Exercise-Induced Hypoalgesia in People with Chronic Low Back Pain

By

Pauline Kuithan

A thesis submitted to the University of Birmingham for the degree of
DOCTOR OF PHILOSOPHY

Centre of Precision Rehabilitation for Spinal Pain

School of Sport, Exercise and Rehabilitation Sciences

College of Life and Environmental Sciences

University of Birmingham

March 2022

Abstract

Chronic low back pain (CLBP) is one of the most prevalent musculoskeletal disorders and a major contributor to disability worldwide. Exercise is recommended in guidelines as a cornerstone of the management of CLBP. One of the manifold benefits of exercise is its influence on endogenous pain modulation. An acute bout of exercise elicits a temporary decrease in pain sensitivity, described as exercise-induced hypoalgesia (EIH). This thesis explores EIH in people with CLBP via a systematic review and observational studies.

The systematic review included 17 studies in people with spinal pain. Of those, four studies considered people with CLBP revealing very low quality evidence with conflicting results. EIH was elicited following remote cycling tasks (two studies, fair risk of bias), but EIH was altered following local repetitive lifting tasks (two studies, good/fair risk of bias).

The observational studies investigated EIH following three different tasks in participants with and without CLBP and explored the stability of EIH results. Conflicting results from quantitative sensory testing were found for whether EIH is impaired in people with CLBP. EIH was only elicited in asymptomatic participants following a repeated lifting task, but both participants with and without CLBP showed EIH following a lumbar resistance and a brisk walking task. This thesis demonstrates the first evidence of stability of EIH over multiple sessions. However, the interpretation of the results can be challenging as stability was poor and changes in lumbar pressure pain thresholds also occurred after rest only.

These findings are important to inform future studies contributing to the elucidation of the complex phenomenon of EIH in people with/without CLBP, specifically as the stability is a prerequisite for future research.

Acknowledgement

When I applied for the PhD position, my presentation included a picture of me on a multiple-day hike carrying a huge backpack up a mountain as an analogy for my academic journey. I experienced all the ups and downs, the highs and lows, my backpack became bigger, full of knowledge and tools; I have learnt and grown up. There were moments full of joy, excitement, and enthusiasm, but it would not be an expedition without storms, blisters, sweat, and tears. When I thought there was no path and felt lost in a whiteout my supervisors reassured me and provided a safety rope to get me back on track. Thank you, Professor Deborah Falla, Professor Ali Rushton, and Dr Nicola Heneghan, for your extraordinary guidance on so many different levels. Your continuous support made this journey safe and was beyond what I could ever ask for. "Doktormutter" Nicola, thank you for your trust in me and the opportunity to further develop my teaching career. You are true role models, and I hope to pass on some of this knowledge to the next generation of physiotherapists.

My friends and family always supported me during my voyages, walked with me, listened to me, were part of many mini adventures along the way, gave me a safe belay, sent me food, shared their dog, cheered me up, accepted me for the free spirit I am, and believed in me even when I could not believe in myself. Thank you for always being there!

I want to thank Dr Nicola Middlebrook and Dr Andy Sanderson for being faithful companions. Thanks to the entire CPR Spine/ UoB team for the time and all the friendships I have made. A special thank goes to Nadège Haouidji-Javaux for creating magical spreadsheets. David McIntyre and Steve Allen, thank you for all the emergency repairs and support. For the trunk rotation project, I want to thank Andy Sanderson for all the help with data collection, and Alessandro de Nunzio and Eduardo Martinez-Valdez for the assistance with the study set up. Nicola Middlebrook, thank you for the great teamwork organising equipment. I want to thank Deepa Abichandani for her contribution as a second reviewer.

Lastly, I want to thank all my participants for their contribution despite multiple sessions of inflicting pain. Without them my research would have not been possible.

I hope after my hardest journey the best views are waiting. As Sir Edmund Hillary said

"It is not the mountain we conquer but ourselves"

List of Publications

The list below provides work which has either been published, presented at conferences, or is in preparation/under review and relates to this thesis directly. At the start of each Chapter a summary will be provided with the use within this thesis. Some sections of this thesis are written verbatim from published work. Further sections of the thesis have been developed from published work and will resemble the published work in terms of structure and content. Copyright permissions are included in Appendix 20.

Published Articles

– Kuithan, P., Heneghan, N. R., Rushton, A., Sanderson, A. & Falla, D. 2019. Lack of exercise induced hypoalgesia to repetitive back movement in people with chronic low back pain. *Pain Practice*, 19, 740-750. DOI: 10.1111/papr.12804

– Kuithan, P., Rushton, A., Heneghan, N.R. 2022 Schmerzmodellierung durch Bewegung - Bewegungs-induzierte Hypoalgesie in der Physiotherapie [Pain modulation through exercise - Exercise-induced hypoalgesia in Physiotherapy] Article in German. *Der Schmerz* DOI 10.1007/s00482-022-00623-3

Additional articles external to the PhD

– Sanderson, A., Cescon, C., Heneghan, N. R., Kuithan, P., Martinez-Valdes, E., Rushton, A., Barbero, M., Falla, D. 2019. People with Low Back Pain Display a Different Distribution of Erector Spinae Activity During a Singular Mono-Planar Lifting Task. Frontiers in Sports and Active Living, 1. Reprinted in Frontiers in Sports and Active Living: Anniversary Edition (May 2020) DOI 10.3389/fspor.2019.00065

Conference Presentations

– Kuithan, P., Heneghan, N.R., Rushton, A., Falla, D. Exercise induced hypoalgesia: stability of measures with functional lumbar spine resistance training. Physiotherapy UK 2019. Birmingham, UK, November 2019 DOI: 10.1016/j.physio.2020.03.068

– Kuithan, P., Rushton, A., Nicola R. Heneghan, N.R., Falla, D. Investigating the repeatability and stability of exercise induced hypoalgesia in healthy adults. Pain Science in Motion III (PSIM). Savona, Italy, May 2019. DOI 10.1097/PR9.0000000000000753

– Kuithan, P., Heneghan, N.R., Sanderson, A., Rushton, A., Falla, D. Patienten mit Kreuzschmerzen erreichen keine bewegungsinduzierte Hypoalgesie durch eine wiederholte Hebeuebung. [Lack of Exercise-Induced Hypoalgesia to Repetitive Back Movement in People with Chronic Low Back Pain] German Society for Physiotherapy Science Research Symposium. Luebeck, Germany, November 2018. Available at http://www.dgptw.org/images/downloads/Wirbelsaeule.pdf

Poster Presentations

– Kuithan, P., Heneghan, N.R., Rushton, A., Falla, D. Stability of Exercise-induced Hypoalgesic Effects in Chronic Low Back Pain. International Association for the study of Pain (IASP) World Congress. Virtual, June 2021

– Kuithan, P., Heneghan, N.R., Sanderson, A., Rushton, A., Falla, D. A repetitive lifting task reveals impaired exercise induced hypoalgesia in individuals with chronic low back pain. World Confederation for Physical Therapy Congress (WCPT). Geneva, Switzerland, May 2019. Available at https://www.abstractstosubmit.com/wcpt2019/archive/#/viewer/abstract/575

– Kuithan, P., Rushton, A., Sanderson, A., Heneghan, N.R., Falla, D. Lack of exercise induced hypoalgesia in response to repeated lifting in individuals with low back pain. Physiotherapy UK 2018. Birmingham, UK, October 2018. DOI: 10.1016/j.physio.2018.11.185

Submitted manuscripts/ poster abstracts under review

– Kuithan, P., Rushton, A., Abichandani, D., Heneghan, N.R., Falla, D. Exercise-induced hypoalgesia in individuals with spinal pain: a systematic review and data synthesis (October 2021) submitted to European Journal of Pain, currently under review

– Kuithan, P., Rushton, A., Abichandani, D., Heneghan, N.R., Falla, D. Exercise-Induced Hypoalgesia in People with Spinal Pain: a Systematic Review and Data Synthesis (March 2022) submitted as poster abstract at the "2022 World Congress on Pain" (International Association for the Study of Pain) in Toronto, Canada

Relevant Awards

– Awarded third best oral presentation at German Society for Physiotherapy Science Research Symposium. Luebeck, Germany, November 2018 for
Kuithan, P., Heneghan, N.R., Sanderson, A., Rushton, A., Falla, D. Patienten mit Kreuzschmerzen erreichen keine bewegungsinduzierte Hypoalgesie durch eine wiederholte Hebeuebung. [Lack of Exercise-Induced Hypoalgesia to Repetitive Back Movement in People with Chronic Low Back Pain] German Society for Physiotherapy Science Research Symposium. Luebeck, Germany, November 2018. Available at http://www.dgptw.org/images/downloads/Wirbelsaeule.pdf

Table of Content

List of Figures

List of Tables

List of Abbreviations

AMSTAR 2= A Measurement Tool to Assess Systematic Reviews 2

ANOVA= Analysis of Variance

BC= Bonferroni Corrections

CDT= Cold Detection Threshold

CI= Confidence Interval

CLBP= Chronic Low Back Pain

CNP= Chronic Neck Pain

CON= Control Group

CPM= Conditioned Pain Modulation

CPT= Cold Pain Thresholds

CSI=Central Sensitisation Inventory

DASS= Depression, Anxiety and Stress Scale

EIH= Exercise-Induced Hypoalgesia

EPM= Endogenous Pain Modulation

ES= Effect Size

FABQ= Fear Avoidance Beliefs Questionnaire

fMRI= Functional Magnetic Resonance Imaging

GRADE= Grading of Recommendations Assessment, Development & Evaluation

HPT= Heat Pain Thresholds

IASP= International Association for the Study of Pain

ICC= Intraclass Correlation Coefficient

ICF= International Classification of Function, Disability and Health

IPAQ= International Physical Activity Questionnaire

IQR= Interquartile Range

L1-5= First to Fifth Lumbar Vertebrae

LBP= Low Back Pain

MD= Mean Difference

MESH= Medical Subject Heading

MDC= Minimal Detectable Change

MRC= Medical Research Council

MVIC= Maximum Voluntary Isometric Contraction

NICE= National Institute for Health and Care Excellence

NOS= Newcastle-Ottawa Scale

NRS= Numeric Rating Scale

ODI= Oswestry Disability Index

PCS= Pain Catastrophizing Scale

PPI= Patient and Public Involvement

PPT= Pressure Pain Thresholds

PPTOL= Pressure Pain Tolerances

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

PSEQ= Pain Self-Efficacy Questionnaire

QST= Quantitative Sensory Testing

RCT= Randomised Controlled Trial

RM-ANOVA= Repeated Measures Analysis of Variance

ROB= Risk of Bias

SD= Standard Deviation

SNK= Student Newman Keuls

SE= Standard Error

SEM= Standard Error of Measurement

SF-36v2=Short Form Health Survey 36 item, version 2

STarT-Back= Subgroups for Targeted Treatment Back (Screening Tool)

STROBE= Strengthening the Reporting of Observational Studies in Epidemiology

TPT= Thermal Pain Thresholds

TS= Temporal Summation of Pain

UK= United Kingdom of Great Britain and Northern Ireland

VAS= Visual Analogue Scale

WAD= Whiplash Associated Disorders

WHO= World Health Organisation

WDT= Warmth Detection Threshold

Chapter One

Introduction

Parts of this introduction, including Figure 1.2, relate to the article cited below. The publication (in German) is attached as Appendix 1 and copyright permission in Appendix 20.

Publication

Kuithan, P., Rushton, A., Heneghan, N.R. Schmerzmodellierung durch Bewegung-Bewegungs-induzierte Hypoalgesie in der Physiotherapie [Pain modulation through exercise - Exercise-induced hypoalgesia in Physiotherapy] Article in German. Invited for special issue "Physiotherapy" in *Der Schmerz (2022)* DOI 10.1007/s00482-022-00623-3

1.1 Low Back Pain

Pain is defined by the International Association for the Study of Pain (IASP) Taxonomy working group as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" (IASP, 2011). It is a complex biopsychosocial experience and usually serves an adaptative role (IASP, 2011). Nociception is different from pain referring to "the neural process of encoding noxious stimuli" (IASP, 2011). A nociceptive stimulus is therefore an actual or potential damaging event which can be detected by nociceptors, high-threshold sensory receptors in the peripheral nervous system (IASP, 2011). From a clinical perspective, musculoskeletal pain may be described in terms of its origins or mechanisms, i.e., nociceptive, peripheral neuropathic, and central sensitisation, or nociplastic (IASP, 2021; IASP, 2011; Smart et al., 2011; Vardeh et al., 2016).

Pain, and specifically low back pain (LBP), is a common complaint of people seeking healthcare treatment (Hartvigsen et al., 2018). LBP is commonly described as pain in the posterior area between the caudal border of the 12th rib and the gluteal folds (Hoy et al., 2014). Up to 90% of all LBP is labelled non-specific LBP, ruling out specific pathologies and also challenging clinical diagnosis, as a specific pathoanatomical cause is unknown (Maher et al., 2017). As a result, management is not targeted at a pathoanatomical cause and instead aims to improve function and reduce pain and/or disability (Maher et al., 2017).

LBP contributes to the high disability worldwide causing a high financial burden and immense reduction of quality of life (Hoy et al., 2014; Vos et al., 2016). LBP is common across all age groups, with a global point prevalence of 540 million people worldwide

(Hartvigsen et al., 2018). Reported lifetime prevalence is up to 85%, with most adults experiencing LBP at some point (Hartvigsen et al., 2018; Roussel et al., 2013). Most people will recover within six weeks, although recurrence rates are high (Hartvigsen et al., 2018). Commonly chronic pain is described as pain persisting for a minimum of twelve weeks (National Institute for Health and Care Excellence (NICE), 2020). This does not fully reflect the complexity of chronic pain, with recurrent chronic pain, (e.g., episodic bouts) not fulfilling the criteria of this classification (Dionne et al., 2008; Stanton et al., 2010). Moreover, the transition from acute pain to chronic pain is not fully understood; it is unlikely a linear process with considerable inter-person variability (Gatchel et al., 2018; Jull et al., 2015), which is influenced by an individual's psychological profile (e.g., fear or anxiety) and can contribute to a mal-adaptive pain response (Hartvigsen et al., 2018; Hasenbring et al., 2014). Nevertheless, it has been purported that 33 to 66% of people with LBP develop chronic low back pain (CLBP) (Marcuzzi et al., 2015); with one study reporting that up to 25% of participants with LBP develop chronic widespread pain within five years (Kindler et al., 2010). This contributes to high direct and indirect costs (Hartvigsen et al., 2018).

The relationship between pain and disability and the tipping point of when pain causes disability is not sufficiently studied and might highly depend on the individual person. Factors such as self-efficacy, fear, or psychological distress should be considered (Lee et al., 2015; O'Sullivan et al., 2016). Worldwide only 28% of people have LBP which is considered as severe, but those account for 77% of LBP related disability leading to over 46,000,000 years lived with disability (Hartvigsen et al., 2018). In primary care, patients with minimal or moderate disability or severity of symptoms are common. For example, in a randomised controlled trial (RCT) of stratified care for the management of LBP in the United Kingdom of Great Britain and Northern Ireland (UK), the mean pain intensity was 5.3/10 and 5.2/10 for

the intervention and control group respectively (Hill et al., 2011). The stratification of 851 participants classified 26% of them as of low risk of persistent disability (mean pain intensity of 3.4/10 and 3.5/10; Roland Morris Disability questionnaire indicated minimal disability 4.6/24 and 4.2/24) (Hill et al., 2011). Findings reveal that people with low to moderate levels of pain or disability also contribute to the burden of healthcare.

A range of classification systems exists to guide clinicians with management decisions, with most centred on movement and/ or psychological factors (Hill et al., 2011; O'Sullivan, 2005; O'Sullivan, 2012; Schafer et al., 2014; Stanton et al., 2011). However, to meet the demands of a biopsychosocially informed management, multiple factors should be combined (Falla and Hodges, 2017). For example, the Subgroups for Targeted Treatment Back (STarT-Back) screening tool, a brief questionnaire to stratify care, includes psychological factors and body function (Hill et al., 2011). Another example is the classification of lower back related leg pain, which includes measures of pain sensitivity (Schafer et al., 2014). Changes in pain sensitivity, specifically the acute response to exercise, are currently not reflected in classification approaches.

1.1.1 Biopsychosocial Implications of Low Back Pain

A biopsychosocial approach to the management of LBP has been advocated for many years (Jull et al., 2015; Waddell, 1987) with all domains (biomedical, psychological, and social) needing to be considered. The International Classification of Function, Disability and Health (ICF) promotes a holistic approach (World Health Organisation (WHO), 2002) where a model to facilitate personalised care comprises a biopsychosocial management approach (Figure 1.1).

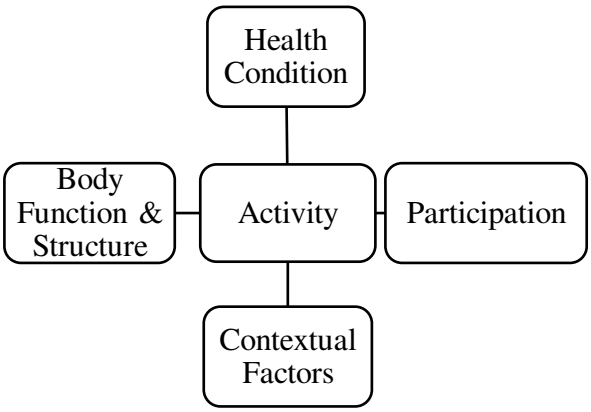


Figure 1.1 Model of Disability

Adapted from the World Health Organisation (2002)

Biological factors (e.g., genetic predisposition, degeneration, such as endplate lesions, chronic conditions, poor mental health, and lower health literacy) are risk factors for the development of CLBP (Hartvigsen et al., 2018; Pincus et al., 2013). Furthermore, altered kinematics, such as increased stiffness of the spine, and altered neurophysiological responses, such as changes in the distribution of muscular activity or greater fatigue, have been observed in people with LBP (Falla et al., 2014; Goubert et al., 2016; Haddas et al., 2016; Masse-Alarie et al., 2016; O'Sullivan, 2012; Shojaei et al., 2017). Interactions between psychological factors and motor behaviour have been identified in a recent systematic review (Christe et al., 2021); the effect size was small, but implied the interdependence of the two domains.

Psychological distress (e.g., fear avoidance beliefs, depression, or catastrophising), is associated with disability in people with LBP (Hartvigsen et al., 2018). Patient reported outcome measures are recommended as routine in the UK as part of stratified care to inform management planning (NICE, 2020). Focussing on chronic presentations, in about 50% of people with CLBP psychological distress plays a major role and often requires additional specialised treatment (Apeldoorn et al., 2012).

Social factors exist at an individual and group level (Pincus et al., 2013). The individual's social and cultural identity as well as not fulfilling social expectations can lead to substantial social consequences such as social withdrawal or family strain (Hartvigsen et al., 2018). Additional social factors are located within the occupational setting and thus linked to socioeconomic status (Hartvigsen et al., 2018). Employment, and especially job satisfaction, incapacity legislation, or benefits can negatively impact on the treatment outcome (Edwards et al., 2016; Pincus et al., 2013). This goes beyond the actual occupational task, which is often discussed to provoke the onset of LBP. This could include manual labour, awkward positions, or heavy lifting (Hartvigsen et al., 2018). Repetitive lifting, which could also account for a biological factor, has been considered as a potential factor associated with the development but also perpetuation of LBP (Power et al., 2001). However, level one evidence based on eight studies could not support this hypothesis revealing no causation for lifting and pain in people with LBP (Kwon et al., 2011).

1.1.2 Exercise for the Management of Low Back Pain

Exercise is the cornerstone of physiotherapy management of LBP (Foster et al., 2018). Physical activity describes any movement requiring energy expenditure by skeletal muscles (Caspersen et al., 1985). Exercise is a sub-category of physical activity which aims to maintain or improve a minimum of one component of physical fitness and is characterised as planned, structured, or repetitive (Caspersen et al., 1985; Geneen et al., 2017).

Exercise is well established as having positive effects on all three domains of the biopsychosocial model. Public Health England (2020) summarises improvement of biological

factors such as strength and endurance, psychological factors, such as mental well-being and self-efficacy, as well as social factors, such as social inclusion and employability. Thus, it is important to understand, that the effects of exercise are not solely based on musculoskeletal structural changes alone (Steiger et al., 2012) and in line with the ICF model, holistic changes should be considered.

Multiple national and international best practice guidelines and recommendation for the management of LBP advocate exercise as a first line recommendation (NICE, 2020; Oliveira et al., 2018; Qaseem et al., 2017). Numerous different exercises have been investigated (Table 1.1), but precise recommendations supported by a body of high-quality evidence have yet to be determined.

Table 1.1 Common exercises for the management of low back pain

References (Hayden et al., 2021b; Owen et al., 2020)

Exercise	**Definition**	**Supported in review**
Resistance/ strength	Increase ability to exert or resist force using load bearing or weight	+
Aerobic	Improvement of cardiovascular fitness	+
Yoga	Principle with different styles such as strengthening, stretching, or breathing	
Directional Preferences/ McKenzie	Specific loading/ postural training/ traditional principle	+
Functional training/ restoration	Focus on function and activities, especially in chronic pain populations	+
(Core) Stabilisation/ Pilates/ Motor control/	Improve control, coordination, strength within the "core" region	++
Stretching	Elongation of (soft) tissue	
Flexibility	Active mobilisation of joints	
Water-based	Aqua therapy	
Multimodal	Any combination	

Legend: *+= supported by one review; ++= supported by two reviews*

A recent Cochrane review (249 trials, participants n=24486) of exercise therapy for people with CLBP (Hayden et al., 2021a) reported moderate certainty evidence supporting the

positive effect of exercise compared with no, usual, or placebo treatment for pain (mean difference (MD) -15.2, 95% Confidence Interval (CI) [-18.3; -12.2]) and functional outcomes (-6.8 [-8.3; -5.3]). A subsequent network analysis (217 RCTs, participants n=20969) found greater effects for regaining function and decreasing pain after Pilates, McKenzie (repeated directional preference exercises), flexibility (function only), and functional exercise (pain only) (Hayden et al., 2021b). Another network analysis by Owen et al. (2020) (89 RCTs, participants n=5578) found low quality evidence that the most effective exercises for reducing pain compared with a control group was Pilates (MD -1.86 95% CI [-2.5; -1.2]) and resistance exercise (-1.14 [-1.7; -0.6]). Stabilisation/ motor control had the highest probability to improve physical function (-1.13 [-1.5; -0.74]); and aerobic (-1.18 [-2.2; -0.2]) and resistance exercise (-1.26 [-2.1; -0.4]) had the highest probability to improve mental health (Owen et al., 2020).

Previous reviews have focussed on specific exercises: Therapeutic exercise, consisting mainly of various forms of resistance exercise, reduced pain in the short term based on a meta-analysis (6 RCTs, participants n= 664; Hedges g=-0.53 95% CI [-.9; -0.2]) (Bertozzi et al., 2013). Another meta-analysis (45 RCTs, participants n= 4462) found exercise effective to reduce pain compared to control or other treatments (MD -0.32 95% CI [-0.4; -0.2]; subgroup analysis favoured resistance (11 RCTs, n=885, Effect Size (ES) -.50 [-0.8; -0.2]) and coordination (12 RCTs, n=1343, -0.47 [-0.8; -0.2] protocols and did not support aerobic and combined programs (Searle et al., 2015). However, a more recent review (5 RCTs, participants n= 329) suggested walking as an alternative for exercise as results did not differ significantly compared to other exercise or exercise plus walking (Vanti et al., 2019). Stabilisation exercises have been shown to be successful for the management of participants with CLBP (11 RCTs, participants n=413, pain: weighted MD -1.03 95% CI [-1.3; -0.3];

disability -5.41 [-8.3; -2.5]) (Gomes-Neto et al., 2017). A previous Cochrane review of motor control exercises found effectiveness to only reduce pain in the short-term (13 RCTs, participants n=872, MD -7.53 95% CI [-10.5; -4.5]; but found no clinical superiority over other forms of exercise (Saragiotto et al., 2016).

This section highlights the effectiveness of exercise for the management of LBP, but no specific form of exercise has yet been found to be superior to another (Foster et al., 2018; Hayden et al., 2021a). Furthermore, it highlights that terminology around exercise has been used inconsistently. Whilst general goals for exercise (e.g., improved motor control, strength, endurance, flexibility) have been described (Falla and Hodges, 2017), a definitive classification for spinal exercises, such as that proposed by Spencer et al. (2016), has not yet been comprehensively investigated to inform implementation. Additionally, the immediate analgesic effects should also be considered when prescribing exercise (Falla et al., 2014).

1.2 Endogenous Pain Modulation

Endogenous pain modulation (EPM) refers to the ability of the body to inhibit or facilitate the experience of pain (Ossipov, 2012). Occurring across multiple different peripheral, spinal, and supraspinal levels and structures (Bingel and Tracey, 2008), EPM involves both sensory (i.e., nociception) and affective systems (i.e., lived pain experience) (Ossipov, 2012) (See Figure 1.2). EPM can contribute to survival in extreme situations and to the evaluation of whether nociception is still a source of danger (Woolf, 2011). However, pain can also persist or be evoked without external stimuli (Woolf, 2011). In asymptomatic people, pain inhibition and facilitation build a balanced equilibrium (Li et al., 2019).

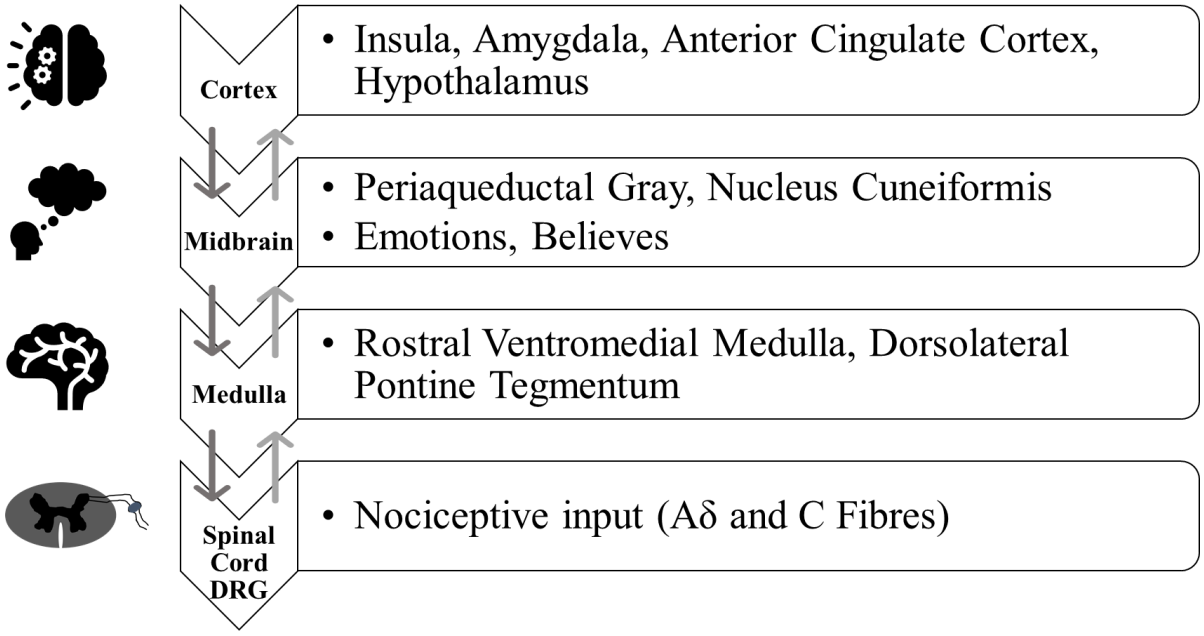


Figure 1.2 Overview of Pain Modulation

Translated from German (Kuithan et al., 2022); DRG= Dorsal root ganglion, arrows indicate ascending and descending pathways

Complex facilitating and inhibiting ascending and descending pathways are involved in pain processing, leading to different experiences or perceptions of pain as outlined in further detail by Kwon et al. (2014). Top-down pain modulation is mainly controlled by monoaminergic pathways, which include serotonin (5-HT), norepinephrine, and dopamine (Kwon et al., 2014; Li et al., 2019). While research investigating EPM commonly involves these biomarkers, different approaches have been used in laboratory settings to reproduce and investigate EPM such as exercise-induced hypoalgesia (EIH) and conditioned pain modulation (CPM) for pain inhibition, or temporal summation of pain (TS) for facilitation of pain. Clinically, pain modulation has also been investigated as an inhibitory effect of treatment interventions, including manual therapy (Bialosky et al., 2018; Bishop et al., 2015).

1.2.1 Sensitisation

Mal-adaptive EPM has been associated with the term sensitisation and with a subgroup of participants with CLBP (Roussel et al., 2013). The IASP defines sensitisation as "increased responsiveness of nociceptive neurons to their normal input, and/or recruitment of a response to normally subthreshold inputs" (2011). Central sensitisation however is defined as an "increased responsiveness of nociceptive neurons in the central nervous system to their normal or sub-threshold afferent input" (IASP, 2011). Peripheral sensitisation is considered a local phenomenon which is linked to decreased thresholds of nociceptors and therefore increased responsiveness due to changes in transducer receptors and ion channels (Vardeh et al., 2016). This is linked to the protection of damaged or inflamed tissue and is also referred to as the zone of primary hyperalgesia (Vardeh et al., 2016); an increased response to a stimulus which would normally be perceived painful (IASP, 2011). In central sensitisation, both ascending and descending pathways are involved and lead to different patterns of brain activity, in turn this affects both peripheral and central reorganisation, and descending inhibition (Apkarian et al., 2009).

1.3 Exercise-Induced Hypoalgesia

1.3.1 Definition and Overview

The phenomenon of EIH is described by Naugle et al. (2012) as an acute hypoalgesic response to a bout of exercise which reduces sensitivity to painful stimuli. Therefore, EIH refers to a temporary change in pain sensitivity. Hypoalgesia is defined as "diminished pain in

response to a normally painful stimulus" by the IASP (2011), thus implying that lower sensitivity or a lower response to the testing stimulus is found immediately following exercise. Alternatively worded, exercise leads to a raised pain threshold or tolerance.

EIH is described as an acute response, reflecting within-session changes in pain sensitivity (Naugle et al., 2012), which will be considered in this thesis. However, the term EIH has also been used to describe changes over multiple sessions. For example, there is level one evidence confirming changes in pain sensitivity after multiple sessions of exercise over a longer period of time (Barros Dos Santos et al., 2021; Belavy et al., 2021; Polaski et al., 2019). Terms used interchangeably in the literature with EIH comprising any of the following: 1) endogenous pain inhibition/ modulation, 2) diffuse noxious inhibitory control (DNIC), a term originating from inhibition of wide dynamic range neurons in the dorsal horn which was first researched in rodents (Cummins et al., 2020), or 3) change in sensitivity to physical activity (Wideman et al., 2014; Woznowski-Vu et al., 2019). However, some of these terms are also used for CPM, highlighting the inconsistency of use of terminology around the phenomenon of EIH.

The first published overview of EIH was in 1996; Janal summarised 15 studies, most supported the occurrence of EIH after aerobic exercise in healthy men (Janal, 1996). A meta-analytic review was published by Naugle et al. in 2012 (25 studies, participants n= 622). For asymptomatic participants the mean effect size was moderate for aerobic exercise (11 studies, n= 136; pain threshold: ES=0.41; pain intensity: ES=0.59) but large for isometric exercise (12 studies, n=267, ES=1.02; ES=0.72) and dynamic resistance exercise (2 studies, n=34, ES=0.83; ES=0.73) (Naugle et al., 2012). The interest in the phenomenon of EIH is evident with numerous review publications since (Lima et al., 2017; Nijs et al., 2012; Rice et al., 2019; Roussel et al., 2013; Sluka et al., 2018). The most recent review identified over 150

publications on EIH (Vaegter and Jones, 2020) and highlighted inconsistency in the design and outcome of those studies. Across the included studies in that review, some reported EIH, but others showed hyperalgesia or no change in pain sensitivity (Vaegter and Jones, 2020).

No systematic review had been published at the beginning of this doctoral study (2017), as the meta-analytic review was not reported systematically (Naugle et al., 2012). An overview of systematic reviews published is provided in Table 1.2. The quality was rated applying A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2) (Shea et al., 2017). A high quality systematic review reported large EIH effects for aerobic (7 RCTs , participants n= 236; Hedges' g =-.85 95% CI [-1.58; -.13]) and small effects following dynamic resistance exercise (2 RCTs, n=23; g =-.45 [-.69; -.22]), but no effects for isometric exercises (3 studies, n=177, g =-.16) in asymptomatic participants (Wewege and Jones, 2021). Another systematic review of moderate quality, including 36 studies of different designs, found a homogenous and statistically significant effect for EIH in asymptomatic participants (n= 1326, ES=0.19, 95% CI [0.11; 0.27]) (Pacheco-Barrios et al., 2020).

Table 1.2 Overview of systematic reviews on Exercise-Induced Hypoalgesia

Review	Objective	Included study designs	Population/ Sample size	Exercise	Comparison	Outcome	Result	AMSTAR 2 Quality
(Bonello et al., 2021) Studies= 13	1) do isometric exercises produce EIH 2) the effect on patient reported measures of pain	RCT non-randomised repeated measures trials	Participants with local MSK pain Participants n= 346	Isometric exercise	Any non-isometric interven-tion	Experimental induced pain thresholds, measures of pain sensiti-vity; post-test within 2hrs	No consistent evidence	Overall good Uncertainty about eligibility criteria & synthesis of evidence
(Pacheco-Barrios et al., 2020) Studies= 36	To evaluate exercise pain perception modulation indexed by pain threshold change	RCT (parallel, crossover and pilot) and quasi experimenta l studies	Asymptomatic participants n= 1326	any	unclear	Pain threshold	Small to mod-erate effects for EIH, higher for resistance exercise, mod-erate intensity, & women	Overall moderate Some uncertainty on protocol, comparison, risk of bias tool, synthesis, & peer review process
(Wewege and Jones, 2021) Studies= 13	Does exercise cause a reduction in experimentally induced pain	RCT (crossover or parallel)	Participants with & without chronic MSK pain n= 423 without/ 114 with pain	Standar-dised bout of exercise	non-exercise control condition	Sensitivity to any form of quantitative sensory testing Pre/ post-test within 1hr	Low confidence that aerobic & dynamic exer-cises reduce experimental pain in asymptomatic participants	Overall high List of excluded studies not provided
(Munneke et al., 2020) Studies= 9	To investigate the association between psycho-social factors and EIH	Cross sectional studies	Participants with & without MSK pain; n= 220 without/ 151 with pain	Single exercise session	N/A	EIH and ≥1 psycho-social factor Post-test within 0.5 hr	No conclusion due to poor quality and high heterogeneity	Overall good Some uncertainty about eligibility & synthesis

Reviews included since 2017 and assessed with AMSTAR 2 (Shea et al., 2017)

Abbreviations: *RCT= Randomised Controlled Trial; EIH= Exercise-induced Hypoalgesia; MSK= Musculoskeletal, hrs= hours, N/A= Not Applicable; AMSTAR 2=A Measurement Tool to Assess Systematic Reviews 2*

1.3.2 Mechanisms of Exercise-Induced Hypoalgesia

Underlying mechanisms of EIH are manifold, complex, and still not fully understood (Vaegter and Jones, 2020). An overview of common mechanisms discussed in the literature is presented in Table 1.3 at the end of this section. Further physiological details are beyond the scope of this thesis, but are outlined by Da Silva Santos and Galdino (2018) or Cooper et al. (2016). Briefly summarised, when a skeletal muscle contracts, it facilitates mechanosensitive afferents triggering a cascade of descending opioid pathways and release of endocannabinoids in both the peripheral and central nervous system (Vaegter and Jones, 2020). Activation of the central inhibitory pathways is facilitated via opioid, serotonin, and N-methyl-D-aspartate (NMDA) mechanisms in the rostral ventromedial medulla and periaqueductal gray (Figure 1.2, section 1.2) (Lima et al., 2017). Peripheral mechanoreceptors can be activated by exercise and might be a contributing factor (Baeske, 2016). Moreover, central and muscular fatigue are thought to be related to an increase of non-nociceptive C-fibre activity, which could facilitate descending inhibition (Viggiani and Callaghan, 2021).

A recent review further supports some of the mechanisms behind EIH and provides explanatory evidence based on animal models (Lesnak and Sluka, 2020). One of the key challenges in animal studies is the differentiation between EIH and stress-induced hypoalgesia. In free-running animals voluntary exercise elicited EIH, and was shown to be able to prevent or reverse hyperalgesia in inflicted conditions such as neuropathic pain (Lesnak and Sluka, 2020). The intensity of training was linked to the extent of EIH, whereas the frequency of exercise did not alter EIH (Lesnak and Sluka, 2020). This is partially in contrast to findings from a review of human participants with chronic pain, that indicates that the increase of frequency improves outcomes (Polaski et al., 2019). Performance until

exhaustion might block hypoalgesia and lead to hyperalgesia instead, which was found to a greater extent in sedentary animals (Lesnak and Sluka, 2020). Further research is required to have confidence of the relevance of these findings to humans.

It is hypothesised that the equilibrium of ascending and descending pathways can be disturbed in people with chronic pain (Lima et al., 2017; Sluka et al., 2018). For example due to a lesser amount of M2 macrophages fewer anti-inflammatory cytokines are released, which inhibit nociceptors at injured sites (Sluka et al., 2018). This is further associated with chronic pain conditions or sedentary behaviour and may partially explain why some participants present with hyperalgesia as a response to an exercise task which normally leads to hypoalgesia (Lima et al., 2017; Sluka et al., 2018).

Table 1.3 Mechanisms of Exercise-Induced Hypoalgesia

References: (Baeske, 2016; Cooper et al., 2016; Ellingson et al., 2016; Gajsar et al., 2020; Geisler et al., 2019; Jones et al., 2017; Koltyn et al., 2014; Lesnak and Sluka, 2020; Padawer and Levine, 1992; Rice et al., 2019; Vaegter et al., 2020b; Van Oosterwijck et al., 2013; Viggiani and Callaghan, 2021)

Interaction between central mechanisms	**Central mechanisms** multi-segmental and segmental
	Opioidergic system endorphins and enkephalins • Opioid receptor antagonists (naloxone) blocked analgesic effects systematically and in RVM and PAG • Mu-opioid receptors activation involved in EIH • Peptides, beta-endorphin, met-enkephalin and leu-enkephalin, in PAG, RVM, hypothalamus, cortex, and/or DRG
	Serotonergic system (5-HT) • elevated post exercise in brainstem, spinal cord, cortex, cerebellum, and midbrain • RVM serotonin transmitter, reduced by opioid expression, facilitates EIH
	Endocannabinoids in PAG, RVM and dorsal horn • ligands, anandamide, and 2-arachidonylglycerol bind cannabinoid receptors (1,2) receptors producing analgesic effects • interaction with opioid system suggested
	NDMA/ excitatory glutamate receptors • exercise can block NR1 (subunit of NMDA receptor) preventing activation of NMDA receptors/ hyperalgesia
	Noradrenergic system

	• increase release of catecholamines (α1, α2, β2 adrenergic receptors) • found in PAG, locus coeruleus, dorsal raphe, spinal cord, DRG
	Adenosine receptors • A1 adenosine receptors produce EIH centrally and peripherally
	Spinal cord/ DRG (rather long-term changes, than acute bout) • Neurotransmitter, intracellular messengers, transcription factors, and growth factors • Mechanisms due to alternating electrophysiological changes from injury
	Brain: BDNF, TrkB, IGF-1, NMDA noradrenergic system increase in brain, Spinal cord: GDNF increase, nitric Oxide increased in cerebrospinal fluid, HSP70 increase, decrease of IL6, TNF-a, NR1 DRG: Increase of BDNF, NT-3, SNAP1, GAP43, HSP70; decrease NGF, Substance P, NR1, TRPV1, TRPM8, phosphorylated-p38, IL6, IL1β
	Neuroimmune mechanisms (central and peripheral)
	Reduced Pro-inflammatory cytokine (TNF-a, IL-1b, and IL-6)
	Central: increased anti-inflammatory cytokine (IL-4, IL-1ra, IL-5, and IL-10) Peripheral: decreased in anti-inflammatory cytokines (IL-4, IL1ra, and IL-10)
	Increased pro-inflammatory cytokines (TNF-a, IL-1b, and IL6) and chemokine CCL2
	Increased number of M2 vs M1 macrophages, increased serum IL-10,
	Decreased IL-1b and CCL2 in the serum and sciatic nerve
	Decrease of IL-1b, TNFa, and leptin
	Increase T-cells, decrease mechanical and thermal hyperalgesia
	Peripheral mechanisms
	Peripheral opioid antagonist showed no effect on EIH in animals
	Peripheral A1 adenosine receptors
	Peripheral mechanoreceptors activated potentially inhibiting nociceptors
	Axon: Increase of Axonal growth, GDNF and BDNF, Schwann Cell Proliferation Free nerve endings: Normalisation Trka positive fibres, increase epidermal innervation, decrease NGF
	Nitrergic system: nitric oxide in plasma increases
	Others
	Education (pain or EIH) and expectation
	Cognitive inhibition ability
	Fatigue
	Stress: release of stress-hormones / plasma change might facilitate EIH
	Artefact from testing
	Cardiovascular system: Elevated blood pressure activates baroreceptors affecting pain modulation in the brain, would not explain longer effects
	Gate Control Theory as exercise activates large diameter afferent nerve fibres
	Stimulation of primary motor cortex, corticospinal tracts, high threshold motor units

Abbreviations: *RVM= rostral ventromedial medulla; PAG= periaqueductal gray; EIH= Exercise-induced hypoalgesia; 5-HT= 5-hydroxytryptamine/ serotonin receptors; DRG= dorsal root ganglion; NDMA= N-methyl-D-aspartate ; BDNF= Brain Derived Neurotrophic Factor; TrkB= Tropomyosin receptor kinase B, IGF-1= Insulin-like growth factor 1; GDNF= Glial cell-derived neurotrophic factor; HSP70= Heat shock protein 70; IL= Interleukin, TNF-a= Tumor necrosis factor; NT-3= Neurotrophin-3; SNAP1= Soluble NSF Attachment Protein, GAP43= Growth Associated Protein 43; NGF= Nerve growth factor; TRPV1= Transient receptor potential cation channel subfamily V member 1; TRPM8= Transient receptor potential cation channel subfamily M, CCL2= C-C Motif Chemokine Ligand 2; Trka= Tropomyosin receptor kinase A*

1.3.3 Assessment of Exercise-Induced Hypoalgesia

The phenomenon EIH cannot be directly measured, but pre-/post exercise testing of pain sensitivity has been commonly used as a means of assessment (Naugle et al., 2012; Wewege and Jones, 2021). Quantitative sensory testing (QST) is commonly used, typically comprising test modalities of pressure pain thresholds (PPT) or thermal pain thresholds (TPT) (Wewege and Jones, 2021). Other approaches include pharmacological approaches such as interactions with opioid antagonists (Bruehl et al., 2020; Crombie et al., 2018; Koltyn et al., 2014), blood tests or invasive microdialysis (Gerdle et al., 2014; Meeus et al., 2010), functional magnetic resonance imaging (fMRI) (Ellingson et al., 2016; Scheef et al., 2012), and somatosensory or laser evoked potentials (Jones et al., 2016). No validated or recommended test battery has yet been published with the express aim to assess EIH. Furthermore, there is limited evidence examining the appropriateness or equivalence of approaches to assess EIH (Baiamonte et al., 2017; Hviid et al., 2019; Jones et al., 2019). This also applies for the test site, with optimal testing sites yet to be determined. Data triangulation in the form of different test modalities and sites can enhance reliability and validity and reduce bias towards a specific hypothesis (Sim and Wright, 2002).

There is no consensus on which level of a pre-post change in pain sensitivity following exercise can be accounted for as EIH. Some studies refer to statistically significant differences, most commonly for the repeated measures analysis of variance (RM-ANOVA) (Meeus et al., 2010; Vaegter et al., 2016). In line with research on CPM, a percentage increase of baseline PPT based on the standard error of measurement (SEM) was calculated to identify a meaningful change (Locke et al., 2014). A similar approach to SEM has been applied in some studies on EIH by one research group; in these studies, a meaningful change was

considered if the absolute change was greater than the SEM (Vaegter et al., 2018; Vaegter et al., 2019b).

When considering the time point of the post-test it is important to consider the duration of the effect of EIH. This is not clearly defined, although an upper limit of 30 minutes has been suggested, however, this might depend on intensity and stimulus (Naugle et al., 2012). With robust evidence lacking and 30 minutes derived from a single study which used an ergometer task with and without administration of dexamethasone assessing dental pain thresholds in six asymptomatic participants, caution should be taken regarding generalisability to other populations and exercise tasks (Kemppainen et al., 1990). Nevertheless, it is postulated that effects are most pronounced in the first 15 minutes after the exercise (Naugle et al., 2012). However, this might be dependent on other factors, such as exercise intensity or type. One study confirmed the presence of EIH after five minutes of resistance training, but not 15 minutes after the task (Koltyn and Arbogast, 1998). Another study showed that EIH persisted five and 15 minutes following an aerobic task (Koltyn et al., 1996). Additionally, a more recent study showed changes in pain sensitivity after arm cycling for up to 24 hrs (Grimby-Ekman et al., 2020). However, systematic reviews restricted the timeframe for post-tests from immediate to 120-minutes post-exercise (Bonello et al., 2021; Munneke et al., 2020; Pacheco-Barrios et al., 2020; Wewege and Jones, 2021).

1.3.3.1 Quantitative Sensory Testing

QST describes psychophysical tests of different somatosensory functions, where the participant reports perception of a controlled stimulus (Mucke et al., 2016; Rolke et al., 2006b). A peripheral nociceptive or sensational stimulus is used to gain information about

pain processing, and loss or change in function reported by the individual (Mucke et al., 2016). Given the psychophysical nature of QST, it is considered a performance-based outcome measure and suited to pain sensitivity evaluation in a laboratory setting and feasible in clinical practice (Reimer et al., 2020; Zhu et al., 2019). QST has been used to cluster participants to different phenotypes based on sensory characteristic (Baron et al., 2017; Coronado et al., 2014; Finnern et al., 2021; O'Neill et al., 2014; Rabey et al., 2015; Smith et al., 2017c; Vaegter and Graven-Nielsen, 2016).

QST can identify different levels of sensory thresholds including:

- *Detection threshold* - refers to the first perceived change in sensation when applying a tactile stimulus (Mucke et al., 2016). Higher acuity has been noted for noxious stimuli (Adamczyk et al., 2021).
- *Pain threshold* - refers to the lowest stimulus intensity which will be perceived as pain (IASP, 2011).
- *Pain tolerance* - refers to the highest stimulus intensity a subject is willing to tolerate (IASP, 2011).

For pain thresholds slower Aδ and unmyelinated C fibres and their projection pathways, i.e., spinothalamic tract, are tested (Table 1.4) (Hubscher et al., 2013). Next to static QST measures, where one stimulus is applied, dynamic QST can further assess the response to prolonged or repetitive stimuli (Cruz-Almeida and Fillingim, 2014; Mucke et al., 2016).

Table 1.4 Overview of stimuli and fibres for pain thresholds

References (Cruz-Almeida and Fillingim, 2014; Mucke et al., 2016; Rolke et al., 2006b)

Stimulus	Fibre type	Central/ peripheral sensitisation	Device (example)
Pressure Blunt for deeper tissues	C, Aδ	Centrally not examinable or unchanged, evidence unknown Peripherally sensitisation increased, evidence unknown	Pressure algometer or pressure gauge device [Somedic, Sweden/ Wagner, USA], pin prick (skin), cuff pressure
Thermal heat skin	C, Aδ	Centrally not examinable or unchanged, evidence unknown Peripheral sensitisation with increased sensitivity	Thermal tester [Medoc, Israel]
Thermal cold skin	C, Aδ	Central sensitisation increased Peripherally not examinable or unchanged	Thermal tester [Medoc, Israel]

Amongst other factors, ethnicity, gender, age, mood, sleep, reaction time, and stress potentially influence QST measures (Cruz-Almeida et al., 2013; George et al., 2007; Geva et al., 2014; Hansen et al., 2015; Onen et al., 2001). Level one evidence (16 studies, participants n=1965) confirmed that psychological factors, such as catastrophising, depression, and pain related fear, negatively influence QST measures (Othman et al., 2020).

Studies evaluating baseline QST in people with LBP indicate that at least one subgroup exist with those presenting with peripheral and/or central sensitisation (Gerhardt et al., 2016; Imamura et al., 2013; Lewis et al., 2010; Puta et al., 2013; Roussel et al., 2013). Some studies showed that baseline QST in people with CLBP differed from those with chronic widespread pain or fibromyalgia (Finnern et al., 2021; Gerhardt et al., 2016; Smart et al., 2011). High inter-individual variation of baseline measures is common in QST testing and, moreover, there is insufficient evidence that individual pain sensitivity levels affect treatment outcome (Klyne et al., 2019; O'Leary et al., 2017). Commonly applied QST assessment approaches are outlined in the following sections.

Guidelines now exist for QST primarily with the aim to detect neuropathic pain or central sensitisation and have been modified for clinical use over one impaired and one unimpaired test site using different test modalities (Maier et al., 2010; Rolke et al., 2006a; Rolke et al., 2006b). The pre-requisites for EIH evaluation should usefully consider or include the following: short testing duration as effects of EIH might not be present for longer than 30 minutes; sensitisation of tissue due to repeated testing; or interference from the exercise due to other factors such as changes in temperature. There is a lack of consensus about the optimum test site, and whether the test site matters (local or remote in relation to the painful body region or exercise (Hubscher et al., 2013). Some research indicates that topographical maps, a visualised representation of multiple test sites over a muscle or body region may better represent changes in QST (Binderup et al., 2011; Koo et al., 2013; Ribeiro et al., 2016).

1.3.3.1.1 Mechanical Stimuli

PPT and Pressure Pain Tolerances (PPTOL) are the most used mechanical stimuli and can both be tested with an algometer (Table 1.4.).

Testing PPT activates myofascial afferents, which are sensitive to pressure, and can be used to assess both peripheral and central sensitisation (Rabey et al., 2015). Schmitt et al. (2020) hypothesised that PPT better detect EIH over cutaneous (thermal) stimuli, as nociceptors in muscles present with stronger descending inhibition. Most mechanical assessments have sufficient to very good test-re-test reliability (different forms of analysis), including tests in people with LBP or other pain populations, and over shorter time periods, such as within day or between day reliability (Cruz-Almeida and Fillingim, 2014; Middlebrook et al., 2020; Vuilleumier et al., 2015; Walton et al., 2011). Within-session test-

re-test reliability (stability) has been tested within studies including a rest period. For example, a recent study assessed reliability of PPT over the lumbar region and forearm with a 20 minute rest in asymptomatic participants (Mailloux et al., 2021a). In agreement with findings stated above, for PPT the intraclass correlation coefficient (ICC) were excellent (ICC 2,1 ≥.80) based on two or three measurements, although only moderate reliability was noted for the first measurement (Mailloux et al., 2021a). The use of the mean of two consecutively repeated pressure pain tests over the lower back has been further supported previously (Balaguier et al., 2016a; Balaguier et al., 2016b). However, validity has been investigated less in people with spinal pain (Jorgensen et al., 2014; Schenk et al., 2007). For example, criterion related validity has been shown for a handheld algometer based on a force plate or compared with a computer controlled algometer confirming the clinical use of handhold algometry (Kinser et al., 2009; Koo et al., 2013).

Level one evidence synthesis based on 24 studies found lower PPT over remote test sites in people with LBP (PPT scapula: 6 studies, n=464 asymptomatic/ 229 LBP, MD 119.20 kPa 95% CI [91.8; 146.6]; arm: five studies, n= 203/ 314, 36.32 kPa [2.27; 70.37]; gluteal: four studies, n= 173/ 190, 218.93 kPa [49.69; 387.57]; lower leg: five studies, n= 91/ 112, 68.71kPa [19.15; 117.86], but not over the hand) (den Bandt et al., 2019).

Considering the approach of producing topographical maps, the lumbar spine area has only been explored in a few studies (Balaguier et al., 2016a; Balaguier et al., 2016b; Binderup et al., 2011; Falla et al., 2014; O'Neill et al., 2019; Schenk et al., 2007). Five studies included participants with and without LBP. Of those, two showed that PPT varied between locations (Binderup et al., 2011; O'Neill et al., 2019), whereas three studies did not show any difference between the test sites (Falla et al., 2014; Koo et al., 2013; Schenk et al., 2007). Only one study tested EIH in people with and without CLBP (Falla et al., 2014).

Less research has been conducted testing PPTOL. One of the reported challenges is that tolerance thresholds are not reached within the safety limitations of the device (Middlebrook et al., 2020), or some studies limit the pain tolerance, for example to 1000 kPa (Neziri et al., 2012). Alternatively, cuff pressure has been applied for pain tolerance testing (Hviid et al., 2019; Vaegter and Graven-Nielsen, 2016). One study suggested that pain tolerances were more indicative of EIH related changes than PPT after a dynamic circuit training (Baiamonte et al., 2017), but the effect was only present immediately, and had disappeared for repeated measures at five and 15 minutes. Similar results were found in another study in asymptomatic people immediately after submaximal isometric knee extension (Vaegter et al., 2017a). Hviid et al. (2019) showed changes in PPTOL but not PPT after a walking task. Therefore, pain tolerance might be different to pain thresholds based on findings in these studies and could add further insight about underlying EIH mechanisms.

1.3.3.1.2 Thermal Stimuli

Altered TPTs have been found in participants with LBP (Hubscher et al., 2014; Rabey et al., 2021; Roussel et al., 2013). There is level one evidence (21 studies) showing fair to excellent reliability for TPT based on multiple forms of analysis, but slightly lower reliability for thermal detection thresholds (Moloney et al., 2012). More recent studies have supported the reliability of TPT in different populations and over the lower back (Knutti et al., 2014; Middlebrook et al., 2020; Vuilleumier et al., 2015). However, thermal testing devices' safety limitations are often within pain-free ranges. Up to 38% of participants reached the maximum for thermal testing as reported in a study in participants with LBP (Vuilleumier et al., 2015). Even higher numbers were reported in asymptomatic or acute musculoskeletal trauma

participants for cold pain thresholds (CPT) (Middlebrook et al., 2020). TPT can be an important measure in testing EIH via a different pathway avoiding effects on pain sensitivity from local changes within the muscle tissue, such as fatigue.

1.3.3.1.3 Dynamic Quantitative Sensory Testing

Dynamic testing, such as TS or CPM (Rabey et al., 2021), can add to the understanding of processing or responsiveness of the nervous system with assessing real time EPM. The testing and standardisation are complex; one possible reason that the long-term reliability in asymptomatic people was lower for dynamic compared to static measurements (Marcuzzi et al., 2017). Moreover, measurement of the phenomenon EIH itself could be accounted for dynamic pain modulation, and therefore used as a potential outcome measure for EPM (Koltyn et al., 2014).

1.3.3.1.3.1 Temporal Summation of Pain

TS, also known as wind-up, refers to a series of repetitive or prolonged noxious stimuli leading to decreased thresholds due to spatial and temporal summation of dorsal horn neurons/ C-fibre-evoked responses (Cruz-Almeida and Fillingim, 2014; Hubscher et al., 2014). Various protocols and test batteries are described in the literature, which differ based on frequency and duration of a stimulus (Adnadjevic and Graven-Nielsen, 2015; Cruz-Almeida and Fillingim, 2014; Nie et al., 2009). Both mechanical and thermal stimuli have been used for TS (Koltyn et al., 2014; Naugle et al., 2014a; Vaegter et al., 2015; Vaegter et al., 2016). Reliability has been assessed for different modalities, with outcomes ranging from

poor to excellent reliability but showing overall good reliability (Cathcart et al., 2009; Graven-Nielsen et al., 2015; Kong et al., 2013; Mailloux et al., 2021a; Middlebrook et al., 2020). A systematic review and meta-analysis included 29 articles (participants n=1507) on TS with a variety of test modalities (mechanical n=16, electric n=9, and heat n=5) in participants with LBP (McPhee et al., 2020); TS was facilitated at all stages, but the standardised MD was small (standardised MD 0.50 95% CI [0.29; 0.72]). A different systematic review including seven studies, found that TS was increased in participants with CLBP over the lumbar area but not over the hand (den Bandt et al., 2019). Further research is required on standardisation and measurement properties as well as elucidation of the clinical relevance (McPhee et al., 2020).

1.3.3.1.3.2 Conditioned Pain Modulation

CPM refers to a decrease in sensitivity of a test stimulus after a remote conditioning stimulus (Cruz-Almeida and Fillingim, 2014). This follows the principle that pain inhibits pain (Kennedy et al., 2016). Inhibitory descending pathways activated in the brainstem level can lead to hypoalgesia similar to EIH (Ellingson et al., 2014; Lemley et al., 2015; Stolzman and Bement, 2016; Vaegter et al., 2014). CPM has been shown to be a reliable measure in both asymptomatic people and people with CLBP (Kennedy et al., 2016). A recent systematic review evaluated 20 studies and showed impaired CPM response across all participants with LBP, post-hoc analysis confirmed this only for participants with CLBP (McPhee et al., 2020). As was the case for TS, measurement properties and the clinical relevance of CPM should be further evaluated as between group changes were small (McPhee et al., 2020). Based on current research on validity, CPM should not be used as a biomarker for chronic pain alone as

future research on correlation between CPM outcome (standardisation, and lack of normative data) and clinical manifestation of pain are required prior a diagnostic or prognostic role (Fernandes et al., 2019).

1.3.4 Factors affecting Exercise-Induced Hypoalgesia

In the absence of a deeper understanding of the underlying mechanisms of EIH, as with QST, many different factors have been discussed to influence EIH such as age, gender, psychological stage, activity level (professional athletes), ethnicity, mood, food, expectations, sleep, as well as menstrual cycle and pain (Brellenthin et al., 2017; Hoeger Bement et al., 2009; Lemley et al., 2015; Naugle et al., 2014a; Ohlman et al., 2018; Stolzman et al., 2015; Travers et al., 2018; Umeda et al., 2016). In asymptomatic participants, higher EIH has been found for women (12 studies, ES=0.36, 95% CI [0.15; 0.56]) (Pacheco-Barrios et al., 2020). As a modifiable factor, levels of physical activity have been discussed equivocally in individual studies to both affect or not affect EIH (Black et al., 2017; Peterson et al., 2019; Schmitt et al., 2020; Umeda et al., 2016), but this evidence base has not previously been systematically synthesised. It has been suggested that EIH might be different in athletes (Vaegter and Jones, 2020), where for example increased CPM effects were shown (Flood et al., 2017).

Pain self-efficacy, coping strategies, fear of pain, and perceived stress have been also discussed to affect EIH (Vaegter and Jones, 2020). However, a systematic review (Table 1.2) did not reveal any interaction between psychosocial factors and EIH based on limited evidence (nine studies) and high heterogeneity (Munneke et al., 2020). However,

psychological factors have been shown to influence QST measures in people with LBP (section 1.3.3). Therefore, it could potentially also affect EIH assessment.

Two RCTs investigated changes in EIH by influencing the participants' expectations; these studies found that education or knowledge provided prior to the exercise altered the effects of EIH (Jones et al., 2017; Vaegter et al., 2020b). An aerobic and a squat task led to significantly different changes in pain sensitivity based on the information provided. This highlights a cognitive component in the phenomenon of EIH, and therefore, consistent information should be considered for standardisation.

1.3.5 Exercise Task Characteristics

The term 'task' is used in the following Chapters to describe the exercise investigated to elicit EIH. Whilst exercise is linked to conditioning or performance related goals (see 1.1.2), this only relates partially to the phenomenon of EIH, a natural course where the exercise task is utilised to elicit a temporary change in pain sensitivity. As this is not a common aim of exercise, the umbrella term physical activity task was used.

A variety of task have been used to elicit EIH (Naugle et al., 2012; Pacheco-Barrios et al., 2020; Wewege and Jones, 2021), but no clear consensus has been gained in asymptomatic people on task characteristics, such as the type of task, intensity and duration, as well as whether the task should be painful. There is even less research in people with pain (see section 1.3.6). Most previous studies have assessed laboratory tasks such as cycling protocols or isometric contractions, few protocols have used a combination of tasks such as circuit training or dynamic exercises (Pacheco-Barrios et al., 2020; Vaegter and Jones, 2020; Wewege and Jones, 2021). This is not necessarily reflective of real-world clinical

management of people with pain but facilitates standardisation of the tasks. Very few studies examined standardised tasks linked to spinal pain, such as the Biering Soerensen test (Gajsar et al., 2017), rehabilitative exercises for deep neck flexors (O'Leary et al., 2007), or static stretching of the lower back in flexion (Larouche et al., 2020).

Mixed evidence exists regarding task characteristics for type of task (such as aerobic or resistance), intensity, and duration. It is commonly assumed that aerobic exercise tasks elicit a systemic response, whereas resistance tasks produce a local response in the muscle group involved in the task (Rice et al., 2019). A recent high quality systematic review did not find an effect for isometric tasks in asymptomatic participants, but for aerobic tasks (Wewege and Jones, 2021). Contradictory, another systematic review found higher effects of EIH following resistance exercise but not aerobic exercise (Pacheco-Barrios et al., 2020). However, interpretation of these results should be done cautiously due to very low quality evidence and methodological concerns (Table 1.2).

It is further synthesised that tasks of moderate intensity are best to produce EIH in asymptomatic participants (ES=0.27; 95% CI [0.16; 0.38]) (Pacheco-Barrios et al., 2020). Only a few studies have explored different intensities in the same population group indicating more announced EIH with higher intensities (Micalos and Arendt-Nielsen, 2016; Naugle et al., 2014b; Schmitt et al., 2020). This provides limited evidence for the discussed dose-response rate of EIH. The review by Rice et al. (2019) states that for aerobic exercises higher intensities such as 200W or 70% of the maximum oxygen consumption elicit EIH based on work by Koltyn (2002). For isometric contractions the review indicates that 10-30% of maximum voluntary contraction might be sufficient, often held till exhaustion or for ≤ five minutes (Rice et al., 2019). But for example, a study (n=134) showed that also a two-minute sub-maximal isometric task could reduce pain sensitivity (Foxen-Craft and Dahlquist, 2017).

The appropriate duration and intensity of a task to elicit EIH has not been sufficiently explored.

Lastly, the interaction of the pain perceived with the task requires further research. For example. in asymptomatic participants EIH could not be elicited after receiving a painful stimulus in one study (Gajsar et al., 2018), this indicates an influence of pain on EIH, or shared pathways as associated with CPM. Vaegter and Jones (2020) summarise in their review that firstly, tasks producing EIH often are moderately painful, with peak pain intensity of 5-6/10 on a numeric rating scale (NRS); secondly, that in asymptomatic people painful tasks led to higher EIH; and thirdly, this might be different for people with chronic pain.

1.3.6 Exercise-Induced Hypoalgesia in People with Chronic Pain

It can be assumed that in at least some people with chronic pain, descending endogenous pain inhibitory pathways are impaired, as for example, shown in participants with fibromyalgia (Hoeger Bement et al., 2011; Staud et al., 2005). Additionally, in a chronic pain population, a task which would normally lead to EIH might have the opposite effect and cause hyperalgesia at lower intensities than expected due to altered sensitisation (Lima et al., 2017). A recent systematic review of 13 randomised and non-randomised studies, of which seven were lower limb, three upper limb, two neck related pain, and one mixed musculoskeletal disorders, could not draw any definitive conclusion due to high heterogeneity, with both hypo- and hyperalgesia found following isometric contractions (Bonello et al., 2021). Another review included studies with participants with epicondylopathy, knee osteoarthritis, and plantar fasciopathy (Wewege and Jones, 2021); one study used a dynamic task (1 RCT, no effect), but a meta-analysis was only performed for isometric exercises and revealed no effect

(3 RCTs, participants n=114, g= -41 95% CI [-1.08; 25]). A recent overview included over fifty articles with different pain conditions such as chronic fatigue syndrome, temporo-mandibular dysfunction, painful neuropathy, patellar tendinopathy, or shoulder pain (Vaegter and Jones, 2020). Across these studies, changes in pain sensitivity varied from hypo- to hyperalgesia, as well as a difference or no difference to an asymptomatic control group, or absence of an effect. However, the results indicate that more widespread pain conditions, such as fibromyalgia or whiplash associated disorders (WAD) might lead to hyperalgesia rather than hypoalgesia (Vaegter and Jones, 2020). Furthermore, the body region performing the task and its relation to the painful area might influence the findings (Bonello et al., 2021; Rice et al., 2019; Vaegter and Jones, 2020). For example, in knee osteoarthritis, level one evidence confirmed EIH local to the exercised limb (five studies, participants n=159, standardised MD 0.26 95% CI [0.02; 0.051]) but not at a remote test site (0.09, [-0.11; 0.29], n = 90 participants, four studies) (Hall et al., 2020). However, the type of exercise (aerobic: two studies or resistance: five studies) did not significantly affect EIH (Hall et al., 2020). Overall, this highlights a lack of consistent results in research on EIH in people with chronic pain, and high heterogeneity of studies limiting synthesis of evidence.

1.3.7 Exercise-Induced Hypoalgesia in People with Low Back Pain

Evidence for EIH in people with LBP is scarce. At the beginning of this doctoral study a summary dated back to 2013 (Roussel et al.) included the same two studies included by Naugle et al. (2012), both evaluating cycling protocols. The first study found that 21 participants with CLBP did not present abnormal central pain processing during submaximal aerobic exercise (Meeus et al., 2010). The second study included eight participants with LBP

of low to moderate disability; aerobic exercise (25 minutes of cycling) demonstrated EIH effects lasting for more than 30 minutes (Hoffmann et al., 2005). The latter study included a control group, but these participants did not perform the cycling task. Both studies indicated that EIH was present in participants with CLBP (Hoffmann et al., 2005; Meeus et al., 2010) and was not impaired in comparison with a control group (Meeus et al., 2010). A third study has been published since these reviews. Falla et al. (2014) investigated a three-minute repeated lifting task, which is the first evidence of altered EIH in response to a back specific lifting task. Participants with CLBP (n=19) showed lower lumbar PPT after the task, whereas asymptomatic participants (n=17) showed no change in PPT. Instead of hypoalgesia, hyperalgesia was found indicating an altered EIH as response to a local task (Falla et al., 2014). However, this task was likely of inadequate intensity to produce EIH, since no change occurred in the asymptomatic group.

More recent research by Vaegter et al. (2016) included 37 participants with LBP in addition to other musculoskeletal conditions (total n= 61). Participants experienced EIH after isometric knee extension and 15 minutes cycling. However, when the group was split according to high and low pain sensitivity based on their PPT, participants with high pain sensitivity presented with relatively less/ impaired EIH (Vaegter et al., 2016). This indicates that baseline pain sensitivity could be a mediating factor for EIH.

Overall, this highlights a clear lack of research of EIH in people with LBP with only four studies in total with inception to 2017. Moreover, none of the included studies reflect exercises commonly used for the management of CLBP as outlined in section 1.1.2. Only one study explored an occupational task (i.e., repeated lifting) which targeted the back specifically (Falla et al., 2014); findings indicated that EIH might be impaired in people with CLBP as participants responded with hyperalgesia. However, due to the short duration of the task and

no change in the control group further research should explore the response, when EIH can be elicited in the asymptomatic control group.

1.3.8 Reliability and Validity of Exercise-Induced Hypoalgesia

Reliability should be assessed prior to validity (Mokkink et al., 2018; Sim and Arnell, 1993). Stability is a sub term of reliability; identifying that EIH should be consistent and therefore the value of the entity should not change on repeated occasions (Sim and Wright, 2002). Stability therefore precedes the assessment of intra-rater reliability, where the focus is on the tester rather than the effect. Since measurement properties for most QST modalities show moderate to excellent intra- and inter-rater reliability (section 1.3.3), it could be assumed that it can be translated to EIH. However, considering the complexity of the phenomenon of EIH, stability should be explored first (Sim and Wright, 2002).

At the commencement of this doctoral study in 2017, no study had investigated stability of EIH. However, some emerging evidence has been published assessing the stability of EIH over two sessions of aerobic or isometric tasks in asymptomatic participants with overall moderate ICC values (Gomolka et al., 2019; Hviid et al., 2019; Vaegter et al., 2019a; Vaegter et al., 2018; Vaegter et al., 2019b). The findings will be discussed in further detail in Chapters four and five as those are directly linked to the specific thesis objective of examining stability of EIH.

Some studies have examined the validity of EIH, but none have included participants with LBP. After rest no differences in pain sensitivity were found in several studies but performance of the exercise task did alter pain sensitivity (Ellingson et al., 2014; Hviid et al.,

2019; Naugle et al., 2012; Smith et al., 2017a; Smith et al., 2020; Vaegter et al., 2016). This provides evidence for adequate construct validity across different study designs (Sim and Wright, 2002) and confirms feasibility of the test protocol applied in those studies.

1.4 Aim of the Thesis

The overall aim of the thesis is to explore EIH in people with CLBP.

The exploration of EIH is important and in the future, a RCT could establish the effectiveness of what is the best intervention to elicit EIH in people with CLBP. However, further knowledge of two different areas is required prior to testing this. Firstly, EIH in symptomatic people, specifically CLBP, needs to be further explored, as it is not known if it occurs to the same extent as in asymptomatic people. Secondly, more evidence is needed around the "best task" to produce EIH and the best assessment.

This thesis is of an exploratory nature and contributes to the emerging body of evidence on EIH in people with and without CLBP. In line with recommendations from the Medical Research Council (MRC) it is placed mainly within phase I (Campbell et al., 2000; Craig, 2019) (see Figure 1.3). Only when sufficient evidence is gathered for phase I, feasibility trials can be planned and conducted as the next step (phase II - exploratory trial) (Campbell et al., 2000; Craig, 2019; Skivington et al., 2021). Phase I covers three key areas (Craig, 2019). Firstly, identification of the research base: Empirical evidence is synthesised to support the phenomenon of EIH in an asymptomatic population (Naugle et al., 2012; Pacheco-Barrios et al., 2020; Wewege and Jones, 2021); but evidence in people with chronic musculoskeletal pain conditions, specifically CLBP, is scarce (Bonello et al., 2021; Wewege

and Jones, 2021). This gap will be addressed in a systematic review (Chapter three). The second area is the identification and development of the theory. Despite over 150 publications, specific recommendations, for both outcome measures and task characteristics are missing (Vaegter and Jones, 2020). These components, including for example different test sites, have only been partially explored in asymptomatic people and require further elucidation. Regarding measurement properties, the first step towards phase II is to assess the stability of EIH over multiple sessions. The third key area is modelling process and outcome, which also requires further elucidation of feasibility and the interacting factors of EIH. It needs to be further explored whether people with CLBP have impaired or normal EIH, especially following exercise tasks representing current management of CLBP.

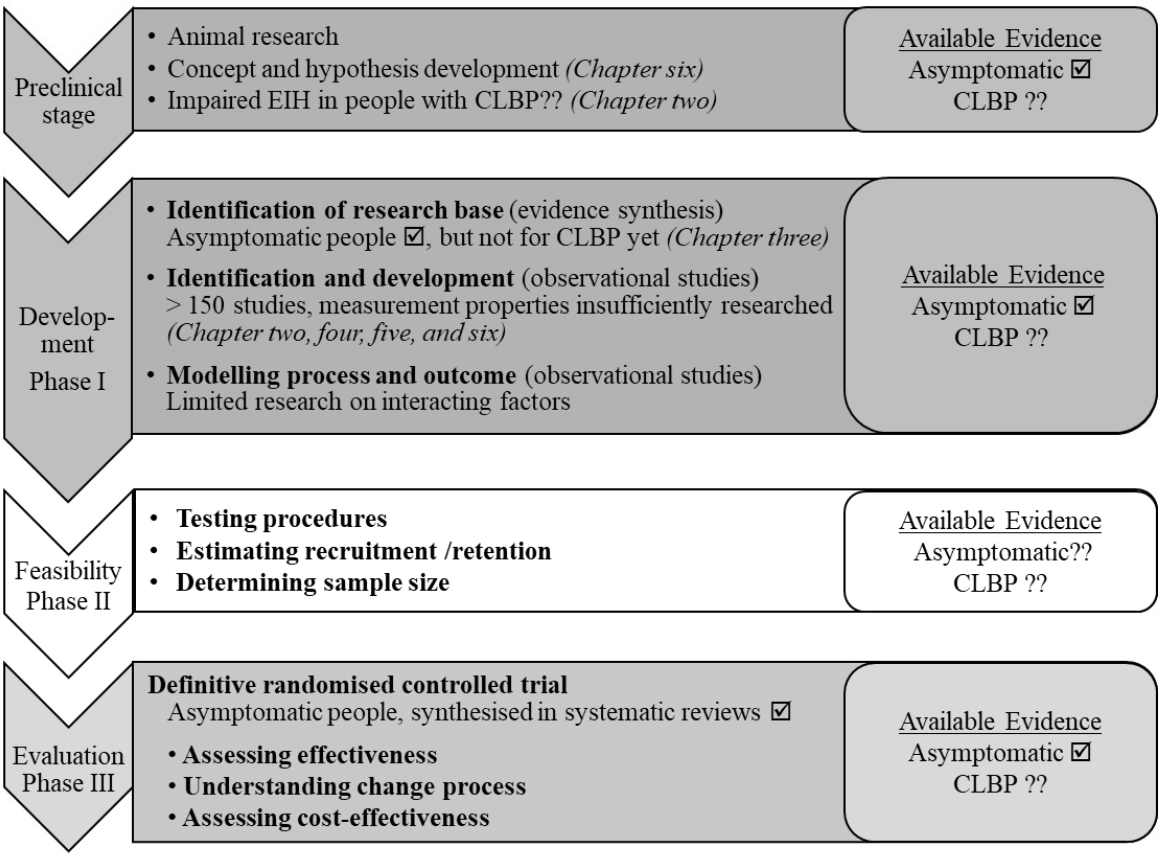


Figure 1.3 Application of the Medical Research Council (MRC) Framework

EIH= Exercise-induced Hypoalgesia, CLBP= Chronic Low Back Pain

1.4.1 Objectives of the Thesis

The objectives for this thesis are outlined below and visualised in Figure 1.4

1. to quantify whether a repetitive lifting task elicits EIH in participants with and without CLBP
2. to synthesise existing evidence for EIH in participants with spinal pain
3. to empirically explore tasks to produce EIH in participants with and without CLBP over multiple sessions
4. to investigate the stability of EIH over multiple sessions in participants with and without CLBP
5. to analyse the test protocol over multiple session in non-exercising asymptomatic participants

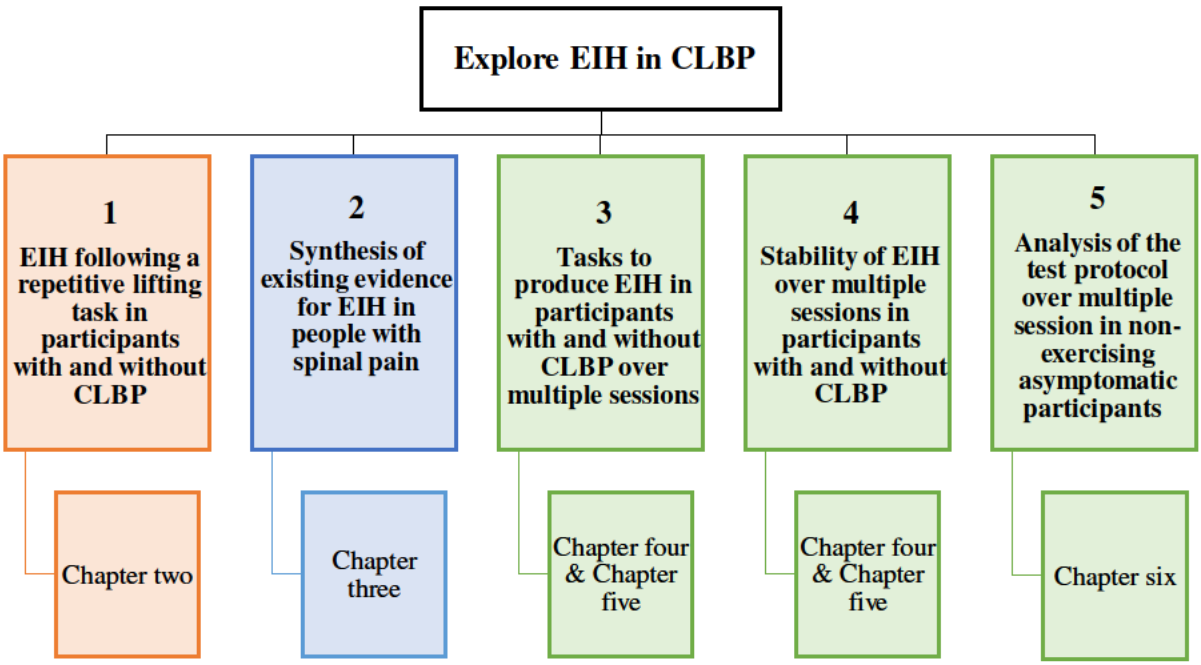


Figure 1.4 Aim and Objectives of the Thesis linked to the relevant Chapter

Abbreviations: EIH= Exercise-induced Hypoalgesia; CLBP= Chronic Low Back Pain

1.4.2 Overview of Thesis' Chapters

Chapter one has provided a background and rationale for this thesis outlining LBP, EPM, and the phenomenon of EIH. For Chapter two, empirical research is conducted first. When this research was initiated in March 2017, scoping searches revealed limited studies on EIH in people with CLBP. QST was assessed at local lumbar and remote sites, exploring whether asymptomatic participants demonstrate EIH in response to repeated movement of the trunk and whether the response is abnormal in participants with CLBP (objective one). The third Chapter reports an evidence synthesis based on the finding of impaired EIH in participants with CLBP, a systematic review is extended to all spinal pathologies due to the relatively limited research in LBP (objective two).

Findings from Chapter three confirmed a lack of research on EIH in participants with CLBP, specifically on tasks targeting the lower back region or walking tasks. The following Chapters four to six are related to one study. This pragmatic observational study explores changes in pain sensitivity over local lumbar and remote test sites in participants with and without CLBP (objective three). The tasks to elicit EIH comprise of either a lumbar resistance task (Chapter four) or a brisk walking task on a treadmill (Chapter five). Objective four is related to the stability of EIH over multiple sessions. The sixth Chapter (objective five) analysed the testing protocol to inform findings from the previous two Chapters.

The final Chapter, the discussion, provides a summary for each Chapter followed by a reflection of the objectives and relevant methodological considerations. Strengths and limitations of this thesis are discussed. The Chapter closes with the clinical implications of the overall findings, recommendations for future research, and conclusions of this thesis.

Chapter Two

Lack of Exercise-Induced Hypoalgesia to Repetitive Back Movement in People with and without Chronic Low Back Pain

This study was presented at different national and international conferences as listed at the beginning of this thesis and has been published in a peer-reviewed journal (Kuithan et al., 2019). Some elements, such as the introduction, have been re-worded for the aim for this thesis to avoid repetition as an extensive background was provided in the previous Chapter. The methods, results, discussion, and conclusion largely reflect the publication verbatim.

The publication in its original form is attached as Appendix 2.

Publication

Kuithan, P., Heneghan, N. R., Rushton, A., Sanderson, A. & Falla, D. 2019. Lack of Exercise-Induced Hypoalgesia to Repetitive Back Movement in People with Chronic Low Back Pain. *Pain Practice,* 19**,** 740-750.

2.1 Abstract

The lack of research on exercise-induced hypoalgesia (EIH) in people with chronic low back pain (CLBP) was outlined in Chapter one.

This cross-sectional observational study was conducted on asymptomatic participants (CON) (n=18) and participants with CLBP (n=21). Quantitative sensory testing (QST) was applied extensively over the lumbar region and a remote area before and after the task, which involved repetitive back movement in form of lifting of a 5kg box for approximately seven minutes. QST included pressure pain thresholds (PPT), thermal detection and pain thresholds and measures of temporal summation. Topographical maps of the percentage change in PPT detected at 16 locations over the lumbar region were generated to explore regional differences and compared between groups.

Mean PPT measured from 16 sites over the lower back, changed significantly in asymptomatic participants (+29.78 kPa ±41.4) following task completion indicative of EIH, whereas no statistically significant change was observed for the CLBP group (-14.87 kPa ±61.2). No changes were detected at the remote site for either group. No changes were revealed for the thermal tests. Temporal summation data revealed decreasing pain sensitivity within the test, but the test response did not change after the task for both group.

Unlike asymptomatic participants, participants with CLBP showed impaired EIH over the lumbar erector spinae muscles following repeated lifting. Although these results should be considered in relation to the study limitations, particularly the absence of a control group not performing the task, the findings support impaired EIH in people with CLBP.

2.2. Introduction

As outlined in Chapter one, the effects of EIH, a short-term endogenous pain inhibitory response after exercise, are well documented in asymptomatic people. The EIH response can be detected with QST, but the extent of the EIH response depends on several factors including the type, intensity, and dosage of the exercise (Micalos and Arendt-Nielsen, 2016; Naugle et al., 2014b). Only three studies have examined EIH specifically in participants with CLBP (Chapter one section 1.3.7), although exercise is recommended as a fundamental treatment for the management of LBP in national and international guidelines (NICE, 2020; Qaseem et al., 2017). Looking at tasks targeting the lumbar region, only one study indicated hyperalgesia after a repetitive lifting task (Falla et al., 2014). However, no EIH was found in the asymptomatic group, which should be further investigated. A longer task is hypothesised to elicit EIH and therefore, the task was modified accordingly. A study has investigated the response to a 2-minute isometric back extension task (Biering Soerensen test) (Gajsar et al., 2017). EIH was found at remote but not local lumbar sites (Gajsar et al., 2017), however this study was limited to asymptomatic participants. Further research is therefore needed to fully understand the hypoalgesic response to back-specific task and whether this is affected in people with CLBP.

2.2.1 Chapter Objectives

The Chapter objective of this study was to quantify via QST, assessed at local and remote sites, whether asymptomatic participants demonstrate EIH in response to repeated movement of the trunk and whether the response is dysfunctional in participants with CLBP.

This reflects thesis objective one. Based on the study by Falla et al. (2014), the task involved repeated lifting of a 5 kg box for approximately seven minutes. The knowledge gained from this study may facilitate a greater understanding of the mechanisms contributing to varied response to exercise in participants with LBP (i.e., those that lack EIH) and the exacerbation of symptoms in some participants with LBP following repeated mechanical work (Gerhardt et al., 2016; Hubscher et al., 2014; Puta et al., 2013; Roussel et al., 2013).

2.3 Methods

2.3.1 Study Design and Setting

This observational cross-sectional study was approved by the Ethics committee of the University of Birmingham (ERN_16-1389) and was conducted according to the Declaration of Helsinki. This report follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for observational studies (von Elm et al., 2014) (Appendix 5). All tests were conducted in a single session by the same investigator between July 2017 and March 2018. The relevant documentation for ethical approval is attached as Appendix 4.

2.3.2 Participants

Participants with CLBP and asymptomatic controls were recruited from the University staff and student population. All participants gave written consent prior to data collection and

were reimbursed for their time (Appendix 4). Inclusion criteria for both groups were age between 18 and 65 years, not being pregnant, and able to communicate in English. Participants were considered asymptomatic if they had no previous history of back or lower limb pain which warranted treatment from a health care practitioner and no neurological disorders.

Inclusion criteria for the participants with CLBP were back pain lasting more than three months, and pain experienced on more than 90 days out of the past six months. A history of spinal fractures, spinal stenosis, and radiating leg pain were exclusion criteria as were concurrent systemic, rheumatic, or neurological disorders which may have confounded testing. They should not have been undergoing active management for CLBP or on higher doses of pain medication (> 30 mg of morphine equivalent dose).

2.3.3 Questionnaires

A custom designed questionnaire (Appendix 3) was firstly completed by the CLBP participants to assess their average of the last 24hrs, during their latest episode, as well as their current pain intensity, all rated on an 11–item NRS, with 0 for no pain and 10 for the worst pain imaginable (Breivik et al., 2008). CLBP participants were also asked to rate their perceived disability with the Oswestry Disability Index (ODI) (Fairbank and Pynsent, 2000). In addition, the following established questionnaires were used to describe the study population: The International Physical Activity Questionnaire (IPAQ) (Craig et al., 2003); Short Form Health Survey (SF-36v2) for perception of health and wellbeing, comprising of the Physical and Mental Component Scale (Scoggins and Patrick, 2009); the 21-item depression, anxiety and stress scale (DASS-21) (Henry and Crawford, 2005), the fear

avoidance beliefs questionnaire (FABQ) (Osman et al., 2000); and pain catastrophizing scale (PCS) (Waddell et al., 1993).

2.3.4 Quantitative Sensory Testing

QST was performed in a consistent order which was PPT testing followed by thermal detection and TPT testing starting at the periphery and finishing at the back. TS of repeated thermal stimuli was performed last. The tests were chosen based on previous studies and pilot testing (Falla et al., 2014; Owens et al., 2016; Rolke et al., 2006a). QST is an established method to evaluate EIH and its reliability has been demonstrated in Chapter one (section 1.3.3).

2.3.4.1 Pressure Pain Thresholds

After a familiarisation period, PPT were measured with an algometer (1 cm^2 probe, 30 kPa/sec) (Somedic Production, Stockholm, Sweden). Firstly, PPT were tested over the thenar eminence on the right side for the asymptomatic group, and on the most painful side for the CLBP participants. In the case of bilateral and symmetrical pain, the right side was selected. A grid, orientated on the spinous process of the 5^{th} lumbar vertebrae, was used to mark 16 testing locations over the lumbar region (Figure 2.1) to explore regional differences in PPT changes following the exercise. This was based on a similar approach used previously (Falla et al., 2014) but applied bilaterally, with two vertical rows of four points on each side. The medial row was directly placed over the erector spinae muscles. Testing was alternated across

participants in two different patterns on each side. From test site one the next test site was caudal, for test site four the next test site was cranial, this pattern was the same for the right side. For all PPT tests, the participants were instructed to push a button as soon as they perceived that the sensation of pressure had turned to one of pain. The mean of two consecutive readings over each site was used for data analysis (Chapter one, section 1.3.3). Topographical maps of the percentage change in PPT for each location were generated based on the mean value (Falla et al., 2014).

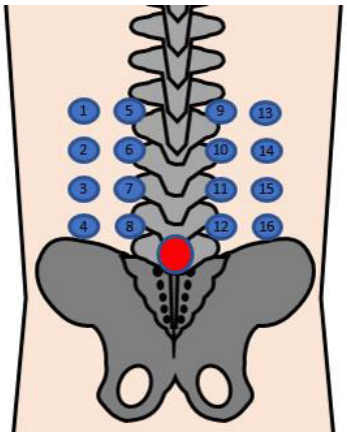


Figure 2.1 Schematic Representation of the Area over the Lumbar Region for Pressure Pain Threshold Testing

The distance between two testing sites was 2.5 cm, and the first sites were 2.5 cm cranial to the spinous process of the fifth lumbar vertebrae

2.3.4.2 Thermal Detection and Pain Thresholds

A Thermal analyser TSA-II (Medoc, Israel) with a 30x30mm Peltier thermode was applied over the thenar eminence on the right or most painful side as described above, after a demonstration on the contralateral side. Three randomised stimuli of either warm or cold were

applied for the detection threshold (WDT/ CDT) and then for the pain threshold. Baseline temperature was set at 32°C, and the temperature increased or decreased by 1°C and returned with a rate of 8°C/s with a five second interstimulus interval. For the pain threshold an increase / decrease of 1.5°C/s and return of 8°C/s with ten seconds interval was chosen to avoid TS. The minimum temperature was set to 0°C and the maximum to 50°C. The same test was then conducted for both groups over the back on the right side corresponding to the PPT locations 11-16 (Figure 2.1). For analysis, the mean of three measurements was taken for each site.

2.3.4.3 Temporal Summation

Firstly, a familiarisation test was performed on the contralateral side with five stimuli of 46°C with the same thermal tester described above. Participants were asked to rate their perceived pain on an NRS from 0-100 for each of the stimuli with 0 for no pain and 100 as worst pain imaginable. Then the thermode was placed under the volar mid-forearm on the right or most painful side. Ten consecutive stimuli were applied starting at a baseline temperature of 40°C increasing within 8°C/s to 48°C, and at the same rate to return to baseline. Inter stimulus interval was set as 2.5s adapted from a protocol by Owens et al. (2016).

2.3.5 Repeated Lifting Task

Measurements of the sternomanubrial joint line for the top shelves, and the height of the lateral epicondyle of the femur for the lower shelves, and the length from the acromion to

the head of the ulna for distance from the feet to the shelves were taken to determine the set-up for the lifting task (Figure 2.2 A).

Participants performed ten cycles lifting a 5kg box (35.5 cm x 29 cm x 13.5 cm) with reinforced handles between six different shelves for approximately seven minutes in total. To the beat of a metronome, the participant lifted the box to the top shelf over 2 seconds and then could rest for two seconds with the box on the shelf. Figure 2.2 B shows the pattern for each cycle. The task was based on a task described in a previous study (Falla et al., 2014), but was extended to represent a more functional movement by adding rotation using six instead of two shelves. During the task, the participant was asked every minute to rate their pain on an NRS from 0-10 and their perceived exertion after the lifting task on a printed Borg scale (Borg, 1982). They were informed that they could end the lifting task at any time.

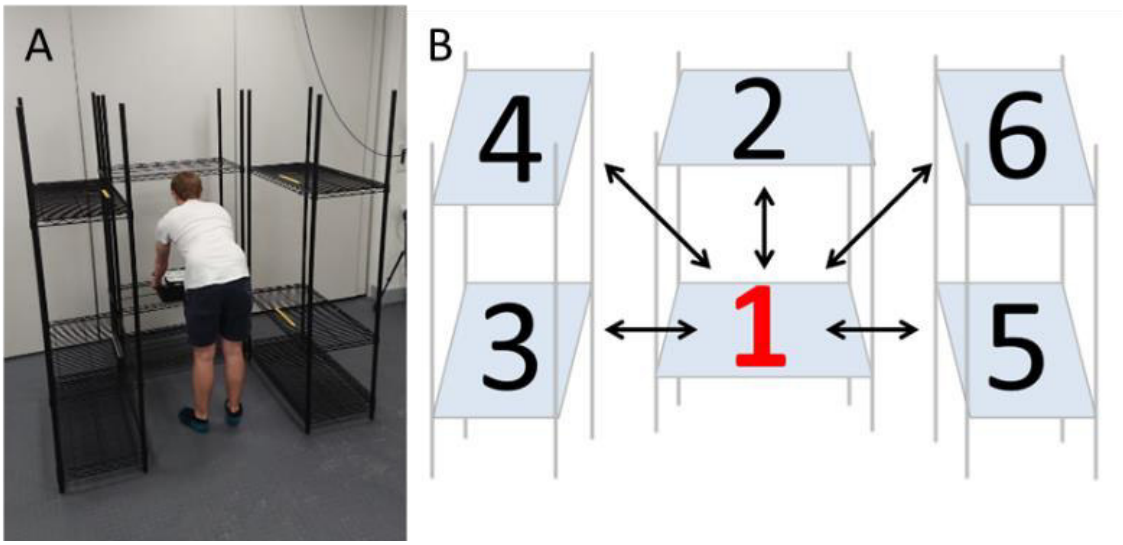


Figure 2.2 A-B Repeated Lifting Task

(A) Participant demonstrating the starting position of the lifting task, (B) schematic illustration of the lifting sequence

Within five minutes of completion of the lifting task, the QST tests were repeated as described above, but in the following order: Lumbar PPT followed by thermal tests over the lumbar area with the participant in supine. Then the PPT and thermal measurements were performed over the hand. This sequence was selected for efficiency of testing, to minimise movement of the participant and prioritise testing of the lumbar region. TS testing was conducted last avoiding any potential interference with the other tests. The duration of the pre-test protocol was slightly longer than the post-test protocol because of the familiarisation period. The entire duration varied between 20 to 30 minutes.

2.3.6 Statistical Analysis

For descriptive analysis participants characteristics were summarised for each group. Data was checked for normality (Kolmogorov –Smirnov test). If necessary, outliers were removed from the analysis based on a z-score >3.29 and reported as such (Field, 2007). For rating the SF-36 the provider's software was used to generate the score for the physical and mental component subscales. To detect changes between the two groups, independent t-tests/ Kruskal-Wallis test were applied with significance set as $p<0.05$ (IBM SPSS Statistics Version 24).

A mean of the PPT across the 16 locations of their back was calculated for each participant and in addition, the percentage change in PPT was determined for each location and displayed as a topographical map (Falla et al., 2014). For the thermal testing, if any reading did not meet the pain threshold at 0/50 °C (limit of the equipment), then the data were excluded from further analysis.

A three-way RM-ANOVA was conducted for the lumbar PPT (local test site) with group, time, and location (locations 1-16) as factors. A two-way RM-ANOVA was conducted to evaluate changes in PPT detected over the hand with group (CON/CLBP) and time (pre/post) as factors. Two-way RM-ANOVAs were also applied for the thermal detection - and pain thresholds with group and time as factors. For TS, a three-way RM-ANOVA with group, time, and sequence of heat impulse (1-10) was applied. Statistically significant differences were followed by Student Newman Keuls (SNK) post hoc analyses and Bonferroni corrections (BC) for multiple comparisons. Finally, the correlation of pain, perceived exertion, and change in percentage for the QST measurements was tested using the Pearson correlation coefficient. Significance was set as $p < .05$.

2.4 Results

2.4.1 Participants

Participant characteristics of 18 asymptomatic participants (8 men, 10 women) and 21 participants with CLBP (9 men, 12 women) are presented in Table 2.1. One further participant was recruited but only pre QST measures were taken due to technical issues and this participant was therefore excluded. The ODI indicated minimal disability (≤20%) in the group with CLBP and only two participants reported moderate disability. Participants with CLBP reported statistically significantly higher scores on the Borg Scale (mean ± standard deviation (SD) CON: 11.1 ± 2.2, CLBP: 13.1 ±1.7; p=.005).

In contrast to all asymptomatic participants who successfully completed the full task, three participants with CLBP terminated the task due to provocation of their LBP during the

fourth, sixth, and nineth cycle. In line with the ethical approval, participants were monitored during the post-testing, which settled pain, and were given generic advice. However, as participants performed the task for as long as they could, their data were retained in the analysis and QST was still performed after their final task cycle.

2.4.2 Pain

Four control participants experienced discomfort during the task (peak LBP intensity of 2/10 reported by three participants and 8/10 by one participant, group mean: 0.8 ±2.0). Overall, the reported peak pain intensity during the task was 4.78 ±2.0 for the CLBP group and only one CLBP participant did not perceive LBP during the task.

Table 2.1 Demographic characteristics of the study population

Characteristic/Questionnaire	**CON Mean± SD**	**CLBP Mean± SD**	**Group Difference *p- value***
Age	28.2± 12.5	31.7± 13.3	= .406
BMI	23.3± 4.0	25.4± 3.4	= .084
DASS21 (Range: 0 to 126)	9.4± 10.1	19.3± 22.5	= .095
FABQ (0 to 96)	2.6± 5.7	27.2± 11.6	< .001*
PCS (0 to 52)	5.7± 6.9	14.9± 9.2	< .001*
Peak Pain Lifting (0 to 10)	0.8± 2.0	4.8± 2.0	< .001*
Borg Scale Lifting (6 to 20)	11.1± 2.2	13.1± 1.7	=.004*
SF36-PCS	58.43 ± 3.9	49.36 ± 5.3	< .001*
SF36-MCS	51.82 ± 4.4	46.51± 13.0	= .091
IPAQ	14 high, 4 med.	18 high, 4 med.	=.0525
ODI (0 to100)		16.0± 6.8	
Pain last 24hrs		3.9± 2.1	
Pain before task		3.1± 2.0	
Pain episode		4.9± 1.9	

***Abbreviations**: CON= Asymptomatic Control Group; CLBP= Chronic Low Back Pain Group; BMI=Body Mass Index; DASS21= Depression Anxiety Stress Scales; FABQ= Fear Avoidance Believe Questionnaire; PCS= Pain Catastrophizing Scale; SF36-PCS= Short Form Health Survey Physical Component Score; SF36-MCS= Short Form Health Survey Mental Component Scale; IPAQ= International Physical Activity Questionnaire; ODI= Oswestry Disability Index; All independent t-test, except Kruskal-Wallis test for IPAQ*

2.4.3 Pressure Pain Thresholds (Local and Remote)

For PPT collected over the lower back, the overall scores (mean of 16 locations) were pre-test 341.39 kPa ±116.9 and post-test 371.16 kPa ±130.4 for asymptomatic (n=18) and 320.08 kPa ±113.7 and 305.20 kPa ±101.0 for participants with CLBP (n=20). This led to a difference of 29.78kPa ±41.4 for the asymptomatic participants and -14.87 kPa ±61.2 for the participants with CLBP. The percentage changes in PPT are displayed in Figure 2.3 illustrating a mean change for the asymptomatic group of +9.43% ±13.4, 95% CI [2.8; 16.1] and -2.10% ±18.4 [-10.7; 6.5] for the CLBP group.

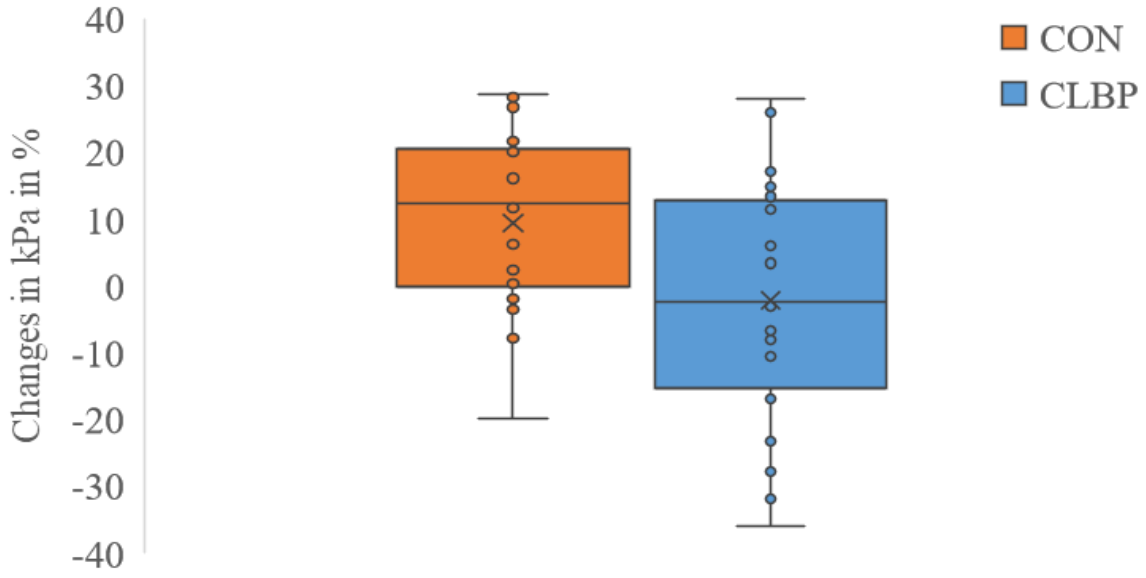


Figure 2.3 Boxplot of the Percentage Change in Pressure Pain Sensitivity

The percentage change of the overall mean of 16 locations for each participant within the two groups is shown. A higher percentage change represents signs of exercise-induced hypoalgesia. At the group level, the mean change (illustrated by the x) was (mean± SD) +9.43% ±13.4 for the asymptomatic group (CON) and -2.10% ±18.4 for the participants with chronic low back pain (CLBP). The lower and upper extreme was -19.80% and 28.20% for asymptomatic compared to -35.95% and 28.13% for the group with CLBP

A three-way RM-ANOVA showed statistically significant interactions for location, location and group, and time and location (F= 1.85 – 10.81, $p \leq .001 – .025$). The significance of location/ time and location indicates the heterogeneous response of different test sites over the lumbar area. However, for the purposes of this study, the most relevant finding was a group and time interaction (F=6.78, p=.001) and the post hoc analysis revealed a statistically significant increase in PPT after the task but only for the control group (CON: SNK: p=.019; CLBP: SNK: p=.228). However, Bonferroni correction for multiple comparisons revealed no statistically significant interaction for time and group (CON: +29.78, Standard Error (SE): 12.44, 95% CI [-5.0; 64.5] p=.132; CLBP: -14.87, SE: 11.80, [-47.8; 18.1] p=1.00).

Topographical maps showing the percent change in PPT between pre- and post-test over the 16 different locations over the lumbar spine are presented in Figure 2.4.

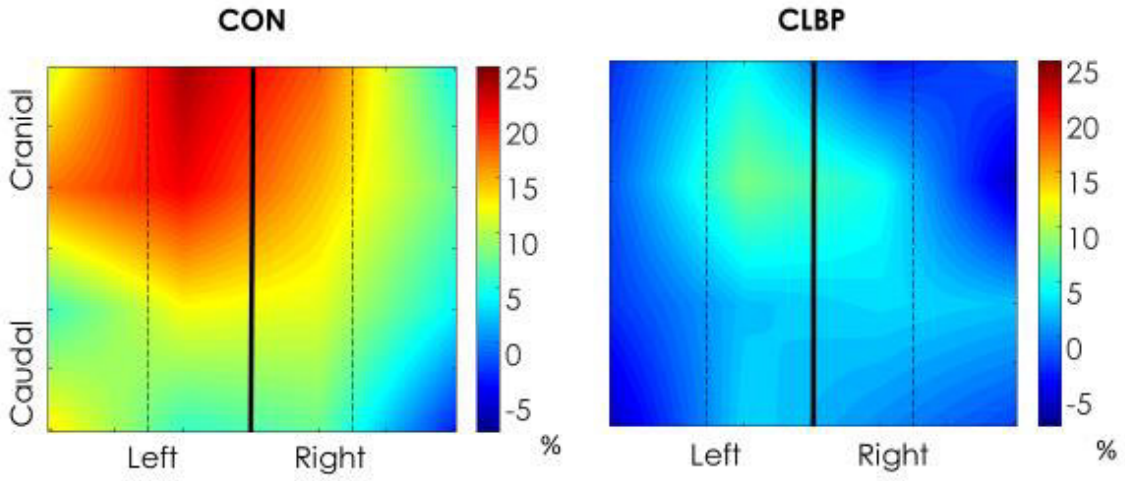


Figure 2.4 Topographical Maps showing the Percentage Change in Pressure Pain Thresholds

Pre-and post-test change over the 16 different locations over the lumbar spine as determined in Figure 2.1. The vertical line represents the midline of the spine. The left side shows the asymptomatic group (CON), the right side the group with chronic low back pain (CLBP)

Based on observation of the topographical maps, further analysis was conducted to evaluate changes only within the cranial half of the map. There was an interaction of time and group (F=10.23, *p*=.003; SNK: CON: *p*=.002, CLBP: *p*=.265). Correction for multiple comparisons confirmed changes for the asymptomatic group (CON: +43.05, SE 13.03, 95% CI [6.69; 79.42]*; p*=.132).

By separating the medial and lateral row, a statistically significant change was observed over the medial (PPT test sites 5-12) column only. A statistically significant interaction between time and group was found (F= 8.12, *p*=.007). The post-hoc analysis showed a statistically significant change only for the asymptomatic group (SNK: CON: *p*=.001, CLBP: *p*=.643). Adjustment for multiple comparisons confirmed a statistically significant post-task increase in PPT only for the asymptomatic group (CON: +46.93, SE 13.5, 95% CI [9.18; 84.68]; *p*=.008).

For PPT measured over the thenar eminence, the mean ± SD pre-test values were 259.33 kPa ±77.8 and post-test values 281.94 kPa ±117.4 for the asymptomatic group with a difference of +22.61 kPa ±93.1. For participants with CLBP the mean pre-test value was 276.55 kPa ±88.84 and 278.50 ±72.2 for the post-test with a difference of +1.95 kPa ±40.2. A two-way RM-ANOVA revealed no statistically significant differences between groups and no statistically significant change over time.

There was a statistically significant correlation between change in the PPT percentage over the hand and the back only in asymptomatic participants (r=.783, *p*< .001, n=18). However, in both groups there was no statistically significant correlation between baseline PPT and the percent change in PPT indicating that an EIH response was not dependent on baseline sensitivity.

2.4.4 Thermal Testing

Results for the cold and warm detection and pain thresholds are presented in Table 2.2. Two CDT readings from the hand and one from the back were identified as outliers (z-score> 3.29) and were removed from the analysis. A two-way RM-ANOVA revealed a statistically significant difference for group (F=4.18, *p*=.049) for the CDT detected over the hand yet further post-hoc analysis revealed no further statistically significant differences between groups and there was no effect of time. No statistically significant differences and interactions between group or time were observed for the CDT performed over the lumbar region nor warm detection over the hand and the lumbar area.

Due to limitations of the device with a safety limit of 0 °C/ 50°C completed data sets were limited in both groups for CPT. The difference in CPT between pre- and post-tests was +1.6 °C ±5.6 for the asymptomatic participants and a +2.5°C ±4.9 for CLBP group. A two-way RM-ANOVA showed a statistically significant change over time (F=5.31, *p*=.028) for both groups but there were no differences between groups.

For the lumbar area, a RM-ANOVA showed no statistically significant group difference, although the overall change between pre- and post-task measures across both groups was close to statistically significant (F=4.24, *p*=.054). Imputing 0°C for the missed scores did not affect the result.

For the thenar heat pain thresholds (HPT) the overall difference between pre- and post-test was -1.2°C ±2.5 for the asymptomatic group and -1.1°C ±2.7 for those with CLBP. A two-way RM-ANOVA showed a statistically significant interaction between group and time (F=8.739, *p*=.006) with the post-hoc analysis confirming a reduction of the HPT for the

asymptomatic group only (SNK: p=.037). However, correction for multiple comparisons showed no significance (BC: p=.144). No statistically significant changes in HPT were measured over the lumbar region.

Table 2.2 Results for thermal detection and pain threshold testing

Modality & Time	Test Site	CON			CLBP	
		N	Mean± SD (°C)		N	Mean± SD (°C)
CDT pre	Hand	17	30.2 ± 1.0		20	30.5± 0.6
CDT post			29.9± 1.1			30.5± 0.6
WDT pre		18	33.9± 1.1		21	34.1± 0.9
WDT post			33.8± 0.8			33.9± 0.6
CPT pre		16	14.0± 7.5		18	15.4± 7.6
CPT post			15.8± 8.5			17.8± 6.2
HPT pre		14	43.0± 2.9		21	43.5± 3.9
HPT post			41.2± 3.7			42.4± 2.5
CDT pre	Lumbar	18	29.6± 2.0		20	29.8± 1.6
CDT post			29.7± 2.0			29.3± 2.0
WDT pre		18	35.3± 1.3		21	35.5± 1.1
WDT post			35.0± 1.1			35.2± 1.4
CPT pre		12	21.5± 6.1		8	24.8± 4.4
CPT post			19.6± 6.8			22.7± 6.8
HPT pre		17	43.3± 3.9		20	43.7± 4.1
HPT post			43.7± 3.5			43.5± 3.0

Abbreviations: *CON= Asymptomatic Control Group; CLBP= Chronic Low Back Pain Group; CDT= Cold Detection Threshold, WDT= Warm Detection Threshold, CPT= Cold Pain Threshold, HPT= Heat Pain Threshold, pre= pre-test, post= post-test*

2.4.5 Temporal Summation

TS data was obtained from 15 asymptomatic and 18 participants with CLBP. Overall, a reduction in pain sensitivity to the same stimulus was found over time (Figure 2.5). A three-way RM-ANOVA revealed interactions for sequence only (F= 22.69, p< .001) with the post hoc analysis revealing statistically significant changes between the first and third to tenth stimulus (SNK: p< .034). No differences were observed between groups and there was no effect of the task on TS.

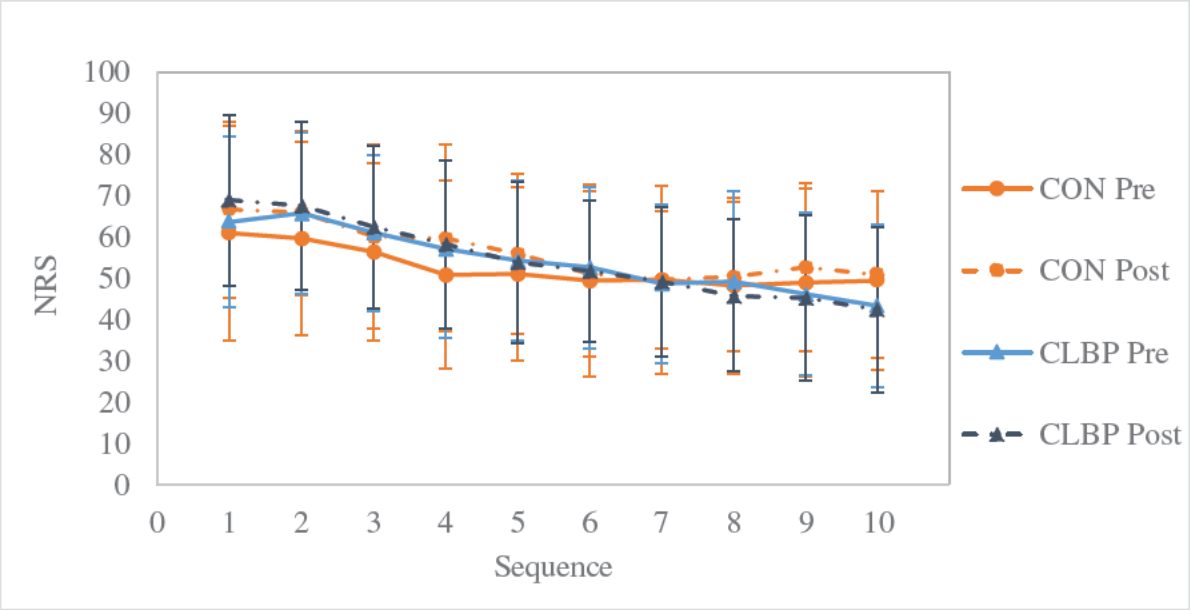


Figure 2.5 Results of Temporal Summation

The graph depicts pain scores (NRS 0-100) over ten heat pulses (Sequence) in healthy asymptomatic participants and in those with chronic low back pain (CLBP) pre- and post- the repetitive lifting task. Asymptomatic participants (CON) started with an average pain score of mean ± SD 60.93 ±26.1 and rated the tenth stimulus as 49.4 ±21.7 in the pre-test, and 66.67 ±21.4 and 50.80 ±20.2 for the post-test. The CLBP group changed respectively from 63.67 ±20.0 to 43.28 ±21.9, and in the post test from 68.94 ±22.3 to 42.33 ±21.2. There was neither a statistically significant difference between pre- and post-task test nor between groups

2.5 Discussion

This is the first study to rigorously utilise different quantitative sensory measures to evaluate whether a repeated lifting exercise induces EIH and whether this effect differs in people with CLBP. The findings from this study confirmed that the hypoalgesic effect gained from back-specific exercise induced by repeated lifting is impaired in participants with CLBP which has important implications for those performing repeated lifting in an occupational setting.

The study population comprised mainly participants with minimal disability due to their LBP (ODI≤20). At baseline, no consistent differences in any of the QST measures between groups were observed indicating that the sample of participants with CLBP in this study did not show obvious signs of peripheral or central sensitisation. This is in contrast with previous work using multiple PPT over the lumbar region which showed lower PPT for participants with CLBP in a comparable population (Falla et al., 2014; O'Neill et al., 2019). The high inter-individual differences and the relatively low levels of pain and disability in this sample could explain this. Moreover, no correlation between baseline PPT and changes in PPT post-task in this study population was found indicating that the extent of EIH was independent of baseline sensitivity.

The task was perceived by the participants as easy to moderate exercise according to the Borg Scale. This is in contrast to most other studies which have examined EIH in response to more demanding exercises (Naugle et al., 2012; Vaegter et al., 2015). Yet the current study clearly demonstrated an EIH response for the asymptomatic population as seen by the statistically significant increase in lumbar PPT measured after completion of the repetitive task.

Furthermore, findings are in contrast to previous studies that did not find evidence of impaired EIH in participants with LBP, however no other study has examined the response to exercise specifically targeting the back muscles or utilising a functional task (Hoffmann et al., 2005; Meeus et al., 2010). In a study which evaluated changes in PPT following a lifting task albeit of shorter duration and only lifting in the sagittal plane (Falla et al., 2014), a statistically significant local decrease in PPT over the lumbar area was shown in participants with CLBP. The trend was shown in this study. However, changes were not statistically significant.

Differences were observed for the change in PPT between medial and lateral testing sites in the asymptomatic group with statistically significant changes observed only for medial sites. This is likely because the lateral column was located to a lesser extent over the erector spinae, i.e., the iliocostalis lumborum, which were engaged in the task (Bogduk, 2005). Moreover, EIH was more evident at cranial sites. This underlines the importance of multiple PPT test sites, as interactions of time and location were found. If only a single test site is used changes might not be depicted.

The absence of EIH in this cohort of people with CLBP does not necessarily imply that the participants with CLBP lacked descending pain inhibition. It rather could be caused by their erector spinae muscles becoming sensitised after the task due to localised muscle fatigue. Especially since studies indicate that the erector spinae are more fatigable in people with CLBP and changes in muscles activity were found with fatigue or pain (Abboud et al., 2014; Boucher et al., 2015; Sanderson et al., 2019).

Research on changes in pain sensitivity over the lumbar region after exercise is limited. Comparing the results from this study with the findings from Gajsar et al. (2017), similar baseline scores and changes in lumbar PPT (absolute change: men: 34.2 kPa: women: 18.9 kPa) were found in this study. However, in the study by Gajsar et al.(2017), the increase in PPT over the lower back after exercise did not reach statistical significance, unlike the current findings. The isometric back extension task used in this previous study also engages the hip extensor muscles, over which they found a statistically significant increase in PPT. Additionally, Gajsar et al.(2017) examined the PPT at only one site over the lumbar region (adjacent to the third lumbar vertebrae (L3)). The findings of this study indicate that test site has a statistically significant influence on outcome and that testing sites directly over the muscle belly are more likely to demonstrate a change.

There was no statistically significant change in pressure pain sensitivity measured at a remote site (hand), likely because of the low intensity and duration of the task since remote changes are typically seen after excessive or vigorous exercise (Micalos and Arendt-Nielsen, 2016; Naugle et al., 2014b).

In contrast to pressure testing, the sensitivity to thermal stimuli did not show a clear pattern and was restricted by the temperature range of the equipment used. In line with this study, most other studies have used PPT as an outcome measurement for EIH which seems more responsive as an outcome measurement (Naugle et al., 2012). This is likely because mechanical pressure stimulates receptors within an exercised muscle, whereas the thermal stimuli stimulate superficial receptors of the skin. Changes in temperature pain thresholds may be caused by exercise-induced changes in skin or body temperature rather than inhibitory pain mechanisms (Naugle et al., 2012). Furthermore, the randomisation of stimuli might have affected the results (Heldestad et al., 2010).

The TS of heat stimuli did not differ between groups and did not change pre- and post-exercise but did decrease over the series of stimuli. These results are in contrast to those from a similar protocol in a similar population without an exercise intervention (Owens et al., 2016). Other studies also showed an increase in pain intensity using different protocols (Brellenthin et al., 2017; Reynolds et al., 2017). However, consistent with findings of this study, a reverse effect of TS has been reported in other studies as a reduced wind-up or habituation in healthy controls (Penza et al., 2017; Staud et al., 2005). As the protocol applied in this study did not induce TS, changes cannot be related to EIH to inform the TS response after a repeated lifting task.

It is worthwhile to note that there was large variability in QST responses. Some participants with CLBP did show increased PPT after the task reflecting the large variability in presentation found in any CLBP cohort (Falla and Hodges, 2017). However, the findings of this study highlight that even people experiencing chronic symptoms of low severity and normal baseline sensitivity can lack an EIH response. It will be relevant in future research to investigate if the absence of EIH is associated with poorer outcome to exercise interventions in people with LBP. Potentially, the response to a short bout of back-specific exercise could be used to understand whether or not a participant is likely to have a positive analgesic response to an exercise programme targeting their back muscles. Although, subgrouping based on EIH response needs to be fully investigated in future work.

2.5.1 Strengths and Limitations

This is the first study to investigate the effects of repetitive lifting on pain sensitivity with an extensive QST test battery including tests of sensitivity to both mechanical and thermal stimuli. Nevertheless, there are some methodological considerations that should be noted. An *a priori* sample size was not determined, and it is therefore possible that the sample size prevented some differences from reaching statistical significance. It could be argued that the average change in PPT measured from the 16 sites over the lower back for the asymptomatic participants (i.e., +29.78 kPa) is low and although statistically significant, is not a relevant change. Moreover, based on the RM-ANOVA there was no interaction at the remote test site for time (CON: +22.61 kPa/ CLBP: +1.95 kPa), even though change in the asymptomatic group is somewhat similar to the change over the lumbar region. Nevertheless, it should be noted that the average change in PPT for the CLBP group was in the opposite

direction (i.e., -14.87 kPa) suggesting a real and relevant difference in response between groups.

No control condition was included in this study; thus, it is uncertain whether the changes in PPT are actually due to the exercise performed. The change in PPT at the back could be partially attributed to habituation, due to induction of pain itself from the extensive psychophysical testing or even expectation effects. Participants were verbally encouraged and instructed participants to lift with their back. Therefore, changes in QST might be influenced by underlying biomechanical or muscular activations pattern which were not considered in this study. Participants were recruited from a University environment and therefore the data cannot be generalised to other CLBP populations including those exposed to manual labour and heavy lifting or to people with more severe LBP.

Even in the asymptomatic group, the task produced mild back discomfort in some participants. This suggests that the task targeted the right region. However, the duration and intensity of the task might not have been extensive enough to produce high levels of EIH, as shown for a task with higher discomfort in asymptomatic people (Ellingson et al., 2014). This could explain the lack of a systemic effect measured at the remote site.

Missing data were due to technical limitations of the equipment used but were relatively even between groups and thus this did not likely have a statistically significant effect on the results. The order of QST was the same for both groups and cannot explain group differences. However, it cannot be out ruled that different test modalities have an effect on the subsequent test. Finally, the full QST was completed within 30 minutes, which has been indicated as the minimum persistence of EIH (Naugle et al., 2012). As thermal tests

were performed last, any effects might have been disappeared by that time. It is still not clearly defined how long the effects of EIH can be maintained.

2.6 Conclusion

Asymptomatic participants displayed evidence of EIH as revealed by a statistically significant reduction in pressure pain sensitivity over the erector spinae, in response to a short, repeated lifting task. In contrast, this phenomenon was absent in participants with CLBP who presented with low severity pain and disability. This is the first evidence of a longer functional task eliciting EIH and future research should be conducted considering similar tasks in participants with CLBP to strengthen the available evidence. A systematic analysis of EIH in this population can contribute to reduce this gap in research and identify specific needs for future research. Due to paucity of studies available evidence from similar pathologies could inform the current knowledge of EIH in people with CLBP.

Chapter Three

Exercise-Induced Hypoalgesia in People with Spinal Pain: A Systematic Review and Data Synthesis

The protocol for this systematic review has been registered with PROSPERO and is available as Appendix 6 or online under https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019145586

Publication

This study has been submitted to the European Journal of Pain and is currently under review. Some elements have been re-worded for the aim of this thesis to avoid repetition with previous Chapters. This Chapter largely reflects the submitted manuscript verbatim and parts of the registered protocol but contains additional in-text information of the methods and result sections. Furthermore, an abstract of this Chapter has been submitted at the "2022 World Congress on Pain" (International Association for the Study of Pain).

3.1 Abstract

This Chapter presents a systematic review on exercise-induced hypoalgesia (EIH) in people with spinal pain. Findings from the previous Chapters highlight a lack of research on EIH in people with chronic low back pain (CLBP), but an emerging body of evidence has examined EIH in recent years. The Chapter objective was to investigate the phenomenon of EIH in people with spinal pain reflecting the following three Chapter objectives considering 1) the region of the task and the type of the task 2) type of spinal complaint; and 3) location of test sites in respect to the affected body region.

A sensitive search strategy of six databases and search engines and hand search was conducted including grey literature. Eligibility criteria were any spinal pain complaint, physical activity aiming to alter pain sensitivity, observational studies, and within-session re-test. Risk of bias and cumulative evidence (GRADE) informed the narrative synthesis. This review was planned, conducted, and reported following PRISMA guidelines.

Seventeen studies (four good, ten fair, and three poor risk of bias) were included. Low quality evidence supports impaired EIH following isometric tasks and in people with whiplash associated disorders; conflicting results for remote and aerobic tasks were found. Very low quality evidence supports altered EIH after a local task, hyperalgesia after a regional/ work-mimicking tasks, with conflicting results for people with CLBP and chronic neck pain. Very low quality evidence supports no difference between local and remote sites.

As a conclusion, confidence in the existing quality of evidence is low to very low for the presence of EIH in people with spinal pain across all three objectives. There is a clear need for high quality studies to further elucidate whether EIH occurs in people with spinal pain and to establish the role of EIH in rehabilitation.

3.2 Introduction

As there is little available evidence for EIH in people with CLBP, this systematic review includes all types of spinal pain. Although spinal regions and their pathologies differ in their anatomy and function, regional interdependences exist and thus they are commonly combined (Heneghan and Rushton, 2016; Hubscher et al., 2013; Marcuzzi et al., 2015). CLBP and chronic neck pain (CNP) are common and relevant problems affecting the quality of life of people and leading to high costs for the healthcare and social systems (Hoy et al., 2014). Moreover, people with chronic spinal pain often present with peripheral and/or central sensitisation potentially affecting EPM (Roussel et al., 2013; Uddin et al., 2014). The presence of sensitisation has been hypothesised as one of the factors explaining why some people with pain do not respond as favourably to exercise as others (Rice et al., 2019).

To date, one systematic review with meta-analysis limited to RCTs has been conducted investigating whether EIH occurs in people with chronic musculoskeletal pain and asymptomatic people (Wewege and Jones, 2021). A large summary effect size (Hedges' g>.8) was demonstrated for the presence of EIH in asymptomatic people following aerobic exercises, whereas dynamic resistance exercise lead to small EIH (g <.2), and no evidence of EIH was found after isometric exercise (Wewege and Jones, 2021). For people with musculoskeletal pain, EIH did not occur after isometric exercise based on three studies (Wewege and Jones, 2021). However, none of these studies considered people with spinal pain; the review included tendino-/fasciopathy or degenerative disorders which may present differently to spinal pain. A previous meta-analytic review by Naugle et al. (2012) included observational studies on people with spinal pain and recent key focus articles referred to further observational studies (Rice et al., 2019; Vaegter et al., 2020a). Recommendations from

reviews of clinical trials and observational studies are important to contribute to the overall body of evidence (Craig, 2019; Guyatt et al., 2011a).

Thus, there is currently equivocal evidence ranging from hypoalgesic to hyperalgesic effects to no effect following exercise in people with chronic pain (Bonello et al., 2021; Naugle et al., 2012; Pacheco-Barrios et al., 2020; Rice et al., 2019; Vaegter and Jones, 2020; Wewege and Jones, 2021), but no systematic review to date firstly, investigated spinal pain specifically or secondly, investigated if EIH differs depending on whether the exercise was performed by the affected body region or not. This is important as current clinical management for spinal pain often specifically targets the symptomatic region (Falla and Hodges, 2017). Resistance exercise has been hypothesised to elicit localised EIH, whereas aerobic exercise produces a systemic response (Naugle et al., 2012). It is also largely unknown if EIH differs when tested over the affected body region (local) compared to unaffected regions (remote).

3.2.1 Chapter Objectives

The overall objective of the systematic review is to investigate if people presenting with spinal pain gain EIH following a bout of a physical activity as outlined as the second objective of this thesis. The Chapter objective to synthesise current evidence from observational studies is broken down into these three specific Chapter objectives:

1) to synthesise current evidence from observational studies to determine whether EIH occurs in people with spinal pain and whether this is dependent on the region (e.g., local or remote to the affected body region) of the exercise performed and the type of task (e.g., aerobic or isometric)

2) to investigate whether these results vary depending on the specific spinal pain complaint i.e., CLBP versus CNP as it remains unclear whether there are systematic differences in EIH between CLBP and CNP.
3) to evaluate differences in test sites with different spatial relation to the affected spinal region (i.e., local versus remote sites).

3.3 Methods

3.3.1 Design

This systematic review was designed and reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) and protocols, Cochrane recommendations by the back pain review group, and STROBE guidelines applying a pre-defined and registered protocol (Furlan et al., 2009; Hutton et al., 2015; Moher et al., 2015; Page et al., 2021; von Elm et al., 2008). The review was first registered on PROSPERO on the 16th of August 2019 (CRD42019145586) (Appendix 6). Minor changes in synthesis and definitions as well as a search update are outlined online, but no major changes were conducted for the rest of the methodology with the final updates in November 2020. This Chapter followed the updated PRISMA guideline (Page et al., 2021) and is presented in Appendix 7.

3.3.2 Eligibility Criteria

Eligibility criteria were defined using PIPOS and are summarised in Table 3.1 comprising of: population, intervention (task), phenomenon of interest: EIH, outcome measurement, and study design. Cochrane recommends the use of PIC(O(S)) for systematic reviews on therapeutic interventions but this does not fully represent EIH as the objective of this study as it is not the aim of an intervention (Eriksen and Frandsen, 2018). Therefore, phenomenon of interest was added from "SPIDER", which has been shown to be superior for qualitative or narrative synthesis (Methley et al., 2014).

Observational studies with and without a control group were included as the research question did not aim for a comparison between people with and without spinal pain, therefore this domain was not used. Only observational studies were included as this was deemed most appropriate to answer the research aim (Koenders et al., 2016). Based on scoping searches, multiple studies did not clearly state their study design. Due to this ambiguity, study design and language were evaluated in the second screening stage.

Whilst different methods have been employed to determine EIH, currently no gold standard exists (Lima et al., 2017; Rice et al., 2019; Sluka et al., 2018; Vaegter et al., 2020a). Repeated QST, including PPT or TPT, has most commonly been used to determine EIH (Wewege and Jones, 2021). Furthermore, tasks including all forms of physical activity were included (see Chapter one, section 1.3.5).

Table 3.1 Eligibility criteria

PIPOS	Inclusion	Exclusion
Population	• ≥ 18 years old • Pain in the lumbar, thoracic, or cervical region • Specific, non-specific, and traumatic pain • Any level of severity, disability, and stage (acute/ chronic) • Multiple regions of bodily pain not excluded • Mixed presentation ≥80% spinal pain	• Fibromyalgia • Post-traumatic stress disorder • Non-musculoskeletal disorders • Neurological injuries
Intervention/ task	• Any form of physical activity with the aim of altering pain sensitivity and of any duration performed in any part of the body (region) e.g., isometric, concentric, eccentric exercise, or combined/ functional/ occupational tasks with or without resistance/weights, and/ or aerobic exercise (type)	• Passive, psychological, or mental exercises, such cognitive tasks, or educational programmes
Phenomenon of interest	• EIH, as change in pain sensitivity/ pain modulation/ pain inhibition after a single bout of exercise • No restriction in elapsed time between the task and post-test • Test sites could be at the painful region or over remote test sites	• No within-session change • No EIH
Outcome measurement	• Performance-based psychophysical measures such as pain threshold or tolerance of mechanical (pressure), thermal, electrical stimuli or dynamic measurements such as TS • Assessments such as the nociceptive withdrawal reflex, CPM, invasive techniques, or imaging techniques • Patient reported outcome measurement as for example pain score (VAS/ NRS) and pain drawings measuring changes in pain sensitivity due to physical activity	• Only measuring perceived pain using a pain scale such as VAS/NRS without any further relation to pain sensitivity as not linked to a specific stimulus to quantify pain sensitivity
Study type	• Observational studies • In case no or "less conventional" study design was stated, reviewers agreed on eligibility • Full-text available and written in English	• Randomised and cross-over trials and case studies

Abbreviations: *EIH= Exercise-induced Hypoalgesia; TS= Temporal Summation; CPM= Conditioned Pain Modulation; VAS= Visual Analogue Scale; NRS= Numeric Rating Scale*

3.3.3 Information Sources

The following databases and search engines were searched independently by two researchers (PK; AD): MEDLINE (OVID interface), EMBASE (OVID interface), CINAHL (EBSCO interface), Web of Science, PubMed. The search included all results from inception to the 2nd of July 2020, with two independent researchers performing searches on Google Scholar to the 22nd July 2020. Additionally, hand searches of the following key journals complemented the search: The Journal of Pain, Scandinavian Journal of Pain, PAIN, The Clinical Journal of Pain, and European Journal of Pain. Moreover, Grey literature search included Ethos for dissertation abstracts, Open Grey, ZETOC and British National Bibliography for unpublished research. Further hand searches were conducted for relevant key reviews in the area and their reference list (Lima et al., 2017; Naugle et al., 2012; Nijs et al., 2012; Rice et al., 2019; Roussel et al., 2013; Sluka et al., 2018).

3.3.4 Search Strategy

The search strategy was developed by the lead author (PK) in discussion with the supervisors. Where appropriate, medical subject headings (MESH), text words, and unique searching filters of individual databases were used (Baumann, 2016). The concepts searched considered the eligibility criteria (PIPO) for the strategy and included 1) population (spinal pain or related terms) 2) intervention/ physical activity (task) 3) EIH, or endogenous pain inhibition, or pain sensitivity to activity 4) outcome measurements linked to EIH. PICO(S)/ PIPOS is limited due to the fact that outcome measures might not be stated in the abstract,

therefore a sensitive search with a wide range of terms was used and the search was not limited to title and abstract depending on the search engine (Eriksen and Frandsen, 2018). Search terms were informed by previous reviews or protocols (Naugle et al., 2012; Wewege and Jones, 2021) but further refined for this specific research question. No restrictions were applied for the year of publication, study design, or language. Hand searching followed by the same two independent researchers. All full line-by-line search strategies are presented in Appendix 8.

3.3.5 Selection Process

All references were imported to Endnote X9 (Clarivate Analytics), and duplicates were removed by the lead author using the software's own function followed by visual inspection and manual removal. At the first stage of screening two independent researchers (PK, AD) screened titles and abstracts, and full-text in the second stage using a pre-designed and piloted screening tool of eligibility criteria for each stage. Decisions were made according to "include", "exclude", and "unsure". If "unsure" the full-text was considered. If articles were considered for the full-text screening stage, the PDF of the full-text was obtained. Authors were contacted by email if the determination of eligibility was unclear. For the full-text screening stage, the same procedure of evaluating eligibility was followed using a pre-designed screening form. At all stages, an experienced researcher (AR) mediated in case of disagreement, or a study was still considered as "unsure".

3.3.6 Data Collection Process

Relevant data from all included studies were extracted independently by two reviewers (PK, AD) according to a bespoke proforma. Where further information/ data needed to be obtained, the authors of the relevant study were contacted by email. In case of no reply, a second request was sent out after two weeks. If not obtained, values from published figures were estimated using "WebPlotDigitizer 4.2" by one reviewer (PK) and checked by a second reviewer (DA).

3.3.7 Data Items

Data items were defined *a priori* in the registered protocol. Extracted data items included: authors, year, country, spinal complaint, study design, setting, population (size, gender, age, spinal pain relevant characteristics), task (region of the task in respect to spinal complaint, type, duration, intensity, perceived exertion), outcome measurement for each mechanical, thermal, or blood/others testing naming the device, unit, and test sites and timepoint of post-test. For the results if available mean and SD, results in change in percentage, pre-post score, or absolute difference with effect size and/ or confidence intervals were reported.

For data extraction, results of EIH were presented within 1) the local affected area and 2) remote area. As a third category 3) the results were compared to the control group if available.

3.3.8 Risk of Bias in Individual Studies

Both reviewers independently assessed ROB of the included studies using a modified version of the Newcastle Ottawa Scale (NOS) for observational studies (Wells, 2009). The NOS is a well-established tool, but its reliability can be challenged and therefore, further modifications are recommended (Hartling et al., 2013; Zeng et al., 2015). Modifications for this systematic review included the three domains of selection (*case definition, *representativeness, *selection, and *definition of controls), comparability (not considered for overall score), and exposure/ outcome (*outcome measurement, and *intervention, *consistent for both groups) (Appendix 9). Applying the modified NOS, studies were rated as good, fair, or poor. Percentage agreement between reviewers was calculated based on each item of the first and third domain as well as the overall score. All disagreement were mediated by a third reviewer (NRH).

3.3.9 Effect Measures

Differences from pre/ and post-test/ or absolute or relative change were used as presented in the analysis of each individual study or applied analysis model output. Results were described within five categories: no EIH (no statistically significant difference between pre and post scores in any group); normal EIH (change in EIH, but no statistically significant group difference between symptomatic and asymptomatic group) and altered EIH consisting of impaired EIH (reduced or no EIH with a statistically significant difference to the asymptomatic group, which experienced EIH); increased EIH (more pronounced EIH than the asymptomatic group); and hyperalgesia (significantly increased pain sensitivity with or without a statistically significant group difference).

3.3.10 Synthesis methods

Due to clinical and methodological heterogeneity, meta-analysis was not appropriate (McKenzie and Brennan, 2020). For the narrative analyses, data were organised based on the three objectives. For the first objective, region of task, commonly used terminology has been adopted (Bonello et al., 2021) differentiating between local, within the affected area, and remote tasks. However, a third category was derived to better reflect the data defined as regional exercise tasks; definitions are outlined in Table 3.2. For the second objective of spinal regions, the cervical region was subdivided into CNP and WAD. Differences between CNP and WAD have been shown before (for example see Anstey et al., 2016; Chien and Sterling, 2010), but have not been investigated for EIH. All studies were evaluated on each of the three objectives and if needed, further sub-categories were derived.

Table 3.2 Data synthesis structure based on the three objectives and themes

Objective		**Definitions**		
1a	Region	**Local** Affected region of the spine is targeted within the task as for example deep neck flexor exercise for people with CNP (Falla et al., 2013)	**Remote** For example, cycling in a population with CLBP	**Regional** Tasks not directly in the local area, but the task is designed to target the affected region such as shoulder movements for people with CNP
1b	Type	Aerobic	Isometric	Others
2	Spinal complaint	CLBP	CNP	WAD
3	Test site	**Local** Within the region of spinal pain	**Remote** Outside the region of spinal pain	

***Abbreviations**: CLBP = Chronic Low Back Pain; CNP= Chronic Neck Pain; WAD= Whiplash Associated Disorders*

3.3.11 Meta-Biases

To avoid publication bias, the grey literature, conference abstracts, and the internet were searched including potential study protocols. Currently no study register exists for observational studies.

3.3.12 Risk of Bias across Studies/ Confidence in Cumulative Evidence

Following the Grading Recommendations, Assessment Development and Evaluation (GRADE) the strength of the overall body of evidence using "very low", "low", "moderate" and "high" were reported considering all five domains: study limitations, inconsistency, imprecision, indirectness, and publication bias. Based on the design of observational studies, the starting point for evaluation of quality is "low" (Guyatt et al., 2011a). For narrative synthesis, definitions were modified as recommended (Murad et al., 2017). For study limitations, sample sizes were considered, defined by power calculation/ a priori calculation of sample size or justification from the STROBE guidelines (Vandenbroucke et al., 2014; von Elm et al., 2014). These were not covered by the modified NOS for assessment of ROB. Inconsistency was based on results of the individual studies (Guyatt et al., 2011d). Imprecision was defined as lack of reporting or wide ranges of 95% confidence interval and effect size, and numbers of participants (continuous defined as pre/post) ≥400 (Guyatt et al., 2011b). Indirectness referred to substantial differences in population, intervention (duration and intensity) to produce EIH, feasibility of outcome measurement and/or relevance for recommended management for people with spinal pain and levels of disability and severity (Guyatt et al., 2011c). The fifth domain was publication bias. A huge variety of results

reduces the risk of positive reporting, whereas a low number of studies in general might increase publication bias; additionally, conflict from industry funding was considered (Guyatt et al., 2011e). Serious concerns in more than one domain downgraded the confidence to very low quality of evidence.

3.4 Results

3.4.1 Study Selection

The search resulted in 9173 articles for screening; and 119 were reviewed at the full-text stage. Twenty-eight articles representing 17 studies were included; Figure 3.1 displays the PRISMA flow diagram (Page et al., 2021).

When one study presented data across multiple publications, all articles were included as one study (studies n=6) (Table 3.3). To improve clarity and facilitate reading the following studies are only referenced with the main relevant or most recent study only in text and tables. The full list of excluded studies including justification can be found in Appendix 10.

Table 3.3 Studies resulting in multiple publications

In text cited as	Comprising of publications
Gerdle et al., 2008a	(Gerdle et al., 2008a; Gerdle et al., 2008b; Rosendal et al., 2005; Rosendal et al., 2004)
Ghafouri et al., 2013	(Gerdle et al., 2010; Ghafouri et al., 2013)
Grimby-Ekman et al., 2020	(Grimby-Ekman et al., 2020; Grimby-Ekman et al., 2017; Stensson and Grimby-Ekman, 2019)
Persson et al., 2009	(Persson et al., 2000; Persson et al., 2003; Persson et al., 2009)
Strom et al., 2012	(Strom et al., 2009a; Strom et al., 2009b; Strom et al., 2012)
Vaegter et al., 2016	(Vaegter et al., 2016; Vaegter et al., 2017b)

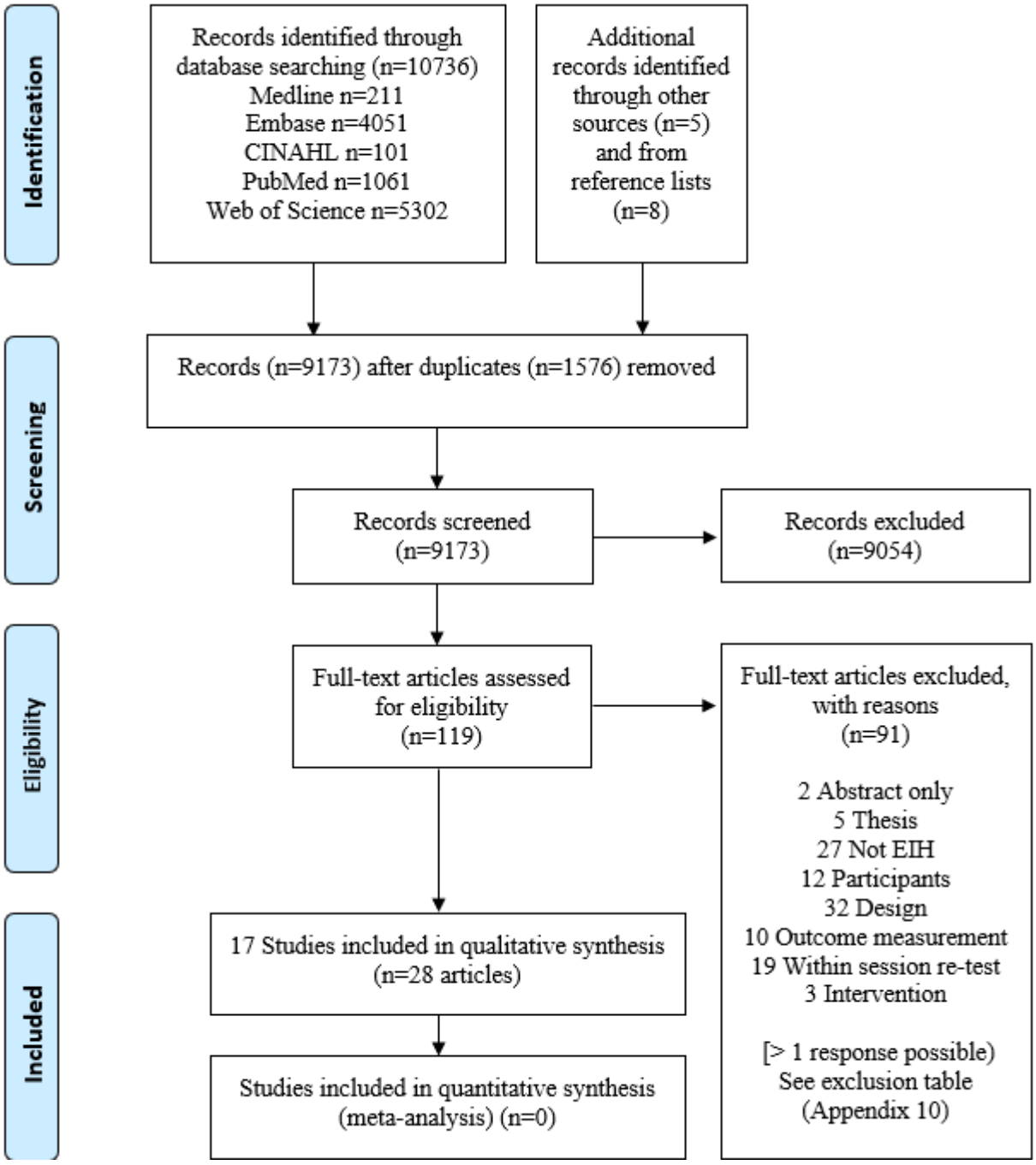


Figure 3.1 Selection Process

PRISMA flow diagram adapted from (Page et al., 2021); EIH= Exercise-induced Hypoalgesia

3.4.2 Study Characteristics

The 17 included studies reflect 434 participants (73% female) (Christensen et al., 2017; Falla et al., 2014; Gerdle et al., 2008a; Ghafouri et al., 2013; Grimby-Ekman et al., 2020; Hoffman et al., 2005; Ickmans et al., 2017; Kemppainen et al., 1998; Kuithan et al., 2019; Larsson et al., 2008; Meeus et al., 2010; Persson et al., 2009; Smith et al., 2017a; Smith et al., 2020; Strom et al., 2012; Vaegter et al., 2016; Van Oosterwijck et al., 2012).

Study characteristics are presented in Table 3.4 for all individual studies, additional details are presented in Appendix 11.

Table 3.4 Study characteristics

Study	Spinal Pain	Participants n= (women)	Age (years Mean /SD or (Range))	Task	
Christensen et al., 2017	CNP WAD	16 (10) 9 (7)	27.6± 1.8 33.8± 2.5	Glenohumeral Abduction	
Falla et al., 2014	LBP	19 (11)	32.2± 9.5	Lifting	
Gerdle et al. 2008a	CNP WAD	19 (19) 22 (22)	41 (21-61) 36 (24-45)	Peg Board	
Ghafouri et al., 2013	CNP	34 (34)	45 (29-60)	Peg Board	
Grimby-Ekman et al., 2020	CNP	26 (19)	51± 5.12	Arm Cycling	
Hoffman et al. 2005	LBP	8 (0)	40± 10	Cycling	
Ickmans et al., 2017	WAD	26 (15)	43.5 (IQR 30.8–47.3)	Cycling	
Kemppainen et al., 1998	CNP	8 (0)	(22-35)	Cycling	
Kuithan et al., 2019	LBP	21 (12)	31.7± 13.3	Lifting	
Larsson et al, 2008	CNP	20 (20)	43.8± 9.8	Workday	
Meeus et al., 2010	LBP	21 (11)	41.55± 12.4	Cycling	
Persson et al., 2009	CNP	17 (17)	47± 14.8	Isometric	
Smith et al. 2017	WAD	21 (55%)	44.5± 10.5	Cycling	ISO
Smith et al. 2020	WAD	40 (28)	37.3± 13.6	Treadmill	ISO
Strom et al., 2012	CNP	24 (14)	39± 6	PC task	
Van Oosterwijck et al., 2012	WAD	22 (22)	38.4± 9.2	Cycling	
Vaegter et al., 2016	Mixed	61 (42)	45.4± 11.2	Cycling	ISO

Abbreviations: *CNP= Chronic non-specific Neck Pain; WAD= Whiplash Associated Disorders; CLBP = Chronic non-specific Low Back Pain; IQR= Interquartile Range; ISO= Isometric*

Nine studies reported an average pain intensity before the task as 3.5/10 on a visual analogue scale (VAS)/ numeric rating scale (NRS) (Hjermstad et al., 2011). Sample sizes varied from 8 to 61 participants. For most studies, a comparison could be made to an asymptomatic control group representing a normal EIH response, but two studies had a non-exercising control group (Hoffman et al., 2005; Vaegter et al., 2016). Twelve studies included participants with CNP and/or WAD. One study included chronic musculoskeletal pain but fulfilled eligibility with 87% of participants presenting with spinal pain; participants were divided in groups of high and low pain sensitivity based on their PPT scores.

The tasks used to produce EIH comprised of aerobic exercises (n=9), isometric exercises (n=4), a peg-board task (n=2), and a lifting task (n=2). Additionally, one study investigated repeated shoulder abduction, a working day, and a computer task. All studies reported task duration, which ranged from 90 seconds to eight hours. Studies assessing two tasks were analysed individually, as studies either confirmed scores returned to the baseline level or the other session was on a different day.

3.4.3 Risk of Bias within Included Studies

The NOS rating of studies was poor (n=3), fair (n=10), and good (n=4), with good indicating a low ROB, and poor a high ROB. The overall ROB rating is outlined in Figure 3.2 confirming selection bias, full information is provided in Appendix 12. Agreement between the two researchers (PK, AD) was 87%, a third researcher (NRH) resolved all disagreements through discussion. Only two studies (Ickmans et al., 2017; Kuithan et al., 2019) mentioned reporting guidelines (von Elm et al., 2008), the lack of adherence to those impacted data

synthesis and thus increased ROB. Some studies reported equivocal sample sizes between publications (Gerdle et al., 2008a; Ghafouri et al., 2013; Grimby-Ekman et al., 2020; Strom et al., 2012; Vaegter et al., 2016).

Study	Selection				Exposure/ Outcome			Overall Risk of Bias
	Case definition	Represen-tiveness	Selection of control	Definition of controls	Description of outcome measurement	Identical for outcome and intervention	Description of task	
Christensen et al., 2017	+	+	?	+	+	+	+	GOOD
Falla et al., 2014	+	-	?	+	+	+	+	FAIR
Gerdle et al., 2008a	-	-	-	+	+	+	+	POOR
Ghafouri et al., 2013	-	-	+	+	+	+	+	FAIR
Grimby-Ekman et al., 2020	+	-	-	+	+	+	+	FAIR
Hoffman et al., 2005	+	?	?	+	+	-	+	FAIR
Ickmans et al., 2017	+	-	-	+	+	+	+	FAIR
Kemppainen et al., 1998	-	-	+	+	+	+	-	FAIR
Kuithan et al., 2019	+	-	+	+	+	+	+	GOOD
Larsson et al., 2008	?	-	+	+	+	?	-	POOR
Meeus et al., 2010	+	-	-	+	+	+	?	FAIR
Persson et al., 2009	+	-	?	+	+	-	+	FAIR
Smith et al., 2017	+	-	?	+	+	+	+	FAIR
Smith et al., 2020	+	-	-	+	+	+	+	FAIR
Strom et al., 2012	+	-	+	+	-	+	+	GOOD
Van Oosterwijck et al., 2012	+	-	+	+	-	+	+	GOOD
Vaegter et al., 2016	+	-	NA	NA	+	NA	+	POOR

Figure 3.2 Modified Risk of Bias Scale for all included Studies

Green (+) indicates criteria are met, red (-) that criteria are not met, and yellow (?) unclear; NA= Not applicable

3.4.4 Results of Individual Studies

Results of all individual studies included in the synthesis outlining all data items are presented in a table in Appendix 11. For five studies data could not be obtained or authors did

not reply, and results were estimated and marked as such. Relevant information for synthesis is presented in the next section.

3.4.5 Confidence in Cumulative Evidence

3.4.5.1 Objective one – Exercise-Induced Hypoalgesia in respect to Task Region and Type

Two studies (Falla et al., 2014; Kuithan et al., 2019) investigated local tasks, eight investigated remote tasks (Hoffman et al., 2005; Ickmans et al., 2017; Kemppainen et al., 1998; Meeus et al., 2010; Smith et al., 2017a; Smith et al., 2020; Vaegter et al., 2016; Van Oosterwijck et al., 2012), and seven investigated regional tasks (Christensen et al., 2017; Gerdle et al., 2008a; Ghafouri et al., 2013; Grimby-Ekman et al., 2020; Larsson et al., 2008; Persson et al., 2009; Strom et al., 2012). For the type of exercise, nine studies included aerobic exercises (Grimby-Ekman et al., 2020; Hoffman et al., 2005; Ickmans et al., 2017; Kemppainen et al., 1998; Meeus et al., 2010; Smith et al., 2017a; Smith et al., 2020; Vaegter et al., 2016; Van Oosterwijck et al., 2012), four isometric exercises (Persson et al., 2009; Smith et al., 2017a; Smith et al., 2020; Vaegter et al., 2016), three studies included work mimicking tasks (Gerdle et al., 2008a; Ghafouri et al., 2013; Strom et al., 2012), and two studies lifting tasks (Falla et al., 2014; Kuithan et al., 2019). Results are shown in Table 3.5 with overall quality of evidence determined by GRADE.

Table 3.5 Evidence synthesis task and type (first objective)

Task region	Author & year	Sample	Task type	Duration	Intensity	Outcome	Spinal com-plaint	Result			ROB	GRADE: 1) study limitation 2) Inconsistency 3) Indirectness 4) Imprecision 5) publication bias					
								No EIH	Normal EIH	Altered EIH		1	2	3	4	5	Overall evidence
Local N=40	Falla et al., 2014	19	Lifting	~200s	5kg	PPT	CLBP	CON		↑	FAIR	++	+	++	++	++	Very low quality for altered EIH to a local lifting task [2 studies of good /fair ROB]
	Kuithan et al., 2019	21	Lifting	~7min	5kg	PPT, TPT	CLBP			↓	GOOD						
Remote N=207	Hoffman et al., 2005	8	Cycling	25min	70% VO2max	Pressure	CLBP		X no CON		FAIR	+	+ +	+	+		Low quality for remote tasks with conflicting evidence to lead to normal or impaired EIH. [5 studies (7 tasks) normal EIH (1 good, three fair ROB); 4 studies (six tasks) altered EIH (1 good, 2 fair, 1poor ROB), 2 studies no EIH (fair ROB)]
	Meeus et al., 2010	21	Cycling	~27.5 min	Max 130W	PPT	CLBP		X		FAIR						
	Ickmans et al., 2017	26	Cycling	Median 5 min	75% HR	PPT	WAD	X			FAIR						
	Van Oosterwijck et al., 2012	22	Cycling	~4.3min	75% HR/	PPT	WAD			↓	GOOD						
				~10.3min	self-paced				1test site								
	Kemppainen et al., 1998	8	Cycling	20-32 min	Max 200W	TPT	CNP			I	FAIR						
	Smith et al., 2017	21	Cycling	30min	75% HR	PPT	WAD	X			FAIR						
			Isometric squat	≤3min	Body weight				X								
	Smith et al., 2020	40	Treadmill	30min	75% HR	PPT	WAD			↓	FAIR						
			Isometric Quads	≤3min	20-25% MVC					↓							
	Vaegter et al., 2016	61	Cycling	15min	75% Vo2max	PPT, TPT, Pressure	Mixed		X no CON	↓ HS vs LS	POOR (No CON)						
			Isometric Quads	90s	30% MVC												

Regional Total N=159	Persson et al., 2009	17	Isometric GH ABD	Maximal (~209s)	1kg on wrist	PPT	CNP			↓ Less sites	FAIR	++	++	++	++	+	Very low quality that regional exercises lead to altered, i.e., hyper-algesia. [Altered EIH 5 studies of those 2 impaired EIH (fair and good ROB) and 4 hyperalgesia (2 good, fair, and poor ROB); 3 studies with no EIH (2 fair, 1 poor ROB)]
	Christensen et al., 2017	16+9	G/H ABD	~30min breaks	Arm weight	PPT	CNP WAD			↓ WAD ↑ CNP	GOOD						
	Larsson et al., 2008	20	Workday	8hrs	Task exposure scale	MD	CNP	*			POOR						
	Strom et al., 2012	22	PC task	90min	low	PPT	CNP			↑ as CON	GOOD						
	Ghafouri et al., 2013	34	Peg Board	20min	low	MD	CNP	CNP*		↑ WAD*	FAIR						
	Gerdle et al., 2008a	19+22	Peg Board	20min	low	MD	CNP WAD			*	POOR						
	Grimby - Ekman et al., 2020	26	Arm Cycling	30min	25 laps/min; load 100-600gr	PPT Blood test	CNP	X			FAIR						
	Summary type of task																
	Aerobic n=233, [4 studies normal EIH (3 fair, 1 good/poor ROB), 4 studies altered EIH (2 fair, 1 good/poor ROB), 3 studies showed no EIH (fair ROB)]											+	++	+	+		Low quality with conflicting results for aerobic exercises
	Isometric n=139 [3 studies altered (all impaired) EIH (2 fair, 1 poor ROB), 2 studies (fair and poor ROB) normal EIH]											+	+	+	++	+	Low quality that EIH is impaired after isometric exercises
	Work mimicking tasks n= 97 [3 studies altered (hyperalgesia) (poor, fair, and good ROB), 1 study no EIH (fair ROB)]											++	++	+	+	++	Very low quality that work mimicking tasks lead to hyperalgesia
	Lifting n=40, see local tasks																

Abbreviations: *ROB= Risk of Bias; ↓= Impaired; I= Increased, ↑Hyperalgesia; *=Increased Anti-nociceptive Markers; GRADE + = Concern; ++ = Serious concern: more than one serious concern downgrades the level of confidence, CLBP= Chronic Low Back Pain; WAD= Whiplash Associated Disorders; CNP= Chronic Neck Pain; CMSK= Chronic Musculoskeletal Pain; CON= Control Group; GH= Glenohumeral; ABD= Abduction; Quads= Quadriceps; PPT= Pressure Pain Threshold; TPT= Thermal Pain Threshold; MD = Microdialysis; EIH= Exercise-Induced Hypoalgesia; HS= High Pain Sensitivity Group; LS= Low Pain Sensitivity Group*

3.4.5.1.1 Local Tasks

Local tasks (2 studies, n=40 participants with CLBP) were an occupationally informed lifting task but of different durations. Both local tasks revealed an altered response; a local task revealed impaired EIH in one study of good ROB (Kuithan et al., 2019) and hyperalgesia in one study of fair ROB with a shorter task (Falla et al., 2014). Publication bias should be considered. Overall, there is very low quality evidence for altered EIH in response to a local lifting task in people with spinal pain, specifically CLBP.

3.4.5.1.2 Remote Tasks

Remote tasks (8 studies) included aerobic (cycling and treadmill, n= 233) and/ or isometric tasks (n=139) showing conflicting results. Five studies evaluating seven tasks (three fair, one good, one poor ROB) showed normal EIH (Hoffman et al., 2005; Meeus et al., 2010; Smith et al., 2017a; Vaegter et al., 2016; Van Oosterwijck et al., 2012). Four studies evaluating six tasks (two fair, one good, one poor ROB) showed altered EIH (Kemppainen et al., 1998; Smith et al., 2020; Vaegter et al., 2016; Van Oosterwijck et al., 2012). An altered response, specifically impaired EIH, was observed in all studies except for one study (fair ROB). Vaegter et al. (2016) found either normal or impaired EIH depending on high or low pain sensitivity at baseline, this was the same for aerobic and isometric tasks. No EIH was found in two studies (fair ROB) (Ickmans et al., 2017; Smith et al., 2017a). As detailed above, a difference between people with high and low pain sensitivity was found in one of the studies (Vaegter et al., 2016). Overall, there is low quality evidence for conflicting results that remote exercise leads to normal or impaired EIH in people with spinal pain.

3.4.5.1.3 Regional Tasks

Seven studies were included involving the following tasks: peg board (n=75), shoulder movements (n=25), a PC task (n=22), a working day (n=20), isometric shoulder contractions (n=17), and arm cycling (n=26). The purpose of these tasks was of different nature, with protocols aiming for hypo- and hyperalgesic responses and some mimicking occupational tasks. Regional tasks led to altered EIH in five studies. Of these, four showed hyperalgesia (two good, one fair, one poor ROB) (Christensen et al., 2017; Gerdle et al., 2008a; Ghafouri et al., 2013; Strom et al., 2012), and two showed impaired EIH (one good, one fair ROB) (Christensen et al., 2017; Persson et al., 2009). Three studies did not show EIH (two fair, one poor ROB) (Gerdle et al., 2008a; Grimby-Ekman et al., 2020; Larsson et al., 2008). Overall, there is very low quality evidence that regional tasks lead to altered EIH, specifically hyperalgesia.

3.4.5.1.4 Objective One – Exercise-Induced Hypoalgesia in respect to Task Type

3.4.5.1.5 Aerobic Tasks

Regarding the type of task, nine studies evaluated ten aerobic tasks. Task duration varied from five (median) to thirty minutes. Results were conflicting, with four studies showing normal EIH (two fair, one good, one poor ROB) (Hoffman et al., 2005; Meeus et al., 2010; Vaegter et al., 2016; Van Oosterwijck et al., 2012); four studies showing altered EIH (two fair, one good, one poor ROB) (Kemppainen et al., 1998; Smith et al., 2020; Vaegter et al., 2016; Van Oosterwijck et al., 2012); and three studies showing no EIH (fair ROB) (Grimby-Ekman et al., 2020; Ickmans et al., 2017; Smith et al., 2017a). Overall, there is low

quality evidence with conflicting results for either altered or no EIH following aerobic exercise in people with spinal pain.

3.4.5.1.6 Isometric Tasks

Four studies included isometric tasks, and all elicit EIH. Of those three studies showed an impaired response following an isometric task (two fair, one poor ROB) (Persson et al., 2009; Smith et al., 2020; Vaegter et al., 2016), and two studies showed normal EIH (fair and poor ROB) (Smith et al., 2017a; Vaegter et al., 2016). Overall, there is low quality evidence that EIH is impaired in people with spinal pain after an isometric task.

3.4.5.1.7 Work Mimicking Tasks

Work mimicking static tasks, such as peg board exercise (n=2, 20 minutes) or a computer task for 90-minutes, showed hyperalgesia in three studies (one good, one fair, one poor ROB) (Gerdle et al., 2008a; Ghafouri et al., 2013; Strom et al., 2012); however, one study also showed hyperalgesia in the control group (Strom et al., 2012). Microdialysis showed hyperalgesia only in the WAD group, but normal EIH in CNP (one study, fair ROB) (Ghafouri et al., 2013). Overall, there is very low quality evidence that work mimicking tasks lead to hyperalgesia in people with spinal pain.

3.4.5.1.8 Other Tasks

Two studies (good and fair ROB) used a lifting task as a local task (Falla et al., 2014; Kuithan et al., 2019). There is very low quality evidence that EIH is altered based on the two

contrasting studies (hypo-and hyper-algesia) as discussed above. All other tasks were only represented in one study only.

3.4.5.2 Objective Two – Exercise-Induced Hypoalgesia in respect to Spinal Complaint

All seventeen studies examined people with spinal pain as per the eligibility criteria, comprising of CLBP (Falla et al., 2014; Hoffman et al., 2005; Kuithan et al., 2019; Meeus et al., 2010), CNP (Christensen et al., 2017; Gerdle et al., 2008a; Ghafouri et al., 2013; Grimby-Ekman et al., 2020; Kemppainen et al., 1998; Larsson et al., 2008; Persson et al., 2009; Strom et al., 2012), WAD (Christensen et al., 2017; Gerdle et al., 2008a; Ickmans et al., 2017; Smith et al., 2017a; Smith et al., 2020; Van Oosterwijck et al., 2012), and chronic mixed pathologies (Vaegter et al., 2016). No other spinal regions, i.e., the thoracic, were examined (Table 3.6).

3.4.5.2.1 Lumbar Region/ Chronic Low Back Pain

For the lumbar region, four studies included participants with CLBP. Two (good and fair ROB) are discussed above for local tasks showing altered EIH, with both hypo- and hyperalgesic responses (Falla et al., 2014; Kuithan et al., 2019). In addition, two studies of fair ROB showed EIH (Hoffman et al., 2005; Meeus et al., 2010) following aerobic/ remote tasks. Findings indicate that EIH response might be dependent on the task. Overall, there is very low quality evidence with conflicting results for EIH in people with CLBP that EIH is normal or altered.

Table 3.6 Evidence synthesis spinal complaint (second objective)

Spinal Com-plaint	Author & year	Sample	Task type	Region of Task	Outcome	Finding			ROB	GRADE 1) study limitation 2) Inconsistency 3) Indirectness 4) Imprecision 5) publication bias					
						No EIH	Normal EIH	Altered EIH		1	2	3	4	5	Overall evidence
CLBP N=69	Falla et al., 2014	19	Lifting	Local	PPT	CON		↑	FAIR	++	+	+	++	+	Very low quality with conflicting results EIH in CLBP [2 studies altered EIH (good and fair ROB, both local tasks) and 2 studies normal EIH (Fair ROB, both remote tasks)]
	Kuithan et al., 2019	21	Lifting	Local	PPT, TPT			↓	GOOD						
	Hoffman et al., 2005	8	Cycling	Remote	Pressure		X no CON		FAIR						
	Meeus et al., 2010	21	Cycling	Remote	PPT		X		FAIR						
WAD N=140	Ickmans et al., 2017	26	Cycling	Remote	PPT	X			FAIR	+	+	+	++		Low quality of impaired EIH in WAD [4 studies (5 tasks) altered EIH; of those showed 4 impaired EIH (2 good, 2 fair ROB) and 1 hyperalgesia (poor ROB), 2 studies normal EIH (good/fair ROB), 2 studies no EIH (fair ROB)].
	Van Oosterwijck et al., 2012	22	Cycling	Remote	PPT			↓	GOOD						
							1 test site self-paced								
	Smith et al., 2017	21	Cycling	Remote	PPT	X			FAIR						
			Isometric	Remote			X								
	Smith et al., 2020	40	Treadmill	Remote	PPT			↓	FAIR						
			Isometric	Remote				↓							
	Christensen et al., 2017	9	G/H ABD	Regional	PPT			↓	GOOD						
	Gerdle et al., 2008a	22	Peg Board	Regional	MD			*	POOR						

CNP N=162	Kemppainen et al., 1998	8	Cycling	Remote	TPT			I	FAIR	++	++	+	++	+	Very low quality for EIH in CNP with conflicting results. [5 studies altered EIH (3 hyperalgesia (2 good, 1 fair ROB) and 1 impaired (fair ROB) and 1 increased EIH (fair ROB), 3 studies no EIH (2 fair, 1 poor ROB)]
	Strom et al., 2012	22	PC task	Regional	PPT			↑ as CON	GOOD						
	Persson et al., 2009	17	G/H isometric	Regional	PPT			↓less test sites	FAIR						
	Christensen et al., 2017	16	G/H ABD	Regional	PPT			↑	GOOD						
	Ghafouri et al., 2013	34	Peg Board	Regional	MD	*			FAIR						
	Larsson et al., 2008	20	Workday	Regiona	MD	*			POOR						
	Gerdle et al., 2008a	19	Peg Board	Regiona	MD			*	POOR						
	Grimby -Ekman et al. 2020	26	Arm cycling	Regiona	PPT/ Blood	X			FAIR						
Mixed N=61	Vaegter et al., 2016	61	Cycling	Remote	PPT, TPT Pressure		X no CON	↓ HS	POOR (No CON)						Single study
			Isometric	Remote											

Abbreviations: *ROB= Risk of Bias; ↓= Impaired EIH; I= Increased EIH; ↑Hyperalgesia;*=Increased anti-nociceptive markers with/ without group difference to CON; GRADE + = Concern; ++ = Serious Concern: more than one serious concern downgrades the level of confidence, CLBP= Chronic Low Back Pain; WAD= Whiplash Associated Disorders; Mixed= Chronic Musculoskeletal Pain; CNP= Chronic non-specific Neck Pain; CON= Control Group; G/H= Glenohumeral; ABD= Abduction; PPT= Pressure Pain Threshold; TPT= Thermal Pain Threshold; MD = Microdialysis; EIH= Exercise-induced Hypoalgesia; HS= High Pain Sensitivity Group*

3.4.5.2.2 Cervical Region

3.4.5.2.2.1 Whiplash Associated Disorders

Six studies with nine tasks were conducted in people with WAD. Four studies with five tasks showed altered EIH, with three studies showing impaired EIH in four tasks (two good, two fair ROB) (Christensen et al., 2017; Smith et al., 2020; Van Oosterwijck et al., 2012). One study (poor ROB) found hyperalgesia after a peg board exercise and therefore is quite different to the other tasks analysed in this population (Gerdle et al., 2008a). Two studies (two fair ROB) showed no EIH (Ickmans et al., 2017; Smith et al., 2017a) and two studies (good and fair ROB) normal EIH (Smith et al., 2017a; Van Oosterwijck et al., 2012). Overall, there is low quality evidence that EIH is impaired in people with WAD.

3.4.5.2.2.2 Chronic Neck Pain

Eight studies included participants with CNP. Five studies showed altered EIH. Of those three studies (one good, one fair, one poor ROB) found hyperalgesia (Christensen et al., 2017; Gerdle et al., 2008a; Strom et al., 2012), one study (fair ROB) impaired EIH (Persson et al., 2009), and one study (fair ROB) increased EIH (Kemppainen et al., 1998). EIH could not be elicited in three studies (two fair, one poor ROB) with two using microdialysis as an outcome (Ghafouri et al., 2013; Grimby-Ekman et al., 2020; Larsson et al., 2008). Overall, there is very low quality evidence with conflicting results for altered or no EIH.

Two studies included participants with WAD and CNP. Christensen et al. (2017) found that participants with WAD (n=9) showed hyperalgesia, but participants with CNP (n=16) showed impaired EIH (good ROB). A microdialysis study found different nociceptive

changes for participants with CNP and WAD after a peg board task (Gerdle et al., 2008a) (poor ROB).

3.4.5.2.3 Mixed Spinal Complaints

One study (poor ROB) considered chronic mixed musculoskeletal pathologies, mainly including people with CNP or LBP. Higher pain sensitivity, based on the participants' PPT, showed impaired EIH in contrast to the lower pain sensitivity group, which was classed as normal EIH in absence of a control group for both aerobic and isometric tasks (Vaegter et al., 2016).

3.4.5.3 Objective Three - Test Sites in Spatial Relation to the Painful Spinal Region

Eight studies (ten tasks) included both local and remote test sites (Christensen et al., 2017; Ickmans et al., 2017; Kuithan et al., 2019; Meeus et al., 2010; Persson et al., 2009; Smith et al., 2017a; Smith et al., 2020). Four studies evaluating six tasks (one good, three fair ROB) showed no differences in the response between the two test regions and remote tasks (Christensen et al., 2017; Ickmans et al., 2017; Smith et al., 2017a; Smith et al., 2020). Another two studies found unclear results (two fair ROB) due to the amount of test sites or the exposed site being the local test site, but both sites were over the neck (Meeus et al., 2010; Persson et al., 2009). Two studies showed a different response (two good ROB) after a local and regional task, although task region dependence is indicated (Kuithan et al., 2019; Strom et al., 2012). Overall, there is very low quality evidence that there is no difference in response at local and remote test sites (Table 3.7).

Table 3.7 Evidence synthesis test site (third objective)

Author & year	Task region	Spinal com-plaint	Sample	Task type	Test site (in relation to spinal pain region)			ROB	GRADE 1) study limitation 2) Inconsistency 3) Indirectness 4) Imprecision 5) publication bias					
					Change Local	Change Remote	Difference		1	2	3	4	5	Overall evidence (n=193)
Kuithan et al., 2019	Local	CLBP	21	Lifting	EIH	No EIH	Yes	GOOD	+	+	++	++	+	Very low quality that the test site in relation to the spinal region of complaint does not affect EIH [4 studies (6 tasks) no difference (2 good, 4 fair ROB), 2 studies showed difference (both good ROB), 2 studies unclear results (fair ROB)]
Meeus et al., 2010	Remote		21	Cycling	EIH	2/3 test sites showed EIH	Amount test sites	FAIR						
Ickmans et al., 2017		WAD	26	Cycling	No EIH	No EIH	No	FAIR						
Smith et al., 2017			21	Cycling	↓ EIH	↓ EIH	No	FAIR						
				Isometric	EIH	EIH	No							
Smith et al., 2020			40	Treadmill	↓ EIH	↓ EIH	No	FAIR						
				Isometric	↓ EIH	↓ EIH	No							
Christensen et al., 2017	Regional		9	G/H ABD	↓ EIH	↓ EIH	No	GOOD						
		CNP	16		↑	↑								
Persson et al., 2009			17	G/H isometric	↓ EIH	↓ EIH	Exposed test site	FAIR						
Strom et al., 2012			22	PC task	↑	No change	Yes	GOOD						

Abbreviations: *ROB= Risk of Bias; ↓= Impaired EIH; ↑Hyperalgesia, GRADE + = Concern; ++ = Serious Concern; PPT= Pressure Pain Threshold; MD= Microdialysis; CLBP= Chronic Low Back Pain; CNP= Chronic non-specific Neck Pain; WAD= Whiplash Associated Disorders; CMSK= Chronic Musculoskeletal Pain; CON= Control Group; G/H = Glenohumeral; ABD= Abduction; EIH= Exercise-induced Hypoalgesia*

3.5 Discussion

This is the first systematic review which examines the evidence for EIH in people with spinal pain. Low quality evidence was found with conflicting results for remote and aerobic tasks, and impaired EIH following isometric tasks and in people with WAD. Very low quality evidence was found for altered EIH after a local task, hyperalgesia after a regional/ work-mimicking tasks, and conflicting results were found for people with CLBP or CNP. Very low quality evidence was found for no difference in response at local and remote test sites. This indicates the need for further high-quality research investigating EIH in people with spinal pain following different types of exercise.

3.5.1.1 First Objective Task Region

The duration of the task could have been a reason why the response varied for local tasks, as a dose response relationship has been discussed for EIH (Naugle et al., 2014b; Vaegter and Jones, 2020). Both tasks were pain provocative and the perception of pain could have interfered with EIH, but other research has showed that EIH can occur in presence of high pain levels (Vaegter and Jones, 2020). The conflicting results for remote tasks could be explained by many different factors such as sample size, disability of participants, determination of EIH, outcome measures, or task intensity (Vaegter and Jones, 2020). Overall, very low quality evidence was found for regional tasks eliciting hyperalgesia. As some of the included studies differed substantially from commonly applied exercises, it remains arguable if changes can be directly related to the task. Hyperalgesia has been shown in other patient populations (Meeus et al., 2010; Wideman et al., 2014), and could indicate an

impaired endogenous response rather than a physiological response of fatigue (Lima et al., 2017). Studies using microdialysis should be interpreted with caution due to publication bias, and further study information could not be obtained; however, this could add a new dimension to the understanding EIH and the role of biochemical biomarkers (Gerdle et al., 2014).

3.5.1.2 First Objective Task Type

The findings for aerobic tasks are partly in contrast to findings from a recent review in asymptomatic people showing a large effect for EIH after aerobic exercises based on RCTs (Wewege and Jones, 2021). It remains unclear why EIH was not produced in some studies, but this might be due to methodological considerations including the chosen task or outcome measurement. Alternatively, the spinal complaint itself could be a factor, as results differed between people with CLBP (normal) or impaired EIH in people with WAD. Both chronic and widespread pain have been associated with impaired EIH (Vaegter and Jones, 2020). For isometric tasks, the findings of this systematic review differ from those of Wewege and Jones (2021), but different pathologies were considered. Another systematic review focussing on isometric exercises showed inconsistent EIH in people with localised musculoskeletal pain (Bonello et al., 2021). Only one study was commonly eligible (Smith et al., 2017a). Hyperalgesia following work mimicking tasks comprised of rather static positions, and this contrasts with the phenomenon of EIH. Some research in asymptomatic participants showed that a twenty-minute computer task led to decreased PPT (Park and Yoo, 2013). This concurs with an included study (good ROB) showing hyperalgesia in asymptomatic people (Strom et al., 2012). Interestingly, adding stationary cycling while performing a computer task did not

lead to hyperalgesia and no changes in PPT occurred (Yoon et al., 2019). This could indicate that EIH might also counteract an underlying hyperalgesic response; an interesting finding meriting further investigation in a patient population.

3.5.2 Second Objective Spinal Pain Complaint

In context with the nature of WAD, central sensitisation and widespread pain are commonly discussed (Anstey et al., 2016) and impaired EIH has been shown for example in people with chronic fatigue syndrome (Meeus et al., 2010). A study of good ROB found impaired EIH after a standardised task, when this task was repeated on a self-paced base, the test site over the calf showed normal EIH (Van Oosterwijck et al., 2012). This might either be due to different modalities, the nature of self-pacing, or adaptation. A study of fair ROB assessed a short cycling protocol, but the interpretation of the results can be challenged. In the absence of a statistically significant pre-post difference, findings were not considered as EIH, although the absolute difference over the calf muscle differed between groups (Ickmans et al., 2017).

Conflicting results for people with CNP showed the presence of changes in pain sensitivity following an acute bout of exercise, but mainly hyperalgesic responses. Although most research was undertaken on people with CNP, one study of fair ROB in fighter pilots (n=16) assessed a remote intervention (Kemppainen et al., 1998). This might not represent the general CNP population. Furthermore, the study used the cold pressor test as outcome measurement, which is commonly applied for CPM, and thus might interfere with EIH (Kennedy et al., 2016; Vaegter et al., 2014). However, it was observed that hyperalgesia

occurred, i.e., after a static and work mimicking tasks as discussed for regional task and type of task. There could be a difference in response between WAD and CNP based on two studies. However, further comparisons are beyond the scope of this review.

Only four studies investigated people with CLBP, revealing that EIH is underexplored in this population. Very low quality of the overall evidence for conflicting results of either normal or altered EIH could indicate that region or type of task play a role in eliciting EIH. Finally, PPT pain sensitivity and overall widespread pain could be considered as a relevant factor for EIH, as discussed in other reviews (Bonello et al., 2021; Vaegter and Jones, 2020) and supported from findings of one study in this review (Vaegter et al., 2016).

3.5.3 Third Objective - Test Sites in Spatial Relation to the Painful Spinal Region

No differences between local or remote sites in relation to the spinal complaint could be detected in this review. In the absence of an agreed testing protocol for EIH, both test sites and test modalities could affect the EIH response (Jones et al., 2019). For example, Meeus et al. (2010) showed a statistically significant change over larger muscles, but not over the thumb web space. Small muscle belly size might affect PPT as shown over the thenar eminence (Kuithan et al., 2019). Additionally, some people might only show localised impairment of pain modulation (Hubscher et al., 2013; Roussel et al., 2013). There could be an altered EIH after a local or regional task based on the findings of this systematic review. The nature of exercise plays an additional role, as for resistance exercises the effect are more pronounced locally (Rice et al., 2019). On the other hand, Lannersten and Kosek (2010) showed that following an isometric shoulder task, PPT did not increase consistently over all

test sites, whereas after a lower limb task, PPT increased over all test sites in participants with shoulder myalgia. This indicates that the task could be more relevant than the test site.

3.5.4 Limitations

Some limitations of this systematic review need to be considered. The lack of adherence to reporting standards of included studies increased the ROB. This is in line with study limitations, where only three studies reported a sample size calculation (Ickmans et al., 2017; Smith et al., 2017a; Smith et al., 2020). The overall ROB was a concern due to only four of seventeen studies being categorised as good. Further concerns were caused by reporting, imprecision, inconsistency of results, the highly heterogeneous exercise tasks, as well as timepoints and characteristics of outcome measures. Despite the sensitive search strategy, studies classified as "shoulder pain" for trapezius myalgia, could have been missed. The definition of EIH as 'no', 'normal', or 'altered' might have been overly simplistic as the definition of these effect measures depend on statistical significance and therefore on the sample size. However, it represents the heterogeneous findings and facilitates readability. Only the first post-test was considered for analysis in this synthesis, additional responses in pain sensitivity over time following the exercises were therefore not considered. In absence of normative data, results from a control group were used to inform interpretation of the results. Some protocols did not elicit EIH in asymptomatic people, however comparison between groups is beyond the scope of this review.

The variation of EIH assessment is an important issue and there is no clear definition of when changes can be considered as constituting a hypoalgesic effect. There is a lack of clear protocols to elicit EIH as well as measurement properties of the outcome characteristics, thus no restrictions were applied. Some research supports a dose-response relationship

(Naugle et al., 2014b), but also low task intensities have been shown to produce EIH (Foxen-Craft and Dahlquist, 2017). However, it is also discussed that some asymptomatic people seem not to respond with EIH, whereas others do (Vaegter et al., 2018). Lastly, it is important to mention that participants' awareness of the hypothesis can affect EIH outcomes (Vaegter et al., 2020b, Jones et al., 2017). Most studies did not report if any information had been given to participants regardless of a hyper/hypoalgesic effect.

Overall, an AMSTAR 2 self-assessment confirmed moderate quality of the completed review (Shea et al., 2017). A weakness was that the protocol did not further outline a meta-analysis but based on scoping searches this was unlikely to be conducted. In addition to it, researchers considered as experts in that area were not contacted specifically. Some experts were contacted to gain further study information for data extraction.

3.6 Conclusion

For EIH in people with spinal pain, low to very low quality evidence exists for the region and type of task, the spinal complaint, and test sites and does not allow specific recommendations to be made for the management of people with spinal pain. A lack of research was found especially for people with CLBP due to the conflicting results based on a small sample (n=69) and two cycling and two lifting tasks only. Further exploration of local and remote tasks is suggested for people with CLBP. There is a clear need for high quality studies, following reporting guidelines, applying clearly defined protocols for outcome measures considering measurement properties.

4.0 Outlook Chapters Four to Six

The following Chapters four to six reflect one pragmatic observational study exploring different tasks over multiple sessions in participants with and without CLBP, ensuring consistent methods e.g., a consistent QST protocol. A qualitative component utilising a questionnaire was embedded to evaluate the participants' perceptions of taking part in the study. One ethical approval (Appendix 13) therefore encompasses the studies reported in Chapters four to six.

A summary of the project was presented at the Centre of Precision Rehabilitation for Spinal Pain's (CPR Spine) Patient and Public Involvement (PPI) day at the University of Birmingham in March 2018. A short overview of the study was presented to the PPI group. Then the PPI group provided feedback specifically on the recruitment announcement and participant information leaflet documents. Recommendations on language and design of these documents are reflected in the current version (Appendix 13). The Table 4.0 on the following page shows relevant characteristics of all 78 recruited participants as well as pain and disability for the participants with CLBP.

Chapter four investigates a lumbar resistance task over six identical sessions, and Chapter five investigates a brisk walking task over five sessions; addressing thesis objectives three and four. Thirty-three asymptomatic controls and thirty-five participants with CLBP were randomly allocated either to the lumbar resistance or the brisk walking task on a treadmill by a computer-generated sequence.

Chapter six investigated the same QST protocol in asymptomatic participants who did not perform a task and rested instead; addressing thesis objective five. These participants were recruited independently and were not part of the randomisation process. The pragmatic observational study methodology is detailed fully in Chapter four using STROBE guidelines (Appendix 15).

Table 4.0 Characteristics of all recruited participants

		CLBP n= 35		**Asymptomatic n= 33**		**Asymptomatic n= 10**
Task		Lumbar Resistance	Brisk Walking	Lumbar Resistance	Brisk Walking	Rest
Participants		n=18	n=17	n=16	n=17	n=10
Age (years)		25.94± 6.17	27.41± 9.54	22.88± 4.16	25.71 ± 5.14	25.20± 3.97
BMI		23.67± 2.47	22.09± 6.35	23.36± 2.70	23.53± 2.15	25.79± 4.07
Gender		10 women, 8 men	10 women, 7 men	8 women, 8 men	10 women, 7 men	5 women, 5 men
SF-36	Physical functioning	77.78± 14.57	88.24± 10.45	97.16± 4.94	94.36± 11.19	98.00± 4.83
	Pain	63.89± 11.92	68.82± 16.87	83.59± 13.26	86.76± 14.84	95.00± 5.27
	General Health	66.39± 16.25	70.59± 13.21	72.19± 18.25	80.88± 14.60	86.50± 10.55
IPAQ		5 high, 11 moderate, 2 low	9 high, 4 moderate, 4 low	4 high, 12 moderate	8 high, 9 moderate,	5 high, 4 moderate, 1 low
FABQ		28.78± 13.34	26.53± 12.71			
ODI		14.44± 7.78	10.30±5.79			
PCS		9.61± 8.14	8.24±6.68			
TAMPA		35.00± 6.56	31.00± 5.41			
PSEQ		48.00± 7.40	53.65± 5.85			
VAS pain pre first session		38.39± 24.67	21.24± 20.35			
VAS worst pain past four weeks		52.39± 26.07	50.65± 23.34			
VAS average last 24 hours		42.50± 23.80	28.24± 21.86			

All Mean ±SD except for categorical data

Abbreviations: *CLBP= Chronic Low Back Pain Group; BMI=Body Mass Index; SF-36= SF-36 v2 Health Survey; IPAQ=International Physical Activity Questionnaire; FABQ= Fear Avoidance Believes Questionnaire; ODI= Oswestry Disability Index; PCS= Pain Catastrophizing Scale; TAMPA= Tampa scale of Kinesiophobia; PSEQ= Pain Self-Efficacy Questionnaire; VAS= Visual Analogue Scale (0-100)*

Chapter Four
Exercise-Induced Hypoalgesia and its Stability in People with and without Chronic Low Back Pain after a Lumbar Resistance Exercise Task

The abstract related to this Chapter was presented at the IASP World Congress Pain in June 2021. Some elements have been re-worded for the aim for this Chapter, but it largely reflects the abstract verbatim.

– Kuithan, P., Heneghan, N.R., Rushton, A., Falla, D. Stability of Exercise-induced Hypoalgesic Effects in Chronic Low Back Pain. International Association for the study of Pain (IASP) World Congress. Virtual, June 2021

Additionally, elements of this Chapter were presented at international and national conferences.

– Kuithan, P., Heneghan, N.R., Rushton, A., Falla, D. Exercise induced hypoalgesia: stability of measures with functional lumbar spine resistance training. Physiotherapy UK 2019. Birmingham, UK, November 2019 DOI: 10.1016/j.physio.2020.03.068

– Kuithan, P., Rushton, A., Nicola R. Heneghan, N.R., Falla, D. Investigating the repeatability and stability of exercise induced hypoalgesia in healthy adults. Pain Science in Motion III (PSIM). Savona, Italy, May 2019. DOI 10.1097/PR9.0000000000000753

4.1 Abstract

Chapter three highlighted the need for further empirical evidence for local tasks in people with chronic low back pain (CLBP). Therefore, the objectives of this pragmatic observational study were to investigate if participants with CLBP and without (CON) experience exercise-induced hypoalgesia (EIH) after a lumbar resistance exercise task and to assess the stability of EIH over six sessions in both groups. The two groups (n=15, each) performed six sessions of a lumbar resistance exercise task over a period of three weeks. A standardised test battery was applied pre-and post-exercise in each session. The primary outcome was local pressure pain thresholds (PPT) over eight sites across the lumbar region. A RM-ANOVA with factors for group, time, session, and location was applied for local PPT and non-parametric tests were used for all other outcome measurements. Intraclass correlation coefficient (ICC 3,1) of baseline quantitative sensory testing and absolute pre-post changes were used to assess stability of EIH.

PPT increased after resistance training over the lumbar area for both groups ($p < .001$; absolute difference CLBP: +42.30 kPa 95% CI [7.20; 77.40] CON: +63.44 kPa [28.33; 98.54]). EIH was present regardless of the session, group, or test site. An increase was found across all six sessions. Pressure pain tolerance thresholds were increased in the CLBP group only. In contrast, heat pain thresholds changed only in the CON group. However, when individual sessions were considered, changes were not statistically significant in most sessions for secondary outcomes. For all outcome measures, the stability of baseline measures was moderate to good (ICC range 0.512 - 0.876). However, stability of EIH was poor for all outcomes.

EIH was found to be present over the lumbar area following a lumbar resistance exercise task. Findings suggest that localised exercise of the back muscles can elicit EIH in participants with and without CLBP. Findings at remote sites were less consistent. No adaptation occurred as local EIH remained present when exposed to the same task over six sessions. The poor stability of absolute changes, indicative of EIH, raises a concern about the use of EIH in research. Prior to application in clinical research, further elucidation of the measurement and effect of EIH and the stability of the measures is required.

4.2 Introduction

Although resistance exercise is commonly used in clinical practice and recommended in guidelines as part of the prevention and rehabilitation of LBP (Chapter one, section 1.1.2), its effect on EIH has received little attention. A recent systematic review of RCTs by Wewege and Jones (2021) revealed that there was no study on people with CLBP but did show that dynamic resistance exercises led to EIH (g =-.45 95% CI [-.69; -.22]) based on two studies in asymptomatic participants. Both included studies did not use an isolated task, but utilised a combination of different exercises, including a pull-down task targeting trunk muscles (Koltyn and Arbogast, 1998; Lee, 2014). Only one study was included which examined EIH in participants with chronic musculoskeletal pain, i.e., plantar fasciopathy (Wewege and Jones, 2021). Additionally, for isometric exercises, three studies each were included for asymptomatic participants and participants with musculoskeletal pain, concluding that isometric exercises did not induce EIH for both groups (Wewege and Jones, 2021). This is in line with another recent systematic review of good quality (Chapter one, Table 1.2) focusing on isometric exercise in participants with and without chronic musculoskeletal pain; no studies included people with LBP (Bonello et al., 2021). Findings from the review reported in Chapter three revealed that there is very low quality evidence for impaired EIH in people with spinal pain after an isometric task, based on four studies, none included people with CLBP.

As outlined in Chapter three and summarised above, EIH of tasks localised to the lumbar region are underexplored. The review identified two primary studies which investigated whether EIH occurred in response to a lifting task. The first study showed decreased lumbar PPT in participants with CLBP following a lifting task (approximately 200 seconds), but no change occurred in the asymptomatic group (Falla et al., 2014). The second

study (Chapter two) (Kuithan et al., 2019) used an adaptation of the lifting task which was implemented for approximately seven minutes; no change in PPT was observed in the CLBP group but the asymptomatic group did show EIH, as evidenced by an increase in PPT (see Chapter three, section 3.4.5.1.1). Although this lifting task involved movement of the lumbar region, it could be considered a provocative task for participants with CLBP given that it involved repeated lifting. Additionally, this type of task would rather be classified as an occupational task with a functional relevance rather than representing a traditional exercise for the management of CLBP. The only other two primary studies investigating EIH in participants with CLBP (Hoffmann et al., 2005; Meeus et al., 2010) which were included in the systematic review (Chapter three), used a cycling protocol in participants with mild to moderate LBP symptoms.

A systematic review by Pacheco-Barrios et al. (2020) which evaluated EIH in asymptomatic participants concluded that PPT increased following exercise (36 studies, n=1326; Hedge's effect size =0.19 [0.11; 0.27]); further subgroup analysis revealed greater EIH predominately in women, after moderate intensity exercise and particularly for resistance exercise. This was based on very low quality evidence due to the high ROB of non-randomised studies (Pacheco-Barrios et al., 2020). The review referred to one additional relevant study by Gajsar et al. (2017) which examined the effects of a local lumbar task in asymptomatic participants; that study showed that the isometric Biering Soerensen test led to EIH over the hamstrings, but not over the right lower back at L3 level (p= .007).

It is evident that further research is necessary to understand whether people with and without CLBP experience EIH specifically in response to a lumbar resistance task of their back muscles. Meanwhile, the EIH response has been shown to be reliable in asymptomatic participants after an isometric task (Vaegter et al., 2019b). No study has examined the

stability of the results when people with CLBP perform the same task over repeated sessions. Stability of the results is important to inform further measurement properties (Chapter one, section 1.3.8).

Exploring participants' views can help to explore feasibility for future clinical studies and is often underdeveloped in musculoskeletal research (Petty et al., 2012). A feasibility study reflects the next phase (II) of the MRC framework (Chapter 1, section 1.4.1) and should integrate a qualitative component (Eldridge et al., 2016). Participants' perception of EIH has not been investigated in asymptomatic people previously nor in people with musculoskeletal pain disorders. Furthermore, the experience of exercise for patients with LBP needs to be further investigated with a qualitative approach (Slade and Keating, 2010). Preliminary evaluation of a small sample of the heterogenous LBP population will contribute to working towards Phase II of the MRC Framework.

4.2.1 Chapter Objectives

The first objective of this Chapter was to determine whether participants with and without CLBP experience EIH immediately following the performance of a resistance exercise task of their back muscles. A second objective is whether EIH can be achieved repeatedly when performing the same task over six separate sessions. This reflects objectives three and four of the thesis. Embedded within this study, the participants' perception of the exercise task and their participation in the study were examined.

4.3 Methods

4.3.1 Design

This study gained full ethical approval from the University of Birmingham (ERN_18-0833) and followed criteria set by the Declaration of Helsinki. All participants gave written informed consent and were reimbursed for their time. Full details are provided in Appendices 13 and 14.

This study is a pragmatic observational study with repeated measures and is reported adapting the STROBE guidelines (von Elm et al., 2014) (Appendix 15). Participants attended six sessions over three weeks, as up to six represent standard amount of clinical session for people with LBP in the UK (Hill et al., 2011). Allocation to either this resistance task or a brisk walking task (Chapter five) was randomised via a computer generated sequence. There was a minimum of 48 hours rest in between each session to provide sufficient recovery time and to minimise potential carry-over and learning effects which can occur up to 24 hours after an exercise (Grimby-Ekman et al., 2020). The first session was used to familiarise participants with the test procedures in addition to the baseline assessments. Participants also completed a series of questionnaires (see below) during this initial session with subsequent sessions being identical in term of completing the test procedure.

All participants were informed about the aim of the study, i.e., potential hypoalgesic effects and for those with CLBP, it was outlined that the task might temporarily increase their symptoms.

4.3.2 Setting and Participants

Data collection took place in a laboratory setting at the University of Birmingham between October 2018 and December 2019. A convenience sample of asymptomatic participants was recruited via poster announcements on campus (Appendix 13), social media, and via word of mouth. Inclusion criteria were men and women aged between 18 and 65 years. This age range was limited to 65 years, as is commonplace in musculoskeletal research and in line with Chapter two (Kuithan et al., 2019). People aged 65 and older are often classified as "older adults" (Wong et al., 2017), and attributed to the likelihood of degenerative changes, increasing numbers of comorbidities, as well as a higher prevalence of specific spinal pathologies (Hartvigsen et al., 2018; Maher et al., 2017). Existing research involving adults with an age range from 60 to 70 years revealed that EIH was impaired, especially in those with lower activity levels (Ohlman et al., 2018), Further inclusion criteria were, no relevant history of musculoskeletal complaints in the last two years, no systemic or cardiovascular diseases or regular medication such as corticosteroids or beta blockers, as such have been shown to alter the heart rate during exercise (Wonisch et al., 2003). Participants who were competitive athletes or performed more than 90 minutes of vigorous exercise per day were also excluded, as some evidence suggest that EIH might be altered in athletes (Flood et al., 2017; Peterson et al., 2019), as well as keeping task performance comparable within and between groups.

Participants with CLBP were recruited via the same approaches as for the asymptomatic group as well as via an internal University register of the Centre of Precision Rehabilitation for Spinal Pain (https://www.birmingham.ac.uk/research/cpr-spine/opportunities.aspx) for participants with spinal pain in context of patient and public

engagement and a database for research. Inclusion criteria for participants with CLBP were the same but participants had to have experienced LBP for the past three months, and on more than 90 days out of the past six months as used before in Chapter two. Additional exclusion criteria for the CLBP group were radiating leg pain, or low back pain related to trauma, fractures, spinal stenosis, and being under active management of their CLBP through specific medications prescribed by a GP or receiving therapies e.g., physiotherapy or the use of higher doses of opioids (> 30 mg of morphine equivalent dose).

4.3.3 Lumbar Resistance Exercise Task

A functional dynamometer (Primus, BTE Technologies, US) was used to perform isotonic resistance exercise. Participants' individual data were used to design a standardised, but individually tailored, protocol for all six sessions. The task comprised of dynamic as well as isometric components and allowed the participant to move individually but was also highly standardised. From a standardised starting position with an individually comfortable width of stance, the task started at knee level with no resistance added (Figure 4.1 A).

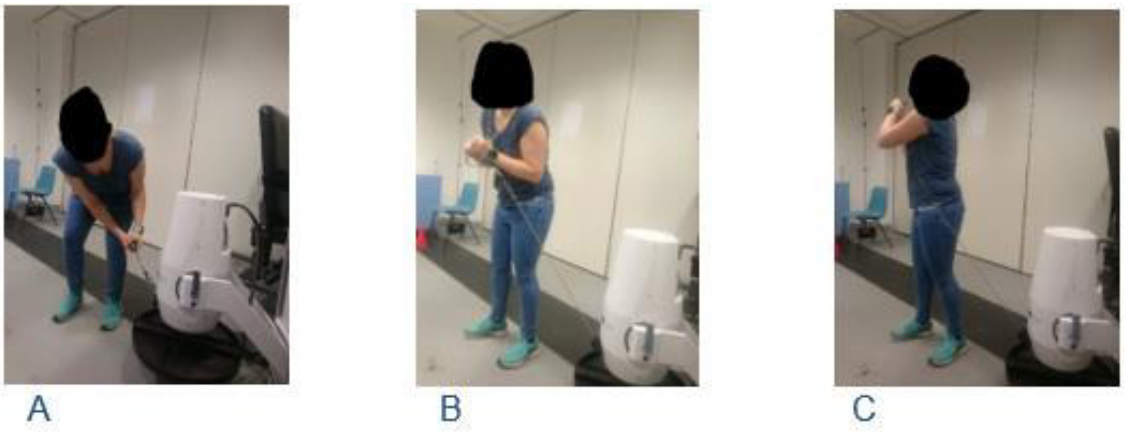


Figure 4.1 A-C Lumbar Resistance Exercise Task

Start (A), mid (B), and end position (C) of the task with the Primus RS

The participants then moved in a diagonal pattern pulling the handle up and away towards their chest on the contralateral side by rotating and extending their trunk (Figure 4.1 B - C). The participant returned to the start position in the same way resisting the pull of the device working eccentrically.

Maximum voluntary isometric strength (MVIC) of the trunk for that particular movement was tested in the mid position (Figure 4.1 B) on each side at the beginning of each session with two consecutive readings and two minutes of rest between attempts as commonly practiced (Martinez-Valdes et al., 2017). Following performance of the MVIC, five minutes rest was provided before the participant started the resistance exercise task to avoid any fatigue from the MVIC testing. The starting position was alternated between left and right between participants but remained constant for the individual participant to counteract a potentially more announced response on the side which was targeted last. The task was divided into four sets (alternating two on each side) with a short rest in between sets lasting for approximately 12-minutes in total. The load was based on the individual's maximal trunk strength for each side (50 % of MVIC) and consisted of eight cycles of the movement pattern to the beat of a metronome (30 bpm). Each of the following phases lasted two seconds: 1) concentric lifting to the middle 2) isometric hold (Figure 4.1 B) 3) concentric lifting to the end position 4) isometric hold (Figure 4.1 C) 5) eccentric return to middle 6) isometric hold (Figure 4.1 B) 7) eccentric return 8) rest for four seconds (Figure 4.1 A).

4.3.4 Evaluation of Demographics and Low Back Pain related Characteristics

To characterise the sample, demographic details were recorded and all participants completed the SF-36 v2 Health Survey as a measure of their general health status (Brazier et

al., 1992; Jenkinson et al., 1999) and the IPAQ (Booth, 2000) to determine their physical activity levels. During each session, a printed Borg Scale was used immediately after the lumbar resistance task for participants to self-rate level of perceived exertion (Borg, 1982). Furthermore, outcome expectations for exercise were assessed pre and post participation in the study with an modified questionnaire (Resnick et al., 2000), mood and perception after the task were assessed each session (Appendix 14).

Additionally, the CLBP participants completed a custom-designed questionnaire (Appendix 14) and the following standardised questionnaires which are commonly used in this population: FABQ, ODI, PCS, Tampa scale of Kinesiophobia, Pain Self-Efficacy Questionnaire (PSEQ), and Central Sensitisation Inventory (CSI) (Fairbank and Pynsent, 2000; Mayer et al., 2012; Nicholas, 2007; Sullivan et al., 1995; Vlaeyen et al., 1995; Waddell et al., 1993). Data for participants with CLBP were collected digitally using the University of Birmingham's electronic data capture tool REDCap (REDCap consortium, Vanderbilt University, Nashville, TN, USA).

LBP intensity was assessed in those with CLBP using a digital VAS, with 0 indicating no pain and 100 being the worst pain. This was performed at the beginning of each session. Furthermore, perceived LBP intensity based on a verbal NRS (0-11) was assessed after each set and at the end of each session. Although the VAS has been shown to be superior to the verbal NRS, it might reflect rather unpleasantness than pain (Hjermstad et al., 2011; Thong et al., 2018). Due to practical reasons, the NRS was easier to implement during the lumbar resistance task as no extra display was required. A final measure of pain intensity was recorded with the digital post-session questionnaire at the end of each session approximately 20 minutes after completion of the task.

4.3.5 Qualitative Evaluation of Participants' Perceptions

At the end of the final testing session the participants were asked to describe their experience on a five-item questionnaire to explore their perceptions of taking part in the study for preliminary evaluation. For the qualitative analysis, a pragmatic content analysis (outlined in section 4.3.9.4) based on a naturalistic research paradigm was applied. The questions included (Appendix 14):

1. How would you describe your experience over the six sessions?
2. Were you pleased with the allocation/ your exercise intervention?
3. Do you think you would have had a different outcome from the other exercise?
4. If you could change anything in this study, what would it be?
5. a. CLBP group: Do you think this programme is feasible for people with severe low back pain and why?

   b. Asymptomatic group: Do you think this programme is feasible for people with low back pain and why?

4.3.6 Quantitative Sensory Testing

Chapter one (section 1.3.3) outlines the absence of a gold standard for outcome measurements to assess EIH, although PPT are favoured in some research (Vaegter et al., 2020a; Wewege and Jones, 2021). In this study, a comprehensive QST assessment was used

which included both pressure and thermal testing adapted from the test battery in Chapter two. PPT measured over the lumbar region were selected as the primary outcome measure.

All tests were conducted by the same researcher and author (PK), an experienced physiotherapist with expertise in QST. The order of QST was randomised via a computer generated sequence into three sections based on the position of the participant. The first block of testing was randomised into three different starting positions for PPT and TPT (prone, sitting, supine). Testing within a position followed the same order with pain tolerance taken last. Measures of TS and the nociceptive withdrawal reflex were always assessed after that block. The testing order was the same for pre- and post-tests but varied between sessions and participants.

All test sites were marked with a surgical pen and the participants were encouraged to remark the sites in between sessions to improve consistency of the test site. Tests over the lumbar region were performed bilaterally whereas for all other test sites, the right side was chosen for asymptomatic participants. For those with CLBP, the most dominant pain side was chosen, in case both sides were equally affected the right side was chosen.

The first laboratory session included a familiarisation period with each of the modalities. Due to concerns about the validity of the results and low sample size, TS of heat pain and data collected from the nociceptive withdrawal reflex are reported in the Appendix 16.

4.3.6.1 Pressure Pain Thresholds

PPT were tested with a Somedic algometer (Somedic Production, Stockholm, Sweden) which was applied perpendicular to the skin with a 1 cm^2 probe (approximately 30 kPa/Sec) (Falla et al., 2014; Vaegter et al., 2019a). Once the pain threshold was recorded via the participant pushing a button, the device was removed. Two consecutive measurements were taken at the same site with a short interval between repeated measures (Chapter one, section 1.3.3).

The primary outcome was the PPT measured over the lumbar region which was tested over four points bilaterally over the erector spinae muscles (total of eight sites) adapted from a previous protocol (Falla et al., 2014). The starting position was kept constant for each participant but randomised between sites one, four, five, and eight, between participants following the sequence on the ipsilateral side first (1-4 and 5-8, or 4-1, 8-5, and vice versa on the right) (Figure 4.2). The pooled mean PPT across the eight test sites was used to assess the stability of baseline measures. For stability of EIH, the absolute difference (post-pre) of the pooled mean PPT was calculated as commonly used in the field (Wewege and Jones, 2021).

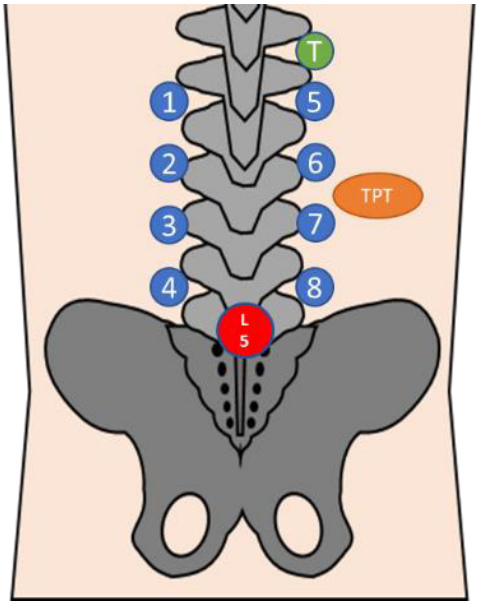


Figure 4.2 Overview of Quantitative Sensory Testing Test Sites over the Lumbar Region

Blue circles indicate test sites 1-8 for Pressure Pain Thresholds, which where 2.5cm apart (vertically) and 5 cm horizontally each. The green circle (T) marks the test site for lumbar pain tolerance and the orange (TPT) indicates the test site for lumbar heat pain threshold for both groups.

Remote PPT test sites were defined as outside the painful region. For the upper trapezius, the participant was seated and the PPT was performed over the muscle, at a position approximately two centimetres lateral to the levator scapulae muscle. PPT was tested over the wrist extensors, detected via palpation of the extensor carpi radialis muscles below the lateral epicondyle with the forearm pronated and the palm resting on a plinth. The third test site was over the tibialis anterior muscle belly, approximately 8 centimetres below the tibial tuberosity, test sites were adapted from previous protocols (Fernandez-Carnero et al., 2010; Nie et al., 2009). The mean of two consecutive measures was used for data analysis for each site as described above.

4.3.6.2 Pressure Pain Tolerances

PPTOL were assessed over the lumbar region, 2.5cm cranial to the most cranial PPT test site (5) on the right side (Figure 4.2), and over the wrist extensors, 2.5cm caudal to the PPT test site in line with the orientation of the tendon. The participant identified the maximum level of pain that could be tolerated with the instruction *"only press the button when the pain is so intense that you cannot tolerate it anymore, your maximum"*. In contrast to thresholds, this modality has been shown in few individual studies to increase the detection of changes in pain sensitivity after an exercise task (Baiamonte et al., 2017; Hviid et al., 2019; Vaegter et al., 2017a). The safety limit for the device was set at 2000 kPa by the manufacturer.

4.3.6.3 Thermal Pain Thresholds

A TSA-II NeuroSensory Analyzer thermal stimulator and accompanying software (Medoc Ltd, Israel) with a 30 x 30mm Peltier thermode was used to determine TPT. For the HPT and CPT, the temperature of the thermode was gradually de- or increased (1°C/sec) from a baseline temperature of 32°C until the participant perceived pain or the safety limit of 50.5°C/ 0°C was reached. The return to baseline was set as 8°C/sec. Two consecutive measurements, each with 30 seconds of rest, were conducted in a randomised order with a 15 second rest interval between measurements over the lumbar area (Figure 4.2) and thenar eminence. Heat pain was tested over the lumbar area only, as previous studies and internal pilot testing revealed that the minimum temperature of 0°C was not low enough to provoke

pain in most participants (Chapter two). The mean of two consecutive measures at each site was used for analysis.

4.3.7 Bias

The rigorous study design reduced bias by emphasis of not only a high standardisation of both the testing procedure and the exercise task, but also for information and instructions given to the participants. No additional issues arose during conduction of the study.

4.3.8 Study Size

The sample size was estimated using the software G*power (3.1), based on previous PPT data over the same lumbar test sites (Chapter two) (Kuithan et al., 2019), applying an a priori within-between interaction repeated measures analysis (effect size f(U)= .475). Analysis specified a minimum of 14 participants for each group. Allowing for a potential dropout, the aim was to collect 15 full data sets for each group. This sample size (n=15 in each group) also fulfilled the prerequisite requirements for assessment of the stability of measures (Walter et al., 1998).

4.3.9 Statistical Analysis

Statistical analysis was conducted with Statistica v13.3 and IBM SPSS 26. The level of statistical significance was set as $p < 0.05$.

4.3.9.1 Descriptive Statistics

Baseline demographics and participant characteristics were analysed with an independent t-test to assess for group differences. Only full data sets of all six sessions were considered for analysis. Specifically, if the safety limit of the devices was reached or data were missing, it was accounted for as missing in pairwise consideration.

Exercise task characteristics were examined with a three-way RM-ANOVA with group (CLBP, CON), session (one to six) and side (right, left) as factors. Perceived pain intensity at five timepoints during and after the lumbar resistance task were assessed with a one-way RM-ANOVA. Analysis of questionnaires was descriptive only and participants' perception of the study were summarised. Participants' views on taking part in the study were summarised.

4.3.9.2 Exercise-Induced Hypoalgesia

Data were checked for normality using the Kolmogorov-Smirnov test, as a non-normal distribution of the data is a common problem within QST due to high inter-variability of the data (Mucke et al., 2016). Only PPT over the lumbar region were normally distributed and a four-way RM-ANOVA was performed with factors group (CLBP, CON), session (one to six), time (pre/post), and location (eight test sites over the lumbar region (Figure 4.2)). RM-ANOVA was followed by a post hoc analysis to correct for multiple dependent variables (Wilks' lambda) and post hoc correction for multiple comparisons (Bonferroni).

Data from all other outcome measures (remote PPT, TPT, PPTOL) were not normally distributed and removal of outliers (based on a z-score of 3.29) did not contribute to the normality of the data. Hence non-parametric tests were applied to full data sets. A Friedman two-way analysis of variance (ANOVA) was used to assess pre- and post-changes in each variable for each group across all six sessions for each group (CLBP, CON) and as a separate analysis for each individual session (one to six) with time (pre/post) as factor. Furthermore, for changes in response between groups, the absolute change considering all six sessions were compared using a Kruskal-Wallis test. For all figures mean and SD are reported for consistency and comparison for Lx data and the second objective of stability.

The presence of EIH was defined as a statistically significant change between pre- and post-test as used in the previous Chapters.

4.3.9.3 Stability

To examine the stability of the baseline-measures across each session, ICCs, defined as test re-test reliability, were conducted (Sim and Wright, 2002). For this purpose, a two-way mixed single score for each outcome (ICC 3,1) based on a consistent rater (PK) for each participant was used (Rankin and Stokes, 1998; Weir, 2005). Consistency was chosen over agreement, as the previous conducted analysis would detect systematic errors. Normal distribution is not a requirement for ICC (Mehta et al., 2018). ICC values were set as poor reliability when < 0.5, moderate for < 0.75, good for < 0.9 and excellent with ICC >0.9 (Koo and Li, 2016). Absolute consistency was expressed by the SEM, based on the calculation of $SEM = SD * \sqrt{1 - ICC}$ (Weir, 2005). Only full data sets were considered for the analysis.

The same approach was applied to assess the stability of the absolute changes in PPT, PPTOL, and TPT for sessions one to six using the same ICC (3,1) model as described above.

4.3.9.4 Qualitative Analysis of Participants' Perceptions

Notwithstanding the preliminary nature of the study, data were analysed with a pragmatic content analysis by counting answers and developing themes and codes for open parts of the questions by the lead researcher (Bengtsson, 2016). A content analysis is positioned within a naturalistic research paradigm, which fits the exploratory nature of the thesis (Chapter one section 1.4). Data are collected in a natural setting with little contamination by the researcher with the aim to organise collected data and to elicit the meanings to then draw realistic conclusions (Bengtsson, 2016; Sim and Wright, 2002). A manifest analysis was chosen as only the surface structure of the provided responses were analysed (Bengtsson, 2016). For questions two, three, and five frequencies of the responses "yes", "no", and "unsure" were counted. Further text was used to support this with codes if available. Participants' responses for the open questions one and four were analysed inductively. Themes and codes and were generated for each group via de- and re-contextualisation, followed by categorisation of data (Bengtsson, 2016). This approach fits with the aim of gaining preliminary data in this area as well as providing insights to inform the design of qualitative components of a future feasibility study.

4.4. Results

4.4.1. Participant Characteristics

A total of 30 participants were considered for analysis (CLBP n=15, CON n=15). Participant characteristics are reported in Table 4.1. Groups were comparable for gender and BMI, although there was a difference between groups in age, with the CLBP group being slightly older. Data from dropouts during the study were excluded as not all six sessions were completed (additional recruited participants CLBP=2, CON=1, drop out due to time constraints or no information provided). One further participant with CLBP was excluded, as, although meeting the inclusion criteria at beginning of the study based on one episode of LBP, the participant reported no pain and disability (ODI=0) during the course of the study.

For the CLBP group, the ODI score revealed that the overall disability was minimal (<20 %) (Fairbank and Pynsent, 2000). Pain scores based on a VAS are presented in Table 4.1 reflecting moderate severity.

Table 4.1: Baseline characteristics

* indicates a statistically significant difference based on a student's t-test/ Chi Square test

Group		**CLBP n=15**	**CON n=15**	**P value**
		Mean± SD	**Mean± SD**	
Age (years)		27.00± 6.20	22.93± 4.30	.046*
BMI		23.51± 2.65	23.71± 2.38	.833
Gender		7 men, 8 women	7 men, 8 women	1.0
SF-36	Physical functioning	75.67± 14.38	96.97± 5.06	<.001*
	Pain	60.83± 8.11	83.17± 13.61	<.001*
	General Health	66.00± 17.44	71.67± 18.77	.399
IPAQ		2 low, 10 moderate, 3 high	11 moderate, 4 high	.121
IPAQ MET		2421.37± 2360.04	2372.77± 1494.60	.947
FABQ		31.33± 12.69		
FABQ Work		13.47± 7.07		
FABQ Physical activity		12.00± 4.87		
ODI		14.93± 6.50		
PCS		10.33± 8.52		
TAMPA		35.13± 6.92		
PSEQ		48.73± 7.09		
CSI A		32.60± 14.20		
VAS average most recent episode		52.73± 21.09		
VAS pain present time		41.47± 23.69		
VAS worst pain past four weeks		57.20± 23.84		
VAS average last 24 hours		46.33± 21.86		
Dominant pain side		Left n=6; right n=9		

Abbreviations: *BMI=Body Mass Index; SF-36= SF-36 v2 Health Survey; IPAQ=International Physical Activity Questionnaire; MET= Metabolic Equivalent of Task; FABQ= Fear Avoidance Believes Questionnaire; ODI= Oswestry Disability Index; PCS= Pain Catastrophizing Scale; TAMPA= Tampa Scale of Kinesiophobia; PSEQ= Pain Self-Efficacy Questionnaire; CSI=Central Sensitisation Inventory; VAS= Visual Analogue Scale (0-100)*

No group differences were found for the IPAQ or SF-36. Further relevant characteristics were below the cut off score for TAMPA and CSI, which was used previously in a chronic pain population (Vlaeyen et al., 1995, Neblett et al., 2015), or within scores close to normal values for FABQ, PCS, PSEQ. There were four days (median, CLBP: Interquartile Range (IQR)= 3;4.5; CON: IQR= 4;5) between sessions for both groups.

4.4.2 Lumbar Resistance Task Parameters

There was an increase of the MVIC over the six sessions (Wilks 0.53, F=4.30, p= .006) in both groups; the post hoc analysis verified a change from the first session to sessions three to six (p< .001) (Table 4.2).

Table 4.2: Maximal voluntary isometric contraction and perceived exertion

CLBP (Mean± SD)							
	Session 1	**Session 2**	**Session 3**	**Session 4**	**Session 5**	**Session 6**	**Mean**
Borg scale	12.67± 1.99	12.93± 2.28	12.80± 1.86	12.87± 1.68	13.13± 2.07	13.13± 1.81	12.92± 1.51
MVIC Left (N)	365.45 ±137.48	414.00 ±157.23	418.38 ±172.43	445.38 ±175.42	438.49 ±164.86	439.87 ± 152.51	420.26 ± 152.01
MVIC Right (N)	362.45 ±112.16	398.04 ±145.36	407.01 ±150.70	427.31 ±177.52	446.17 ±170.13	448.74 ± 179.73	414.95 ± 150.28
CON (Mean± SD)							
Borg scale	12.87± 2.42	12.8± 2.18	13.27± 1.91	12.47± 1.60	12.8± 2.08	12.6± 1.96	12.8± 1.73
MVIC Left (N)	468.91 ± 118.61	471.19 ±160.63	507.84 ± 182.45	512.45 ± 180.82	507.54 ±158.60	513.31± 181.85	496.87 ± 156.6
MVIC Right (N)	427.58 ± 131.17	458.27 ± 152.14	501.21± 158.11	504.13 ± 179.95	507.61 ± 171.80	509.88 ± 166.32	484.78 ± 153.04

Abbreviations: *CLBP= Chronic Low Back Pain Group; CON= Asymptomatic Control Group; MVIC= Maximal Voluntary Isometric Contraction*

Although the CON group presented with higher MVIC, this difference was not statistically significant (F=1.74, p= .198). There was no difference in perceived exertion between groups, or between the MVIC recorded on the left and right side for either group. One participant of the CLBP group stopped the final set after four/ five of eight repetitions in the first two sessions due to pain; their results were included in the analysis.

4.4.3 Perceived Pain during Exercise Task

The perceived pain intensity experienced by the CLBP participants during the task was described as their normal pain by most participants. Only in 13/90 cases, no pain or pain which was described to be different from their usual LBP, was reported. Analysis showed a statistically significant interaction for session ($F=3.55$, $p= .006$) and timepoints ($F=10.23$, $p< .001$). Post hoc test revealed that perceived pain ratings for the second set on each side were statistically significantly higher compared to the first set ($p< .003$) but were not different to the pain experienced after the task. The decrease over the six sessions was not statistically significant for pain intensity during the task in the post hoc analysis (Figure 4.3).

In 33 cases, no pain after the task was reported when asked in the following session. If pain was present it was reported to last usually for about 20 minutes up to a few hours. Only on four occasions, pain was experienced longer than 12 hours; these occurred in the first two sessions but did not affect adherence to the study.

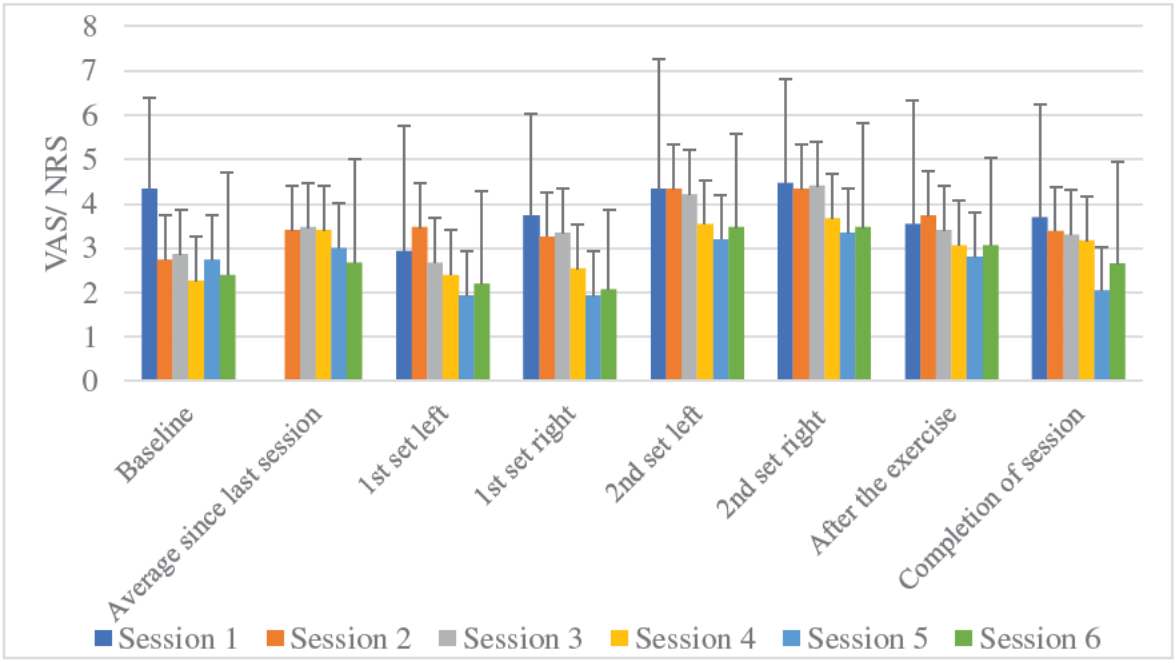


Figure 4.3 Pain Intensity during the Lumbar Resistance Task

NRS (Numeric Rating Scale) score was taken after each set (alternated start between participants) and after completion of the exercise task for the chronic low back pain group. Separate from the analysis the VAS (Visual Analogue Scale) on arrival and the average pain since the last session are displayed. Completion score represents the post testing (20-30 min after task) converted from the 0-100 VAS

4.4.4 Exercise-Induced Hypoalgesia

4.4.4.1 Lumbar Pressure Pain Thresholds – Primary Outcome

A RM-ANOVA showed a statistically significant effect for time (Wilks= 0.43, F=37.25, p< .001), session (Wilks= 0.55, F= 3.88, p= .010), and location (Wilks= 0.42, F=4.35, p= .004) but not group (F=3.60, p= .068). An interaction was found between time*location*group (Wilks= 0.54, F= 2.71, p=.035). Post hoc analysis for time revealed that a statistically significant increase in PPT occurred post the lumbar resistance task for both

groups ($p < .001$), demonstrating the presence of EIH regardless of the session, group, or specific testing location. The absolute change in PPT averaged over the six sessions was +42.30 kPa 95% CI [7.20; 77.40] for the CLBP and +63.44 kPa [28.33; 98.54] for the CON group (Figure 4.4).

Post hoc analysis for session, considering pre- and post PPT, revealed an increase in PPT measurements across the lumbar region for both groups (session one to sessions four, five, and six $p \leq .030$), but no interaction was found for group or session. The absolute increase of PPT baseline measures from the first to the sixth session was 111.39 kPa [54.80; 167.97] in the CLBP group and 66.03 kPa [9.44; 122.62] for the CON group. A post hoc analysis for location revealed that PPT increased at all eight locations over the lumbar region post performance of the lumbar resistance task (all $p < .001$). The interaction between time*location*group revealed a statistically significant increase in PPT at all eight of the tested sites over the lumbar region for both groups (all $p \leq .025$).

No statistically significant effect was found for *time*session*group ($p = .232$) indicating EIH did not differ across the six sessions or between groups.

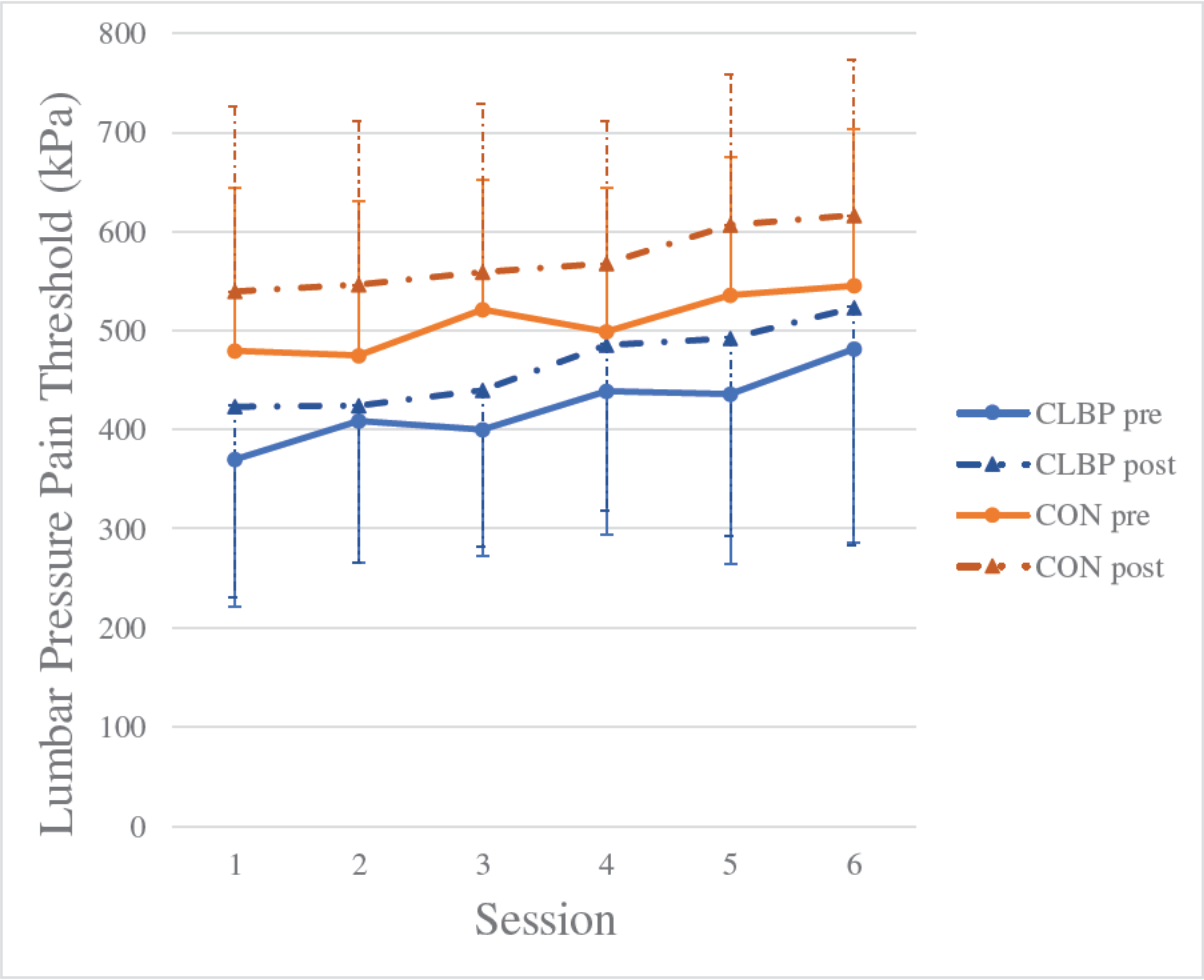


Figure 4.4 Pressure Pain Thresholds across the eight Lumbar Test Sites (Mean/SD)

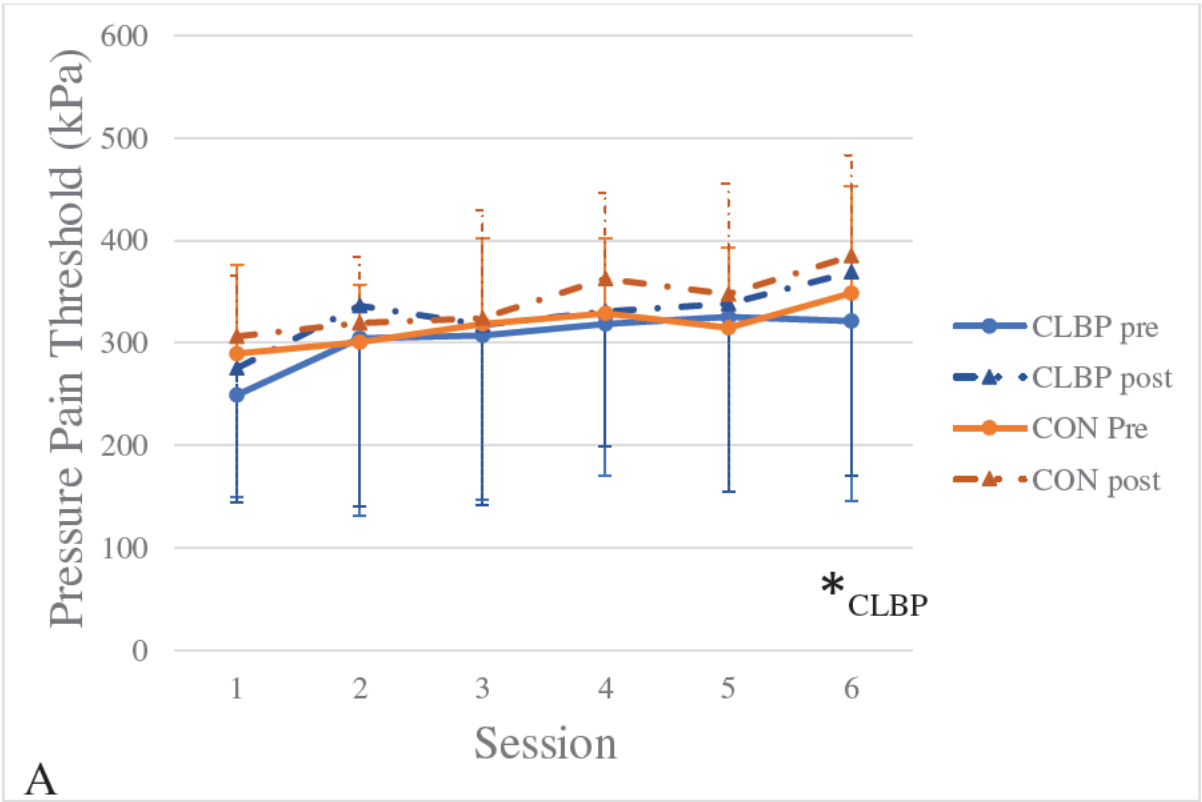
CLBP=Chronic Low Back Pain; CON= Asymptomatic Control

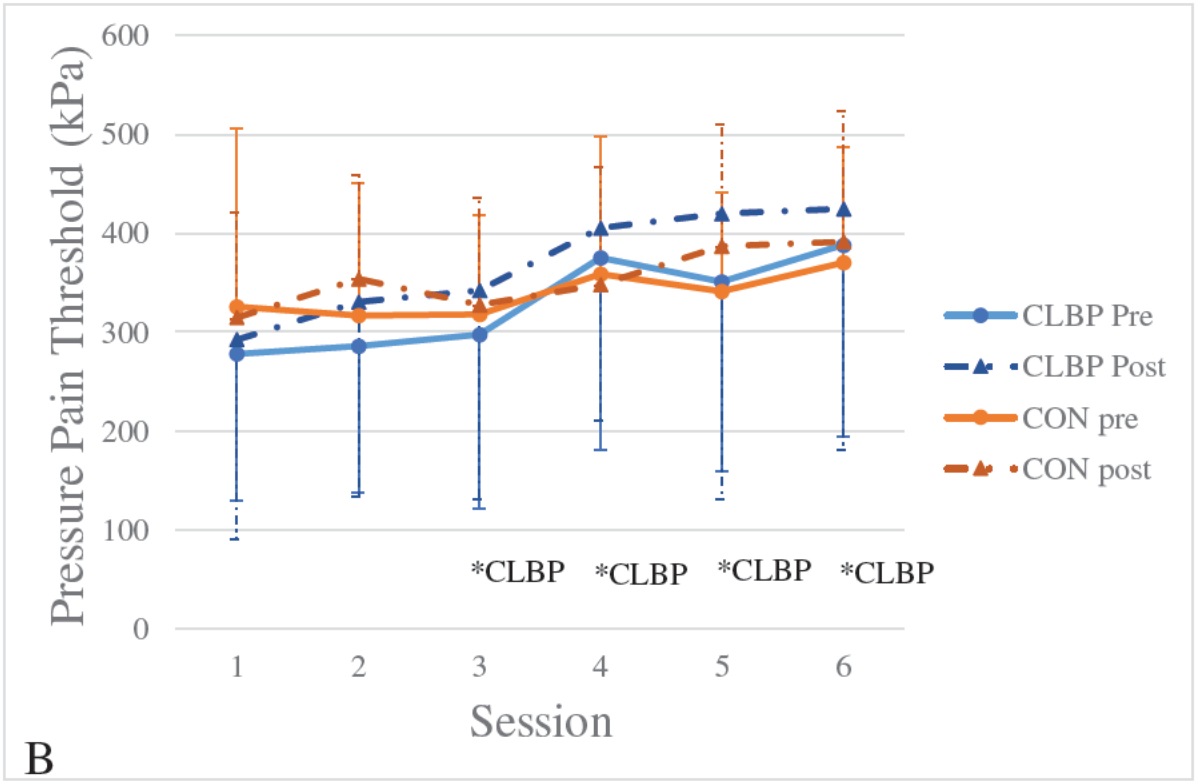
4.4.4.2 Remote Pressure Pain Thresholds

There was a statistically significant increase in absolute PPT over the trapezius after the lumbar resistance task in both groups and across all six sessions ($p \leq .012$). When considering each individual session, the change in PPT was only statistically significant in the sixth session for the CLBP group ($p = .020$) but not for any of the sessions in the CON group (Figure 4.5 A). Kruskal-Wallis test revealed no group differences for the change of PPT.

The same result was found over the wrist extensors in both groups (p≤ .006). Considering each individual session there was a statistically significant increase of PPT within sessions three to six (all p= .020) in the CLBP group, but no intra-session change of PPT was found for the CON group (Figure 4.5 B). Kruskal-Wallis confirmed a difference in absolute changes between the two groups with a higher increase (mean ±SD: 39.72 kPa ± 83.56) for the CLBP group compared to the CON group (15.42 kPa ± 92.23) (p= .049).

Over the tibialis anterior, there was a statistically significant increase of PPT across all six sessions in both groups (p≤ .026). For the CLBP group there was a statistically significant increase only in session five (p= .008), and for the CON in sessions two, five, and six (p= .001 - .033) (Figure 4.5 C). The Kruskal-Wallis test showed no difference between groups for the change of PPT.





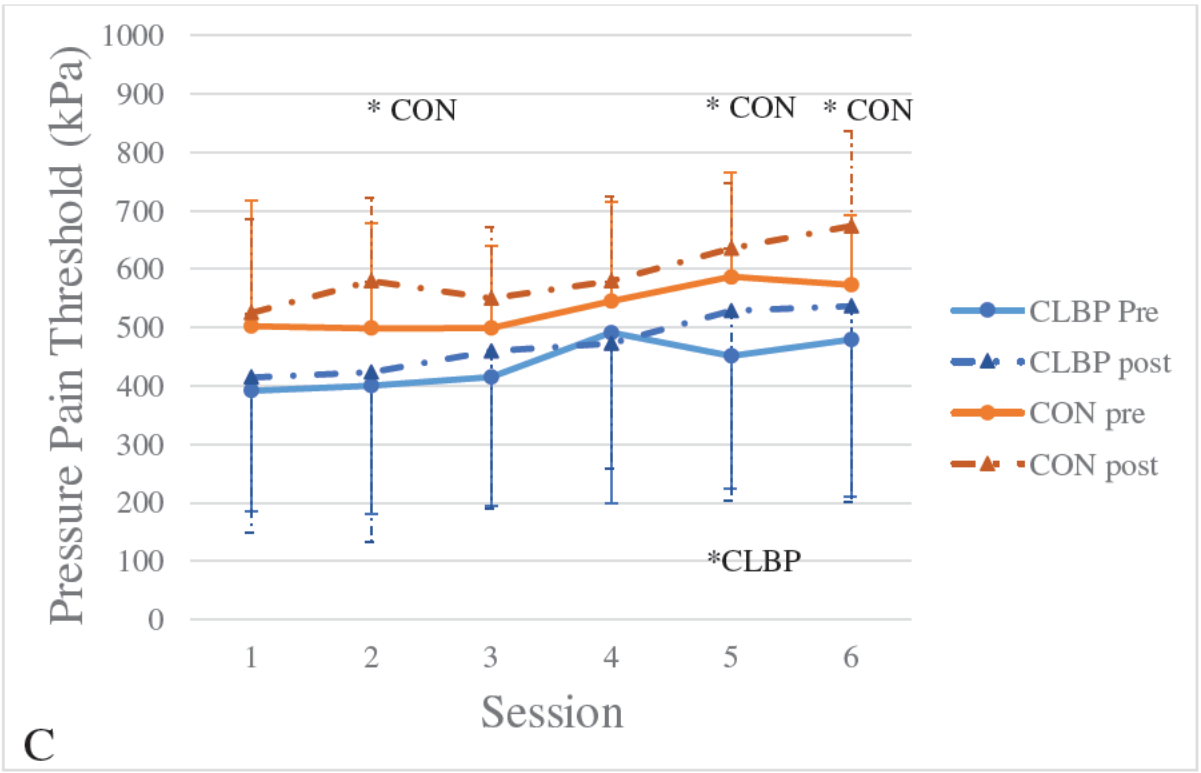


Figure 4.5 A-C Remote Pressure Pain Thresholds (Mean/SD)

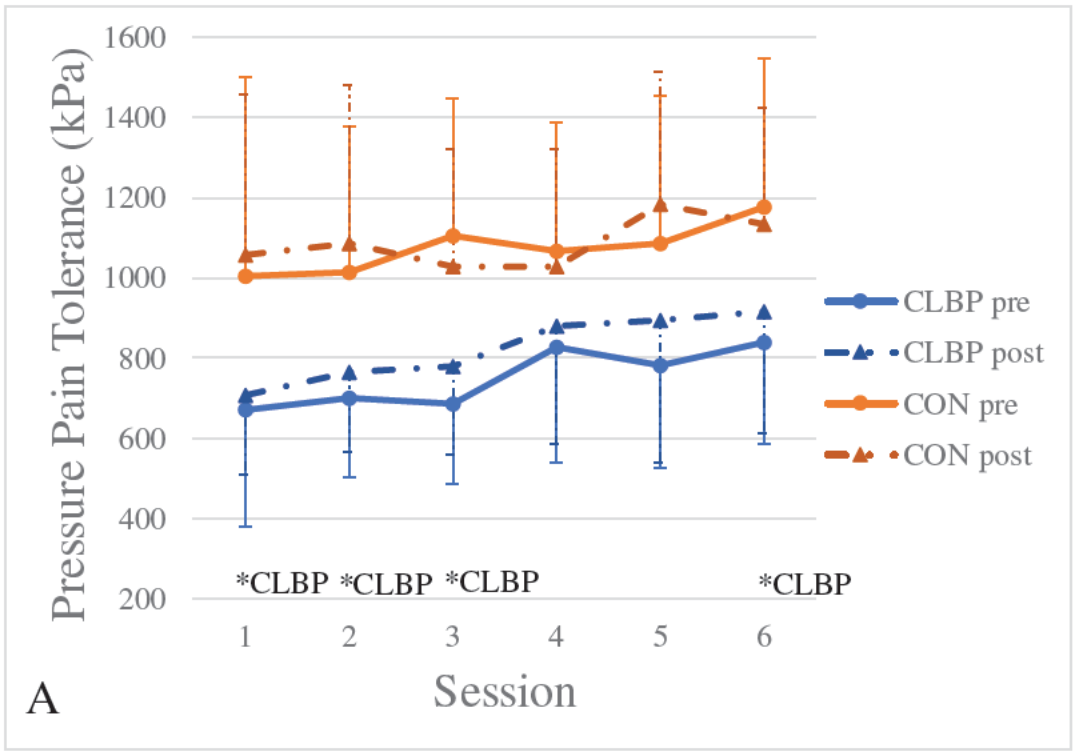
Test sites over (A) Upper Trapezius (B), Wrist Extensors and (C) Tibialis anterior. Significant within-session changes are marked with an *. Note that (C) used a different scaling as Pressue Pain Thresholds were higher. CLBP=Chronic Low Back Pain; CON= Asymptomatic Control

4.4.4.3 Pressure Pain Tolerances

PPTOL data over both test sites were not normally distributed. Many data were missing as either the safety limit of the device was reached, or the test was interrupted due to discomfort from previous sessions or slipping of the algometer due to movement of the participant. Thus, full data were available for all 15 participants over the wrist extensors and 14 participants over the lumbar region in the CLBP group whereas 11 data sets were available for both test sites for the CON group.

Over the lumbar region there was a statistically significant increase in PPTOL after the task in the CLBP group ($p < .001$), but not for the CON group. Considering each individual session, a change in PPTOL was confirmed for sessions one, two, three, and six ($p = .001$ - $.033$) in the CLBP group (Figure 4.6 A). The Kruskal-Wallis test confirmed a statistically significant group difference in PPTOL ($p = .032$) with a larger increase of PPTOL of 72.8 kPa ± 123.33 in the CLBP group compared to 10.41 kPa ± 224.56 in the CON group.

Over the WE, there was a statistically significant increase in PPTOL for the CLBP group ($p = .020$). Friedman ANOVA for individual sessions revealed a statistically significant change only in the final session ($p = .020$) for the CLBP group (Figure 4.6 B). The Kruskal-Wallis test revealed a group difference for the change in PPTOL over the wrist extensors ($p = .005$), with an increase of 40.53 kPa ± 116.78 in the CLBP group and a decrease in the CON group -26.42 kPa ± 186.31.



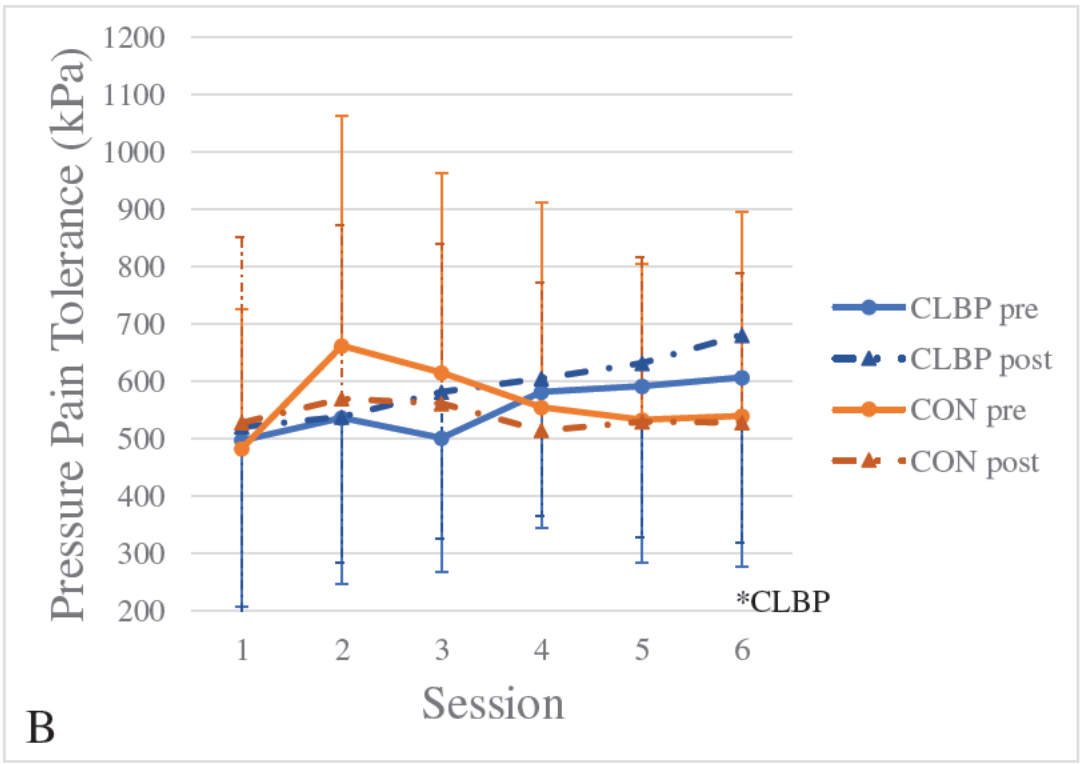


Figure 4.6 A-B Pressure Pain Tolerances (Mean/SD)

Test sites over (A) the lumbar region and (B) the wrist extensors. Significant within-session changes are marked with an *. Note that (B) used a different scaling as values were lower. CLBP=Chronic Low Back Pain; CON= Asymptomatic Control

4.4.4.4 Thermal Pain Thresholds

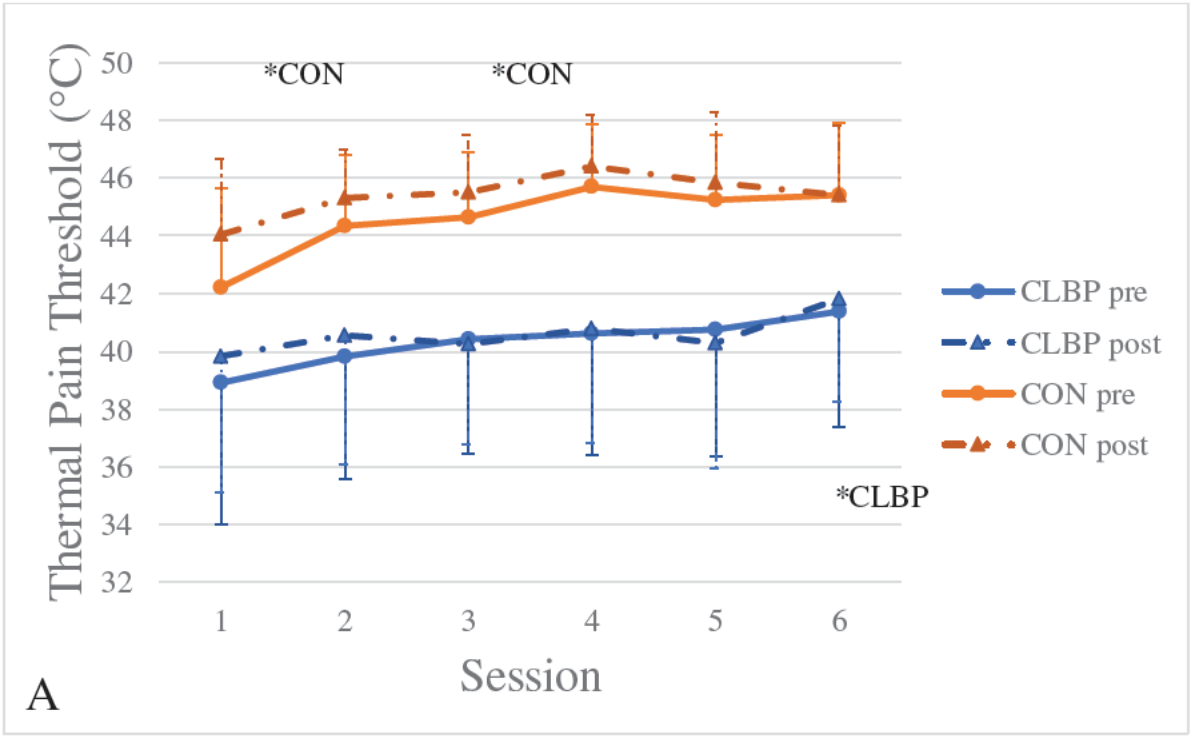
The TPT data were not normally distributed and therefore non-parametric tests were applied. It should be noted that many participants did not reach their pain threshold within the safety limits of the device and therefore numbers included in the analysis differed. For lumbar HPT, data from 13 for CLBP and 9 CON were included in the analysis. Data from 13 participants in each group were analysed for the thenar HPT, and for thenar CPT, data was available for 11 participants with CLBP and eight participants without.

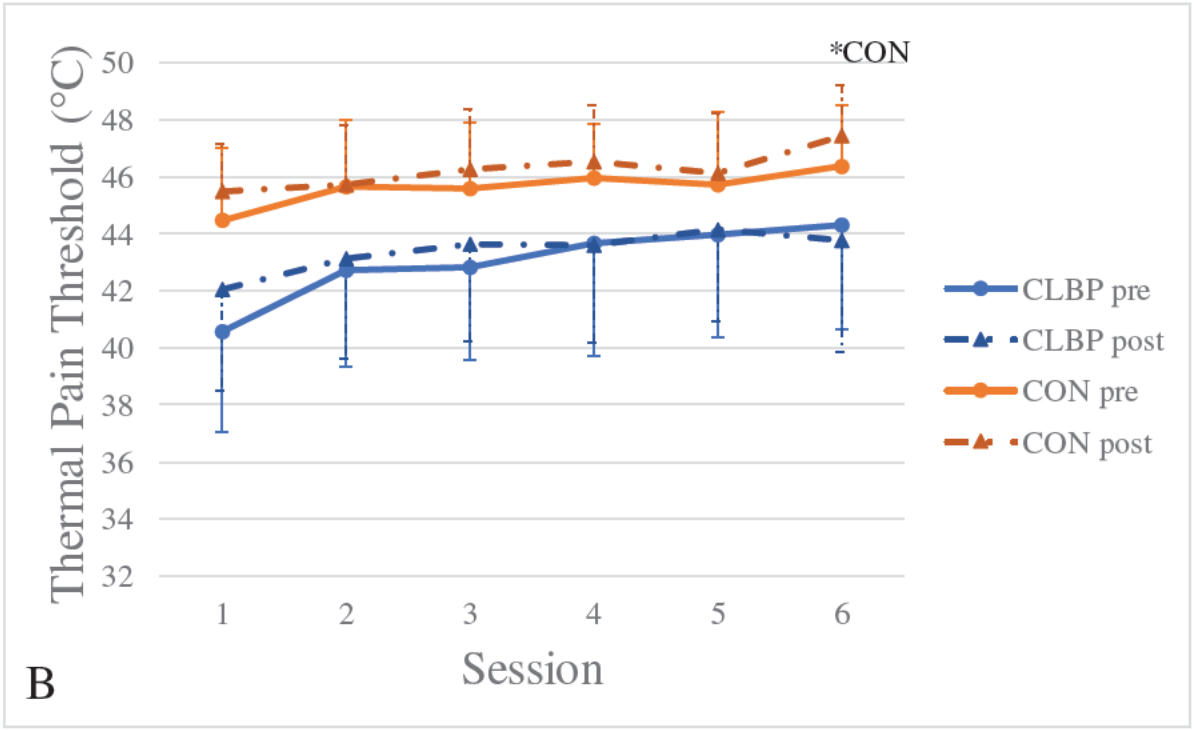
Over the lumbar region there was a statistically significant change in HPT after the task for the CON group across the six sessions ($p < .001$), but not for the CLBP group ($p = .157$). Considering each individual session, the HPT changed in the first ($p = .020$) and third ($p = .034$) session for the CON group. For the CLBP group, there was a statistically significant increase in the HPT only in the sixth session ($p = .021$) (Figure 4.7 A). The Kruskal-Wallis test showed that the changes in lumbar HPT differed between groups with a higher increase in the CON group (mean± SD CON: 0.78°C ± 1.86, CLBP: 0.28°C ± 1.77; $p = .013$).

For the thenar HPT (Figure 4.7 B), there was statistically significant change for the CON group only ($p = .002$). Considering each individual session, the increase in HPT was confirmed for the sixth session in the CON group ($p = .013$). However, the Kruskal-Wallis test revealed no group difference.

Similar results were observed for the thenar CPT (Figure 4.7 C). Across the six sessions a change occurred only for the CON group ($p = .002$). Considering each individual session, a decrease in CPT was confirmed for the third session ($p = .034$) for the CON group and the fourth session in the CLBP group ($p = .035$). The Kruskal-Wallis test revealed a group

difference (p= .018) with an average change of +0.64°C ± 3.72 in the CLBP group and -1.28°C ± 3.56 in the CON group.





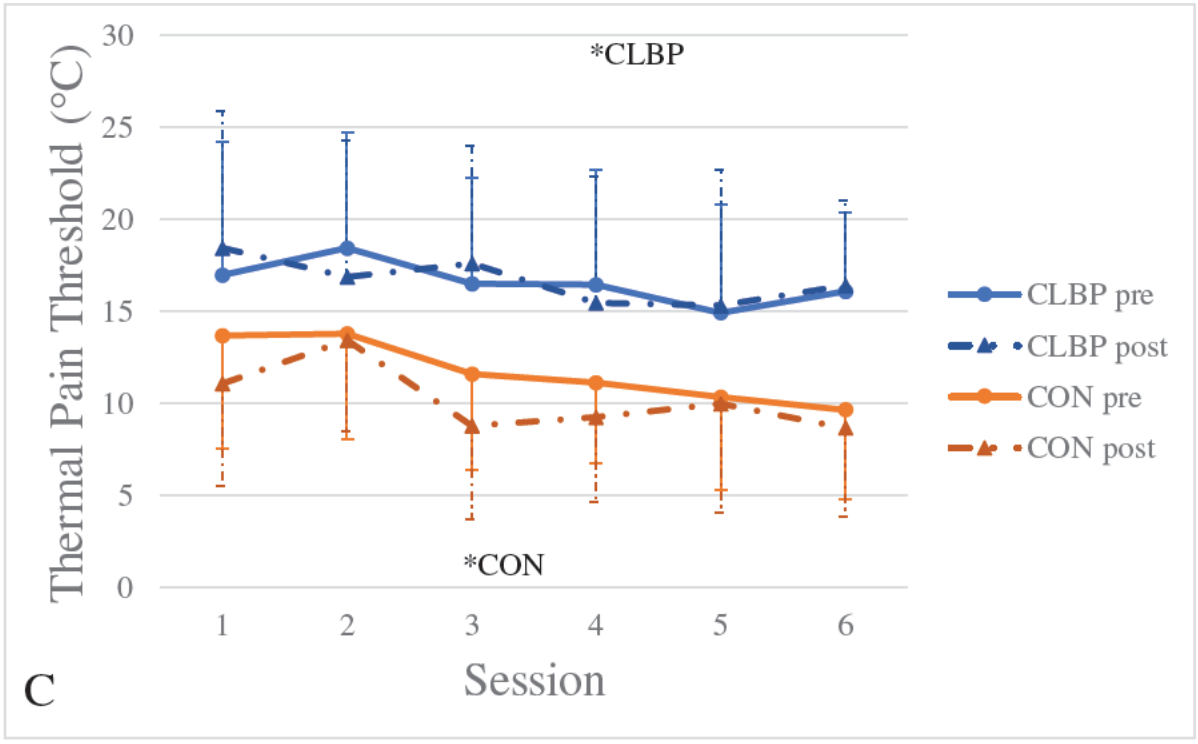


Figure 4.7 A-C Thermal Pain Thresholds (Mean/SD)

(A) lumbar heat pain thresholds, (B) thenar heat pain thresholds, and (C) thenar cold pain thresholds. Significant within-session changes are marked with an *. CLBP=Chronic Low Back Pain; CON= Asymptomatic Control

4.4.5 Stability of the Baseline Measures (pre-measurements within each session)

4.4.5.1 Pressure Pain Thresholds

The ICC for lumbar PPT (average over all eight test sites) baseline-measures across the six sessions were moderate to good with a SEM of 55.51 kPa (CLBP) and 73.15 kPa (CON) (Table 4.3).

For remote PPT, the ICC of the baseline measurements was moderate over the tibialis anterior and the wrist extensors in the CON group and good over the upper trapezius and over all test sites in the CLBP group (Table 4.4). The SEM ranged from 47.82 kPa to 104.48 kPa.

Table 4.3: Stability of the baseline measures of lumbar Pressure Pain Thresholds

	PPT for each session in kPa (Mean± SD)							**ICC 3,1**	**LB**	**UB**	**SEM**
	1	**2**	**3**	**4**	**5**	**6**	**Mean**				
CLBP	370.25± 140.82	408.65± 130.94	400.18± 114.21	438.73± 130.24	436.40± 158.43	481.63± 189.84	422.64± 146.27	.856	.737	.940	55.51
CON	479.36± 155.16	475.18± 148.72	521.83± 113.52	499.15± 135.24	535.64± 119.84	545.39± 137.67	509.42± 134.68	.705	.518	.866	73.15

Abbreviations: *CLBP= Chronic Low Back Pain; CON= Asymptomatic Control Group; PPT= Pressure Pain Threshold; ICC= Intraclass Correlation Coefficient; LB= Lower Bound; UB= Upper Bound; SEM= Standard Error of Measurement*

Table 4.4 Stability of the baseline measures of remote Pressure Pain Thresholds

	Group	**PPT for each session in kPa** (Mean± SD)							**ICC 3,1**	**LB**	**UB**	**SEM**
		1	**2**	**3**	**4**	**5**	**6**	**Mean**				
Upper Trapezius	CLBP	248.73± 99.45	303.67± 172.64	307.20± 160.20	318.50± 148.92	325.03± 169.97	321.03± 175.50	304.03± 154.38	.876	.770	.949	54.36
	CON	289.27± 126.44	300.20± 119.62	317.80± 105.06	328.03± 126.59	314.23± 99.45	348.13± 112.23	316.28± 113.67	.823	.685	.925	47.82
Wrist extensors	CLBP	277.93± 148.82	286.00± 148.61	297.60± 175.49	375.67± 194.96	351.17± 192.33	388.20± 194.37	329.43± 177.48	.868	.756	.945	64.48
	CON	325.23± 181.13	316.80± 133.99	317.77± 100.28	359.03± 139.52	340.83± 99.82	370.23± 116.48	338.32± 129.43	.630	.425	.824	78.73
Tibialis anterior	CLBP	391.07± 206.46	400.40± 219.89	415.00± 220.92	491.00± 293.41	450.47± 226.12	479.03± 269.91	437.83± 237.73	.856	.737	.940	90.21
	CON	502.23± 214.48	497.90± 180.12	498.97± 140.40	544.10± 170.55	586.50± 178.09	573.30± 119.10	533.83± 169.04	.618	.412	.817	104.48

Abbreviations: *CLBP= Chronic Low Back Pain; CON= Asymptomatic Control Group; PPT= Pressure Pain Threshold; ICC= Intraclass Correlation Coefficient; LB= Lower Bound; UB= Upper Bound; SEM= Standard Error of Measurement*

4.4.5.2 Pressure Pain Tolerances

Over the lumbar region PPTOL baseline measures showed good ICC for the CLBP group and moderate ICC for the CON group. Over the wrist extensors, both groups showed good ICC for PPTOL. SEM varied from 122.98 kPa to 215.90 kPa across all PPTOL measurements (Table 4.5).

Table 4.5: Stability of the baseline measures of Pressure Pain Tolerances

	Group	PPTOL for each session in kPa (Mean± SD)							ICC 3,1	UB	LB	SEM
		1	2	3	4	5	6	Mean				
Lumbar region	CLBP n =14	670.71 ± 291.61	701.43 ± 197.47	686.86 ± 201.96	826.64 ± 288.04	781.86 ± 256.33	839.50 ± 251.92	751.17 ± 252.36	.762	.588	.899	123.11
	CON n=11	1004.64 ± 498.16	1015.45 ± 362.60	1105.36 ± 342.97	1067.18 ± 320.91	1038.10 ± 339.15	1177.09 ± 371.59	1075.85 ± 371.55	.725	.510	.898	194.84
Wrist extensors	CLBP n=15	497.33 ± 288.87	537.00 ± 290.98	501.00 ± 233.16	582.07 ± 238.58	591.87 ± 308.45	607.00 ± 329.97	552.71 ± 279.20	.806	.659	.917	122.98
	CON n=11	483.82 ± 242.57	662.27 ± 399.66	616.00 ± 346.66	555.09 ± 357.81	532.91 ± 271.62	539.18 ± 357.10	564.88 ± 325.94	.850	.702	.949	126.24

Abbreviations: *CLBP= Chronic Low Back Pain; CON= Asymptomatic Control Group; PPTOL= Pressure Pain Tolerance; ICC= Intraclass Correlation Coefficient; LB= Lower Bound; UB= Upper Bound; SEM= Standard Error of Measurement*

4.4.5.3 Thermal Pain Thresholds

Both lumbar and thenar HPT showed moderate ICC for the CON group, and good ICC for the CLBP group. For the thenar CPT, the ICC was moderate for both groups. However, it should be noted that this was based on very low numbers due to the safety limit of the device as indicated above. All baseline scores (mean ± SD) and ICC and SEM are presented in Table 4.6.

Table 4.6: Stability of the baseline measures of Thermal Pain Thresholds

	Group	n	TPT for each session in °C (Mean± SD)							ICC 3,1	LB	UB	SEM
			1	2	3	4	5	6	Mean				
Lumbar heat	CLBP	12	38.91± 3.85	39.82± 3.66	40.41 ± 2.78	40.61± 2.79	40.75± 3.79	41.38± 3.33	40.31 ± 3.37	.858	.723	.949	1.27
	CON	9	42.22± 3.54	44.35± 2.74	44.64 ± 1.85	45.69± 2.26	45.25± 2.16	45.41± 2.28	44.59 ± 2.67	.613	.344	.868	1.66
Thenar heat	CLBP	13	40.58± 3.23	42.73± 3.23	42.85 ± 2.85	43.66± 3.78	43.97± 3.58	44.31± 3.67	43.02 ± 3.52	.764	.583	.905	2.37
	CON	13	44.47± 2.49	45.67± 2.26	45.59 ± 2.40	45.95± 1.93	45.74± 2.55	46.38± 2.11	45.63 ± 2.30	.716	.517	.882	2.45
Thenar cold	CLBP	11	16.98± 7.16	18.45± 4.37	16.51 ± 4.29	16.43± 4.42	14.92± 4.58	16.11± 4.24	16.57 ± 4.88	.521	.272	.795	2.33
	CON	8	13.69± 5.02	13.78± 4.31	11.58 ± 5.26	11.13± 4.05	10.36± 4.50	9.64± 4.14	11.70 ± 4.60	.518	.229	.839	1.86

Abbreviations: *CLBP= Chronic Low Back Pain; CON= Asymptomatic Control Group; TPT= Thermal Pain Threshold; ICC= Intraclass Correlation Coefficient; LB= Lower Bound; UB= Upper Bound; SEM= Standard Error of Measurement*

4.4.6 Stability of the Absolute Changes

4.4.6.1 Pressure Pain Thresholds

For the absolute change in PPT measured over the lumbar area (average across all eight test sites), the ICC was poor (CLBP= .062; CON=.204) with a SEM 65.67 kPa for the CLBP group and 73.84 kPa for the CON group (Table 4.7).

Table 4.7: Stability of the absolute changes of lumbar Pressure Pain Thresholds

Group	Absolute change in PPT for each session in kPa (Mean± SD)							ICC 3,1	LB	UB	SEM
	1	2	3	4	5	6	Mean				
CLBP	53.12 ± 100.10	15.43 ± 58.73	40.14 ± 55.44	47.27 ± 43.46	56.29 ± 56.93	41.57 ± 80.09	42.30 ± 67.81	.062	-.056	.305	65.67
CON	60.29 ± 124.42	71.70 ± 64.76	37.05 ± 59.41	68.97 ± 59.60	71.34 ± 51.63	71.28 ± 53.68	63.44 ± 72.38	.204	.037	.482	73.84

Abbreviations: *CLBP= Chronic Low Back Pain; CON= Asymptomatic Control Group; PPT= Pressure Pain Threshold; ICC= Intraclass Correlation Coefficient; LB= Lower Bound; UB= Upper Bound; SEM= Standard Error of Measurement*

The same was found over all three remote test sites for both groups with poor ICC ranging from .114 - .464 and the SEM between 49.37 kPa and 113.02 kPa (Table 4.8).

Table 4.8: Stability of the absolute changes of remote Pressure Pain Thresholds

	Group	Absolute change in PPT for each session in kPa (Mean± SD)							ICC 3,1	LB	UB	SEM
		1	2	3	4	5	6	Mean				
Upper Trapezius	CLBP	26.20± 80.99	32.17± 55.67	9.57± 52.17	11.87± 43.31	12.40± 67.59	47.50± 42.15	23.28 ± 58.55	.114	-.024	.376	55.11
	CON	16.70± 45.59	18.97± 42.85	6.07± 56.28	34.37± 75.88	33.40± 56.57	36.13± 77.56	24.27 ± 59.95	.322	.126	.600	49.37
Wrist Extensors	CLBP	14.40± 83.64	44.43± 84.08	44.33± 72.19	29.67± 45.55	69.00± 114.44	36.50± 90.36	39.72 ± 83.56	.464	.251	.716	61.18
	CON	-10.57± 138.80	37.47± 89.42	9.60± 57.11	-11.40± 95.20	46.27± 81.97	21.13± 68.32	15.42 ± 92.23	.216	.046	.495	81.67
Tibialis Anterior	CLBP	22.87± 120.54	22.43± 130.40	43.43± 135.28	-18.53± 135.17	77.23± 129.06	57.03± 90.78	34.08 ± 124.73	.179	.020	.455	113.02
	CON	22.20± 143.37	81.10± 79.63	50.07± 76.76	34.20± 101.89	48.37± 131.59	99.87± 87.87	55.97 ± 107.00	.198	.033	.476	95.82

Abbreviations: *CLBP= Chronic Low Back Pain; CON= Asymptomatic Control Group; PPT= Pressure Pain Threshold; ICC= Intraclass Correlation Coefficient; LB= Lower Bound; UB= Upper Bound; SEM= Standard Error of Measurement*

4.4.6.2 Pressure Pain Tolerances

The ICC was poor for both groups over both test sites for PPTOL (Table 4.9). The SEM ranged from 127.63 kPa to 227.01 kPa.

Table 4.9: Stability of the absolute changes of Pressure Pain Tolerances

	Group	n	Absolute change in PPTOL for each session in kPa (Mean± SD)							ICC 3,1	UB	LB	SEM
			1	2	3	4	5	6	Mean				
Lumbar	CLBP	14	36.57± 131.54	63.93± 119.91	93.57± 98.03	53.86± 88.44	112.00± 148.54	76.86± 148.02	72.80± 123.33	-.071	-.135	.095	127.63
	CON	11	52.00± 194.06	71.36± 214.76	-77.18± 233.09	-39.00± 276.04	98.00± 156.49	-42.73± 245.59	10.41± 224.56	-.022	-.116	.232	227.01
Wrist extensors	CLBP	15	23.60± 90.97	1.13± 124.23	81.67± 116.45	22.73± 103.34	39.80± 148.64	74.27± 106.34	40.53± 116.78	-.084	-.141	.062	121.58
	CON	11	44.09± 164.30	-92.45± 199.07	-54.64± 206.94	-40.91± 224.34	-3.36± 87.23	-20.00± 116.17	-26.42 ± 186.31	.319	.097	.653	153.75

Abbreviations*: CLBP= Chronic Low Back Pain; CON= Asymptomatic Control Group; PPTOL= Pressure Pain Tolerance; ICC= Intraclass Correlation Coefficient; LB= Lower Bound; UB= Upper Bound; SEM= Standard Error of Measurement*

4.4.6.3 Thermal Pain Thresholds

The ICC for the absolute change in thermal pain thresholds after the lumbar resistance task was poor for all test sites and test stimuli (Table 4.10).

Table 4.10: Stability of the absolute changes of Thermal Pain Thresholds

	Group	n	Absolute change in TPT for each session in °C (Mean± SD)							ICC 3,1	UB	LB	SEM
			1	2	3	4	5	6	Mean				
Lumbar heat	CLBP	12	0.92± 1.32	0.73± 1.84	-0.14± 1.80	0.17± 1.78	-0.46± 1.72	0.44± 2.04	0.28± 1.77	.198	.018	.519	1.58
	CON	9	1.78± 1.20	0.90± 2.26	0.86± 0.76	0.66± 1.71	0.45± 2.97	0.05± 1.56	0.78± 1.86	.380	.124	.739	1.46
Thenar heat	CLBP	13	1.48± 2.09	-0.41± 1.62	0.78± 1.69	-0.07± 2.02	0.19± 1.59	-0.55± 1.93	0.24± 1.91	.057	-.066	.324	1.86
	CON	13	1.02± 1.47	-0.06± 1.74	0.69± 1.96	0.58± 1.79	0.39± 2.42	1.05± 1.27	0.61± 1.86	.138	-.016	.433	1.72
Thenar cold	CLBP	11	-2.70± 4.98	1.58± 4.54	1.11± 3.56	-0.99± 2.76	0.41± 4.45	0.28± 3.14	0.64± 3.72	.029	-.089	.319	3.67
	CON	8	3.79± 11.00	0.04± 3.79	-2.85± 2.75	-1.75± 2.98	0.58± 3.46	-0.98± 2.74	-1.28± 3.56	-.070	-.148	.213	3.69

Abbreviations: *CLBP= Chronic Low Back Pain; CON= Asymptomatic Control Group; TPT= Thermal Pain Threshold; ICC= Intraclass Correlation Coefficient; LB= Lower Bound; UB= Upper Bound; SEM= Standard Error of Measurement*

4.4.7 Qualitative Analysis of Participants' Perceptions

Evaluation of the questionnaire responses from the five questions using a pragmatic content analysis is presented in the following sections. Full quotes are presented in Appendix 16.

4.4.7.1 Question One: Participants' Experience over the Six Sessions

Statements from the 15 participants with CLBP derived four themes (Table 4.11). Twelve participants with CLBP stated the experience as positive (first theme), covering five codes such as enjoyable or interesting. The second theme, covering five codes, was related to the effects from study participation reflecting improved performance or pain sensitivity. However, challenges were reported (third theme, four codes) as the task and testing was perceived as challenging. Two participants stated a reduction in their LBP (fourth theme, two codes), but another participant stated the opposite.

The asymptomatic CON group's statements led to three themes. Overall, there was a positive experience (first theme, eight codes), but it was also challenged as painful, tedious or of not sufficient intensity (third theme, four codes). The effect of the participation was described a positive on both physical and mental status (second theme, six codes).

Table 4.11 Participants' experience over the six sessions

Group	**CLBP (n=15)**			**Asymptomatic (n=15)**	
Theme	**Code**	**n=**	**Theme**	**Code**	**n=**
Positive experience n=12	Good/ Great/ Positive	5	**Positive experience n= 10**	Interesting	4
	Interesting	5		Good/ Positive	4
	Enjoyable	3		Enjoyable/ fun	3
	Safe/ looked after	1		Mixture of calm/very active	2
	Unusual	1		Unique	1
				Good feeling to focus on QST	1
				Rewarding	1
				Professional	1
Effect from participation n=6	Improved task performance	2	**Effect from participation n= 8**	Change in pain sensitivity	6
	Motivation to exercise	2		Improved strength	2
	Getting stronger	1		Improved Memory	1
	Confirmation of own strength	1		Less tired	1
	Back less sensitive	1		Motivation to exercise	1
				Built resistance to pain	1
Challenges n=4	Challenging task	2	**Challenges n= 3**	Slightly painful	1
				Unpleasant QST tests	1
	Challenging to pay attention to pain	1		Tedious task	1
				Too light to feel an impact	1
	Not liking Pressure Pain Testing	1			
	Tiring	1			
LBP reduction n=3	Reduced LBP	2			
	No effect on LBP	1			

Abbreviations: *CLBP= Chronic Low back Pain, LBP= Low Back Pain, QST= Quantitative Sensory Testing*

4.4.7.2 Question Two: Participants' Satisfaction with the Allocation

Satisfaction with group allocation was reported by 13 of the 15 participants with CLBP. Two participants stated additionally that their strength improved (n=2), one reported

reduced LBP (n=1), a sense of accomplishment was stated (n=1), and one participant felt comforted when the pain withdrawal reflex testing was discontinued due to discomfort. One participant was not pleased with the group allocation due to pain, and one participant with CLBP did not have a preference.

In the asymptomatic CON group, 14 participants were satisfied with the group allocation, one participant "did not mind". No additional comments were provided.

4.4.7.3 Question Three: Participants' Expectation on Different Outcome from the other Exercise Task?

Six participants in the CLBP group reported expecting a different outcome from the brisk walking task, i.e., that it would improve walking (n=1), be less painful (n=1), or might encourage people to undertake regular exercise (n=1). Three participants stated not to expect a different outcome, the remaining seven were not sure.

For the asymptomatic CON group, five participants expected a different outcome from the brisk walking task, especially as aerobic exercise has a different aim (n=2), and one expected a lower decrease in pain sensitivity (n=1). Four participants answered with did not expecting a different outcome, and six asymptomatic participants were unsure.

4.4.7.4 Question Four: Participants' Recommendation for Changes to the Study

Statements from five participants emerged three themes around the study design (one code), exercise (two codes) and the QST testing (two codes), ten participants did not provide any suggestions (Table 4.12).

For the asymptomatic group, statements from seven participants led to the derivation of three themes (study design (one code), exercise (four codes), and QST testing (three codes)), eight participants did not indicate a change (Table 4.12).

Table 4.12 Participants' perceptions on change of the study design

Group	**CLBP**		**Group**	**Asymptomatic**	
Theme	**Code**	**n=**	**Theme**	**Code**	**n=**
Study design n=1	Continuous sessions without breaks	1	**Study design n=1**	Longer time allocation, as study took longer than outlined	1
Exercise task n=2	Longer task	1	**Exercise task n=3**	Handle of task device	1
	More exercise tasks	1		Less exercise	1
				Heavier Weights	1
				Less recovery time	1
Testing n=2	Painful skin after testing	1	**Testing n=3**	Cold limitation of thermal tester	1
	Computer controlled testing suggested	1		Less test sites	1
				Less pain tolerance tests	1
No change n=10			**No change n=8**		

***Abbreviations**: CLBP= Chronic Low back Pain*

4.4.7.5 Question Five: Participants' Perceptions of Feasibility and Transferability of the Study Programme

Seven of the 15 participants with CLBP reported that this study was feasible for a population with more severe CLBP (first theme, three codes) as the task was easy (n=1), improved function (n=1), and was individually tailored (n=1). Five participants with CLBP were unsure (second theme, four codes). Three stated that the programme would not be feasible for people with more severe CLBP (third theme, three codes) as the exercise would be too painful (n=2) or difficult (n=1), and the overall pain sensitivity would be too low (n=1) (Table 4.13).

In the asymptomatic CON group, ten participants reported that the programme was feasible for people with LBP (first theme, five codes), two participants were unsure (second theme, two codes), and three participants did not perceive the programme as feasible for people with LBP due to the demand on the back (n=1), pain (n=1), or stiffness (n=1) (third theme, three codes) (Table 4.13).

Table 4.13 Participants' perceptions on feasibility and transferability

Group	**CLBP**		**Group**	**Asymptomatic**	
Theme	**Code**	**n=**	**Theme**	**Code**	**n=**
Yes n=7	Easy task	3	**Yes n=10**	Task feasible/good for LBP	4
	Improvement of function	2		Maybe difficult	2
	Individually shaped protocol	1		Improve pain awareness	1
				Strengthening	1
				Relieve Pain	1
Unsure n=5	Twisting could be uncomfortable	1	**Unsure n=2**	No experience, but easy task	1
	Maybe not doable on days with severe pain	1		Possibly painful	1
	Improved experience, but not severe pain	1			
	Lower loads needed	1			
No n=3	Task too painful	2	**No n=3**	Involves mainly back muscles	1
	Won't be able to do resistance exercise	1		Causes pain	1
	Pressure sensitivity too low	1		Stiffness after task	1

Abbreviations: *CLBP= Chronic Low back Pain, LBP= Low Back Pain*

4.5 Discussion

This study contributes to the emerging body of research on EIH in people with and without CLBP and is the first to assess stability of both baseline quantitative sensory test measures and changes in these measures over six sessions of performing a lumbar resistance task. This study uniquely evaluated whether EIH occurred in response to a functional task which was specifically designed to target the back muscles. Recent reviews (Bonello et al., 2021; Wewege and Jones, 2021) including the systematic review presented in Chapter three have shown that no studies have assessed resistance tasks in people with CLBP. Given the

lack of a gold standard for measuring EIH, a battery of QST was conducted to investigate changes in pain sensitivity induced by the resistance task.

Both groups had similar physical activity levels, one factor discussed to potentially influence the extent of EIH (Chapter one, section 1.3.4). The comparable levels of physical activity between groups could explain their comparable strength assessed at baseline, although there was a trend for lower MVIC in those with CLBP. Other studies have reported poorer performance in participants with CLBP when performing an isometric holding task with bodyweight (Sanderson et al., 2019) or measures of trunk muscle strength using an isokinetic dynamometer (Cho et al., 2014; Moreno Catala et al., 2018). However, deconditioning of the erector spinae muscles is not always present in participants with CLBP based on level one evidence (Smeets et al., 2006). Whereas more recent synthesis in people with recurrent low back pain found very low evidence for changes of deeper trunk muscles including erector spinae, multifidus and transverse abdominis muscles, defined as greater contraction, redistribution of muscle activity, and delayed postural control (Devecchi et al., 2021). It should also be noted that the specific task used in this study was not designed to localise the erector spinae muscles and involved upper body movement which could compensate for lower trunk strength. Additionally, participants in this study presented with relatively low levels of disability which may explain why their performance was comparable to asymptomatic participants. The task was perceived to be of similar intensity between groups across all sessions.

The baseline MVIC increased over the course of the study in both groups, possibly because of familiarisation with the task or neural adaptations which can occur rapidly with resistance training resulting in increased strength (Carroll et al., 2001; Nuzzo et al., 2017).

The increase of MVIC between sessions, demonstrates that both groups adapted positively to the task in terms of an improvement in performance.

4.5.1 Changes in Pressure Pain Thresholds

In this study, both participants with and without CLBP demonstrated EIH in response to the resistance task as demonstrated by an increase in lumbar PPT after the task. It should be noted that the main effect for group was close to significance (p= .068) with high variability of the measures in both groups. The extent of change of PPT over the lumbar region (+42.30 kPa 95% CI [7.20; 77.40] for the CLBP and +63.44 kPa [28.33; 98.54] for the CON group) is similar to the findings from a previous study, considering the same test sites over the lumbar region after a shorter lifting task for the asymptomatic group (+46.93 kPa [9.18; 84.68]) (Chapter two) (Kuithan et al., 2019). However, in the previous study, EIH was not observed in the CLBP group (Chapter two) even though the clinical characteristics of the sample of participants with CLBP were similar between studies (i.e., pain and disability levels). This difference likely relates to the difference in the task performed since in the study presented in Chapter two, the task involved repeated movements, lifting in the sagittal plane a reported risk factor for CLBP (Hartvigsen et al., 2018). In contrast, the task selected in the current Chapter was designed to more closely reflect a resistance exercise that would be offered as part of the rehabilitation programme for people with CLBP.

Other studies have evaluated the effect of different lumbar tasks on PPT, for instance, Paungmali and colleagues (2017) documented a change in lumbar PPT tested over a single site of +35.45 kPa 95% CI [16.33; 54.58] after lumbar core stabilisation exercise performed for approximately 15 minutes. The increase in lumbar PPT following this task was

statistically significantly different to a placebo task (automated passive cycling; -16.93 kPa [-51.56; 17.71]) and control group -36.64 kPa [-62.48; -10.81]). Joseph and colleagues (2018) reported an increase of the PPT assessed over the lumbar area of 19.95 % [15.23; 24.57], 16.92 % [13.54; 20.29] and 15.68 % [13.10; 18.25] over three sessions combining lumbopelvic stability exercises and massage therapy in female elite weight-lifters, changes which were statistically significantly different to massage therapy alone.

The EIH observed over the exercised test sites is potentially linked to local and segmental descending inhibition, whereas changes at remote sites indicate supraspinal pathways (Lima et al., 2017; Rice et al., 2019). In the current study, there was evidence of EIH measured via the PPT at remote sites and this was evident across the six sessions, albeit values were below the SEM. When considering individual sessions, the non-parametric tests for pre-post changes were only statistically significant for approximately 25 % of the sessions. The inconsistent change of PPT at remote sites following the resistance task in this study, is in line with the hypothesis that resistance exercise leads to a localised change in pain sensitivity only, whereas aerobic exercise results in a systemic effect (Rice et al., 2019).

It can be argued that the wrist extensors and trapezius muscles were partially involved in the lumbar resistance task which may explain the variability of results with some evidence of EIH at these sites. Thus, the few signs of EIH over the wrist may represent a local EIH response independent of the resistance task performed by the back muscles (Foxen-Craft and Dahlquist, 2017). That said, some studies have reported changes in PPT at remote sites following lumbar exercises. For example, in the study by Joseph et al. (2018) which examined the effects of lumbopelvic stability exercises combined with massage in weightlifters, the task led to statistically significant changes in PPT over the upper trapezius (25.66 % 95% CI [20.74;30.57]; 18.11 % [14.32; 21.89]; 18.64 % [14.34; 22.93]). Gajsar et al. (2017) also

reported that an isometric back lifting task resulted in an increase of PPT over the hand in asymptomatic women.

4.5.2 Changes in Pressure Pain Tolerances

Less research has been conducted on changes in PPTOL following an exercise task compared to PPT. The statistically significant change in the CLBP group only, which was present in two thirds of the sessions, supports the presence of EIH following the task. However, the absence of changes in PPTOL in the asymptomatic group, despite changes in PPT, raises the question whether the change observed for the CLBP group truly reflects EIH. It is possible that those with CLBP tolerated less pressure at first since this is a painful test over a painful region which may have prompted them to stop the test earlier. Note that in all sessions, the PPTOL scores over the lumbar region were higher in the asymptomatic group. With repeated exposure, they may have learnt to tolerate higher pressure in the post test, however this is speculative. An alternative explanation is that the change in PPTOL for those with CLBP truly reflects EIH. Interestingly, the PPTOL also increased over the wrist in those with CLBP despite comparable baseline measures to the asymptomatic participants. It should be noted that at baseline PPT measured over the lumbar region was not statistically significantly different between groups whereas a difference for PPTOL with lower pressure tolerated for those with CLBP was observed. Thus, the PPTOL may be relevant to determine a change in sensitisation over the painful region and the added benefit of measuring PPTOL in addition to PPT (commonly believed as the gold standard measure of EIH) and should be explored further in future studies. Overall, these results should be interpreted with caution given that the analyses were conducted on a smaller sample size; data from several

participants was either missing as the safety limit of the device was reached, or the test was interrupted due to discomfort from previous sessions or slipping of the algometer due to movement of the participant.

4.5.3 Changes in Temperature Pain Thresholds

Sensitivity to heat pain is thought to reflect a sign of peripheral sensitisation (Mucke et al., 2016), whereas sensitivity to cold is considered as a sign of central sensitisation. At baseline, those with CLBP displayed sensitivity to both heat and cold compared to asymptomatic participants, which also has been found in previous studies (Hubscher et al., 2014; Kuithan et al., 2019). Overall, the results in this study showed that the HPT increased in both groups in some sessions, but the between group analysis revealed the change in HPT was greatest for the control group. Additionally, the HPT tested over the thenar eminence changed for the control group only in some sessions, but the Kruskal-Wallis test revealed no group difference. In contrast, a statistically significant group difference was observed for the CPT tested over the thenar eminence with greater changes observed for the asymptomatic group. Other studies have reported changes in HPT following exercise (Jurgens et al., 2014; Paungmali et al., 2017) but not for CPT. However, considering that many participants did not reach their pain threshold within the safety limits of the device resulting in small sample size for these analyses, the non-parametric test was underpowered. Thus, any firm conclusions based on these results should not be made.

4.5.4 Stability of Measures

The stability of the baseline measurements are consistent with previous literature for both PPT and TPT in people with and without spinal pain (Balaguier et al., 2016a; Balaguier et al., 2016b; Jones et al., 2007; Knutti et al., 2014; Kong et al., 2013; Middlebrook et al., 2020; Moloney et al., 2012; Mutlu and Ozdincler, 2015; Waller et al., 2015; Walton et al., 2011), showing moderate to good ICC over the six sessions for both measures. These findings confirm that baseline PPT and TPT can be used as a reliable measure over repeated sessions.

Although an effect for session with increasing values over the lumbar region was observed, the ICC was still moderate to good (ICC ≥.705). The progressive increase of lumbar PPT which was present in both groups could indicate a favourable response to the task (i.e., EIH) which was maintained until the next session. Besides lasting EIH, this result could also reflect conditioning or habituation with the testing procedure. Previous work has shown that increased PPT were maintained 105 minutes and 24 hours after an arm cycling task in asymptomatic participants, whereas in participants with neck pain, PPT decreased immediately after the task and then returned to baseline level (Grimby-Ekman et al., 2020). Although the factor for time was statistically significant for all analyses in this study, changes at each time point were not further discussed (Grimby-Ekman et al., 2020).

A recent systematic review investigated hypoalgesic effects of exercise over multiple sessions based on outcome measures of VAS for pain intensity and questionnaires assessing quality of life and disability, but not QST (Polaski et al., 2019). Exercise dosing for the treatment of chronic neck pain showed a positive correlation with higher analgesic effects with longer duration, however, the authors acknowledged that further research is required to elucidate the dose effect and its clinical implications (Polaski et al., 2019). Some studies

report that PPT increase over the duration of an exercise programme of multiple sessions (Bodes Pardo et al., 2018; Henriksen et al., 2014). Nevertheless, there is equivocal evidence with other studies reporting unaltered QST findings after an exercise programme (Bobos et al., 2016; Hansen et al., 2020b; Kosek et al., 2013; Kroll et al., 2018; Lluch et al., 2013). Nevertheless, a recent systematic review confirmed that exercise leads to increased PPT, and improved pain sensitivity, with greater effects over the impaired region in participants with chronic pain (Belavy et al., 2021).

In contrast, the stability of EIH, quantified as an absolute change in the measure, was poor for all test sites and outcome measurements for the six sessions regardless of the presence of EIH. A recent study on asymptomatic participants assessed the stability of EIH after a three-minute wall squat; PPT increased by 100 kPa ± 102 95% CI [65; 135] and 96 kPa ± 104 [61; 134] over the exercising quadriceps and by 29 kPa ± 57[9; 48] and 22 kPa ± 50 [4; 39] over the non-exercising trapezius muscle in two identical sessions (Vaegter et al., 2019b). Although no systematic error was found between sessions, re-test reliability was low for both relative and absolute change (Range ICC (3,1) .03 – .43) (Vaegter et al., 2019b). Agreement between sessions was not statistically significant indicating inter-individual inconsistency between sessions (Vaegter et al., 2019b).

The poor reliability highlights a complex issue of testing EIH, as responses seem to vary intra-individually in the presence of large inter-individual disparity. Higher standardisation of the protocol using lactate thresholds and cycling protocols showed better (fair) test-re-test reliability (Vaegter et al., 2019a). However, further validation of the test procedure and EIH as a principle should be conducted first before this is taken into further clinical studies.

4.5.5 Qualitative Analysis of Participants' Perceptions

As this analysis was embedded in the pragmatic observational study, trustworthiness and rigor is limited. Credibility, dependability, and confirmability can be challenged as only one researcher conducted the analysis, and questions were not further developed to gain a deeper insight. Participants provided predominately yes/ no answers but some space for additional comments was provided in the five-item questionnaire. This was not specifically aimed to gain full breadth or depth. Therefore, the stage of data compilation remained close to the text not being able to draw realistic conclusion in the wider context (Bengtsson, 2016).

Most of the participants (CLBP n=7/15, CON n=10/15) felt the study programme would be feasible for people with/ more severe CLBP. However, extrapolation of the findings from healthy participants or participants with mild to moderate disability levels is limited. Concerns were raised not only about a painful demanding exercise task and its intensity, but also around the assessment of EIH, which challenged the extensive test protocol. There is some evidence suggesting that painful exercises have potentially a greater treatment effect in people with chronic musculoskeletal pain (Smith et al., 2017b), and moderate pain levels might further facilitate the EIH response (Vaegter and Jones, (2020). Future research should explore the participants' perceptions of painful exercise and EIH i.e., reflecting a population with more severe LBP/ higher levels of disability.

This preliminary evaluation can inform the qualitative component of a future feasibility study representing the next phase (II) of the MRC framework as well as develop future study protocols shaping the assessment and elicitation of EIH.

4.5.6 Strengths and Limitations

This study was of a pragmatic observational design, following a highly standardised testing procedure and exercise task protocol. This study contributes to the emerging body of research on EIH in people with and without CLBP and implemented a comprehensive QST protocol. The study is the first to assess stability of both baseline QST measures and changes in these measures over six sessions of a lumbar resistance task. Additionally, this study uniquely evaluated whether EIH occurred in response to a functional resistance task which was specifically designed to engage the back muscles. Therefore, no further conclusion can be drawn to other types of exercise such as aerobic tasks, which will be explored in Chapter five.

For reasons of feasibility, practicability, and participants' availability however, it could not be controlled for many confounders which may have affected the stability of the measures. This includes controlling for sport and exercises outside of the study between sessions, time of the day, and providing the same amount of rest days between sessions.

There was a small yet statistically significant difference in age between groups. Nevertheless, both groups were young and in their mid-twenties and therefore it is not expected that the slight difference in mean age impacted on the study results. The participants in this study with CLBP presented with relatively mild pain and disability and therefore these results cannot be generalised to those with more severe symptoms or levels of sensitisation.

Although PPT is often accepted as the gold standard to assess EIH, it cannot entirely be ruled out that the changes in PPT which were interpreted as EIH in this study, are due to habituation with the measures. However, Vaegter et al. (2016) showed that a resting period of 15 minutes did not lead to increased PPT following an initial measure, and therefore this is

unlikely to be a dominant factor in this results. Further validation of the protocol could be conducted by testing a non-exercising asymptomatic control group.

The duration of the QST protocol took up to 30 minutes in some participants and it is possible that any EIH may have been short lived and therefore not captured. As discussed in previous Chapters, EIH lasts likely for approximately 15 minutes, with only minor effects remaining evident up to 30 minutes (Naugle et al., 2012). Sensitisation of the tissue was reported by some participants, particularly noted during the PPTOL test, and some participants reported the test site felt sensitised over the entire duration of the study, which likely influenced their results.

The power analysis indicated that this study included a large enough sample size. Due to the widely dispersed data, it can be argued that a larger sample size could have contributed to normal distribution of the data and thus more accurate analysis. Non-parametric tests had to be applied to most of the data, which is a compromise in terms of data analysis as these tests are known to be less powerful due to the non-normal distribution of data.

4.6 Conclusion

EIH was found to be present locally over the lumbar area in participants with and without CLBP in response to a resistance task of the back muscles, with less consistent findings at remote sites. Local EIH remained present when exposed to the same task over six sessions.

The reliability of baseline measurements was moderate to good offering some preliminary support for clinical practice. However, stability of EIH based on the absolute

change was poor. Prior to application in clinical research, further elucidation of EIH and the stability of the measures are required particularly for other types of exercise such walking.

Chapter Five

Exercise-Induced Hypoalgesia and its Stability in People with and without Chronic Low Back Pain after a Brisk Walking Task

Parts of these results have been published as an abstract and were presented at the Pain Science in motion conference in Savona, Italy in 2019.

– Kuithan, P., Rushton, A., Nicola R. Heneghan, N.R., Falla, D. Investigating the repeatability and stability of exercise induced hypoalgesia in healthy adults. Pain Science in Motion III (PSIM). Savona, Italy, May 2019. DOI 10.1097/PR9.0000000000000753

5.1 Abstract

Where Chapter four focussed on a lumbar resistance task to elicit exercise-induced hypoalgesia (EIH), this Chapter utilises a brisk walking task performed on a treadmill. The first Chapter objective is to investigate if EIH occurs in participants with and without chronic low back pain (CLBP). The second objective of this pragmatic observational study is to explore the stability of baseline, and absolute changes over five sessions as an indicator of EIH for both groups.

The outcome measures were identical to the previous Chapter (four), but the task differed. The walking task was adjusted to 70% ±5 of the age-predicted heart rate for a duration of 15 minutes. The first session included the test protocol to determine exercise parameters for the walking task. Analysis included the following five sessions.

Results obtained from 15 participants in both groups were considered for statistical analysis. Both groups showed EIH after the task for lumbar pressure pain thresholds (PPT) (Wilks=0.53, F=25.11, p< .001; average absolute difference across five sessions CLBP: +35.39 kPa 95% CI [5.58; 65.21]; CON: +39.03 kPa [9.21; 68.84]). Moreover, an increase in PPT over sessions was found (Wilks= 0.51, F=5.99, p= .001). Even though changes for remote PPT, pressure pain tolerances, and thermal pain thresholds over the thenar eminence were statistically significant across five sessions, changes within each session were revealed in only 14 of 60 sessions across these outcome measures. Baseline stability of outcome measures was moderate to good (ICC (3,1) range .502 to .878), but stability of absolute changes was poor (≤ .330). This is consistent with the findings from Chapter four and raises some concerns about the clinical use of the principle of EIH and its role in pain modulation.

5.2 Introduction

Aerobic exercise is commonly used and is effective for the management of chronic musculoskeletal pain, including CLBP (Booth et al., 2017). Walking has been shown to have a positive influence on pain and disability in people with CLBP in the short-term (three months) and long-term (Vanti et al., 2019). As outlined in Chapter three, only two studies have assessed EIH following an acute bout of aerobic exercise in participants with CLBP. Both studies used a cycling protocol as a remote/ aerobic task (Hoffmann et al., 2005; Meeus et al., 2010).

A recent systematic review showed that aerobic exercise resulted in EIH in asymptomatic participants (7 RCTs, n=236, g=-.85 95% CI [-1.58; -.13]) but no studies included people with musculoskeletal disorders (Wewege and Jones, 2021). In contrast, a further systematic review on asymptomatic participants only, including 15 RCTs or quasi-experimental studies, could not support EIH after aerobic exercise (g= .05 [-.0.06; 0.16]) (Pacheco-Barrios et al., 2020). Only three studies were included for both of the two systematic reviews, even though the main eligibility criteria were similar. As outlined in Chapter one (Table 1.2), the review by Wewege and Jones (2021) was of higher quality and also required a control group for comparison, whereas this was not specified for the other review (Pacheco-Barrios et al., 2020). Additionally, the search strategy was less sensitive for the review although eligibility criteria were less strict increasing the bias that relevant studies were not included. One study by Meeus et al. (2010) on EIH after cycling in participants with and without CLBP was considered in the latter systematic review and in this thesis (Chapter three). Overall, most studies across the two reviews used cycling protocols.

In contrast to a resistance exercise task as discussed in Chapter four, there is evidence that after an aerobic task the effects of EIH are often systemic rather than being localised to the exercised area (Rice et al., 2019). However, this has been discussed equivocally and some studies showed EIH in the exercised muscle group, but not in other body regions. Moreover, the intensity of the exercise task has been discussed as a potential factor contributing to discrepancies in study findings (Micalos and Arendt-Nielsen, 2016; Naugle et al., 2014b).

EIH has been assessed in response to a walking task in only two studies assessing asymptomatic participants (Hviid et al., 2019; Nguy et al., 2019). Treadmill walking at low (39% of age predicted heart rate/ Borg Scale 9-10) or moderate (59% of age-predicted heart rate/ Borg Scale 12-13) intensity for 10-25 minutes led to EIH over the biceps and the quadriceps in older adults regardless of the exercise intensity (Nguy et al., 2019). In another study, a six-minute walk test was used to elicit EIH in two separate sessions; no changes of PPT over the trapezius and quadriceps muscles were found but pain tolerance, measured with computer controlled cuff algometry over the lower leg, increased statistically significantly after the walking task (Hviid et al., 2019). The study assessed the stability of effects over two sessions and showed a poor ICC (3,1) for PPT, and ICC values of .60 95% CI [0.21; 0.80] for cuff pressure pain threshold and 0.61 [0.20; 0.81] for cuff pressure pain tolerance (Hviid et al., 2019). Some research in asymptomatic participants showed fair reliability of absolute PPT changes as indicators for EIH after cycling (Gomolka et al., 2019; Vaegter et al., 2018). Furthermore, stricter standardisation based on lactate thresholds improved reliability (ICC (Vaegter et al., 2019a).

So far, no study has examined whether a walking task can induce EIH in people with CLBP. Furthermore, stability of EIH has not been explored in people with CLBP after a brisk walking task.

The same qualitative approach as in the previous Chapter was embedded to explore participants' perceptions of taking part in the study as no qualitative research has investigated EIH specifically following an aerobic task.

5.2.1 Chapter Objectives

The first objective of this study was to determine whether participants with and without CLBP gain EIH immediately following a brisk walking task. The second objective was to determine whether EIH could be achieved repeatedly over five separate sessions. This reflects objectives three and four of the thesis. As part of this study, participants' perceptions of the exercise task and their participation in the study were explored.

5.3 Methods

5.3.1 Design

The methodology was the same as applied in the previous chapter (Chapter four). The study is a pragmatic observational study with repeated measures. The brisk walking task and outcomes linked to the task are outlined below.

5.3.2 Brisk Walking Task

All components were conducted on the same treadmill (The Biodex Gait Trainer 3, USA) and controlled with a Polar heart rate monitor.

5.3.2.1 First Session

The participant started walking on the treadmill at their preferred warm-up speed for two minutes. Then the speed was increased every minute, initially to the nearest whole or half km/h then consequently by 0.5 km/h. If brisk walking could not be maintained or reached by 7km/h an additional increase in treadmill gradient was added every minute by 1%. The test was terminated when >70% ±5 of the age-predicted heart rate (220 – age) was maintained for five minutes (Camarda et al., 2008).

5.3.2.2 Sessions Two to Six

Participants started with a two-minute warm-up at their preferred speed. According to the individual adjusted protocol in the first session, participants then walked for 15 minutes at their designated speed and inclination. At each full minute first the incline / then the speed (1% incline/ decline; ±0.5km/h) was increased or decreased if their heart rate was not within the targeted interval (70% ±5). For sessions two to six, participants listened to the same individually chosen music, as pilot testing indicated this could facilitate study adherence.

5.3.3 Evaluation of Demographics, Low Back Pain related Characteristics, and Qualitative Analysis of Participants' Perceptions

The same battery of questionnaires was used as in Chapter four (section 4.3.4/ Appendix 14) and data on activity levels, general health, and participants demographics were collected. For the CLBP group, the questionnaires (FABQ, ODI, PCS, Tampa scale of Kinesiophobia, PSEQ, CSI) were considered to further explore the disability and impact of their CLBP.

During the 15 minute walking task participants with CLBP were asked to rate their pain on a NRS from zero, no pain, to ten, the worst pain, every minute and immediately after the brisk walking task. Furthermore, participants rated their perceived exertion on a Borg scale (Borg, 1982). Other pain measures were collected with a digital VAS using the University's data capture tool REDCap (REDCap consortium, Vanderbilt University, Nashville, TN, USA) for the CLBP group.

The same qualitative approach was embedded as described in Chapter four (section 4.3.5) comprising of a five-item questionnaire.

5.3.4 Quantitative Sensory Testing

The same QST testing (tests and location) was applied as outlined in the previous Chapter (Chapter four, section 4.3.6). As a summary, PPT were measured over eight local test sites over the lumbar region, and over the tibialis anterior, wrist extensors, and upper trapezius muscle. PPTOL was tested over the lumbar region and over the wrist extensors. TPT were

measured over the thenar eminence and the lumbar region (HPT only). Furthermore, TS of heat stimuli and the nociceptive withdrawal reflex are outlined in Appendix 17.

5.3.5 Statistical Analysis

After the presentation of descriptive statistics and participants' questionnaires, RM-ANOVA/ non-parametric analysis for EIH was conducted. Stability of baseline measures and absolute changes was assessed with ICC (3,1). As outlined in Chapter four, the same methodology was used except for the following modifications:

Task characteristics were analysed with a RM-ANOVA for group, session, and each of the following parameters: pace, heart rate, and incline. Because the first session was used to determine the individual treadmill walking protocol, the time differed preventing a true comparison. Thus, only five sessions (session two to six) were included in the analysis for EIH and stability of absolute change. All figures display the mean and (SD) for consistency and comparison for lumbar data and the second objective of stability regardless of the distribution of the data. To evaluate the participants' perceptions of taking part in the study a pragmatic content analysis was conducted as described in the previous Chapter (section 4.3.9.4).

5.4 Results

5.4.1 Participant Characteristics

For data analysis, 15 participants for each group were considered (Table 5.1). Two additional participants with and without CLBP each dropped out over the course of the study due to non-study related medical reasons or no information given.

The gap between sessions was three days [Median, IQR 3; 5] for the asymptomatic group and four days [3; 5] for the CLBP group. No differences were found between baseline characteristics of the two groups except for general health and pain sub scores of the SF-36 confirmed with an independent t-test. Findings of the CLBP group show minimal disability (ODI) and mild to moderate pain levels.

Table 5.1 Baseline characteristics

* indicates a significant difference based on a student's t-test/ Chi Square test

Group		CLBP n=15	CON n=15	P value
		Mean± SD	Mean± SD	
Age		25.60± 5.28	26.13± 5.34	.785
BMI		21.71± 6.64	23.40± 2.26	.359
Gender		7 men, 8 women	7 men, 8 women	1.0
SF-36 aver-age score	Physical functioning	88.00± 10.99	93.94± 11.86	.166
	Pain	71.17± 16.42	88.67± 14.66	.005*
	General Health	68.67± 12.88	81.67± 15.31	.018*
IPAQ		3 low, 4 moderate, 8 high	9 moderate, 6 high	.074
IPAQ MET		3425.57± 3055.14	4326.43± 4000.12	.494
FABQ		28.20± 12.15		
FABQ Work		11.27± 7.79		
FABQ Physical activity		11.53± 4.87		
ODI		11.01± 5.69		
PCS		9.13± 6.60		
TAMPA		31.60± 5.41		
PSEQ		53.07± 5.96		
CSI A		32.53± 14.73		
VAS average most recent episode		40.20± 22.50		
VAS pain at present		24.00± 20.09		
VAS worst pain past 4 weeks		48.00± 23.63		
VAS average last 24 hours		27.27± 18.91		
Dominant pain side		Left n=6; right n=9		

Abbreviations: *BMI=Body Mass Index; SF-36= SF-36 v2 Health Survey; IPAQ=International Physical Activity Questionnaire; MET= Metabolic Equivalent of Task; FABQ= Fear Avoidance Believes Questionnaire; ODI= Oswestry Disability Index; PCS= Pain Catastrophizing Scale; TAMPA= Tampa Scale of Kinesiophobia; PSEQ= Pain Self-Efficacy Questionnaire; CSI=Central Sensitisation Inventory; VAS= Visual Analogue Scale (0-100)*

5.4.2 Brisk Walking Task Parameters

There was no statistically significant group difference for the performance parameters. However, there was a statistically significant difference for the Borg Scale for session (F=4.87, p= .001) and group*session (F=2.59, p= .004). Post hoc analysis verified a decline in perceived exertion from session two to six in the CON group (p= .028) but not in the CLBP group (p= 1.00) (Table 5.2).

Table 5.2 Walking task parameters

	Session 2	Session 3	Session 4	Session 5	Session 6	Mean across 2-6
CLBP group (Mean± SD)						
Borg scale	11.80± 1.90	12.40± 2.53	11.53± 2.13	10.93± 2.34	11.47± 1.81	11.63± 1.80
Pace (km/h)	6.23± 0.54	6.26± 0.56	6.24± 0.56	6.18± 0.57	6.24± 0.54	6.23± 0.54
Incline (%)	4.77± 3.60	4.62± 3.69	5.24± 3.62	5.22± 3.58	4.95± 3.51	4.96± 3.51
Heart rate (bpm)	135.22± 6.16	135.61± 5.87	134.66± 4.85	134.51± 4.92	135.44± 5.60	135.09± 4.75
CON group (Mean± SD)						
Borg scale	13.07± 2.05	11.87± 1.06	11.53± 1.13	11.67± 1.35	11.53± 1.13	11.93± 1.04
Pace (km/h)	6.57± 0.42	6.54± 0.40	6.55± 0.40	6.54± 0.40	6.56± 0.41	6.55 ± 0.40
Incline (%)	4.25± 2.50	4.32± 2.61	4.48± 2.54	4.25± 2.58	4.57± 2.73	4.38 ± 2.57
Heart rate (bpm)	134.12± 4.33	133.68± 6.17	133.46± 4.59	133.59± 5.30	134.33± 5.35	133.84± 4.60

Abbreviations: *CLBP= Chronic Low Back Pain; CON= Asymptomatic Control Group*

5.4.3 Perceived Pain during the Walking Task in Participants with Chronic Low Back Pain

The perceived pain during the walking task, averaged for the 15 minutes and five sessions, was 1.25± 1.06/10 on a NRS. Pain levels at the beginning of the session were 1.68± 1.33/10 and 1.29± 1.37/10 immediately after the task. The average intensity between sessions was 2.07± 1.37/10 (digital NRS). Pain levels at the completion of the session, after post testing, were 13.51± 14.51/100 (digital VAS). Further analysis was not conducted due to the low pain levels.

5.4.4 Exercise-Induced Hypoalgesia

5.4.4.1 Lumbar Pressure Pain Thresholds – Primary Outcome

A RM-ANOVA showed a statistically significant effect for time (Wilks=0.53, F=25.11, p< .001), session (Wilks= 0.51, F=5.99, p= .001), and location (Wilks= 0.27, F=8.63, p< .001). There was no statistically significant effect for group (p= .150) or any interaction between these factors. Post hoc analysis showed a statistically significant change (p< .001), with a +35.39 kPa CI [5.58; 65.21] for the CLBP group and +39.03 kPa [9.21; 68.84] in the CON group across five sessions. For the factor session, the change was confirmed for sessions two, four, five, and six (p< .006) including both pre- and post-values. Considering the baseline measures only, the increase was +66.00 kPa [7.46; 125.54] in the CLBP group and +73.33 kPa [14.79; 131.87] in the CON group. Post hoc analysis indicated that test site eight (bottom right) was different to test sites one to three, five and six (p< .004), but not four (bottom left) and seven. PPT over test site four (top right) were lower than test site five and six (p< .034). Furthermore, PPT over test site five were statistically significantly higher than test sites seven (p= .016). However, for all locations PPT increased across five sessions from pre to post (p< .008).

The extent of EIH did not differ between groups or between the five sessions as effect for time*group*session was not statistically significant (Wilks= 0.80, p= .223) (Figure 5.1).

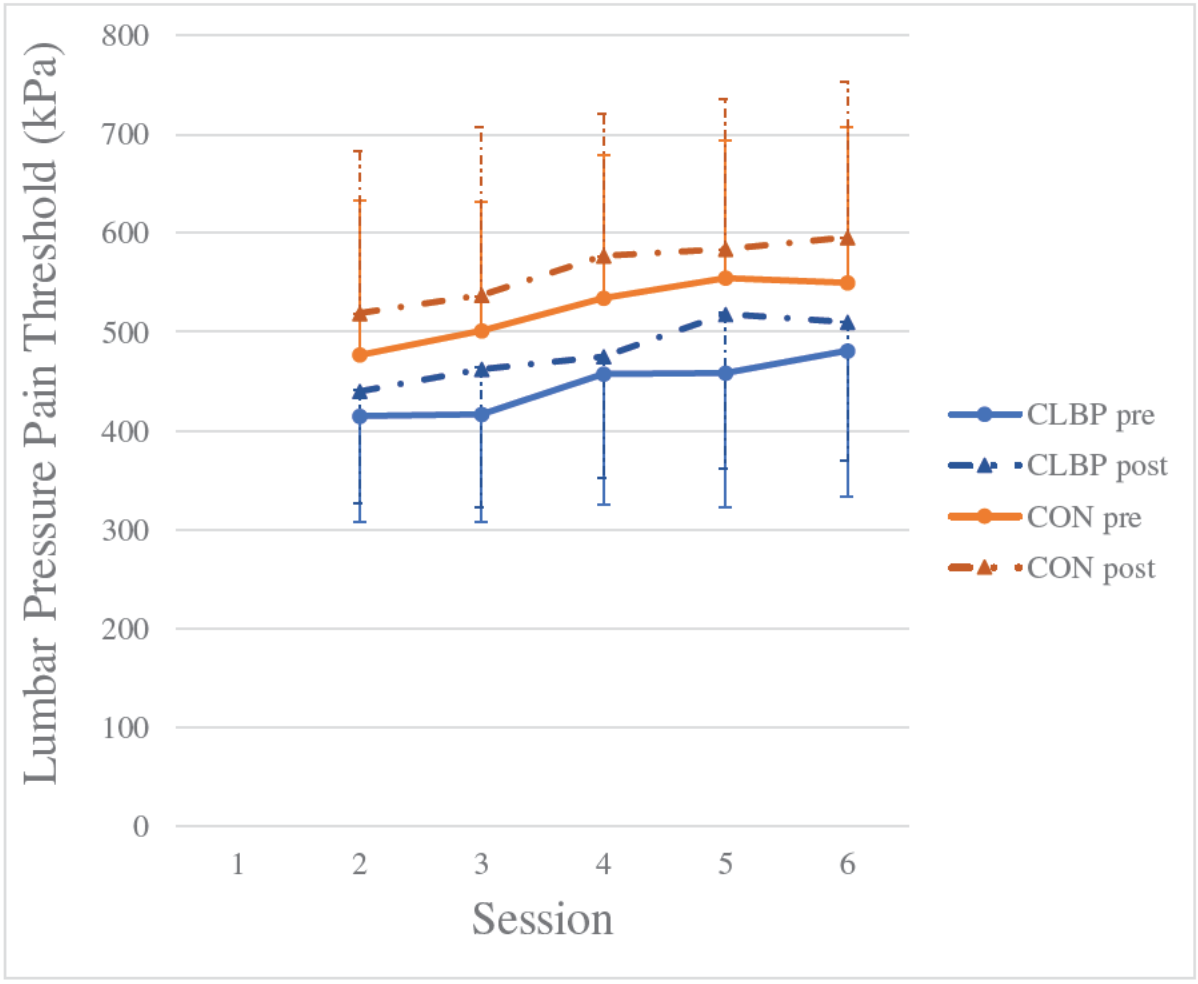


Figure 5.1 Pressure Pain Thresholds across the eight Lumbar Test Sites (Mean/SD)

CLBP=Chronic Low Back Pain; CON= asymptomatic control

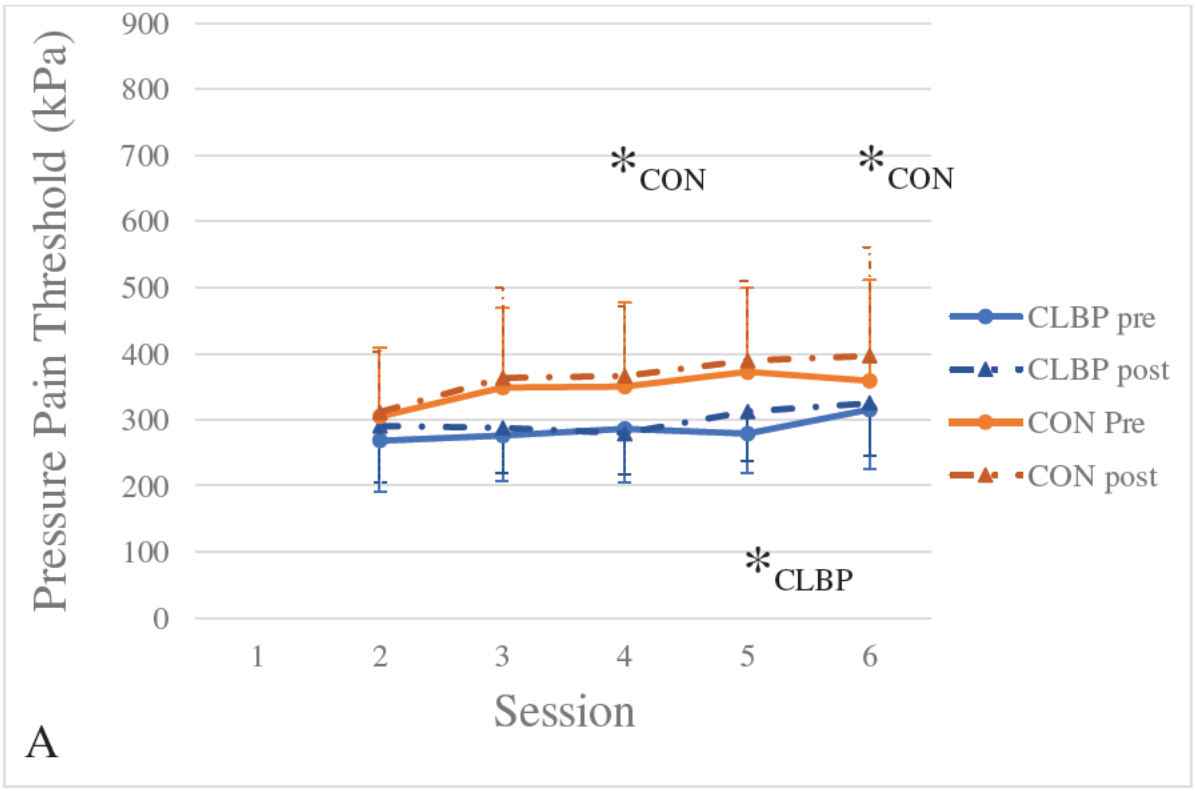
5.4.4.2 Remote Pressure Pain Thresholds

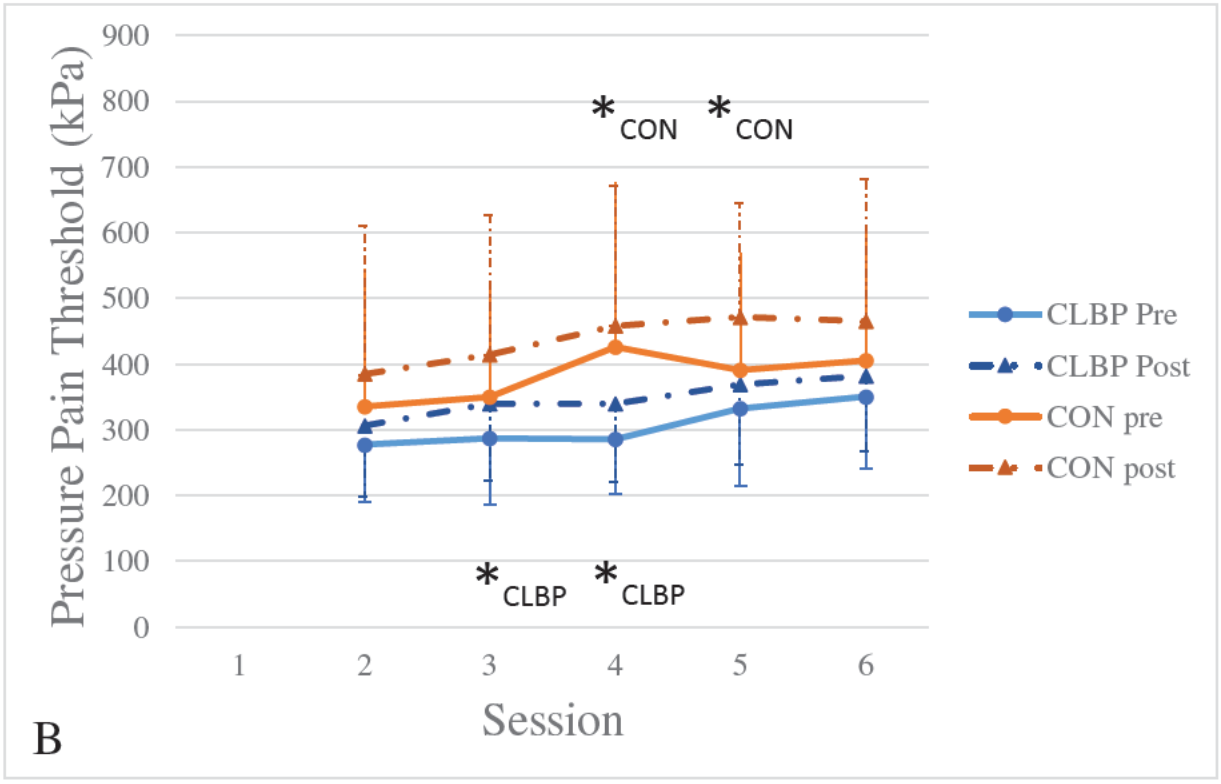
The three remote test sites showed non normal distributed data and hence non-parametric tests were applied. All results are displayed in Figure 5.2 A-C. Both groups showed a statistically significant increase of PPT over the upper trapezius across all five sessions ($p < .004$). When considering each individual session, the CLBP group showed a statistically significant increase only in session five ($p = .008$). The CON group showed a

statistically significant change in sessions four (p= .005) and six (p= .020). The Kruskal-Wallis test did not confirm any group differences for the absolute changes in PPT.

For the wrist extensors test site, both groups showed an increase across the five sessions (p< .001). For the CLBP group the change was statistically significant for sessions three and four (both p= .033). For the CON group increase was statistically significant in sessions four (p= .020) and five (p< .001). Kruskal-Wallis showed no group difference (p= .059) for absolute change over the wrist extensors.

Over the tibialis anterior, the CLBP group showed an increase across the five sessions (p= .015) and the CON group just reached statistical significance (p= .050). None of the individual sessions revealed a significance change. No group difference for absolute change in PPT was present.





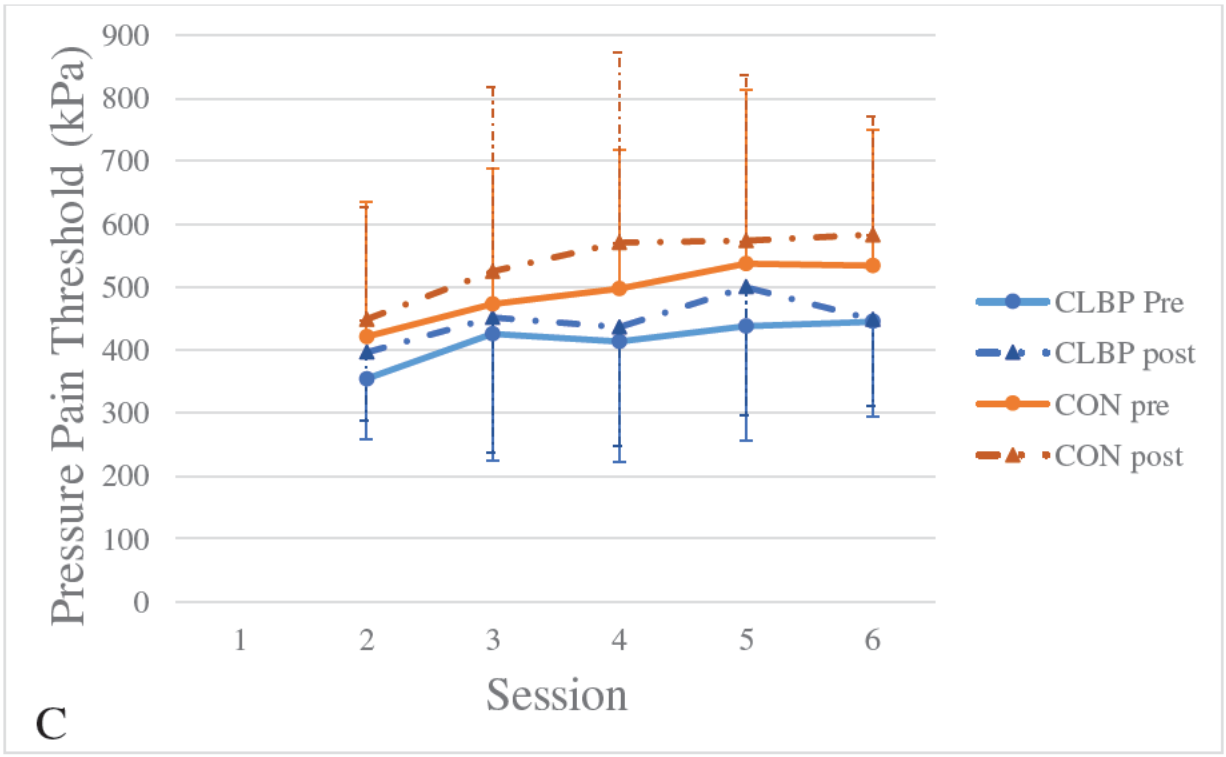


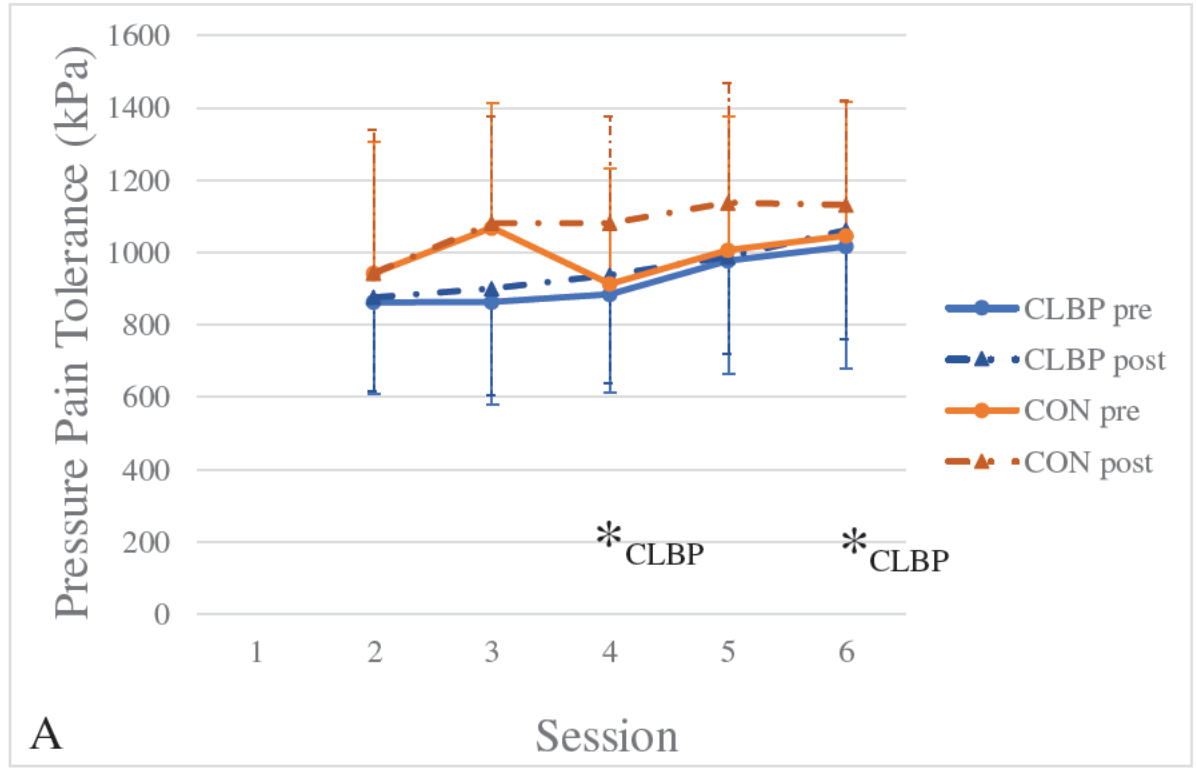
Figure 5.2 A-C Remote Pressure Pain Thresholds (Mean/SD)

Test sites over (A) the Upper Trapezius (B), the Wrist extensors and (C) Tibialis anterior. Significant within-session changes are marked with an *. CLBP=Chronic Low Back Pain; CON= asymptomatic control

5.4.4.3 Pressure Pain Tolerances

All PPTOL data were not normally distributed, hence a Friedman ANOVA and Kruskal-Wallis tests were applied. Results are displayed in Figure 5.3 A-B. PPTOL over the lumbar region included data for all participants of the CLBP group and twelve participants of the CON group. Both groups showed a statistically significant increase in PPTOL after the walking task across the five sessions (CLBP p= .003, CON p= .039). For each individual session, the increase was only statistically significant in the fourth and sixth session (both p= .020) for the CLBP group. In the CON group no individual session showed a statistically significant change. There was no group difference for absolute changes.

For the test site over the wrist extensors, all participants of the CLBP were considered for analysis and eleven of the CON group. Both groups showed a statistically significant increase in PPTOL after the walking task across five sessions (CLBP: p< .001; CON: p= .029). For individual sessions, the increase was statistically significant in sessions four (p= .020) and five (p< .001) for the CLBP group. The CON group showed a statistically significant increase in session five (p= .035). No group difference for absolute changes was found.



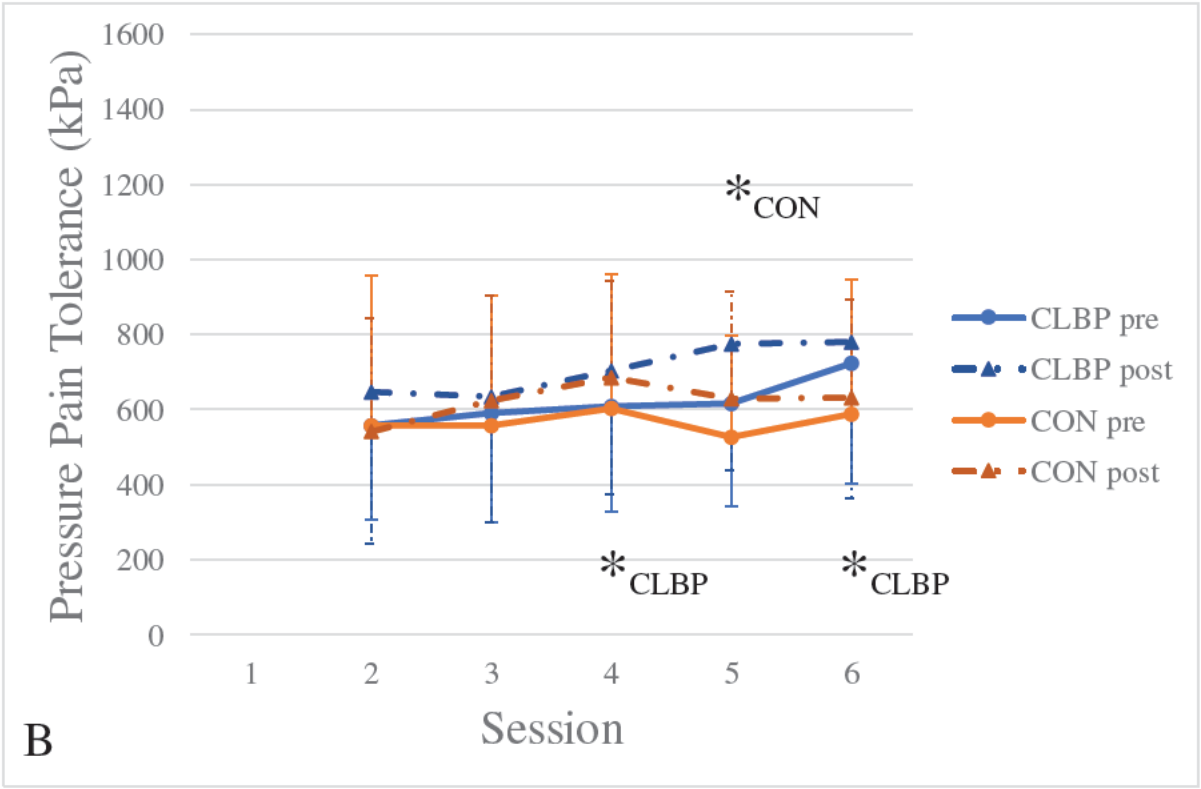


Figure 5.3 A-B Pressure Pain Tolerances (Mean/SD)

Test sites over (A) the lumbar region and (B) the wrist extensor. Significant within-session changes are marked with an *. CLBP=Chronic Low Back Pain; CON= asymptomatic control

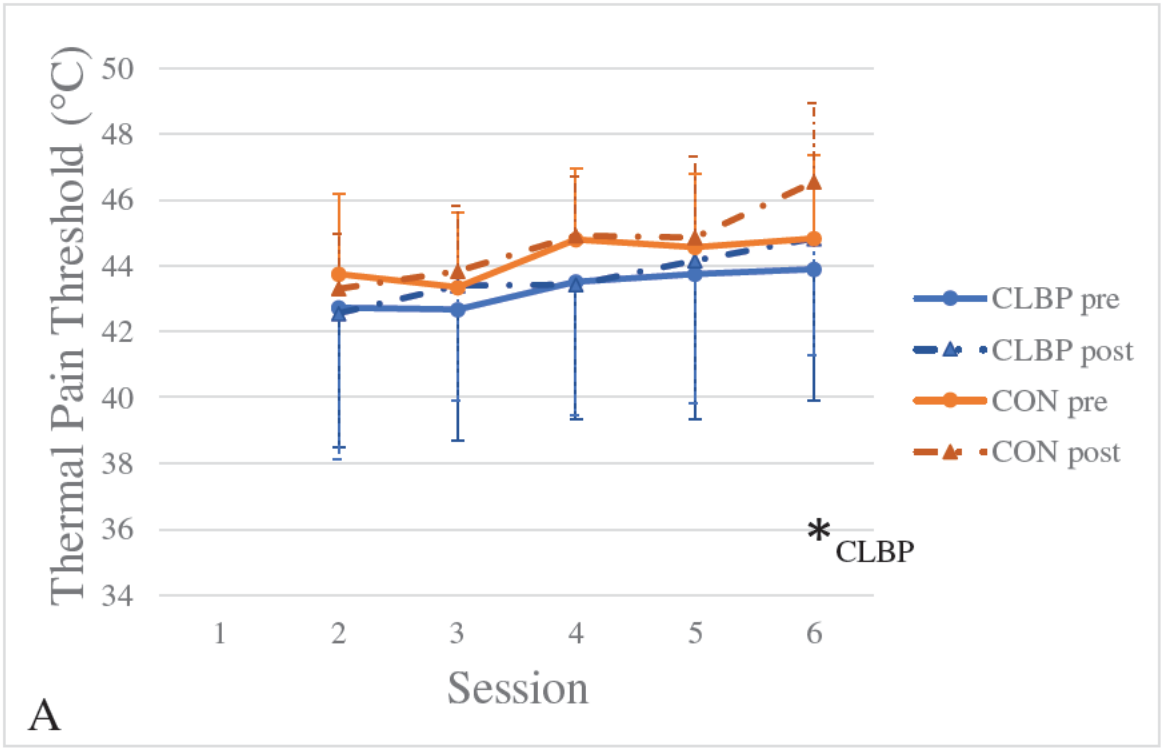
5.4.4.4 Thermal Pain Thresholds

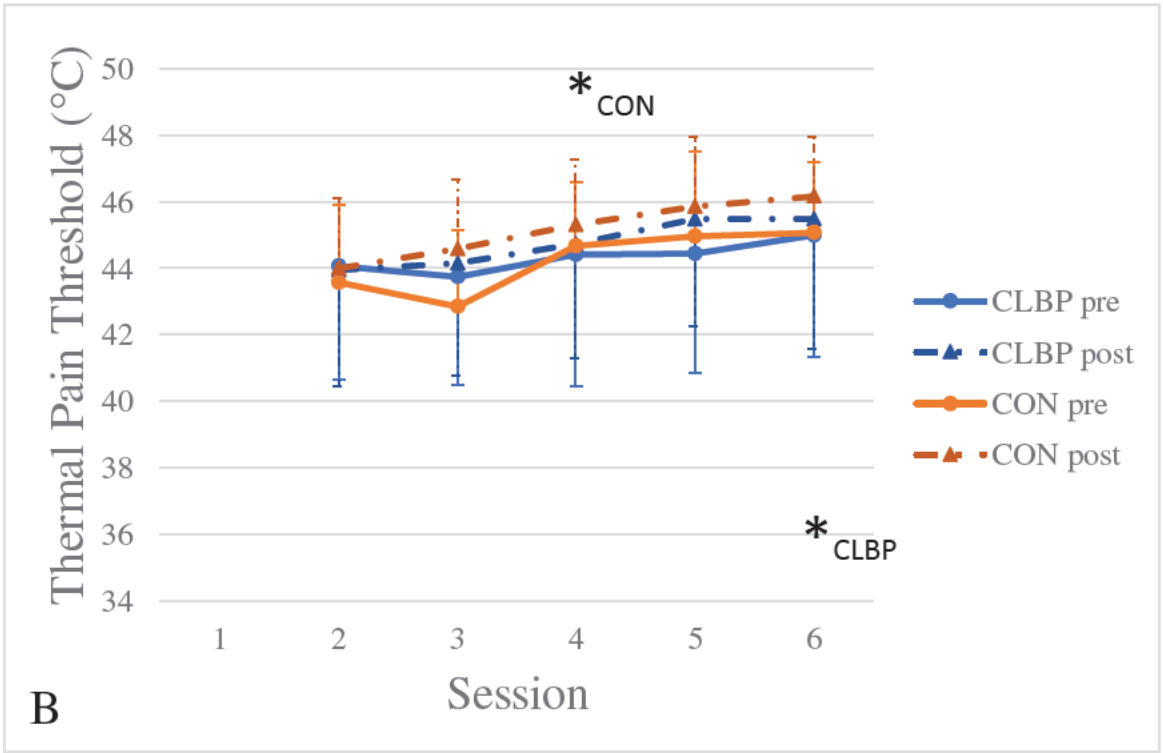
All thermal data were not normally distributed, and hence non-parametric tests were applied. Especially for the CON group, many data sets were excluded from the analysis due to the safety limitations of the device being reached before pain thresholds. Data are displayed in Figure 5.4 A-C.

Lumbar HPT showed no statistically significant change across the five sessions based on data of 14 participants of the CLBP group and six for the CON group. However, in the CLBP group the final session showed a significant increase in temperature ($p = .033$). A Kruskal-Wallis test showed no group difference for absolute differences between groups.

Thenar HPT were considered for 14 participants of the CLBP group and eight of the CON group. There was a statistically significant increase across the five sessions for both groups (both $p = .004$). The CLBP group showed a statistically significant increase in the final session ($p = .033$); and the CON group for the third session ($p = .005$). No group difference was found for absolute changes between groups.

Friedman ANOVA for thenar CPT of 13 participants with CLBP and six asymptomatic participants revealed no change across five or within individual sessions. No group difference was found for pre-post differences.


Thermal Pain Threshold (°C)
50
48
46
44
42
40
38
36
34
1
2
3
4
5
6
Session
*CLBP
CLBP pre
CLBP post
CON pre
CON post
A


Thermal Pain Threshold (°C)
50
48
46
44
42
40
38
36
34
1
2
3
4
5
6
Session
*CON
*CLBP
CLBP pre
CLBP post
CON pre
CON post
B

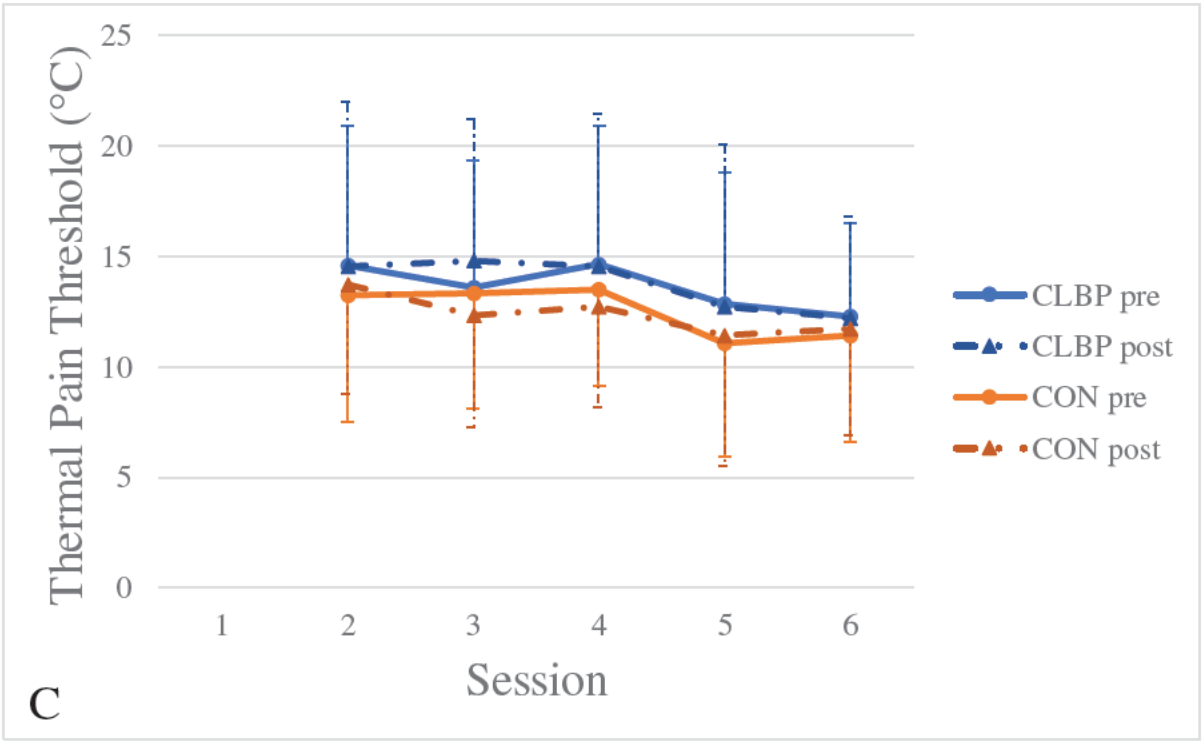


Figure 5.4 A-C Thermal Pain Thresholds (Mean/SD)

(A) lumbar heat pain thresholds (B) heat pain thresholds over the thenar eminence (C) cold pain thresholds over the thenar eminence. Significant within-session changes are marked with an *. CLBP=Chronic Low Back Pain; CON= asymptomatic control

5.4.5 Stability of the Baseline Measures (Pre-measurements within each session)

5.4.5.1 Pressure Pain Thresholds

Across six sessions the ICC for lumbar PPT, pooled across eight test sites, was moderate for the CLBP group and good for the CON group. SEM was 64.17 kPa and 71.63 kPa respectively (Table 5.3).

For all remote PPT the ICC was moderate, and the SEM varied from 70.64 kPa to 128.50 kPa (CON group) compared to 63.00 kPa to 87.23 kPa (CLBP group) (Table 5.4).

Table 5.3 Stability of the baseline measures of lumbar Pressure Pain Thresholds

Group	PPT for each session in kPa (Mean± SD)							ICC 3,1	LB	UB	SEM
	1	2	3	4	5	6	Mean				
CLBP	434.56 ±96.91	415.18 ±89.50	416.83 ±94.27	457.89 ±120.74	458.46 ±125.13	481.18 ±136.52	444.01 ±111.37	.668	.494	.856	64.17
CON	496.87 ±164.07	476.71 ±163.25	501.50 ±205.99	534.88 ±196.23	554.60 ±231.14	550.05 ±206.66	519.10 ±192.70	.856	.737	.940	73.13

Abbreviations: *CLBP= Chronic Low Back Pain; CON= Asymptomatic Control Group; PPT= Pressure Pain Threshold; ICC= Intraclass Correlation Coefficient; LB= Lower Bound; UB= Upper Bound; SEM= Standard Error of Measurement*

Table 5.4 Stability of the baseline measures of remote Pressure Pain Thresholds

	Grou	PPT for each session in kPa (Mean± SD)							ICC 3,1	LB	UB	SEM
		1	2	3	4	5	6	Mean				
Upper Trapezius	CLBP	285.93 ± 141.34	267.90 ± 78.09	275.37 ± 67.64	286.63 ± 81.79	278.93 ± 60.42	315.17 ± 90.82	284.99 ± 89.28	.502	.288	.743	63.00
	CON	326.00 ± 137.75	304.50 ± 103.71	347.80 ± 122.04	350.60 ± 126.07	372.30 ± 127.11	358.73 ± 152.14	343.32 ± 127.28	.692	.501	.859	70.64
Wrist extensors	CLBP	311.10 ± 117.93	277.67 ± 87.98	286.73 ± 101.39	286.13 ± 83.73	332.00 ± 116.38	350.63 ± 109.10	307.38 ± 104.14	.531	.317	.762	71.32
	CON	353.67 ± 189.12	335.57 ± 208.02	349.37 ± 162.35	426.10 ± 249.38	391.07 ± 177.55	405.27 ± 193.91	376.84 ± 195.75	.672	.476	.848	112.11
Tibialis anterior	CLBP	416.63 ± 143.23	353.97 ± 96.26	424.93 ± 200.77	413.73 ± 191.89	438.03 ± 182.95	444.53 ± 150.22	415.31 ± 162.83	.713	.528	.870	87.23
	CON	511.17 ± 281.95	420.93 ± 215.25	473.30 ± 215.23	496.57 ± 222.26	536.90 ± 275.95	534.33 ± 216.09	495.53 ± 236.18	.704	.517	.866	128.50

Abbreviations: *CLBP= Chronic Low Back Pain; CON= Asymptomatic Control Group; PPT= Pressure Pain Threshold; ICC= Intraclass Correlation Coefficient; LB= Lower Bound; UB= Upper Bound; SEM= Standard Error of Measurement*

5.4.5.2 Pressure Pain Tolerances

The ICC for PPTOL was good for both groups over both test sites. Note only full data sets were considered (Table 5.5).

Table 5.5 Stability of the baseline measures of Pressure Pain Tolerances

	Group	PPTOL for each session in kPa (Mean± SD)							ICC 3,1	LB	UB	SEM
		1	2	3	4	5	6	Mean				
Lumbar	CLBP n=15	893.40 ± 230.91	862.47 ± 253.33	862.73 ± 281.69	884.80 ± 269.97	977.20 ± 313.22	1016.87 ± 335.63	916.24 ± 281.32	.757	.588	.893	138.67
	CON n=12	951.92 ± 368.59	944.08 ± 421.97	1069.17± 502.57	913.33 ± 383.37	1006.50 ± 370.44	1045.75± 368.81	988.46 ± 395.09	.799	.628	.925	177.13
Wrist extensors	CLBP n=15	648.33 ± 232.16	558.13 ± 252.71	592.13 ± 290.53	609.40 ± 281.83	617.20 ± 275.44	723.47 ± 321.48	624.78 ± 274.22	.839	.709	.932	110.03
	CON n=11	645.36 ± 329.20	557.18 ± 311.45	557.91 ± 261.01	603.00 ± 360.54	526.91 ± 222.54	588.82 ± 246.19	579.86 ± 283.71	.823	.657	.939	119.36

Abbreviations: *CLBP= Chronic Low Back Pain; CON= Asymptomatic Control Group; PPTOL= Pressure Pain Tolerance; ICC= Intraclass Correlation Coefficient; LB= Lower Bound; UB= Upper Bound; SEM= Standard Error of Measurement*

5.4.5.3 Thermal Pain Thresholds

The ICC for baseline TPT was moderate for both HPT in the CLBP group and good for thenar CPT. For the CON group, the ICC was moderate for thenar HPT, but good for lumbar HPT and thenar CPT (Table 5.6). Note that data sets included vary in number with participants due to violation of safety limitations in the first session for CPT for one participant from the CLBP group.

Table 5.6 Stability of the baseline measures of Thermal Pain Thresholds

	Group	n	TPT for each session in °C (Mean± SD)							ICC 3,1	LB	UB	SEM
			1	2	3	4	5	6	Mean				
Lumbar Heat	CLBP	14	41.34± 2.44	42.73 ± 2.57	42.68 ± 2.47	43.53 ± 2.34	43.75 ± 2.38	43.90 ± 2.72	42.99 ± 2.57	.694	.497	.866	1.42
	CON	6	42.61± 2.45	43.75 ± 3.34	43.35 ± 3.74	44.79 ± 3.22	44.57 ± 3.77	44.83 ± 3.72	43.98 ± 3.26	.845	.620	.972	1.28
Thenar Heat	CLBP	14	42.75± 2.70	44.06 ± 2.27	43.74 ± 2.86	44.40 ± 2.43	44.44 ± 2.44	44.99 ± 2.11	44.06 ± 2.50	.548	.327	.781	1.68
	CON	8	42.74± 2.56	43.56 ± 3.57	42.84 ± 3.42	44.67 ± 3.55	44.95 ± 3.28	45.07 ± 3.44	43.97 ± 3.29	.596	.309	.874	2.09
Thenar cold	CLBP	12	14.25± 7.77	15.05 ± 6.72	14.22 ± 7.15	14.52 ± 7.04	13.16 ± 7.37	12.80 ± 6.27	14.00 ± 6.86	.812	.648	0.931	2.97
	CON	6	11.68± 6.56	13.26 ± 7.40	13.32 ± 7.17	13.50 ± 7.44	11.07 ± 7.26	11.44 ± 7.10	12.38 ± 6.71	.878	.687	.979	2.34

Abbreviations: *CLBP= Chronic Low Back Pain; CON= Asymptomatic Control Group; TPT= Thermal Pain Thresholds; ICC= Intraclass Correlation Coefficient; LB= Lower Bound; UB= Upper Bound; SEM= Standard Error of Measurement*

5.4.6 Stability of the Absolute Changes

5.4.6.1 Pressure Pain Thresholds

The ICC was poor for the absolute change in PPT over the lumbar region (Table 5.7).

This was the same for remote PPT. The ICC was poor for both groups over all remote test sites (Table 5.8).

Table 5.7 Stability of the absolute changes of lumbar Pressure Pain Thresholds

Group	Absolute change in PPT for each session in kPa (Mean± SD)						ICC 3,1	LB	UB	SEM
	2	3	4	5	6	Mean				
CLBP n=15	24.83± 55.39	46.16± 59.72	17.53± 47.63	59.86± 92.98	28.59± 59.60	35.39± 65.07	.091	-.061	.370	62.03
CON n=15	42.53± 63.92	35.67± 78.92	41.95± 50.77	29.19± 64.15	45.80± 85.92	39.03± 68.19	.303	.092	.594	56.93

Abbreviations: *CLBP= Chronic Low Back Pain; CON= Asymptomatic Control Group; PPT= Pressure Pain Threshold; ICC= Intraclass Correlation Coefficient; LB= Lower Bound; UB= Upper Bound; SEM= Standard Error of Measurement*

Table. 5.8 Stability of the absolute changes of remote Pressure Pain Thresholds

	Group	Absolute change in PPT for each session in kPa (Mean± SD)						ICC 3,1	LB	UB	SEM
		2	3	4	5	6	Mean				
Upper Trapezius	CLBP n=15	23.13± 39.43	11.77± 46.19	-7.27± 61.85	33.50± 38.24	9.43± 32.65	14.11± 15.34	.106	-.052	.388	14.51
	CON n=15	6.83± 61.64	15.57± 58.12	16.03± 77.30	17.57± 86.33	37.50± 83.31	18.70± 11.32	-.037	-.139	.187	11.53
Wrist Extensors	CLBP n=15	28.77± 63.30	53.33± 56.55	54.30± 95.15	37.47± 81.12	31.47± 66.20	41.07± 12.06	.046	-.090	.311	11.78
	CON n=15	49.27± 121.01	65.40± 85.45	32.50± 121.28	80.63± 64.07	60.33± 113.77	57.63± 18.02	.135	-.032	.423	16.76
Tibialis anterior	CLBP n=15	41.80± 74.87	25.70± 81.63	21.87± 48.78	61.40± 96.05	3.93± 63.64	30.94± 21.71	.087	-.064	.365	20.74
	CON n=15	27.40± 120.47	51.27± 137.23	74.13± 131.84	36.10± 115.65	48.70± 122.87	47.52± 17.74	.229	.035	.525	15.58

Abbreviations*: CLBP= Chronic Low Back Pain; CON= Asymptomatic Control Group; PPT= Pressure Pain Threshold; ICC= Intraclass Correlation Coefficient; LB= Lower Bound; UB= Upper Bound; SEM= Standard Error of Measurement*

5.4.6.2 Pressure Pain Tolerances

The ICC was poor for all PPTOL test sites and both groups (Table 5.9).

Table 5.9 Stability of the absolute changes of Pressure Pain Tolerances

PPTOL	Group	Absolute change in PPTOL for each session in kPa (Mean± SD)						ICC 3,1	LB	UB	SEM
		2	3	4	5	6	Mean				
Lumbar	CLBP n=15	13.73± 111.75	37.73± 129.54	54.13± 70.48	12.27± 151.72	45.40± 135.36	32.65± 120.78	-.003	-.119	.240	120.96
	CON n=12	-0.08± 113.39	12.75± 211.36	168.58± 289.52	131.67 ± 260.11	84.92± 106.79	79.57± 213.22	.122	-.056	.454	199.79
Wrist extensors	CLBP n=15	89.07± 219.58	42.67± 107.40	94.13± 121.86	158.67± 131.42	56.80± 175.56	88.27± 157.63	.285	.078	.578	133.28
	CON n=11	-16.09± 138.12	66.82± 204.14	82.64± 147.84	101.91± 142.22	41.91± 102.77	55.44± 150.65	-.005	-.134	.303	151.03

Abbreviations: *CLBP= Chronic Low Back Pain; CON= Asymptomatic Control Group; PPTOL= Pressure Pain Tolerance; ICC= Intraclass Correlation Coefficient; LB= Lower Bound; UB= Upper Bound; SEM= Standard Error of Measurement*

5.4.6.3 Thermal Pain Thresholds

The ICC was poor for all thermal pain thresholds regardless of modality, test site, and group (Table 5.10). It is to note that CPT over the thenar eminence and HPT over the lumbar region included only data of six participants in the CON group.

Table 5.10 Stability of the absolute changes of Thermal Pain Thresholds

	Group	n	Absolute change in TPT for each session in °C (Mean± SD)						ICC 3,1	LB	UB	SEM
			2	3	4	5	6	Mean				
Lumbar Heat	CLBP	14	-0.17± 2.08	0.72± 1.21	-0.11± 1.54	0.42± 2.28	0.94± 1.07	0.36± 1.71	.118	-.048	.417	2.33
	CON	6	-0.44± 1.72	0.48± 1.29	0.14± 1.45	0.29± 1.69	1.71± 2.64	0.44± 1.84	-.002	-.162	.513	3.37
Thenar Heat	CLBP	14	0.12± 1.94	0.42± 2.10	0.33± 2.14	1.04± 1.20	0.49± 1.12	0.48± 1.73	.153	-.025	.458	2.21
	CON	8	-0.43± 2.32	1.74± 1.71	0.63± 1.30	0.89± 1.15	1.09± 1.67	0.78± 1.75	.103	-.095	.541	3.21
Thenar Cold	CLBP	13	0.04± 4.58	1.19± 5.55	-0.10± 3.88	-0.15± 3.55	-0.07± 2.90	0.18± 4.09	-.042	-.147	.206	6.80
	CON	6	-0.47± 1.69	-0.98± 1.42	-0.76± 1.91	0.36± 2.32	0.29± 2.30	-0.31± 1.90	.360	.033	.824	5.47

Abbreviations: *CLBP= Chronic Low Back Pain; CON= Asymptomatic Control Group; TPT= Thermal Pain Threshold; ICC= Intraclass Correlation Coefficient; LB= Lower Bound; UB= Upper Bound; SEM= Standard Error of Measurement*

5.4.7 Qualitative Analysis of Participants' Perceptions

Evaluation of the questionnaire via a pragmatic content analysis is presented in the following section. Full quotes are provided in Appendix 18.

5.4.7.1 Question One: Participants' Experience over the Six Sessions

Statements from the 15 participants with CLBP derived four themes (Table 5.11). Most stated the experience as positive, covering seven codes such as enjoyable,

interesting, or professional. The second theme, covering six codes, was related to the effect from participation, which was perceived as improving performance, mood, or pain sensitivity. However, it was reported as a challenge that the testing did not improve the mood (third theme, one code). Two participants stated a reduction in their LBP (fourth theme, two codes).

The asymptomatic CON group's statements led to three themes (Table 5.11). Overall, there was a positive experience (five codes), but it was also challenged as painful or as a challenging walking task (third theme, four codes). The effect of the participation was described positive on both physical and mental status (second theme, eight codes).

Table 5.11 Participants' experience over the six sessions

Group	CLBP (n=15)		Group	Asymptomatic (n=15)	
Theme	**Code**	**n=**	**Theme**	**Code**	**n=**
Positive experience n=14	Enjoyable	6	**Positive experience n=9**	Enjoyable	4
	Good/ Positive	6		Good	1
	Interesting	3		Interesting	5
	Professional	1		Professional	1
	Unusual	1		In control of testing	1
	Useful	1			
	Very friendly	1			
Effect from participation n=6	Task improved mood	1	**Effect from participation n=8**	Higher thresholds in thermal testing	2
	Reduced pain sensitivity	1		Less tired afterwards	1
	Improved work performance	1		Increased confidence in testing	1
	Getting stronger	1		Improved physical and mental status	1
	Hill walking	1		Brighter mood	1
	Motivation	1		Improved concentration	1
				Sense of accomplishment	1
				Easy	1
Challenges n=1	Testing did not improve mood	1	**Challenges n=4**	Painful	1
				Challenging walking	1
				Only few hard parts	1
				Pain tracker too painful	1
LBP reduction n=2	Reduced LBP	2			
	Prevented pain episodes	1			

***Abbreviations**: CLBP= Chronic Low Back Pain, LBP= Low Back Pain*

5.4.7.2 Question Two: Participants' Satisfaction with the Allocation

Satisfaction with group allocation was reported by 12 of the 15 participants with CLBP. One participant was not pleased, indicating a preference to have been in the resistance exercise task group, and two participants did not have a preference.

In the asymptomatic CON group, equally 12 participants were satisfied with the group allocation, two participants did not have a preference and one participant would have preferred the resistance task.

5.4.7.3 Question Three: Participants' Expectation on Different Outcome from the other Exercise Task?

Six participants with CLBP expected a different outcome from the lumbar resistance task and equally six did not expect a different outcome. The remaining three participants were not sure, indicating the comparability of the intensity (n=2). Further codes indicated, that strengthening was found to either help or aggravate back pain (n=1 each), but the other task would be more beneficial to improve strength (n=2).

For the asymptomatic CON group, seven participants expected a different outcome from the lumbar resistance task, three participants did not. Five participants indicated "do not know". Comments indicated that increased intensity of the exercise task might be needed to facilitate strength (n=1), or the exercise task could be more tiring (n=1) or too difficult (n=1).

5.4.7.4 Question Four: Participants' Recommendation for Changes to the Study

Statements from five participants derived one theme around the exercise task (five codes) and 10 participants did not provide any suggestions (Table 5.12). Codes derived were around the task duration, the task variation, the incline of the treadmill, as well as the music.

For the asymptomatic CON group, statements from eight participants led to the derivation of two themes, exercise task (four codes) and testing (six codes). Seven participants did not indicate a change (Table 5.12). For the first theme codes covered the task duration, the incline and speed of the treadmill, as well as music. Codes for the theme testing were mainly around the test modalities as well as study setup.

Table 5.12 Participants' perceptions on change of the study design

Group	**CLBP**		**Group**	**Asymptomatic**	
Theme	**Code**	**n=**	**Theme**	**Code**	**n=**
Exercise task n=5	Longer task	1	**Exercise task n=4**	Longer task	1
	Less/ no incline on treadmill	1		Incline treadmill challenging muscles	1
	More task variation	1		Running instead	1
	Changing music	1		Changing music	1
	Headphones for music	1			
Testing n=0			**Testing n=4**	Thermal tester not reaching limits	1
				Did not like Pain Tolerance	1
				Consistency measuring PPT/tolerance	1
				No nociceptive withdrawal reflex	1
				Even number of days between sessions	1
No change n=10	NA	3	**No change n=7**	NA	1
	Nothing	7		Nothing	6

Abbreviations: *CLBP= Chronic Low Back Pain, NA= Not Available, PPT= Pressure Pain Threshold*

5.4.7.5 Question Five: Participants' Perceptions of Feasibility and Transferability of the Study Programme

Of the 15 participants with CLBP eight reported that this study programme was feasible for people with more severe CLBP (first theme, eight codes). Four were unsure,

including if testing could be tolerated by individuals with more severe CLBP (second theme, four codes). Three stated that the study programme would not be feasible for people with more severe pain, due to the positioning for testing, or the desired intensity could not be reached (third theme, five codes) (Table 5.13).

In the asymptomatic CON group, nine participants reported that the study programme was feasible for people with LBP (first theme, eight codes), three were unsure (second theme, three codes), and another three participants reported that the study programme would not be feasible for people with LBP, due to the exercise intensity, the testing, or overall volunteering to participate (third theme, four codes) (Table 5.13).

Table 5.13 Participants' perceptions on feasibility and transferability

Group	CLBP		Group	Asymptomatic	
Theme	**Code**	**n=**	**Theme**	**Code**	**n=**
Yes n=8	Low intensity	2	**Yes n=9**	No back aggravation	2
	No stress (rotation) on back	2		Easy task	2
	Accurately measures back pain pre/post exercise	1		Facilitation of exercise usually not performed because afraid of pain	1
	Inform physiotherapy	1		People with LBP could tolerate	1
	Change of pain tolerance	1		Younger people	1
	Feasibility of walking	1		Realistic amount of exercise	1
	Realising what stimulates back pain	1		Tailored programme	1
	Can stop if uncomfortable	1		Good for physical/mental health	1
Unsure n=4	Unsure	1	**Unsure n=3**	Running would be aggravating	1
	Tolerating pressure on lower back	1		Running slower and longer	1
	Testing over lower back uncomfortable	1		Lower intensity needed	1
	Gradual build up for severe pain	1			
No n=3	Struggle with testing position	1	**No n=3**	Walking speed difficult	1
	Moving between positions	1		Pain tolerance test difficult	1
	Struggle with intensity/ heart rate	1		Not willing to take part	1
	Pressure tolerance so low that it can't be measured	1		Pressure pain exacerbates symptoms	1
	Incline walking aggravated back pain	1			

Abbreviations: *CLBP= Chronic Low Back Pain, LBP= Low Back Pain*

5.5. Discussion

This is the first study examining whether EIH occurs over multiple sessions following a brisk walking task in asymptomatic participants and those with CLBP. This adds important

insights about the stability of baseline measures and absolute changes as an indicator for EIH. The individually adjusted brisk walking task elicited EIH in both groups. This is in line with previous studies in people with and without spinal pain (Wewege and Jones, 2021) (Chapter three). The stability of baseline measures was moderate to good, but stability of absolute changes was poor.

The CON group showed some adaptations to the walking task for perceived exertion across the sessions, which was not present in the CLBP group. It can be argued that the change from 13.07± 2.05 to 11.53± 1.13 is small, but research on the minimal detectable change (MDC) for the Borg Scale is scarce (Ries, 2005). However, the mean across sessions did not differ between groups (CON: 11.93± 1.04; CLBP= 11.63± 1.80). For all the other walking task parameters, there was no statistically significant difference between groups. Pain levels were low during the walking task, which has been discussed controversially in the literature for walking tasks (Taylor et al., 2003; Wittink et al., 2001).

5.5.1 Changes in Pressure Pain Thresholds

EIH was found over the lumbar region as well as the over remote areas for PPT and both groups responded the same. However, except for the lumbar PPT, changes were not present in most sessions when analysed for individual sessions (remote test sites 7/30). This is in line with results found previously (Chapter four). The test site over the tibialis anterior muscle is directly involved in the walking task. Although there was a statistically significant change across five sessions, individual sessions did not show a statistically significant pre-post change. In contrast, test sites over the upper trapezius and wrist extensors showed statistically significant within-session changes in seven out of twenty sessions across both

groups. These findings support the notion that aerobic tasks led to systemic changes (Lima et al., 2017; Rice et al., 2019).

Differences between lumbar test sites were found, even though all test sites showed statistically significant pre-post changes confirming the presence of EIH. As outlined in previous work (Chapter two), changes might be explained by anatomical location, as the most caudal test sites might be over ligament structures rather than the muscle, and the most cranial sites might be already in the area of floating ribs depending on the height of the participant (Bogduk, 2005). Different tissues and underlying structures/ tissue might explain the changes, as well as different activation of the trunk muscles during walking (Crawford et al., 2016). However, this did not affect the EIH response.

The systematic review (Chapter three) revealed two studies which examined aerobic tasks in participants with CLBP. However, the pressure pain test used by Hoffman and colleagues (2005) is not comparable to the PPT applied in this study. The other study showed changes after a cycle ergometer over the lumbar test sites (0.76 kg/cm3 ± 2.04 95% CI [-0.16; 1.69], reflecting percentage change 9.64%± 29.36 [-1.29; 20.58]), the deltoid (+9.05%± 25.83 [-2.71; 20.81]) and triceps surae (10.76%±29.36 [-2.61; 24.12]) but not over the test site over the thumb (Meeus et al., 2010) (Chapter three). These changes are comparable with findings in this study. After a walking task, similar changes were found regardless of the intensity of walking with PPT changes of 8 % over the biceps and 7 % over the quadriceps (Nguy et al., 2019).

Research from cycling protocols showed similar results. In 34 asymptomatic participants, 15 minutes of cycling (Borg scale intensity =16) led to an increase in PPT over the quadriceps by 51 kPa± 84, 95% CI [22; 80] in the first and in an identical second session

by 104 kPa± 117 [63;145], changes over the trapezius were 18 kPa± 54 [-1; 36] and 27 kPa± 96 [-6; -61] respectively (Vaegter et al., 2018). In a second study with 15 minutes based on their age-related heart rate (85.9 %) (Borg scale average 15), absolute change over the leg was 84.5 kPa± 86.15 in the first and 81.67 kPa± 103.77 in the second session, over the back 31.15 kPa± 77.22 and 93.52 kPa± 101.68 respectively (Gomolka et al., 2019). Changes over the back were not statistically significant in the first session, but in the second session; over the hand no statistical significance was found (Gomolka et al., 2019). It was shown in a third study that with further standardisation, based on lactate threshold determination, stability increased, but EIH was only found over the quadriceps (55 kPa± 70 95% CI [30; 79] and 80 kPa± 110 [41; 118]) but not the trapezius (10 kPa± 35 [-2; 22] and 15 kPa± 29 [5; 25]) (Vaegter et al., 2019a). However, this is in slight contrast to findings from this Chapter. Firstly, different test sites where used, and the tibialis anterior muscle and the quadriceps muscle differ in their function and activity between tasks. Secondly, should a dose intensity response exist, these tasks had a higher intensity than the brisk walking task used in the current study.

A study in asymptomatic participants, which used the six minute walk test, did not find PPT changes over the quadriceps or trapezius muscle when analysed in comparison to quiet rest (Hviid et al., 2019). A recently published study (Vaegter et al., 2021) used the six minute walk test in participants with CLBP. The results of that study showed no overall effect for PPT, but interestingly of 96 participants only 27 reported an increase of ≥2/10 (NRS) in pain and those differed statistically significantly from those with a smaller increase or decrease of pain and did not show EIH over both lower back and leg. No further analysis was conducted for pain levels in this study, as only two participants had a NRS of >2.2 across the five sessions. Moreover, a study comparing painful with non-painful aerobic exercise tasks

could not find a different response in asymptomatic participants (Ellingson et al., 2014). However, the study used repeated heat stimuli to rate pain intensity and unpleasantness.

5.5.2 Changes in Pressure Pain Tolerances

Both groups showed a statistically significant change in PPTOL across five sessions, supporting EIH. However, when considering individual sessions, the CLBP group showed statistically significant changes in four out of ten sessions, whereas the CON group only showed changes in one session. PPTOL over the lumbar region were also consistently lower than in the CON group despite the fact that no group difference occurred for absolute changes. Moreover, the safety limit was only reached in participants of the CON group. It should be considered that higher forces in application of the algometer have been shown to affect reliability of scores (Middlebrook et al., 2020). Alternatively, a cuff could be used; following a six-minute walk test PPTOL changed statistically significantly, but no change was revealed for PPT (Hviid et al., 2019). This was not tested in a similar study in participants with CLBP (Vaegter et al., 2021). Pain tolerance, shown as the duration of a constant applied stimulus, was prolonged after an aerobic step test (Gurevich et al., 1994), but this test stimulus, as well as a cuff pressure, is very different to the PPTOL as applied in this study.

5.5.3 Changes in Thermal Pain Thresholds

Sensitivity for thermal stimuli changed only for the HPT over the thenar eminence in both groups supporting the presence of EIH. However, the results must be interpreted cautiously. Due to safety limitations of the device, data sets were reduced to six for thenar

CPT and lumbar HPT and eight participants (lumbar HPT) for the CON group. The non-parametric analysis was therefore underpowered. Compared to Chapter four, more data sets had to be excluded due to safety limitations of the device. But in agreement with those results, data in the CLBP group, especially over the lumbar area, were lower than in the CON group, which could be an indicator for peripheral sensitisation (Hubscher et al., 2013; Roussel et al., 2013). However, there was no difference in absolute changes between the two groups.

A cycling task (five minutes, 60-70 rpm) in participants currently experiencing LBP (n=12) elicited no changes in TPT over the lumbar and cervical innervated region (Bialosky et al., 2009). Outcome measures were heat stimuli of three seconds over the forearm and calf which differed from the TPT testing in this study.

The findings in this Chapter agree with a study by Jones et al. (2019), which showed that PPT were more sensitive after cycling compared to heat pain stimulation. However, the study used brief laser stimuli (Jones et al., 2019), which is likely to be different to the thermal testing used in this study. Nevertheless, for heat pain sensation laser application would not be limited to the same extent as experienced with the safety restrictions of the device used in the current study.

5.5.4 Stability of Measures

Moderate to good ICC was found for baseline measures, which have been shown in various studies for QST in people with and without musculoskeletal pain as outlined in Chapter one (section 1.3.3). This further supports that QST can be used for baseline measures in a laboratory setting in a reliable way.

This is the first study to assess the stability of EIH following a brisk walking task over five consecutive sessions in participants with and without CLBP. In contrast to the baseline measures, the ICC was poor for all absolute changes. This was the same after a lumbar resistance task performed over six sessions (Chapter four). The SEM was higher than the change within each session except for remote PPT over the wrist extensors, tibialis anterior muscle, and the upper trapezius (CON group only). This could indicate a meaningful change, as this classification has been used previously to identify participants with a change greater than the SEM (Gomolka et al., 2019; Hviid et al., 2019; Vaegter et al., 2018).

Overall, the results in this study might be lower due to the higher number of sessions and the variability of responses. To date, the stability of EIH has been investigated in three studies with cycling protocols over two sessions each (Gomolka et al., 2019; Vaegter et al., 2019a; Vaegter et al., 2018). Firstly, after 15 minutes of cycling the ICC (3,1) was .45 95% CI [-0.1; 0.73]) with an SEM of 86 kPa over the quadriceps and .046 [-.01; 0.73] and a SEM of 65 kPa over the trapezius (Vaegter et al., 2018). The agreement for participants with a meaningful change of pre- and post-test indicating EIH over both test sites based on the SEM for each individual session was not statistically significant. In a second study, absolute change over the leg had an ICC (3,1) value of .540 ([0.224; -0.752]; SEM 65.23 kPa), and over the back of .400 ([0.032; 0.669]; SEM 64.54 kPa), and over the hand of .317 ([-0.023; 0.598]; SEM 30.14 kPa) (Gomolka et al., 2019). Based on the same criteria as in the above-mentioned study, agreement in participants with a meaningful change based on the SEM over the leg and the back was not statistically significant. It was shown in a third study that with further standardisation, based on lactate threshold determination, reliability increased over the quadriceps (ICC 3,1: .45 [0.1; 0.72] SEM Session two 43 kPa/ Session three 57 kPa) and the trapezius (.57 [0.1; 0.79], SEM 19 kPa/ 27 kPa) (Vaegter et al., 2019a). In this case agreement

between participants with a meaningful change was statistically significant, but still 25% of participants showed a different response across the two sessions. The only study examining stability after a 6-minute walk test showed poor reliability for PPT but fair to good (ICC 3,1 .60 and .61) for computer controlled cuff algometry (Hviid et al., 2019). Moreover, this study did not show a statistically significant agreement of participants with or without a meaningful change. Using computer-controlled cuff pressure would also avoid inaccuracy due to manual handling as it would avoid applying high manual pressure. Furthermore, participants' involuntary activation of muscles within the tested area would not affect the measurement. This could be considered as a more appropriate measure for mechanical pain tolerance. The poor stability of the measures has an impact on the concept of EIH, as this has been used for example to predict outcomes similar to CPM (Fingleton et al., 2017).

5.5.5 Qualitative Analysis of Participants' Perceptions

Considering the limitations of this qualitative study as outlined in Chapter four (section 4.5.5) the evaluation can inform future study designs. Participants stated an overall positive experience (codes such as enjoyable, interesting, and good) of taking part in the study. Challenges were highlighted regarding the testing i.e., around the pain associated with testing and some modalities such as the pain withdrawal reflex and pain tolerance. Although reproduction of pain is an essential feature of pain sensitivity testing, the participants' perceptions of the amount of testing and different modalities should be considered when shaping future protocols. For the exercise task the walking speed and incline could be considered as highlighted by some participants (CLBP n=2, CON n=1). An increased incline and higher walking speed could trigger the lumbar erector spinae muscles more than a flat

brisk walking protocol (Lee et al., 2014). To avoid this impact but allow for a sufficient exercise intensity, stationary cycling protocols are a feasible alternative, despite being less functional and not as feasible to integrate into daily activities. Overall, more concerns about the QST testing in a back pain population were raised, which could be due to the nature of a less provocative task in contrast to findings from Chapter four. Within the limitations of the pragmatic content analysis, the limited possible extrapolation of these findings to a population with more severe pain/ higher levels of disability can only inform qualitative components embedded in future feasibility studies as well as contribute to the development of protocols to assess and elicit EIH. The preliminary insights support that qualitative studies are needed in this area.

5.5.6 Strengths and Limitations

This is the first study to assess EIH over more than two sessions in participants with and without CLBP after an aerobic walking task. A standardised QST battery was applied in each session. Moreover, the walking task was individualised but also standardised to meet different performance levels.

However, this study faces some limitations. First, it can be argued that the walking task itself might have been not strenuous enough to produce EIH. However, considering the transferability to the management of CLBP it was deliberately chosen over, for example, a running task used in asymptomatic people (Hoffman et al., 2004). Considering feasibility, a walking task could also be implemented in daily life outside laboratory settings as no equipment would be required. EIH was found over the lumbar area in every session, and the extent was comparable to some cycling protocols (Chapter three). Some research favours

resistance and coordination protocols and does not endorse aerobic and combined programs for the management of CLBP (Searle et al., 2015). But other research shows that aerobic interventions decrease pain and increase function in people with CLBP (Meng and Yue, 2015; Vanti et al., 2019). A further limitation of this study is that the CLBP group had minimal to moderate disability levels and thus does not represent a population within secondary care. This could further explain why there was no difference between groups in this study.

Standardisation of this study did not extend to some between-sessions factors such as caffeine intake, time of day, exercise outside the study, and rest between sessions was not considered. Additionally, group size was based on calculations from Chapter four and the primary outcome of lumbar PPT, so secondary outcome measures might be underpowered in addition to less sensitive non-parametric analysis. Lastly, in the absence of a non-exercising asymptomatic control group, findings could have occurred from testing itself rather than the task. However, no change in QST after a rest period has been shown by others as outlined in Chapter one.

5.6 Conclusion

In response to a brisk walking task on a treadmill, EIH was found as demonstrated by a change in lumbar PPT regardless of group, session, or test site. In addition, remote PPT, HPT over the thenar eminence, and PPTOL increased across the five sessions. However, the results for individual sessions were less consistent in both participants with and without CLBP. Baseline measures showed good stability indicating the potential benefit of these pain sensitivity measures in clinical research. However, absolute changes showed poor stability

and therefore, further research should elucidate the underlying mechanisms of EIH and its role in pain modulation for future research.

Chapter Six

Analysis of the Protocol in Asymptomatic People

6.1 Abstract

Chapters four and five showed exercise-induced hypoalgesia (EIH) after a lumbar resistance and a brisk walking task in participants with and without chronic low back pain (CLBP). However, the findings were inconsistent for secondary outcome measures. Furthermore, it was observed that pain sensitivity decreased across sessions. This Chapter reflects thesis objective five and aims to analyse the test protocol in asymptomatic participants. To explore if these changes were due to the exercise tasks and not attributed to other factors associated with multiple testing, the same test battery was applied. In this pragmatic observational study, instead of performing an exercise task, the participants rested for 20-30 minutes for all six sessions.

The findings showed a statistically significant change of lumbar pressure pain thresholds (PPT), but no change for most of the other outcome measures. The decreased pain sensitivity over the lumbar region raises the question if the changes observed in Chapters four and five can be attributed to the exercise task. In absence of a physical task, no increase in pain thresholds was observed across the six sessions. This highlights that the increase across the six sessions observed in Chapters four and five is likely caused by the exercise task. Stability of baseline measures was moderate to good, but stability of the absolute difference of pre- to post-test was poor. This emphasises that the test protocol with the quantitative sensory testing battery should be further tested before applying it to assess EIH especially when repeated PPT are applied.

6.2 Introduction

Chapters four and five investigated whether EIH exists in participants with and without CLBP, however, the consistent but small increase of lumbar PPT measures across sessions prompted the need to investigate whether this phenomenon was indeed real or alternatively, was related to repeated testing. Therefore, a sample of asymptomatic non-exercising participants was recruited with the aim to observe if a similar change occurred in the absence of an exercise task. Most changes found after the lumbar resistance or brisk walking task in Chapters four and five were below the SEM, hence further testing was planned even though a substantial amount of studies have shown no effect on pain sensitivity after a resting period using different QST protocols (Ellingson et al., 2014; Mailloux et al., 2021a; Naugle et al., 2012; Smith et al., 2017a; Smith et al., 2020; Vaegter et al., 2016). An increase in pain thresholds which was found across the sessions in the groups who did perform an exercise task, could also be caused by adaptation to the testing procedure instead of the exercise task.

6.2.1 Chapter Objectives

To analyse the test protocol over multiple session in non-exercising asymptomatic participants. Furthermore, stability of baseline measurements and absolute changes were evaluated in line with the previous Chapters.

6.3 Methods

6.3.1 Design and Participants

As with the two previous Chapters four and five (section 4.3.1/ 5.3.1), a pragmatic observational study with repeated measures was chosen. However, participants did not perform an exercise task in between pre- and post-testing.

All participants were asymptomatic based on the same inclusion criteria and the same recruitment pathway for asymptomatic participants as outlined in Chapters four and five (section 4.3.2/ 5.3.2) was followed. All participants were aware that they would take part as a non-exercising participant. As within previous Chapters, characteristics regarding general health (SF-36) and physical activity (IPAQ) and demographics were collected.

6.3.2 Sessions

The six sessions were the same except for the introduction and familiarisation in the first session as well as task related questionnaires. Participants rested for 20-30 minutes between pre and post-tests without performing any exercise in contrast to the tasks outlined in Chapters four and five (section 4.3.3/ 5.3.3).

6.3.3 Quantitative Sensory Testing

The same standardised QST battery was applied as outlined in detail in Chapter four (section 4.3.6). Briefly summarised, it comprised of PPT over eight test sites across the

lumbar region and three remote test sites, TPT over the back and hand, PPTOL over the wrist extensors and the lumbar region, TS over the forearm and lumbar region, and the nociceptive withdrawal reflex. The latter two modalities are presented in Appendix 18.

6.3.4 Statistical Analysis

Descriptive data were presented for the participants demographics and characteristics. Data analysis was conducted with a three-way RM-ANOVA for lumbar PPT considering factors for time, location, and session. Non-parametric Friedman ANOVA was applied for all other outcome measurements considering both changes across six sessions and within individual sessions. All figures show mean and SD to facilitate comparability. For stability ICC (3,1) was applied for baseline measures and absolute changes. As within previous Chapters, ICC values were considered as poor with an ICC score < 0.5, moderate < 0.75, good < 0.9, and excellent > 0.9 (Koo and Li, 2016). It was decided to test only ten participants as less variation was expected due to the lack of the exercise task.

6.4 Results

6.4.1 Participants Characteristics

Baseline characteristics of the ten included participants are presented in Table 6.1. These were comparable to the asymptomatic groups of Chapter four (Age: 23± 4; BMI: 24±2; 47% men; IPAQ 73%moderate) and Chapter five (Age 26±5; BMI 23±2; 47% men; 60%

moderate IPAQ). No dropouts occurred. There was a median of three [IQR 2; 3] days of rest between sessions.

Table 6.1 Characteristics of asymptomatic participants

		Mean± SD
Participants		n=10
Age		25.20± 3.97
BMI		25.79± 4.07
Gender		5 women; 5 men
SF-36 average score	Physical functioning	98.00± 4.83
	Pain	95.00± 5.27
	General Health	86.50± 10.55
IPAQ		5 high, 4 moderate, 1 low
IPAQ MET		3815.50± 2849.42

Abbreviations: *BMI=Body Mass Index; SF-36= SF-36 v2 Health Survey; IPAQ=International Physical Activity Questionnaire, MET= Metabolic Equivalent of Task*

6.4.2 Protocol

6.4.2.1 Lumbar Pressure Pain Thresholds

A RM-ANOVA revealed a statistically significant effect for time (Wilks=0.34, F=17.64, p= .002), which was confirmed in the post hoc test (p= .002) with an average of +35.46 kPa 95% CI [16.36; 54.55] across the six sessions (Figure 6.1). No effect was found for session or location, and no interactions were present.

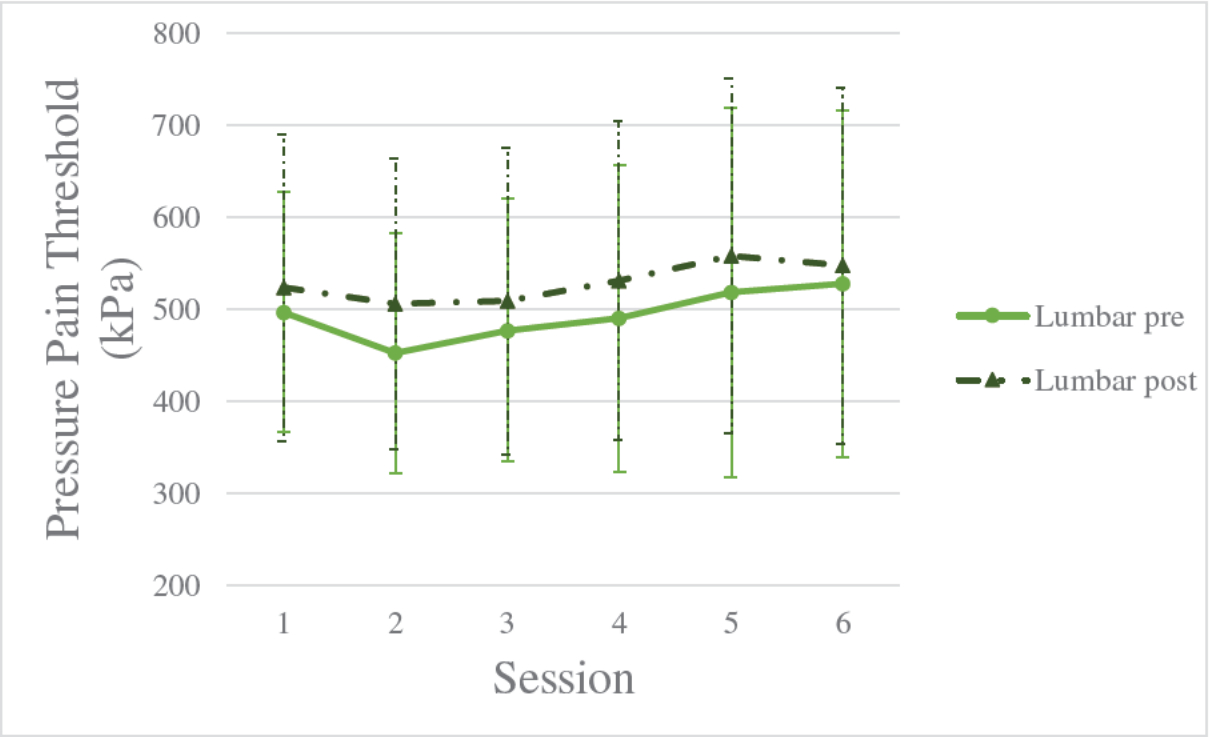


Figure 6.1 Pressure Pain Thresholds across the eight Lumbar Test Sites (Mean/SD)

6.4.2.2 Remote Pressure Pain Thresholds

Non-parametric Friedman ANOVA revealed no increase in PPT over the trapezius (p= .439), the wrist extensors (p= .302), or the tibialis anterior (p= .051) across six sessions. For individual sessions, only in the final session a statistically significant increase in PPT over the tibialis anterior was found (p= .011). For one participant the test side over the tibialis anterior muscle was on the left instead of the right due to a sensory deficit from an old injury.

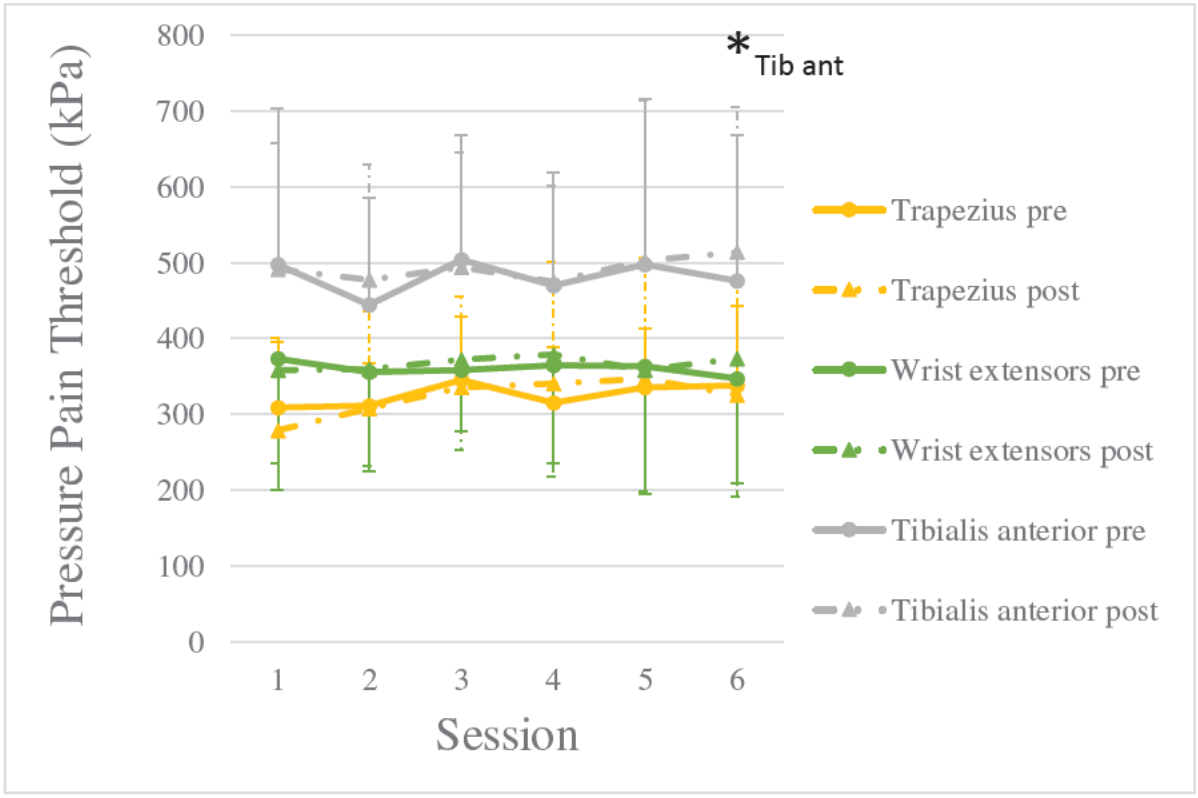


Figure 6.2 Remote Pressure Pain Thresholds (Mean/SD)

Significant within-session changes are marked with an *

6.4.2.3 Pressure Pain Tolerances

Data were not normally distributed, and Friedman ANOVA was applied for data of all ten participants over both test sites. No participant reached the safety limitation of the device (2000 kPa). Neither lumbar nor PPTOL over the wrist extensors changed across the six sessions, or within individual sessions (Figure 6.3).

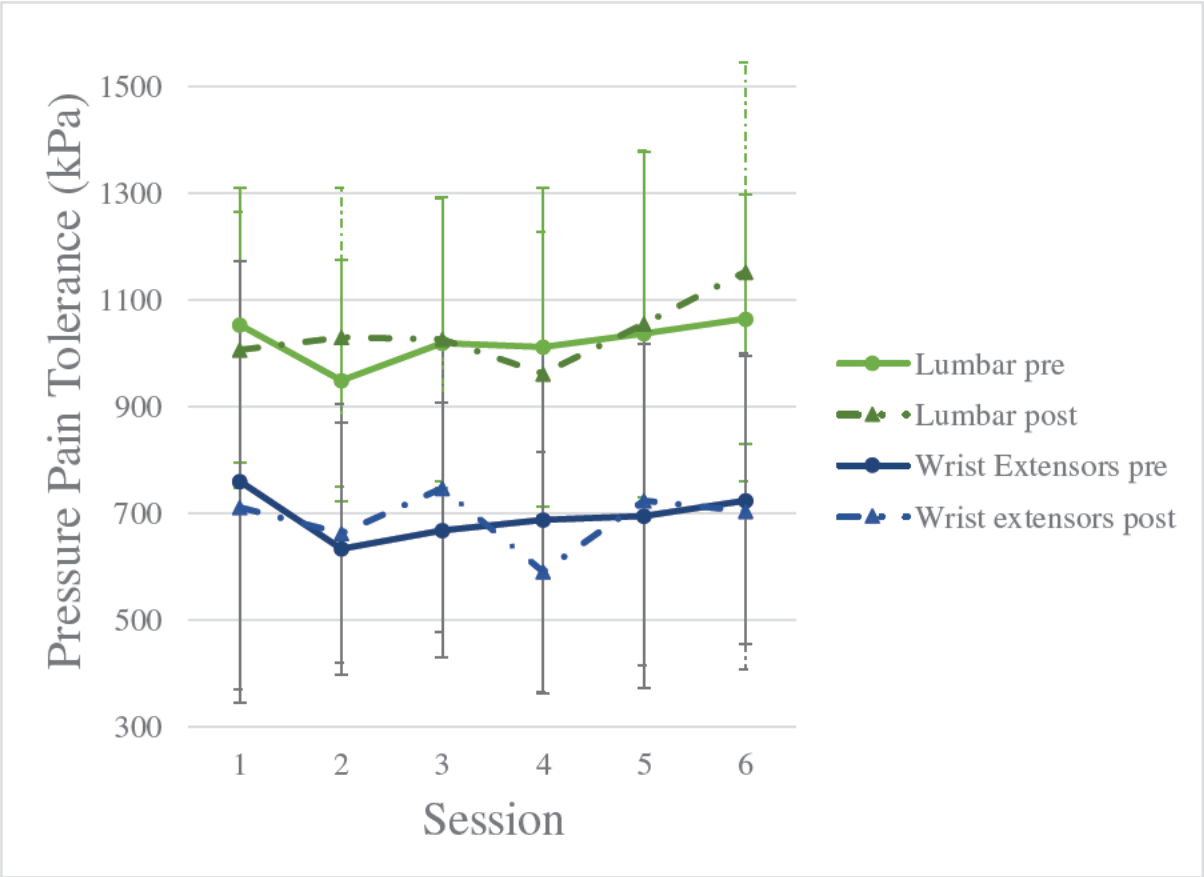


Figure 6.3 Pressure Pain Tolerances (Mean/SD)

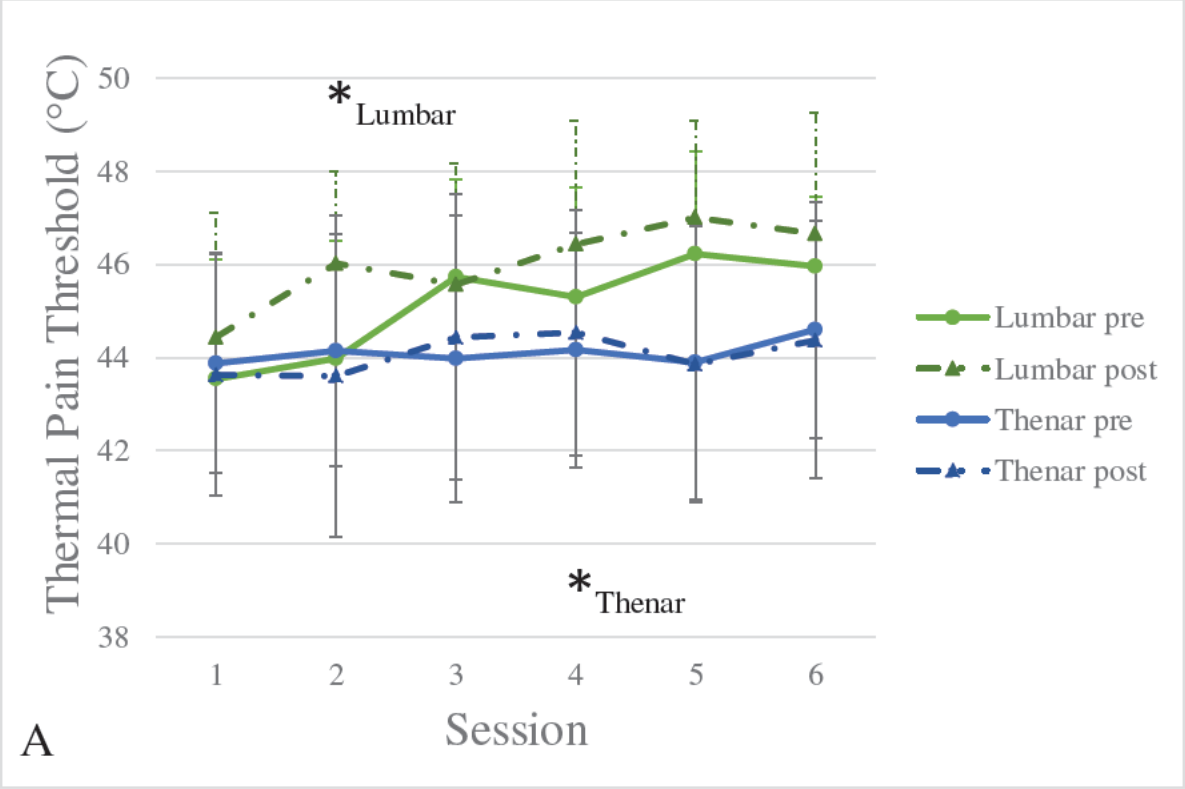
6.4.2.4 Thermal Pain Thresholds

For all TPT non-parametric tests were applied. Only participants with full data sets are displayed in Figure 6.4, due to safety limitations of the device threshold were not reached in many participants.

For lumbar HPT there was a statistically significant increase across the six sessions based on eight participants (p= .009). This was confirmed only for session two (p= .034). Eight participants were considered for HPT over the thenar eminence, and no change occurred

across the six sessions, but the fourth session showed a statistically significant increase from pre- to post-test (p= .034). For one participant the test site over the thenar was on the left instead of the right due to a minor skin injury.

Based on the data from five participants only, there was a statistically significant increase of CPT (p= .028) representing hyperalgesic changes, which was confirmed for session two (p= .025).



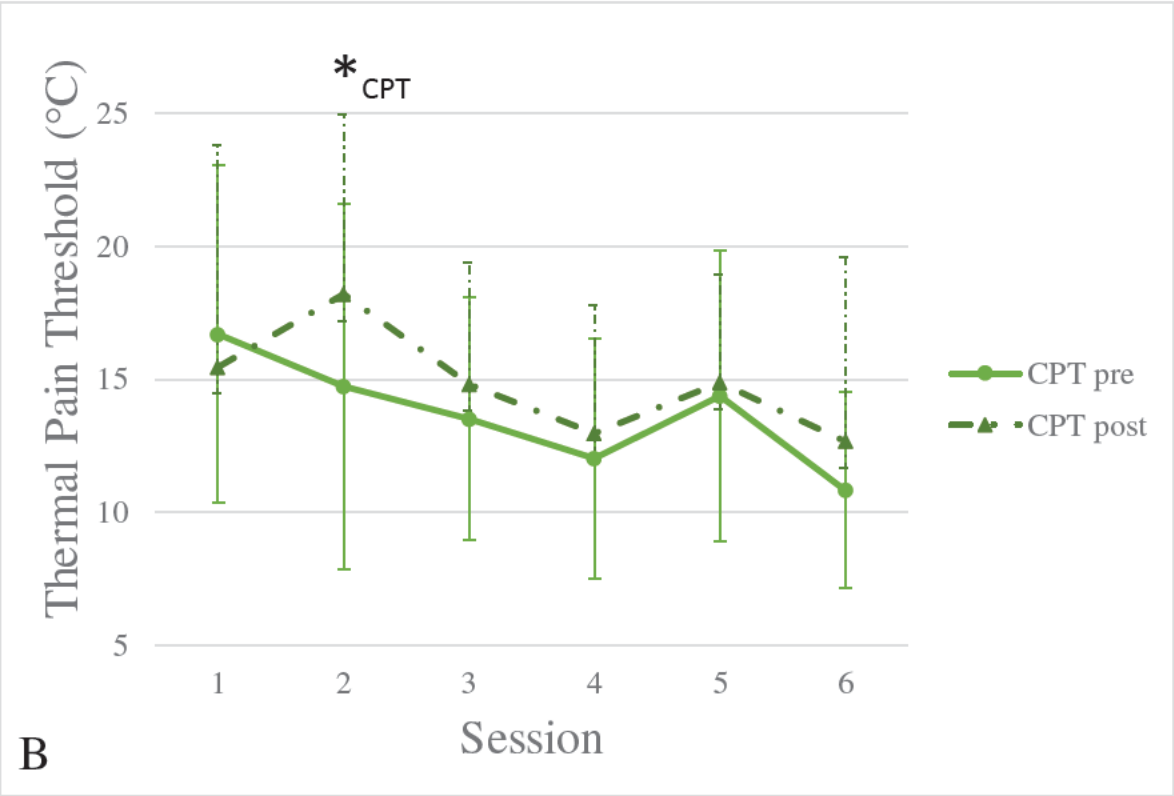


Figure 6.4 A-B Thermal Pain Thresholds (Mean/SD)

(A) Heat pain thresholds over the lumbar area and the thenar eminence (B) Cold Pain Thresholds (CPT) over the thenar eminence. Significant within-session changes are marked with an *

6.4.3 Stability

6.4.3.1 Baseline Measures

6.4.3.1.1 Lumbar Pressure Pain Thresholds

The ICC was moderate (ICC= .741) with a SEM of 76.58 kPa (Table 6.2).

Table 6.2 Stability of the baseline measures of lumbar Pressure Pain Thresholds

	PPT for each session in kPa (Mean± SD)							**ICC 3,1**	**LB**	**UB**	**SEM**
	1	**2**	**3**	**4**	**5**	**6**	**Mean**				
Lumbar PPT	496.77 ± 121.84	452.23 ± 123.43	476.97 ± 138.63	490.06 ± 155.11	518.31 ± 193.51	527.71 ± 182.79	493.67 ± 150.47	.741	.521	.912	76.58

Abbreviations: *PPT=Pressure Pain Thresholds; ICC= Intraclass Correlation Coefficient; LB= Lower Bound; UB= Upper Bound; SEM= Standard Error of Measurement*

6.4.3.1.2 Remote Pressure Pain Thresholds

ICC was moderate for test sites over the trapezius and wrist extensors, and good over the tibialis anterior (Table 6.3).

Table 6.3 Stability of the baseline measures of remote Pressure Pain Thresholds

	PPT for each session in kPa (Mean± SD)							**ICC 3,1**	**LB**	**UB**	**SEM**
	1	**2**	**3**	**4**	**5**	**6**	**Mean**				
Trapezius	309.00 ± 86.60	310.80 ± 90.60	345.35 ± 94.60	315.30 ± 98.60	335.95 ± 102.60	338.30 ± 106.60	325.78 ± 79.53	.597	.340	.848	50.49
Wrist extensors	373.35 ± 173.06	355.50 ± 130.85	358.90 ± 80.47	365.30 ± 130.26	363.85 ± 169.74	347.35 ± 138.39	360.71 ± 134.69	.684	.445	.889	75.71
Tibialis anterior	497.50 ± 205.92	444.35 ± 142.08	504.10 ± 164.92	470.25 ± 148.54	497.25 ± 218.06	476.80 ± 192.22	481.71 ± 174.31	.764	.555	.921	84.68

Abbreviations: *PPT=Pressure Pain Threshold; ICC= Intraclass Correlation Coefficient; LB= Lower Bound; UB= Upper Bound; SEM= Standard Error of Measurement*

6.4.3.1.3 Pressure Pain Tolerances

Full data sets were obtained for both test sites with moderate ICC (Lumbar: ICC= .686; Wrist extensors: ICC=.674) and a SEM of 148.71 kPa and 169.67 kPa (Table 6.4).

Table 6.4 Stability of the baseline measures of Pressure Pain Tolerances

	PPTOL for each session in kPa (Mean± SD)							**ICC 3,1**	**LB**	**UB**	**SEM**
	1	**2**	**3**	**4**	**5**	**6**	**Mean**				
Lumbar	1053.10 ± 258.66	949.40 ± 226.23	1020.20± 273.28	1011.50± 299.6	1038.10± 339.15	1065.20 ± 233.94	1022.92± 265.38	.686	.447	.889	148.71
Wrist extensors	760.30 ± 413.96	633.80 ± 236.62	668.70 ± 238.95	688.70 ± 326.19	695.50 ± 323.31	724.70 ± 269.85	695.28 ± 297.16	.674	.432	.884	169.67

Abbreviations: *PPTOL= Pressure Pain Tolerance; ICC= Intraclass Correlation Coefficient; LB= Lower Bound; UB= Upper Bound; SEM= Standard Error of Measurement*

6.4.3.1.4 Thermal Pain Thresholds

For TPT baseline measures, data was reduced due to the safety limitations of the device. However, the ICC was moderate for all outcomes (Table 6.5).

Table 6.5 Stability of the baseline measures of Thermal Pain Thresholds

	n	**TPT for each session in °C** (mean± SD)							**ICC 3,1**	**LB**	**UB**	**SEM**
		1	**2**	**3**	**4**	**5**	**6**	**Mean**				
Lumbar heat pain threshold	8	43.53 ± 2.53	43.97 ± 2.32	45.72 ± 1.88	45.30 ± 2.07	46.22 ± 2.34	45.96 ± 1.49	45.12 ± 2.26	.639	.358	.892	1.36
Thenar heat pain threshold	8	43.87 ± 2.26	44.15 ± 1.77	43.97 ± 2.40	44.16 ± 2.02	43.90 ± 2.60	44.60 ± 2.32	44.11 ± 2.14	.612	.326	.881	1.33
Thenar cold pain threshold	5	16.69 ± 6.93	14.73 ± 6.89	13.50 ± 4.86	12.03 ± 4.54	14.37 ± 6.09	10.82 ± 3.08	13.69 ± 5.43	.515	.155	.912	3.78

Abbreviations*: TPT= Thermal Pain Threshold; ICC= Intraclass Correlation Coefficient; LB= Lower Bound; UB= Upper Bound; SEM= Standard Error of Measurement*

6.4.3.2 Stability of Absolute Changes

6.4.3.2.1 Lumbar Pressure Pain Thresholds

Stability of the absolute change in PPT pooled across the eight test sites over the lumbar region was poor (Table 6.6).

Table 6.6 Stability of the absolute changes of lumbar Pressure Pain Thresholds

	Absolute Change of lumbar PPT in kPa (mean± SD)							**ICC 3,1**	**LB**	**UB**	**SEM**
	1	**2**	**3**	**4**	**5**	**6**	**Mean**				
Lumbar PPT	26.59± 72.46	53.60± 59.55	32.38± 45.26	41.12± 29.81	39.58± 23.04	19.47± 26.20	63.44± 72.38	-.041	-.129	.216	73.84

Abbreviations: *PPT= Pressure Pain Threshold; ICC= Intraclass Correlation Coefficient; LB= Lower Bound; UB= Upper Bound; SEM= Standard Error of Measurement*

6.4.3.2.2 Remote Pressure Pain Thresholds

Stability of the absolute changes over remote PPT sites was poor (ICC ≤ .145) (Table 6.7).

Table 6.7 Stability of the absolute changes of remote Pressure Pain Thresholds

	Absolute Change of lumbar PPT in kPa (mean± SD)							**ICC 3,1**	**LB**	**UB**	**SEM**
	1	**2**	**3**	**4**	**5**	**6**	**Mean**				
Trapezius	-30.25 ± 46.30	-2.55 ±37.79	-9.55 ±49.02	25.05 ±45.62	11.00 ±51.17	-12.35 ±53.51	-3.11 ±48.78	-.082	-.148	.130	50.74
Wrist extensors	-14.65 ± 108.28	4.10 ±46.05	13.05 ±68.61	13.65 ±41.53	-5.40 ±64.89	25.95 ±64.32	6.12± 67.43	.145	-.028	.502	62.35
Tibialis anterior	-6.05 ± 101.11	33.75 ±42.74	-10.30 ±78.41	4.70 ±67.63	5.40 ±88.66	37.05 ±29.09	10.76± 71.71	.102	-.053	.448	67.96

Abbreviations: *PPT= Pressure Pain Threshold; ICC= Intraclass Correlation Coefficient; LB= Lower Bound; UB= Upper Bound; SEM= Standard Error of Measurement*

6.4.3.2.3 Pressure Pain Tolerances

Absolute changes for PPTOL are presented in Table 6.8. The ICC was poor.

Table 6.8 Stability of the absolute changes of Pressure Pain Tolerances

	Absolute Change of PPTOL in kPa (mean± SD)							**ICC 3,1**	**LB**	**UB**	**SEM**
	1	**2**	**3**	**4**	**5**	**6**	**Mean**				
Lumbar	-45.50 ± 116.15	80.60 ± 184.54	5.80 ± 103.40	-49.10 ± 114.70	18.20 ± 161.03	87.90 ± 182.54	16.32 ± 151.29	.130	-.037	.484	141.12
Wrist extensors	-49.10 ± 174.64	28.70 ± 66.91	78.90 ± 84.89	-97.70 ± 224.74	28.60 ± 123.51	-20.00 ± 116.17	-5.10 ± 148.08	.003	-.107	.298	147.85

***Abbreviations**: PPTOL= Pressure Pain Tolerance; ICC= Intraclass Correlation Coefficient; LB= Lower Bound; UB= Upper Bound; SEM= Standard Error of Measurement*

6.4.3.2.4 Thermal Pain Thresholds

Due to safety limitations of the device, data sets were reduced to eight and five participants, and thus should be interpreted cautiously. The ICC was poor (Table 6.9).

Table 6.9 Stability of the absolute changes of Thermal Pain Thresholds

	n	**Absolute Change of TPT in °C** (mean± SD)							**ICC 3,1**	**LB**	**UB**	**SEM**
		1	**2**	**3**	**4**	**5**	**6**	**Mean**				
Lumbar heat pain threshold	8	0.90 ± 1.35	2.04 ± 1.91	-0.17 ± 1.85	1.13 ± 2.08	0.78 ± 1.64	0.70 ± 1.91	0.90 ± 1.83	-.087	-.155	.173	1.91
Thenar heat pain threshold	8	-0.24 ± 1.47	0.55 ± 2.05	0.46 ± 1.03	0.38 ± 0.89	-0.05 ± 1.51	-0.23 ± 2.16	0.14 ± 1.54	.108	-.063	.520	1.45
Thenar cold pain threshold	5	-1.24 ± 5.06	-3.47 ± 3.38	1.31 ± 3.33	0.94 ± 1.35	0.49 ± 2.27	1.84 ± 5.34	-0.02 ± 3.87	-.015	-.141	.532	3.90

***Abbreviations:** TPT= Thermal Pain Threshold; ICC= Intraclass Correlation Coefficient; LB= Lower Bound; UB= Upper Bound; SEM= Standard Error of Measurement*

6.5 Discussion

The results of this pragmatic observational study add to the evaluation of the findings presented in Chapters four and five and provide further insight into the stability of the data. An increase of lumbar PPT was found despite the lack of an exercise task. However, pain sensitivity did not decrease across the sessions. The stability of results was poor, which was consistent with findings of Chapters four and five.

6.5.1 Protocol

6.5.1.1 Mechanical Stimuli

An increase of PPT over the lumbar region (+35.46 kPa 95% CI [16.36; 54.55]) was found after the task. These changes were similar to the changes in Chapter four (CLBP: +42.30 kPa [7.20; 77.40], CON: +63.44 kPa [28.33; 98.54]) and Chapter five (CLBP: +35.39 kPa [5.58; 65.21], CON: +39.03 kPa [9.21; 68.84]; five sessions). In both Chapters no differences between participants with and without CLBP were found for the EIH response. This is in contrast to findings from Chapter two, which did not show an increase in the CLBP group.

Other studies assessing topographical maps for QST, i.e., PPT, did not report within-session sensitisation and an increase from repetitive testing across one region for baseline measures or EIH response (Balaguier et al., 2016a; Falla et al., 2014; O'Neill et al., 2019), as in agreement with findings from Chapter two. Therefore, findings in this Chapter challenge that changes observed in the previous chapters were really caused by the exercise task.

Potentially this was simply due to repeated measurements and the amount of test sites across the lumbar region.

In this Chapter, no changes were found over remote test sites indicating that the change present in previous Chapters was likely due to the exercise tasks. Although changes were not present for most individual sessions, across the five/ six sessions the brisk walking or lumbar resistance task led to a significant increase in remote PPT.

In contrast to previous Chapters, no increase was found across sessions, indicating that the exercise task was likely the reason for increased PPT across multiple sessions due to the repeated task. This is in line with current level one evidence (Belavy et al., 2021; Polaski et al., 2019). However, this study was of a shorter duration and tested within-session changes, whereas both systematic reviews assessed changes in pain sensitivity after exercise programmes over multiple weeks. However, the clinical relevance of increased PPT following exercise requires further research.

For PPTOL no within-session or change across sessions was found in this study. This reinforces that the findings from previous Chapters on PPTOL were caused by the lumbar resistance or brisk walking task.

6.5.1.2 Thermal Stimuli

Lumbar HPT showed a statistically significant increase between pre- and post-measurements indicating a hypoalgesic response after the rest. However, this could also have been caused by the TS test site over the back; this is in line with the group performing the resistance task (Chapter four), but not the walking task (Chapter five). The test site over the

back was the same for both procedures. The exposure from TS could be the cause why thresholds increased. No changes were found for thenar HPT, which was not exposed to TS. CPT showed a hyperalgesic change, as this was based on only five participants, it should be interpreted cautiously.

6.5.2 Stability

Baseline measurements were similar to the findings from the previous two Chapters, indicating that the test battery was a reliable approach across the six sessions over three weeks. However, the same issue arose with data sets being excluded due to safety limitations for thermal outcomes, but complete data sets could be obtained for PPTOL. Although no absolute changes were expected, the ICC values for absolute changes were poor for all outcome measurements. Nevertheless, this could be because overall changes were small, and responses varied between positive and negative responses. A statistically significant effect for time was found for lumbar PPT, which could further affect stability.

6.5.3 Strengths and Limitations

This study followed the same highly standardised QST battery and is therefore unique to be tested across six sessions over three weeks. This informs the evaluation of the EIH effects, i.e., if effects were potentially caused by testing, as well as stability of baseline measures. However, as in Chapters four and five, standardisation of participants' daily activities between sessions was not further controlled. Furthermore, participants were able to

choose the resting time for any nonphysical tasks such as studying. Moreover, it should be noted that this study had a small sample size, which should be considered when interpretating these findings.

6.6 Conclusion

This study adds to the evaluation of the findings of EIH reported in Chapters four and five. The protocol used in previous Chapters did not lead to changes for most outcome measurements but PPT over the lumbar region increased for each session. This challenges the idea of whether the changes reported in previous Chapters are really representing EIH. Nevertheless, the increase across sessions was likely caused by the exercise tasks, as no changes were found in this Chapter in asymptomatic participants, who did not perform an exercise task. The stability of baseline measures was moderate to good, but absolute effects were poor in agreement with findings from the two previous Chapters. Future research should aim to establish a robust testing protocol to be able to analyse changes of EIH in further depth as repeated testing might influence the assessment of EIH.

Chapter Seven

Discussion

7.1 Summary of Findings

The aim of this thesis was to explore whether EIH occurs in people with CLBP. There is minimal research on EIH in people with CLBP despite being one of the most common musculoskeletal disorders, with exercise advocated as the first line of management (Hartvigsen et al., 2018; NICE, 2020). Despite the recognisable body of evidence in EIH for asymptomatic people, no gold standard has been determined for outcome measurements and task characteristics (Rice et al., 2019; Vaegter and Jones, 2020). Findings from each Chapter will be presented (Figure 7.1).

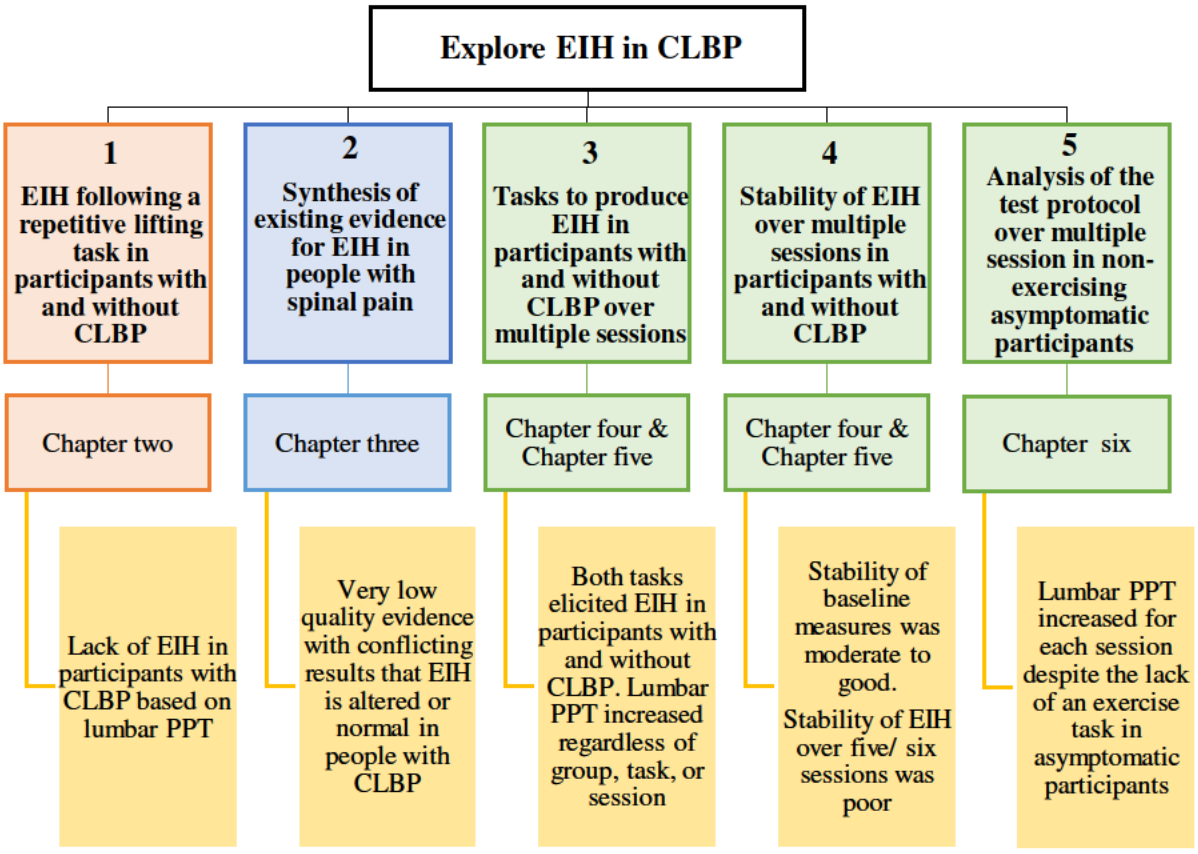


Figure 7.1 Aim of the Thesis and Objectives with key findings

EIH= Exercise-Induced Hypoalgesia; CLBP= Chronic Low Back Pain; PPT= Pressure Pain Thresholds

7.1.1 Chapter One - Introduction

The first Chapter introduced the phenomenon of EIH and provided an overview of CLBP and EPM. The Chapter concluded with the thesis aims seeking to further explore EIH in people with CLBP. Drawing on the MRC framework (see Chapter one, Figure 1.4), currently available evidence differed between asymptomatic people (phase I, early phase III) and people with CLBP (preclinical stage, early phase I). This then supported the need for further empirical evidence from observational studies and a synthesis of available evidence in people with spinal pain.

7.1.2 Chapter Two - Lack of Exercise-Induced Hypoalgesia to Repetitive Back Movement in People with and without Chronic Low Back Pain

This Chapter focused on a functional lifting task to elicit EIH in participants with and without CLBP. Drawing on findings from an earlier study (Falla et al., 2014), Chapter two provides the first evidence that EIH is impaired in participants with CLBP after a repeated lifting task especially when PPT over the lumbar region were considered. Based on 16 test sites an increase of +29.78 kPa ± 41.4 95% CI [-5.0; 64.5] was found following task completion in asymptomatic participants over local but not remote test sites. No statistically significant change was observed for the CLBP group over both test sites. However, in line with Falla et al. (2014) lumbar PPT decreased indicating potential hyperalgesia (-14.87 kPa ± 61.2 [-47.8; 18.1]). As EIH was present in asymptomatic people, it was concluded that impairment of EIH was evident in those with CLBP.

7.1.3 Chapter Three - Exercise-Induced Hypoalgesia in People with Spinal Pain: A Systematic Review and Data Synthesis

A systematic review of EIH, inclusive of all spinal regions, investigated: 1) local, regional, and remote tasks as well as different types of exercise tasks, 2) the spinal region of impairment, and 3) the location of test site in relation to the impaired body region. Seventeen studies were included (participants n=434 (73% female)). Considerable variation between the studies in terms of exercise tasks, outcome characteristics, and results were observed, therefore no meta-analysis was conducted. Key findings with the focus on CLBP were:

1. *Task region*: There was very low quality evidence for altered EIH after a local lifting task based on two studies including participants with CLBP (Falla et al., 2014; Kuithan et al., 2019). Furthermore, these were the only studies for local/lifting tasks, highlighting the demand for further research on tasks commonly used in rehabilitation. Low quality evidence for remote tasks was found with conflicting evidence to lead to normal or impaired EIH. Two of those eight studies included participants with CLBP, which both demonstrated normal EIH following a cycling task (Hoffman et al., 2005; Meeus et al., 2010).

Task type: There was low quality evidence for aerobic (conflicting results with either normal, altered, or no EIH) and isometric (impaired EIH) tasks. Only two studies included CLBP as outlined above for the remote/ cycling as well as local tasks.

2. *Spinal region:* Very low quality evidence was found for people with CLBP based on four studies with conflicting evidence as outlined above. Two studies showed altered EIH as response to a local/ lifting task, whereas two studies with an aerobic task showed normal EIH. Furthermore, comparisons from other spinal pain conditions were restricted. For WAD there was low quality evidence for impaired EIH and very low quality evidence with conflicting

results for CNP with either altered or no EIH. One study included mixed pathologies and revealed that EIH was impaired in participants with lower baseline PPT (Vaegter et al., 2016).

3. *Test site*: There was very low quality evidence that the test site does not affect EIH. However, two studies including participants with CLBP assessed both local and remote test sites (Kuithan et al., 2019; Meeus et al., 2010). A potential difference was indicated, as one study found EIH only over the local test site (Chapter two), whereas the other study found EIH over local but not over all remote test sites (Meeus et al., 2010).

There is a need for further studies firstly, in people with CLBP and secondly, for local tasks. Cumulative evidence was impacted by (serious) concerns across all GRADE domains. Following reporting guidelines and an appropriate sample size could improve quality. This prompted the conduction of the next observational study assessing different tasks in people with and without CLBP.

7.1.4 Chapters Four and Five - Exercise-Induced Hypoalgesia and its Stability in People with and without Chronic Low Back Pain

Chapters four and five explored EIH following a lumbar resistance or brisk walking task in participants with and without CLBP (thesis objective three). The study was the first to assess the stability of EIH over multiple sessions (thesis objective four).

7.1.4.1 Exercise-Induced Hypoalgesia

For both lumbar resistance and brisk walking tasks PPT confirmed EIH, regardless of session or group. Following the resistance task lumbar PPT increased across six sessions by

+42.30 kPa 95% CI [7.2; 77.4] in the CLBP group and by +63.44 kPa [28.3; 98.5]) for the asymptomatic group. Equally, lumbar PPT changed after the walking task across five sessions by +35.39 kPa [5.6; 65.2] and +39.03 kPa [9.2; 68.8] respectively. Findings of secondary outcome measures (remote PPT, PPTOL, and TPT) were less consistent; changes were statistically significant across five/six sessions, but not within individual sessions. Overall, changes were invariably small, often within the SEM.

In contrast to Chapter two despite testing a comparable population, there was no difference in EIH between people with and without CLBP. Regardless of whether the task was pain provocative, i.e., lumbar resistance task, both tasks elicited EIH.

A decrease in baseline sensitivity over the duration of the study was found. Both Chapters confirmed that lumbar PPT increased over the six sessions.

7.1.4.2 Stability of Measures

The fourth thesis objective was to assess the stability of EIH. Baseline measure of all outcome measurements showed moderate to good ICC values (3,1) indicating appropriate stability across sessions (Chapters four to six). However, the response to the task, indicative of EIH, revealed poor ICC (3,1) values across all outcome measurements regardless of group or task. The poor stability raises concerns about the interpretation of EIH and should be considered in future studies.

7.1.4.3 Qualitative Evaluation of Participants' Perceptions

Evaluation of the participants' perceptions of both exercise task groups provided some valuable data, which can be used to inform future studies, specifically around the duration or intensity of the exercise tasks. Some participants felt sensitised from the repeated testing, explicitly PPTOL and the pain withdrawal reflex were not tolerated well. Future research should be conducted to determine a valid test protocol integrating findings from this study. Overall, most participants stated that the study programme including both lumbar resistance and brisk walking exercise tasks would be feasible for people with/more severe CLBP. Considering the limited possible extrapolation these findings are preliminary and not representative for the general back pain population. Analysis of the current version of the questionnaire does not allow for further breadth or depth of data. This restricted compilation of data, and no realistic conclusions could be drawn. However, it informs future qualitative protocols developing a more rigorous way of data collection. Considering the patient experience as well as the overall findings of Chapters four and five, it was decided to analyse the test protocol (Chapter six).

7.1.5 Chapter Six - Analysis of the Protocol in Asymptomatic People

Chapter six was conducted to analyse the test protocol applied in Chapters four and five. The same protocol to assess EIH was tested in ten asymptomatic participants, who rested for a similar duration instead of performing a task. A statistically significant increase in PPT over the lumbar region (+35.46 kPa 95% CI [16.36; 54.55]) was found across six sessions, similar to the findings of participants who performed a task (see above). No statistically

significant changes were found for most of the secondary outcome measures. Stability of the measures of the baseline protocol was similar with moderate to good stability, but poor for absolute changes. No increase across sessions was found for lumbar PPT in absence of an exercise task. This implies that changes across sessions were a result of the exercise task.

7.2 Exercise-Induced Hypoalgesia in People with Chronic Low Back Pain

Overall, findings of this thesis revealed equivocal results for EIH in people with CLBP. The first exploratory study (Chapter two) contributed to the systematic review (Chapter three). Very low quality evidence with conflicting results was found, using the terminology outlined in Chapter three, EIH might be altered after a local lifting task but not after an aerobic task. Therefore, another pragmatic observational study was conducted (Chapters four to six), with good ROB based on the modified NOS applied in Chapter three (section 3.3.8). However, due to randomisation of participants, the studies cannot directly be compared. Both lumbar resistance and brisk walking tasks elicited EIH in participants with and without CLBP. Despite the findings of Chapter six challenging that the results of Chapters four and five confidently reflect EIH, they support the hypothesis that EIH is normal, i.e., not altered, in people with CLBP regardless of the type or region of task.

An increase in lumbar PPT over time was observed for both exercising protocols (Chapters four and five), but not for non-exercising asymptomatic participants (Chapter six). This is in line with current level one evidence that exercise over longer periods decreases pain sensitivity (Belavy et al., 2021; Polaski et al., 2019). On the other hand, in asymptomatic

participants repeated measurements have been shown to increase pain sensitivity over two and four months (Marcuzzi et al., 2017). Contrarily in this thesis, PPT remained consistent across sessions over three weeks in absence of an exercise task (Chapter six).

The phenomenon of EIH is still not fully understood (Vaegter and Jones, 2020). The plethora of contextual factors as outlined in the introduction, and huge variation of tasks and outcome measures make research complex. The confidence in the available evidence remains very low.

7.2.1 Do Findings Present Exercise-Induced Hypoalgesia?

Multiple factors should be considered to answer whether the findings of this thesis as well as cumulated evidence truly present EIH. This thesis provides an important rationale, and the following aspects should be considered to design feasible protocols for future studies.

7.2.1.1 Study Design and Quality of Reporting

Although multiple articles on EIH have been published (Vaegter and Jones, 2020), very few examined the task characteristics or outcome measures. Most studies had firstly, methodological issues, such as small ample size and high risk of bias, and secondly, did not follow reporting standards. Overall evidence was downgraded consistently across previous systematic reviews (Bonello et al., 2021; Pacheco-Barrios et al., 2020; Wewege and Jones, 2021). The systematic review in Chapter three also showed similar findings, as only four of

17 studies were of good ROB, three studies did a power analysis, and two stated reporting guidelines. Concerns (serious) across all GRADE domains were found.

By applying an observational study design the effect of EIH can be overestimated (Vaegter and Jones, 2020), thus a power analysis should be conducted. This was implemented in Chapter four, after being recognised as a limitation in Chapter two (Kuithan et al., 2019). The final study was randomised for feasibility and to accommodate for participation bias of a pain provoking task. While this can reduce selection bias, it increases randomisation bias (Odgaard-Jensen et al., 2011). RCTs (MRC phase III) rank higher in the hierarchy of evidence, but the research on EIH is still not sufficiently answered for phase I, bypassing phase II. Therefore, observational studies were adequate to answer the thesis' aim (Faraoni and Schaefer, 2016; Koenders et al., 2019). Currently there is a gap in the research on EIH for phase II. Feasibility studies can include qualitative approaches (Eldridge et al., 2016). The patients' experience of exercise is underexplored in people with LBP (Slade and Keating, 2010). Despite being a preliminary evaluation via a simple questionnaire of a small non-representative sample of the wider population with CLBP, participants' perceptions in this thesis provided valuable feedback on the exercise tasks and outcome measures for shaping future studies. This supports integration of qualitative approaches into research on EIH.

Further explorative research should allow for an appropriate sample size, adhere to reporting guidelines, and carefully choose the design based on the research question and position within the MRC framework.

7.2.1.2 Psychosocial Factors

The role of the psychosocial factors on EIH needs to be further explored as currently there is insufficient evidence (Munneke et al., 2020). Factors such as mood or sleep have been associated with altered QST results, therefore, it could equally affect EIH (see Chapter one, section 1.3.3/1.3.4). Findings from this thesis did not observe any obvious relationship on any recorded demographic characteristics (Chapter two). Additionally, results of a brief mood and an exercise expectation questionnaire were comparable for groups and sessions (Chapters four and five), however, it can be argued that those were not specific enough. A recent study (asymptomatic men, n=33) found that physical activity level but not mood influenced EIH (Schmitt et al., 2020). This goes beyond the scope of this thesis but warrants further investigation.

Additionally, a cognitive component of EIH has been suggested (see Chapter one, section 1.3.4), which should be considered when informing participants about the study and potential hypoalgesic effects.

7.2.1.3 Task Characteristics

This thesis contributes to the understanding of EIH and showed an increase of lumbar PPT after a local lifting (asymptomatic only), a lumbar resistance, and a brisk walking task. Statistically significant changes were found for all tasks, implying the presence of EIH. However, due to the complexity of EIH and manifold factors influencing both outcome measures and the task, it is still unknown to what extent the change can be referred to the task itself. When reflecting upon the results from Chapter six, one factor why PPT changed only to

a small extent could have been that the tasks simply were not adequate in intensity, duration, or type. However, this would not explain the increase in baseline PPT across sessions and as outlined for each Chapter, tasks were comparable to tasks which previously elicited EIH (Naugle et al., 2012; Pacheco-Barrios et al., 2020; Wewege and Jones, 2021). Moreover, current recommendations, despite uncertain generalisability (Chapter one, section 1.3), were followed (Rice et al., 2019).

A few studies in asymptomatic participants considered local tasks for the lumbar region (Gajsar et al., 2017; Larouche et al., 2020; Mailloux et al., 2021b). Following the Biering Soerensen task, EIH was not elicited over lumbar test sites, but over the hamstrings (Gajsar et al., 2017). No EIH was found following either an anterior pelvic tilt or resistance in extension locally over the back or over the wrist, whereas isometric contraction of the wrist elicited EIH (Mailloux et al., 2021b). A lumbar stretch led to increased PPT over the back and wrist, whereas a stretch of the wrist only led to increased PPT over the wrist (Larouche et al., 2020). Studies replicating these tasks in participants with CLBP have not been published yet. It could be argued that lower back tasks might be less favourable to elicit EIH over the lumbar region compared to peripheral exercises, where a wider body of literature is available. Equivocally, Chapters two and four confirmed EIH over the lumbar region after a local task. There is a lack of evidence on lower back tasks to confidently answer this.

Chapter three synthesised that there is very low quality evidence that work mimicking tasks lead to hyperalgesic responses in people with CNP. These tasks, such as a peg board task, do not represent management of spinal pain. The study by Falla et al. (2014) is as yet the only study which reported hyperalgesia in people with CLBP following an exercise task. No further evidence was found in this thesis, but findings from Chapter two indicated hyperalgesia rather than hypoalgesia, however, this was not statistically significant. Further

research is required to understand why some people respond with hyperalgesia (Lima et al., 2017).

Overall, this thesis highlights the problems of designing a suitable task to produce EIH, which can be highly standardised, but also allows transferability into a clinical setting.

7.2.1.4 When do changes account for EIH?

Some methodological considerations emerged around the assessment of EIH. Most studies did not further investigate the applied QST protocol to assess EIH. Research outlined in Chapter one (section 1.3.8), has shown no statistically significant changes after rest for various test modalities. However, this was retrospectively analysed in Chapter six.

There is no clear definition as to when changes in QST are defined as EIH. As in common practice, statistically significant changes were obtained from RM-ANOVA/ non-parametric tests within this thesis. One research group defined a meaningful change based on a change greater than the SEM (Vaegter et al., 2018). However, the MDC would be most appropriate to reflect a real meaningful difference, as the MDC considers errors from both pre- and post-measures, but thus requires a greater change to count as meaningful (Weir, 2005). Some researchers have already applied this to asymptomatic participants (Mailloux et al., 2021a). Relative changes of PPT over the wrist (8 % ± 16) and back (7 % ± 12) were slightly above the MDC (7-9 %) following an isometric wrist task (n= 23), and after a back exercise (n=11, lumbar PPT change 8 % ± 12) (Mailloux et al., 2021a); relative changes were similar to findings from this thesis. It is common that a substantial number of individuals do

not elicit EIH, for unknown reasons (Vaegter et al., 2019a; Vaegter et al., 2018; Vaegter et al., 2019b). Especially for studies with a small sample size this can lead to misinterpretation.

In this thesis, the focus was on absolute changes as commonly reported for EIH. It can be argued that the relative change is more representative accounting for baseline differences. As baseline PPT increased over the duration of the second study, this could have affected the outcome. On the other hand, relative changes are in general smaller, and fluctuations will have a bigger impact on the analysis. Nevertheless, analysis for relative changes did not lead to different results in this thesis and are consequently not reported in further detail.

7.2.1.4.1 Test Site

Optimal outcome measures also include agreement on the optimal test site. It is hypothesised that people with widespread body pain or WAD often present with local and global dysfunction of EIH or even hyperalgesia (Rice et al., 2019; Vaegter and Jones, 2020). Features of central sensitisation are less prevalent in people with CLBP (Chapter one, section 1.3.3) and could affect pain modulation. A study on baseline QST showed that participants with local LBP had lower PPT over the back, whereas participants with widespread LBP pain showed increased sensitivity over local and remote test sites as well as to thermal stimuli (Gerhardt et al., 2016). In this thesis, no remote changes occurred (Chapter two) or at least were not present in each session (Chapters four and five), although Chapter three synthesised, based on very low quality evidence, that there was no difference in outcome for different test sites (i.e., local and remote). However, there was not sufficient evidence for people with CLBP and functional tasks. Rice et al. (2019) refer to a study with participants with shoulder myalgia, where local EIH over the exercised shoulder muscles was impaired, but not remote

EIH following a quadriceps task (Lannersten and Kosek, 2010). This would support the hypothesis of differences between local and remote test sites in respect to the painful body region and exercise group for at least a subgroup of participants. Further studies assessing both local and remote test sites are listed in reviews (Rice et al., 2019; Vaegter and Jones, 2020); however, a pattern was not identified. Future research on EIH should include test sites in both exercised and painful regions as well as over a remote muscle.

Regarding the optimal test site, various structures have been used including soft tissue, i.e., muscle, or periosteum/ bone (Arendt-Nielsen, 2015; Waller et al., 2015). One factor which should be considered is creep or hardness of tissues and changes from both testing and task (Andersen et al., 2006; Viggiani and Callaghan, 2021). The test site over the thenar eminence (Chapter two) was replaced, as in line with other studies no signs of EIH were found over the thumb (Meeus et al., 2010). Smaller amounts of muscle tissue might be a disadvantage. However, there is little research on PPT over different parts of the muscle and if they respond to EIH, but sensitivity might be higher over the muscle belly (Andersen et al., 2006). Retrospectively, the test site over the wrist extensors and tibialis anterior were less optimal for application of higher pressures due to handling of the device and direction of force applied. Future research should consider different test sites, such as the quadriceps for the lower limb (Bonello et al., 2021; Vaegter and Jones, 2020). Furthermore, standardised test sites could contribute to consistency for future syntheses.

The amount of test sites over the lumbar region were reduced from eight to four on each side (medial rows) for Chapters four to six. Location showed a significant interaction in Chapter two (16 test sites, $F=10.81$, $p< .001$), Chapter four (Wilks= 0.42, $F=4.35$, $p= .004$) and Chapter five (Wilks= 0.27, $F=8.63$, $p< .001$). Post hoc analysis revealed that EIH did not differ between locations for Chapter four, but did for Chapter five, although EIH occurred

over all test sites. Most previous studies tested only one lumbar PPT site lateral of L3 (Gajsar et al., 2017; Meeus et al., 2010). Consequently, a test site 2.5- 3.0 cm lateral of the spinous process of L3 should be included in future research to facilitate direct comparison. Further recommendations for test sites could be achieved through an evidence synthesis or through expert consensus.

7.2.1.4.2 Pressure Pain Thresholds

PPT are acknowledged to assess pain sensitivity (Smith et al., 2017c). Compared to the other test modalities it is a quick, clinically applicable, and relatively inexpensive method (Beales et al., 2021; Zhu et al., 2019). In all empirical studies of this thesis no difference in baseline PPT between participants with and without CLBP was observed. This is in contrast to level one evidence (den Bandt et al., 2019), but could be explained by high variability of inter-individual PPT (Cruz-Almeida and Fillingim, 2014), a small sample size, or lower levels of disability of participants included in this thesis.

The most relevant aspect to critically reflect upon is the amount of test sites. Applying topographical maps could facilitate the increase in PPT irrespective of EIH (Chapter six). So far only a few studies have used a similar amount of test sites (Chapter one, section 1.3.3). In this thesis, within- and between-session adaptation instead of sensitisation was found as PPT pain sensitivity decreased instead of increased. In contrast, no change in asymptomatic participants and hyperalgesia in participants with CLBP was found over eight lumbar test sites (Falla et al., 2014). Protocols testing PPT slightly differed in this thesis, especially, the short interstimulus interval could have led to effects similar to TS. Computer-controlled PPT

produced TS with intervals between one and ten seconds (Nie et al., 2005); one second compared to three seconds showed a higher increase (Nie et al., 2006). However, the interstimulus interval used in this thesis for PPT was longer than one second and only two stimuli were applied over the same test site. Experimental analysis of PPT considering only the first of the two measures did not lead to different results (Chapters two, and four to six). No increase between the first and second test was reported in a different study measuring PPT over multiple lumbar test sites (O'Neill et al., 2019). To further support this, no other studies reported adaptation or sensitisation within or between test sites even if the topographical map included more test sites (Balaguier et al., 2016a; Binderup et al., 2011). Further research is required to explore the effect of multiple test sites.

The assessor was trained to apply the pressure at a rate of 30 kPa/sec which has shown to be reliable (Chesterton et al., 2007), other protocols applied a higher rate, i.e., 50 kPa/sec (Rolke et al., 2006b). It can only be hypothesised that a higher rate would have led to less sensitisation of tissue due to reduced contact time.

7.2.1.4.3 Secondary Outcome Measures

For secondary outcome measures two problems occurred. Firstly, safety limitations reduced the amount of data sets, and secondly, data was not normally distributed.

Notwithstanding the expense of the equipment and a methodological concern due to safety limitations, it is suggested that TPT changes do not show EIH as well as mechanical stimuli (Jones et al., 2019; Kuithan et al., 2019; Schmitt et al., 2020). However, based on the current understanding of EIH and underlying mechanisms, measures should not rely on PPT

alone. As commonly tested over a muscle, this could reflect physiological changes within the muscles, such as performance fatigability (Berardi et al., 2021), rather than EPM.

Although CPT have been shown to be impaired in at least some people with spinal pain (Hubscher et al., 2014), it might not be an appropriate outcome measure for EIH. Even a different thermal tester (ATS PATHWAY, Medoc Ltd, Israel) allowing for lower temperatures of minus 10°C was not sufficiently cold to elicit pain thresholds (unpublished data, University of Birmingham). A considered alternative was the cold pressor test, but this is also commonly used for CPM and therefore could interfere with EIH (Mlekusch et al., 2016; Pokhrel et al., 2013; Vaegter et al., 2016). CPT and HPT were randomised with only a short interstimulus interval. Randomisation of the parameters seems only to affect detection thresholds (Heldestad et al., 2010), but other research suggests that HPT could affect CPT as well as repeated testing led to habituation and decreased sensitivity (Kuhtz-Buschbeck et al., 2010). Adaptation was shown for HPT over the back in another study with multiple test sites, as the second stimulus had a statistically significantly higher mean threshold (O'Neill et al., 2019). In this thesis, the interaction of TS with a series of heat stimuli potentially affected HPT over the lumbar area (Chapters four to six) and therefore limit the validity of the results.

Chapter two included detection thresholds, the physical activity of the task could have changed body temperature, and transpiration or perception of the skin, this has potentially a greater impact on detection than pain thresholds (Bakkers et al., 2013; Pertovaara et al., 1996). Due to inconclusive results and the extensive test protocol, detection thresholds were not included in Chapters four to six. A slower rate of increases or decreases in temperature or a bigger thermode could have reduced the number of missing data (Bakkers et al., 2013). An alternative solution could be to incorporate prolonged heat exposure, or the application of a

laser as described in other studies (Bialosky et al., 2009; Jones et al., 2016). This could be considered for future laboratory studies but should avoid any form of CPM.

PPTOL was not only limited by the safety limitations of the device, some test sites also showed bruising and therefore, could either not be tested, or areas might have been sensitised from previous sessions. Moreover, greater inaccuracy in testing has been reported with higher intensities for PPT (Middlebrook et al., 2020). Another study used a pressure algometer and tested over the web space of the hand; no complications were reported in that study, although multiple trials were conducted (Baiamonte et al., 2017). However, it has been indicated that PPTOL might be superior to PPT in detecting EIH (Hviid et al., 2019; Vaegter et al., 2017a). There is less research on PPTOL, but these studies mainly used cuff pressure, which could lead to blood flow restrictions rather than soft tissue impairment.

From a communication and participants' perspective, pain tolerance tests are very different to testing pain thresholds. The understanding of maximal pain or tolerance was interpreted quite differently at an individual participant level in this thesis despite standardised instructions. Based on findings on PPT, participants' control of the application of pressure as well as psychological factors might be relevant to further understand PPTOL (Lalouni et al., 2021). From that point of view, further exploration of the difference between threshold and tolerance is of interest, e.g., to explore people with different pain perceptions and considering the impact of different psychological models on pain processing (Hasenbring et al., 2014). Measurement properties of PPTOL require further investigation in terms of reliability, but also on tissue recovery time after each test, where cuff pressure might be advantageous.

There was a series of issues with TS and the nociceptive withdrawal reflex. TS did not lead to an increase in perceived pain, the opposite was found in this thesis. Furthermore, the nociceptive reflex was not further analysed due to the amount of data, as some participants did not tolerate the test, or no reflex could be elicited. Findings for both tests are further discussed in Appendix 19.

7.2.1.4.4 Alternative Outcome Measures

As an alternative to EIH, EPM could be measured with CPM. Some research indicates that EIH is correlated to CPM results in healthy controls and might be caused by experienced pain during the exercise equivalent to the conditioning stimulus (Lemley et al., 2015). However, the opposite was reported in other studies (Ellingson et al., 2014; Szikszay et al., 2020; Vaegter et al., 2014). CPM measures EPM but might be less suitable to assess EIH due to potential shared pathways (Alsouhibani et al., 2019; Gajsar et al., 2018; Samuelly-Leichtag et al., 2018; Vaegter et al., 2014).

Another form to test EPM is 'off-set analgesia', which refers to a local disproportional reduction in perceived pain after a small decrease of the noxious stimulus by descending EPM (Szikszay et al., 2020; Yelle et al., 2009). In asymptomatic people, the Biering Soerensen test led to no direct or indirect changes in off-set analgesia responses (Szikszay et al., 2020), which therefore might not share the same pathways as EIH. An isometric quadriceps task showed changes in PPT but not in off-set analgesia and no further correlation (EIH, offset analgesia) was found (Harris et al., 2018); fMRI showed different activation patterns indicating spatial filtering of nociceptive information for EIH and non-opioidergic off-set

analgesia (Harris et al., 2018). Similar problems with the test protocol occur as in EIH, and therefore, would not be a current alternative. All these methods did not involve an exercise task, and therefore do not relate to changes within intervention programmes/ clinical practice.

Next to performance-based outcome measures such as QST, additional outcome measures have been discussed, e.g., blood tests or imaging. Test modalities such as cortisol levels have been systematically reviewed (Barros Dos Santos et al., 2021). The understanding of hyperalgesia instead of EIH still needs to be explored further, including the role of anti- and pro-inflammatory cytokines (Docherty et al., 2022). Microdialysis has been assessed by mainly one research group (Gerdle et al., 2014). It is likely that especially Interleukin-6 is mainly produced locally in the muscle and peripheral circulation is less pronounced which would support local investigations (Docherty et al., 2022). Even though this is a promising approach, it is unlikely to be implemented in clinical practice due to its invasive nature. Further high quality studies are needed to investigate underlying physiological mechanisms by applying both exploratory and explanatory approaches (Lesnak and Sluka, 2020). Alternative methods could investigate cortical structures/functions, such as fMRI (Ellingson et al., 2016; Geisler et al., 2019; Scheef et al., 2012), and provide further insight into EIH.

7.2.2 Newly Emerging Evidence

Four additional relevant studies have been published since the inception date of Chapter three. Woznowski-Vu et al. (2021) focussed on sensitivity to physical activity in 97 participants with LBP (< six months). Perceived pain on a NRS, psychological factors, and a *SPA-Sensory item*, including PPT, were outcome measures to assess pre- post-changes

following a two-stage lifting task (duration not specified) (Woznowski-Vu et al., 2021). In contrast to findings from Chapter two, changes were found over the remote test site over the web space between the thumb and index finger indicating a hyperalgesic response (MD -18.80 kPa ± 73.10; p= .007), but not over the lumbar test site (3.97 kPa ± 97.29; p= .597) (Woznowski-Vu et al., 2021). This study also included a three-month follow-up, in contrast to psychological factors and the pain responses, no statistically significant correlation was found for EIH. This adds to the evidence that EIH might be altered in some people with CLBP, specifically after a local task, and adds to conflicting results in people with CLBP in general. However, based on the modified NOS (Chapter three) the ROB was poor.

As discussed in Chapter five, in a study by Vaegter et al. (2021) EIH was not present after a walking task considering all 96 participants with CLBP; but when the task increased pain levels, participants (27/96) showed impaired EIH, whereas if not, EIH was present (72%). As outlined in Chapter three, pain sensitivity might affect EIH (Vaegter et al., 2016). A recently published RCT did not show differences in EIH following a three-minute wall squat task by injecting either hyper- or isotonic saline (Hansen et al., 2021). Findings of Chapter two did not show significant correlations. Chapters four and five showed no difference for a painful task, but no further analysis was conducted due to the small sample size and focus on multiple sessions. Future research should explore the interaction of pain perceived during the exercise and its effect on EIH, as this might be relevant for managing people with musculoskeletal pain. Adding this finding to the available evidence in people with LBP, it supports that aerobic/remote tasks might lead to normal EIH (based on the 72%). An upgrade of the recommendation to low quality evidence could be considered, as this was a well conducted study (ROB= poor; but due to no control group) with a large a priori calculated sample size.

In addition, two randomised studies have been published including only participants with CLBP. In a pseudorandomised clinical trial (n=81), no changes in PPT after each of the three exercise modalities (walking (20 minutes, 65.85%±7 HR, Borg Scale= 3), resistance (mix of core stability and general body weight exercises), and stretching (major back/hip muscles)) were found, the same as for the group with a control condition (Sitges et al., 2021). Another randomised experimental study investigated different intensities of lumbo-pelvic coordination training, similar to an isometric contraction (*high* (10 min, 180 mmHG) and *low* (5 min 100 mmHG)), and a sham task (Xu et al., 2021). Changes in PPT were found over four out of ten trunk muscles for high intensity, over three muscles for low intensity, and no change for the sham condition (total n=42). Interpretation of the results were questionable due to test sites over deep muscles as well as reporting and interpretation of the results, i.e., for the sham group. Overall, the Cochrane ROB 2 tool showed that both studies had some concerns, especially for the randomisation process. ROB was subsequently high (Sterne et al., 2019), limiting the internal validity of the results.

Despite the difference in study design, there is conflicting evidence that there is altered EIH in response to a local task in people with CLBP. Chapter three (two studies) and one additional study (Woznowski-Vu et al., 2021) found altered EIH, whereas two studies revealed normal EIH (Chapter four) (Xu et al., 2021) and one study revealed no EIH (Sitges et al., 2021). In contrast to Chapter three (two studies) and Chapter five which showed normal EIH, two further studies showed no EIH after an aerobic/ remote task (Sitges et al., 2021; Vaegter et al., 2021); however, the study by Vaegter et al. (2021) showed normal EIH for the majority of participants, i.e., for those where walking did not increase pain intensity.

7.2.3 Stability of Exercise-Induced Hypoalgesia

Despite numerous published studies, basic principles of research methodology, such as establishing measurement properties, have not been sufficiently explored. This thesis provides the first evidence for stability of EIH over multiple sessions, and the first evidence in people with CLBP. Stability was poor across all outcome measures for all groups. This is in contrast to evidence in asymptomatic participants, which showed moderate ICC (3,1) values (range = 0.33 – 0.61) for absolute changes in PPT following aerobic exercise (Gomolka et al., 2019; Hviid et al., 2019; Vaegter et al., 2019a; Vaegter et al., 2018), and ICC (3,1) ranging from 0.03 to 0.43 for relative changes after resistance exercise (Vaegter et al., 2019b). However, the categories for ICC values differed. Based on ICC values in this thesis poor stability was defined as a ICC value < 0.5 (Koo and Li, 2016). The other research group around Vaegter et al. had a less conservative approach defining poor as < 0.40. In this thesis, five and six sessions were evaluated, whereas the other studies only considered two sessions (Gomolka et al., 2019; Hviid et al., 2019; Vaegter et al., 2019a; Vaegter et al., 2018), this could further explain the difference in outcome. Stability of measures is of high importance for any further assessment of validity (Sim and Arnell, 1993). If EIH was used as a treatment goal for EPM, it would need to be reproduced in every session. Due to the poor stability, it can be argued that EIH can confidently be used for future purposes, such as stratification of care, or prediction of treatment outcome, as reported in knee osteoarthritis (Hansen et al., 2020b; Wideman et al., 2014).

Chapters four to six were a pragmatic observational study informed by current guidelines for reliability (Kottner et al., 2011) and ICC were used (Koo and Li, 2016). The randomisation of testing could explain lower ICC values for baseline measures compared to

other literature focussing purely on reliability of baseline measures (Chapter one section 1.3.3), as little is known of the interactions of different test modalities (Heldestad et al., 2010). This highlights the importance of standardised protocols and further elucidation of interactions.

Different numbers of rest days between the sessions could have sensitised tissue to a different extent. Additionally, there might have been a training effect across sessions. This was avoided in studies by the other research group by having two sessions only. Less functional tasks allowed for higher standardisation, which has been shown to increase stability (Vaegter et al., 2019a).

An effect from exercise programmes on EIH over multiple weeks has been shown in recent studies. Hansen et al. (2020a) showed that military training (seven weeks) increased EIH in asymptomatic participants (n=38); interestingly those who presented with hyperalgesia in the first session (26%) regained EIH and presented with greater increase in PPT following a wall-squat. Another study showed that EIH was greater after high intensity stationary cycling over the quadriceps femoris, whereas after the programme (six sessions over two weeks) the EIH response was the same for high and low intensity in cancer survivors (n=19) (Clifford et al., 2021). It can be argued that findings from Chapters four and five were adaptations, where the sessions accounted for the "exercise programme", but a RM-ANOVA confirmed the same EIH response across sessions. It would be interesting to explore this further, as it indicates that EIH might be responsive to exercise programmes, which could play a role in rehabilitation. However, this remains speculative.

7.3 Strength and Limitations

7.3.1 Strengths

This thesis is unique in testing EIH after different functional and clinically relevant tasks in people with CLBP, adding to the empirical body of evidence from findings of observational studies (Chapters two, four, and five) as well as synthesising the existing current evidence (Chapter three). Secondly, it is the first evidence of stability of EIH over multiple sessions. It therefore adds one more piece to the complex puzzle of elucidating EIH.

A standardised testing protocol was used informed by existing research, which was analysed in Chapter six, and standardised tasks were applied. The researcher was a highly experienced musculoskeletal physiotherapist with relevant training in QST. This reduces the chance of systematic errors. Recommendations for future studies such as location and amount of test sites were outlined.

Methodologies and reporting followed latest guidelines for observational studies and systematic reviews (Page et al., 2021; von Elm et al., 2008). The designs were chosen to better reflect rehabilitation settings focusing on functional tasks as outlined for the ICF. Furthermore, the work has been published and cited in peer-reviewed journals and was presented at national and international conferences.

7.3.2 Limitations

There are some limitations which should be considered. The recruitment was within a University setting representing people of younger age and lower levels of pain and disability. Therefore, the results might not be transferrable to people with more severe pain/higher disability and the wider non-University population. Participants self-selected for the different tasks and had a very positive attitude towards exercise in general.

The same researcher conducted both QST tests, controlled the tasks, and performed the data analysis, which increases the potential for bias. Nevertheless, outcomes were performance based and participant controlled by pressing a button to indicate pain thresholds, consequently the researcher has only an indirect impact. Control of random errors was only partially feasible. Further standardisation was not always possible, for example restricting participants to other activities between sessions (Chapters four to six).

The testing itself could have led to changes due to adaptation or sensitisation considering results from the non-exercising participants in Chapter six. At the beginning of the thesis sufficient evidence based on individual studies confirmed construct validity (Chapter one section 1.3.8), but retrospectively Chapter six could have been conducted prior to Chapters four and five.

A power analysis was conducted for Chapter four based on the primary outcome measure data (lumbar PPT) presented in Chapter two (Kuithan et al., 2019). However, for most other outcome measures data sets were reduced due to safety limitations, and non-normative distribution limited the power of interpretation of the results.

Lastly, the terminology and the classification used for EIH in this thesis, might be slightly simplistic. Based on the findings, and additional evidence also showing hyperalgesia after an exercise task in people with and without spinal pain, the terminology of the phenomenon of EIH might be not entirely appropriate, as it does not reflect all changes in pain sensitivity specifically considering people with pain.

7.4 Clinical Implications

Currently, there is still limited evidence on EIH. Poor stability of EIH raises concerns for clinical implications. However, this thesis provided preliminary insights in both task characteristics and outcome measures, but the weak evidence base currently precludes this being used with confidence in a clinical or rehabilitation setting. It is beyond the scope of this thesis to evaluate the clinical relevance of the effects of EIH.

7.5 Future Research

Findings from this thesis contribute to a rapidly emerging body of evidence on EIH and specifically in people with CLBP (Phase I MRC, see Chapter one Figure 1.3). Overall, further high quality studies are required, applying validated protocols to optimise study designs.

Some points of interest for future research were raised in recent reviews (Bonello et al., 2021; Rice et al., 2019; Vaegter and Jones, 2020): understanding pain sensitivity and

perception of the effects of EIH; mediating factors such as pain perception or activity level; or the relationship to CPM. Aspects specifically addressed in this thesis comprised of stability, clinically relevant protocols, and local tasks. Further RCTs were recommended to reduce bias and not to overestimate the effects of EIH (Vaegter and Jones, 2020). Based on the MRC (Craig, 2019) it is recommend to explore the phenomenon first via observational studies to inform subsequent high-priced RCTs. Nevertheless, this thesis agrees on the need for validated protocols and comparable interventions, using PPT as outcome measures over both local and remote test sites (Vaegter and Jones, 2020). EIH is not an unidimensional factor (Woznowski-Vu et al., 2021) and research should fully reflect the biopsychosocial model.

Once the phenomenon of EIH is better understood, it could contribute to prognostic factors. However, research should address the following aspects before a RCT can establish the effectiveness of what the best intervention is to elicit EIH in people with CLBP.

First, a synthesis of evidence is needed to further elucidate appropriate tasks to produce EIH and what outcome measures can be applied to assess this. Based on the heterogeneity of current literature, the preferred design is a Delphi Consensus Study which allows experts from different research groups to develop a framework i.e., a test protocol. The project should follow guidelines for Delphi studies (Junger et al., 2017; Spranger et al., 2022). An international conference such as the International Association for the Study of Pain World Congress could connect researchers/experts from different groups and continents to discuss this in a workshop (first round) allowing open discussions and sharing of experiences (Mars et al., 2015). This could then be followed by a more standard Delphi approach (round two and three) finding consensus via a survey to determine content of a new test protocol.

As mentioned previously the reporting quality of studies and case series in the field of EIH is often poor stressing the importance of following reporting guidelines. Furthermore, it can be argued that positive reporting/ publication bias might be present. Additionally, it is unlikely that another review would lead to a consensus. Several reviews (Bonello et al., 2021; Naugle et al., 2012; Pacheco-Barrios et al., 2020; Rice et al., 2019; Vaegter and Jones, 2020; Wewege and Jones, 2021) synthesising different study designs did neither allow recommendations with moderate or high level of confidence nor provided specific recommendations for the intervention to elicit EIH or the best outcome measures. Pressure cuff testing for pain thresholds and tolerance should be included as an outcome measurement which was not utilised in this thesis. The amount of test sites should be considered carefully and not be excessive and further research would be needed to explore the effects of topographical testing. A less functional task, such as isokinetic exercise or cycling, might help to improve the stability of EIH as it can be standardised to a greater extent.

Once a test protocol is established an observational study can assess stability and validity of the newly developed test protocol, the pre-requisite for future studies (second step). This would finalise phase I of the MRC Framework allowing to initiate phase II (feasibility study). As part of a future feasibility study, the qualitative component can be informed by the preliminary evaluation of participants' perceptions. Once completed, it can then be transferred to people with musculoskeletal conditions, i.e., CLBP.

7.6 Conclusion

This thesis outlined important and unique findings of EIH in people with and without CLBP. Evidence synthesis (Chapter three) found low to very low quality evidence with

conflicting results. For people with CLBP there was very low evidence that aerobic cycling tasks led to normal EIH (two studies, fair ROB) and that local tasks (repetitive lifting) elicited altered EIH (two studies, one good, one fair ROB). Local tasks are relevant as they better reflect normal management for people with spinal pain. One of the two included studies was Chapter two; the first study which demonstrated impaired EIH in participants with CLBP following a local task while asymptomatic participants showed EIH. Altogether, the systematic review highlighted a paucity of studies assessing EIH in people with spinal pain, specifically CLBP. Across included studies the ROB was high, and sample size calculations and use of reporting guidelines were lacking.

Integrating the additional empirical findings into the existing body of literature showed equivocal results. After a lumbar resistance and brisk walking task both participants with and without CLBP showed EIH across multiple sessions (Chapters four and five). As the increase of lumbar PPT was also present after rest (Chapter six), interpretation of the results should be done cautiously. Analysis of the test protocol is recommended prior to future research on EIH. Finally, stability of absolute changes was poor, although the effect occurred in each session. This outlines a challenge for future studies and needs to be addressed first.

This thesis further underlines the complexity of assessing and eliciting EIH in presence of many unexplored interacting factors in asymptomatic people and those with CLBP. Overall, findings of this thesis are important to inform future studies contributing to the elucidation of EIH in people with and without CLBP, specifically on the stability, a prerequisite for further research.

References

ABBOUD, J., NOUGAROU, F., PAGE, I., CANTIN, V., MASSICOTTE, D. & DESCARREAUX, M. 2014. Trunk motor variability in patients with non-specific chronic low back pain. *European Journal of Applied Physiology,* 114**,** 2645-54. doi: 10.1007/s00421-014-2985-8

ADAMCZYK, W. M., SZIKSZAY, T. M., KUNG, T., CARVALHO, G. F. & LUEDTKE, K. 2021. Not as "blurred" as expected? Acuity and spatial summation in the pain system. *Pain,* 162**,** 794-802. doi: 10.1097/j.pain.0000000000002069

ADNADJEVIC, D. & GRAVEN-NIELSEN, T. 2015. Temporal summation of muscle pain evoked by very fast pressure sequences and rotation. *Somatosensory and Motor Research,* 32**,** 99-105. doi: 10.3109/08990220.2014.981650

ALSOUHIBANI, A., VAEGTER, H. B. & HOEGER BEMENT, M. 2019. Systemic Exercise-Induced Hypoalgesia Following Isometric Exercise Reduces Conditioned Pain Modulation. *Pain Medicine,* 20**,** 180-190. doi: 10.1093/pm/pny057

ANDERSEN, H., ARENDT-NIELSEN, L., DANNESKIOLD-SAMSOE, B. & GRAVEN-NIELSEN, T. 2006. Pressure pain sensitivity and hardness along human normal and sensitized muscle. *Somatosensory and Motor Research,* 23**,** 97-109. doi: 10.1080/08990220600856255

ANSTEY, R., KONGSTED, A., KAMPER, S. & HANCOCK, M. J. 2016. Are People With Whiplash-Associated Neck Pain Different From People With Nonspecific Neck Pain? *Journal of Orthopaedic and Sports Physical Therapy,* 46**,** 894-901. doi: 10.2519/jospt.2016.6588

APELDOORN, A. T., BOSSELAAR, H., OSTELO, R. W., BLOM-LUBERTI, T., VAN DER PLOEG, T., FRITZ, J. M., DE VET, H. C. & VAN TULDER, M. W. 2012. Identification of patients with chronic low back pain who might benefit from additional psychological assessment. *Clinical Journal of Pain,* 28**,** 23-31. doi: 10.1097/AJP.0b013e31822019d0

APKARIAN, A. V., BALIKI, M. N. & GEHA, P. Y. 2009. Towards a theory of chronic pain. *Progress in Neurobiology,* 87**,** 81-97. doi: 10.1016/j.pneurobio.2008.09.018

ARENDT-NIELSEN, L. 2015. Reliability of pressure pain threshold testing (PPT) in healthy pain free young adults. *Scandinavian Journal of Pain,* 9**,** 28-29. doi: 10.1016/j.sjpain.2015.06.002

BAESKE, R. 2016. Mobilisation with movement: a step towards understanding the importance of peripheral mechanoreceptors. *Physical Therapy Reviews,* 20**,** 299-305. doi: 10.1080/10833196.2015.1121014

BAIAMONTE, B. A., KRAEMER, R. R., CHABRECK, C. N., REYNOLDS, M. L., MCCALEB, K. M., SHAHEEN, G. L. & HOLLANDER, D. B. 2017. Exercise-induced hypoalgesia: Pain tolerance, preference and tolerance for exercise intensity, and physiological correlates following dynamic circuit resistance exercise. *Journal of Sports Sciences,* 35**,** 1-7. doi: 10.1080/02640414.2016.1239833

BAKKERS, M., FABER, C. G., PETERS, M. J., REULEN, J. P., FRANSSEN, H., FISCHER, T. Z. & MERKIES, I. S. 2013. Temperature threshold testing: a systematic review. *Journal of the Peripheral Nervous System,* 18**,** 7-18. doi: 10.1111/jns5.12001

BALAGUIER, R., MADELEINE, P. & VUILLERME, N. 2016a. 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,* 17**,** 350. doi: 10.1186/s12891-016-1212-7

BALAGUIER, R., MADELEINE, P. & VUILLERME, N. 2016b. Is One Trial Sufficient to Obtain Excellent Pressure Pain Threshold Reliability in the Low Back of Asymptomatic Individuals? A Test-Retest Study. *PloS One,* 11**,** e0160866. doi: 10.1371/journal.pone.0160866

BARON, R., MAIER, C., ATTAL, N., BINDER, A., BOUHASSIRA, D., CRUCCU, G., FINNERUP, N. B., HAANPAA, M., HANSSON, P., HULLEMANN, P., JENSEN, T. S., FREYNHAGEN, R., KENNEDY, J. D., MAGERL, W., MAINKA, T., REIMER, M., RICE, A. S. C., SEGERDAHL, M., SERRA, J., SINDRUP, S., SOMMER, C., TOLLE, T., VOLLERT, J. & TREEDE, R. D. 2017. Peripheral neuropathic pain: a

mechanism-related organizing principle based on sensory profiles. *Pain,* 158**,** 261-272. doi: 10.1097/j.pain.0000000000000753

BARROS DOS SANTOS, A. O., PINTO DE CASTRO, J. B., LIMA, V. P., DA SILVA, E. B. & DE SOUZA VALE, R. G. 2021. Effects of physical exercise on low back pain and cortisol levels: a systematic review with meta-analysis of randomized controlled trials. *Pain Managament,* 11**,** 49-57. doi: 10.2217/pmt-2020-0020

BAUMANN, N. 2016. How to use the medical subject headings (MeSH). *International Journal of Clinical Practice,* 70**,** 171-4. doi: 10.1111/ijcp.12767

BEALES, D., MITCHELL, T., MOLONEY, N., RABEY, M., NG, W. & REBBECK, T. 2021. Masterclass: A pragmatic approach to pain sensitivity in people with musculoskeletal disorders and implications for clinical management for musculoskeletal clinicians. *Musculoskeletal Science and Practice,* 51**,** 102221. doi: 10.1016/j.msksp.2020.102221

BELAVY, D. L., VAN OOSTERWIJCK, J., CLARKSON, M., DHONDT, E., MUNDELL, N. L., MILLER, C. T. & OWEN, P. J. 2021. Pain sensitivity is reduced by exercise training: Evidence from a systematic review and meta-analysis. *Neuroscience and Biobehavioral Reviews,* 120**,** 100-108. doi: 10.1016/j.neubiorev.2020.11.012

BENGTSSON, M. 2016. How to plan and perform a qualitative study using content analysis. *NursingPlus Open,* 2**,** 8-14. doi: 10.1016/j.npls.2016.01.001

BERARDI, G., SENEFELD, J. W., HUNTER, S. K. & BEMENT, M. K. H. 2021. Impact of isometric and concentric resistance exercise on pain and fatigue in fibromyalgia. *European Journal of Applied Physiology,* 121**,** 1389-1404. doi: 10.1007/s00421-021-04600-z

BERTOZZI, L., GARDENGHI, I., TURONI, F., VILLAFANE, J. H., CAPRA, F., GUCCIONE, A. A. & PILLASTRINI, P. 2013. Effect of therapeutic exercise on pain and disability in the management of chronic nonspecific neck pain: systematic review and meta-analysis of randomized trials. *Physical Therapy,* 93**,** 1026-36. doi: 10.2522/ptj.20120412

BIALOSKY, J. E., BENECIUK, J. M., BISHOP, M. D., CORONADO, R. A., PENZA, C. W., SIMON, C. B. & GEORGE, S. Z. 2018. Unraveling the Mechanisms of Manual Therapy: Modeling an Approach. *Journal of Orthopaedic and Sports Physical Therapy,* 48**,** 8-18. doi: 10.2519/jospt.2018.7476

BIALOSKY, J. E., BISHOP, M. D., ROBINSON, M. E., ZEPPIERI, G., JR. & GEORGE, S. Z. 2009. Spinal manipulative therapy has an immediate effect on thermal pain sensitivity in people with low back pain: a randomized controlled trial. *Physical Therapy,* 89**,** 1292-303. doi: 10.2522/ptj.20090058

BINDERUP, A. T., HOLTERMANN, A., SOGAARD, K. & MADELEINE, P. 2011. Pressure pain sensitivity maps, self-reported musculoskeletal disorders and sickness absence among cleaners. *International Archives of Occupational and Environmental Health,* 84**,** 647-54. doi: 10.1007/s00420-011-0627-6

BINGEL, U. & TRACEY, I. 2008. Imaging CNS modulation of pain in humans. *Physiology,* 23**,** 371-80. doi: 10.1152/physiol.00024.2008

BISHOP, M. D., TORRES-CUECO, R., GAY, C. W., LLUCH-GIRBES, E., BENECIUK, J. M. & BIALOSKY, J. E. 2015. What effect can manual therapy have on a patient's pain experience? *Pain Managament,* 5**,** 455-64. doi: 10.2217/pmt.15.39

BLACK, C. D., HUBER, J. K., ELLINGSON, L. D., ADE, C. J., TAYLOR, E. L., GRIFFETH, E. M., JANZEN, N. R. & SUTTERFIELD, S. L. 2017. Exercise-Induced Hypoalgesia Is Not Influenced by Physical Activity Type and Amount. *Medicine and Science in Sports and Exercise,* 49**,** 975-982. doi: 10.1249/MSS.0000000000001186

BOBOS, P., BILLIS, E., PAPANIKOLAOU, D. T., KOUTSOJANNIS, C. & MACDERMID, J. C. 2016. Does Deep Cervical Flexor Muscle Training Affect Pain Pressure Thresholds of Myofascial Trigger Points in Patients with Chronic Neck Pain? A Prospective Randomized Controlled Trial. *Rehabilitation Research and Practice,* 2016 doi: 10.1155/2016/6480826

BODES PARDO, G., LLUCH GIRBES, E., ROUSSEL, N. A., GALLEGO IZQUIERDO, T., JIMENEZ PENICK, V. & PECOS MARTIN, D. 2018. Pain Neurophysiology Education and Therapeutic Exercise for Patients With Chronic Low Back Pain: A Single-Blind Randomized Controlled Trial. *Archives of Physical Medicine and Rehabilitation,* 99**,** 338-347. doi: 10.1016/j.apmr.2017.10.016

BOGDUK, N. 2005. *Clinical anatomy of the lumbar spine and sacrum,* Edinburgh, Elsevier/Churchill Livingstone.

BONELLO, C., GIRDWOOD, M., DE SOUZA, K., TRINDER, N. K., LEWIS, J., LAZARCZUK, S. L., GAIDA, J. E., DOCKING, S. I. & RIO, E. K. 2021. Does isometric exercise result in exercise induced hypoalgesia in people with local musculoskeletal pain? A systematic review. *Physical Therapy in Sport* 49**,** 51-61. doi: 10.1016/j.ptsp.2020.09.008

BOOTH, J., MOSELEY, G. L., SCHILTENWOLF, M., CASHIN, A., DAVIES, M. & HUBSCHER, M. 2017. Exercise for chronic musculoskeletal pain: A biopsychosocial approach. *Musculoskeletal Care,* 15**,** 413-421. doi: 10.1002/msc.1191

BOOTH, M. 2000. Assessment of physical activity: An international perspective. *Research Quarterly for Exercise and Sport,* 71**,** 312-312. doi: 10.1080/02701367.2000.11082794

BORG, G. A. 1982. Psychophysical bases of perceived exertion. *Medicine and Science in Sports and Exercise,* 14**,** 377-81.

BOUCHER, J. A., ABBOUD, J., NOUGAROU, F., NORMAND, M. C. & DESCARREAUX, M. 2015. The Effects of Vibration and Muscle Fatigue on Trunk Sensorimotor Control in Low Back Pain Patients. *PloS One,* 10**,** e0135838. doi: 10.1371/journal.pone.0135838

BRAZIER, J. E., HARPER, R., JONES, N. M., O'CATHAIN, A., THOMAS, K. J., USHERWOOD, T. & WESTLAKE, L. 1992. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ,* 305**,** 160-4. doi: 10.1136/bmj.305.6846.160

BREIVIK, H., BORCHGREVINK, P. C., ALLEN, S. M., ROSSELAND, L. A., ROMUNDSTAD, L., HALS, E. K., KVARSTEIN, G. & STUBHAUG, A. 2008. Assessment of pain. *British Journal of Anaesthesia,* 101**,** 17-24. doi: 10.1093/bja/aen103

BRELLENTHIN, A. G., CROMBIE, K. M., COOK, D. B., SEHGAL, N. & KOLTYN, K. F. 2017. Psychosocial Influences on Exercise-Induced Hypoalgesia. *Pain Medicine,* 18**,** 538-550. doi: 10.1093/pm/pnw275

BRUEHL, S., BURNS, J. W., KOLTYN, K., GUPTA, R., BUVANENDRAN, A., EDWARDS, D., CHONT, M., WU, Y. H., QU'D, D. & STONE, A. 2020. Are endogenous opioid mechanisms involved in the effects of aerobic exercise training on chronic low back pain? A randomized controlled trial. *Pain,* 161**,** 2887-2897. doi: 10.1097/j.pain.0000000000001969

CAMARDA, S. R., TEBEXRENI, A. S., PAFARO, C. N., SASAI, F. B., TAMBEIRO, V. L., JULIANO, Y. & BARROS NETO, T. L. 2008. Comparison of maximal heart rate using the prediction equations proposed by Karvonen and Tanaka. *Arquivos Brasileiros de Cardiologia,* 91**,** 311-4. doi: 10.1590/s0066-782x2008001700005

CAMPBELL, M., FITZPATRICK, R., HAINES, A., KINMONTH, A. L., SANDERCOCK, P., SPIEGELHALTER, D. & TYRER, P. 2000. Framework for design and evaluation of complex interventions to improve health. *BMJ,* 321**,** 694-6. doi: 10.1136/bmj.321.7262.694

CARROLL, T. J., RIEK, S. & CARSON, R. G. 2001. Neural adaptations to resistance training: implications for movement control. *Sports Medicine,* 31**,** 829-40. doi: 10.2165/00007256-200131120-00001

CASPERSEN, C. J., POWELL, K. E. & CHRISTENSON, G. M. 1985. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Reports,* 100**,** 126-31.

CATHCART, S., WINEFIELD, A. H., ROLAN, P. & LUSHINGTON, K. 2009. Reliability of temporal summation and diffuse noxious inhibitory control. *Pain Research and Management,* 14**,** 433-8. doi: 10.1155/2009/523098

CHESTERTON, L. S., SIM, J., WRIGHT, C. C. & FOSTER, N. E. 2007. Interrater reliability of algometry in measuring pressure pain thresholds in healthy humans, using multiple raters. *Clinical Journal of Pain,* 23**,** 760-6. doi: 10.1097/AJP.0b013e318154b6ae

CHIEN, A. & STERLING, M. 2010. Sensory hypoaesthesia is a feature of chronic whiplash but not chronic idiopathic neck pain. *Manual Therapy,* 15**,** 48-53. doi: 10.1016/j.math.2009.05.012

CHO, K. H., BEOM, J. W., LEE, T. S., LIM, J. H., LEE, T. H. & YUK, J. H. 2014. Trunk muscles strength as a risk factor for nonspecific low back pain: a pilot study. *Annals of Rehabilitation Medicine,* 38**,** 234-40. doi: 10.5535/arm.2014.38.2.234

CHRISTE, G., CROMBEZ, G., EDD, S., OPSOMMER, E., JOLLES, B. M. & FAVRE, J. 2021. Relationship between psychological factors and spinal motor behaviour in low back pain: a systematic review and meta-analysis. *Pain,* 162**,** 672-686. doi: 10.1097/j.pain.0000000000002065

CHRISTENSEN, S. W., HIRATA, R. P. & GRAVEN-NIELSEN, T. 2017. Altered pain sensitivity and axioscapular muscle activity in neck pain patients compared with healthy controls. *European Journal of Pain,* 21**,** 1763-1771. doi: 10.1002/ejp.1088

CLIFFORD, B. K., JONES, M. D., SIMAR, D., BARRY, B. K. & GOLDSTEIN, D. 2021. The effect of exercise intensity on exercise-induced hypoalgesia in cancer survivors: A randomized crossover trial. *Physiological Reports,* 9**,** e15047. doi: 10.14814/phy2.15047

COOPER, M. A., KLUDING, P. M. & WRIGHT, D. E. 2016. Emerging Relationships between Exercise, Sensory Nerves, and Neuropathic Pain. *Frontiers in Neuroscience,* 10**,** 372. doi: 10.3389/fnins.2016.00372

CORONADO, R. A., BIALOSKY, J. E., ROBINSON, M. E. & GEORGE, S. Z. 2014. Pain sensitivity subgroups in individuals with spine pain: potential relevance to short-term clinical outcome. *Physical Therapy,* 94**,** 1111-22. doi: 10.2522/ptj.20130372

CRAIG, C. L., MARSHALL, A. L., SJOSTROM, M., BAUMAN, A. E., BOOTH, M. L., AINSWORTH, B. E., PRATT, M., EKELUND, U., YNGVE, A., SALLIS, J. F. & OJA, P. 2003. International physical activity questionnaire: 12-country reliability and validity. *Medicine and Science in Sports and Exercise,* 35**,** 1381-95. doi: 10.1249/01.MSS.0000078924.61453.FB

CRAIG, P. D., P.; MICHIE, S. ; NAZARETH, I.; PETTICREW, M. 2019. Developing and evaluating complex interventions. Available: https://mrc.ukri.org/documents/pdf/complex-interventions-guidance/ [Last accessed 05/11/2021].

CRAWFORD, R. J., GIZZI, L., MHUIRIS, A. N. & FALLA, D. 2016. Are regions of the lumbar multifidus differentially activated during walking at varied speed and inclination? *Journal of Electromyography and Kinesiology,* 30**,** 177-83. doi: 10.1016/j.jelekin.2016.07.006

CROMBIE, K. M., BRELLENTHIN, A. G., HILLARD, C. J. & KOLTYN, K. F. 2018. Endocannabinoid and Opioid System Interactions in Exercise-Induced Hypoalgesia. *Pain Medicine,* 19**,** 118-123. doi: 10.1093/pm/pnx058

CRUZ-ALMEIDA, Y. & FILLINGIM, R. B. 2014. Can quantitative sensory testing move us closer to mechanism-based pain management? *Pain Medicine,* 15**,** 61-72. doi: 10.1111/pme.12230

CRUZ-ALMEIDA, Y., RILEY, J. L., 3RD & FILLINGIM, R. B. 2013. Experimental pain phenotype profiles in a racially and ethnically diverse sample of healthy adults. *Pain Medicine,* 14**,** 1708-18. doi: 10.1111/pme.12203

CUMMINS, T. M., KUCHARCZYK, M. M., GRAVEN-NIELSEN, T. & BANNISTER, K. 2020. Activation of the descending pain modulatory system using cuff pressure algometry: Back translation from man to rat. *European Journal of Pain,* 24**,** 1330-1338. doi: 10.1002/ejp.1580

DA SILVA SANTOS, R. & GALDINO, G. 2018. Endogenous systems involved in exercise-induced analgesia. *Journal of Physiology and Pharmacology,* 69**,** 3-13. doi: 10.26402/jpp.2018.1.01

DEN BANDT, H. L., PAULIS, W. D., BECKWEE, D., ICKMANS, K., NIJS, J. & VOOGT, L. 2019. Pain Mechanisms in Low Back Pain: A Systematic Review With Meta-analysis of Mechanical Quantitative Sensory Testing Outcomes in People With Nonspecific Low Back Pain. *Journal of Orthopaedic and Sports Physical Therapy,* 49**,** 698-715. doi: 10.2519/jospt.2019.8876

DEVECCHI, V., RUSHTON, A. B., GALLINA, A., HENEGHAN, N. R. & FALLA, D. 2021. Are neuromuscular adaptations present in people with recurrent spinal pain during a period of remission? a systematic review. *PloS One,* 16**,** e0249220. doi: 10.1371/journal.pone.0249220

DIONNE, C. E., DUNN, K. M., CROFT, P. R., NACHEMSON, A. L., BUCHBINDER, R., WALKER, B. F., WYATT, M., CASSIDY, J. D., ROSSIGNOL, M., LEBOEUF-YDE, C., HARTVIGSEN, J., LEINO-ARJAS, P., LATZA, U., REIS, S., GIL DEL REAL, M. T., KOVACS, F. M., OBERG, B., CEDRASCHI, C., BOUTER, L. M., KOES, B. W., PICAVET, H. S., VAN TULDER, M. W., BURTON, K., FOSTER, N. E., MACFARLANE, G. J., THOMAS, E., UNDERWOOD, M., WADDELL, G., SHEKELLE, P., VOLINN, E. & VON KORFF, M. 2008. A consensus approach toward the standardization of back pain definitions for use in prevalence studies. *Spine,* 33**,** 95-103. doi: 10.1097/BRS.0b013e31815e7f94

DOCHERTY, S., HARLEY, R., MCAULEY, J. J., CROWE, L. A. N., PEDRET, C., KIRWAN, P. D., SIEBERT, S. & MILLAR, N. L. 2022. The effect of exercise on cytokines: implications for musculoskeletal health: a narrative review. *BMC Sports Science, Medicine and Rehabilitation,* 14**,** 5. doi: 10.1186/s13102-022-00397-2

EDWARDS, R. R., DWORKIN, R. H., SULLIVAN, M. D., TURK, D. C. & WASAN, A. D. 2016. The Role of Psychosocial Processes in the Development and Maintenance of Chronic Pain. *Journal of Pain,* 17**,** T70-92. doi: 10.1016/j.jpain.2016.01.001

ELDRIDGE, S. M., LANCASTER, G. A., CAMPBELL, M. J., THABANE, L., HOPEWELL, S., COLEMAN, C. L. & BOND, C. M. 2016. Defining Feasibility and Pilot Studies in Preparation for Randomised Controlled Trials: Development of a Conceptual Framework. *PloS One,* 11**,** e0150205. doi: 10.1371/journal.pone.0150205

ELLINGSON, L. D., KOLTYN, K. F., KIM, J. S. & COOK, D. B. 2014. Does exercise induce hypoalgesia through conditioned pain modulation? *Psychophysiology,* 51**,** 267-76. doi: 10.1111/psyp.12168

ELLINGSON, L. D., STEGNER, A. J., SCHWABACHER, I. J., KOLTYN, K. F. & COOK, D. B. 2016. Exercise Strengthens Central Nervous System Modulation of Pain in Fibromyalgia. *Brain Sciences,* 6 doi: 10.3390/brainsci6010008

ERIKSEN, M. B. & FRANDSEN, T. F. 2018. The impact of patient, intervention, comparison, outcome (PICO) as a search strategy tool on literature search quality: a systematic review. *Journal of the Medical Library Association,* 106**,** 420-431. doi: 10.5195/jmla.2018.345

FAIRBANK, J. C. & PYNSENT, P. B. 2000. The Oswestry Disability Index. *Spine,* 25**,** 2940-52. doi: 10.1097/00007632-200011150-00017

FALLA, D., GIZZI, L., TSCHAPEK, M., ERLENWEIN, J. & PETZKE, F. 2014. Reduced task-induced variations in the distribution of activity across back muscle regions in individuals with low back pain. *Pain,* 155**,** 944-953. doi: 10.1016/j.pain.2014.01.027

FALLA, D. & HODGES, P. W. 2017. Individualized Exercise Interventions for Spinal Pain. *Exercise and Sport Sciences Reviews,* 45**,** 105-115. doi: 10.1249/JES.0000000000000103

FALLA, D., LINDSTROM, R., RECHTER, L., BOUDREAU, S. & PETZKE, F. 2013. Effectiveness of an 8-week exercise programme on pain and specificity of neck muscle activity in patients with chronic neck pain: a randomized controlled study. *European Journal of Pain,* 17**,** 1517-28. doi: 10.1002/j.1532-2149.2013.00321.x

FARAONI, D. & SCHAEFER, S. T. 2016. Randomized controlled trials vs. observational studies: why not just live together? *BMC Anesthesiology,* 16**,** 102. doi: 10.1186/s12871-016-0265-3

FERNANDES, C., PIDAL-MIRANDA, M., SAMARTIN-VEIGA, N. & CARRILLO-DE-LA-PENA, M. T. 2019. Conditioned pain modulation as a biomarker of chronic pain: a systematic review of its concurrent validity. *Pain,* 160**,** 2679-2690. doi: 10.1097/j.pain.0000000000001664

FERNANDEZ-CARNERO, J., BINDERUP, A. T., GE, H. Y., FERNANDEZ-DE-LAS-PENAS, C., ARENDT-NIELSEN, L. & MADELEINE, P. 2010. Pressure pain sensitivity mapping in experimentally

induced lateral epicondylalgia. *Medicine and Science in Sports and Exercise,* 42**,** 922-7. doi: 10.1249/MSS.0b013e3181c29eab
FIELD, A. 2007. Discovering Statistics Using SPSS. ProQuest Ebook Central: SAGE Publications.
FINGLETON, C., SMART, K. M. & DOODY, C. M. 2017. Exercise-induced Hypoalgesia in People With Knee Osteoarthritis With Normal and Abnormal Conditioned Pain Modulation. *Clinical Journal of Pain,* 33**,** 395-404. doi: 10.1097/AJP.0000000000000418
FINNERN, M. M., KLEINBOHL, D., FLOR, H., BENRATH, J. & HOLZL, R. 2021. Differential sensory and clinical phenotypes of patients with chronic widespread and regional musculoskeletal pain. *Pain,* 162**,** 56-70. doi: 10.1097/j.pain.0000000000002018
FLOOD, A., WADDINGTON, G., THOMPSON, K. & CATHCART, S. 2017. Increased conditioned pain modulation in athletes. *Journal of Sports Sciences,* 35**,** 1066-1072. doi: 10.1080/02640414.2016.1210196
FOSTER, N. E., ANEMA, J. R., CHERKIN, D., CHOU, R., COHEN, S. P., GROSS, D. P., FERREIRA, P. H., FRITZ, J. M., KOES, B. W., PEUL, W., TURNER, J. A. & MAHER, C. G. 2018. Prevention and treatment of low back pain: evidence, challenges, and promising directions. *The Lancet,* 391**,** 2368-2383. doi: 10.1016/S0140-6736(18)30489-6
FOXEN-CRAFT, E. & DAHLQUIST, L. M. 2017. Brief submaximal isometric exercise improves cold pressor pain tolerance. *Journal of Behavioral Medicine,* 40**,** 760-771. doi: 10.1007/s10865-017-9842-2
FURLAN, A. D., PENNICK, V., BOMBARDIER, C. & VAN TULDER, M. 2009. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. *Spine,* 34**,** 1929-41. doi: 10.1097/BRS.0b013e3181b1c99f
GAJSAR, H., NAHRWOLD, K., TITZE, C., HASENBRING, M. I. & VAEGTER, H. B. 2018. Exercise does not produce hypoalgesia when performed immediately after a painful stimulus. *Scandinavian Journal of Pain,* 18**,** 311-320. doi: 10.1515/sjpain-2018-0024
GAJSAR, H., TITZE, C., HASENBRING, M. I. & VAEGTER, H. B. 2017. Isometric Back Exercise Has Different Effect on Pressure Pain Thresholds in Healthy Men and Women. *Pain Medicine,* 18**,** 917-923. doi: 10.1093/pm/pnw176
GAJSAR, H., TITZE, C., KONIETZNY, K., MEYER, M., VAEGTER, H. B. & HASENBRING, M. I. 2020. Cognitive Inhibition Correlates with Exercise-Induced Hypoalgesia After Aerobic Bicycling in Pain-Free Participants. *Journal of Pain Research,* 13**,** 847-858. doi: 10.2147/JPR.S238718
GATCHEL, R. J., BEVERS, K., LICCIARDONE, J. C., SU, J., DU, Y. & BROTTO, M. 2018. Transitioning from Acute to Chronic Pain: An Examination of Different Trajectories of Low-Back Pain. *Healthcare,* 6 doi: 10.3390/healthcare6020048
GEISLER, M., EICHELKRAUT, L., MILTNER, W. H. R. & WEISS, T. 2019. Expectation of exercise in trained athletes results in a reduction of central processing to nociceptive stimulation. *Behavioural Brain Research,* 356**,** 314-321. doi: 10.1016/j.bbr.2018.08.036
GENEEN, L. J., MOORE, R. A., CLARKE, C., MARTIN, D., COLVIN, L. A. & SMITH, B. H. 2017. Physical activity and exercise for chronic pain in adults: an overview of Cochrane Reviews. *Cochrane Database of Systematic Reviews,* 4**,** CD011279. doi: 10.1002/14651858.CD011279.pub3
GEORGE, S. Z., WITTMER, V. T., FILLINGIM, R. B. & ROBINSON, M. E. 2007. Sex and pain-related psychological variables are associated with thermal pain sensitivity for patients with chronic low back pain. *Journal of Pain,* 8**,** 2-10. doi: 10.1016/j.jpain.2006.05.009
GERDLE, B., GHAFOURI, B., ERNBERG, M. & LARSSON, B. 2014. Chronic musculoskeletal pain: review of mechanisms and biochemical biomarkers as assessed by the microdialysis technique. *Journal of Pain Research,* 7**,** 313-26. doi: 10.2147/JPR.S59144
GERDLE, B., HILGENFELDT, U., LARSSON, B., KRISTIANSEN, J., SOGAARD, K. & ROSENDAL, L. 2008a. Bradykinin and kallidin levels in the trapezius muscle in patients with work-related trapezius myalgia, in patients with whiplash associated pain, and in healthy controls - A microdialysis study of women. *Pain,* 139**,** 578-587. doi: 10.1016/j.pain.2008.06.012

GERDLE, B., LEMMING, D., KRISTIANSEN, J., LARSSON, B., PEOLSSON, M. & ROSENDAL, L. 2008b. Biochemical alterations in the trapezius muscle of patients with chronic whiplash associated disorders (WAD)--a microdialysis study. *European Journal of Pain,* 12**,** 82-93. doi: 10.1016/j.ejpain.2007.03.009

GERDLE, B., SODERBERG, K., SALVADOR PUIGVERT, L., ROSENDAL, L. & LARSSON, B. 2010. Increased interstitial concentrations of pyruvate and lactate in the trapezius muscle of patients with fibromyalgia: a microdialysis study. *Journal of Rehabilitation Medicine,* 42**,** 679-87. doi: 10.2340/16501977-0581

GERHARDT, A., EICH, W., JANKE, S., LEISNER, S., TREEDE, R. D. & TESARZ, J. 2016. Chronic Widespread Back Pain is Distinct From Chronic Local Back Pain: Evidence From Quantitative Sensory Testing, Pain Drawings, and Psychometrics. *Clinical Journal of Pain,* 32**,** 568-79. doi: 10.1097/AJP.0000000000000300

GEVA, N., PRUESSNER, J. & DEFRIN, R. 2014. Acute psychosocial stress reduces pain modulation capabilities in healthy men. *Pain,* 155**,** 2418-25. doi: 10.1016/j.pain.2014.09.023

GHAFOURI, N., GHAFOURI, B., LARSSON, B., STENSSON, N., FOWLER, C. J. & GERDLE, B. 2013. Palmitoylethanolamide and stearoylethanolamide levels in the interstitium of the trapezius muscle of women with chronic widespread pain and chronic neck-shoulder pain correlate with pain intensity and sensitivity. *Pain,* 154**,** 1649-1658. doi: 10.1016/j.pain.2013.05.002

GOMES-NETO, M., LOPES, J. M., CONCEICAO, C. S., ARAUJO, A., BRASILEIRO, A., SOUSA, C., CARVALHO, V. O. & ARCANJO, F. L. 2017. Stabilization exercise compared to general exercises or manual therapy for the management of low back pain: A systematic review and meta-analysis. *Physical Therapy in Sport* 23**,** 136-142. doi: 10.1016/j.ptsp.2016.08.004

GOMOLKA, S., VAEGTER, H. B., NIJS, J., MEEUS, M., GAJSAR, H., HASENBRING, M. I. & TITZE, C. 2019. Assessing Endogenous Pain Inhibition: Test-Retest Reliability of Exercise-Induced Hypoalgesia in Local and Remote Body Parts After Aerobic Cycling. *Pain Medicine,* 20**,** 2272-2282. doi: 10.1093/pm/pnz131

GOUBERT, D., OOSTERWIJCK, J. V., MEEUS, M. & DANNEELS, L. 2016. Structural Changes of Lumbar Muscles in Non-specific Low Back Pain: A Systematic Review. *Pain Physician,* 19**,** E985-E1000.

GRAVEN-NIELSEN, T., VAEGTER, H. B., FINOCCHIETTI, S., HANDBERG, G. & ARENDT-NIELSEN, L. 2015. Assessment of musculoskeletal pain sensitivity and temporal summation by cuff pressure algometry: a reliability study. *Pain,* 156**,** 2193-2202. doi: 10.1097/j.pain.0000000000000294

GRIMBY-EKMAN, A., AHLSTRAND, C., GERDLE, B., LARSSON, B. & SANDEN, H. 2020. Pain intensity and pressure pain thresholds after a light dynamic physical load in patients with chronic neck-shoulder pain. *BMC Musculoskeletal Disorders,* 21**,** 266. doi: 10.1186/s12891-020-03298-y

GRIMBY-EKMAN, A., GHAFOURI, B., SANDEN, H., LARSSON, B. & GERDLE, B. 2017. Different DHEA-S Levels and Response Patterns in Individuals with Chronic Neck Pain, Compared with a Pain Free Group-a Pilot Study. *Pain Medicine,* 18**,** 846-855. doi: 10.1093/pm/pnw162

GUREVICH, M., KOHN, P. M. & DAVIS, C. 1994. Exercise-induced analgesia and the role of reactivity in pain sensitivity. *Journal of Sports Sciences,* 12**,** 549-59. doi: 10.1080/02640419408732205

GUYATT, G., OXMAN, A. D., AKL, E. A., KUNZ, R., VIST, G., BROZEK, J., NORRIS, S., FALCK-YTTER, Y., GLASZIOU, P., DEBEER, H., JAESCHKE, R., RIND, D., MEERPOHL, J., DAHM, P. & SCHUNEMANN, H. J. 2011a. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology,* 64**,** 383-94. doi: 10.1016/j.jclinepi.2010.04.026

GUYATT, G. H., OXMAN, A. D., KUNZ, R., BROZEK, J., ALONSO-COELLO, P., RIND, D., DEVEREAUX, P. J., MONTORI, V. M., FREYSCHUSS, B., VIST, G., JAESCHKE, R., WILLIAMS, J. W., JR., MURAD, M. H., SINCLAIR, D., FALCK-YTTER, Y., MEERPOHL, J., WHITTINGTON, C., THORLUND, K., ANDREWS, J. & SCHUNEMANN, H. J. 2011b. GRADE guidelines 6. Rating the quality of evidence--imprecision. *Journal of Clinical Epidemiology,* 64**,** 1283-93. doi: 10.1016/j.jclinepi.2011.01.012

GUYATT, G. H., OXMAN, A. D., KUNZ, R., WOODCOCK, J., BROZEK, J., HELFAND, M., ALONSO-COELLO, P., FALCK-YTTER, Y., JAESCHKE, R., VIST, G., AKL, E. A., POST, P. N., NORRIS, S., MEERPOHL, J., SHUKLA, V. K., NASSER, M., SCHUNEMANN, H. J. & GROUP, G. W. 2011c. GRADE guidelines: 8. Rating the quality of evidence--indirectness. *Journal of Clinical Epidemiology,* 64**,** 1303-10. doi: 10.1016/j.jclinepi.2011.04.014

GUYATT, G. H., OXMAN, A. D., KUNZ, R., WOODCOCK, J., BROZEK, J., HELFAND, M., ALONSO-COELLO, P., GLASZIOU, P., JAESCHKE, R., AKL, E. A., NORRIS, S., VIST, G., DAHM, P., SHUKLA, V. K., HIGGINS, J., FALCK-YTTER, Y., SCHUNEMANN, H. J. & GROUP, G. W. 2011d. GRADE guidelines: 7. Rating the quality of evidence--inconsistency. *Journal of Clinical Epidemiology,* 64**,** 1294-302. doi: 10.1016/j.jclinepi.2011.03.017

GUYATT, G. H., OXMAN, A. D., MONTORI, V., VIST, G., KUNZ, R., BROZEK, J., ALONSO-COELLO, P., DJULBEGOVIC, B., ATKINS, D., FALCK-YTTER, Y., WILLIAMS, J. W., JR., MEERPOHL, J., NORRIS, S. L., AKL, E. A. & SCHUNEMANN, H. J. 2011e. GRADE guidelines: 5. Rating the quality of evidence--publication bias. *Journal of Clinical Epidemiology,* 64**,** 1277-82. doi: 10.1016/j.jclinepi.2011.01.011

HADDAS, R., SAWYER, S. F., SIZER, P. S., JR., BROOKS, T., CHYU, M. C. & JAMES, C. R. 2016. Effects of Volitional Spine Stabilization and Lower Extremity Fatigue on Trunk Control During Landing in Individuals With Recurrent Low Back Pain. *Journal of Orthopaedic and Sports Physical Therapy,* 46**,** 71-8. doi: 10.2519/jospt.2016.6048

HALL, M., DOBSON, F., PLINSINGA, M., MAILLOUX, C., STARKEY, S., SMITS, E., HODGES, P., VICENZINO, B., SCHABRUN, S. M. & MASSE-ALARIE, H. 2020. Effect of exercise on pain processing and motor output in people with knee osteoarthritis: a systematic review and meta-analysis. *Osteoarthritis and Cartilage,* 28**,** 1501-1513. doi: 10.1016/j.joca.2020.07.009

HANSEN, M. S., HORJALES-ARAUJO, E. & DAHL, J. B. 2015. Associations between psychological variables and pain in experimental pain models. A systematic review. *Acta Anaesthesiologica Scandinavica,* 59**,** 1094-102. doi: 10.1111/aas.12555

HANSEN, S., DALGAARD, R. C., MIKKELSEN, P. S., SORENSEN, M. B. & PETERSEN, K. K. 2020a. Modulation of Exercise-Induced Hypoalgesia Following an Exercise Intervention in Healthy Subjects. *Pain Medicine,* doi: 10.1093/pm/pnaa212

HANSEN, S., PETERSEN, K. K., SLOTH, E., MANUM, L. A., MCDONALD, A. K., ANDERSEN, P. G. & VAEGTER, H. B. 2021. Hypoalgesia after exercises with painful vs. non-painful muscles in healthy subjects - a randomized cross-over study. *Scandinavian Journal of Pain,* doi: 10.1515/sjpain-2021-0161

HANSEN, S., VAEGTER, H. B. & PETERSEN, K. K. 2020b. Pretreatment Exercise-induced Hypoalgesia is Associated With Change in Pain and Function After Standardized Exercise Therapy in Painful Knee Osteoarthritis. *Clinical Journal of Pain,* 36**,** 16-24. doi: 10.1097/AJP.0000000000000771

HARRIS, S., STERLING, M., FARRELL, S. F., PEDLER, A. & SMITH, A. D. 2018. The influence of isometric exercise on endogenous pain modulation: comparing exercise-induced hypoalgesia and offset analgesia in young, active adults. *Scandinavian Journal of Pain,* 18**,** 513-523. doi: 10.1515/sjpain-2017-0177

HARTLING, L., MILNE, A., HAMM, M. P., VANDERMEER, B., ANSARI, M., TSERTSVADZE, A. & DRYDEN, D. M. 2013. Testing the Newcastle Ottawa Scale showed low reliability between individual reviewers. *Journal of Clinical Epidemiology,* 66**,** 982-93. doi: 10.1016/j.jclinepi.2013.03.003

HARTVIGSEN, J., HANCOCK, M., KONGSTED, A., LOUW, Q., FERREIRA, M., GENEVAY, S., HOY, D., KARPPINEN, J., PRANSKY, G., SIEPER, J., SMEETS, R., UNDERWOOD, M. & LANCET LOW BACK PAIN SERIES WORKING GROUP 2018. What low back pain is and why we need to pay attention. *The Lancet,* 391**,** 2356-2367. doi: 10.1016/s0140-6736(18)30480-x

HASENBRING, M. I., CHEHADI, O., TITZE, C. & KREDDIG, N. 2014. Fear and anxiety in the transition from acute to chronic pain: there is evidence for endurance besides avoidance. *Pain Managament,* 4**,** 363-74. doi: 10.2217/pmt.14.36

HAYDEN, J. A., ELLIS, J., OGILVIE, R., MALMIVAARA, A. & VAN TULDER, M. W. 2021a. Exercise therapy for chronic low back pain. *Cochrane Database of Systematic Reviews,* 9**,** CD009790. doi: 10.1002/14651858.CD009790.pub2

HAYDEN, J. A., ELLIS, J., OGILVIE, R., STEWART, S. A., BAGG, M. K., STANOJEVIC, S., YAMATO, T. P. & SARAGIOTTO, B. T. 2021b. Some types of exercise are more effective than others in people with chronic low back pain: a network meta-analysis. *Journal of Physiotherapy,* 67**,** 252-262. doi: 10.1016/j.jphys.2021.09.004

HELDESTAD, V., LINDER, J., SELLERSJO, L. & NORDH, E. 2010. Reproducibility and influence of test modality order on thermal perception and thermal pain thresholds in quantitative sensory testing. *Clinical Neurophysiology,* 121**,** 1878-85. doi: 10.1016/j.clinph.2010.03.055

HENEGHAN, N. R. & RUSHTON, A. 2016. Understanding why the thoracic region is the 'Cinderella' region of the spine. *Manual Therapy,* 21**,** 274-6. doi: 10.1016/j.math.2015.06.010

HENRIKSEN, M., KLOKKER, L., GRAVEN-NIELSEN, T., BARTHOLDY, C., SCHJODT JORGENSEN, T., BANDAK, E., DANNESKIOLD-SAMSOE, B., CHRISTENSEN, R. & BLIDDAL, H. 2014. Association of exercise therapy and reduction of pain sensitivity in patients with knee osteoarthritis: a randomized controlled trial. *Arthritis Care & Research,* 66**,** 1836-43. doi: 10.1002/acr.22375

HENRY, J. D. & CRAWFORD, J. R. 2005. The short-form version of the Depression Anxiety Stress Scales (DASS-21): construct validity and normative data in a large non-clinical sample. *British Journal of Clinical Psychology,* 44**,** 227-39. doi: 10.1348/014466505X29657

HILL, J. C., WHITEHURST, D. G., LEWIS, M., BRYAN, S., DUNN, K. M., FOSTER, N. E., KONSTANTINOU, K., MAIN, C. J., MASON, E., SOMERVILLE, S., SOWDEN, G., VOHORA, K. & HAY, E. M. 2011. Comparison of stratified primary care management for low back pain with current best practice (STarT Back): a randomised controlled trial. *The Lancet,* 378**,** 1560-71. doi: 10.1016/S0140-6736(11)60937-9

HJERMSTAD, M. J., FAYERS, P. M., HAUGEN, D. F., CARACENI, A., HANKS, G. W., LOGE, J. H., FAINSINGER, R., AASS, N., KAASA, S. & EUROPEAN PALLIATIVE CARE RESEARCH, C. 2011. Studies comparing Numerical Rating Scales, Verbal Rating Scales, and Visual Analogue Scales for assessment of pain intensity in adults: a systematic literature review. *Journal of Pain and Symptom Management,* 41**,** 1073-93. doi: 10.1016/j.jpainsymman.2010.08.016

HOEGER BEMENT, M. K., RASIARMOS, R. L., DICAPO, J. M., LEWIS, A., KELLER, M. L., HARKINS, A. L. & HUNTER, S. K. 2009. The role of the menstrual cycle phase in pain perception before and after an isometric fatiguing contraction. *European Journal of Applied Physiology,* 106**,** 105-12. doi: 10.1007/s00421-009-0995-8

HOEGER BEMENT, M. K., WEYER, A., HARTLEY, S., DREWEK, B., HARKINS, A. L. & HUNTER, S. K. 2011. Pain perception after isometric exercise in women with fibromyalgia. *Archives of Physical Medicine and Rehabilitation,* 92**,** 89-95. doi: 10.1016/j.apmr.2010.10.006

HOFFMAN, M. D., SHEPANSKI, M. A., MACKENZIE, S. P. & CLIFFORD, P. S. 2005. Experimentally induced pain perception is acutely reduced by aerobic exercise in people with chronic low back pain. *Journal of Rehabilitation Research and Development,* 42**,** 183-90. doi: 10.1682/jrrd.2004.06.0065

HOFFMAN, M. D., SHEPANSKI, M. A., RUBLE, S. B., VALIC, Z., BUCKWALTER, J. B. & CLIFFORD, P. S. 2004. Intensity and duration threshold for aerobic exercise-induced analgesia to pressure pain. *Archives of Physical Medicine and Rehabilitation,* 85**,** 1183-7. doi: 10.1016/j.apmr.2003.09.010

HOFFMANN, M. D., SHEPANSKI, M. A., MACKENZIE, S. P. & CLIFFORD, P. S. 2005. Experimentally-induced pain perception is acutely reduced by aerobic exercise in persons with chronic low back pain. *Journal of Rehabilitation Research and Development,* 42**,** 183-190.

HOY, D., MARCH, L., BROOKS, P., BLYTH, F., WOOLF, A., BAIN, C., WILLIAMS, G., SMITH, E., VOS, T., BARENDREGT, J., MURRAY, C., BURSTEIN, R. & BUCHBINDER, R. 2014. The global burden of

low back pain: estimates from the Global Burden of Disease 2010 study. *Annals of the Rheumatic Diseases,* 73**,** 968-74. doi: 10.1136/annrheumdis-2013-204428

HUBSCHER, M., MOLONEY, N., LEAVER, A., REBBECK, T., MCAULEY, J. H. & REFSHAUGE, K. M. 2013. Relationship between quantitative sensory testing and pain or disability in people with spinal pain-a systematic review and meta-analysis. *Pain,* 154**,** 1497-1504. doi: 10.1016/j.pain.2013.05.031

HUBSCHER, M., MOLONEY, N., REBBECK, T., TRAEGER, A. & REFSHAUGE, K. M. 2014. 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,* 30**,** 886-93. doi: 10.1097/AJP.0000000000000045

HUTTON, B., SALANTI, G., CALDWELL, D. M., CHAIMANI, A., SCHMID, C. H., CAMERON, C., IOANNIDIS, J. P., STRAUS, S., THORLUND, K., JANSEN, J. P., MULROW, C., CATALA-LOPEZ, F., GOTZSCHE, P. C., DICKERSIN, K., BOUTRON, I., ALTMAN, D. G. & MOHER, D. 2015. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Annals of Internal Medicine,* 162**,** 777-84. doi: 10.7326/M14-2385

HVIID, J. T., THORLUND, J. B. & VAEGTER, H. B. 2019. Walking increases pain tolerance in humans: an experimental cross-over study. *Scandinavian Journal of Pain,* 19**,** 813-822. doi: 10.1515/sjpain-2019-0070

ICKMANS, K., MALFLIET, A., DE KOONING, M., GOUDMAN, L., HUBLOUE, I., SCHMITZ, T., GOUBERT, D. & AGUILAR-FERRANDIZ, M. E. 2017. Lack of Gender and Age Differences in Pain Measurements Following Exercise in People with Chronic Whiplash-Associated Disorders. *Pain Physician,* 20**,** E829-E840.

IMAMURA, M., CHEN, J., MATSUBAYASHI, S. R., TARGINO, R. A., ALFIERI, F. M., BUENO, D. K. & HSING, W. T. 2013. Changes in pressure pain threshold in patients with chronic nonspecific low back pain. *Spine,* 38**,** 2098-107. doi: 10.1097/01.brs.0000435027.50317.d7

INTERNATIONAL ASSOCIATION FOR THE STUDY OF PAIN. 2021. *Terminology* [Online]. Available: https://www.iasp-pain.org/resources/terminology/ [Last accessed 20/03/2022].

INTERNATIONAL ASSOCIATION FOR THE STUDY OF PAIN TERMINOLOGY WORKING GROUP 2011. Part III: Pain Terms, A Current List with Definitions and Notes on Usage. *Classification of Chronic Pain.* 3rd ed. https://iaspfiles.s3.amazonaws.com/production/public/2021/Part_III-PainTerms.pdf: [Last accessed 20/03/2022].

JANAL, M. N. 1996. Pain sensitivity, exercise and stoicism. *Journal of the Royal Society of Medicine,* 89**,** 376-81.

JENKINSON, C., STEWART-BROWN, S., PETERSEN, S. & PAICE, C. 1999. Assessment of the SF-36 version 2 in the United Kingdom. *Journal of Epidemiology and Community Health,* 53**,** 46-50. doi: 10.1136/jech.53.1.46

JONES, D. H., KILGOUR, R. D. & COMTOIS, A. S. 2007. Test-retest reliability of pressure pain threshold measurements of the upper limb and torso in young healthy women. *Journal of Pain,* 8**,** 650-6. doi: 10.1016/j.jpain.2007.04.003

JONES, M. D., NUZZO, J. L., TAYLOR, J. L. & BARRY, B. K. 2019. Aerobic Exercise Reduces Pressure More Than Heat Pain Sensitivity in Healthy Adults. *Pain Medicine,* 20**,** 1534-1546. doi: 10.1093/pm/pny289

JONES, M. D., TAYLOR, J. L., BOOTH, J. & BARRY, B. K. 2016. Exploring the Mechanisms of Exercise-Induced Hypoalgesia Using Somatosensory and Laser Evoked Potentials. *Frontiers in Physiology,* 7**,** 581. doi: 10.3389/fphys.2016.00581

JONES, M. D., VALENZUELA, T., BOOTH, J., TAYLOR, J. L. & BARRY, B. K. 2017. Explicit Education About Exercise-Induced Hypoalgesia Influences Pain Responses to Acute Exercise in Healthy Adults: A Randomized Controlled Trial. *Journal of Pain,* 18**,** 1409-1416. doi: 10.1016/j.jpain.2017.07.006

JORGENSEN, R., RIS, I., FALLA, D. & JUUL-KRISTENSEN, B. 2014. Reliability, construct and discriminative validity of clinical testing in subjects with and without chronic neck pain. *BMC Musculoskeletal Disorders,* 15**,** 408. doi: 10.1186/1471-2474-15-408

JOSEPH, L. H., BENJAMAPORN, H., PATRAPORN, S., UBON, P. & AATIT, P. 2018. 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,* 11**,** 16-22.

JULL, G. A., MOORE, A., FALLA, D., LEWIS, J., MCCARTHY, C. & STERLING, M. 2015. *Grieve's Modern Musculoskeletal Physiotherapy, 4th Edition,* Edinburgh, London, New York, Oxford, Philadelphia, St Louis, Sydney, Toronto, Elsevier.

JUNGER, S., PAYNE, S. A., BRINE, J., RADBRUCH, L. & BREARLEY, S. G. 2017. Guidance on Conducting and REporting DElphi Studies (CREDES) in palliative care: Recommendations based on a methodological systematic review. *Palliative Medicine,* 31**,** 684-706. doi: 10.1177/0269216317690685

JURGENS, T. P., SAWATZKI, A., HENRICH, F., MAGERL, W. & MAY, A. 2014. An improved model of heat-induced hyperalgesia--repetitive phasic heat pain causing primary hyperalgesia to heat and secondary hyperalgesia to pinprick and light touch. *PloS One,* 9**,** e99507. doi: 10.1371/journal.pone.0099507

KEMPPAINEN, P., HAMALAINEN, O. & KONONEN, M. 1998. Different effects of physical exercise on cold pain sensitivity in fighter pilots with and without the history of acute in-flight neck pain attacks. *Medicine and Science in Sports and Exercise,* 30**,** 577-82. doi: 10.1097/00005768-199804000-00016

KEMPPAINEN, P., PAALASMAA, P., PERTOVAARA, A., ALILA, A. & JOHANSSON, G. 1990. Dexamethasone attenuates exercise-induced dental analgesia in man. *Brain Research,* 519**,** 329-32. doi: 10.1016/0006-8993(90)90096-t

KENNEDY, D. L., KEMP, H. I., RIDOUT, D., YARNITSKY, D. & RICE, A. S. C. 2016. Reliability of conditioned pain modulation: a systematic review. *Pain,* 157**,** 2410-2419. doi: 10.1097/j.pain.0000000000000689

KINDLER, L. L., JONES, K. D., PERRIN, N. & BENNETT, R. M. 2010. Risk factors predicting the development of widespread pain from chronic back or neck pain. *Journal of Pain,* 11**,** 1320-8. doi: 10.1016/j.jpain.2010.03.007

KINSER, A. M., SANDS, W. A. & STONE, M. H. 2009. Reliability and validity of a pressure algometer. *Journal of Strength and Conditioning Research,* 23**,** 312-4. doi: 10.1519/jsc.0b013e31818f051c

KLYNE, D. M., MOSELEY, G. L., STERLING, M., BARBE, M. F. & HODGES, P. W. 2019. Are Signs of Central Sensitization in Acute Low Back Pain a Precursor to Poor Outcome? *Journal of Pain,* 20**,** 994-1009. doi: 10.1016/j.jpain.2019.03.001

KNUTTI, I. A., SUTER, M. R. & OPSOMMER, E. 2014. Test-retest reliability of thermal quantitative sensory testing on two sites within the L5 dermatome of the lumbar spine and lower extremity. *Neuroscience Letters,* 579**,** 157-62. doi: 10.1016/j.neulet.2014.07.023

KOENDERS, N., RUSHTON, A., VERRA, M. L., WILLEMS, P. C., HOOGEBOOM, T. J. & STAAL, J. B. 2019. Pain and disability after first-time spinal fusion for lumbar degenerative disorders: a systematic review and meta-analysis. *European Spine Journal,* 28**,** 696-709. doi: 10.1007/s00586-018-5680-3

KOLTYN, K. F. 2002. Exercise-induced hypoalgesia and intensity of exercise. *Sports Medicine,* 32**,** 477-87. doi: 10.2165/00007256-200232080-00001

KOLTYN, K. F. & ARBOGAST, R. W. 1998. Perception of pain after resistance exercise. *British Journal of Sports Medicine,* 32**,** 20-4. doi: 10.1136/bjsm.32.1.20

KOLTYN, K. F., BRELLENTHIN, A. G., COOK, D. B., SEHGAL, N. & HILLARD, C. 2014. Mechanisms of exercise-induced hypoalgesia. *Journal of Pain,* 15**,** 1294-1304. doi: 10.1016/j.jpain.2014.09.006

KOLTYN, K. F., GARVIN, A. W., GARDINER, R. L. & NELSON, T. F. 1996. Perception of pain following aerobic exercise. *Medicine and Science in Sports and Exercise,* 28**,** 1418-21. doi: 10.1097/00005768-199611000-00011

KONG, J. T., JOHNSON, K. A., BALISE, R. R. & MACKEY, S. 2013. Test-retest reliability of thermal temporal summation using an individualized protocol. *Journal of Pain,* 14**,** 79-88. doi: 10.1016/j.jpain.2012.10.010

KOO, T. K., GUO, J. Y. & BROWN, C. M. 2013. Test-retest reliability, repeatability, and sensitivity of an automated deformation-controlled indentation on pressure pain threshold measurement. *Journal of Manipulative and Physiological Therapeutics,* 36**,** 84-90. doi: 10.1016/j.jmpt.2013.01.001

KOO, T. K. & LI, M. Y. 2016. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. *Journal of Chiropractic Medicine,* 15**,** 155-63. doi: 10.1016/j.jcm.2016.02.012

KOSEK, E., ROOS, E. M., AGEBERG, E. & NILSDOTTER, A. 2013. Increased pain sensitivity but normal function of exercise induced analgesia in hip and knee osteoarthritis--treatment effects of neuromuscular exercise and total joint replacement. *Osteoarthritis and Cartilage,* 21**,** 1299-307. doi: 10.1016/j.joca.2013.06.019

KOTTNER, J., AUDIGE, L., BRORSON, S., DONNER, A., GAJEWSKI, B. J., HROBJARTSSON, A., ROBERTS, C., SHOUKRI, M. & STREINER, D. L. 2011. Guidelines for Reporting Reliability and Agreement Studies (GRRAS) were proposed. *International Journal of Nursing Studies,* 48**,** 661-71. doi: 10.1016/j.ijnurstu.2011.01.016

KROLL, L. S., SJODAHL HAMMARLUND, C., GARD, G., JENSEN, R. H. & BENDTSEN, L. 2018. Has aerobic exercise effect on pain perception in persons with migraine and coexisting tension-type headache and neck pain? A randomized, controlled, clinical trial. *European Journal of Pain,* 22**,** 1399-1408. doi: 10.1002/ejp.1228

KUHTZ-BUSCHBECK, J. P., ANDRESEN, W., GOBEL, S., GILSTER, R. & STICK, C. 2010. Thermoreception and nociception of the skin: a classic paper of Bessou and Perl and analyses of thermal sensitivity during a student laboratory exercise. *Advances in Physiology Education,* 34**,** 25-34. doi: 10.1152/advan.00002.2010

KUITHAN, P., HENEGHAN, N. R., RUSHTON, A., SANDERSON, A. & FALLA, D. 2019. Lack of Exercise-Induced Hypoalgesia to Repetitive Back Movement in People with Chronic Low Back Pain. *Pain Practice,* 19**,** 740-750. doi: 10.1111/papr.12804

KUITHAN, P., RUSHTON, A. & HENEGHAN, N. R. 2022. Schmerzmodellierung durch Bewegung-Bewegungs-induzierte Hypoalgesie in der Physiotherapie [Pain modulation through exercise - Exercise-induced hypoalgesia in Physiotherapy]. *Der Schmerz,* doi: 10.1007/s00482-022-00623-3

KWON, B. K., ROFFEY, D. M., BISHOP, P. B., DAGENAIS, S. & WAI, E. K. 2011. Systematic review: occupational physical activity and low back pain. *Occupational Medicine,* 61**,** 541-8. doi: 10.1093/occmed/kqr092

KWON, M., ALTIN, M., DUENAS, H. & ALEV, L. 2014. The role of descending inhibitory pathways on chronic pain modulation and clinical implications. *Pain Practice,* 14**,** 656-67. doi: 10.1111/papr.12145

LALOUNI, M., FUST, J., VADENMARK-LUNDQVIST, V., EHRSSON, H. H., KILTENI, K. & BIRGITTA JENSEN, K. 2021. Predicting pain: differential pain thresholds during self-induced, externally induced, and imagined self-induced pressure pain. *Pain,* 162**,** 1539-1544. doi: 10.1097/j.pain.0000000000002151

LANNERSTEN, L. & KOSEK, E. 2010. Dysfunction of endogenous pain inhibition during exercise with painful muscles in patients with shoulder myalgia and fibromyalgia. *Pain,* 151**,** 77-86. doi: 10.1016/j.pain.2010.06.021

LAROUCHE, M. C., CAMIRE BERNIER, S., RACINE, R., COLLIN, O., DESMONS, M., MAILLOUX, C. & MASSE-ALARIE, H. 2020. Stretch-induced hypoalgesia: a pilot study. *Scandinavian Journal of Pain,* 20**,** 837-845. doi: 10.1515/sjpain-2020-0018

LARSSON, B., ROSENDAL, L., KRISTIANSEN, J., SJOGAARD, G., SOGAARD, K., GHAFOURI, B., ABDIU, A., KJAER, M. & GERDLE, B. 2008. Responses of algesic and metabolic substances to 8 h of repetitive manual work in myalgic human trapezius muscle. *Pain,* 140**,** 479-490. doi: 10.1016/j.pain.2008.10.001

LEE, H., HUBSCHER, M., MOSELEY, G. L., KAMPER, S. J., TRAEGER, A. C., MANSELL, G. & MCAULEY, J. H. 2015. How does pain lead to disability? A systematic review and meta-analysis of mediation studies in people with back and neck pain. *Pain,* 156**,** 988-997. doi: 10.1097/j.pain.0000000000000146

LEE, H. S. 2014. The effects of aerobic exercise and strengthening exercise on pain pressure thresholds. *Journal of Physical Therapy Science,* 26**,** 1107-11. doi: 10.1589/jpts.26.1107

LEE, H. S., SHIM, J. S., LEE, S. T., KIM, M. & RYU, J. S. 2014. Facilitating effects of fast and slope walking on paraspinal muscles. *Annals of Rehabilitation Medicine,* 38**,** 514-22. doi: 10.5535/arm.2014.38.4.514

LEMLEY, K. J., HUNTER, S. K. & BEMENT, M. K. 2015. Conditioned pain modulation predicts exercise-induced hypoalgesia in healthy adults. *Medicine and Science in Sports and Exercise,* 47**,** 176-84. doi: 10.1249/MSS.0000000000000381

LESNAK, J. B. & SLUKA, K. A. 2020. Mechanism of exercise-induced analgesia: what we can learn from physically active animals. *PAIN reports,* 5**,** e850. doi: 10.1097/PR9.0000000000000850

LEWIS, C., SOUVLIS, T. & STERLING, M. 2010. Sensory characteristics of tender points in the lower back. *Manual Therapy,* 15**,** 451-6. doi: 10.1016/j.math.2010.03.006

LI, C., LIU, S., LU, X. & TAO, F. 2019. Role of Descending Dopaminergic Pathways in Pain Modulation. *Current Neuropharmacology,* 17**,** 1176-1182. doi: 10.2174/1570159X17666190430102531

LIMA, L. V., ABNER, T. S. S. & SLUKA, K. A. 2017. Does exercise increase or decrease pain? Central mechanisms underlying these two phenomena. *Journal of Physiology,* 595**,** 4141-4150. doi: 10.1113/JP273355

LLUCH, E., ARGUISUELAS, M. D., COLOMA, P. S., PALMA, F., REY, A. & FALLA, D. 2013. Effects of deep cervical flexor training on pressure pain thresholds over myofascial trigger points in patients with chronic neck pain. *Journal of Manipulative and Physiological Therapeutics,* 36**,** 604-11. doi: 10.1016/j.jmpt.2013.08.004

LOCKE, D., GIBSON, W., MOSS, P., MUNYARD, K., MAMOTTE, C. & WRIGHT, A. 2014. Analysis of meaningful conditioned pain modulation effect in a pain-free adult population. *Journal of Pain,* 15**,** 1190-1198. doi: 10.1016/j.jpain.2014.09.001

MAHER, C., UNDERWOOD, M. & BUCHBINDER, R. 2017. Non-specific low back pain. *The Lancet,* 389**,** 736-747. doi: 10.1016/S0140-6736(16)30970-9

MAIER, C., BARON, R., TOLLE, T. R., BINDER, A., BIRBAUMER, N., BIRKLEIN, F., GIERTHMUHLEN, J., FLOR, H., GEBER, C., HUGE, V., KRUMOVA, E. K., LANDWEHRMEYER, G. B., MAGERL, W., MAIHOFNER, C., RICHTER, H., ROLKE, R., SCHERENS, A., SCHWARZ, A., SOMMER, C., TRONNIER, V., UCEYLER, N., VALET, M., WASNER, G. & TREEDE, D. R. 2010. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes. *Pain,* 150**,** 439-450. doi: 10.1016/j.pain.2010.05.002

MAILLOUX, C., BEAULIEU, L. D., WIDEMAN, T. H. & MASSE-ALARIE, H. 2021a. Within-session test-retest reliability of pressure pain threshold and mechanical temporal summation in healthy subjects. *PloS One,* 16**,** e0245278. doi: 10.1371/journal.pone.0245278

MAILLOUX, C., WIDEMAN, T. H. & MASSÉ-ALARIE, H. 2021b. Wrist, but Not Back, Isometric Contraction Induced Widespread Hypoalgesia in Healthy Participants. *Frontiers in Pain Research,* 2 doi: 10.3389/fpain.2021.701830

MARCUZZI, A., DEAN, C. M., WRIGLEY, P. J. & HUSH, J. M. 2015. Early changes in somatosensory function in spinal pain: a systematic review and meta-analysis. *Pain,* 156**,** 203-214. doi: 10.1097/01.j.pain.0000460300.10583.f6

MARCUZZI, A., WRIGLEY, P. J., DEAN, C. M., ADAMS, R. & HUSH, J. M. 2017. The long-term reliability of static and dynamic quantitative sensory testing in healthy individuals. *Pain,* 158**,** 1217-1223. doi: 10.1097/j.pain.0000000000000901

MARS, T., ELLARD, D. R., ANTROBUS, J. H., CAIRNS, M., UNDERWOOD, M., HAYWOOD, K., KEOHANE, S., SANDHU, H. & GRIFFITHS, F. 2015. Intraarticular Facet Injections for Low Back Pain: Design Considerations, Consensus Methodology to Develop the Protocol for a Randomized Controlled Trial. *Pain Physician,* 18**,** 473-93.

MARTINEZ-VALDES, E., FALLA, D., NEGRO, F., MAYER, F. & FARINA, D. 2017. Differential Motor Unit Changes after Endurance or High-Intensity Interval Training. *Medicine and Science in Sports and Exercise,* 49**,** 1126-1136. doi: 10.1249/MSS.0000000000001209

MASSE-ALARIE, H., BEAULIEU, L. D., PREUSS, R. & SCHNEIDER, C. 2016. Corticomotor control of lumbar multifidus muscles is impaired in chronic low back pain: concurrent evidence from ultrasound imaging and double-pulse transcranial magnetic stimulation. *Experimental Brain Research,* 234**,** 1033-45. doi: 10.1007/s00221-015-4528-x

MAYER, T. G., NEBLETT, R., COHEN, H., HOWARD, K. J., CHOI, Y. H., WILLIAMS, M. J., PEREZ, Y. & GATCHEL, R. J. 2012. The development and psychometric validation of the central sensitization inventory. *Pain Practice,* 12**,** 276-85. doi: 10.1111/j.1533-2500.2011.00493.x

MCKENZIE, J. E. & BRENNAN, S. E. 2020. Chapter 12: Synthesizing and presenting findings using other methods. *In:* HIGGINS, J. P. T. T., J.; CHANDLER, J.; CUMPSTON, M.; LI, T.; PAGE, M. J.; WELCH, V.A. (ed.) *Cochrane Handbook for Systematic Reviews of Interventions version 6.1.* https://training.cochrane.org/handbook [Last accessed 21/10/2021].

MCPHEE, M. E., VAEGTER, H. B. & GRAVEN-NIELSEN, T. 2020. Alterations in pronociceptive and antinociceptive mechanisms in patients with low back pain: a systematic review with meta-analysis. *Pain,* 161**,** 464-475. doi: 10.1097/j.pain.0000000000001737

MEEUS, M., ROUSSEL, N. A., TRUIJEN, S. & NIJS, J. 2010. Reduced pressure pain thresholds in response to exercise in chronic fatigue syndrome but not in chronic low back pain: an experimental study. *Journal of Rehabilitation Medicine,* 42**,** 884-90. doi: 10.2340/16501977-0595

MEHTA, S., BASTERO-CABALLERO, R. F., SUN, Y., ZHU, R., MURPHY, D. K., HARDAS, B. & KOCH, G. 2018. Performance of intraclass correlation coefficient (ICC) as a reliability index under various distributions in scale reliability studies. *Statistics in Medicine,* 37**,** 2734-2752. doi: 10.1002/sim.7679

MENG, X. G. & YUE, S. W. 2015. Efficacy of aerobic exercise for treatment of chronic low back pain: a meta-analysis. *American Journal of Physical Medicine and Rehabilitation,* 94**,** 358-65. doi: 10.1097/PHM.0000000000000188

METHLEY, A. M., CAMPBELL, S., CHEW-GRAHAM, C., MCNALLY, R. & CHERAGHI-SOHI, S. 2014. PICO, PICOS and SPIDER: a comparison study of specificity and sensitivity in three search tools for qualitative systematic reviews. *BMC Health Services Research,* 14**,** 579. doi: 10.1186/s12913-014-0579-0

MICALOS, P. S. & ARENDT-NIELSEN, L. 2016. Differential pain response at local and remote muscle sites following aerobic cycling exercise at mild and moderate intensity. *Springerplus,* 5**,** 91. doi: 10.1186/s40064-016-1721-8

MIDDLEBROOK, N., HENEGHAN, N. R., EVANS, D. W., RUSHTON, A. & FALLA, D. 2020. Reliability of temporal summation, thermal and pressure pain thresholds in a healthy cohort and

musculoskeletal trauma population. *PloS One,* 15**,** e0233521. doi: 10.1371/journal.pone.0233521

MLEKUSCH, S., NEZIRI, A. Y., LIMACHER, A., JUNI, P., ARENDT-NIELSEN, L. & CURATOLO, M. 2016. Conditioned Pain Modulation in Patients With Acute and Chronic Low Back Pain. *Clinical Journal of Pain,* 32**,** 116-21. doi: 10.1097/AJP.0000000000000238

MOHER, D., SHAMSEER, L., CLARKE, M., GHERSI, D., LIBERATI, A., PETTICREW, M., SHEKELLE, P., STEWART, L. A. & GROUP, P.-P. 2015. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews,* 4**,** 1. doi: 10.1186/2046-4053-4-1

MOKKINK, L. B., PRINSEN, A. C. C., PATRICK, D. L., ALONSO, J., BOUTER, L. M., DE VET, H. C. W. & TERWEE, C. B. 2018. COSMIN methodology for systematic reviews of Patient-Reported Outcome Measures (PROMs). Available: https://cosmin.nl/wp-content/uploads/COSMIN-syst-review-for-PROMs-manual_version-1_feb-2018.pdf [Last accessed 20/02/2022].

MOLONEY, N. A., HALL, T. M. & DOODY, C. M. 2012. Reliability of thermal quantitative sensory testing: a systematic review. *Journal of Rehabilitation Research and Development,* 49**,** 191-207. doi: 10.1682/jrrd.2011.03.0044

MORENO CATALA, M., SCHROLL, A., LAUBE, G. & ARAMPATZIS, A. 2018. Muscle Strength and Neuromuscular Control in Low-Back Pain: Elite Athletes Versus General Population. *Frontiers in Neuroscience,* 12**,** 436. doi: 10.3389/fnins.2018.00436

MUCKE, M., CUHLS, H., RADBRUCH, L., BARON, R., MAIER, C., TOLLE, T., TREEDE, R. D. & ROLKE, R. 2016. Quantitative sensory testing (QST). English version. *Der Schmerz,* 35**,** 153-160. doi: 10.1007/s00482-015-0093-2

MUNNEKE, W., ICKMANS, K. & VOOGT, L. 2020. The Association of Psychosocial Factors and Exercise-Induced Hypoalgesia in Healthy People and People With Musculoskeletal Pain: A Systematic Review. *Pain Practice,* 20**,** 676-694. doi: 10.1111/papr.12894

MURAD, M. H., MUSTAFA, R. A., SCHUNEMANN, H. J., SULTAN, S. & SANTESSO, N. 2017. Rating the certainty in evidence in the absence of a single estimate of effect. *BMJ Evidence-Based Medicine,* 22**,** 85-87. doi: 10.1136/ebmed-2017-110668

MUTLU, E. K. & OZDINCLER, A. R. 2015. Reliability and responsiveness of algometry for measuring pressure pain threshold in patients with knee osteoarthritis. *Journal of Physical Therapy Science,* 27**,** 1961-5. doi: 10.1589/jpts.27.1961

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE. 2020. *NICE guideline 59. Low back pain and sciatica in over 16s: assessment and management.* [Online]. Available: https://www.nice.org.uk/guidance/ng59# [Last accessed 04.03.2022].

NAUGLE, K. M., FILLINGIM, R. B. & RILEY, J. L. 2012. A meta-analytic review of the hypoalgesic effects of exercise. *Journal of Pain,* 13**,** 1139-50. doi: 10.1016/j.jpain.2012.09.006

NAUGLE, K. M., NAUGLE, K. E., FILLINGIM, R. B. & RILEY, J. L. 2014a. Isometric exercise as a test of pain modulation: effects of experimental pain test, psychological variables, and sex. *Pain Medicine,* 15**,** 692-701. doi: 10.1111/pme.12312

NAUGLE, K. M., NAUGLE, K. E., FILLINGIM, R. B., SAMUELS, B. & RILEY, J. L. 2014b. Intensity thresholds for aerobic exercise-induced hypoalgesia. *Medicine and Science in Sports and Exercise,* 46**,** 817-25. doi: 10.1249/MSS.0000000000000143

NEZIRI, A. Y., CURATOLO, M., LIMACHER, A., NUESCH, E., RADANOV, B., ANDERSEN, O. K., ARENDT-NIELSEN, L. & JUNI, P. 2012. Ranking of parameters of pain hypersensitivity according to their discriminative ability in chronic low back pain. *Pain,* 153**,** 2083-2091. doi: 10.1016/j.pain.2012.06.025

NGUY, V., BARRY, B. K., MOLONEY, N., HASSETT, L. M., CANNING, C. G., LEWIS, S. J. G. & ALLEN, N. E. 2019. Exercise-induced hypoalgesia is present in people with Parkinson's disease: Two observational cross-sectional studies. *European Journal of Pain,* 23**,** 1329-1339. doi: 10.1002/ejp.1400

NICHOLAS, M. K. 2007. The pain self-efficacy questionnaire: Taking pain into account. *European Journal of Pain,* 11**,** 153-63. doi: 10.1016/j.ejpain.2005.12.008
NIE, H., ARENDT-NIELSEN, L., ANDERSEN, H. & GRAVEN-NIELSEN, T. 2005. Temporal summation of pain evoked by mechanical stimulation in deep and superficial tissue. *Journal of Pain,* 6**,** 348-55. doi: 10.1016/j.jpain.2005.01.352
NIE, H., ARENDT-NIELSEN, L., MADELEINE, P. & GRAVEN-NIELSEN, T. 2006. Enhanced temporal summation of pressure pain in the trapezius muscle after delayed onset muscle soreness. *Experimental Brain Research,* 170**,** 182-90. doi: 10.1007/s00221-005-0196-6
NIE, H., GRAVEN-NIELSEN, T. & ARENDT-NIELSEN, L. 2009. Spatial and temporal summation of pain evoked by mechanical pressure stimulation. *European Journal of Pain,* 13**,** 592-9. doi: 10.1016/j.ejpain.2008.07.013
NIJS, J., KOSEK, E., VAN OOSTERWIJCK, J. & MEEUS, M. 2012. Dysfunctional endogenous analgesia during exercise in patients with chronic pain: to exercise or not to exercise? *Pain Physician,* 15**,** ES205-13.
NUZZO, J. L., BARRY, B. K., JONES, M. D., GANDEVIA, S. C. & TAYLOR, J. L. 2017. Effects of Four Weeks of Strength Training on the Corticomotoneuronal Pathway. *Medicine and Science in Sports and Exercise,* 49**,** 2286-2296. doi: 10.1249/MSS.0000000000001367
O'LEARY, H., SMART, K. M., MOLONEY, N. A. & DOODY, C. M. 2017. Nervous System Sensitization as a Predictor of Outcome in the Treatment of Peripheral Musculoskeletal Conditions: A Systematic Review. *Pain Practice,* 17**,** 249-266. doi: 10.1111/papr.12484
O'LEARY, S., FALLA, D., HODGES, P. W., JULL, G. & VICENZINO, B. 2007. Specific therapeutic exercise of the neck induces immediate local hypoalgesia. *Journal of Pain,* 8**,** 832-9. doi: 10.1016/j.jpain.2007.05.014
O'NEILL, S., LARSEN, J. B., NIM, C. & ARENDT-NIELSEN, L. 2019. 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,* 19**,** 25-37. doi: 10.1515/sjpain-2018-0113
O'NEILL, S., MANNICHE, C., GRAVEN-NIELSEN, T. & ARENDT-NIELSEN, L. 2014. Association between a composite score of pain sensitivity and clinical parameters in low-back pain. *Clinical Journal of Pain,* 30**,** 831-8. doi: 10.1097/AJP.0000000000000042
O'SULLIVAN, P. 2005. Diagnosis and classification of chronic low back pain disorders: maladaptive movement and motor control impairments as underlying mechanism. *Manual Therapy,* 10**,** 242-55. doi: 10.1016/j.math.2005.07.001
O'SULLIVAN, P. 2012. It's time for change with the management of non-specific chronic low back pain. *British Journal of Sports Medicine,* 46**,** 224-7. doi: 10.1136/bjsm.2010.081638
O'SULLIVAN, P., CANEIRO, J. P., O'KEEFFE, M. & O'SULLIVAN, K. 2016. Unraveling the Complexity of Low Back Pain. *Journal of Orthopaedic and Sports Physical Therapy,* 46**,** 932-937. doi: 10.2519/jospt.2016.0609
ODGAARD-JENSEN, J., VIST, G. E., TIMMER, A., KUNZ, R., AKL, E. A., SCHUNEMANN, H., BRIEL, M., NORDMANN, A. J., PREGNO, S. & OXMAN, A. D. 2011. Randomisation to protect against selection bias in healthcare trials. *Cochrane Database of Systematic Reviews***,** MR000012. doi: 10.1002/14651858.MR000012.pub3
OHLMAN, T., MILLER, L., NAUGLE, K. E. & NAUGLE, K. M. 2018. Physical Activity Levels Predict Exercise-induced Hypoalgesia in Older Adults. *Medicine and Science in Sports and Exercise,* 50**,** 2101-2109. doi: 10.1249/MSS.0000000000001661
OLIVEIRA, C. B., MAHER, C. G., PINTO, R. Z., TRAEGER, A. C., LIN, C. C., CHENOT, J. F., VAN TULDER, M. & KOES, B. W. 2018. Clinical practice guidelines for the management of non-specific low back pain in primary care: an updated overview. *European Spine Journal,* 27**,** 2791-2803. doi: 10.1007/s00586-018-5673-2

ONEN, S. H., ALLOUI, A., GROSS, A., ESCHALLIER, A. & DUBRAY, C. 2001. The effects of total sleep deprivation, selective sleep interruption and sleep recovery on pain tolerance thresholds in healthy subjects. *Journal of Sleep Research,* 10**,** 35-42. doi: 10.1046/j.1365-2869.2001.00240.x

OSMAN, A., BARRIOS, F. X., GUTIERREZ, P. M., KOPPER, B. A., MERRIFIELD, T. & GRITTMANN, L. 2000. The Pain Catastrophizing Scale: further psychometric evaluation with adult samples. *Journal of Behavioral Medicine,* 23**,** 351-65. doi: 10.1023/a:1005548801037

OSSIPOV, M. H. 2012. The perception and endogenous modulation of pain. *Scientifica,* 2012**,** 561761. doi: 10.6064/2012/561761

OTHMAN, R., DASSANAYAKE, S., JAYAKARAN, P., TUMILTY, S., SWAIN, N. & MANI, R. 2020. Relationships Between Psychological, Social, Physical Activity, and Sleep Measures and Somatosensory Function in Individuals With Spinal Pain: A Systematic Review and Meta-analysis. *Clinical Journal of Pain,* 36**,** 124-134. doi: 10.1097/AJP.0000000000000775

OWEN, P. J., MILLER, C. T., MUNDELL, N. L., VERSWIJVEREN, S., TAGLIAFERRI, S. D., BRISBY, H., BOWE, S. J. & BELAVY, D. L. 2020. Which specific modes of exercise training are most effective for treating low back pain? Network meta-analysis. *British Journal of Sports Medicine,* 54**,** 1279-1287. doi: 10.1136/bjsports-2019-100886

OWENS, M. A., BULLS, H. W., TROST, Z., TERRY, S. C., GOSSETT, E. W., WESSON-SIDES, K. M. & GOODIN, B. R. 2016. An Examination of Pain Catastrophizing and Endogenous Pain Modulatory Processes in Adults with Chronic Low Back Pain. *Pain Medicine,* 17**,** 1452-64. doi: 10.1093/pm/pnv074

PACHECO-BARRIOS, K., GIANLORENCO, A. C., MACHADO, R., QUEIROGA, M., ZENG, H., SHAIKH, E., YANG, Y., NOGUEIRA, B., CASTELO-BRANCO, L. & FREGNI, F. 2020. Exercise-induced pain threshold modulation in healthy subjects: a systematic review and meta-analysis. *Principles and Practice of Clinical Research,* 6**,** 11-28. doi: 10.21801/ppcrj.2020.63.2

PADAWER, W. J. & LEVINE, F. M. 1992. Exercise-induced analgesia: fact or artifact? *Pain,* 48**,** 131-135. doi: 10.1016/0304-3959(92)90048-G

PAGE, M. J., MCKENZIE, J. E., BOSSUYT, P. M., BOUTRON, I., HOFFMANN, T. C., MULROW, C. D., SHAMSEER, L., TETZLAFF, J. M., AKL, E. A., BRENNAN, S. E., CHOU, R., GLANVILLE, J., GRIMSHAW, J. M., HROBJARTSSON, A., LALU, M. M., LI, T., LODER, E. W., MAYO-WILSON, E., MCDONALD, S., MCGUINNESS, L. A., STEWART, L. A., THOMAS, J., TRICCO, A. C., WELCH, V. A., WHITING, P. & MOHER, D. 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ,* 372**,** n71. doi: 10.1136/bmj.n71

PAUNGMALI, A., JOSEPH, L. H., SITILERTPISAN, P., PIRUNSAN, U. & UTHAIKHUP, S. 2017. Lumbopelvic Core Stabilization Exercise and Pain Modulation Among Individuals with Chronic Nonspecific Low Back Pain. *Pain Practice,* 17**,** 1008-1014. doi: 10.1111/papr.12552

PENZA, C. W., HORN, M. E., GEORGE, S. Z. & BISHOP, M. D. 2017. Comparison of 2 Lumbar Manual Therapies on Temporal Summation of Pain in Healthy Volunteers. *Journal of Pain,* 18**,** 1397-1408. doi: 10.1016/j.jpain.2017.07.007

PERSSON, A. L., HANSSON, G. A., KALLIOMAKI, A., MORITZ, U. & SJOLUND, B. H. 2000. Pressure pain thresholds and electromyographically defined muscular fatigue induced by a muscular endurance test in normal women. *Clinical Journal of Pain,* 16**,** 155-63. doi: 10.1097/00002508-200006000-00009

PERSSON, A. L., HANSSON, G. A., KALLIOMAKI, J. & SJOLUND, B. H. 2003. Increases in local pressure pain thresholds after muscle exertion in women with chronic shoulder pain. *Archives of Physical Medicine and Rehabilitation,* 84**,** 1515-22. doi: 10.1016/s0003-9993(03)00273-9

PERSSON, A. L., SJÖLUND, B. H. & LARSSON, B. K. 2009. Three Clusters of Different Properties Characterize Women with Chronic Trapezius Myalgia. *Journal of Musculoskeletal Pain,* 16**,** 287-297. doi: 10.1080/10582450802479768

PERTOVAARA, A., KAUPPILA, T. & HAMALAINEN, M. M. 1996. Influence of skin temperature on heat pain threshold in humans. *Experimental Brain Research,* 107**,** 497-503. doi: 10.1007/BF00230429

PETERSON, J. A., SCHUBERT, D. J., CAMPBELL, J., BEMBEN, M. G. & BLACK, C. D. 2019. Endogenous Pain Inhibitory Function: Endurance-Trained Athletes vs Active Controls. *Pain Medicine,* 20**,** 1822-1830. doi: 10.1093/pm/pnz014

PETTY, N. J., THOMSON, O. P. & STEW, G. 2012. Ready for a paradigm shift? Part 1: introducing the philosophy of qualitative research. *Manual Therapy,* 17**,** 267-74. doi: 10.1016/j.math.2012.03.006

PINCUS, T., KENT, P., BRONFORT, G., LOISEL, P., PRANSKY, G. & HARTVIGSEN, J. 2013. Twenty-five years with the biopsychosocial model of low back pain-is it time to celebrate? A report from the twelfth international forum for primary care research on low back pain. *Spine,* 38**,** 2118-23. doi: 10.1097/BRS.0b013e3182a8c5d6

POKHREL, B. R., MALIK, S. L., ANSARI, A. H., PAUDEL, B. H., SINHA, R. & SINHA, M. 2013. Effect of sub-maximal exercise stress on cold pressor pain: a gender based study. *Kathmandu University Medical Journal,* 11**,** 54-9. doi: 10.3126/kumj.v11i1.11028

POLASKI, A. M., PHELPS, A. L., KOSTEK, M. C., SZUCS, K. A. & KOLBER, B. J. 2019. Exercise-induced hypoalgesia: A meta-analysis of exercise dosing for the treatment of chronic pain. *PloS One,* 14**,** e0210418. doi: 10.1371/journal.pone.0210418

POWER, C., FRANK, J., HERTZMAN, C., SCHIERHOUT, G. & LI, L. 2001. Predictors of low back pain onset in a prospective British study. *American Journal of Public Health,* 91**,** 1671-8. doi: 10.2105/ajph.91.10.1671

PUBLIC HEALTH ENGLAND. 2020. *Health matters: physical activity - prevention and management of long-term conditions* [Online]. Public Health England. Available: https://www.gov.uk/government/publications/health-matters-physical-activity/health-matters-physical-activity-prevention-and-management-of-long-term-conditions [Last accessed 04.03.2022].

PUTA, C., SCHULZ, B., SCHOELER, S., MAGERL, W., GABRIEL, B., GABRIEL, H. H., MILTNER, W. H. & WEISS, T. 2013. Somatosensory abnormalities for painful and innocuous stimuli at the back and at a site distinct from the region of pain in chronic back pain patients. *PloS One,* 8**,** e58885. doi: 10.1371/journal.pone.0058885

QASEEM, A., WILT, T. J., MCLEAN, R. M., FORCIEA, M. A., CLINICAL GUIDELINES COMMITTEE OF THE AMERICAN COLLEGE OF, P., DENBERG, T. D., BARRY, M. J., BOYD, C., CHOW, R. D., FITTERMAN, N., HARRIS, R. P., HUMPHREY, L. L. & VIJAN, S. 2017. Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline From the American College of Physicians. *Annals of Internal Medicine,* 166**,** 514-530. doi: 10.7326/M16-2367

RABEY, M., KENDELL, M., KOREN, S., SILVA, I., WATTS, L., WONG, C., SLATER, H., SMITH, A. & BEALES, D. 2021. Do chronic low back pain subgroups derived from dynamic quantitative sensory testing exhibit differing multidimensional profiles? *Scandinavian Journal of Pain,* 21**,** 474-484. doi: 10.1515/sjpain-2020-0126

RABEY, M., SLATER, H., O'SULLIVAN, P., BEALES, D. & SMITH, A. 2015. Somatosensory nociceptive characteristics differentiate subgroups in people with chronic low back pain: a cluster analysis. *Pain,* 156**,** 1874-1884. doi: 10.1097/j.pain.0000000000000244

RANKIN, G. & STOKES, M. 1998. Reliability of assessment tools in rehabilitation: an illustration of appropriate statistical analyses. *Clinical Rehabilitation,* 12**,** 187-99. doi: 10.1191/026921598672178340

REIMER, M., FORSTENPOINTNER, J., HARTMANN, A., OTTO, J. C., VOLLERT, J., GIERTHMUHLEN, J., KLEIN, T., HULLEMANN, P. & BARON, R. 2020. Sensory bedside testing: a simple stratification approach for sensory phenotyping. *PAIN reports,* 5**,** e820. doi: 10.1097/PR9.0000000000000820

RESNICK, B., ZIMMERMAN, S. I., ORWIG, D., FURSTENBERG, A. L. & MAGAZINER, J. 2000. Outcome expectations for exercise scale: utility and psychometrics. *Journals of Gerontology. Series B: Psychological Sciences and Social Sciences,* 55**,** S352-6. doi: 10.1093/geronb/55.6.s352

REYNOLDS, W. S., BROWN, E. T., DANFORD, J., KAUFMAN, M., WEIN, A., DMOCHOWSKI, R. & BRUEHL, S. 2017. Temporal summation to thermal stimuli is elevated in women with overactive bladder syndrome. *Neurourology and Urodynamics,* 36**,** 1108-1112. doi: 10.1002/nau.23059

RIBEIRO, I. L., CAMARGO, P. R., ALBURQUERQUE-SENDIN, F., MADELEINE, P., FERNANDEZ-DE-LAS-PENAS, C. & SALVINI, T. F. 2016. Topographical pressure pain sensitivity maps of the shoulder region in individuals with subacromial pain syndrome. *Manual Therapy,* 21**,** 134-43. doi: 10.1016/j.math.2015.07.002

RICE, D., NIJS, J., KOSEK, E., WIDEMAN, T., HASENBRING, M. I., KOLTYN, K., GRAVEN-NIELSEN, T. & POLLI, A. 2019. Exercise-Induced Hypoalgesia in Pain-Free and Chronic Pain Populations: State of the Art and Future Directions. *Journal of Pain,* 20**,** 1249-1266. doi: 10.1016/j.jpain.2019.03.005

RIES, A. L. 2005. Minimally clinically important difference for the UCSD Shortness of Breath Questionnaire, Borg Scale, and Visual Analog Scale. *Journal of Chronic Obstructive Pulmonary Disease,* 2**,** 105-10. doi: 10.1081/copd-200050655

ROLKE, R., BARON, R., MAIER, C., TOLLE, T. R., TREEDE, D. R., BEYER, A., BINDER, A., BIRBAUMER, N., BIRKLEIN, F., BOTEFUR, I. C., BRAUNE, S., FLOR, H., HUGE, V., KLUG, R., LANDWEHRMEYER, G. B., MAGERL, W., MAIHOFNER, C., ROLKO, C., SCHAUB, C., SCHERENS, A., SPRENGER, T., VALET, M. & WASSERKA, B. 2006a. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. *Pain,* 123**,** 231-243. doi: 10.1016/j.pain.2006.01.041

ROLKE, R., MAGERL, W., CAMPBELL, K. A., SCHALBER, C., CASPARI, S., BIRKLEIN, F. & TREEDE, R. D. 2006b. Quantitative sensory testing: a comprehensive protocol for clinical trials. *European Journal of Pain,* 10**,** 77-88. doi: 10.1016/j.ejpain.2005.02.003

ROSENDAL, L., KRISTIANSEN, J., GERDLE, B., SOGAARD, K., PEOLSSON, M., KJAER, M., SORENSEN, J. & LARSSON, B. 2005. Increased levels of interstitial potassium but normal levels of muscle IL-6 and LDH in patients with trapezius myalgia. *Pain,* 119**,** 201-209. doi: 10.1016/j.pain.2005.09.026

ROSENDAL, L., LARSSON, B., KRISTIANSEN, J., PEOLSSON, M., SOGAARD, K., KJAER, M., SORENSEN, J. & GERDLE, B. 2004. Increase in muscle nociceptive substances and anaerobic metabolism in patients with trapezius myalgia: microdialysis in rest and during exercise. *Pain,* 112**,** 324-334. doi: 10.1016/j.pain.2004.09.017

ROUSSEL, N. A., NIJS, J., MEEUS, M., MYLIUS, V., FAYT, C. & OOSTENDORP, R. 2013. Central sensitization and altered central pain processing in chronic low back pain: fact or myth? *Clinical Journal of Pain,* 29**,** 625-38. doi: 10.1097/AJP.0b013e31826f9a71

SAMUELLY-LEICHTAG, G., KODESH, E., MECKEL, Y. & WEISSMAN-FOGEL, I. 2018. A Fast Track to Hypoalgesia - The Anaerobic Exercise Effect on Pain Sensitivity. *International Journal of Sports Medicine,* 39**,** 473-481. doi: 10.1055/s-0043-123645

SANDERSON, A., MARTINEZ-VALDES, E., HENEGHAN, N. R., MURILLO, C., RUSHTON, A. & FALLA, D. 2019. Variation in the spatial distribution of erector spinae activity during a lumbar endurance task in people with low back pain. *Journal of Anatomy,* 234**,** 532-542. doi: 10.1111/joa.12935

SARAGIOTTO, B. T., MAHER, C. G., YAMATO, T. P., COSTA, L. O. P., COSTA, L. C. M., OSTELO, R. & MACEDO, L. G. 2016. Motor Control Exercise for Nonspecific Low Back Pain: A Cochrane Review. *Spine,* 41**,** 1284-1295. doi: 10.1097/BRS.0000000000001645

SCHAFER, A. G., HALL, T. M., ROLKE, R., TREEDE, R. D., LUDTKE, K., MALLWITZ, J. & BRIFFA, K. N. 2014. Low back related leg pain: an investigation of construct validity of a new classification

system. *Journal of Back and Musculoskeletal Rehabilitation,* 27**,** 409-18. doi: 10.3233/BMR-140461

SCHEEF, L., JANKOWSKI, J., DAAMEN, M., WEYER, G., KLINGENBERG, M., RENNER, J., MUECKTER, S., SCHURMANN, B., MUSSHOFF, F., WAGNER, M., SCHILD, H. H., ZIMMER, A. & BOECKER, H. 2012. An fMRI study on the acute effects of exercise on pain processing in trained athletes. *Pain,* 153**,** 1702-1714. doi: 10.1016/j.pain.2012.05.008

SCHENK, P., LAEUBLI, T. & KLIPSTEIN, A. 2007. Validity of pressure pain thresholds in female workers with and without recurrent low back pain. *European Spine Journal,* 16**,** 267-75. doi: 10.1007/s00586-006-0124-x

SCHMITT, A., WALLAT, D., STANGIER, C., MARTIN, J. A., SCHLESINGER-IRSCH, U. & BOECKER, H. 2020. Effects of fitness level and exercise intensity on pain and mood responses. *European Journal of Pain,* 24**,** 568-579. doi: 10.1002/ejp.1508

SCOGGINS, J. F. & PATRICK, D. L. 2009. The use of patient-reported outcomes instruments in registered clinical trials: evidence from ClinicalTrials.gov. *Contemporary Clinical Trials,* 30**,** 289-92. doi: 10.1016/j.cct.2009.02.005

SEARLE, A., SPINK, M., HO, A. & CHUTER, V. 2015. Exercise interventions for the treatment of chronic low back pain: a systematic review and meta-analysis of randomised controlled trials. *Clinical Rehabilitation,* 29**,** 1155-67. doi: 10.1177/0269215515570379

SHEA, B. J., REEVES, B. C., WELLS, G., THUKU, M., HAMEL, C., MORAN, J., MOHER, D., TUGWELL, P., WELCH, V., KRISTJANSSON, E. & HENRY, D. A. 2017. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ,* 358**,** j4008. doi: 10.1136/bmj.j4008

SHOJAEI, I., SALT, E. G., HOOKER, Q., VAN DILLEN, L. R. & BAZRGARI, B. 2017. Comparison of lumbo-pelvic kinematics during trunk forward bending and backward return between patients with acute low back pain and asymptomatic controls. *Clinical Biomechanics,* 41**,** 66-71. doi: 10.1016/j.clinbiomech.2016.12.005

SIM, J. & ARNELL, P. 1993. Measurement validity in physical therapy research. *Physical Therapy,* 73**,** 102-10. doi: 10.1093/ptj/73.2.102

SIM, J. & WRIGHT, C. 2002. *Research in health care: concepts, design and methods,* Cheltenham, Nelson Thornes Ltd.

SITGES, C., VELASCO-ROLDAN, O., CRESPI, J., GARCIA-DOPICO, N., SEGUR-FERRER, J., GONZALEZ-ROLDAN, A. M. & MONTOYA, P. 2021. Acute Effects of a Brief Physical Exercise Intervention on Somatosensory Perception, Lumbar Strength, and Flexibility in Patients with Nonspecific Chronic Low-Back Pain. *Journal of Pain Research,* 14**,** 487-500. doi: 10.2147/JPR.S274134

SKIVINGTON, K., MATTHEWS, L., SIMPSON, S. A., CRAIG, P., BAIRD, J., BLAZEBY, J. M., BOYD, K. A., CRAIG, N., FRENCH, D. P., MCINTOSH, E., PETTICREW, M., RYCROFT-MALONE, J., WHITE, M. & MOORE, L. 2021. Framework for the development and evaluation of complex interventions: gap analysis, workshop and consultation-informed update. *Health Technology Assessment,* 25**,** 1-132. doi: 10.3310/hta25570

SLADE, S. C. & KEATING, J. L. 2010. Measurement of participant experience and satisfaction of exercise programs for low back pain: a structured literature review. *Pain Medicine,* 11**,** 1489-99. doi: 10.1111/j.1526-4637.2010.00951.x

SLUKA, K. A., FREY-LAW, L. & HOEGER BEMENT, M. 2018. Exercise-induced pain and analgesia? Underlying mechanisms and clinical translation. *Pain,* 159**,** S91-S97. doi: 10.1097/j.pain.0000000000001235

SMART, K. M., BLAKE, C., STAINES, A. & DOODY, C. 2011. The Discriminative validity of "nociceptive," "peripheral neuropathic," and "central sensitization" as mechanisms-based classifications of musculoskeletal pain. *Clinical Journal of Pain,* 27**,** 655-63. doi: 10.1097/AJP.0b013e318215f16a

SMEETS, R. J., WADE, D., HIDDING, A., VAN LEEUWEN, P. J., VLAEYEN, J. W. & KNOTTNERUS, J. A. 2006. The association of physical deconditioning and chronic low back pain: a hypothesis-oriented systematic review. *Disability and Rehabilitation,* 28**,** 673-93. doi: 10.1080/09638280500264782

SMITH, A., RITCHIE, C., PEDLER, A., MCCAMLEY, K., ROBERTS, K. & STERLING, M. 2017a. Exercise induced hypoalgesia is elicited by isometric, but not aerobic exercise in individuals with chronic whiplash associated disorders. *Scandinavian Journal of Pain,* 15**,** 14-21. doi: 10.1016/j.sjpain.2016.11.007

SMITH, A., RITCHIE, C., WARREN, J. & STERLING, M. 2020. Exercise-induced Hypoalgesia Is Impaired in Chronic Whiplash-associated Disorders (WAD) With Both Aerobic and Isometric Exercise. *Clinical Journal of Pain,* 36**,** 601-611. doi: 10.1097/AJP.0000000000000845

SMITH, B. E., HENDRICK, P., SMITH, T. O., BATEMAN, M., MOFFATT, F., RATHLEFF, M. S., SELFE, J. & LOGAN, P. 2017b. Should exercises be painful in the management of chronic musculoskeletal pain? A systematic review and meta-analysis. *British Journal of Sports Medicine,* 51**,** 1679-1687. doi: 10.1136/bjsports-2016-097383

SMITH, S. M., DWORKIN, R. H., TURK, D. C., BARON, R., POLYDEFKIS, M., TRACEY, I., BORSOOK, D., EDWARDS, R. R., HARRIS, R. E., WAGER, T. D., ARENDT-NIELSEN, L., BURKE, L. B., CARR, D. B., CHAPPELL, A., FARRAR, J. T., FREEMAN, R., GILRON, I., GOLI, V., HAEUSSLER, J., JENSEN, T., KATZ, N. P., KENT, J., KOPECKY, E. A., LEE, D. A., MAIXNER, W., MARKMAN, J. D., MCARTHUR, J. C., MCDERMOTT, M. P., PARVATHENANI, L., RAJA, S. N., RAPPAPORT, B. A., RICE, A. S. C., ROWBOTHAM, M. C., TOBIAS, J. K., WASAN, A. D. & WITTER, J. 2017c. The Potential Role of Sensory Testing, Skin Biopsy, and Functional Brain Imaging as Biomarkers in Chronic Pain Clinical Trials: IMMPACT Considerations. *Journal of Pain,* 18**,** 757-777. doi: 10.1016/j.jpain.2017.02.429

SPENCER, S., WOLF, A. & RUSHTON, A. 2016. Spinal-Exercise Prescription in Sport: Classifying Physical Training and Rehabilitation by Intention and Outcome. *Journal of Athletic Training,* 51**,** 613-628. doi: 10.4085/1062-6050-51.10.03

SPRANGER, J., HOMBERG, A., SONNBERGER, M. & NIEDERBERGER, M. 2022. Reporting guidelines for Delphi techniques in health sciences: A methodological review. *Zeitschrift fuer Evidenz, Fortbildung und Qualitaet im Gesundheitswesen,* 172**,** 1-11. doi: 10.1016/j.zefq.2022.04.025

STANTON, T. R., FRITZ, J. M., HANCOCK, M. J., LATIMER, J., MAHER, C. G., WAND, B. M. & PARENT, E. C. 2011. Evaluation of a treatment-based classification algorithm for low back pain: a cross-sectional study. *Physical Therapy,* 91**,** 496-509. doi: 10.2522/ptj.20100272

STANTON, T. R., LATIMER, J., MAHER, C. G. & HANCOCK, M. J. 2010. How do we define the condition 'recurrent low back pain'? A systematic review. *European Spine Journal,* 19**,** 533-9. doi: 10.1007/s00586-009-1214-3

STAUD, R., ROBINSON, M. E. & PRICE, D. D. 2005. Isometric exercise has opposite effects on central pain mechanisms in fibromyalgia patients compared to normal controls. *Pain,* 118**,** 176-84. doi: 10.1016/j.pain.2005.08.007

STEIGER, F., WIRTH, B., DE BRUIN, E. D. & MANNION, A. F. 2012. Is a positive clinical outcome after exercise therapy for chronic non-specific low back pain contingent upon a corresponding improvement in the targeted aspect(s) of performance? A systematic review. *European Spine Journal,* 21**,** 575-98. doi: 10.1007/s00586-011-2045-6

STENSSON, N. & GRIMBY-EKMAN, A. 2019. Altered relationship between anandamide and glutamate in circulation after 30 min of arm cycling: A comparison of chronic pain subject with healthy controls. *Molecular Pain,* 15 doi: 10.1177/1744806919898360

STERNE, J. A. C., SAVOVIC, J., PAGE, M. J., ELBERS, R. G., BLENCOWE, N. S., BOUTRON, I., CATES, C. J., CHENG, H. Y., CORBETT, M. S., ELDRIDGE, S. M., EMBERSON, J. R., HERNAN, M. A., HOPEWELL, S., HROBJARTSSON, A., JUNQUEIRA, D. R., JUNI, P., KIRKHAM, J. J., LASSERSON, T., LI, T., MCALEENAN, A., REEVES, B. C., SHEPPERD, S., SHRIER, I., STEWART, L. A., TILLING, K.,

WHITE, I. R., WHITING, P. F. & HIGGINS, J. P. T. 2019. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ,* 366**,** l4898. doi: 10.1136/bmj.l4898
STOLZMAN, S. & BEMENT, M. H. 2016. Does Exercise Decrease Pain via Conditioned Pain Modulation in Adolescents? *Pediatric Physical Therapy,* 28**,** 470-3. doi: 10.1097/PEP.0000000000000312
STOLZMAN, S., DANDURAN, M., HUNTER, S. K. & BEMENT, M. H. 2015. Pain Response after Maximal Aerobic Exercise in Adolescents across Weight Status. *Medicine and Science in Sports and Exercise,* 47**,** 2431-40. doi: 10.1249/MSS.0000000000000678
STROM, V., KNARDAHL, S., STANGHELLE, J. K. & ROE, C. 2009a. Pain induced by a single simulated office-work session: time course and association with muscle blood flux and muscle activity. *European Journal of Pain,* 13**,** 843-52. doi: 10.1016/j.ejpain.2008.11.003
STROM, V., ROE, C. & KNARDAHL, S. 2009b. Work-induced pain, trapezius blood flux, and muscle activity in workers with chronic shoulder and neck pain. *Pain,* 144**,** 147-55. doi: 10.1016/j.pain.2009.04.002
STROM, V., ROE, C., MATRE, D. & KNARDAHL, S. 2012. Deep tissue hyperalgesia after computer work. *Scandinavian Journal of Pain,* 3**,** 53-60. doi: 10.1016/j.sjpain.2011.08.005
SULLIVAN, M. J. L., BISHOP, S. R. & PIVIK, J. 1995. The Pain Catastrophizing Scale: Development and validation. *Psychological Assessment,* 7**,** 524-532. doi: 10.1037/1040-3590.7.4.524
SZIKSZAY, T. M., ADAMCZYK, W. M., WOJTYNA, E. & LUEDTKE, K. 2020. Pain inhibition is not affected by exercise-induced pain. *PAIN reports,* 5**,** e817. doi: 10.1097/PR9.0000000000000817
TAYLOR, N. F., EVANS, O. M. & GOLDIE, P. A. 2003. The effect of walking faster on people with acute low back pain. *European Spine Journal,* 12**,** 166-72. doi: 10.1007/s00586-002-0498-3
THONG, I. S. K., JENSEN, M. P., MIRO, J. & TAN, G. 2018. The validity of pain intensity measures: what do the NRS, VAS, VRS, and FPS-R measure? *Scandinavian Journal of Pain,* 18**,** 99-107. doi: 10.1515/sjpain-2018-0012
TRAVERS, M., MOSS, P., GIBSON, W., HINCE, D., YORKE, S., CHUNG, C., LANGFORD, R., TAN, E. E. W., NG, J. & PALSSON, T. S. 2018. Exercise-induced hypoalgesia in women with varying levels of menstrual pain. *Scandinavian Journal of Pain,* 18**,** 303-310. doi: 10.1515/sjpain-2018-0020
UDDIN, Z., MACDERMID, J. C., WOODHOUSE, L. J., TRIANO, J. J., GALEA, V. & GROSS, A. R. 2014. The effect of pressure pain sensitivity and patient factors on self-reported pain-disability in patients with chronic neck pain. *Open Orthopaedics Journal,* 8**,** 302-9. doi: 10.2174/1874325001408010302
UMEDA, M., KEMPKA, L. E., GREENLEE, B. T. & WEATHERBY, A. C. 2016. A smaller magnitude of exercise-induced hypoalgesia in African Americans compared to non-Hispanic Whites: A potential influence of physical activity. *Biological Psychology,* 113**,** 46-51. doi: 10.1016/j.biopsycho.2015.11.006
VAEGTER, H. B., BJERREGAARD, L. K., REDIN, M. M., RASMUSSEN, S. H. & GRAVEN-NIELSEN, T. 2019a. Hypoalgesia after bicycling at lactate threshold is reliable between sessions. *European Journal of Applied Physiology,* 119**,** 91-102. doi: 10.1007/s00421-018-4002-0
VAEGTER, H. B., DORGE, D. B., SCHMIDT, K. S., JENSEN, A. H. & GRAVEN-NIELSEN, T. 2018. Test-Retest Reliabilty of Exercise-Induced Hypoalgesia After Aerobic Exercise. *Pain Medicine,* 19**,** 2212-2222. doi: 10.1093/pm/pny009
VAEGTER, H. B., FEHRMANN, E., GAJSAR, H. & KREDDIG, N. 2020a. Endogenous Modulation of Pain: The Role of Exercise, Stress, and Cognitions in Humans. *Clinical Journal of Pain,* 36**,** 150-161. doi: 10.1097/AJP.0000000000000788
VAEGTER, H. B. & GRAVEN-NIELSEN, T. 2016. Pain modulatory phenotypes differentiate subgroups with different clinical and experimental pain sensitivity. *Pain,* 157**,** 1480-1488. doi: 10.1097/j.pain.0000000000000543
VAEGTER, H. B., HANDBERG, G. & GRAVEN-NIELSEN, T. 2014. Similarities between exercise-induced hypoalgesia and conditioned pain modulation in humans. *Pain,* 155**,** 158-167. doi: 10.1016/j.pain.2013.09.023

VAEGTER, H. B., HANDBERG, G. & GRAVEN-NIELSEN, T. 2015. Isometric exercises reduce temporal summation of pressure pain in humans. *European Journal of Pain,* 19**,** 973-83. doi: 10.1002/ejp.623

VAEGTER, H. B., HANDBERG, G. & GRAVEN-NIELSEN, T. 2016. Hypoalgesia After Exercise and the Cold Pressor Test is Reduced in Chronic Musculoskeletal Pain Patients With High Pain Sensitivity. *Clinical Journal of Pain,* 32**,** 58-69. doi: 10.1097/AJP.0000000000000223

VAEGTER, H. B., HOEGER BEMENT, M., MADSEN, A. B., FRIDRIKSSON, J., DASA, M. & GRAVEN-NIELSEN, T. 2017a. Exercise increases pressure pain tolerance but not pressure and heat pain thresholds in healthy young men. *European Journal of Pain,* 21**,** 73-81. doi: 10.1002/ejp.901

VAEGTER, H. B. & JONES, M. D. 2020. Exercise-induced hypoalgesia after acute and regular exercise: experimental and clinical manifestations and possible mechanisms in individuals with and without pain. *PAIN reports,* 5**,** e823. doi: 10.1097/PR9.0000000000000823

VAEGTER, H. B., LYNG, K. D., YTTERENG, F. W., CHRISTENSEN, M. H., SORENSEN, M. B. & GRAVEN-NIELSEN, T. 2019b. Exercise-Induced Hypoalgesia After Isometric Wall Squat Exercise: A Test-Retest Reliabilty Study. *Pain Medicine,* 20**,** 129-137. doi: 10.1093/pm/pny087

VAEGTER, H. B., MADSEN, A. B., HANDBERG, G. & GRAVEN-NIELSEN, T. 2017b. Kinesiophobia is associated with pain intensity but not pain sensitivity before and after exercise: an explorative analysis. *Physiotherapy,* doi: 10.1016/j.physio.2017.10.001

VAEGTER, H. B., PETERSEN, K. K., SJODSHOLM, L. V., SCHOU, P., ANDERSEN, M. B. & GRAVEN-NIELSEN, T. 2021. Impaired exercise-induced hypoalgesia in individuals reporting an increase in low back pain during acute exercise. *European Journal of Pain,* 25**,** 1053-1063. doi: 10.1002/ejp.1726

VAEGTER, H. B., THINGGAARD, P., MADSEN, C. H., HASENBRING, M. & THORLUND, J. B. 2020b. Power of Words: Influence of Preexercise Information on Hypoalgesia after Exercise-Randomized Controlled Trial. *Medicine and Science in Sports and Exercise,* 52**,** 2373-2379. doi: 10.1249/MSS.0000000000002396

VAN OOSTERWIJCK, J., MEEUS, M., PAUL, L., DE SCHRYVER, M., PASCAL, A., LAMBRECHT, L. & NIJS, J. 2013. Pain physiology education improves health status and endogenous pain inhibition in fibromyalgia: a double-blind randomized controlled trial. *Clinical Journal of Pain,* 29**,** 873-82. doi: 10.1097/AJP.0b013e31827c7a7d

VAN OOSTERWIJCK, J., NIJS, J., MEEUS, M., VAN LOO, M. & PAUL, L. 2012. Lack of endogenous pain inhibition during exercise in people with chronic whiplash associated disorders: an experimental study. *Journal of Pain,* 13**,** 242-54. doi: 10.1016/j.jpain.2011.11.006

VANDENBROUCKE, J. P., VON ELM, E., ALTMAN, D. G., GOTZSCHE, P. C., MULROW, C. D., POCOCK, S. J., POOLE, C., SCHLESSELMAN, J. J., EGGER, M. & INITIATIVE, S. 2014. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *International Journal of Surgery,* 12**,** 1500-24. doi: 10.1016/j.ijsu.2014.07.014

VANTI, C., ANDREATTA, S., BORGHI, S., GUCCIONE, A. A., PILLASTRINI, P. & BERTOZZI, L. 2019. The effectiveness of walking versus exercise on pain and function in chronic low back pain: a systematic review and meta-analysis of randomized trials. *Disability and Rehabilitation,* 41**,** 622-632. doi: 10.1080/09638288.2017.1410730

VARDEH, D., MANNION, R. J. & WOOLF, C. J. 2016. Toward a Mechanism-Based Approach to Pain Diagnosis. *Journal of Pain,* 17**,** T50-69. doi: 10.1016/j.jpain.2016.03.001

VIGGIANI, D. & CALLAGHAN, J. P. 2021. Interrelated hypoalgesia, creep, and muscle fatigue following a repetitive trunk flexion exposure. *Journal of Electromyography and Kinesiology,* 57**,** 102531. doi: 10.1016/j.jelekin.2021.102531

VLAEYEN, J. W. S., KOLE-SNIJDERS, A. M. J., BOEREN, R. G. B. & VAN EEK, H. 1995. Fear of movement/(re)injury in chronic low back pain and its relation to behavioral performance. *Pain,* 62**,** 363-372. doi: 10.1016/0304-3959(94)00279-N

VON ELM, E., ALTMAN, D. G., EGGER, M., POCOCK, S. J., GOTZSCHE, P. C., VANDENBROUCKE, J. P. & INITIATIVE, S. 2008. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Journal of Clinal Epidemiology,* 61**,** 344-9. doi: 10.1016/j.jclinepi.2007.11.008

VON ELM, E., ALTMAN, D. G., EGGER, M., POCOCK, S. J., GOTZSCHE, P. C., VANDENBROUCKE, J. P. & INITIATIVE, S. 2014. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. *International Journal of Surgery,* 12**,** 1495-9. doi: 10.1016/j.ijsu.2014.07.013

VOS, T., et al. 2016. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *The Lancet,* 388**,** 1545-1602. doi: 10.1016/s0140-6736(16)31678-6

VUILLEUMIER, P. H., BIURRUN MANRESA, J. A., GHAMRI, Y., MLEKUSCH, S., SIEGENTHALER, A., ARENDT-NIELSEN, L. & CURATOLO, M. 2015. Reliability of Quantitative Sensory Tests in a Low Back Pain Population. *Regional Anesthesia and Pain Medicine,* 40**,** 665-73. doi: 10.1097/AAP.0000000000000289

WADDELL, G. 1987. 1987 Volvo award in clinical sciences. A new clinical model for the treatment of low-back pain. *Spine,* 12**,** 632-44. doi: 10.1097/00007632-198709000-00002

WADDELL, G., NEWTON, M., HENDERSON, I., SOMERVILLE, D. & MAIN, C. J. 1993. A Fear-Avoidance Beliefs Questionnaire (FABQ) and the role of fear-avoidance beliefs in chronic low back pain and disability. *Pain,* 52**,** 157-168. doi: 10.1016/0304-3959(93)90127-B

WALLER, R., STRAKER, L., O'SULLIVAN, P., STERLING, M. & SMITH, A. 2015. Reliability of pressure pain threshold testing in healthy pain free young adults. *Scandinavian Journal of Pain,* 9**,** 38-41. doi: 10.1016/j.sjpain.2015.05.004

WALTER, S. D., ELIASZIW, M. & DONNER, A. 1998. Sample size and optimal designs for reliability studies. *Statistics in Medicine,* 17**,** 101-10.

WALTON, D. M., MACDERMID, J. C., NIELSON, W., TEASELL, R. W., CHIASSON, M. & BROWN, L. 2011. Reliability, standard error, and minimum detectable change of clinical pressure pain threshold testing in people with and without acute neck pain. *Journal of Orthopaedic and Sports Physical Therapy,* 41**,** 644-50. doi: 10.2519/jospt.2011.3666

WEIR, J. P. 2005. Quantifying test-retest reliability using the intraclass correlation coefficient and the SEM. *Journal of Strength and Conditioning Research,* 19**,** 231-40. doi: 10.1519/15184.1

WELLS, G. A., SHEA, B., O'CONNEL, D., PETERSON,J., WELCH, V., LOSOS, M., TUGWELL, P. 2009. *The Newcastle-Ottawa scale (NOS) for assessing the quailty of nonrandomised studies in meta-analyses.* [Online]. Available: http://www.ohri.ca/programs/clinical_epidemiology/nosgen.pdf [Last accessed 20/02/2022].

WEWEGE, M. A. & JONES, M. D. 2021. Exercise-Induced Hypoalgesia in Healthy Individuals and People With Chronic Musculoskeletal Pain: A Systematic Review and Meta-Analysis. *Journal of Pain,* 22**,** 21-31. doi: 10.1016/j.jpain.2020.04.003

WIDEMAN, T. H., FINAN, P. H., EDWARDS, R. R., QUARTANA, P. J., BUENAVER, L. F., HAYTHORNTHWAITE, J. A. & SMITH, M. T. 2014. Increased sensitivity to physical activity among individuals with knee osteoarthritis: relation to pain outcomes, psychological factors, and responses to quantitative sensory testing. *Pain,* 155**,** 703-711. doi: 10.1016/j.pain.2013.12.028

WITTINK, H., ROGERS, W., GASCON, C., SUKIENNIK, A., CYNN, D. & CARR, D. B. 2001. Relative contribution of mental health and exercise-related pain increment to treadmill test intolerance in patients with chronic low back pain. *Spine,* 26**,** 2368-74. doi: 10.1097/00007632-200111010-00014

WONG, A. Y. L., KARPPINEN, J. & SAMARTZIS, D. 2017. Low back pain in older adults: risk factors, management options and future directions. *Scoliosis and Spinal Disorders,* 12**,** 14. doi: 10.1186/s13013-017-0121-3

WONISCH, M., HOFMANN, P., FRUHWALD, F. M., KRAXNER, W., HODL, R., POKAN, R. & KLEIN, W. 2003. Influence of beta-blocker use on percentage of target heart rate exercise prescription. *European Journal of Cardiovascular Prevention and Rehabilitation,* 10**,** 296-301. doi: 10.1097/00149831-200308000-00013

WOOLF, C. J. 2011. Central sensitization: implications for the diagnosis and treatment of pain. *Pain,* 152**,** S2-S15. doi: 10.1016/j.pain.2010.09.030

WORLD HEALTH ORGANIZATION. 2002. *Towards a Common Language for Functioning, Disability and Health ICF* [Online]. World Health Organization. Available: https://cdn.who.int/media/docs/default-source/classification/icf/icfbeginnersguide.pdf?sfvrsn=eead63d3_4 [Last accessed 31.10.2021].

WOZNOWSKI-VU, A., ATERNALI, A., GERVAIS, A., PAVILANIS, A. D. S., NIJS, J., SULLIVAN, M. J. L. & WIDEMAN, T. H. 2021. The Prospective Prognostic Value of Biopsychosocial Indices of Sensitivity to Physical Activity Among People With Back Pain. *Clinical Journal of Pain,* 37**,** 719-729. doi: 10.1097/AJP.0000000000000965

WOZNOWSKI-VU, A., UDDIN, Z., FLEGG, D., ATERNALI, A., WICKENS, R., SULLIVAN, M. J. L., SWEET, S. N., SKOU, S. T. & WIDEMAN, T. H. 2019. Comparing Novel and Existing Measures of Sensitivity to Physical Activity Among People With Chronic Musculoskeletal Pain: The Importance of Tailoring Activity to Pain. *Clinical Journal of Pain,* 35**,** 656-667. doi: 10.1097/AJP.0000000000000732

XU, C., FU, Z. & WANG, X. 2021. Effect of Transversus abdominis muscle training on pressure-pain threshold in patients with chronic low Back pain. *BMC Sports Science, Medicine and Rehabilitation,* 13**,** 35. doi: 10.1186/s13102-021-00262-8

YELLE, M. D., OSHIRO, Y., KRAFT, R. A. & COGHILL, R. C. 2009. Temporal filtering of nociceptive information by dynamic activation of endogenous pain modulatory systems. *Journal of Neuroscience,* 29**,** 10264-71. doi: 10.1523/JNEUROSCI.4648-08.2009

ZENG, X., ZHANG, Y., KWONG, J. S., ZHANG, C., LI, S., SUN, F., NIU, Y. & DU, L. 2015. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. *Journal of Evidence-Based Medicine,* 8**,** 2-10. doi: 10.1111/jebm.12141

ZHU, G. C., BOTTGER, K., SLATER, H., COOK, C., FARRELL, S. F., HAILEY, L., TAMPIN, B. & SCHMID, A. B. 2019. Concurrent validity of a low-cost and time-efficient clinical sensory test battery to evaluate somatosensory dysfunction. *European Journal of Pain,* 23**,** 1826-1838. doi: 10.1002/ejp.1456

Appendices

Table of Appendices

Appendix 1 Kuithan et al. 2022 Chapter one

Schmerz
https://doi.org/10.1007/s00482-022-00623-3
Eingegangen: 28. Juli 2021
Überarbeitet: 5. Oktober 2021
Angenommen: 2. Januar 2022

Schmerzmodellierung durch Bewegung

Bewegungsinduzierte Hypoalgesie in der Physiotherapie

Pauline Kuithan[1,2] · Alison Rushton[1,3] · Nicola R. Heneghan[1]

[1] Centre of Precision Rehabilitation for Spinal Pain, School of Sport, Exercise and Rehabilitation Sciences, College of Life and Environmental Sciences, University of Birmingham, Edgbaston, Birmingham, Großbritannien

[2] School of Nursing, Midwifery and Health, Faculty of Health and Life Sciences, Coventry University, Coventry, Großbritannien

[3] School of Physical Therapy, Faculty of Health Science, Western University, London, Kanada

Zusammenfassung

Übungen sind ein Kernbestandteil von Physiotherapie. Eine der vielen positiven Wirkungen von Übungsprogrammen ist der Effekt auf die endogene Schmerzmodellierung. Bewegungsinduzierte Hypoalgesie (BIH) ist definiert als eine kurzzeitige Erhöhung der Schmerzschwelle als direkte Antwort auf eine Bewegungsübung. Das Phänomen BIH hat in den letzten Jahren große Aufmerksamkeit in der Forschung bekommen mit über 150 publizierten Studien. Vier systematische Übersichtsarbeiten wurden allein im Jahr 2020 veröffentlicht.

Dieses narrative Review liefert einen Überblick über das Phänomen BIH und fasst die zugrunde liegenden Mechanismen und Einflussfaktoren zusammen. Aktuelle systematische Übersichtsarbeiten bei gesunden Teilnehmern und Patienten wurden anhand von AMSTAR2 bewertet. Das Phänomen BIH ist wissenschaftlich fundiert, aber es besteht niedrige bis sehr niedrige Konfidenz, dass BIH bei Gesunden auftritt. Große Heterogenität, hohes Verzerrungsrisiko und das Nichterfüllen der Einschlusskriterien für die systematischen Übersichtsarbeiten beeinträchtigen die Auswertung. Für Menschen mit Erkrankungen besteht sehr niedrige Konfidenz, bestenfalls zeigen Subgruppen oder isometrische Übungen geänderte BIH. Trotz des großen Interesses an der Thematik konnten Probleme mit der aktuellen Studienlage durch die Komplexität von BIH aufgezeigt werden. Es fehlen Empfehlungen für Messinstrumente und Übungsparameter, zudem wurden Reliabilität und Validität bisher wenig erforscht. Weitere Grundlagenforschung zu BIH-Parametern und Kontextfaktoren wird benötigt und kann zum Verständnis von BIH beitragen, um dann in klinische Forschung, insbesondere bei Patientengruppen, und anschließend die Rehabilitation übertragen werden zu können.

Schlüsselwörter
Review · Übungsprogramm · Schmerzhemmung · Rehabilitation · Schmerzempfindlichkeit

In diesem Beitrag

Der Artikel wurde von der Erstautorin verfasst und ist Teil ihrer Promotionsarbeit *Exercise-Induced Hypoalgesia in Chronic Low Back Pain* an der University of Birmingham (UK). Die weiteren Autorinnen sind Supervisoren und haben inhaltlich und methodisch zur Erstellung des Artikels beigetragen.

Zur Vereinfachung für den Leser wird anstatt gendergerechter Sprache die männliche Variante gewählt.

QR-Code scannen & Beitrag online lesen

Bewegungsübungen sind ein Kernbestandteil der Physiotherapie. Eine der Wirkweisen ist der Einfluss auf die Schmerzmodellierung, welche in den letzten Jahren viel untersucht wurde [38]. Bewegungsinduzierte Hypoalgesie bezeichnet eine temporäre Senkung der Schmerzempfindlichkeit nach einem Übungsprogramm [23]. Allein im Jahr 2020 sind zu diesem Thema vier systematische Übersichtsarbeiten veröffentlicht worden [7, 22, 25, 42].

Physiotherapie und Schmerzmodellierung

Physiotherapie wird oft in passive und aktive Maßnahmen unterteilt. Der Fokus dieses Artikels liegt auf der endogenen Schmerzhemmung, welche durch Physiotherapie

Published online: 15 February 2022

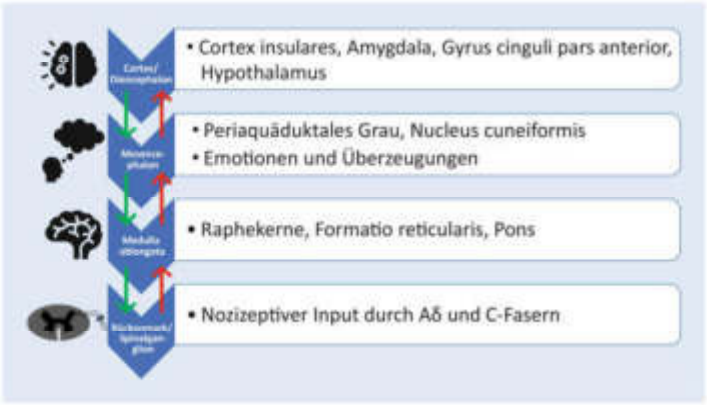


Abb. 1 ▲ Übersicht über eine Auswahl von Faktoren und Strukturen auf verschiedenen Ebenen der Schmerzmodellierung. *Rote* und *grüne Pfeile* zeigen auf- und absteigende Projektionsneurone. (Inhaltlich adaptiert nach [6])

beeinflusst [2] und auf peripherer, spinaler und/oder supraspinaler Eben moduliert werden kann (◘ **Abb. 1**). Verschiedene auf- und absteigende Bahnen sind zum Beispiel durch Transmitter wie Serotonin, Noradrenalin oder Dopamin gesteuert [19].

Passive Maßnahmen wie die manuelle Therapie, welche Weichteiltechniken (Muskeln, Faszien) und arthrogene Techniken beinhaltet, haben einen kurzeitigen Effekt auf die Schmerzinhibierung [41]. Aktive Maßnahmen sind ebenso Bestandteil der Therapie und das Durchführen von Übungsprogrammen wird empfohlen. Der allgemeine Nutzen von Bewegung auf allen Ebenen des biopsychosozialen Modells ist ausreichend bewiesen; neben den klassischen motorischen Fähigkeiten Kraft, Ausdauer, Schnelligkeit, Beweglichkeit und Koordination können auch soziale und psychologische Faktoren positiv beeinflusst werden [9]. Ein weiterer Effekt, der in der Therapie berücksichtigt werden sollte, ist die Schmerzmodellierung [4]. Training über längere Zeiträume hat positive Auswirkungen auf die Schmerzempfindlichkeit [3, 5, 26], jedoch liegt der Schwerpunkt dieser Arbeit auf dem kurzzeitigen Effekt einer körperlichen Aktivität.

Bewegungsinduzierte Hypoalgesie

Die International Association for the Study of Pain (IASP) definiert Hypoalgesie als abgeschwächte Schmerzreaktion auf einen normalerweisen schmerzhaften Stimulus [14]. Die bewegungsinduzierte Hypoalgesie (BIH), wurde von Naugle und Kollegen als eine hypoalgetische Reaktion, die einer akuten Bewegungsübung folgt, definiert [23]. Dies führt zu einer Reduzierung der Schmerzempfindlichkeit oder, anders formuliert, zu einer Erhöhung der Schmerzschwelle.

Die erste Metaanalyse aus dem Jahr 2012 zur BIH umfasste 25 Studien [23]. Bei gesunden Teilnehmern wurden ein moderater Effekt für Ausdauerübungen und große Effekte für isometrische und dynamische Kraftübungen gezeigt, wohingegen die Ergebnisse in Patienten mit chronischen Schmerzen stark variierten [23]. Erste Untersuchungen gab es jedoch bereits 1996, in 13 Studien wurde BIH bei gesunden männlichen Probanden untersucht [16]. Eine aktuelle Übersichtsarbeit aus dem Jahr 2020 zeigt, dass inzwischen über 150 Studien zum Thema BIH publiziert wurden [38]. Dies spricht für ein großes Interesse an dem Phänomen, aber neuere Übersichtsarbeiten zeigen, dass viele Studien aufgrund der Methodik und unklarer Protokolle die Einschlusskriterien nicht erfüllen [7, 25, 42]. Die zugrunde liegenden Mechanismen sind komplex und basieren oft auf Ergebnissen aus der Tierforschung [20, 38]. Als potenzielle Mechanismen auf peripherer und zentraler Ebene für die Schmerzmodellierung werden unter anderem die Wirkung von Opiaten, Cannabinoiden, Serotonin und Stresshormonen (Noradrenalin), das Immunsystem, die Herzratenvariabilität und zerebrale Blutverteilung diskutiert [20, 27, 30, 33, 38]. Veränderungen des Blutdrucks durch Aktivität von Barorezeptoren sind als weitere Ursache diskutiert worden, jedoch würde dies nicht erklären, weshalb die Effekte von BIH länger als 15 Minuten anhalten [23, 38]. Auch psychologische Faktoren spielen eine Rolle, zum Beispiel bezüglich des Verständnisses und der Erwartungshaltung von Probanden und des Auftretens von Schmerz durch manche Übungen [38]. Eine randomisierte kontrollierte Studie hat so zum Beispiel gezeigt, dass Probanden mit der Erwartungshaltung, eine Schmerzreduktion zu erreichen, eine ausgeprägtere Hypoalgesie nach einem 20-minütigen Ergometertraining zeigten als Probanden mit neutraler Information [17]. Zudem werden überlappende Mechanismen und eine Interaktion mit konditionierter Schmerzmodellierung („conditioned pain modulation") – dem Prinzip „Schmerz hemmt Schmerz" – kontrovers diskutiert [8, 28, 32, 37]. Einige Studien zeigen, dass nach einem schmerzhaften Stimulus die BIH beeinträchtigt ist [1, 10]. Eine andere Studie fand hingegen eine ausgeprägtere hypoalgetische Reaktion, wenn Übungen schmerzhaft waren [8].

Quantitative sensorische Testungen (QST) werden oft als Messinstrument für BIH genutzt. Primär werden dabei Druckschmerzschwellen über verschiedenen Körperregionen vor und nach der Übung getestet [42]. Andere Messinstrumente sind thermische Schmerzschwellen, Schmerztoleranz, fMRT oder Blutproben [23, 38]. Die Messzeitpunkte nach der Übung variieren stark, mit Einschränkungen in systematischen Übersichtsarbeiten von bis zu zwei-Stunden [7], wobei die Effekte vermutlich nicht länger als 30 Minuten ausgeprägt sind [23]. Es ist bisher jedoch nicht klar definiert, ab wann Veränderungen auf BIH zurückgeführt werden können. Viele Studien nutzen statistische Verfahren, um signifikante Vorher/Nachher-Veränderungen zu zeigen. Andere Studien nutzen den Standardmessfehler als Indikator, ob tatsächlich eine hypoalgetische Wirkung für individuelle Probanden stattgefunden hat [34, 39]. Anhand dieser Methode konn-

te jedoch bei vielen Probanden keine hypoalgetische Reaktion gezeigt werden.

Als Maßnahme werden oft Ausdauerprogramme auf einem Ergometer, isometrische Kontraktionen oder Kombinationen wie Zirkeltraining getestet, wohingegen wenige Studien Protokolle getestet haben, die in der Rehabilitation/Physiotherapie zur Behandlung von Patienten genutzt werden [7, 18, 23, 38, 42]. Es gibt keine klare Empfehlung zur Intensität, obwohl eine Dosis-Wirkungs-Kurve diskutiert wird, welche mit höherer Übungsintensität bei Ausdauersport stärkere Hypoalgesie versuchen könnte [23, 38]. Des Weiteren wird angenommen, dass Krafttraining sowie isometrische Kontraktionen oder dynamische Übungen zu lokaler Hypoalgesie in dem trainierten Bereich führen [18, 27], aber durch Ausdauertraining die Hypoalgesie eher systemisch auch außerhalb der trainierten Region gefunden werden kann [27].

Viele weitere Faktoren, wie zum Beispiel Aktivitätslevel oder ethnische Herkunft, sind diskutiert worden [38]. Eine systematische Auswertung dieser Faktoren hat jedoch nicht stattgefunden, und Ergebnisse basieren auf einzelnen Studien mit oft kleiner Fallzahl. Psychosoziale Faktoren wie Selbstwirksamkeit, Coping-Strategien, Angst vor Schmerzen oder Stressbewältigung können zum Beispiel in Leistungssportlern unterschiedlich ausgeprägt sein [38]. Eine aktuelle Übersichtsarbeit zu psychosozialen Faktoren und BIH konnte keinen Zusammenhang bei Gesunden und Patienten mit muskuloskelettalen Schmerzen zeigen [22]. Neun Studien wurden berücksichtigt, jedoch hatten alle Studien ein hohes Verzerrungsrisiko, und aufgrund der großen Heterogenität konnten keine weiteren Schlussfolgerungen gezogen werden [22]. Die Qualität dieser Übersichtsarbeit, bewertet mit dem AMSTAR2-Instrument [29], ist gut, es gibt jedoch kleinere Unklarheiten bezüglich der Einschlusskriterien und Datenauswertung.

Validität und Reliabilität

Allgemein zeigt QST eine moderate bis exzellente Reliabilität, und es liegt nahe, dass dies auch eine reliable Messung für BIH ist [11, 15, 34, 35, 39]. Die Stabilität von BIH ist bisher über zwei Zeitpunkte untersucht worden. Bei gesunden Probanden konnte eine moderate Intraklassenkorrelation (ICC [3,1]= 0,33–0,61) für absolute Veränderungen nach Ausdauertraining gezeigt werden [11, 15, 34, 35], und nach einer Wandsitzübung für relative Veränderungen (ICC [3,1]= 0,03–0,43) [39]. Die als „responder" gewerteten Probanden konnten dies in der folgenden Testung nicht systematisch reproduzieren.

Die Konstruktvalidität von BIH-Messungen wurde in einzelnen Studien anhand einer Ruheperiode getestet, so konnten Veränderungen durch das Testprogramm ausgeschlossen werden [8, 31, 36]. Jedoch fehlen weiterhin konkrete Empfehlungen für die Erstellung eines Goldstandards. Weitere Forschung zur Stabilität und Validität von BIH sollte unternommen werden und kann so auch die Qualität der Studien verbessern.

Der Einsatz von BIH als Prädiktor für Therapieresultate klingt vielversprechend [13], aber noch mangelt es an Grundlagenforschung zur BIH bei Gesunden und in Menschen mit Erkrankungen.

Übersicht über aktuelle Literatur

Die meiste Forschung ist an gesunden Probanden unter Laborbedingungen durchgeführt worden. Dies ist von Vorteil, da die Variabilität dadurch besser kontrolliert werden kann, zum Beispiel mit präziser Standardisierung und homogener Probandengruppe. Der Nachteil ist, dass diese Bedingungen oft nicht dem klinischen Alltag entsprechen und somit Rückschlüsse auf therapeutische Interventionen nur eingeschränkt möglich sind. Drei systematische Übersichtsarbeiten zu den Effekten der BIH sind in den letzten Jahren publiziert worden [7, 25, 42]. Die methodisch hochwertigste Studie mit Berücksichtigung von randomisierten Studien publizierte die Liste der ausgeschlossenen Studien nicht, dies war die einzige Schwachstelle anhand AMSTAR2 [29, 42]. Bei gesunden Probanden wurde eine stark ausgeprägte hypoalgetische Antwort nach Ausdauerinterventionen gefunden (7 Studien, 236 Probanden; Hedges 'g = −0,85 95 % Konfidenzintervall [−1,58; −0,13]) [42]. Dahingegen wurde für dynamische Kraftübungen nur ein geringer Effekt gezeigt (2 Studien, 23 Teilnehmer; g = −0,45 [−0,69; −0,22]). Kein Effekt wurde für isometrische Kontraktionen gezeigt (3 Studien, 177 Probanden; g = −0,16 [−0,36; 0,05]) [42]. Jedoch ist die Konfidenz für alle Ergebnisse anhand von GRADE auf sehr niedrig zurückgestuft worden [12, 42].

Eine andere systematische Übersichtsarbeit hingegen hatte weniger Begrenzungen im Studiendesign [25]. Die Ausweitung auf andere Studiendesigns hat klare Vorteile, da ein Großteil der Literatur keine randomisiert kontrollierten Studien sind. Datenauswertung von verschieden Studiendesigns birgt aber dafür andere Komplikationen. So ist zum Beispiel anhand von GRADE die Evidenz von Beobachtungsstudien nur als niedrig oder sehr niedrig eingestuft [12]. Die AMSTAR2-Bewertung zeigte Limitationen im Protokoll, der Kontrollbedingung, dem Instrument zur Erhebung des Verzerrungsrisikos, in der Datensynthese und dem Peer-Review-Verfahren auf [25, 29]. Moderate Effekte auf die Schmerzschwelle wurden in der Analyse gezeigt (36 Studien, 1326 Probanden, g = 0,19 [0,11; 0,27]), mit stärker ausgeprägten Effekten für Kraftübungen im Vergleich zu Ausdauerübungen (ES = 0,034 [0,23; 0,44]), moderater Intensität (ES = 0,45 [0,27; 0,64]) und in Frauen (ES = 0,36, [0,15; 0,56]), aber keinem signifikanten Effekt für Alter [25]. Die Konfidenz wurde durch Limitationen im Verzerrungsrisiko von niedrig auf sehr niedrig reduziert. Trotz ähnlicher Einschlusskriterien waren nur drei Studien in beiden Arbeiten vertreten [25, 42].

Bewegungsinduzierte Hypoalgesie in Patienten

Im Vergleich zur BIH bei gesunden Probanden gibt es nur wenig Forschung, die das Phänomen in Probanden mit Erkrankungen untersucht. Menschen mit chronischen Schmerzen haben eine größere Variabilität; es kann vermutet werden, dass zumindest bei einer Untergruppe von Patienten mit chronischen Schmerzen die Schmerzhemmung beeinträchtigt ist, wie zum Beispiel Studien bei Patienten mit chronischen Kreuzschmerzen, Schleudertrauma oder Fibromyalgie gezeigt haben [18, 38]. Es gibt Hinweise, dass Patienten mit niedriger Schmerzempfindlichkeit beeinträchtigte BIH aufzeigen [36, 40]. An-

derseits wurde zum Beispiel bei Patienten mit Parkinson BIH erfolgreich durch isometrische Kontraktion oder Laufbandtraining ausgelöst, ähnlich wie in der Kontrollgruppe mit gesunden Probanden [24].

Über 50 Artikel mit verschieden Studiendesigns und Pathologien, wie kraniomandibuläre Dysfunktion, Schulterschmerzen oder Patella-Tendinopathie, wurden in 2020 aufgelistet [38]. Für die systematische Übersichtsarbeit erfüllten lediglich vier randomisierte Studien zur Epikondylopathie, Gonarthrose und Plantarfasziitis ($N = 2$) die Einschlusskriterien [42]. Metaanalysen für isometrische Übungen zeigten keinen Effekt (drei Studien, Probanden $N = 114$; $g = -0{,}41$ [−1,08; 0,25]) mit sehr niedriger Konfidenz und unklarem Verzerrungsrisiko [42]. Die dritte systematische Übersichtsarbeit, mit 13 randomisierten und nichtrandomisierten Studien (346 Teilnehmer), untersuchte isometrische Übungen in Patienten mit muskuloskelettalen Beschwerden [7]. Anhand von AMSTAR2 gab es lediglich Unklarheiten zu den Einschlusskriterien und der Datensynthese [7]. Aufgrund der großen Heterogenität konnte jedoch keine Schlussfolgerung gezogen werden [7]. Im Gegensatz zu vorherigen Arbeiten [23] wurde keine Hyperalgesie gefunden, jedoch wurden in der Studie Schmerzen auf eine lokale Region begrenzt [7]. Anderseits wurde in einer Subgruppe von Patienten mit Gonarthrose eine hyperalgetische Reaktion gezeigt [43]. Es wird vermutet, dass in chronischen Patienten mit mehreren schmerzhaften Regionen vermutlich eher eine hyperalgetische Antwort gefunden werden kann [23, 30, 38]. Übungen, die BIH auslösen, sind oft schmerzhaft (Schmerzskala bis zu 5–6/10) und dies kann zumindest bei Gesunden zu stärkerer Schmerzmodellierung führen. Dies ist jedoch bei Patienten noch nicht ausreichend erforscht [38]. Zum Beispiel hat unsere Arbeit zu einer Hebeübung bei Patienten mit Kreuzschmerzen gezeigt, dass sich in der Kontrollgruppe eine Erhöhung der Druckschmerzschwellen über der lumbalen Region zeigte, aber in der Gruppe mit chronischem unspezifischen Kreuzschmerzen nicht [18]. Im Gegensatz dazu wurde nach einem Ergometer-Protokoll in einer anderen Studie keine Beeinträchtigung der BIH bei Probanden mit Kreuzschmerzen, aber dafür bei Teilnehmern mit chronischem Ermüdungssyndrom gefunden [21]. Die Auswahl der Übung könnte demnach für die Therapie von chronischen Patienten mit starker Beeinträchtigung der Lebensqualität und starken Symptomen relevant sein.

Fazit für die Praxis

- **Bewegungsinduzierte Hypoalgesie (BIH) ist ein Phänomen, das einen weiteren positiven Effekt von Übungsprogrammen unterstreicht und von Physiotherapeuten in der Praxis genutzt und mit Patienten kommuniziert werden kann.**
- **Es besteht ein großes wissenschaftliches Interesse, jedoch sind Methodik und Qualität der Studien zu verbessern, um konkrete Empfehlungen für die Praxis liefern zu können.**
- **Viele Komponenten und Faktoren bleiben durch die große Komplexität ungeklärt. Es gibt weder für das Messinstrument noch für die Übung/Maßnahme einen Goldstandard.**
- **Weitere Grundlagenforschung sollte die zugrunde liegenden Mechanismen und Kontextfaktoren erforschen. Des Weiteren sollte die Reliabilität und Validität von BIH tiefergehend erforscht werden.**
- **Weitere klinische Forschung in Patientengruppen ist erforderlich, um dies dann schlussendlich in die Rehabilitation übertragen zu können.**

Korrespondenzadresse

Pauline Kuithan
School of Nursing, Midwifery and Health, Faculty of Health and Life Sciences, Coventry University
Jordan Well, CV1 5RW, Coventry, Großbritannien
ad8146@coventry.ac.uk

Danksagung. Ein spezieller Dank geht an Dr. Julia Wolska für das Korrekturlesen des Manuskripts.

Einhaltung ethischer Richtlinien

Interessenkonflikt. P. Kuithan, A. Rushton und N.R. Heneghan geben an, dass kein Interessenkonflikt besteht.

Für diesen Beitrag wurden von den Autoren keine Studien an Menschen oder Tieren durchgeführt. Für die aufgeführten Studien gelten die jeweils dort angegebenen ethischen Richtlinien.

Literatur

1. Alsouhibani A, Vaegter HB, Hoeger Bement M (2019) Systemic exercise-induced hypoalgesia following isometric exercise reduces conditioned pain modulation. Pain Med 20:180–190
2. Arribas-Romano A, Fernandez-Carnero J, Molina-Rueda F et al (2020) Efficacy of physical therapy on nociceptive pain processing alterations in patients with chronic musculoskeletal pain: a systematic review and meta-analysis. Pain Med 21:2502–2517
3. Barros Dos Santos AO, Pinto de Castro JB, Lima VP et al (2021) Effects of physical exercise on low back pain and cortisol levels: a systematic review with meta-analysis of randomized controlled trials. Pain Manag 11:49–57
4. Beales D, Mitchell T, Moloney N et al (2021) Masterclass: a pragmatic approach to pain sensitivity in people with musculoskeletal disorders and implications for clinical management for musculoskeletal clinicians. Musculoskelet Sci Pract 51:102221
5. Belavy DL, Van Oosterwijck J, Clarkson M et al (2021) Pain sensitivity is reduced by exercise training: evidence from a systematic review and meta-analysis. Neurosci Biobehav Rev 120:100–108
6. Bingel U, Tracey I (2008) Imaging CNS modulation of pain in humans. Physiology 23:371–380
7. Bonello C, Girdwood M, De Souza K et al (2021) Does isometric exercise result in exercise induced hypoalgesia in people with local musculoskeletal pain? A systematic review. Phys Ther Sport 49:51–61
8. Ellingson LD, Koltyn KF, Kim JS et al (2014) Does exercise induce hypoalgesia through conditioned pain modulation? Psychophysiology 51:267–276
9. Falla D, Hodges PW (2017) Individualized exercise interventions for spinal pain. Exerc Sport Sci Rev 45:105–115
10. Gajsar H, Nahrwold K, Titze C et al (2018) Exercise does not produce hypoalgesia when performed immediately after a painful stimulus. Scand J Pain 18:311–320
11. Gomolka S, Vaegter HB, Nijs J et al (2019) Assessing endogenous pain inhibition: test-retest reliability of exercise-induced hypoalgesia in local and remote body parts after aerobic cycling. Pain Med 20:2272–2282
12. Guyatt G, Oxman AD, Akl EA et al (2011) GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 64:383–394
13. Hansen S, Vaegter HB, Petersen KK (2020) Pretreatment exercise-induced hypoalgesia is associated with change in pain and function after standardized exercise therapy in painful knee osteoarthritis. Clin J Pain 36:16–24
14. IASP (2021) Terminology. https://www.iasp-Pain.Org/Resources/Terminology/#Hypoalgesia. Zugegriffen: 24. Juli 2021
15. Hvid JT, Thorlund JB, Vaegter HB (2019) Walking increases pain tolerance in humans: an experimental cross-over study. Scand J Pain 19:813–822
16. Janal MN (1996) Pain sensitivity, exercise and stoicism. J R Soc Med 89:376–381
17. Jones MD, Valenzuela T, Booth J et al (2017) Explicit education about exercise-induced hypoalgesia influences pain responses to acute exercise in healthy adults: a randomized controlled trial. J Pain 18:1409–1416
18. Kuithan P, Heneghan NR, Rushton A et al (2019) Lack of exercise-induced hypoalgesia to repetitive back movement in people with chronic low back pain. Pain Pract 19:740–750

Abstract

Pain modulation through exercise. Exercise-induced hypoalgesia in physiotherapy

Exercise prescription is a central tenet of physiotherapy. One of the numerous benefits of exercise is its influence on endogenous pain modulation. Exercise-induced hypoalgesia (EIH) refers to a short-term change in pain sensitivity following an acute bout of exercise. Interest in this phenomenon has grown considerably with over 150 articles published, including four systematic reviews in 2020 alone.
This narrative review provides an overview of EIH including a definition and summary of the underlying mechanisms and mediating factors. Recent systematic reviews assessing EIH in people with and without musculoskeletal complaints were evaluated using AMSTAR2. Review findings confirm the presence of EIH. For asymptomatic people, confidence in the evidence was low to very low due to high heterogeneity of included studies, risk of bias, and study eligibility. For people with pain, there is very low confidence, at best, that subgroups or isometric exercise show altered EIH. Despite the growing body of evidence, challenges within the available evidence due to its complex nature are highlighted. Recommendations regarding outcome measures and exercise parameters are required, and further understanding of reliability and validity of EIH is needed. There is a demand to further elucidate these parameters and contextual factors to advance our understanding of EIH. Additional clinical research, especially in patient populations, is required to then provide implications for rehabilitation.

Keywords
Review · Exercise program · Pain inhibition · Rehabilitation · Pain sensitivity

19. Kwon M, Altin M, Duenas H et al (2014) The role of descending inhibitory pathways on chronic pain modulation and clinical implications. Pain Pract 14:656–667
20. Lesnak JB, Sluka KA (2020) Mechanism of exercise-induced analgesia: what we can learn from physically active animals. Pain Rep 5:e850
21. Meeus M, Roussel NA, Truijen S et al (2010) Reduced pressure pain thresholds in response to exercise in chronic fatigue syndrome but not in chronic low back pain: an experimental study. J Rehabil Med 42:884–890
22. Munneke W, Ickmans K, Voogt L (2020) The association of psychosocial factors and exercise-induced hypoalgesia in healthy people and people with musculoskeletal pain: a systematic review. Pain Pract 20:676–694
23. Naugle KM, Fillingim RB, Riley JL 3rd (2012) A meta-analytic review of the hypoalgesic effects of exercise. J Pain 13:1139–1150
24. Nguy V, Barry BK, Moloney N et al (2019) Exercise-induced hypoalgesia is present in people with Parkinson's disease: two observational cross-sectional studies. Eur J Pain 23:1329–1339
25. Pacheco-Barrios K, Carolyna Gianlorenco A, Machado R et al (2020) Exercise-induced pain threshold modulation in healthy subjects: a systematic review and meta-analysis. Princ Pract Clin Res 6:11–28
26. Polaski AM, Phelps AL, Kostek MC et al (2019) Exercise-induced hypoalgesia: a meta-analysis of exercise dosing for the treatment of chronic pain. PLoS ONE 14:e210418
27. Rice D, Nijs J, Kosek E et al (2019) Exercise-induced hypoalgesia in pain-free and chronic pain populations: state of the art and future directions. J Pain 20:1249–1266
28. Samuelly-Leichtag G, Kodesh E, Meckel Y et al (2018) A fast track to hypoalgesia—the anaerobic exercise effect on pain sensitivity. Int J Sports Med 39:473–481
29. Shea BJ, Reeves BC, Wells G et al (2017) AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 358:j4008
30. Sluka KA, Frey-Law L, Hoeger Bement M (2018) Exercise-induced pain and analgesia? Underlying mechanisms and clinical translation. Pain 159(1):S91–S97
31. Smith A, Ritchie C, Warren J et al (2020) Exercise induced hypoalgesia is impaired in chronic whiplash associated disorders (wad) with both aerobic and isometric exercise. Clin J Pain 36(8):601–611
32. Szikszay TM, Adamczyk WM, Wojtyna E et al (2020) Pain inhibition is not affected by exercise-induced pain. Pain Rep 5:e817
33. Titze C, Gajsar H, Hasenbring MI (2016) Physical activity and musculoskeletal pain : a focus review within the Mispex research group. Schmerz 30:421–428
34. Vaegter HB, Bjerregaard LK, Redin MM et al (2019) Hypoalgesia after bicycling at lactate threshold is reliable between sessions. Eur J Appl Physiol 119:91–102
35. Vaegter HB, Dorge DB, Schmidt KS et al (2018) Test-retest reliability of exercise-induced hypoalgesia after aerobic exercise. Pain Med 19:2212–2222
36. Vaegter HB, Handberg G, Graven-Nielsen T (2016) Hypoalgesia after exercise and the cold pressor test is reduced in chronic musculoskeletal pain patients with high pain sensitivity. Clin J Pain 32:58–69
37. Vaegter HB, Handberg G, Graven-Nielsen T (2014) Similarities between exercise-induced hypoalgesia and conditioned pain modulation in humans. Pain 155:158–167
38. Vaegter HB, Jones MD (2020) Exercise-induced hypoalgesia after acute and regular exercise: experimental and clinical manifestations and possible mechanisms in individuals with and without pain. Pain Rep 5:e823
39. Vaegter HB, Lyng KD, Yttereng FW et al (2019) Exercise-induced hypoalgesia after isometric wall squat exercise: a test-retest reliability study. Pain Med 20:129–137
40. Vaegter HB, Pittersen KK, Sjodsholm LV et al (2021) Impaired exercise-induced hypoalgesia in individuals reporting an increase in low back pain during acute exercise. Eur J Pain 25:1053–1063
41. Voogt L, de Vries J, Meeus M et al (2015) Analgesic effects of manual therapy in patients with musculoskeletal pain: a systematic review. Man Ther 20:250–256
42. Wewege MA, Jones MD (2021) Exercise-induced hypoalgesia in healthy individuals and people with chronic musculoskeletal pain: a systematic review and meta-analysis. J Pain 22:21–31
43. Wideman TH, Finan PH, Edwards RR et al (2014) Increased sensitivity to physical activity among individuals with knee osteoarthritis: relation to pain outcomes, psychological factors, and responses to quantitative sensory testing. Pain 155:703–711

Appendix 2 Kuithan et al. 2019 Chapter two

ORIGINAL ARTICLE

Lack of Exercise-Induced Hypoalgesia to Repetitive Back Movement in People with Chronic Low Back Pain

Pauline Kuithan, MSc; Nicola R. Heneghan, PhD; Alison Rushton, PhD; Andy Sanderson, BSc; Deborah Falla, PhD

Centre of Precision Rehabilitation for Spinal Pain (CPR Spine), School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, Birmingham, U.K

■ **Abstract**

Purpose: To investigate whether people with chronic low back pain (LBP) show dysfunctional exercise-induced hypoalgesia (EIH) in response to repeated contractions of their back muscles during a lifting task.

Methods: In this cross-sectional observational study conducted on asymptomatic participants (n = 18) and participants with chronic LBP (n = 21), quantitative sensory testing (QST) was applied extensively over the lumbar region and a remote area before and after a repeated task that involved lifting a 5-kg box for ~7 minutes. QST included pressure pain thresholds (PPTs), thermal detection, pain thresholds, and measures of temporal summation. Topographical maps of the percentage change in PPT detected at 16 locations over the lumbar region were generated to explore regional differences and compared between groups.

Results: Mean (standard deviation) PPTs measured from 16 sites over the lower back changed significantly in asymptomatic participants (+29.78 kPa [41.4]) following task completion, indicative of EIH, whereas no significant change was observed for the low back pain (LBP) group (−14.87 kPa [61.2]). No changes were detected at the remote site for either group. No changes were revealed for the thermal tests. Temporal summation data revealed decreasing pain sensitivity as the test progressed, but the test response did not change after the exercise for either group.

Conclusion(s): Unlike asymptomatic individuals, participants with LBP lacked EIH over the lumbar erector spinae muscles following repeated lifting. Although these results should be considered in relation to the study limitations, particularly the absence of a control group, the findings support impaired EIH in patients with LBP. ■

Key Words: exercise-induced hypoalgesia, quantitative sensory testing, low back pain

Address correspondence and reprint requests to: Deborah Falla, PhD, Centre of Precision Rehabilitation for Spinal Pain (CPR Spine), School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, Birmingham B15 2TT, U.K. E-mail: [redacted]

Submitted: February 19, 2019; Revised May 21, 2019; Revision accepted: May 29, 2019

DOI. 10.1111/papr.12804

INTRODUCTION

The effects of exercise-induced hypoalgesia (EIH), a short-term endogenous pain inhibitory response after exercise, are well documented in healthy individuals.[1] The EIH response can be detected with quantitative sensory testing (QST), revealed as a change in pain threshold after exercise. The extent of the EIH response depends on several factors, including the type, dosage and intensity of the exercise.[2,3]

Studies have revealed that EIH can be impaired in different musculoskeletal pain disorders, including whiplash, osteoarthritis of the knee, or shoulder pain,[4–7] which can explain the varied response to exercise, and has important implications for exercise

prescription. On the contrary, very few studies have examined EIH in people with low back pain (LBP), even though exercise is recommended as a fundamental treatment for the management of LBP in national and international guidelines.[8,9] Two studies evaluated EIH in people with relatively mild LBP, and both showed a similar analgesic response in people with LBP compared to a control group following submaximal aerobic exercise on an ergometer for ~30 minutes.[10,11] In contrast, a 3-minute repeated lifting task that was designed to target activation of the back muscles led to higher pain sensitivity to pressure over the lumbar region in participants with mild chronic low back pain (LBP) and no changes in the control group,[12] suggesting that EIH to back-specific tasks could be impaired in LBP. However, this task was likely of inadequate intensity to produce EIH, since no change in pain sensitivity occurred in the asymptomatic control group. A further study examined the response to a 2-minute isometric back extension exercise (Biering Soerensen test) and showed evidence of EIH at remote but not local sites[13]; however, this study was limited to asymptomatic individuals. Further research is therefore needed to fully understand the analgesic response to back-specific exercise and whether this is affected in people with chronic LBP.

The aim of this study was to quantify, via QST assessed at local and remote sites, whether asymptomatic people demonstrate EIH in response to repeated movement of the trunk and whether the response is dysfunctional in participants with chronic LBP. Based on the earlier study by Falla et al.,[12] we used a task that involved repeated lifting of a 5-kg box for ~7 minutes. The knowledge gained from this study may facilitate a greater understanding of the mechanisms contributing to varied responses to exercise in people with LBP (ie, those who lack EIH) and the exacerbation of symptoms in some people with LBP following repeated mechanical work.[14–17]

METHODS

Study Design and Setting

This observational cross-sectional study was approved by the Ethics Committee of the University of Birmingham (ERN_16-1389) and was conducted according to the Declaration of Helsinki. All tests were conducted in a single session by the same 2 investigators (P.K. and A.S.) between July 2017 and March 2018. This report follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for observational studies.[18]

Participants

Participants with chronic LBP and asymptomatic controls were recruited from the university staff and student population. All participants gave written consent prior to data collection. Inclusion criteria for both groups were age between 18 and 65 years, not being pregnant, and able to communicate in English. Participants were considered asymptomatic if they had no previous history of back or lower limb pain that warranted treatment from a healthcare practitioner and no neurological disorders.

Inclusion criteria for the participants with chronic LBP were back pain lasting more than 3 months and pain experienced on more than 90 days in the preceding 6 months. A history of spinal fractures or spinal stenosis and radiating leg pain were exclusion criteria, as were concurrent systemic, rheumatic, or neurological disorders, which may have confounded testing. They should not have been undergoing active management for chronic LBP or on higher doses of pain medication (>30 mg of morphine equivalent dose).

Questionnaires

A custom-designed questionnaire was first completed by the participants with LBP to assess their average pain in the preceding 24 hours, during their latest episode, as well as their current pain intensity, all rated on an 11-item numeric rating scale (NRS), with 0 signifying no pain and 10 the worst pain imaginable.[19] Participants with LBP were also asked to rate their perceived disability using the Oswestry Disability Index (ODI).[20] In addition, the following established questionnaires were used to describe the study population: the International Physical Activity Questionnaire (IPAQ)[21]; perception of health and wellbeing (SF-36v2) using the Physical and Mental Component Scale[22]; 21-item Depression, Anxiety and Stress Scale (DASS-21),[23] Fear Avoidance Beliefs Questionnaire (FABQ)[24]; and Pain Catastrophizing Scale (PCS).[25]

Quantitative Sensory Testing

Quantitative sensory testing was performed in a consistent order, which was pressure pain threshold (PPT)

testing, followed by thermal detection and thermal pain threshold testing, starting at the periphery and finishing at the back. Temporal summation of repeated thermal stimuli was performed last. The tests were chosen based on previous studies and pilot testing.[12,26,27] Reliability of QST has been demonstrated previously and is an established method to evaluate EIH.[1,28–31]

Pressure Pain Thresholds

After a familiarization period, PPTs were measured with an algometer (1-cm^2 probe, 30 kPa/s; Somedic Production, Stockholm, Sweden). First, PPT was tested over the thenar eminence on the right side in the asymptomatic group, and on the most painful side in the participants with LBP. In the case of bilateral and symmetrical pain, the right side was selected. A grid, orientated on the spinous process of the 5th lumbar vertebra, was used to mark 16 testing locations over the lumbar region (Figure 1) to explore regional differences in PPT changes following the exercise. This was based on a similar approach used previously[12] but applied bilaterally, with 2 vertical rows of 4 points on each side. The medial row was directly placed over the erector spinae muscles. Testing was alternated across participants in 4 different patterns. For all PPT tests, the participants were instructed to push a button as soon as they perceived that the sensation of pressure had turned to one of pain. The mean of 2 consecutive readings over each site was used for data analysis. Topographical maps of the percentage change in PPT for each location were generated as previously described.[12]

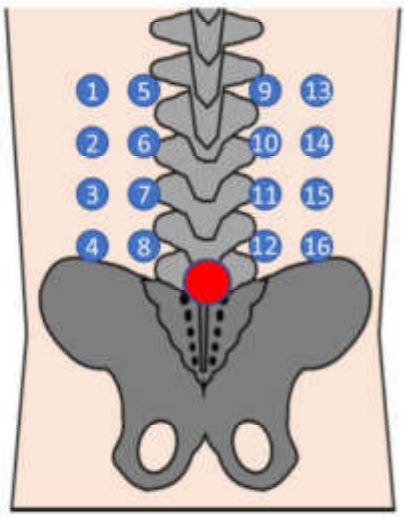


Figure 1. Schematic representation of the area over the lumbar region for pressure pain threshold testing. The distance between two testing sites was 2.5 cm, and the first sites were 2.5 cm cranial to the spinous process of L5.

Thermal Detection and Pain Thresholds

A TSA-II thermal analyzer (Medoc, Ramat Yishai, Israel) with a 30 × 30 mm Peltier thermode was applied over the thenar eminence on the right or most painful side as described above, after a demonstration on the contralateral side. Three randomized stimuli of either warm or cold were applied for the detection threshold and then for the pain threshold. Baseline temperature was set at 32°C, and the temperature was increased or decreased by 1°C and returned at a rate of 8°C/s with a 5-second interstimulus interval. For the pain threshold, an increase/decrease of 1.5°C/s and return of 8°C/s with a 10-second interval were chosen to avoid temporal summation. The minimum temperature was set to 0°C and the maximum to 50°C. The same test was then conducted for both groups over the back on the right side corresponding to PPT locations 11 to 16 (see Figure 1). For analysis, the mean of 3 measurements was taken for each site.

Temporal Summation

First, a familiarization test was performed on the contralateral side with 5 stimuli of 46°C with the same thermal tester described above. Participants were asked to rate their perceived pain on an NRS from 0 to 100 for each of the stimuli, with 0 signifying no pain and 100 the worst pain imaginable. Then the thermode was placed under the volar mid-forearm on the right or most painful side. Ten consecutive stimuli were applied starting at a baseline temperature of 40°C and increasing within 8°C/s to 48°C, and returning to baseline at the same rate. The interstimulus interval was set at 2.5 seconds, adapted from a protocol by Owens et al.[26]

Repeated Lifting Task

Measurements of the sternomanubrial joint line for the top shelves, the height of the lateral epicondyle of the femur for the lower shelves, and the length from the acromion to the head of the ulna for distance from the feet to the shelves were taken to determine the set-up for the lifting task (Figure 2A).

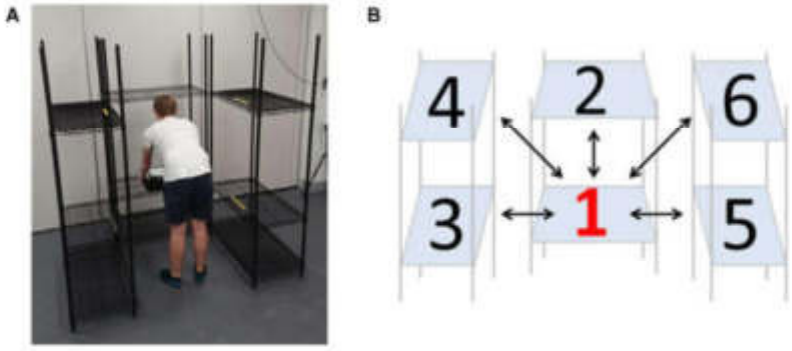


Figure 2. A, Participant demonstrating the starting position of the lifting task. B, Schematic illustration of the lifting sequence.

Participants performed 10 cycles of lifting a 5-kg box (35.5 × 29 × 13.5 cm) with reinforced handles between 6 different shelves for approximately 7 minutes in total. To the beat of a metronome, the participant lifted the box to the top shelf over 2 seconds and then could rest for 2 seconds with the box on the shelf. Figure 2B shows the pattern for each cycle. The task was based on a task described in a previous study,[12] but was extended to represent a more functional movement by adding rotation using 6 instead of 2 shelves. During the task, participants were asked every minute to rate their pain on an NRS from 0 to 10 and their perceived exhaustion after the lifting task on a printed Borg scale.[32] They were informed that they could end the lifting task at any time.

Within 5 minutes of completion of the lifting task, the QST tests were repeated as described above, but in the following order: lumbar PPTs, followed by thermal tests over the lumbar area with the participant in supine; then the PPTs and thermal measurements were performed over the hand. This sequence was selected for efficiency of testing to minimize movement of the participant and prioritize testing of the lumbar region. Temporal summation testing was conducted last, avoiding any potential interference with the other tests. The duration of the pre-test protocol was slightly longer than the post-test protocol because of the familiarization period. The entire duration varied between 20 and 30 minutes.

Statistical Analysis

Independent *t*-tests were applied to detect possible differences between the participant characteristics of the 2 groups (IBM SPSS Statistics version 24, IBM Corp., Armonk, NY, U.S.A.). Data were analyzed for normality, and if necessary, outliers were removed from the analysis based on a *z*-score > 3.29 and reported as such.[33]

The mean PPT across the 16 locations of the back was calculated for each participant; in addition, the percentage change in PPT was determined for each location. For the thermal testing, if any reading did not meet the pain threshold at 0/50°C (limit of the equipment), then the data were excluded from further analysis.

A 2-way repeated measurement analysis of variance (RM-ANOVA) was conducted to evaluate changes in PPT detected over the hand, with group (asymptomatic/LBP) and time (pre/post) as factors. A 3-way RM-ANOVA was conducted for the lumbar PPT, with group, time, and location (locations 1 to 16) as factors. Two-way RM-ANOVAs were also applied for the thermal detection, and for pain thresholds, with group and time as factors. For temporal summation, a 3-way RM-ANOVA, with group, time, and sequence of heat impulse (1 to 10), was applied. Significant differences were followed by Student–Newman–Keuls (SNK) post hoc analyses and Bonferroni corrections (BCs) for multiple comparisons.

Finally, we tested the correlation of pain, perceived exertion, and change in percentage for the QST measurements using the Pearson correlation coefficient. Significance was set as $P < 0.05$.

RESULTS

Participants

Participant characteristics of 18 asymptomatic participants (8 men, 10 women) and 21 participants with chronic LBP (9 men, 12 women) are presented in Table 1. One further participant was recruited, but only a pre-QST measurement were taken due to technical issues, and this participant was therefore excluded. The

Table 1. Demographic Characteristics of the Study Population

Characteristic/Questionnaire	Asymptomatic		LBP		Group Difference
	Mean	SD	Mean	SD	*P*
Age	28.2	12.5	31.7	13.3	0.406
BMI	23.3	4.0	25.4	3.4	0.084
DASS21 (range 0 to 126)	9.4	10.1	19.3	22.5	0.095
FABQ (range 0 to 96)	2.6	5.7	27.2	11.6	<0.001
PCS (range 0 to 52)	5.7	6.9	14.9	9.2	<0.001
Peak pain lifting (range 0 to 10)	0.8	2.0	4.8	2.0	<0.001
Borg scale lifting (range 6 to 20)	11.1	2.2	13.1	1.7	0.004
SF36-PCS	58.43	3.9	49.36	5.3	<0.001
SF36-MCS	51.82	4.4	46.51	13.0	0.091
IPAQ	14 high, 4 med.		18 high, 4 med.		0.0525
ODI (range 0 to 100; ≤20% = minimal disability)			16.0	6.8	
Pain in last 24 hours			3.9	2.1	
Pain before task			3.1	2.0	
Pain episode			4.9	1.9	

BMI, body mass index; DASS21, Depression Anxiety Stress Scales; FABQ, Fear Avoidance Believe Questionnaire; IPAQ, International Physical Activity Questionnaire; LBP, low back pain; ODI, Oswestry Disability Index; PCS, Pain Catastrophizing Scale; SD, standard deviation; SF36-MCS, Short Form Health Survey Mental Component Scale; SF36-PCS, Short Form Health Survey Physical component score.

ODI indicated minimal disability in the group with LBP, and only 2 participants reported moderate disability. Participants with LBP reported significantly higher scores on the Borg Scale (controls: 11.1, [standard deviation (SD): 2.2], LBP: 13.1 [1.7]; $P = 0.005$).

In contrast to all asymptomatic participants who successfully completed the full task, 3 participants with LBP terminated the task due to provocation of their LBP during the 4th, 6th, and 9th cycles. However, because participants performed the task for as long as they could, their data were retained in the analysis and QST was still performed after their final task cycle.

Pain

Four control participants experienced LBP during the task (peak pain intensity of 2/10 reported by 3 participants and 8/10 by 1 participant, group mean: 0.8 [SD: 2.0]). Overall, the reported peak pain intensity during the task was 4.78 (SD: 2.0) for the LBP group, and only 1 participant with LBP did not perceive LBP during the task.

PPTs (Local and Remote)

For PPTs collected over the lower back, the overall scores (mean of 16 locations) were pre-test 341.39 kPa (SD: 116.9) and post-test 371.16 kPa (130.4) for asymptomatic ($n = 18$) and 320.08 kPa (113.7) and 305.20 kPa (101.0) for participants with LBP ($n = 20$). This led to a difference of 29.78 kPa (41.4) for the asymptomatic participants and −14.87 kPa (61.2) for the participants with LBP. The percentage changes in PPT are displayed in Figure 3, illustrating a mean change for the asymptomatic group of +9.43% (SD: 13.4; confidence interval [CI]: [2.8, 16.1]) and −2.10% (SD: 18.4; CI: [−10.7, 6.5]) for the LBP group.

A 3-way RM-ANOVA showed significant interactions for location, location and group, and time and location ($F = 1.85$ to 10.81, $P = 0.000$ to 0.025). The significance of location/time and location indicates the heterogeneous response of different test sites over the lumbar area. However, for the purposes of this study, the most relevant finding was a group and time interaction ($F = 6.78$, $P = 0.001$), and the post hoc

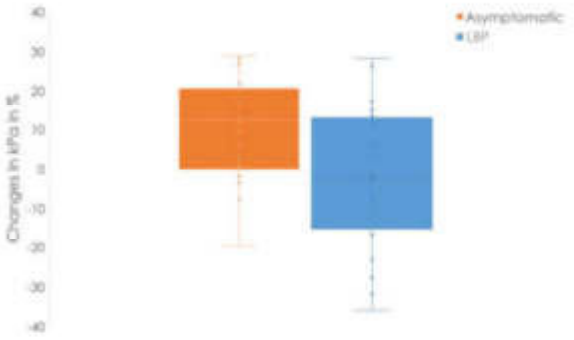


Figure 3. Boxplot of the percentage change in pressure pain sensitivity measured over the back from pre- to post-test based on the overall mean of 16 locations for each individual within the 2 groups. A higher percentage change represents signs of exercise-induced hypoalgesia. At the group level, the mean change (illustrated by the x) was +9.43% (SD: 13.4) for the asymptomatic group and −2.10% (SD: 18.4) for the participants with chronic low back pain (CLBP). The lower and upper extreme was −19.80% and 28.20% for the asymptomatic group compared to −35.95% and 28.13% for the group with CLBP.

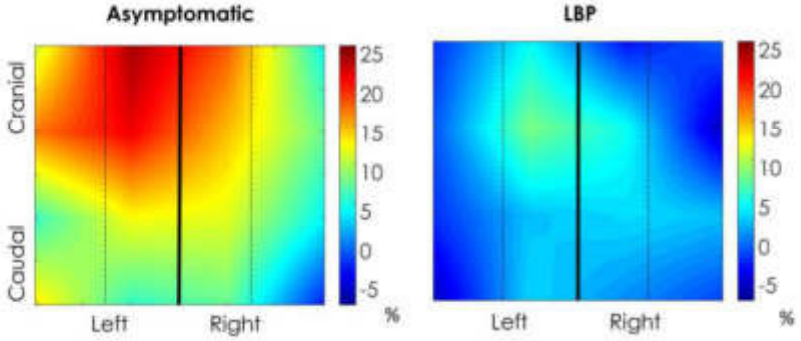


Figure 4. Topographical maps showing the percentage change in pressure pain threshold between pre- and post-test over the 16 different locations over the lumbar spine as determined in Figure 1. The vertical line represents the midline of the spine. CLBP, chronic low back pain.

analysis revealed a significant increase in PPT after the task but only for the control group (controls: SNK test, $P = 0.019$; LBP: SNK test, $P = 0.228$). However, Bonferroni correction for multiple comparisons revealed no significant interaction for time and group (controls: +29.78 [standard error (SE): 12.44], $P = 0.132$ [−5.0, 64.5]; LBP: −14.87 [SE: 11.80], $P = 1.00$; CI: [−47.8, 18.1]).

Topographical maps showing the percentage change in PPT between pre- and post-test over the 16 different locations over the lumbar spine are presented in Figure 4. Based on observation of the topographical maps, we undertook further analysis to evaluate changes only within the cranial half of the map. There was an interaction of time and group ($F = 10.23$, $P = 0.003$; SNK test: controls, $P = 0.002$; LBP, $P = 0.265$). Correction for multiple comparisons confirmed changes for the asymptomatic group only (controls: +43.05 [SE: 13.03], $P = 0.132$; CI: [6.69, 79.42]).

By separating the medial and lateral row, a significant change was observed over the medial (PPT test sites 5 to 12) column only. A significant interaction between time and group was observed ($F = 8.12$, $P = 0.007$). The post hoc analysis showed a significant change only for the asymptomatic group (SNK test: controls, $P = 0.001$; LBP, $P = 0.643$). Adjustment for multiple comparisons confirmed a significant post-task increase in PPT only for the asymptomatic group (controls: +46.93 [SE: 13.5], $P = 0.008$; CI: [9.18, 84.68]).

For PPT measured over the thenar eminence, the mean (SD) pre-test values for the asymptomatic group were 259.33 kPa (77.8) and post-test values for the asymptomatic group were 281.94 kPa (117.4), a difference of +22.61 kPa (93.1). For participants with LBP, the mean pre-test value was 276.55 kPa (88.84) and the mean post-test value was 278.50 (72.2), a difference of +1.95 kPa (40.2). A 2-way RM-ANOVA revealed no significant differences between groups and no significant change over time.

There was a significant correlation between change in the PPT percentage over the hand and the back only in asymptomatic participants ($r = 0.783$, $P = 0.000$, $n = 18$). However, in both groups, there was no significant correlation between baseline PPT and the percentage change in PPT, indicating that an EIH response was not dependent on baseline sensitivity.

Thermal Testing

Results for the cold and warm detection and pain thresholds are presented in Table 2. Two cold detection threshold (CDT) readings from the hand and one from the back were identified as outliers (z-score > 3.29) and were removed from the analysis. A 2-way RM-ANOVA revealed a significant difference for group ($F = 4.18$,

Table 2. Results for Thermal Detection and Pain Threshold Testing

		Asymptomatic			LBP		
Test	Site	*n*	Mean (°C)	SD	*n*	Mean (°C)	SD
CDT pre	Hand	17	30.2	1.0	20	30.5	0.6
CDT post			29.9	1.1		30.5	0.6
WDT pre		18	33.9	1.1	21	34.1	0.9
WDT post			33.8	0.8		33.9	0.6
CPT pre		16	14.0	7.5	18	15.4	7.6
CPT post			15.8	8.5		17.8	6.2
WPT pre		14	43.0	2.9	21	43.5	3.9
WPT post			41.2	3.7		42.4	2.5
CDT pre	Lumbar	18	29.6	2.0	20	29.8	1.6
CDT post			29.7	2.0		29.3	2.0
WDT pre		18	35.3	1.3	21	35.5	1.1
WDT post			35.0	1.1		35.2	1.4
CPT pre		12	21.5	6.1	8	24.8	4.4
CPT post			19.6	6.8		22.7	6.8
WPT pre		17	43.3	3.9	20	43.7	4.1
WPT post			43.7	3.5		43.5	3.0

CDT, cold detection threshold; CPT, cold pain threshold; post, post-test, pre, pre-test; LBP, low back pain; SD, standard deviation; WDT, warm detection threshold; WPT, warm pain threshold.

$P = 0.049$) for the CDT detected over the hand, yet further post hoc analysis revealed no further significant differences between groups, and there was no effect of time. No significant differences and interactions between group and time were observed for the CDT performed over the lumbar region, nor warm detection over the hand and the lumbar area.

Due to limitations of the device with a safety limit of 0/50°C, completed data sets were limited in both groups for the cold pain threshold (CPT). The difference in CPT between pre- and post-tests was +1.6°C (5.6) for the asymptomatic participants and +2.5°C (SD: 4.9) for the LBP group. A 2-way RM-ANOVA showed a significant change over time ($F = 5.31$, $P = 0.028$) for both groups, but there were no differences between groups.

For the lumbar area, an RM-ANOVA showed no significant group difference, although the overall change between pre- and post-task measures across both groups was close to significant ($F = 4.24$, $P = 0.054$). Imputing 0°C for the missed scores did not affect the result.

For the thenar warm pain threshold (WPT), the overall difference between pre- and post-test was −1.2°C (SD: 2.5) for the asymptomatic group and −1.1°C (2.7) for those with LBP. A 2-way RM-ANOVA showed a significant interaction between group and time ($F = 8.739$, $P = 0.006$), with the post hoc analysis confirming a reduction of the WPT for the asymptomatic group only (SNK test: $P = 0.037$). However, correction for multiple comparisons showed no significance (BC: $P = 0.144$). There was no significant change in WPT measured over the lumbar region for either group.

Temporal Summation

Temporal summation data were obtained from 15 asymptomatic participants and 18 participants with LBP. Overall, a reduction in pain sensitivity to the same stimulus was found over time (Figure 5). A 3-way RM-ANOVA revealed interactions for sequence only ($F = 22.69$, $P = 0.000$), with the post hoc analysis revealing significant changes between the 1st and 3rd through 10th stimuli (SNK test: $P < 0.034$). No differences were observed between groups, and there was no effect of the task on temporal summation.

DISCUSSION

This is the first study to rigorously utilize different quantitative sensory measures to evaluate whether a repeated lifting exercise induces EIH and whether this effect differs in people with chronic LBP. Our findings confirmed that the hypoalgesic effect gained from back-specific exercise induced by repeated lifting is impaired in participants with chronic LBP, which has important implications for those performing repeated lifting in an occupational setting.

The study population comprised mainly people with minimal disability due to their LBP (ODI ≤ 20). At baseline, we did not observe any consistent differences in any of the QST measures between groups, indicating that our sample of people with LBP did not show obvious signs of peripheral or central sensitization. This is in contrast with previous work using multiple PPTs over the lumbar region, which showed lower PPTs for people with LBP in a comparable population.[12,34] The high interindividual differences and the relatively low levels of pain and disability in our sample could explain this. Moreover, we did not observe a correlation between baseline PPTs and changes in PPT post-task in our study population, indicating that the extent of EIH was independent of baseline sensitivity.

The task was perceived by the participants as easy to moderate exercise according to the Borg Scale. This is in contrast to most other studies that have examined EIH in response to more demanding exercise.[1,35] Yet, the

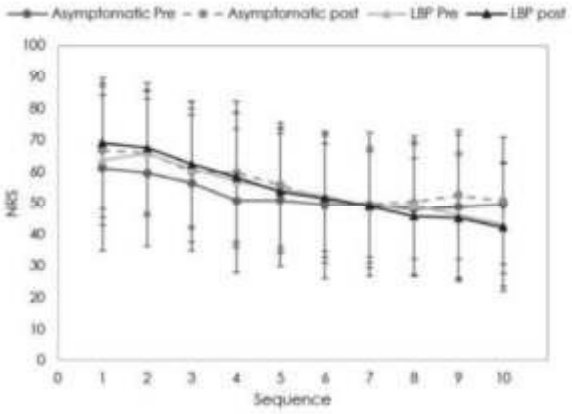


Figure 5. Results of temporal summation. The graph shows pain scores (NRS 0 to 100) over 10 heat pulses (sequence) in healthy asymptomatic participants and in those with low back pain (LBP) before and after the repetitive lifting task. Asymptomatic participants started with an average pain score of 60.93 (standard deviation 26.1) and rated the tenth stimulus as 49.4 (21.7) in the pre-test, and 66.67 (21.4) and 50.80 (20.2) for the post-test, respectively. The LBP group changed from 63.67 (20.0) to 43.28 (21.9) pre-test, and from 68.94 (22.3) to 42.33 (21.2) post-test. There was neither a significant difference between pre- and post-task test results nor between the 2 groups.

current study clearly demonstrated an EIH response for the asymptomatic population as seen by the significant increase in lumbar PPTs measured after completion of the repetitive task.

Furthermore, our results are in contrast to those of previous studies that did not find evidence of impaired EIH in people with LBP; however, no other study has examined the response to exercise specifically targeting the back muscles.[10,11] In a study that evaluated changes in PPT following a lifting task, albeit of shorter duration and only lifting in the sagittal plane,[12] a significant local decrease in PPT over the lumbar area was shown in people with LBP. The trend was shown in our study. However, changes were not statistically significant.

Differences were observed for the change in PPT between medial and lateral testing sites in the asymptomatic group, with significant changes observed only for medial sites. This is likely because the lateral column was located to a lesser extent over the erector spinae (ie, the iliocostalis lumborum), which were engaged in the task.[36] Moreover, EIH was more evident at cranial sites. This underlines the importance of topographical PPT mapping, as changes might not be depicted if only a single test site is used.

The absence of EIH in our cohort of people with LBP does not necessarily imply that the people with LBP lacked descending pain inhibition. It rather could be caused by their erector spinae muscles becoming sensitized after the task due to localized muscle fatigue, especially since studies indicate that the erector spinae are more fatigable in people with LBP and changes in muscles activity were found with fatigue or pain.[37–39]

Research on changes in pain sensitivity over the lumbar region after exercise is limited. Comparing our results with the findings of Gajsar et al.,[13] we found similar baseline scores and changes in lumbar PPTs (absolute change: men, 34.2 kPa; women, 18.9 kPa; from Gajsar et al.[13]). However, in the study by Gajsar et al.,[13] the increase in PPT over the lower back after exercise did not reach statistical significance, unlike our current findings. The isometric back extension task used in this previous study also engages the hip extensor muscles, over which they found a significant increase in PPT. Additionally, Gajsar et al.[13] examined the PPT at only 1 site over the lumbar region (adjacent to L3). Our findings indicate that test site has a significant influence on outcome and that testing sites directly over the muscle belly are more likely to demonstrate a change.

We did not identify a significant change in pressure pain sensitivity measured at a remote site (hand), likely because of the low intensity and duration of the task, since remote changes are typically seen after excessive or vigorous exercise.[2,3]

In contrast to pressure testing, the sensitivity to thermal stimuli did not show a clear pattern and was restricted by the temperature range of the equipment used. In line with our study, most other studies have used PPT as an outcome measurement for EIH, which seems more responsive as an outcome measurement.[1] This is likely because mechanical pressure stimulates receptors within an exercised muscle, whereas the thermal stimuli stimulate superficial receptors of the skin. Changes in temperature pain thresholds may be caused by exercise-induced changes in skin or body temperature rather than inhibitory pain mechanisms.[1] Furthermore, the randomization of stimuli might have affected the results.[40]

The temporal summation of heat stimuli did not differ between groups and did not change pre- and post-exercise but did decrease over the series of stimuli. These results are in contrast to those from a similar protocol in a similar population without an exercise intervention.[26] Other studies also showed an increase in pain intensity using different protocols.[41,42] However, consistent with our findings, a reverse effect of temporal summation has been reported in other studies as a reduced wind-up or habituation in healthy controls.[43,44] We therefore cannot infer any changes in temporal summation because the protocol we used did not induce temporal summation.

It is worthwhile to note that there was large variability in QST responses. Some participants with chronic LBP did show increased PPT after the task, reflecting the large variability in presentation found in any chronic LBP cohort.[45] However, our findings highlight that even people experiencing chronic symptoms of low severity and normal baseline sensitivity can lack an EIH response. It will be relevant in future research to investigate if the absence of EIH is associated with poorer outcome to exercise interventions in people with LBP. Potentially, the response to a short bout of back-specific exercise could be used to understand whether or not patients are likely to have a positive analgesic response to an exercise program targeting their back muscles. However, subgrouping based on EIH response needs to be fully investigated in future work.

Strengths and Limitations

This is the first study to assess the effects of repetitive lifting on pain sensitivity with an extensive QST test

battery, including tests of sensitivity to both mechanical and thermal stimuli. Nevertheless, there are some methodological considerations that should be noted. An a priori sample size was not determined, and it is therefore possible that the sample size prevented some differences from reaching statistical significance. It could be argued that the average change in PPT measured from the 16 sites over the lower back for the asymptomatic participants (ie, +29.78 kPa) is low and, although statistically significant, is not a relevant change. Moreover, based on the RM-ANOVA, there was no interaction at the remote test site for time (controls: +22.61 kPa; LBP: +1.95 kPa), even though change in the asymptomatic group is somewhat similar to the change over the lumbar region. Nevertheless, it should be noted that the average change in PPT for the LBP group was in the opposite direction (ie, −14.87 kPa), suggesting a real and relevant difference in response between groups.

No control condition was included in this study; thus, it is uncertain whether the changes in PPT are actually due to the exercise performed. The change in PPT at the back could be partially attributed to habituation, due to induction of pain itself from the extensive psychophysical testing or even expectation effects. We verbally encouraged and instructed participants to lift with their back. Therefore, changes in QST might be influenced by underlying biomechanical or muscular activation patterns that were not considered in this study. We recruited participants from a university environment; therefore, our data cannot be generalized to other LBP populations, including those exposed to manual labor and heavy lifting, or to people with more severe LBP.

Even in the control group, the task produced mild back pain in some participants. This suggests firstly that the task targeted the right region. On the other hand, the duration and intensity of the task might not have been extensive enough to produce high levels of EIH, especially indications of a systemic effect measured at the remote site.

Missing data were due to technical limitations of the equipment used but were relatively even between groups; thus, this did not likely have a significant effect on the results. The order of QST was the same for both groups and cannot explain group differences. However, we cannot out rule that different test modalities have an effect on the subsequent test. Finally, the full QST was completed within 30 minutes, which has been indicated as the minimum persistence of EIH.[1] Because thermal tests were performed last, any effects might have disappeared by that time. We do not know how long the effects were maintained, and this should be explored in future studies.

CONCLUSION

Asymptomatic people responded favorably to a short repeated lifting task displaying evidence of EIH as revealed by a significant reduction in pressure pain sensitivity over the erector spinae. In contrast, this phenomenon was absent in participants with chronic LBP, even though they presented with low severity pain and disability.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Naugle KM, Fillingim RB, Riley JL 3rd. A meta-analytic review of the hypoalgesic effects of exercise. *J Pain*. 2012;13:1139–1150.

2. Micalos PS, Arendt-Nielsen L. Differential pain response at local and remote muscle sites following aerobic cycling exercise at mild and moderate intensity. *Springerplus*. 2016;5:91.

3. Naugle KM, Naugle KE, Fillingim RB, Samuels B, Riley JL 3rd. Intensity thresholds for aerobic exercise-induced hypoalgesia. *Med Sci Sports Exerc*. 2014;46:817–825.

4. Kuppens K, Struyf F, Nijs J, et al. Exercise- and stress-induced hypoalgesia in musicians with and without shoulder pain: a randomized controlled crossover study. *Pain Physician*. 2016;19:59–68.

5. Ludvigsson ML, Peterson G, Dedering A, Falla D, Peolsson A. Factors associated with pain and disability reduction following exercise interventions in chronic whiplash. *Eur J Pain*. 2016;20:307–315.

6. Vaegter HB, Handberg G, Graven-Nielsen T. Hypoalgesia after exercise and the cold pressor test is reduced in chronic musculoskeletal pain patients with high pain sensitivity. *Clin J Pain*. 2016;32:58–69.

7. Wideman TH, Finan PH, Edwards RR, et al. Increased sensitivity to physical activity among individuals with knee osteoarthritis: relation to pain outcomes, psychological factors, and responses to quantitative sensory testing. *Pain*. 2014;155:703–711.

8. National Institute for Health and Care Excellence. NICE guideline 59. Low back pain and sciatica in over 16s: assessment and management. 2019. https://www.nice.org.uk/guidance/ng59# (accessed February 18, 2019)

9. Qaseem A, Wilt TJ, McLean RM, Forciea MA, Clinical Guidelines Committee of the American College of Physicians. Noninvasive treatments for acute, subacute, and chronic low back pain: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2017;166:514–530.

10. Hoffmann MD, Shepanski MA, MacKenzie SP, Clifford PS. Experimentally-induced pain perception is acutely reduced by aerobic exercise in persons with chronic low back pain. *J Rehabil Res Dev*. 2005;42:183–190.

11. Meeus M, Roussel NA, Truijen S, Nijs J. Reduced pressure pain thresholds in response to exercise in chronic fatigue syndrome but not in chronic low back pain: an experimental study. *J Rehabil Med*. 2010;42:884–890.

12. Falla D, Gizzi L, Tschapek M, Erlenwein J, Petzke F. Reduced task-induced variations in the distribution of activity across back muscle regions in individuals with low back pain. *Pain*. 2014;155:944–953.

13. Gajsar H, Titze C, Hasenbring MI, Vaegter HB. Isometric back exercise has different effect on pressure pain thresholds in healthy men and women. *Pain Med*. 2017;18:917–923.

14. Gerhardt A, Eich W, Janke S, Leisner S, Treede RD, Tesarz J. Chronic widespread back pain is distinct from chronic local back pain: evidence from quantitative sensory testing, pain drawings, and psychometrics. *Clin J Pain*. 2016;32:568–579.

15. Hubscher M, Moloney N, Rebbeck T, Traeger A, Refshauge KM. Contributions of mood, pain catastrophizing, and cold hyperalgesia in acute and chronic low back pain: a comparison with pain-free controls. *Clin J Pain*. 2014;30:886–893.

16. Puta C, Schulz B, Schoeler S, et al. Somatosensory abnormalities for painful and innocuous stimuli at the back and at a site distinct from the region of pain in chronic back pain patients. *PLoS One*. 2013;8:e58885.

17. Roussel NA, Nijs J, Meeus M, Mylius V, Fayt C, Oostendorp R. Central sensitization and altered central pain processing in chronic low back pain: fact or myth? *Clin J Pain*. 2013;29:625–638.

18. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Int J Surg*. 2014;12:1495–1499.

19. Breivik H, Borchgrevink PC, Allen SM, et al. Assessment of pain. *Br J Anaesth*. 2008;101:17–24.

20. Fairbank JC, Pynsent PB. The Oswestry disability index. *Spine (Phila Pa 1976)*. 2000;25:2940–2952; discussion 52.

21. Craig CL, Marshall AL, Sjostrom M, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc*. 2003;35:1381–1395.

22. Scoggins JF, Patrick DL. The use of patient-reported outcomes instruments in registered clinical trials: evidence from ClinicalTrials.gov. *Contemp Clin Trials*. 2009;30:289–292.

23. Henry JD, Crawford JR. The short-form version of the Depression Anxiety Stress Scales (DASS-21): construct validity and normative data in a large non-clinical sample. *Br J Clin Psychol*. 2005;44(Pt 2):227–239.

24. Osman A, Barrios FX, Gutierrez PM, Kopper BA, Merrifield T, Grittmann L. The Pain Catastrophizing Scale: further psychometric evaluation with adult samples. *J Behav Med*. 2000;23:351–365.

25. Waddell G, Newton M, Henderson I, Somerville D, Main CJ. A Fear-Avoidance Beliefs Questionnaire (FABQ) and the role of fear-avoidance beliefs in chronic low back pain and disability. *Pain*. 1993;52:157–168.

26. 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 Med*. 2016;17:1452–1464.

27. 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;123:231–243.

28. Balaguier R, Madeleine P, Vuillerme N. Intra-session absolute and relative reliability of pressure pain thresholds in the low back region of vine-workers: effect of the number of trials. *BMC Musculoskelet Disord*. 2016;17:350.

29. Knutti IA, Suter MR, Opsommer E. Test-retest reliability of thermal quantitative sensory testing on two sites within the L5 dermatome of the lumbar spine and lower extremity. *Neurosci Lett*. 2014;579:157–162.

30. Moloney NA, Hall TM, Doody CM. Reliability of thermal quantitative sensory testing: a systematic review. *J Rehabil Res Dev*. 2012;49:191–207.

31. Vuilleumier PH, Biurrun Manresa JA, Ghamri Y, et al. Reliability of quantitative sensory tests in a low back pain population. *Reg Anesth Pain Med*. 2015;40:665–673.

32. Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc*. 1982;14:377–381.

33. Field A. Discovering Statistics Using SPSS. SAGE Publications, Available from: ProQuest Ebook Central. [13 April 2018]; 2007.

34. O'Neill S, Larsen JB, Nim C, Arendt-Nielsen L. Topographic mapping of pain sensitivity of the lower back—a comparison of healthy controls and patients with chronic non-specific low back pain. *Scand J Pain*. 2019;19:25–37.

35. Vaegter HB, Handberg G, Graven-Nielsen T. Isometric exercises reduce temporal summation of pressure pain in humans. *Eur J Pain*. 2015;19:973–983.

36. Bodgduk N. *Clinical Anatomy of the Lumbar Spine and Sacrum*. Edinburgh: Elsevier/Churchill Livingstone; 2005.

37. Abboud J, Nougarou F, Page I, Cantin V, Massicotte D, Descarreaux M. Trunk motor variability in patients with non-specific chronic low back pain. *Eur J Appl Physiol*. 2014;114:2645–2654.

38. Boucher JA, Abboud J, Nougarou F, Normand MC, Descarreaux M. The effects of vibration and muscle fatigue on

trunk sensorimotor control in low back pain patients. *PLoS One*. 2015;10:e0135838.

39. Sanderson A, Martinez-Valdes E, Heneghan NR, Murillo C, Rushton A, Falla D. Variation in the spatial distribution of erector spinae activity during a lumbar endurance task in people with low back pain. *J Anat*. 2019.

40. Heldestad V, Linder J, Sellersjo L, Nordh E. Reproducibility and influence of test modality order on thermal perception and thermal pain thresholds in quantitative sensory testing. *Clin Neurophysiol*. 2010;121:1878–1885.

41. Brellenthin AG, Crombie KM, Cook DB, Sehgal N, Koltyn KF. Psychosocial influences on exercise-induced hypoalgesia. *Pain Med*. 2017;18:538–550.

42. Reynolds WS, Brown ET, Danford J, et al. Temporal summation to thermal stimuli is elevated in women with overactive bladder syndrome. *Neurourol Urodyn*. 2017;36:1108–1112.

43. Staud R, Robinson ME, Price DD. Isometric exercise has opposite effects on central pain mechanisms in fibromyalgia patients compared to normal controls. *Pain*. 2005;118:176–184.

44. Penza CW, Horn ME, George SZ, Bishop MD. Comparison of 2 lumbar manual therapies on temporal summation of pain in healthy volunteers. *J Pain*. 2017;18:1397–1408.

45. Falla D, Hodges PW. Individualized exercise interventions for spinal pain. *Exerc Sport Sci Rev*. 2017;45:105–115.

Appendix 3 Ethical Review, Consent form, and Participant Information Chapter two

UNIVERSITY OF BIRMINGHAM
APPLICATION FOR ETHICAL REVIEW

Who should use this form:

This form is to be completed by PIs or supervisors (for PGR student research) who have completed the University of Birmingham's Ethical Review of Research Self Assessment Form (SAF) and have decided that further ethical review and approval is required before the commencement of a given Research Project.

Please be aware that all new research projects undertaken by postgraduate research (PGR) students first registered as from 1st September 2008 will be subject to the University's Ethical Review Process. PGR students first registered before 1st September 2008 should refer to their Department/School/College for further advice.

Researchers in the following categories are to use this form:

1. The project is to be conducted by:

- staff of the University of Birmingham; or
- postgraduate research (PGR) students enrolled at the University of Birmingham (to be completed by the student's supervisor);

2. The project is to be conducted at the University of Birmingham by visiting researchers.

Students undertaking undergraduate projects and taught postgraduate (PGT) students should refer to their Department/School for advice.

NOTES:

- An electronic version of the completed form should be submitted to the Research Ethics Officer, at the following email address: aer-ethics@contacts.bham.ac.uk. Please **do not** submit paper copies.
- If, in any section, you find that you have insufficient space, or you wish to supply additional material not specifically requested by the form, please it in a separate file, clearly marked and attached to the submission email.
- If you have any queries about the form, please address them to the Research Ethics Team.

☒ **Before submitting, please tick this box to confirm that you have consulted and**

understood the following information and guidance and that you have taken it into account when completing your application:

- **The information and guidance provided on the University's ethics webpages (https://intranet.birmingham.ac.uk/finance/accounting/Research-Support-Group/Research-Ethics/Ethical-Review-of-Research.aspx)**

- **The University's Code of Practice for Research (http://www.as.bham.ac.uk/legislation/docs/COP_Research.pdf)**

UNIVERSITY OF BIRMINGHAM APPLICATION FOR ETHICAL REVIEW	*OFFICE USE ONLY:* Application No: Date Received:

1. TITLE OF PROJECT

Influences of low back pain on sensory integration and motor control during activities of daily living

2. THIS PROJECT IS:

University of Birmingham Staff Research project ☒
University of Birmingham Postgraduate Research (PGR) Student project ☐
Other ☐ (Please specify):

3. INVESTIGATORS

a) PLEASE GIVE DETAILS OF THE PRINCIPAL INVESTIGATORS OR SUPERVISORS (FOR PGR STUDENT PROJECTS)

Name: Title / first name / family name	Professor Deborah Falla
Highest qualification & position held:	Chair in Rehabilitation Science and Physiotherapy
School/Department	School of Sport, Exercise and Rehabilitation
Telephone:	[redacted]
Email address:	

Name: Title / first name / family	Dr. Alessandro Marco De Nunzio
Highest qualification & position held:	Research Fellow
School/Department	School of Sport, Exercise and Rehabilitation
Telephone:	[redacted]
Email address:	

Name: Title / first name / family name	Dr. Alison Rushton
Highest qualification & position held:	Senior Lecturer
School/Department	School of Sport, Exercise and Rehabilitation
Telephone:	[redacted]
Email address:	

Name: Title / first name / family name	Dr. Nicola Heneghan
Highest qualification & position held:	Lecturer
School/Department	School of Sport, Exercise and Rehabilitation
Telephone:	[redacted]
Email address:	

b) PLEASE GIVE DETAILS OF ANY CO-INVESTIGATORS OR CO-SUPERVISORS (FOR PGR STUDENT PROJECTS)

Name: Title / first name / family name	Nicola Middlebrook
Highest qualification & position held:	MRes student
School/Department	School of Sport, Exercise and Rehabilitation
Telephone:	
Email address:	

c) In the case of PGR student projects, please give details of the student

Name of student:		Student No:	
Course of study:		Email address:	
Principal			

4. ESTIMATED START OF PROJECT Date: 01/01/2017

ESTIMATED END OF PROJECT Date: 31/12/2019

5. FUNDING

List the funding sources (including internal sources) and give the status of each source.

Funding Body	*Approved/Pending /To be submitted*
To be funded from the start-up of Prof. Deborah Falla	Approved

If you are requesting a quick turnaround on your application, please explain the reasons below (including funding-related deadlines). You should be aware that whilst effort will be made in cases of genuine urgency, it will not always be possible for the Ethics Committees to meet such requests.

6. SUMMARY OF PROJECT

Describe the purpose, background rationale for the proposed project, as well as the hypotheses/research questions to be examined and expected outcomes. This description should be in everyday language that is free from jargon. Please explain any technical terms or discipline-specific phrases.

Low back pain (LBP) is a major clinical problem with substantial socio-economic impact. Whilst some individuals seek medical and therapeutic interventions for pain relief, many more live with LBP where there is no specific cause or known pathology, termed non-specific LBP. Current diagnosis of LBP and optimal therapies are insufficient, and knowledge concerning the interaction between musculoskeletal pain and motor performance being incomplete (Hong et al., 2013; Kalichman et al., 2010; Parsons and Courtney, 2014; Vos et al., 2012). Many studies in this field have been performed under static conditions which do not represent patients' daily-life routines (Gallagher and Callaghan, 2015; Gallagher and Callaghan, 2016; Mazaheri et al., 2013). In the present project a series of activities of daily living (ADL) will be analysed using a comprehensive assessment.

Biomechanics of body segments (kinematic and kinetic evaluation), synergistic motor outcome (via high-density electromyography recordings) (EMG) and cortical activity (via electroencephalography) (EEG) will be studied in people with LBP and age-and gender matched control participants.

The general aim of the project is to understand how the brain orchestrates sensory-motor integration and motor control to manage pain. The specific aim of this project is to study the association between changes in motor control abilities and different pain domains (in line with the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials - IMMPACT - recommendations (Dworkin et al., 2005; Gewandter et al., 2014) that including physical functioning, pain quality, pain intensity and emotional functioning). To date, changes in motor control abilities and different pain domains have never been quantified systematically together during ADL.

The project is divided into three separate studies which focus on different motor tasks

1. Postural control in normal and challenged conditions (voluntary holding of a steady inclined position)
2. Gait Initiation and Sudden Unplanned Gait Termination
3. Walking along curvilinear path and turning strategies

SUMMARY OF STUDY 1

1. Postural control in normal and challenged conditions

Working Hypotheses

1. The postural effects, induced via proprioceptive stimulation, are different in LBP compared to healthy participants likely due to a change in body schema.
2. LBP participants will display a limitation in reaching challenging postural conditions (voluntary holding of a steady inclined position) as expression of inability to voluntarily switch to a new postural set

Background working hypothesis 1

Postural control to maintain an upright stance is one of the most important and basic requirements in the daily life of humans. The sensory inputs involved in postural control include visual and vestibular inputs, as well as proprioceptive and tactile somatosensory inputs. These multisensory inputs are integrated to represent the body state (*body schema*) and as reference to generate and control motion (Maurer et al., 2006; Schweigart and Mergner, 2008).

Posture can be tested by measuring movement of the body's center of mass relative to the base of support (controlled by the Center of Pressure (CoP) movements (Winter et al., 1998) in standing under the instruction to stand relaxed or minimize movement, referred as postural sway.

Limiting postural sway requires adequate trunk control, since any rotation around the ankle joints (considering the standing body as an inverted pendulum controlled at ankle joint (Morasso and Schieppati, 1999; Winter et al., 1998) will induce variation in gravitational moments around the spine that have to be controlled by trunk musculature to maintain trunk alignment (Creath et al., 2005; Hodges et al., 2002; Oullier et al., 2002). In addition, small deviations from the single inverted pendulum approximation do occur, as postural sway comprises trunk movements that are coordinated with movements of the lower extremities to reduce excursion of the body's center of mass (Hodges et al., 2002; Oullier et al., 2002). The latter case specifically applies when balance

needs to be achieved under dynamic, critical or unstable conditions (Courtine et al., 2007; De Nunzio et al., 2008; De Nunzio et al., 2005; Mientjes and Frank, 1999; Schieppati et al., 1994).

Niels and Sinnott in 1991 (Nies and Sinnott, 1991) were the first to investigate balance control in patients with LBP, by measuring CoP movements. Subsequently, many comparable studies have been published and a recent review concluded that there is consistent evidence that LBP coincides with increased sway amplitude and/or sway velocity (Ruhe et al., 2011).

However, there are no previous studies investigating whether LBP alters the integration of proprioceptive inflow to create their body schema and manage posture.

Sensory information conveyed along afferent fibres from muscle proprioceptors plays an important role in the control of posture in humans (Kavounoudias et al., 1999; Kavounoudias et al., 1998; Roll et al., 1989b; Schieppati and Nardone, 1999) and jointly contribute to the body schema formation (Roll et al., 1989b). Tendon vibration almost selectively activates muscle spindle primary endings and elicits a discharge in the fast conducting large-diameter group Ia afferent fibers (Roll and Vedel, 1982; Roll et al., 1989a) thereby providing a means to influence proprioceptive inflow. Thus we will evaluate whether proprioceptive information is differently integrated to balance the body in people with LBP versus healthy controls.

Methods working hypothesis 1

To evaluate the 1st working hypothesis, we will apply unilateral vibration to various regions of the body (see methods for details) during a quiet stance condition with eyes open and eyes closed.

Surface EMG will be recorded from the lumbar erector spinae, selected lower limb and neck muscles bilaterally. EEG as well as CoP movements and ankle torque will be recorded.

We will compare the biomechanical differences (especially kinetic: CoP movements and ankle torque) between people with LBP and age and gender-matched participants in exploiting proprioceptive input subserving posture and correlate the differences with measures of motor control (level of muscle activation variability determined from the EMG recordings) and its cortical signature (EEG local field desynchronizations in sensorimotor and parietal cortex (Wagner et al., 2016).

Background working hypothesis 2

To accomplish the 2nd working hypothesis, we will evaluate how balance is maintained under a challenged condition characterized by voluntarily holding a steady, inclined posture, up to the limit of stability (McCollum and Leen, 1989; Schieppati et al., 1994). This condition implies both greater activation of postural muscles than in normal stance to counteract the increased momentum of gravity, and conscious descending input to the spinal cord.

A previous study (Schieppati et al., 1994) has assessed this challenged stance condition in young and elderly healthy people, and in idiopathic parkinsonians; finding that while sway area was minimal during normal stance, it increased progressively when the subjects leant forward or backward showing a clear fine-tuned function of body support from the tibialis anterior and soleus muscles, and sway control from extensor and flexor digitorum muscles. Age influenced the extent of Antero-Posterior (A-P) leaning without changing the relationship between sway area and A-P displacement, while people with Parkinson's showed impairment in achieving this challenged stance condition, still maintaining the same relationship between muscle activity and body inclination (indicating a preserved feedback mechanism reflexly controlling balance (De Nunzio et al., 2008)). These previous findings highlight that posture inclinations represent a clear different postural set as people with Parkinson's fail to integrate normal afferent input into a novel reference system (the critical posture, deliberately assumed).

Methods working hypothesis 2

Based on these premises we will use the challenged posture test to study the ability of people with

LBP to modulate the gain of different postural loops voluntarily reaching a new postural set.

The same experimental set-up of the previous project session will be used to extract information regarding motor control and its neural correlates in switching across different postural sets.

SUMMARY OF STUDY 2

2. Gait Initiation and Sudden Unplanned Gait Termination

Working Hypotheses

1. LBP participants will exhibit a modification of the Anticipatory Postural Adjustments during gait initiation compared to healthy participants as pain may influence the feedforward subcortically-mediated motor actions accomplished during this task.
2. LBP will be associated with an alteration of the Compensatory Postural Adjustments executed during a sudden unplanned gait termination since pain may impair the ability to control a startle response.

Background working hypothesis 1

The identification of biological factors that play a role in the persistence of symptoms is vital for the development of interventions to treat LBP. A plausible biological mechanism that may impede LBP recovery is the control of postural perturbations by the central nervous system (CNS). Ineffective control of postural perturbations increases the risk of excessive forces being experienced by passive structures of the spine (Cholewicki and McGill, 1996; Panjabi, 1992), contributing to the persistence of LBP. During ADL, people may experience postural perturbations in the form of self-initiated movements, standing on a moving bus, or being hit by an external object. Anticipatory (APAs) and compensatory (CPAs) postural adjustments are alterations in muscle activity by the CNS to control forces imparted on the body by postural perturbations (Tisserand et al., 2015; Viton et al., 2000). APAs can be observed prior to a predictable perturbation and serve to minimise the perturbation's effect (MacKinnon et al., 2007), while CPAs are observed following a perturbation and are a mechanism to re-establish postural equilibrium (Alexandrov et al., 2005; Park et al., 2004).

A well-studied example of APAs occurs during the transition from stationary standing to stepping forward to initiate gait (Crenna and Frigo, 1991; Rogers et al., 2001). These APAs involve a sequence of muscle activations and changes in the ground reaction forces (GRFs) that move the net CoP beneath the feet backward and toward the initial swing limb (see Fig. 1). This sequence of activity produces the forces and moments necessary to propel the body forward and toward the single-stance limb for the regulation of whole body balance and posture before and during initiation of the voluntary step.

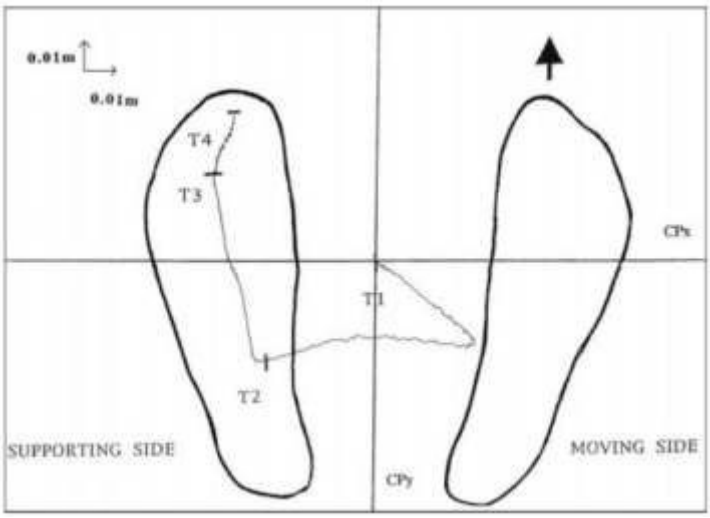


Figure 1 - adapted from Viton et al. 2000

A variety of studies in animals and humans have investigated the neural mechanisms contributing to the generation of the APAs that precede and accompany voluntary movement concluding that the putative regions involved in the control of posture and the intended movement are organized separately (Schepens and Drew, 2003; Schepens and Drew, 2004). Based on the findings of lesion studies, Massion (Massion, 1992) proposed that the neural networks responsible for the control of APAs are organized subcortically. This idea is supported by studies in quadrupeds showing that the pontomedullary reticular formation is involved in the control of posture through brain stem–spinal pathways that may be engaged through motor corticofugal connections (Drew et al., 2004; Matsuyama and Drew, 1997). Thus the motor cortical command for a goal directed movement might include feedforward signals for generating the postural adjustments that anticipate and accompany movements (Massion et al., 2004; Massion et al., 1999). A previous extensive study (MacKinnon et al., 2007) confirms there is an initial phase of movement preparation during which the APA-stepping sequence was progressively assembled, and that this early preparation did not involve the corticomotor pathways which only contribute to the following voluntary initiation of the prepared APA-stepping sequence. These findings are consistent with a feedforward mode of neural control whereby the motor sequence, including the associated postural adjustments, is prepared before voluntary movement.

Methods working hypothesis 1

Preparation of APAs prior to stepping will be studied in people with LBP with the aim of testing the influence on feedforward subcortically-mediated motor actions.

We hypothesise that the APA-stepping sequence could be differently assembled in people with LBP leading to a generation of an impaired voluntary first step action during walking.

Kinetics and kinematics of the body segments, lower limb and trunk muscle activity as well as cortical involvement in voluntary generation of the first walking step will be acquired and analysed. Variability of the onset timing of APAs and the accompanying EMG activity will be correlated with the onset of the volitional first walking step movement to explore if LBP can alter the independency between plan and control of APA and voluntary motor actions.

Background working hypothesis 2

Sudden unplanned gait termination is a dynamic motor task. We stop abruptly in response to unexpected events, such as a car not stopping at a pedestrian crossing, a door closing, an alarming sound, and so on.

Sudden stopping or termination of gait requires abrupt deceleration of the forward progression of the body and the assumption of a stable posture (Hase and Stein, 1998). This task may be particularly demanding individuals with LBP, as it reduces their gait stability and could even lead to an increased incidence of falls (Gryfe et al., 1977; Stenhagen et al., 2013).

Sudden stopping is accomplished in a single step, always with one foot forward (leading leg) and the other back (trailing leg) (Sparrow and Tirosh, 2005). The trailing leg decreases the acceleration and lowers the centre of mass (CoM) (extension synergy), while the leading leg increases the braking force and further decelerates the CoM (flexion synergy (Hase and Stein, 1998; O'Kane et al., 2003). If the effect of these two mechanisms is too weak or they intervene too late in the step cycle, the momentum of the CoM will carry the body forward over the extended leading leg. This will also cause the subject to rise on his toes, thus converting some kinetic energy into potential energy, or moving the arms and rotating the body about the vertical axis (O'Kane et al., 2003; Oates et al., 2010). In any of the previously reported strategies the trunk and its mass play a major role in storing and reducing the CoM momentum.

Moreover, from a neurophysiological perspective a sudden and unexpected gait termination motor action could possibly be characterised as a startle reaction. Therefore, we could expect shorter reaction times than the calculated minimum time for processing of sensory information at the cerebral cortex and therefore an APA followed by a CPA with the first triggered entirely by activity at subcortical levels (probably involving the startle circuit).

Methods working hypothesis 2

In this part of the project, we will explore the hypothesis that LBP may negatively affect a person's ability to abruptly stop walking, in other words, their ability to compensate for the imbalance due to the mechanical perturbations in the sagittal plane and that pain could lead to a different assembly and release of the APA compared to the CPA strategy.

We hypothesise that, in order to compensate for instability in the sagittal plane, they may show a longer and multi-step gait termination strategy and impaired transfer of the forward momentum from the sagittal to the frontal plane. Furthermore, compared with healthy participants, patients may be unable to adequately coordinate trunk movements in order to maintain whole body stability, as well as they may be unable to execute an effective lower limb flexion–extension pattern in order to scale the braking forces needed to decelerate the forward momentum.

This objective will be obtained using the same experimental set-up reported above to study APAs during gait initiation.

SUMMARY OF STUDY 3

3. Walking along a curvilinear path and turnings strategies

Working Hypothesis

1. LBP participants will exhibit an impaired ability to walk along curved trajectory as trunk control and stability are likely affected by pain

Background

Human walking has been extensively studied from kinematic, kinetic and physiological viewpoints (Barker et al., 2006; Coutts, 1999; Ivanenko et al., 2006; Sousa and Tavares, 2015). However, investigations have frequently isolated the walking person from his/her natural context, by studying gait in limited conditions, such as straight-ahead walking, and often on a treadmill.

Even though locomotion along a straight path may represent an easy task for a normal human, it is

rarely encountered in everyday life. Often, humans are faced with changes in path direction, which can be either unexpected or anticipated in advance. In both of the cases, the central nervous system (CNS) must abdicate to the symmetry of the locomotion apparatus, which seems to be adapted to straight-ahead walking (Rossignol, 1996; Rossignol et al., 1996).

Walking in a curved path may thus involve a trade-off between automatic forward progression and voluntary rotation of the body (Domenici et al., 1998; Labruyere and van Hedel, 2012), thereby resulting in the production of smooth, adapted trajectories (Hase and Stein, 1999). Constraints of equilibrium, already present during straight-ahead locomotion (Cavagna and Margaria, 1966; Pozzo et al., 1998), also challenge the CNS during curved walking (Godi et al., 2010; Guglielmetti et al., 2009; Thigpen et al., 2000).

Walking along curved trajectories implies a different spatiotemporal pattern of muscle activation than straight walking. This is due to the constraints of the task (Courtine and Schieppati, 2003a; Courtine and Schieppati, 2003b). Stride length of the inner leg (closer to the centre of curvature) is necessarily shorter than that of the outer leg, because the distance between the feet is not annulled during curved walking and the step frequency is the same for both legs. Swing velocity is greater for the outer than the inner foot. The inner foot is placed on the floor at a greater angle than the outer foot with respect to the trajectory. Stance phase duration is shorter in the outer than inner leg. Ground reaction force is greater for the outer foot at heel strike and toe-off, whereas it is greater for the inner foot during the mid-stance phase (Turcato et al., 2015). Trunk roll is greater towards the inner than the outer side, whereas it is symmetrically and alternately distributed during straight walking. Mediolateral displacement of body centre of mass toward the supporting leg is shifted inwards, to create the centripetal force that keeps the body moving along the circular path (Courtine and Schieppati, 2003a; Courtine and Schieppati, 2003b; Turcato et al., 2015). These kinematic and dynamic constraints require an adapted mode of control. Amplitude and timing characteristics of the muscles' activation are significantly associated with the spatial and temporal adaptations to curvilinear locomotion (Courtine et al., 2006; Courtine and Schieppati, 2004).

Methods

Given i. the substantial complexity of the changes required to smoothly accomplish locomotion along a curved trajectory and ii. the importance of trunk control, mainly operated via proprioceptive inflow integration from paraspinal muscles (Courtine et al., 2007; Schmid et al., 2005), we will investigate the capacity of people with LBP to walk along a 180° curved path.

We hypothesise that LBP could induce poor posturokinetic coordination and affect biomechanics of gait to some extent, showing an impaired control compared to walking straight-ahead or compared to asymptomatic subjects.

Variability of paraspinal muscle activity will be studied via high-density EMG, in conjunction lower limb and neck muscle activity. Sensorimotor and parietal cortex involvement will be studied as controlling an automatic/stereotyped motor task (CPG generation) superimposed on a voluntary synergistic motor modulation to control body rotation (gait adaptation) (Wagner et al., 2016).

7. CONDUCT OF PROJECT

Please give a description of the research methodology that will be used

Design: Cross-sectional.

All studies will be conducted in the human movement laboratory of the School of Sport, Exercise and Rehabilitation Sciences.

For each study, participants will attend a single laboratory session. All measurements will be done as follows:

Study 1: **Postural control in normal and challenged conditions**
Postural assessment will be performed using two Force Platforms (BTS Bioengineering, Italy)

embedded in the floor and positioned at floor level to avoid vivid edges. The quiet upright posture assessment will be performed in order to detect the instant position of the Center of Pressure (CoP). Participants will be asked to stand barefoot on the force platform (one foot on each force platform) with their feet spaced 17 cm apart (measured between heels) and a 14° angle between feet (McIlroy and Maki, 1997), with arms at their sides looking at a visual target adjusted to eye-level height, 40 cm in front. All participants will receive the same instructions: to keep their gaze fixed on the visual target, standing for at least 40 s. In order to ensure accuracy and reiteration across trials, foot positioning will be marked on the platform. During the challenged condition trials the participants will be asked to lean forward or backward as far as possible. To assure safety, an experimenter will stand close to the participant preventing any possible fall, which in any case would be very unlikely.
Inclinations will be accomplished without lifting toes or heels and within minimal bending at the hip or knees, and keeping the trunk as straight as possible.
Eyes-open (EO), and eyes-closed (EC) conditions will be recorded, and 6 consecutive trials (Pinsault and Vuillerme, 2009) (3 EO, 3 EC randomly assigned) will be collected. In order to avoid possible fatigue, a 1-minute rest will be given between trials.

The CoP displacement will be analysed off-line from the unfiltered platform signal by using two different parameterisations techniques (Baratto et al., 2002): i) global parameterisation which numerically expresses the overall size of the sway patterns, in time and frequency domains; and ii) structural parameterisation which identifies subunits of posturographic data related to the underlying motor control process.
In order to compute structural parameters, a Sway Density Plot (SDP) will be calculated by counting the number of consecutive samples of the posturographic trajectory which, for each time instant, fall within a test circle (Ø 2.5 mm) (Baratto et al., 2002). SDP describes a regular series of peaks and valleys. Peaks correspond to time instants in which the ankle torque is relatively stable and is associated to the feed-forward control actions (motor commands); valleys are related to time instants in which the ankle torque rapidly shifts between two consecutive stable points.
The main reason for clinical interest in the analysis of the CoP signal is the fact that its time structure can reveal something of the postural control mechanism and its pathological modifications, because the CoP signal is proportional to the ankle torque (Morasso and Sanguineti, 2002; Morasso and Schieppati, 1999). This torque is the combination of the descending motor commands as well as the mechanical properties of the muscles acting around the ankle. The descending motor commands modulate, at the same time, the ankle torque and the ankle stiffness (Baratto et al., 2002).
The following indices, will be computed for each trial and condition (EO, EC):

- the Sway Path (SP) of the CoP (integrating the instant velocity of the CoP over the total recording time);
- the frequency bandwidth (including the 80% of the amplitude spectrum area (FB1) (Baratto et al., 2002)), separately computed for the antero-posterior (A-P) and medio- lateral (M-L) CoP movements direction;
- the Mean amplitude of the Peaks (MP) of the Sway Density Plot (SDP) - MP is an a-dimensional value which estimates the posture stability degree;
- the Mean Distance (MD) between two consecutive peaks of the SDP (for details see (Baratto et al., 2002)) – it represents the amplitude of the feed-forward control actions (motor commands);
- the Median CoP position along M-L direction will be calculated as index of participants' asymmetrical weight distribution on the feet.
- The Median CoP position along A-P direction will be calculated as index of participants' ability in weight shifting during critical stance condition trials.

Studies 2 and 3: **Gait Initiation, Walking along curvilinear path and Gait Termination**

The participants will undergo a kinematic evaluation of walking with an infrared camera based optoelectronic system (BTS Bioengineering, Italy). Participants, starting with their feet on the force platforms, will be asked to walk barefoot at their usual cadence, along a 6-m rectilinear walkway, making a continuous turn, following a curvilinear path with 120 cm radius of gyration

and walk back to the starting point. A set of at least three repetitions will be acquired. A 2 minutes rest between walking trials will be given to avoid participant exhaustion.
Synchronised with lower limb joint kinematics the coronal and sagittal walking plane will be videotaped. Videotape archiving of the participant's gait is advisable for a number of reasons. For example a videotape record allows a close examination of abnormal foot dynamics such as varus/valgus and mid-foot abnormalities. A videotape of the participant, not encumbered in any way by markers, provides the researcher with an overall or "global" view of the participant and additional documentation for later presentation and discussion. Camera height will be adjusted to exclude face visualisation from the video.
In addition, anthropometric measurements will be taken which include the participant's height, weight and leg length. Data used for the estimation of the joint center locations will be collected, i.e. the knee and ankle widths (as seen in the coronal plane of the limb), the distance between right and left pelvic anterior superior iliac spine (ASIS) and the vertical distance in the sagittal plane of the supine participant between ASIS and the greater trochanter (with the femur rotated such that the greater trochanter is oriented as lateral as possible).
The optoelectronic system consists of 8 infrared cameras (100 Hz sampling rate) that track the 3D motion of passive retroreflective markers. All data will be acquired using BTS SMART Capture software and saved to disk for off-line analysis.
The retroreflective 22 marker set used in the lab will be placed according to the protocol described in Davis et al. (Davis et al., 1991). The markers will be placed on the participant according to the following specifications:
Trunk: 1. right acromion process, 2. left acromion process, 3. 7th cervical spinous process.
Pelvis: 1. right ASIS, 2. left ASIS, 3. over the 5th lumbar spinous process.
Thigh: 1. right greater trochanter, 2. left greater trochanter, 3. right lateral femur epicondyle, 4. left lateral femur epicondyle, 5. along the right femur axis oriented so that the longitudinal axis of the thigh lies in the plane formed by the three markers, 6. along the left femur epicondular axis .
Shank: 1. right head of fibula, 2. left head of fibula, 3. right malleolus, 4. left malleolus, 5. along the right fibula axis oriented so that the longitudinal axis of the shank lies in the plane formed by the three markers, 6. along the left fibula axis.
Foot: 1. right toe, 2. left toe, 3. on the lateral aspect of the right foot at the fifth metatarsal head, 4. on the lateral aspect of the left foot at the fifth metatarsal head, 5. right heel (positioned so that the heel-toe marker vector is parallel to the sole of the foot), 6. left heel (positioned so that the heel-toe marker vector is parallel to the sole of the foot).

Electomyographic (EMG) assessment
Surface EMG measurements will be acquired during walking tests, synchronized with kinematic and kinetic (force) data. Surface electrodes for EMG measurements will be located and placed on the participant following a standard guideline provided by the SENIAM project (www.seniam.org). The SENIAM (Surface ElectroMyoGraphy for the Non-Invasive Assessment of Muscles) is a European concerted action in the Biomedical Health and Research Program (BIOMED II) of the European Union.
Bipolar Ag-AgCl surface electrodes will be used to record EMG bilaterally from:
- Tibialis Anterior (TA)
- Soleus (Sol)
- Gastrocnemius Medialis (GasM)
- Tibialis Posterior (TP),
- Erector Spinae (ES),
- Peroneus Longus (PL),
- Biceps Femoris long head (BF),
- Tensor Fascia Latae (TF)
- Vastus Lateralis (VL).

A completely wireless EMG acquisition system will be used (BTS Bioengineering, Italy). Each skin site will be shaved with disposable razors and cleaned with alcohol before electrode placement (Hermens et al., 1999; Perotto, 1994). All data will be acquired at 1,000 Hz using BTS EMG Analyser software and saved to disk for off-line analysis.

High Density Surface EMG
Surface EMG signals will be detected with semi-disposable adhesive grids of electrodes (OT

Bioelettronica, Torino, Italy) placed over the lumbar erector spinae. Each grid consists of 8 rows and 8 columns of electrodes (1-mm diameter, 10-mm inter-electrode distance in both directions). To characterize the spatial distribution of muscle activity, the following variables will be extracted from the bipolar signals: Root mean square (RMS) and mean frequency (MF) averaged over all signals and the two coordinates of the centroid of the root mean square map (x and y-axis coordinates for the medial-lateral and cranial-caudal direction, respectively (Falla et al., 2008), (Falla et al., 2014).

Kinematics and EMG data reduction and analysis
Synchronised kinematics and EMG acquisition and data processing will be performed using Analyser software (BTSS.p.a.) and custom written routines in LabView National Instruments software.

Kinematics
After the walk is complete and all camera information are collected, the two-dimensional coordinates of the centroid of each marker image will be determined for each frame of optoelectronic camera data. Three dimensional marker coordinates will be computed stereometrically from the two dimensional camera data. The instantaneous orientation of an orthogonal, marker-based, embedded coordinate system will be determined for the trunk and pelvis and each thigh, shank and foot segment. The marker-based embedded coordinate systems for the thigh, shank and foot will then be realigned with the instantaneous, joint center-based, embedded coordinate systems. The angular offset values used in this realignment process will be computed from the standing data that will be collected prior to the walking test. Finally, three dimensional limb rotation angles will be calculated from the embedded coordinate system information.
The analysed Kinematic indexes will be:
- temporal parameters of walking cycle (Davis et al., 1991)
- stance and swing phase duration (% stride cycle) for right and left side,
- double stance phase duration (% stride cycle) for right and left side,
- stance and swing phase duration (time duration of the stride cycle) for right and left side,
- time duration of the stride phase (s) for right and left side,
- walking cadence (step/minutes)

- spatial parameters of walking cycle (Davis et al., 1991)
- step length (m) for right and left side,
- stride velocity (m/s) for right and left side,
- swing velocity (m/s) for right and left side,
- stride length (m) for right and left side,
- step width (m) for right and left side
- walking velocity (m/s)

- three dimensional joint rotation during stride cycle along sagittal, coronal and horizontal anatomical plane, for right and left side (Davis et al., 1991)
- pelvis rotation (deg),
- hip rotation (deg),
- knee rotation (deg),
- ankle rotation (deg),

- elevation angles for right and left side (Borghese et al., 1996; Ivanenko et al., 2008b; Lacquaniti et al., 1999)
- thigh (deg)
- shank (deg)
- foot (deg)

EMG
The EMG signals will be off-line band-pass filtered (fourth-order zero-lag Butterworth digital filter, bandwidth 20 – 400 Hz) to attenuate DC offset, motion artefacts, and high-frequency noise (Hermens et al., 1999). The filtered signals will be full-wave rectified and low-pass filtered (fourth-order zero-lag Butterworth digital filter, cut-off frequency 10 Hz) to obtain the muscle activation patterns. To facilitate comparisons between participants and among different walking

speeds, the EMG from each muscle will be normalized to its peak value from self-selected walking and resampled at each 1% of the gait cycle (Clark et al., 2010).

Matrix Factorisation Algorithm
We will use a version of probabilistic ICA (pICA) that, in addition to allowing estimates of the noise for each data dimension, also allowed the basis vectors and activation coefficients to be constrained to be nonnegative (Hojen-Sorensen et al., 2002; Kolenda et al., 2002) http://mole.imm.dtu.dk/toolbox/menu.html.
The correct number of basis vectors will be indicated by an ad hoc procedure based on variance and likelihood curves. We will apply the above algorithm, varying the number of bases from one to eight. We then calculate the amount of variance and the likelihood of the data set explained by each algorithm with a particular number of bases. However, several studies consistently showed that the EMG activity of trunk and leg muscles during human adult locomotion is adequately reconstructed as a linear combination of four to five basic patterns, each one timed at a different phase of the gait cycle (Cappellini et al., 2006; Clark et al., 2010; Davis and Vaughan, 1993; Gizzi et al., 2011; Ivanenko et al., 2005; Ivanenko et al., 2008a; Ivanenko et al., 2004; McGowan et al., 2010; Olree and Vaughan, 1995; Patla, 1985).
The average shape of each pattern, once it is time-normalized to stride duration, is little affected by changes in walking speed (Ivanenko et al., 2004), direction (walking backwards versus walking forwards, (Ivanenko et al., 2008a)), loading or unloading of the limb and body (McGowan et al., 2010), or changes in locomotion mode (running versus walking; (Cappellini et al., 2006)). The similarity of the average waveforms irrespective of walking or running speed suggests that each command is shaped relative to the overall duration of the gait cycle, so that the resulting muscle activations have a short duration at high speeds and a longer duration at low speeds. Similarity of the average waveforms will be tested according with walking direction conditions (rectilinear or curvilinear).

Activation characteristics contributing to reduced complexity
An examination of the characteristics of muscle activation responsible for possibly reduced locomotor output complexity (Falla et al., 2014) will be realised. LBP participants will be separated into groups based on the number of modules required for EMG reconstruction (2, 3, or 4 modules), performing the Matrix Factorization (pICA) analysis assuming four modules for all of the participants. This procedure will assess how the muscle weightings differed among groups and how activation profiles differed among modules within the same group. The muscle weightings for each module will be correlated across groups to quantify the similarity (i.e., module 1 across groups, module 2 across groups, etc.). High correlations indicate similar module composition. Within each group, correlations of activation timing profiles between modules were computed to assess whether modules are independently active. High correlations indicate a lack of independent module activation.

EMG magnitude
To assess the potential effect of the EMG magnitude on the number of modules identified, raw EMG in millivolts from each muscle will be averaged by condition (i.e., rectilinear or curvilinear) over all the gait cycles for each participant for the respective walking condition. The values from all muscles will be averaged together to obtain a single composite measure for each walking condition of each participant.

Correlation between kinematics and modules of EMG reconstruction
The trajectories of the body Center of Mass (COM) and feet are highly regular and repeatable in human gait (Winter, 1991). They are determined by the combined rotation and translation of the lower limb segments. The pelvis, thigh, shank and foot oscillate back and forth relative to the vertical with a similar waveform, time-shifted across different segments (Bianchi et al., 1998; Borghese et al., 1996), and in so doing they carry the trunk and feet along. When the segment elevation angles are plotted one versus the others, they describe regular loops constrained close to a plane common to both the stance and swing phase (Borghese et al., 1996; Ivanenko et al., 2008b; Lacquaniti et al., 1999). The specific orientation of the planar covariance reflects the phase relationships between the segment elevation angles, and therefore the timing of the inter-segmental coordination (Bianchi et al., 1998).

The planar covariance in walking, with the corresponding muscle activation patterns inserted at the time of occurrence along the gait loop will be also calculated to study the phase coupling between the elevation angles and the muscles activation patterns along rectilinear and curvilinear walking.

The same analysis procedures will be adopted on kinematic, kinetic and EMG data selected around the gait initiation and termination phase.

Kinematic (motion), kinetic (force and torque) and EMG acquisition will be realised in one single session for LBP participants and healthy volunteers.

Pain Domains Assessment
Quantitative sensory tests will be performed including pressure pain thresholds and thermal pain thresholds (Rolke et al., 2006a) over regions of the lumbar spine and at a remote site (non-dominant hand). Pressure pain thresholds will be measured over locations distributed across the lumbar region using a pressure algometer (Somedic, CE). Participants here simply indicate when they perceive pain for the first time during pressure stimulation with slowly increasing intensity (50 kPa/sec). Stimulation will stop with the report of pain. Thermal pain thresholds will be measured with a Thermal Sensory Analyzer II, Medoc, Israel (CE certification enclosed). Temperature change will stop with the report of pain.

Healthy Controls: Self Reports
Questionnaire data as described below will be obtained from the controls:
- SF-12 Health Survey: A measure of the general health status of the patient (Brazier et al., 1992)
- Depression, Anxiety, Stress Scales (DASS): A self-rating measure of depression, anxiety and stress (Lovibond and Lovibond, 1995)
- International Physical Activity Questionnaires (IPAQ) to measure physical activity of participants (Booth, 2000)

LBP participants Self Reports
Questionnaire data as described below will be obtained from the participants:
- Back pain questionnaire: Questions pertaining to back pain area, intensity and duration.
- International Physical Activity Questionnaires (IPAQ) to measure physical activity of participants (Booth, 2000)
- SF-12 Health Survey: A measure of the general health status of the patient (Brazier et al., 1992)
- The Van Korff scale (VKS): A measure to grade severity of chronic pain (Von Korff et al., 1992)
- The Pain Catastrophizing Scale (PCS): A measure of catastrophic thinking related to pain (Osman et al., 1997).
- Depression, Anxiety, Stress Scales (DASS): A self-rating measure of depression, anxiety and stress (Lovibond and Lovibond, 1995)
- The Oswestry Disability Index will be used to assess pain-related disability specifically related to LBP (7 items (Fairbank and Pynsent, 2000))
- Fear Avoidance Believe Questionnaire (Waddell et al., 1993)

Additionally, participants will report the area where the pain is felt by completing a pain drawing through sketch software on an iPad.

Multifactorial fall risk assessment will be realised using the following tools:
- Timed Up and Go test (TUG) (Okubo et al., 2016)
- Tinetti Performance Oriented Mobility Assessment (POMA) (Sterke et al., 2010; Thomas and Lane, 2005)
- Activities-specific Balance Confidence (ABC) Scale (Lajoie and Gallagher, 2004)
- Tinetti Falls Efficacy Scale as measure of fear of falling (Hauer et al., 2010; Tinetti et al., 1990)

8. DOES THE PROJECT INVOLVE PARTICIPATION OF PEOPLE OTHER THAN THE RESEARCHERS AND SUPERVISORS?

Yes ☒ No ☐

Note: 'Participation' includes both active participation (such as when participants take part in an interview) and cases where participants take part in the study without their knowledge and consent at the time (for example, in crowd behaviour research).

If you have answered NO please go to Section 18. If you have answered YES to this question please complete all the following sections.

9. PARTICIPANTS AS THE SUBJECTS OF THE RESEARCH

Describe the number of participants and important characteristics (such as age, gender, location, affiliation, level of fitness, intellectual ability etc.). Specify any inclusion/exclusion criteria to be used.

30 healthy and physically active participants & 30 participants who experience chronic non-specific LBP (NSLBP) will be recruited for study 1. The same group of healthy and physically active participants as well as the 30 participants with non-specific LBP will undergo studies 2 and 3 as the 3 studies could be merged and realised into one single testing session. Resting periods among and within the sessions will prevent for any kind of possible muscular fatigue.

Inclusion criteria:

- Both females and males are eligible for the study.
- The age range will be restricted to 18- 65 years to limit age effects on physical measures of the lumbar region.
- LBP and control participants will have the capacity to give the consent at his/her own will.
- Pain-free participants will be included if they have no relevant history over the last three years of back or lower limb pain or injury that limited their function and/or required treatment from a health profession.
- Individuals with chronic NSLBP will be considered for the study.

The following definition for NSLBP is low back pain which is not related to serious pathology and/or does not have a specific cause (also known as simple or mechanical low back pain). Chronic refers to a sub type where back pain problem may have persisted at least 3 months and has resulted in pain on at least half the days in the past 6 months. If possible, participants should be willing to refrain from analgesic medication on the day of testing.

Exclusion criteria:

- Concurrent systemic, rheumatic or neuro-musculoskeletal disorders which may confound testing or are currently pregnant.
- Radicular low back pain or pain related to trauma, fractures, spinal stenosis.
- Participants with higher doses of opioids (> 30 mg of morphine equivalent dose) will be excluded.
- Participants under active management of LBP through specific medications prescribed by a GP, consultant or therapists (physiotherapist, osteopath, chiropractor) less than 3 months before the possible enrolment.

10. RECRUITMENT

Please state clearly how the participants will be identified, approached and recruited. Include any relationship between the investigator(s) and participant(s) (e.g. instructor-student).

Note: Attach a copy of any poster(s), advertisement(s) or letter(s) to be used for recruitment.

Healthy subjects will be recruited via poster advertisement at the:
-School of Sport, Exercise and Rehabilitation Sciences, College of Life and Environmental Sciences of the University of Birmingham
Research or staff members of the PI of the study will not be recruited as participants.

LBP participants will be recruited, via poster advertisement, from the community and population of staff and students at the University of Birmingham.

Interested volunteers will be asked to contact the PI through email / telephone or face to face.
All information regarding the experiment will be provided in the 'Participant Information Leaflet', that will be provided to interested volunteers.
The investigators involved in this project will explain the experiment procedures to the participants and answer any questions they may have.
The investigators' telephone and e-mail references will be provided on the 'Informed Consent' and 'Participant Information Leaflet'.
Data collection will take place in the School of Sport, Exercise and Rehabilitation Sciences, at the Human Movement Laboratory.

11. CONSENT

a) Describe the process that the investigator(s) will be using to obtain valid consent. If consent is not to be obtained explain why**.** If the participants are minors or for other reasons are not competent to consent, describe the proposed alternate source of consent, including any permission / information letter to be provided to the person(s) providing the consent.

All information regarding the experiment will be provided in the 'Participant Information Leaflet' (see attached) which will include a description of the study, inclusion and exclusion criteria, risk and benefits. The information about the study will also be provided verbally by an investigator. Written informed Consent (see attached) will be obtained after the study has been explained and the volunteers have the opportunity to ask any questions they may have.

Note: Attach a copy of the Participant Information Sheet (if applicable), the Consent Form (if applicable), the content of any telephone script (if applicable) and any other material that will be used in the consent process.

b) Will the participants be deceived in any way about the purpose of the study? **Yes** ☐ **No** ☒

If yes, please describe the nature and extent of the deception involved. Include how and when the deception will be revealed, and who will administer this feedback.

12. PARTICIPANT FEEDBACK

Explain what feedback/ information will be provided to the participants after participation in the research. (For example, a more complete description of the purpose of the research, or access to the results of the research).

Each participating subject will receive a complete explanation of the study and its purpose following the measurements. Participants will be invited to leave their email address to receive the publication of the study results.

13. PARTICIPANT WITHDRAWAL

a) Describe how the participants will be informed of their right to withdraw from the project.

The participants' right to withdraw from taking or continuing the experiment will be clearly reported on the Consent Form and Information leaflet and will also be expressed verbally to the volunteers. Participants will be free to withdraw at any time during the experimental session and will have the right to withdraw their data from the study up to 1 month following data collection without giving a reason.

b) Explain any consequences for the participant of withdrawing from the study and indicate what will be done with the participant's data if they withdraw.

There are no consequences for dropping out or withdrawal from the study. In case of experiment interruption or withdrawal by the participant, personal data for participant identification and all the data acquired until the point of withdrawal will be deleted.

14. COMPENSATION

Will participants receive compensation for participation?

i) Financial **Yes** ☒ **No** ☐

ii) Non-financial **Yes** ☐ **No** ☐

If **Yes** to **either** i) or ii) above, please provide details.

Participants will be reimbursed at a rate of 15 £/ hour for participating in the experiment. Each experimental session is expected to take 1.5 h for LBP participants and healthy volunteers

If participants choose to withdraw, how will you deal with compensation?

Participants will be offered compensation based on the time completed (fraction of the total amount based on the time spent at the laboratory).

15. CONFIDENTIALITY

a) Will all participants be anonymous? **Yes** ☒ **No** ☐

b) Will all data be treated as confidential? **Yes** ☒ **No** ☐

Note: Participants' identity/data will be confidential if an assigned ID code or number is used, but it will not be anonymous. Anonymous data cannot be traced back to an individual participant.

Describe the procedures to be used to ensure anonymity of participants and/or confidentiality of data both during the conduct of the research and in the release of its findings.

To reach complete anonymity of the participants, a table will be created to assign an identification number to each participant before being enrolled in the study. The participant, if enrolled in the study, will be asked to remember the assigned identification number and use it during the evaluation session as a mean of identification. The table (key list) containing the connection between the participants' names and the identification numbers will be kept in a locked cabinet in the office of the Principal Investigator. It will not be given to a third party, and it will be stored for 10 years in line with University of Birmingham Research Governance guidelines. The key list will never be present in electronic form. In case of experiment interruption or withdrawal by the participant, personal data for participant identification will be deleted.
All the data collected during the experiment will be strictly confidential, and will not be disclosed to a third party other than the participant and the Principal Investigator. All data will be collected and stored under the identification number allocated at the recruitment.

If participant anonymity or confidentiality is not appropriate to this research project, explain, providing details of how all participants will be advised of the fact that data will not be anonymous or confidential.

16. STORAGE, ACCESS AND DISPOSAL OF DATA

Describe what research data will be stored, where, for what period of time, the measures that will be put in place to ensure security of the data, who will have access to the data, and the method and timing of disposal of the data.

All data from the experiment will be stored in electronic form. The access to the data will be secured through the use of access password and in any case all the acquired data will be anonymous to fully protect the privacy of the participating subjects. Only PI (Prof. Deborah Falla (DF)) and study supervisors (Dr. Alessandro Marco De Nunzio, Dr. Alison Rushton, Dr. Nicola Heneghan) will be granted with the access to the data. Copy of the encrypted data will be stored on external hard drive and secured in a locked cabinet in the office of the Principal Investigator (DF). It will not be given to a third party, and it will be kept stored for 10 years along with the sheet reporting the access password. Anonymised data will be submitted for publication, where participants will not be identifiable. The results of the study will be presented at conferences and submitted for publication in scientific journals. Copies of publications can be sent to participants upon their request.

OTHER APPROVALS REQUIRED? e.g. Criminal Records Bureau (CRB) checks or NHS R&D approvals.

☐ YES ☒ NO ☐ NOT APPLICABLE

If yes, please specify.

17. SIGNIFICANCE/BENEFITS

Outline the potential significance and/or benefits of the research

There is no immediate benefit to the participants of the study. However the results of this project will increase our understanding of changes in sensory-motor control and muscle synergies behavior in response to LBP. This knowledge is relevant for the development and design of rehabilitation programs for individuals with LBP.

18. RISKS

a) Outline any potential risks to **INDIVIDUALS**, including research staff, research participants, other individuals not involved in the research and the measures that will be taken to minimise any risks and the procedures to be adopted in the event of mishap

We believe that the risk from the procedures proposed within this project is very small.

Non-invasive mounting/attaching procedures of surface electrodes include slight discomfort from minor abrasion of the skin area.

Remote risk of falling:

There could be a remote risk of falling during the postural challenging condition trials as the participants will be asked to lean forward or backward as far as possible. To assure a completely safe environment, an experimenter will stand close to the participant during the entire duration of the tests.
This procedure will prevent any possible fall, which in any case would be very unlikely.

It will be emphasized that participants are free to withdraw at any stage of the study.

Induced anxiety, stress or pain:

Because of their simplicity, motor tasks accomplished by the participants will not lead to anxiety or stress higher than that already expected from everyday life. Scheduled resting periods during the testing sessions will avoid prompting pain or muscular fatigue.

Exacerbation of participant's low back pain:

The participants will be asked to execute simple motor tasks which are usually carried out during a normal daily routine (e.g. standing, walking) and there is a remote risk of little exacerbation of low back pain which will be mitigated just allowing longer resting time and, in the unlikely case that this will not be sufficient and the patient feels uncomfortable , the study session will be immediately stopped and the participant will be disengaged from the study.

Risks induced by pressure and thermal pain threshold test:

The process of evaluating pressure or thermal pain threshold is completely safe, and these tests are commonly applied on people with LBP to elucidate the peripheral and central processing mechanisms that underlie changes in pain sensitivity (Blumenstiel et al., 2011; Hubscher et al., 2014; O'Neill et al., 2011).
There is a remote risk for the participants with LBP to have a further pain sensitization undergoing the thermal and pressure pain threshold evaluation. In the unlikely event of a sensitization and persistent increase of LBP the session will be immediately stopped, and the participant will be disengaged from the study.

Moreover, there is no risk of skin bruising or burning induced by the thermal pain threshold test as the device used (Thermal Sensory Analyzer II, Medoc) features safety standards which prevent from any damage to the skin. The device has a temperature limit of 45 C°, and an analog circuit which overrides the system and lowers the temperature gradually as soon as this limit has been reached.

b) Outline any potential risks to **THE ENVIRONMENT and/or SOCIETY** and the measures that will be taken to minimise any risks and the procedures to be adopted in the event of mishap.

No risks to the environment and/or society can be identified in this study.

19. ARE THERE ANY OTHER ETHICAL ISSUES RAISED BY THE RESEARCH?

Yes ☐ **No** ☒

If yes, please specify

20. EXPERT REVIEWER/OPINION

You may be asked to nominate an expert reviewer for certain types of project, including those of an interventional nature or those involving significant risks. If you anticipate that this may apply to your work and you would like to nominate an expert reviewer at this stage, please provide details below.

Contact details (including email address)
Brief explanation of reasons for nominating and/or nominee's suitability

21. CHECKLIST

Please mark if the study involves any of the following:

- Vulnerable groups, such as children and young people aged under 18 years, those with learning disability, or cognitive impairments ☐
- Research that induces or results in or causes anxiety, stress, **pain** or physical discomfort, or poses a risk of harm to participants (which is more than is expected from everyday life) ☒
- Risk to the personal safety of the researcher ☐
- Deception or research that is conducted without full and informed consent of the participants at time study is carried out ☐
- Administration of a chemical agent or vaccines or other substances (including vitamins or food substances) to human participants. ☐
- Production and/or use of genetically modified plants or microbes ☐
- Results that may have an adverse impact on the environment or food safety ☐
- Results that may be used to develop chemical or biological weapons ☐

Please check that the following documents are attached to your application.

	ATTACHED	**NOT APPLICABLE**
Recruitment advertisement	☒	☐
Participant information sheet	☒	☐
Consent form	☒	☐
Questionnaire	☐	☒
Interview Schedule	☐	☒

22. DECLARATION BY APPLICANTS

I submit this application on the basis that the information it contains is confidential and will be used by the
University of Birmingham for the purposes of ethical review and monitoring of the research project described
herein, and to satisfy reporting requirements to regulatory bodies. The information will not be used for any
other purpose without my prior consent.

I declare that:

- The information in this form together with any accompanying information is complete and correct to the best of my knowledge and belief and I take full responsibility for it.
- I undertake to abide by University Code of Practice for Research (http://www.as.bham.ac.uk/legislation/docs/COP_Research.pdf) alongside any other relevant professional bodies' codes of conduct and/or ethical guidelines.
- I will report any changes affecting the ethical aspects of the project to the University of Birmingham Research Ethics Officer.
- I will report any adverse or unforeseen events which occur to the relevant Ethics Committee via the University of Birmingham Research Ethics Officer.

Name of principal investigator/project supervisor:	
Date:	

Please now save your completed form, print a copy for your records, and then email a copy to the Research Ethics Officer, at aer-ethics@contacts.bham.ac.uk. As noted above, please do not submit a paper copy.

23. REFERENCE LIST

Alexandrov, A. V., Frolov, A. A., Horak, F. B., Carlson-Kuhta, P., & Park, S. (2005). Feedback equilibrium control during human standing. Biol Cybern, 93(5), 309-322. doi: 10.1007/s00422-005-0004-1

Baratto, L., Morasso, P. G., Re, C., & Spada, G. (2002). A new look at posturographic analysis in the clinical context: sway-density versus other parameterization techniques. Motor Control, 6(3), 246-270.

Barker, S., Craik, R., Freedman, W., Herrmann, N., & Hillstrom, H. (2006). Accuracy, reliability, and validity of a spatiotemporal gait analysis system. Med Eng Phys, 28(5), 460-467. doi: 10.1016/j.medengphy.2005.07.017

Bianchi, L., Angelini, D., Orani, G. P., & Lacquaniti, F. (1998). Kinematic coordination in human gait: relation to mechanical energy cost. J Neurophysiol, 79(4), 2155-2170.

Blumenstiel, K., Gerhardt, A., Rolke, R., Bieber, C., Tesarz, J., Friederich, H. C., . . . Treede, R. D. (2011). Quantitative Sensory Testing Profiles in Chronic Back Pain Are Distinct From Those in Fibromyalgia. Clinical Journal of Pain, 27(8), 682-690. doi: 10.1097/AJP.0b013e3182177654

Booth, M. (2000). Assessment of physical activity: An international perspective. (vol 71, pg 114, 2000). Res Q Exerc Sport, 71(3), 312-312.

Borghese, N. A., Bianchi, L., & Lacquaniti, F. (1996). Kinematic determinants of human locomotion. J Physiol, 494 (Pt 3), 863-879.

Brazier, J. E., Harper, R., Jones, N. M., O'Cathain, A., Thomas, K. J., Usherwood, T., & Westlake, L. (1992). Validating the SF-36 health survey questionnaire: new outcome measure for primary care. BMJ, 305(6846), 160-164.

Cappellini, G., Ivanenko, Y. P., Poppele, R. E., & Lacquaniti, F. (2006). Motor patterns in human walking and running. J Neurophysiol, 95(6), 3426-3437. doi: 00081.2006 [pii]
10.1152/jn.00081.2006

Cavagna, G. A., & Margaria, R. (1966). Mechanics of walking. J Appl Physiol, 21(1), 271-278.

Cholewicki, J., & McGill, S. M. (1996). Mechanical stability of the in vivo lumbar spine: implications for injury and chronic low back pain. Clin Biomech (Bristol, Avon), 11(1), 1-15.

Clark, D. J., Ting, L. H., Zajac, F. E., Neptune, R. R., & Kautz, S. A. (2010). Merging of healthy motor modules predicts reduced locomotor performance and muscle coordination complexity post-stroke. J Neurophysiol, 103(2), 844-857. doi: 10.1152/jn.00825.2009
Courtine, G., De Nunzio, A. M., Schmid, M., Beretta, M. V., & Schieppati, M. (2007). Stance- and locomotion-dependent processing of vibration-induced proprioceptive inflow from multiple muscles in humans. J Neurophysiol, 97(1), 772-779. doi: 10.1152/jn.00764.2006
Courtine, G., Papaxanthis, C., & Schieppati, M. (2006). Coordinated modulation of locomotor muscle synergies constructs straight-ahead and curvilinear walking in humans. Exp Brain Res, 170(3), 320-335. doi: 10.1007/s00221-005-0215-7
Courtine, G., & Schieppati, M. (2003a). Human walking along a curved path. I. Body trajectory, segment orientation and the effect of vision. Eur J Neurosci, 18(1), 177-190. doi: 2736 [pii]
Courtine, G., & Schieppati, M. (2003b). Human walking along a curved path. II. Gait features and EMG patterns. Eur J Neurosci, 18(1), 191-205. doi: 2737 [pii]
Courtine, G., & Schieppati, M. (2004). Tuning of a basic coordination pattern constructs straight-ahead and curved walking in humans. J Neurophysiol, 91(4), 1524-1535. doi: 10.1152/jn.00817.2003
00817.2003 [pii]
Coutts, F. (1999). Gait analysis in the therapeutic environment. Man Ther, 4(1), 2-10.
Creath, R., Kiemel, T., Horak, F., Peterka, R., & Jeka, J. (2005). A unified view of quiet and perturbed stance: simultaneous co-existing excitable modes. Neurosci Lett, 377(2), 75-80. doi: S0304-3940(04)01486-7 [pii]
10.1016/j.neulet.2004.11.071
Crenna, P., & Frigo, C. (1991). A motor programme for the initiation of forward-oriented movements in humans. J Physiol, 437, 635-653.
Davis, B. L., & Vaughan, C. L. (1993). Phasic behavior of EMG signals during gait: Use of multivariate statistics. J Electromyogr Kinesiol, 3(1), 51-60. doi: 10.1016/1050-6411(93)90023-P
Davis, R. B., Ounpuu, S., Dennis, T., & Gage, J. R. (1991). A gait analysis data collection and reduction technique. Hum Mov Sci, 10, 575-587.
De Nunzio, A. M., Nardone, A., Picco, D., Nilsson, J., & Schieppati, M. (2008). Alternate trains of postural muscle vibration promote cyclic body displacement in standing parkinsonian patients. Mov Disord, 23(15), 2186-2193. doi: 10.1002/mds.22201
De Nunzio, A. M., Nardone, A., & Schieppati, M. (2005). Head stabilization on a continuously oscillating platform: the effect of a proprioceptive disturbance on the balancing strategy. Exp Brain Res, 165(2), 261-272. doi: 10.1007/s00221-005-2297-7
Domenici, P., Jamon, M., & Clarac, F. (1998). Curve walking in freely moving crayfish (Procambarus clarkii). J Exp Biol, 201 (Pt 9), 1315-1329.
Drew, T., Prentice, S., & Schepens, B. (2004). Cortical and brainstem control of locomotion. Prog Brain Res, 143, 251-261. doi: 10.1016/S0079-6123(03)43025-2
Dworkin, R. H., Turk, D. C., Farrar, J. T., Haythornthwaite, J. A., Jensen, M. P., Katz, N. P., . . . Immpact. (2005). Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain, 113(1-2), 9-19. doi: 10.1016/j.pain.2004.09.012
Fairbank, J. C., & Pynsent, P. B. (2000). The Oswestry Disability Index. Spine (Phila Pa 1976), 25(22), 2940-2952; discussion 2952.
Falla, D., Arendt-Nielsen, L., & Farina, D. (2008). Gender-specific adaptations of upper trapezius muscle activity to acute nociceptive stimulation. Pain, 138(1), 217-225. doi: 10.1016/j.pain.2008.04.004
Falla, D., Gizzi, L., Tschapek, M., Erlenwein, J., & Petzke, F. (2014). Reduced task-induced variations in the distribution of activity across back muscle regions in individuals with low back pain. Pain, 155(5), 944-953. doi: 10.1016/j.pain.2014.01.027
Gallagher, K. M., & Callaghan, J. P. (2015). Early static standing is associated with prolonged standing induced low back pain. Human Movement Science, 44, 111-121. doi: 10.1016/j.humov.2015.08.019
Gallagher, K. M., & Callaghan, J. P. (2016). Standing on a declining surface reduces transient prolonged standing induced low back pain development. Appl Ergon, 56, 76-83. doi: 10.1016/j.apergo.2016.03.014
Gewandter, J. S., Dworkin, R. H., Turk, D. C., McDermott, M. P., Baron, R., Gastonguay, M. R., . . . White, R. E. (2014). Research designs for proof-of-concept chronic pain clinical trials: IMMPACT recommendations. Pain, 155(9), 1683-1695. doi: 10.1016/j.pain.2014.05.025
Gizzi, L., Nielsen, J. F., Felici, F., Ivanenko, Y. P., & Farina, D. (2011). Impulses of activation but not motor modules are preserved in the locomotion of subacute stroke patients. Journal of Neurophysiology, 106(1), 202-210. doi: DOI 10.1152/jn.00727.2010
Godi, M., Nardone, A., & Schieppati, M. (2010). Curved walking in hemiparetic patients. J Rehabil Med, 42(9), 858-865. doi: 10.2340/16501977-0594

Gryfe, C. I., Amies, A., & Ashley, M. J. (1977). A longitudinal study of falls in an elderly population: I. Incidence and morbidity. Age Ageing, 6(4), 201-210.
Guglielmetti, S., Nardone, A., De Nunzio, A. M., Godi, M., & Schieppati, M. (2009). Walking along circular trajectories in Parkinson's disease. Mov Disord, 24(4), 598-604. doi: 10.1002/mds.22424
Hase, K., & Stein, R. B. (1998). Analysis of rapid stopping during human walking. J Neurophysiol, 80(1), 255-261.
Hase, K., & Stein, R. B. (1999). Turning strategies during human walking. J Neurophysiol, 81(6), 2914-2922.
Hermens, H. J., Freriks, B., Merletti, R., Hagg, G. G., Stegeman, D., Blok, J., . . . Disselhorst-Klug, C. (1999). European Recommendations for Surface Electro-MyoGraphy: Results of the SENIAM Project. Enschede, The Netherlands: Roessingh Research and Development.
Hodges, P. W., Gurfinkel, V. S., Brumagne, S., Smith, T. C., & Cordo, P. C. (2002). Coexistence of stability and mobility in postural control: evidence from postural compensation for respiration. Exp Brain Res, 144(3), 293-302. doi: 10.1007/s00221-002-1040-x
Hojen-Sorensen, P. A. D. F. R., Winther, O., & Hansen, L. K. (2002). Mean-field approaches to independent component analysis. Neural Computation, 14(4), 889-918. doi: Doi 10.1162/089976602317319009
Hong, J., Reed, C., Novick, D., & Happich, M. (2013). Costs associated with treatment of chronic low back pain: an analysis of the UK General Practice Research Database. Spine (Phila Pa 1976), 38(1), 75-82. doi: 10.1097/BRS.0b013e318276450f
Hubscher, M., Moloney, N., Rebbeck, T., Traeger, A., & Refshauge, K. M. (2014). 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, 30(10), 886-893. doi: 10.1097/Ajp.0000000000000045
Ivanenko, Y. P., Cappellini, G., Dominici, N., Poppele, R. E., & Lacquaniti, F. (2005). Coordination of locomotion with voluntary movements in humans. J Neurosci, 25(31), 7238-7253. doi: 25/31/7238 [pii] 10.1523/JNEUROSCI.1327-05.2005
Ivanenko, Y. P., Cappellini, G., Poppele, R. E., & Lacquaniti, F. (2008). Spatiotemporal organization of alpha-motoneuron activity in the human spinal cord during different gaits and gait transitions. Eur J Neurosci, 27(12), 3351-3368. doi: EJN6289 [pii]
10.1111/j.1460-9568.2008.06289.x
Ivanenko, Y. P., d'Avella, A., Poppele, R. E., & Lacquaniti, F. (2008). On the origin of planar covariation of elevation angles during human locomotion. J Neurophysiol, 99(4), 1890-1898. doi: 01308.2007 [pii] 10.1152/jn.01308.2007
Ivanenko, Y. P., Poppele, R. E., & Lacquaniti, F. (2004). Five basic muscle activation patterns account for muscle activity during human locomotion. J Physiol, 556(Pt 1), 267-282. doi: 10.1113/jphysiol.2003.057174 jphysiol.2003.057174 [pii]
Ivanenko, Y. P., Poppele, R. E., & Lacquaniti, F. (2006). Motor control programs and walking. Neuroscientist, 12(4), 339-348. doi: 10.1177/1073858406287987
Kalichman, L., Kim, D. H., Li, L., Guermazi, A., & Hunter, D. J. (2010). Computed tomography-evaluated features of spinal degeneration: prevalence, intercorrelation, and association with self-reported low back pain. Spine J, 10(3), 200-208. doi: 10.1016/j.spinee.2009.10.018
Kavounoudias, A., Gilhodes, J. C., Roll, R., & Roll, J. P. (1999). From balance regulation to body orientation: two goals for muscle proprioceptive information processing? Exp Brain Res, 124(1), 80-88.
Kavounoudias, A., Roll, R., & Roll, J. P. (1998). The plantar sole is a 'dynamometric map' for human balance control. Neuroreport, 9(14), 3247-3252.
Kolenda, T., Sigurdsson, S., Winther, O., Hansen, L. K., & Larsen, J. (2002). DTU: Toolbox. Lyngby, Denmark: ISP Group at Institute of Informatics and Mathematical Modeling at the Technical University of Denmark.
Labruyere, R., & van Hedel, H. J. (2012). Curve walking is not better than straight walking in estimating ambulation-related domains after incomplete spinal cord injury. Arch Phys Med Rehabil, 93(5), 796-801. doi: 10.1016/j.apmr.2011.11.009
Lacquaniti, F., Grasso, R., & Zago, M. (1999). Motor Patterns in Walking. News Physiol Sci, 14, 168-174.
Lajoie, Y., & Gallagher, S. P. (2004). Predicting falls within the elderly community: comparison of postural sway, reaction time, the Berg balance scale and the Activities-specific Balance Confidence (ABC) scale for comparing fallers and non-fallers. Archives of Gerontology and Geriatrics, 38(1), 11-26. doi: 10.1016/S0167-4943(03)0082-7
Lovibond, S. H., & Lovibond, P. F. (1995). Manual for the depression anxiety stress scales. Sydney, N.S.W.: Psychology Foundation of Australia.
MacKinnon, C. D., Bissig, D., Chiusano, J., Miller, E., Rudnick, L., Jager, C., . . . Rogers, M. W. (2007). Preparation of anticipatory postural adjustments prior to stepping. J Neurophysiol, 97(6), 4368-4379. doi: 10.1152/jn.01136.2006

Massion, J. (1992). Movement, posture and equilibrium: interaction and coordination. Prog Neurobiol, 38(1), 35-56.
Massion, J., Alexandrov, A., & Frolov, A. (2004). Why and how are posture and movement coordinated? Prog Brain Res, 143, 13-27. doi: 10.1016/S0079-6123(03)43002-1
Massion, J., Ioffe, M., Schmitz, C., Viallet, F., & Gantcheva, R. (1999). Acquisition of anticipatory postural adjustments in a bimanual load-lifting task: normal and pathological aspects. Exp Brain Res, 128(1-2), 229-235. doi: 91280229.221 [pii]
Matsuyama, K., & Drew, T. (1997). Organization of the projections from the pericruciate cortex to the pontomedullary brainstem of the cat: a study using the anterograde tracer Phaseolus vulgaris-leucoagglutinin. J Comp Neurol, 389(4), 617-641.
Maurer, C., Mergner, T., & Peterka, R. J. (2006). Multisensory control of human upright stance. Exp Brain Res, 171(2), 231-250. doi: 10.1007/s00221-005-0256-y
Mazaheri, M., Coenen, P., Parnianpour, M., Kiers, H., & van Dieen, J. H. (2013). Low back pain and postural sway during quiet standing with and without sensory manipulation: a systematic review. Gait Posture, 37(1), 12-22. doi: 10.1016/j.gaitpost.2012.06.013
McCollum, G., & Leen, T. K. (1989). Form and exploration of mechanical stability limits in erect stance. J Mot Behav, 21(3), 225-244.
McGowan, C. P., Neptune, R. R., Clark, D. J., & Kautz, S. A. (2010). Modular control of human walking: Adaptations to altered mechanical demands. J Biomech, 43(3), 412-419. doi: 10.1016/j.jbiomech.2009.10.009
McIlroy, W. E., & Maki, B. E. (1997). Preferred placement of the feet during quiet stance: development of a standardized foot placement for balance testing. Clin Biomech (Bristol, Avon), 12(1), 66-70. doi: S026800339600040X [pii]
Mientjes, M. I., & Frank, J. S. (1999). Balance in chronic low back pain patients compared to healthy people under various conditions in upright standing. Clin Biomech (Bristol, Avon), 14(10), 710-716.
Morasso, P. G., & Sanguineti, V. (2002). Ankle muscle stiffness alone cannot stabilize balance during quiet standing. J Neurophysiol, 88(4), 2157-2162.
Morasso, P. G., & Schieppati, M. (1999). Can muscle stiffness alone stabilize upright standing? J Neurophysiol, 82(3), 1622-1626.
Nies, N., & Sinnott, P. L. (1991). Variations in balance and body sway in middle-aged adults. Subjects with healthy backs compared with subjects with low-back dysfunction. Spine (Phila Pa 1976), 16(3), 325-330.
O'Kane, F. W., McGibbon, C. A., & Krebs, D. E. (2003). Kinetic analysis of planned gait termination in healthy subjects and patients with balance disorders. Gait Posture, 17(2), 170-179.
O'Neill, S., Kjaer, P., Graven-Nielsen, T., Manniche, C., & Arendt-Nielsen, L. (2011). Low pressure pain thresholds are associated with, but does not predispose for, low back pain. Eur Spine J, 20(12), 2120-2125. doi: 10.1007/s00586-011-1796-4
Oates, A. R., Frank, J. S., & Patla, A. E. (2010). Control of dynamic stability during adaptation to gait termination on a slippery surface. Exp Brain Res, 201(1), 47-57. doi: 10.1007/s00221-009-2011-2
Okubo, Y., Schoene, D., & Lord, S. R. (2016). Step training improves reaction time, gait and balance and reduces falls in older people: a systematic review and meta-analysis. Br J Sports Med. doi: 10.1136/bjsports-2015-095452
Olree, K. S., & Vaughan, C. L. (1995). Fundamental patterns of bilateral muscle activity in human locomotion. Biol Cybern, 73(5), 409-414.
Osman, A., Barrios, F. X., Kopper, B. A., Hauptmann, W., Jones, J., & O'Neill, E. (1997). Factor structure, reliability, and validity of the Pain Catastrophizing Scale. J Behav Med, 20(6), 589-605.
Oullier, O., Bardy, B. G., Stoffregen, T. A., & Bootsma, R. J. (2002). Postural coordination in looking and tracking tasks. Hum Mov Sci, 21(2), 147-167.
Panjabi, M. M. (1992). The stabilizing system of the spine. Part I. Function, dysfunction, adaptation, and enhancement. J Spinal Disord, 5(4), 383-389; discussion 397.
Park, S., Horak, F. B., & Kuo, A. D. (2004). Postural feedback responses scale with biomechanical constraints in human standing. Exp Brain Res, 154(4), 417-427. doi: 10.1007/s00221-003-1674-3
Parsons, T. D., & Courtney, C. G. (2014). An initial validation of the Virtual Reality Paced Auditory Serial Addition Test in a college sample. J Neurosci Methods, 222, 15-23. doi: 10.1016/j.jneumeth.2013.10.006
Patla, A. E. (1985). Some characteristics of EMG patterns during locomotion: implications for the locomotor control process. J Mot Behav, 17(4), 443-461.
Perotto, A. O. (1994). Anatomical Guide for the Electromyographer.
Pinsault, N., & Vuillerme, N. (2009). Test-retest reliability of centre of foot pressure measures to assess postural control during unperturbed stance. Med Eng Phys, 31(2), 276-286. doi: 10.1016/j.medengphy.2008.08.003
Pozzo, T., Papaxanthis, C., Stapley, P., & Berthoz, A. (1998). The sensorimotor and cognitive integration of

gravity. Brain Res Brain Res Rev, 28(1-2), 92-101.
Rogers, M. W., Kukulka, C. G., Brunt, D., Cain, T. D., & Hanke, T. A. (2001). The influence of stimulus cue on the initiation of stepping in young and older adults. Arch Phys Med Rehabil, 82(5), 619-624. doi: 10.1053/apmr.2001.20833
Rolke, R., Baron, R., Maier, C., Tolle, T. R., Treede, R. D., Beyer, A., . . . Wasserka, B. (2006). Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. Pain, 123(3), 231-243. doi: 10.1016/j.pain.2006.01.041
Roll, J. P., & Vedel, J. P. (1982). Kinaesthetic role of muscle afferents in man, studied by tendon vibration and microneurography. Exp Brain Res, 47(2), 177-190.
Roll, J. P., Vedel, J. P., & Ribot, E. (1989). Alteration of proprioceptive messages induced by tendon vibration in man: a microneurographic study. Exp Brain Res, 76(1), 213-222.
Roll, J. P., Vedel, J. P., & Roll, R. (1989). Eye, head and skeletal muscle spindle feedback in the elaboration of body references. Prog Brain Res, 80, 113-123; discussion 157-160.
Rossignol, S. (1996). Visuomotor regulation of locomotion. Can J Physiol Pharmacol, 74(4), 418-425.
Rossignol, S., Chau, C., Brustein, E., Belanger, M., Barbeau, H., & Drew, T. (1996). Locomotor capacities after complete and partial lesions of the spinal cord. Acta Neurobiol Exp (Wars), 56(1), 449-463.
Ruhe, A., Fejer, R., & Walker, B. (2011). Center of pressure excursion as a measure of balance performance in patients with non-specific low back pain compared to healthy controls: a systematic review of the literature. Eur Spine J, 20(3), 358-368. doi: 10.1007/s00586-010-1543-2
Schepens, B., & Drew, T. (2003). Strategies for the integration of posture and movement during reaching in the cat. J Neurophysiol, 90(5), 3066-3086. doi: 10.1152/jn.00339.2003
Schepens, B., & Drew, T. (2004). Independent and convergent signals from the pontomedullary reticular formation contribute to the control of posture and movement during reaching in the cat. J Neurophysiol, 92(4), 2217-2238. doi: 10.1152/jn.01189.2003
Schieppati, M., Hugon, M., Grasso, M., Nardone, A., & Galante, M. (1994). The limits of equilibrium in young and elderly normal subjects and in parkinsonians. Electroencephalogr Clin Neurophysiol, 93(4), 286-298.
Schieppati, M., & Nardone, A. (1999). Group II spindle afferent fibers in humans: their possible role in the reflex control of stance. Prog Brain Res, 123, 461-472.
Schmid, M., De Nunzio, A. M., & Schieppati, M. (2005). Trunk muscle proprioceptive input assists steering of locomotion. Neurosci Lett, 384(1-2), 127-132. doi: 10.1016/j.neulet.2005.04.059
Schweigart, G., & Mergner, T. (2008). Human stance control beyond steady state response and inverted pendulum simplification. Exp Brain Res, 185(4), 635-653. doi: 10.1007/s00221-007-1189-4
Sousa, A. S., & Tavares, J. M. (2015). Interlimb Coordination During Step-to-Step Transition and Gait Performance. J Mot Behav, 47(6), 563-574. doi: 10.1080/00222895.2015.1023391
Sparrow, W. A., & Tirosh, O. (2005). Gait termination: a review of experimental methods and the effects of ageing and gait pathologies. Gait Posture, 22(4), 362-371. doi: 10.1016/j.gaitpost.2004.11.005
Stenhagen, M., Ekstrom, H., Nordell, E., & Elmstahl, S. (2013). Falls in the general elderly population: a 3- and 6- year prospective study of risk factors using data from the longitudinal population study 'Good ageing in Skane'. BMC Geriatr, 13, 81. doi: 10.1186/1471-2318-13-81
Sterke, C. S., Huisman, S. L., van Beeck, E. F., Looman, C. W. N., & van der Cammen, T. J. M. (2010). Is the Tinetti Performance Oriented Mobility Assessment (POMA) a feasible and valid predictor of short-term fall risk in nursing home residents with dementia? International Psychogeriatrics, 22(2), 254-263. doi: 10.1017/S1041610209991347
Thigpen, M. T., Light, K. E., Creel, G. L., & Flynn, S. M. (2000). Turning difficulty characteristics of adults aged 65 years or older. Phys Ther, 80(12), 1174-1187.
Thomas, J. I., & Lane, J. V. (2005). A pilot study to explore the predictive validity of 4 measures of falls risk in frail elderly patients. Archives of Physical Medicine and Rehabilitation, 86(8), 1636-1640. doi: 10.1016/j.apmr.2005.03.004
Tisserand, R., Robert, T., Chabaud, P., Livet, P., Bonnefoy, M., & Cheze, L. (2015). Comparison between investigations of induced stepping postural responses and voluntary steps to better detect community-dwelling elderly fallers. Neurophysiologie Clinique-Clinical Neurophysiology, 45(4-5), 269-284. doi: 10.1016/j.neucli.2015.07.003
Turcato, A. M., Godi, M., Giordano, A., Schieppati, M., & Nardone, A. (2015). The generation of centripetal force when walking in a circle: insight from the distribution of ground reaction forces recorded by plantar insoles. Journal of Neuroengineering and Rehabilitation, 12. doi: Unsp 4 10.1186/1743-0003-12-4
Viton, J. M., Timsit, M., Mesure, S., Massion, J., Franceschi, J. P., & Delarque, A. (2000). Asymmetry of gait initiation in patients with unilateral knee arthritis. Arch Phys Med Rehabil, 81(2), 194-200.

Von Korff, M., Ormel, J., Keefe, F. J., & Dworkin, S. F. (1992). Grading the severity of chronic pain. Pain, 50(2), 133-149.
Vos, T., Flaxman, A. D., Naghavi, M., Lozano, R., Michaud, C., Ezzati, M., . . . Memish, Z. A. (2012). Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet, 380(9859), 2163-2196. doi: 10.1016/S0140-6736(12)61729-2
Waddell, G., Newton, M., Henderson, I., Somerville, D., & Main, C. J. (1993). A Fear-Avoidance Beliefs Questionnaire (FABQ) and the role of fear-avoidance beliefs in chronic low back pain and disability. Pain, 52(2), 157-168.
Wagner, J., Makeig, S., Gola, M., Neuper, C., & Muller-Putz, G. (2016). Distinct beta Band Oscillatory Networks Subserving Motor and Cognitive Control during Gait Adaptation. J Neurosci, 36(7), 2212-2226. doi: 10.1523/JNEUROSCI.3543-15.2016
Winter, D. A. (1991). The Biomechanics and Motor Control of Human Gait: Normal, Elderly and Pathological. Waterloo. Ontario: Waterloo Biomechanics.
Winter, D. A., Patla, A. E., Prince, F., Ishac, M., & Gielo-Perczak, K. (1998). Stiffness control of balance in quiet standing. J Neurophysiol, 80(3), 1211-1221.

UNIVERSITY OF BIRMINGHAM
APPLICATION FOR ETHICAL REVIEW –
REQUEST FOR AMENDMENTS

Who should use this form:

- This form is to be completed by PIs or supervisors (for PGR student research) who are requesting ethical approval for amendments to research projects that have previously received ethical approval from the University of Birmingham.

  Please be aware that all new research projects undertaken by postgraduate research (PGR) students first registered as from 1st September 2008 will be subject to the University's Ethical Review Process. PGR students first registered before 1st September 2008 should refer to their Department/School/College for further advice.

- What constitutes an amendment?

  Amendments requiring approval may include, but are not limited to, additions to the research protocol, study population, recruitment of participants, access to personal records, research instruments, or participant information and consent documentation. Amendments must be approved before they are implemented.

NOTES:

- Answers to questions must be entered in the space provided
- An electronic version of the completed form should be submitted to the Research Ethics Officer, at the following email address: aer-ethics@contacts.bham.ac.uk. Please **do not** submit paper copies.
- If, in any section, you find that you have insufficient space, or you wish to supply additional material not specifically requested by the form, please submit it in a separate file, clearly marked and attached to the submission email.
- If you have any queries about the form, please address them to the Research Ethics Team.

UNIVERSITY OF BIRMINGHAM APPLICATION FOR ETHICAL REVIEW - REQUEST FOR AMENDMENTS	*OFFICE USE ONLY:* Application No: Date Received:

1. **TITLE OF PROJECT**

Influences of low back pain on sensory integration and motor control during activities of daily living

2. **APPROVAL DETAILS**

What is the Ethical Review Number (ERN) for the project?

ERN_16-1389

3. **THIS PROJECT IS:**

University of Birmingham Staff Research project ☒
University of Birmingham Postgraduate Research (PGR) student project ☒
Other ☐(Please specify): Please specify):

4. **INVESTIGATORS**

d) PLEASE GIVE DETAILS OF THE PRINCIPAL INVESTIGATORS OR SUPERVISORS (FOR PGR STUDENT PROJECTS)

Name: Title / first name / family name	Professor Deborah Falla
Highest qualification & position	Chair in Rehabilitation Science and
School/Department	School of Sport, Exercise and
Telephone:	[redacted]
Email address:	

Name: Title / first name /	Dr. Alessandro Marco De Nunzio
Highest qualification & position	Research Fellow
School/Department	School of Sport, Exercise and
Telephone:	[redacted]
Email address:	

Name: Title / first name / family name	Dr. Alison Rushton
Highest qualification & position	Senior Lecturer
School/Department	School of Sport, Exercise and
Telephone:	[redacted]
Email address:	

Name: Title / first name / family name	Dr. Nicola Heneghan
Highest qualification & position	Lecturer
School/Department	School of Sport, Exercise and
Telephone:	[redacted]
Email address:	

e) PLEASE GIVE DETAILS OF ANY CO-INVESTIGATORS OR CO-SUPERVISORS (FOR PGR STUDENT PROJECTS)

Name: Title / first name / family name	Nicola Middlebrook
Highest qualification & position	MRes student
School/Department	School of Sport, Exercise and
Telephone:	
Email address:	

Name: Title / first name / family name	Eduardo Martinez Valdes
Highest qualification & position	Research Associate
School/Department	School of Sport, Exercise and
Telephone:	
Email address:	

f) In the case of PGR student projects, please give details of the student

Name of	Andrew	Student	
Course of	PhD	Email	
Principal	Deborah Falla		

Name of	Pauline Kuithan	Student	
Course of	PhD	Email	
Principal	Deborah Falla		

5. **ESTIMATED START OF PROJECT** Date: 01/04/2017

ESTIMATED END OF PROJECT Date: 31/12/2019

6. **ORIGINAL APPLICATION FOR ETHICAL REVIEW AND ANY SUBSEQUENT APPROVED AMENDMENTS:**

Please complete the table below for the original application and any subsequent amendments submitted

Title and reference number of application or amendment	**Key points of application and/or changes made by amendment (include: aims of study, participant details, how participants were recruited and methodology)**	**Ethical considerations arising from these key points (e.g. gaining consent, risks to participants and/or researcher, points raised by Ethical Review Committee during review)**	**How were the ethical considerations addressed?** **(e.g. consent form, participant information, adhering to relevant procedures/clearance required)**
Original application Influences of low back pain on sensory integration and motor control during activities of daily living	**Aims**: To understand how the brain orchestrates sensory-motor integration and motor control to manage pain by studying the association between changes in motor control abilities and different pain domains. **Participants**: Healthy subjects will be recruited via poster advertisement at the: - School of Sport, Exercise and Rehabilitation Sciences, College of Life and Environmental Sciences of the University of Birmingham LBP participants will be recruited, via poster advertisement, from the community and population of staff and students at the University of Birmingham. Control participants will be age and gender matched to the LBP participants. **Methods**: Biomechanics of body segments (kinematic and kinetic evaluation), synergistic motor outcome (via high-density electromyography recordings) (EMG) and cortical activity (via electroencephalography) (EEG) will be studied in people with	**Consent**: Prior to beginning any part of the experiment, it is important that participants will be fully informed of what is expected of them during the experiment. **Risks**: Remote risk of falling; induced anxiety, stress or pain; exacerbation of participant's LBP; risks induced by pressure and thermal pain threshold test	**Consent**: All information regarding the experiment will be provided in the 'Participant Information Leaflet' which will include a description of the study, inclusion and exclusion criteria, risk and benefits. Written informed consent will be obtained after the study has been explained and the volunteers have the opportunity to ask any questions they may have. It will be emphasized that participants are free to withdraw at any stage of the study. **Risks**: *Remote risk of falling*; To assure a completely safe environment, an experimenter will stand close to the participant during the entire duration of the tests. *Induced anxiety, stress or pain*; motor tasks accomplished by the participants will not lead to anxiety or stress higher than that already expected from everyday life. Scheduled resting periods during the testing sessions will avoid prompting pain or muscular fatigue. *Exacerbation of participant's LBP*; motor tasks will replicate those which are usually carried out during a

	LBP and age-and gender matched control participants. Quantitative sensory tests will be performed including pressure pain thresholds and thermal pain thresholds over regions of the lumbar spine and at a remote site. The project is divided into three separate studies which focus on different motor tasks 4. **Postural control in normal and challenged conditions (voluntary holding of a steady inclined position)** 5. **Gait Initiation and Sudden Unplanned Gait Termination** 6. **Walking along curvilinear path and turning strategies**	**Committee Points**: More information required on the methods and equipment used in the quantitative sensory testing. Clarification required for withdrawal deadline, anonymity and exclusion criteria clarified to participants.	normal daily routine. Any exacerbation will lead to a longer rest time and if necessary the participant will be disengaged from the study. *Risks induced by pressure and thermal pain threshold test;* The process of evaluating pressure or thermal pain threshold is completely safe, and these tests are commonly applied on people with LBP. The device used features safety standards which prevent from any damage to the skin **Committee Points**: All committee points were addressed in the final draft of the approved study, as shown above. In addition, a withdrawal deadline of one month following the experiment was clarified and a new system to obtain anonymity was created.

7. DETAILS OF PROPOSED NEW AMENDMENT

Provide details of the proposed new amendment, and clearly and explicitly state how the proposed new amendment will differ from the details of the study as already approved (see Q6 above).

We are requesting two new amendments:
1. Adding a fourth evaluation which investigates a different motor task, and expands on the quantitative sensory testing aspect
2. Amending study recruitment to a] include using social medial as a means of recruitment for this study and b] adjusting recruitment information to accurately reflect the Quantitative sensory tests detailed in the previously approved study.

Amendment 1

SUMMARY OF STUDY 4

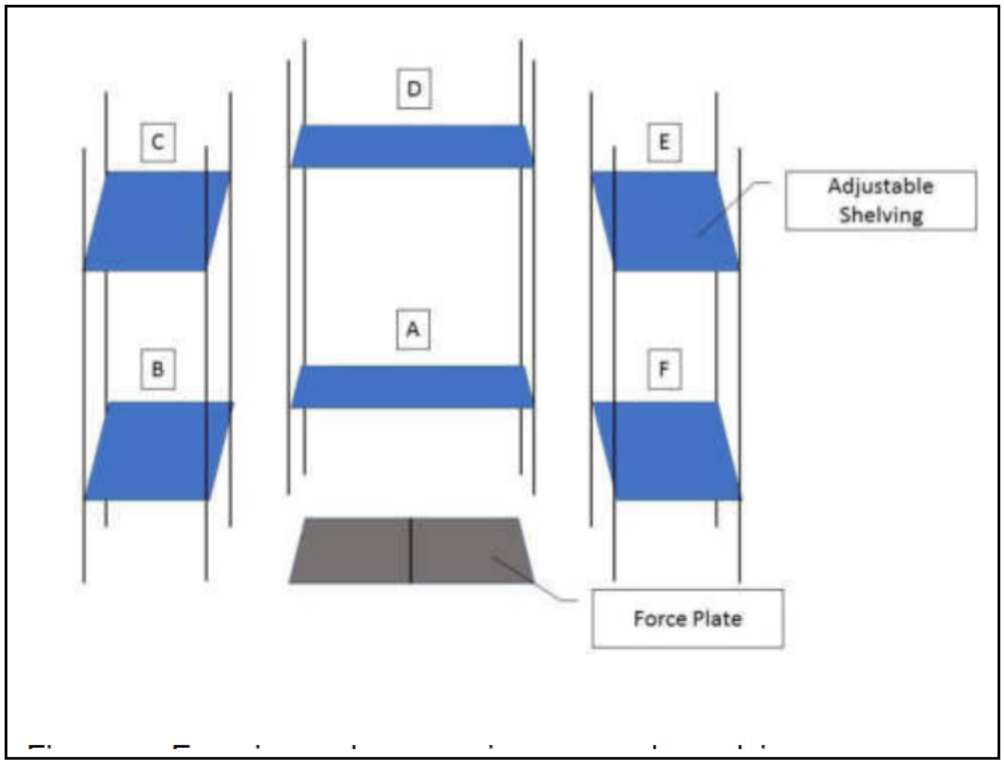
4. Muscle behaviour during a dynamic lifting and rotation task and the effect on pain perception and sensitivity

Working Hypotheses

1. It is hypothesised that the pattern of muscle behaviour will be less varied in individuals with low back pain (LBP) than in control participants.
2. It is hypothesised that individuals with LBP will have less range of motion during the repetitive task than those with no pain.
3. It is hypothesised that individuals with LBP will demonstrate altered pain perception and sensitivity to quantitative sensory testing both before and after the repeated lifting task.

Methods

Subjects will be required to stand on a force plate while lifting a weighted box with handles (the weight of the box will be standardised to 5kg to represent a task of daily life) between different levels of shelving in both the sagittal and horizontal plane. Adjustable shelving will be situated around the participant and with the lower shelf at the participant's knee height, level with the lateral epicondyle of the femur, and the higher shelf at shoulder height while



standing, level with the acromion. One set of shelving will be anterior to the participant, with further sets lateral to the participant on each side centred on the force plate (**Figure 1**).

For the duration of the experimental session, subjects will be instructed to stand barefoot on embedded floor level force plates (BTS Bioengineering, Italy). Participants will be asked to stand with one foot on each force plate with their heels separated by 17cm and at a 14º angle to each other (McIlroy and Maki, 1997). Participants will be asked initially to adopt a 'resting stance' with arms lowered whilst looking at a target placed 40 cm anteriorly.

In line with existing research we will use the following procedure which is adapted slightly from Falla et al. (2014). At the beginning of the task, the weighted box will be placed on shelf 'A', participants will be instructed to lift the box and move it from A to B, rest for 2 seconds and then return the box to A. This movement task will be repeated for A-C, A-D, A-E and A-F. At this point participants have completed a full cycle of the task and will continue by again moving the box from A-B. In order to allow inter- and intra-participant

comparisons, the movements will be timed with an audible metronome as a reference (Falla et al., 2014). Participants will be instructed to complete each movement within two seconds and then will be allowed to rest for two seconds prior to completing the next movement. On this basis, with the maximum of 15 repetitions the entire task will take approximately 10 minutes. Patients will be advised that if the task provokes more discomfort than they would normally experience during activities of daily living, they can stop the task any time, either to rest or stop the task completely. However, a previous comparable study demonstrated no lasting effects beyond some temporary discomfort for some participants (Falla et al., 2014). In addition to this, pilot studies will be used to determine the optimal timing for movements and repetitions to allow for successful completion of the task.

EMG
EMG acquisition and processing will be the same as previously described in the methodology presented for the approved study. The key differences are as follows:

- Arrays of surface electrodes will be used to record EMG from the erector spinae instead of the bipolar EMG previously described
- Bipolar EMG surface electrodes will be used to record EMG signals from additional trunk musculature bilaterally, including the External Oblique (EO) and the Rectus Abdominis (RA)

Kinematics
Movement analysis and processing will be the same as previously described in the methodology presented for studies 2 and 3. The key differences will be as follows:

- The focus of this study is in the movement of the trunk; therefore, the analysed kinematic index will reflect this. The spine will be divided into three triangular segments for analysis of rotation and range of motion (Muller et al., 2016).Thus additional markers will be placed over the spinous processes of S1, T12, T6 and C7 and 10 cm lateral to the spinous processes of T12, T6 and C7.

Data will be acquired in a single session for all participants lasting approximately 2 hours per participant.

Quantitative sensory testing
Pain pressure threshold with an Algometer, thermal pain threshold testing with a thermal stimulator and detection of vibration using a vibrameter over multiple sites of the lower back, within lumbar dermatomes and over a remote side (hand) will be tested before the task referring to standardised protocols (Falla et al., 2014; O' Conaire et al., 2011; Rolke et al., 2006b). Pain threshold measurements and detection of vibration will be repeated immediately following the lifting task.

Amendment 2

Amending study recruitment to a] include using social medial as a means of recruitment for this study and b] adjusting recruitment information to accurately reflect the Quantitative sensory tests detailed in the previously approved study.

a] Recruitment will be conducted, as previously stated in the approved study, through poster recruitment at the University of Birmingham.
This will now include posters being displayed both in the physical space within the University

of Birmingham and through associated accounts on social media websites. This recruitment information will be posted passively (not as paid-for adverts) on social media websites including Facebook and Twitter. These posts will be visible to anybody who views or subscribes to the accounts but will not be posted excessively or onto a page or group where it is not appropriate.
b] These posters have also been amended slightly to include information relating to the quantitative sensory testing.

7. JUSTIFICATION FOR PROPOSED NEW AMENDMENT

Amendment 1

This new amendment will allow the addition a new investigation to the experimental procedure which represents a lifting task which broadly reflects a functional activity of daily living.

Muscle behaviour is known to be altered with fatigue and pain (Hodson-Tole and Wakeling, 2009; Tucker et al., 2009). Recent advances in high density electromyography (HDEMG), has allowed researches to investigate muscle behaviour in a more comprehensive manner (Falla et al., 2014; Martinez-Valdes et al., 2016). Using this technique, it has also been shown that there are significant differences in the activation of the lumbar erector spinae in participants with LBP during a repeated dynamic movement when compared to pain free participants (Falla et al., 2014). In this previous experiment it was shown that the activation of this muscle in individuals with LBP remained stationary during movement, while in pain free participants the distribution of activity changed and this difference in muscle behaviour was also associated with greater muscle fatigue for the patient group. However, this study only assessed the lumbar erector spinae unilaterally during a task which included only sagittal movement (Falla et al., 2014).

Previous studies have shown that there is also a link between the rotation of the trunk and LBP. This link includes a decreased range of motion during rotation in the both pelvic and lumbar region in patients with LBP (Shojaei et al., 2017a; Shojaei et al., 2017b; Sung, 2014). Furthermore it was also found that manual labourers who lift loads whilst undergoing trunk rotation were more likely to develop LBP (Hoogendoorn et al., 2000). Yet currently no studies have evaluated the distribution of erector spinae muscle activity during repeated rotational movements in people with LBP. Such knowledge will allow for a deeper understanding of how a dynamic movement is completed in individuals with and without LBP and inform future research.

To investigate the second working hypothesis, it is necessary to complete a kinematic analysis of the movement required to investigate the first working hypothesis. This kinematic analysis is important because the participants will not be forced to conform in their movement strategy; instead a suggested movement will be demonstrated prior to commencement of the experiment. It is expected that while most participants will copy the demonstrated strategy

initially; individuals who have LBP may utilise adaptive movement strategies as has been demonstrated in previous studies (Basques et al., 2016; Falla et al., 2014; Koes et al., 2006; van Tulder and Koes, 2006).

Regarding the third hypothesis, research provided evidence that at least some patients with low back pain present altered pain thresholds, decreased endogenous pain inhibition as well as facilitated temporal summation (Falla et al., 2014; Nijs et al., 2015; Rabey et al., 2015; Roussel et al., 2013; Vaegter and Graven-Nielsen, 2016). However, the changes in pain thresholds and mechanical detection after repeated movements has not been well investigated in LBP. Such knowledge could inform the establishment of subgroups for pain-mechanism based treatment approaches.

Amendment 2

This new means of disseminating the recruitment material is intended to better reflect the daily habits of potential participants. It has previously been shown that recruitment though social media is an effective means of reaching and recruiting more participants over a short period of time (Khatri et al., 2015). This means of advertising will also allow for the recruitment of a sample which is more representative of the population, as it is not limited to individuals who visit the University of Birmingham campus. The recruitment information which will be displayed through social media will not differ from that displayed on the physical campus.
The slight amendments to the content of the recruitment posters has enabled accurate presentation of the study.

8. **ETHICAL CONSIDERATIONS**

What ethical considerations, if any, are raised by the proposed new amendment?

The task may contribute to a temporary exacerbation of a participant's LBP consistent with how their pain may be exacerbated through normal physical activity.

The trunk rotation and lifting task presented has been designed to reflect normal function and is not expected to cause symptoms beyond those that participants may experience during routine activities of daily living or physical exercise. Participants will however be advised to immediately stop the task and rest until they feel able to continue and they will also have the option to stop and withdraw from the study at any time. Participants will be monitored carefully for symptom reproduction by the research team which includes experienced clinicians and researchers.

9. **DECLARATION BY APPLICANTS**

I make this application on the basis that the information it contains is confidential and will be used by the

University of Birmingham for the purposes of ethical review and monitoring of the research project described

herein, and to satisfy reporting requirements to regulatory bodies. The information will not be used for any

other purpose without my prior consent.

I declare that:

- The information in this form together with any accompanying information is complete and correct to the best of my knowledge and belief and I take full responsibility for it.
- I undertake to abide by University Code of Conduct for Research (http://www.birmingham.ac.uk/Documents/university/legal/research.pdf) alongside any other relevant professional bodies' codes of conduct and/or ethical guidelines.
- I will report any changes affecting the ethical aspects of the project to the University of Birmingham Research Ethics Officer.
- I will report any adverse or unforeseen events which occur to the relevant Ethics Committee project to the University of Birmingham Research Ethics Officer.

Signature of Principal investigator/project supervisor:	
Date:	12/04/17

REFERENCES

BASQUES, B. A., ESPINOZA ORIAS, A. A., SHIFFLETT, G. D., FICE, M. P., ANDERSSON, G. B., AN, H. S. & INOUE, N. 2016. The Kinematics and Spondylosis of the Lumbar Spine Vary Depending on the Levels of Motion Segments in Individuals with Low Back Pain. *Spine (Phila Pa 1976).*

FALLA, D., GIZZI, L., TSCHAPEK, M., ERLENWEIN, J. & PETZKE, F. 2014. Reduced task-induced variations in the distribution of activity across back muscle regions in individuals with low back pain. *Pain,* 155**,** 944-53.

HODSON-TOLE, E. F. & WAKELING, J. M. 2009. Motor unit recruitment for dynamic tasks: current understanding and future directions. *J Comp Physiol B,* 179**,** 57-66.

HOOGENDOORN, W. E., BONGERS, P. M., DE VET, H. C., DOUWES, M., KOES, B. W., MIEDEMA, M. C., ARIENS, G. A. & BOUTER, L. M. 2000. Flexion and rotation of the trunk and lifting at work are risk factors for low back pain: results of a prospective cohort study. *Spine (Phila Pa 1976),* 25**,** 3087-92.

KHATRI, C., CHAPMAN, S. J., GLASBEY, J., KELLY, M., NEPOGODIEV, D., BHANGU, A., FITZGERALD, J. E. & ON BEHALF OF THE, S. C. 2015. Social Media and Internet Driven Study Recruitment: Evaluating a New Model for Promoting Collaborator Engagement and Participation. *PLOS ONE,* 10**,** e0118899.
KOES, B. W., VAN TULDER, M. W. & THOMAS, S. 2006. Diagnosis and treatment of low back pain. *BMJ,* 332**,** 1430-4.
MARTINEZ-VALDES, E., LAINE, C. M., FALLA, D., MAYER, F. & FARINA, D. 2016. High-density surface electromyography provides reliable estimates of motor unit behavior. *Clin Neurophysiol,* 127**,** 2534-41.
MCILROY, W. E. & MAKI, B. E. 1997. Preferred placement of the feet during quiet stance: development of a standardized foot placement for balance testing. *Clin Biomech (Bristol, Avon),* 12**,** 66-70.
MULLER, J., MULLER, S., ENGEL, T., RESCHKE, A., BAUR, H. & MAYER, F. 2016. Stumbling reactions during perturbed walking: Neuromuscular reflex activity and 3-D kinematics of the trunk - A pilot study. *J Biomech,* 49**,** 933-8.
NIJS, J., APELDOORN, A., HALLEGRAEFF, H., CLARK, J., SMEETS, R., MALFLIET, A., GIRBES, E. L., DE KOONING, M. & ICKMANS, K. 2015. Low back pain: guidelines for the clinical classification of predominant neuropathic, nociceptive, or central sensitization pain. *Pain Physician,* 18**,** E333-46.
O' CONAIRE, E., RUSHTON, A. & WRIGHT, C. 2011. The assessment of vibration sense in the musculoskeletal examination: Moving towards a valid and reliable quantitative approach to vibration testing in clinical practice. *Man Ther,* 16**,** 296-300.
RABEY, M., SLATER, H., O'SULLIVAN, P., BEALES, D. & SMITH, A. 2015. Somatosensory nociceptive characteristics differentiate subgroups in people with chronic low back pain: a cluster analysis. *Pain,* 156**,** 1874-84.
ROLKE, R., MAGERL, W., CAMPBELL, K. A., SCHALBER, C., CASPARI, S., BIRKLEIN, F. & TREEDE, R. D. 2006. Quantitative sensory testing: a comprehensive protocol for clinical trials. *Eur J Pain,* 10**,** 77-88.
ROUSSEL, N. A., NIJS, J., MEEUS, M., MYLIUS, V., FAYT, C. & OOSTENDORP, R. 2013. Central sensitization and altered central pain processing in chronic low back pain: fact or myth? *Clin J Pain,* 29**,** 625-38.
SHOJAEI, I., SALT, E. G., HOOKER, Q., VAN DILLEN, L. R. & BAZRGARI, B. 2017a. Comparison of lumbo-pelvic kinematics during trunk forward bending and backward return between patients with acute low back pain and asymptomatic controls. *Clin Biomech (Bristol, Avon),* 41**,** 66-71.
SHOJAEI, I., VAZIRIAN, M., SALT, E. G., VAN DILLEN, L. R. & BAZRGARI, B. 2017b. Timing and magnitude of lumbar spine contribution to trunk forward bending and backward return in patients with acute low back pain. *J Biomech,* 53**,** 71-77.
SUNG, P. S. 2014. A kinematic analysis for shoulder and pelvis coordination during axial trunk rotation in subjects with and without recurrent low back pain. *Gait Posture,* 40**,** 493-8.
TUCKER, K., BUTLER, J., GRAVEN-NIELSEN, T., RIEK, S. & HODGES, P. 2009. Motor unit recruitment strategies are altered during deep-tissue pain. *J Neurosci,* 29**,** 10820-6.
VAEGTER, H. B. & GRAVEN-NIELSEN, T. 2016. Pain modulatory phenotypes differentiate subgroups with different clinical and experimental pain sensitivity. *Pain,* 157**,** 1480-8.
VAN TULDER, M. & KOES, B. 2006. Chronic low back pain. *Am Fam Physician,* 74**,** 1577-9.

From: [redacted]
Sent: 28 April 2017 09:29
To: Deborah Falla
Cc: Alessandro De Nunzio; Alison Rushton; Nicola Heneghan
Subject: Application for amendment ERN_16-1389A

Dear Professor Falla

Re: "Influences of low back pain on sensory integration and motor control during activities of daily living"
Application for amendment ERN_16-1389A

Thank you for the above application for amendment, which was reviewed by the Science, Technology, Engineering and Mathematics Ethical Review Committee.

On behalf of the Committee, I can confirm that this amendment now has full ethical approval.

I would like to remind you that any substantive changes to the nature of the study as now amended, and/or any adverse events occurring during the study should be promptly bought to the Committee's attention by the Principal Investigator and may necessitate further ethical review. A revised amendment application form is now available at https://intranet.birmingham.ac.uk/finance/accounting/Research-Support-Group/Research-Ethics/Ethical-Review-Forms.aspx . Please ensure this form is submitted for any further amendments.

Please also ensure that the relevant requirements within the University's Code of Practice for Research and the information and guidance provided on the University's ethics webpages (available at https://intranet.birmingham.ac.uk/finance/accounting/Research-Support-Group/Research-Ethics/Links-and-Resources.aspx) are adhered to and referred to in any future applications for ethical review. It is now a requirement on the revised application form (https://intranet.birmingham.ac.uk/finance/accounting/Research-Support-Group/Research-Ethics/Ethical-Review-Forms.aspx) to confirm that this guidance has been consulted and is understood, and that it has been taken into account when completing your application for ethical review.

Please be aware that whilst Health and Safety (H&S) issues may be considered during the ethical review process, you are still required to follow the University's guidance on H&S and to ensure that H&S risk assessments have been carried out as appropriate. For further information about this, please contact your School H&S representative or the University's H&S Unit at healthandsafety@contacts.bham.ac.uk.

If you require a hard copy of this correspondence, please let me know.

Kind regards,

[redacted]
Deputy Research Ethics Officer
Research Support Group
C Block Dome (room 132)
Aston Webb Building

Application for amendment ERN_16-1389B

[redacted]

To: Deborah Falla; Nicola Heneghan; Alessandro De Nunzio; Alison Rushton

Cc: Pauline Kuithan

Reply | Reply All | Forward | ...

Tue 15/08/2017 08:39

Follow up. Completed on 16 August 2017.
You forwarded this message on 17/08/2017 12:14.

Dear Professor Deborah Falla, Dr. Alessandro Marco De Nunzio, Dr. Alison Rushton& Dr. Nicola Heneghan

Re: "Influences of low back pain on sensory integration and motor control during activities of daily living"
Application for amendment ERN_16-1389B

Thank you for the above application for amendment, which was reviewed by the Science, Technology, Engineering and Mathematics Ethical Review Committee.

On behalf of the Committee, I can confirm that this amendment now has full ethical approval.

I would like to remind you that any substantive changes to the nature of the study as now amended, and/or any adverse events occurring during the study should be promptly bought to the Committee's attention by the Principal Investigator and may necesstate further ethical review. A revised amendment application form is now available at https://intranet.birmingham.ac.uk/finance/accounting/Research-Support-Group/Research-Ethics/Ethical-Review-Forms.aspx . Please ensure this form is submitted for any further amendments.

Please also ensure that the relevant requirements within the University's Code of Practice for Research and the information and guidance provided on the University's ethics webpages (available at https://intranet.birmingham.ac.uk/finance/accounting/Research-Support-Group/Research-Ethics/Links-and-Resources.aspx) are adhered to and referred to in any future applications for ethical review. It is now a requirement on the revised application form (https://intranet.birmingham.ac.uk/finance/accounting/Research-Support-Group/Research-Ethics/Ethical-Review-Forms.aspx) to confirm that this guidance has been consulted and is understood, and that it has been taken into account when completing your application for ethical review.

Please be aware that whilst Health and Safety (H&S) issues may be considered during the ethical review process, you are still required to follow the University's guidance on H&S and to ensure that H&S risk assessments have been carried out as appropriate. For further information about this, please contact your School H&S representative or the University's H&S Unit at healthandsafety@contacts.bham.ac.uk.

If you require a hard copy of this correspondence, please let me know.

Kind regards,

[redacted]
Aston Webb Building
University of Birmingham
Edgbaston B15 2TT
[redacted]
Web: https://intranet.birmingham.ac.uk/finance/accounting/research-support-group/Research-Ethics

Consent Form

Study ID:

Influences of Low Back Pain on Sensory Integration and Motor Control during activities of daily living

This information is being collected as part of a research project concerned with the investigation of sensory-motor integration processes and its changes to manage chronic LBP during the execution of activities of daily living (ADL) tasks, by the School of Sport, Exercise and Rehabilitation Sciences at the University of Birmingham. The information which you supply and that which may be collected as part of the research project will be entered into a filing system or database and will only be accessed by authorised personnel involved in the project. The information will be retained by the University of Birmingham and will only be used for the purpose of research and statistical and audit purposes. By supplying this information you are consenting to the University storing your information for the purposes stated above. The information will be processed by the University of Birmingham in accordance with the provisions of the Data Protection Act 1998. No identifiable personal data will be published.

- I confirm that I have read and understand the participant information leaflet for this study. I have had the opportunity to ask questions if necessary and have had these answered satisfactorily.
- I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason as I will have the right to withdraw my data from the study up to 1 month following data collection. If I withdraw my data will be removed from the study and will be destroyed. Participants will be free to withdraw at any time during the experimental session and.
- I understand that my personal data will be processed for the purposes detailed above, in accordance with the Data Protection Act 1998.
- Based upon the above, I agree to take part in this study.

Name of participant……	Date……	Signature……..
Name of researcher/ individual obtaining consent……	Date……	Signature……..

Contact details of participant

Contact number:

Email address:

UNIVERSITY OF BIRMINGHAM | CENTRE OF PRECISION REHABILITATION FOR SPINAL PAIN

Participants wanted

Healthy and physically active people without low back pain (aged 18 - 65)

Purpose: Investigating how Low Back Pain influences sensation and movement during day to day activities.

Testing will take place in one session lasting 2-3 hours

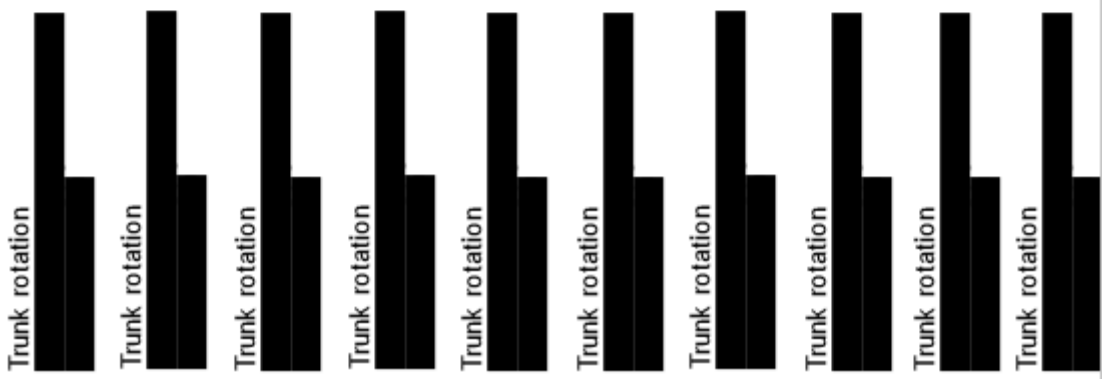
What do I have to do?

You will be asked to perform some tasks e.g. standing, walking, lifting and rotating. The experiment will also test your sensory system, for example your pressure thresholds.

Participants will be compensated £15 for their time.

Contact details
Andy Sanderson and Pauline Kuithan,
PhD students supervised by Professor Deborah Falla.

Interested? Please contact [redacted] or [redacted]



UNIVERSITY OF BIRMINGHAM | CENTRE OF PRECISION REHABILITATION FOR SPINAL PAIN

The University of Birmingham

School of Sport, Exercise and Rehabilitation Sciences

Participant Information Leaflet

Study title

Influences of Low Back Pain on Sensory Integration and Motor Control during activities of daily living

1. Invitation

You are being invited to take part in a research study. Before you decide to participate it is important you understand why the research is being done and what it will involve. Please take time to read the following information sheet carefully and discuss it with the researcher or others if you wish.

2. What is the purpose of the study?

Low back pain (LBP) is a major clinical problem with substantial socio-economic impact. Current diagnosis and therapy are insufficient, and knowledge concerning the interaction between musculoskeletal pain and motor performance is incomplete. Therefore, the aim of this study is to investigate how sensory information is used by the brain to manage and control the execution of activities of daily living in presence of LBP.

3. Why have I been chosen?

You have been chosen because we understand that you, as healthy and physically active subject could represent a control in this study.

Inclusion criteria include:

- Aged between 18 and 65 years

While exclusion criteria include:

- Current or previous history of back or lower limb pain
- Neuromuscular disorders
- Musculoskeletal impairment.

4. Do I have to take part?

You are free to decide whether you participate or not. If you agree to take part you are free to withdraw at any time during the experimental session and you can withdraw your data for up to 1 month following data collection without giving a reason. Any decision to

withdraw will not in any way affect any future care with the health service. If you withdraw from the study all the data acquired will be destroyed immediately.

5. What do I have to do?

You will be asked to visit the Human Movement Laboratory in the School of Sport, Exercise and Rehabilitation Sciences for approximately 120 minutes. During this time you will be asked to do the following

- Complete a brief questionnaire where eligibility will be confirmed.
- Complete some clinical measures to rate your skin sensitivity. Among these clinical measures, a pressure pain threshold,a thermal pain threshold test, and a test for the sense of vibration are included. The pressure pain threshold test is executed using a hand-held probe pushed on the skin at a constant pressure (CE marked device). You have to indicate when pain is perceived for the first time. The thermal threshold test is executed using a heating probe placed on the skin (CE marked device) on the same spot previously used for the pressure threshold test. You have to indicate when pain is perceived for the first time during the thermal stimulation. In addition to it, we use thermal stimuli to provoke a serious of minor painful stimuli to investigate the change of pain levels you perceive. You can stop the test at any time.

- Perform a range of simple tasks to measure your movement control e.g. lifting a small weight between shelves in a cyclical pattern, and walking in a circular motion.

6. Will my taking part in this study be kept confidential?

All information collected on you will be kept strictly confidential. Personal information will be retained, but only available to the researchers using password protected files. All data for presentation will be anonymised and aggregated, so your identity will not be revealed in any way.

7. What will happen to the results of the research study?

The findings from this study will be presented, or shared with other researchers in the form of presentations and scientific papers as appropriate. These will be used to help inform about new possible findings regarding LBP, its evolution and effect on motor control during ADL.

8. Does the study follow Ethics prescriptions?

This study, as all the research involving human subjects, underwent the ethical review processes of the University of Birmingham and received official approval from the University Ethics Committee

9. Who is organising and funding the research?

The study has been designed and organised by Prof. Deborah Falla, Dr. Alessandro De Nunzio, Dr. Nicola Heneghan and Dr. Alison Rushton and supported by PhD students from the School of Sport, Exercise and Rehabilitation Sciences.

As a participant, you will receive a reimbursement of £15. In case of withdraw you will be offered compensation based on the time completed (fraction of the total amount based on the time spent at the laboratory).

Contact details for further information, please contact Andy Sanderson

Project Supervisor Prof. Deborah Falla Chair in Rehabilitation Science and Physiotherapy School of Sport, Exercise and Rehabilitation Sciences University of Birmingham	
Project co-investigator Dr. Alessandro M. De Nunzio Senior Research Fellow School of Sport, Exercise and Rehabilitation Sciences University of Birmingham	
Project co-investigator Dr. Alison Rushton Senior Lecturer School of Sport, Exercise and Rehabilitation Sciences University of Birmingham	
Project co-investigator Dr. Nicola Heneghan Lecturer School of Sport, Exercise and Rehabilitation Sciences University of Birmingham	
PhD Student **Andy Sanderson** **School of Sport, Exercise and Rehabilitation Sciences** **University of Birmingham**	**T:** **E:**
PhD Student Pauline Kuithan School of Sport, Exercise and Rehabilitation Sciences University of Birmingham	E:

Thank you for taking time to read this and considering taking part in the study.

UNIVERSITY OF BIRMINGHAM | CENTRE OF PRECISION REHABILITATION FOR SPINAL PAIN

Are you suffering from Low Back Pain?

Purpose: Investigating how Low Back Pain influences sensation and movement during day to day activities.

We are looking for

- People aged 18 – 65
- Low back pain for more than 3 of the past 6 months
- Not currently seeking treatment
- No radicular low back pain or pain related to trauma, fractures or spinal stenosis

Testing will take place in one session lasting 2-3 hours.

What do I have to do?

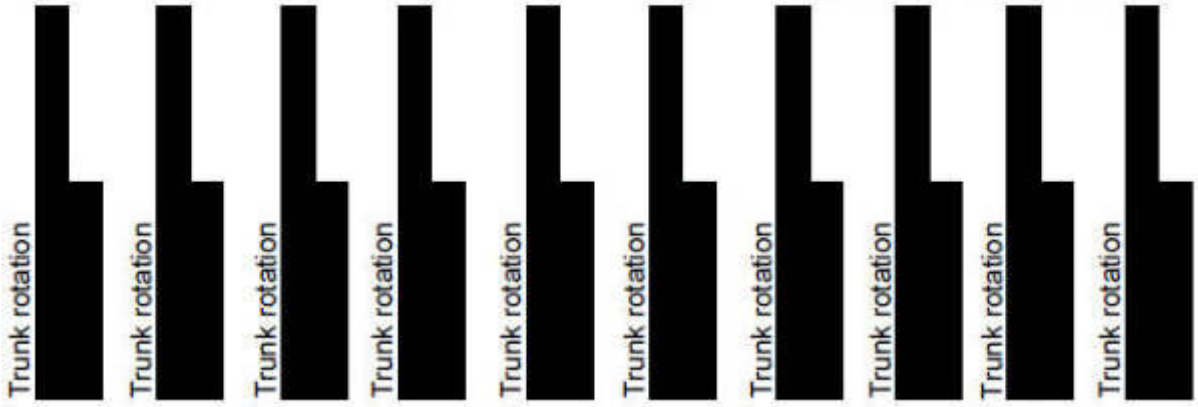
You will be asked to perform some tasks e.g. standing, walking, lifting and rotating. The experiment will also test your sensory system, for example your pressure thresholds.

Participants will be compensated £15 for their time.

Contact details
Andy Sanderson and Pauline Kuithan,
PhD students supervised by Professor Deborah Falla.

Interested? Please contact Andy

[redacted]



UNIVERSITY OF BIRMINGHAM | CENTRE OF PRECISION REHABILITATION FOR SPINAL PAIN

The University of Birmingham

School of Sport, Exercise and Rehabilitation Sciences

Participant Information Leaflet

Study title

Influences of Low Back Pain on Sensory Integration and Motor Control during activities of daily living

1. Invitation

You are being invited to take part in a research study. Before you decide to participate it is important you understand why the research is being done and what it will involve. Please take time to read the following information sheet carefully and discuss it with the researcher or others if you wish.

2. What is the purpose of the study?

Low back pain (LBP) is a major clinical problem with substantial socio-economic impact. Current diagnosis and therapy are insufficient, and knowledge concerning the interaction between musculoskeletal pain and movement is incomplete. Therefore, the aim of this study is to investigate how sensations, e.g. vision, touch, are used by the brain to manage and control the execution of activities of daily living in presence of LBP.

3. Why have I been chosen?

You have been chosen because we understand you have previously experienced a back pain problem that has the following characteristics:

- It has lasted more than 3 months,
- You have experienced pain on more than 90 days out of the past 6 months

Other inclusion criteria include:

- Aged between 18 and 65 years

While exclusion criteria include:

- Concurrent systemic, rheumatic or neuro-musculoskeletal disorders which may confound testing or if you are currently pregnant.
- Radiating leg pain, or low back pain related to trauma, fractures, spinal stenosis.
- Higher doses of pain killers (> 30 mg of morphine equivalent dose)
- Being under active management of LBP through specific medications prescribed by a GP or receiving therapies e.g. physiotherapy.

4. Do I have to take part?

You are free to decide whether you participate or not. If you agree to take part you are free to withdraw at any time during the experimental session and you can withdraw your data up to 1 month following data collection without giving a reason. Any decision to withdraw will not in any way affect any future care with the health service. If you withdraw from the study all the data acquired will be destroyed immediately.

5. What do I have to do?

You will be asked to visit the Human Movement Laboratory in the School of Sport, Exercise and Rehabilitation Sciences for approximately 2-3 hours. During this time you will be asked to do the following

- Complete a brief questionnaire where eligibility will be confirmed.
- Complete some clinical measures to rate and evaluate your LBP condition. Among these clinical measures, a pressure pain threshold, a thermal pain threshold test, and a test for the sense of vibration are included. The pressure pain threshold test is executed using a hand-held probe pushed on the skin at a constant pressure (CE marked device). You have to indicate when pain is perceived for the first time. The thermal threshold test is executed using a heating probe placed on the skin (CE marked device) on the same spot previously used for the pressure threshold test. You have to indicate when pain is perceived for the first time during the thermal stimulation. In addition to it, we use thermal stimuli to provoke a serious of minor painful stimuli to investigate the change of pain levels you perceive. You can stop the test at any time.
- Perform a range of simple tasks to measure your movement control e.g. lifting a small weight between shelves in a cyclical pattern, and walking in a circular motion.

6. Will my taking part in this study be kept confidential?

All information collected on you will be kept strictly confidential. Personal information will be retained, but only available to the researchers using password protected files. All data for presentation will be anonymised, so your identity will not be revealed in any way.

7. What will happen to the results of the research study?

The findings from this study will be presented, or shared with other researchers in the form of presentations and scientific papers as appropriate. These will be used to help inform about new possible findings regarding LBP, its evolution and effect on movement control during daily activities.

8. Does the study follow Ethics prescriptions?

This study, as all the research involving human subjects, underwent the ethical review processes of the University of Birmingham and received official approval from the University Ethics Committee.

9. Who is organising and funding the research?

The study has been designed and organised by Prof. Deborah Falla, Dr. Alessandro De Nunzio, Dr. Nicola Heneghan and Dr. Alison Rushton and supported by PhD students from the School of Sport, Exercise and Rehabilitation Sciences.

As a participant, you will receive a reimbursement of £15. In case of early withdrawal you will be offered compensation based on the time completed (fraction of the total amount based on the time spent at the laboratory).

Contact details for further information, please contact Andy Sanderson

Project Supervisor Prof. Deborah Falla Chair in Rehabilitation Science and Physiotherapy School of Sport, Exercise and Rehabilitation Sciences University of Birmingham	[redacted]
Project co-investigator Dr. Alessandro M. De Nunzio Senior Research Fellow School of Sport, Exercise and Rehabilitation Sciences University of Birmingham	[redacted]
Project co-investigator Dr. Alison Rushton Senior Lecturer School of Sport, Exercise and Rehabilitation Sciences University of Birmingham	[redacted]
Project co-investigator Dr. Nicola Heneghan Lecturer School of Sport, Exercise and Rehabilitation Sciences University of Birmingham	[redacted]
PhD Student **Andy Sanderson** **School of Sport, Exercise and Rehabilitation Sciences** **University of Birmingham**	**T:** [redacted] **E:** [redacted]
PhD Student Pauline Kuithan School of Sport, Exercise and Rehabilitation Sciences University of Birmingham	E: [redacted]

Thank you for taking time to read this and considering taking part in the study.

Appendix 4 Questionnaire Chapter two

Study ID:

Profession: _____ employed □ unemployed □ student □

Highest level of education attained: _____ Ethnicity: _____

Date of Birth: Gender: m □ f□ currently pregnant □

Height: Weight: BMI: (Calculated by us)

Sternum Height: Knee Height: Distance between elbows:

Arm length:

Have you ever experienced low back pain in your life? **Yes □ No □**

1. Within the **last three years** have you had **low back pain** or **lower limb pain or injury** that has limited function and/or **required treatment** from a health profession?
   No □ Yes □ _____
2. Have you been diagnosed with
   - radicular low back pain **Yes □ No □**
   - pain related to trauma, fractures or spinal stenosis **Yes □ No □**
   - concurrent systemic, rheumatic or neuro-musculoskeletal disorders **Yes □ No □**
3. Have you taken specific medications prescribed by a GP, consultant or therapists or higher doses of opioids (> 30 mg of morphine equivalent dose) within the last three months? **Yes □ No □**
4. Are you currently seeking treatment/ under active management? **Yes □ No □**

Back pain

5. Has your pain persisted at least 3 months and resulted in pain on at least half the days in the past 6 months? (if no skip the following questions) **Yes □ No □**
6. When was your first episode of back pain? What caused it?
   Year: cause: _____
7. How often do you get episodes of low back pain?
   Constant pain □ almost constant pain □ _____ year _____months
8. How long does your back pain usually last for if not constant?
   _____ years _____ months_____ weeks _____ days
9. Have you ever experienced any of those features with your back pain?
   numbness □ weakness □ pins and needles □ burning □ leg pain □

Most recent episode

10. When did this episode start?
    ____ years ____ months ____ weeks ____ days
11. How would you rate the average intensity of your most recent episode of back pain?
    Please rate your pain levels from 0 'no pain' and 10 'pain as bad as it could be'

0 1 2 3 4 5 6 7 8 9 10

Back pain questionnaire – University of Birmingham

Current back pain

12. What best describes your current low back pain state within the last 4 weeks?
    stable □ getting better □ getting worse □
    fluctuant with pain free episodes □ fluctuant without pain free episodes □
13. How would you describe your pain (most painful area)?
    _____
14. Which activities provoke your pain?
    _____
15. If an activity provokes your pain, how long does it last for?
    ____ days ____ hours ____ minutes ____ seconds
16. If you think of the following activities, do you think they could increase your back pain?
    Bending □ Trunk Rotation □ Sitting □ Standing □ Standing Up □ Lifting □
    Sitting Down □ Carrying □ Picking Something Up □ Overhead Activity □
17. Which activities or techniques do you use to alleviate your pain?
    _____
18. Have you taken any pain medication within the last 24 hours? Please specify if so.
    No □ **Yes** □ _____

Please rate your pain levels from 0 'no pain' and 10 'pain as bad as it could be'

19. How would you rate your back pain right now?

0 1 2 3 4 5 6 7 8 9 10

20. How would you rate the average intensity of your back pain during the last 24 hours?

0 1 2 3 4 5 6 7 8 9 10

21. In the previous four weeks, how intense was your worst pain?

0 1 2 3 4 5 6 7 8 9 10

Treatment history

In the past, did you ever receive any of the following treatments and if so, did they contribute to your health?

	no	Yes, with success	Yes, with temporary success	Yes, but no improvement
Pain medication				
Physiotherapy				
Advice on bending				
Advice on lifting				

Thank you very much!

Appendix 5 STROBE Guidelines Chapter two

Checklist of items that should be included in reports of **cross-sectional studies**

Retrieved from https://www.strobe-statement.org/download/strobe-checklist-cross-sectional-studies-doc

	Item No	Recommendation	Section
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2.1 abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2.1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2.2
Objectives	3	State specific objectives, including any prespecified hypotheses	2.2.1
Methods			
Study design	4	Present key elements of study design early in the paper	2.3.1
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	2.3.1
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	2.3.2
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	2.3.3; 2.3.4; 2.3.5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	2.3.3; 2.3.4; 2.3.5
Bias	9	Describe any efforts to address potential sources of bias	Chapter three includes RoB
Study size	10	Explain how the study size was arrived at	2.5.1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	2.3.6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	2.3.6
		(*b*) Describe any methods used to examine subgroups and interactions	2.3.6
		(*c*) Explain how missing data were addressed	2.3.6
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	2.3.6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	2.4.1
		(b) Give reasons for non-participation at each stage	2.4.1

		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	2.4.1; 2.4.2
		(b) Indicate number of participants with missing data for each variable of interest	2.4
Outcome data	15*	Report numbers of outcome events or summary measures	2.4.3; 2.4.4.; 2.4.5
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	2.4.3; 2.4.4.; 2.4.5
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	2.4.3
Discussion			
Key results	18	Summarise key results with reference to study objectives	2.5
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	2.5.1
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	2.5; 2.6
Generalisability	21	Discuss the generalisability (external validity) of the study results	2.5; 2.6
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NA see publication

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Appendix 6 PROSPERO Chapter three

Citation

Pauline Kuithan, Nicola R Heneghan, Deepa Abichandani, Alison Rushton, Deborah Falla. Exercise induced hypoalgesia in individuals with spinal pain: a systematic review and data synthesis. PROSPERO 2019 CRD42019145586 Available from:
https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019145586

Review question

This systematic review investigates the presence of exercise induced hypoalgesia in individuals with spinal pain. Exercise induced hypoalgesia has been demonstrated in healthy individuals. Currently, it is unknown whether individuals with spinal pain present with exercise induced hypoalgesia. Therefore, our research question is: Do individuals with spinal pain experience exercise induced hypoalgesia following physical activity? Physical activity is being investigated that is an umbrella term to encompass exercise, training, occupational tasks and similar activities.

Searches

Search engines and databases will include the following MEDLINE (OVID interface), EMBASE (OVID interface), CINAHL (EBSCO interface), Web of Science, PubMed and Google Scholar. No restrictions will be applied for the year of publication, design or language; with databases searched from inception to 15/08/2019 at this stage. If available, we will use medical subject headings (MeSH) and relevant text words referring to exercise induced hypoalgesia, or endogenous pain inhibition, or pain sensitivity to activity. If appropriate, we will use recommended search filters. Furthermore, hand searching of key journals, identified from a previous review (Naugle et al., 2012), will be conducted. Additional searches will include Grey literature, encompassing dissertation abstracts and Ethos, OpenGrey, ZETOC and British National bibliography.
A search update was conducted in July 2020.

Types of study to be included

We will include observational studies, allowing to make comparable recommendations. Based on our scoping searches, no eligible published or registered randomised or non-randomised trials were found solely focussing on the effects of EIH.
Studies where the full manuscript is not written in English will be excluded. Furthermore, case studies, and randomised or cross-over studies will be excluded.

Condition or domain being studied

Spinal pain is a major problem internationally. Low back and neck pain are the most common musculoskeletal disorders with the highest years lived with disability.
According to international guidelines, physical activity is key to conservative management for specific and non-specific back and neck pain. This is usually addressed in the form of exercise, or training. However, the underlying beneficial mechanisms of physical activity and exercise are still not fully understood. In people with chronic pain, responses to physical activity and exercise are likely to be altered, as some people do not respond as favourably to exercise regimes. Even though multiple factors within the biopsychosocial model need to be considered, one cause could be impaired endogenous pain inhibition pathways.

In healthy people it has been shown that physical activity leads to a temporary decrease of pain sensitivity, also referred as exercise induced hypoalgesia, reflecting endogenous pain inhibition.

Further work is needed to fully understand whether exercise induced hypoalgesia is impaired in individuals with spinal pain. These findings could help to further explain the variability in response to physical activity in individuals with spinal pain.

Participants/population

Inclusion criteria
• Human adults, of 18 years of age and older
• Complaint of spinal pain - cervical, thoracic, lumbar, sacral, or coccygeal areas including spinal structures such as trapezius or erector spinae muscles
• Any stage, from acute to chronic
• Including specific conditions of spinal pain originating from, for example, spinal stenosis but also non-specific pain
• Including traumatic injuries such as whiplash injury
• Multiple regions of pain are not excluded
• If population is mixed, a majority of people, defined as at least 80% of the included participants have to have spinal complaints.
Exclusion Criteria
Non-musculoskeletal disorders such as neurological injuries will be excluded.
Furthermore, people with a diagnosis of fibromyalgia will be excluded, as this is rather considered as a chronic pain disease than a spinal disease. This is the same for people diagnosed with Post-traumatic stress disorder (PTSD).

Intervention(s), exposure(s)

Inclusion Criteria
To investigate the effect of exercise induced hypoalgesia, an exposure to physical activity for participants is required to detect changes in pain sensitivity. Physical activity is the umbrella term for exercise, training, occupational tasks and similar activities. This includes all forms of isometric, concentric, eccentric, or combined/ functional movements as related to strengthening with or without resistance/weights and/ or endurance/ aerobic exercise as cycling or walking. In addition, this also includes occupational tasks such as lifting or manual labour.
For all interventions we will distinguish between a local or remote form of physical activity. For local forms, the affected region of the spine is targeted within the activity as for example deep neck flexor exercise in a population with neck pain; or remote forms such as a walking activity in a population with neck pain. The third subcategory will be regional exercises such as exercises not directly in the local area, but targeting the affected region such as shoulder movements for people with neck pain.
Exclusion Criteria
Interventions which are passive or do not include activity e.g. continuous passive motion or manual therapy, will be excluded; as will psychological or mental exercises, such as cognitive tasks and educational programmes.

Comparator(s)/control

Where available, results will be compared to a healthy control group, defined as comprising of individuals without spinal pain, undergoing the same protocol to produce EIH and observed in the same study.

Context

• Effect of exercise induced hypoalgesia, endogenous pain inhibition, or altered (in-/ decreased) sensitivity to physical activity (Question)
• Observational studies (Study design)
• Population comprised of individuals with spinal pain (Population)
• Any kind of physical activity/ exercise intervention/ movement task, such as different strength or endurance training programmes, applied with the aim of modifying pain sensitivity (Intervention)
• Comparison to a healthy control group if available (Comparison)
• Any kind of outcome measurement, used within-in subject and session to assess pain sensitivity (Outcome)

Main outcome(s)

Measurements include performance-based outcomes such as quantitative sensory testing (QST), in which

thermal, electrical or pressure stimuli will be applied until the pain threshold or tolerance of the individual participant is reached. This includes dynamic QST such as temporal summation of heat or pressure stimuli. Furthermore, we will include similar assessments, such as the nociceptive reflex, or dynamic measurements such as conditional pain modulation or offset analgesia.
Moreover, we will include patient reported outcome measures as e.g. pain score (VAS/ NRS), pain drawings or questionnaires measuring changes in pain sensitivity due to physical activity.
Likewise, invasive techniques such as blood samples or non-invasive imaging techniques such as fMRI will be included.
Exclusion criteria
The outcome must be in direct context with a single session and related to the single bout of exercise. Therefore, changes representing the course over multiple sessions are excluded.

Measures of effect

As specified. Results were defined as no EIH, if there was no significant difference between pre and post scores of any relevant outcome measurement for people with spinal pain or healthy controls. Impaired EIH was based on no EIH or significant group difference compared to the control group (if available). Normal EIH represented a change in EIH, but no group difference. If the symptomatic group showed significant hyper- instead of hypoalgesia, this was considered as hypersensitivity.

Additional outcome(s)

None.

Measures of effect

Not applicable.

Data extraction (selection and coding)

We will use Endnote X8 to save our search strategy and data files, including abstracts and full text pdf and to identify and remove duplicates. A screening tool considering inclusion and exclusion criteria, for title, abstract and full text screenings has been designed. Based on title/ abstract, two reviewers will independently screen the results and mark them as either include/exclude/ or unsure. At all stages, inclusion has to be confirmed by both reviewers. In case of disagreement, a consensus meeting will be held, and if unsuccessful a further independent reviewer will be asked. For all eligible articles, the full-text will be obtained. In case of uncertainty, the full text will be used to clarify inclusion and exclusion criteria. If further data or details are required, the corresponding author will be contacted. The same approach will be conducted to screen full texts based on the eligibility criteria.
Data from all included studies will be extracted independently by two researchers according to a bespoke standardised form based on the eligibility criteria.
For all excluded studies, the criteria for exclusion will be summarised.
We will extract data on
• General study information authors and year of publication
• Study characteristics such as design and sample size
• Population and participants characteristics (spinal pain, disability, sex, age, etc.)
• Intervention (type of physical activity, intensity, remote or local)
• Outcome measurement (performance-based outcome measurement such as pressure pain or thermal threshold, or patient reported outcome measurement as pain scales). In case that a study covers multiple sessions such as reliability studies, these will be considered individually. If data is sufficient pooling will be based on those categories.
• Data: mean and SD will be used for change in percentage and/or difference between pre-and post-test and if possible effect size and 95% confidence intervals.

Risk of bias (quality) assessment

The risk of bias for each included study will be independently assessed by two reviewers. If discrepancies in assessment cannot be resolved through discussion a third reviewer will act as a mediator.

Risk of bias in individual studies
Included studies will be assessed using an appropriate and commonly used tool, the Newcastle Ottawa Scale, for observational studies.

Meta-Biases
To avoid reporting bias, we will look for unpublished studies at past conference proceedings in the last ten years as well as by internet research and explicit search for grey literature.

Confidence in Cumulative Evidence
To report the strength of the overall body of evidence we will use "very low", "low", "moderate" and "high" following the Grading Recommendations, Assessment Development and Evaluation (GRADE) considering risk of bias, inconsistency, imprecision, indirectness, and publication bias. Based on the design of observational studies, the starting point for evaluation of quality will be "low" in line with GRADE. However, based on the assessment of the quality of individual studies, studies can be up- or down-graded.

Strategy for data synthesis
First impressions from scoping searches and data from a previous study from 2012 by Naugle et al. indicate that pooling of data could be problematic due to low number of studies, and high heterogeneity of studies. If a meta-analytic approach is therefore not feasible, a narrative analysis will be conducted based on PRISMA recommendations.
Data will be pooled according to exercise induced hypoalgesia from the physical activity chosen to produce these effects (remote, local, regional and type of exercise such as cardio or isometric exercise). Potential other factors of the list of extracted data such as region of spinal complaint or test site might be considered depending on the search result.

Analysis of subgroups or subsets
Not applicable.

Contact details for further information
Pauline Kuithan
pxk634@student.bham.ac.uk

Organisational affiliation of the review
Centre of Precision Rehabilitation for Spinal Pain University of Birmingham
https://www.birmingham.ac.uk/research/activity/cpr-spine/index.aspx

Review team members and their organisational affiliations
Ms Pauline Kuithan. Centre of Precision Rehabilitation for Spinal Pain, University of Birmingham
Dr Nicola R Heneghan. Centre of Precision Rehabilitation for Spinal Pain, Univeristy of Birmingham
Ms Deepa Abichandani. Centre of Precision Rehabilitation for Spinal Pain, Univeristy of Birmingham
Dr Alison Rushton. Centre of Precision Rehabilitation for Spinal Pain, Univeristy of Birmingham
Professor Deborah Falla. Centre of Precision Rehabilitation for Spinal Pain, Univeristy of Birmingham

Type and method of review
Narrative synthesis, Systematic review

Anticipated or actual start date
15 July 2019

Anticipated completion date
31 January 2021

Funding sources/sponsors
None.

Conflicts of interest

Language
English

Country
England

Stage of review
Review Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Humans; Hypesthesia; Pain

Date of registration in PROSPERO
16 August 2019

Date of first submission
01 August 2019

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Revision note
A search update was conducted in July 2020 as original search was one year old. Additionally, a few minor changes haven been conducted to improve clarity of the protocol.

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.
The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions
16 August 2019
25 February 2020
23 July 2020
05 November 2020

Appendix 7 PRISMA GUIDELINES Chapter three

PRISMA 2020 Checklist

Word document available under http://prisma-statement.org/PRISMAstatement/checklist.aspx

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Yes
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	3.1 not further assessed in this thesis
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3,2,1
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	3.2.2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	3.3.2
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	3.3.3
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	3.3.4
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	3.3.5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	3.3.6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	3.3.7
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	3.3.7

Section and Topic	Item #	Checklist item	Location where item is reported
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	3.3.8
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	3.3.9
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	3.3.10
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	NA
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	NA
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	3.3.10
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	3.3.11 meta biases
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	3.3.12
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	3.4.1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Discussion of thesis
Study characteristics	17	Cite each included study and present its characteristics.	3.4.2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	3.4.3
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	3.4.4
	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	3.4.4

Section and Topic	Item #	Checklist item	Location where item is reported
Results of syntheses	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	3.4.5
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	3.4.5
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	3.4.5
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	3.4.2-5
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	3.4.5
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	3.5.1-3
	23b	Discuss any limitations of the evidence included in the review.	3.5.4
	23c	Discuss any limitations of the review processes used.	3.5.4
	23d	Discuss implications of the results for practice, policy, and future research.	Discussion of thesis
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	3.3.1/ Appendix 6
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	3.3.1 Appendix 6
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	3.3.1
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	NA
Competing interests	26	Declare any competing interests of review authors.	NA
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Appendices

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71 For more information, visit: http://www.prisma-statement.org/

Appendix 8 Full Search Strategy Chapter three

Full line-by- line search strategy for Medline and EMBASE

Medline (Ovid Interface)			EMBASE (OVID interface)	
1. 1	Exp Back Pain		Exp backache	
2.	Exp low back pain		Exp low back pain	
3.	Exp neck pain		Exp neck pain	
4.	Exp Neck injuries		Exp neck injury	
5.	Exp Back injuries		Exp back injury	
6.	Exp thoracic injuries		Exp thoracic injury	
7.	Thoracic pain	mp	Exp Thorax pain	
8.	Exp Sacrococcygeal		Exp Sacrococcygeal region	
9.	Spinal Pain	mp	Exp Sacroiliac Joint	
10.	Exp Chronic pain		Exp Spinal pain	
11.	Exp Sacroiliac joint		Exp chronic pain	
12.	1-11 OR	Population	1-11OR	Population
13.	Exp Exercise		Exp Exercise	
14.	Activity	mp	Activity	mp
15.	Training	mp	Exp Training	
16.	Task	mp	Task	mp
17.	Exp Muscle		Exp Muscle Contraction	
18.	Exp Movement		Exp Movement	
19.	13 18 OR	Task	13 18 OR	Task
20.	Exercise Induced	mp	Exercise Induced hypoalgesia	mp
21.	Exercise-Induced	mp	Exercise-Induced hypoalgesia	mp
22.	Endogenous pain	mp	Endogenous pain inhibition	mp
23.	Pain sensitivity	mp	Exp Nociception	
24.	Hypoalgesic	mp	Hypoalgesic	mp
25.	Hypoalgesia	mp	Exp hypoalgesia	
26.	Exp analgesia		Exp analgesia	
27.	Antinociception	mp	Exp antinociception	
28.	Exp Pain perception		Pain modulation	mp
29.	Pain modulation	mp	20- 28 OR	Phenomenon
30.	20- 29 OR	Phenomenon	Exp Pain threshold	
31.	Exp Pain threshold		Quantitative sensory testing	mp
32.	Quantitative sensory	mp	Exp Pain measurement	
33.	Exp Pain		Pain rating	mp
34.	Pain rating	mp	Exp Magnetic Resonance	
35.	Exp Magnetic		Exp Endorphins	
36.	Exp Endorphins		Exp opiate	
37.	Opioid	mp	Exp Hematologic Tests	
38.	Exp Hematologic		Exp Endocannabinoids	
39.	Exp		Exp Serotonergic system	
40.	Serotonergic system	mp	Exp Immune system	

41.	Exp Immune system		Exp Autonomic nervous system	
42.	Exp Autonomic		30 – 41 OR	Outcome
43.	31- 42 OR	Outcome	12, 19, 29, 42 AND	
44.	12, 19, 30, 43 AND		Limitations to humans	
45.	Filter HUMAN			

Search strategy for CINAHL Plus (EBSCO interface)

Population	MH"back pain+" or MH"low back pain+" or MH"neck pain+" or MH"back injuries+" or MH"neck injuries+" or “thoracic” or MH "thoracic injuries+" or MH"sacrum+" or MH"sacroiliac joint+" or MH"coccyx+" or MH"chronic pain+"	AND
Task	MH”exercise+” or MH”physical activity” or “training” or “task” or MH”muscle contraction+” or MH”movement+”	AND
Phenomenon	“Exercise Induced hypoalgesia” or “Exercise-Induced hypoalgesia” or “Endogenous pain inhibition” or “pain sensitivity” or “hypoalgesic” or “hypoalgesia” or “analgesia” or “antinociception” or “pain perception” or “pain modulation”	AND
Outcome	MH”pain threshold” or “quantitative sensory testing” or MH“pain measurement” or “pain rating” or MH”magnetic resonance imaging+” or MH”endorphins” or MH”opioid Peptides+” or MH”hematologic tests+” or “endocannabinoid” or “serotonergic system” or MH”immune system+” or MH”autonomic nervous system+”	

Search strategy Web of Science (all data bases Clarivate Analysis)

Phenomenon	(TS=exercise induced hypoalegsia) OR (TS=Exercise-induced hypoalgesia) OR (TS=endogenous pain inhibition) OR (TS=Pain sensitivity) OR (TS=Pain modulation) OR (TS=Hypoalgesic) OR (TS=Hypoalgesia) OR (TS=Analgesic) OR (TS=Antinociception) OR (TS=Pain perception)	AND
Population	(TS=Back Pain) OR (TS=Low back pain) OR (TS= Neck Pain) OR (TS=Neck injury) OR (TS=Back Injury) OR (TS= Thoracic Injury) OR (TS= thoracic Pain) OR (TS= sacro coccygeal) OR (TS=Sacroiliac joint) OR (TS=Spinal Pain) OR (TS=Chronic Pain)	AND
Task	(TS=Exercise) OR (TS=Activity) OR (TS=Training) OR (TS=Task) OR (TS=Muscle Contraction) OR (TS=Movement)	AND
Outcome	(TS=Pain threshold) OR (TS=Quantitative sensory testing) OR (TS=Pain measurement) OR (TS=Pain rating) OR (TS=Magnetic Resonance Imaging) OR (TS=Endorphins) OR (TS= Opioid) OR (TS=Hematologic Tests) OR (TS=Endocannabinoids) OR (TS=Serotonergic system) OR (TS=Immune system) OR (TS=Autonomic nervous system)	

Search strategy PubMed CENTRAL

Population	("back pain"[MeSH Terms] OR back pain[Text Word] OR "neck pain"[MeSH Terms] OR neck pain[Text Word] OR “Spinal Pain” OR "neck injuries"[MeSH Terms] OR neck injury[Text Word] OR "back injuries"[MeSH Terms] OR back injury[Text Word] OR "thoracic injuries"[MeSH Terms] OR thoracic injury[Text Word] OR “Thoracic Pain “ OR "chronic pain"[MeSH Terms] OR chronic pain[Text Word] OR "sacroiliac joint"[MeSH Terms] OR sacroiliac joint[Text Word] OR "sacrococcygeal region"[MeSH Terms] OR coccygeal region[Text Word])	AND
Task	("exercise"[MeSH Terms] OR exercise[Text Word] OR activity[Text Word] OR training[Text Word] OR “Task” OR "muscle contraction"[MeSH Terms] OR muscle contraction[Text Word] OR "movement"[MeSH Terms] OR movement[Text Word])	AND

Phenomenon	(“exercise induced hypoalgesia” OR “exercise-induced hypoalgesia” OR "pain threshold"[MeSH Terms] OR “Pain sensitivity” OR “Hypoalgesic” OR “Hypoalgesia” OR "analgesia"[MeSH Terms] OR analgesia[Text Word] OR “antinociception” OR "pain perception"[MeSH Terms] OR pain perception[Text Word] OR “Pain modulation”)	AND
Outcome	("pain threshold"[MeSH Terms] OR pain threshold[Text Word] OR “Quantitative Sensory Testing” OR "pain measurement"[MeSH Terms] OR Pain measurement[Text Word] OR "magnetic resonance imaging"[MeSH Terms] OR Magnetic Resonance Imaging[Text Word] OR "endorphins"[MeSH Terms] OR Endorphins[Text Word] OR "Opioid Peptides"[Mesh] OR "hematologic tests"[MeSH Terms] OR Hematologic Test[Text Word] OR "endocannabinoids"[MeSH Terms] OR Endocannabinoids[Text Word] OR “Serotonergic system“ OR "immune system"[MeSH Terms] OR immune system[Text Word] OR "autonomic nervous system"[MeSH Terms] OR autonomic nervous system[Text Word])	

Search Strategy Google

“Exercise induced hypoalgesia” AND (back or neck)
“endogenous pain inhibition” AND (exercise or activity) AND (back or neck)
“pain sensitivity” AND "exercise" AND ("back pain" or "neck pain")
“pain modulation” AND (exercise or activity) AND (back or neck)

Search strategy grey literature, encompassing dissertation abstracts

Source	Search term
Ethos	
	exercise induced hypoalgesia
	endogenous pain inhibition
	pain sensitivity and exercise
	pain modulation and exercise
Open Grey	
	exercise induced hypoalgesia
	endogenous pain inhibition
	pain sensitivity and exercise
	pain modulation
ZETOC	
	exercise induced hypoalgesia
	“endogenous pain inhibition” AND “Exercise”
	“pain sensitivity” and “exercise”
	“pain modulation” and “exercise”
British National bibliography	
	exercise induced hypoalgesia
	endogenous pain inhibition
	pain sensitivity and exercise
	pain modulation and exercise

Journals for hand searches

The Journal of Pain	Scandinavian Journal of Pain	The Clinical Journal of Pain	European Journal of pain	PAIN

Appendix 9 Modification Newcastle- Ottawa Scale Chapter three

Modified Newcastle-Ottawa- Scale (NOS) (Wells, 2009)

SECTION ONE SELECTION		Score
1 Case Definition (Justification: Spinal pain is usually non-specific, and imaging or hospitalisation is not common, and most cases will be self-reported)		
a	Requires some validation e.g. ≥2 parameter regarding dysfunction, such as e.g. VAS, NDI/ODI, pain drawing, years of complain and results are reported in the article to get an overview of the included population and severity/ disability levels	*
b	Self-report with no reference to severity or disability, or only inclusion criteria stated but no results reported	
c	No description	
2 Representativeness of the Cases		
a	All eligible cases with outcome of interest over a defined period of time, all cases in a defined catchment area, all cases in a defined hospital or clinic, group of hospitals, health maintenance organisation, or an appropriate sample of those cases (e.g. random sample)	*
b	This excludes any study recruiting via a register and not reporting numbers of contacted/responded/ included as well as self-referral/ or a convenient sample	
c	Not satisfying requirements in part (a), or not stated.	
3 Selection of Controls (Justification: Hospitalisation is not relevant) This item assesses whether the control series used in the study is derived from the same population as the cases and essentially would have been cases had the outcome been present.		
a	Community controls (i.e. same community as cases and would be cases if had outcome)	*
b	No description or different community to recruit healthy controls	
4 Definition of Controls		
a	If cases are first occurrence of outcome, then it must explicitly state that controls have no history of this outcome. If cases have new (not necessarily first) occurrence of outcome, then controls with previous occurrences of outcome of interest should not be excluded.	*
b	No mentioning of history of outcome	
SECTION TWO COMPARABILITY "Either cases and controls must be matched in the design and/or confounders must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability. "**That implies that it has to be controlled prior to study, not only a comparison after data collection**)		
	Controlled for age	*
	Controlled of for gender	*
SECTION THREE EXPOSURE/ OUTCOME		
1 Description of EIH outcome measurement, as there is no validated tool for EIH		
a	Outcome measurement and test points clearly described and standardised in both groups to reproduce the testing procedure	*

b	Outcome measurement and test points are not sufficiently described and/or not standardised to reproduce the procedure e.g. test location not specified, order/ randomisation not clear	
2 Same methods and intervention for both groups?		
yes		*
3 Description of Physical Activity Intervention		
a	Physical Activity to produce EIH is well described and implemented in a standardised way in both groups to reproduce the testing procedure	*
b	Physical Activity to produce EIH is not sufficiently described and/or not standardised in terms of parameters such as e.g. position, duration, intensity	

Table for Quality rating Scoring algorithm modified (McPheeters et al., 2012)

Available from https://www.ncbi.nlm.nih.gov/books/NBK107322/ Last accessed 24.03.2022

Rating	* Points in Selection Domain	* Points in Outcome Domain
Good	≥3	≥2
Fair	2	≥2
Poor	0-1	0-1

For the research question the control group is not relevant. Therefore, the second category was removed. The lowest grade was accounted for risk of bias.

References

MCPHEETERS, M. L., KRIPALANI, S., PETERSON, N. B., IDOWU, R. T., JEROME, R. N., POTTER, S. A. & ANDREWS, J. C. 2012. Closing the quality gap: revisiting the state of the science (vol. 3: quality improvement interventions to address health disparities). Evid Rep Technol Assess (Full Rep), 1-475.

WELLS, G. A., SHEA, B., O'CONNEL, D. ET AL. . 2009. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. [Online]. Available: http://www.ohri.ca/programs/clinical_epidemiology/nosgen.pdf [Accessed].

Appendix 10 Excluded Studies Chapter three

Eligibility criteria	Reason	Number	N=	Total N=
Phenomenon	Not EIH Note: not listed for other reasons	(Balaguier et al., 2017b) (Bruehl et al., 2002; Bruehl et al., 2013; Bruehl and Chung 2006; Bruehl et al., 2003; Bruehl et al., 2004) (Daenen et al., 2012) (de-la-Puente-Ranea et al., 2016) (Do et al., 2018) (Flor et al., 1999) (Franco et al., 2018) (Fuller and Robinson 1995) (Gross et al., 2008) (Ibrahim 2018) (Kumar and Prasad 2010) (Lackner and Carosella 1999) (Ljungquist et al., 2003) (McCracken et al., 1998) (Saha et al., 2019) (Smith et al., 2016) (Tang et al., 2008) (Vincent et al., 2013) (Cichon et al., 2019) (Goudman et al., 2020) (Harvie et al., 2020) (Jones et al., 2020) (Qu et al., 2020)	27	27
Phenomenon	No within session retest	(Balaguier et al., 2017a) (Bobos et al., 2016) (Bodes Pardo et al., 2018) (Calixtre et al., 2016) (Celenay et al., 2016) (Jeong et al., 2016) (Knost et al., 1999) (Kroll et al., 2018) (Lima et al., 2018) (Marshall and Murphy 2008) (Moseley 2005) (Murray et al., 2017) (Rabey et al., 2017; Schreiber et al., 2014) (Tsauo et al., 2004) (Waling et al., 2000) (Woznowski-Vu et al., 2019b) (Karlsson et al., 2015) (Perez-Cabezas et al., 2020)	19	19
Population	Healthy Participants	(Binderup et al., 2010) (Bishop et al., 2012) (Foxen-Craft and Dahlquist 2017) (Gajsar et al., 2018) (Koltyn et al., 2013) (Lemley et al., 2014) (Park and Yoo 2013) (Yoon et al., 2019)	8	12
	No spinal pain	(Calixtre et al., 2016) (Cook et al., 2010) (Scioli-Salter et al., 2016) (Deering et al., 2019)	4	
Task	Not physical task	(Dissanayaka et al., 2016) (Fernandez-Carnero et al., 2019) (Perez-Cabezas et al., 2020)	3	3
Outcome	Not pain sensitivity	(Danneels et al., 2016) (Lima et al., 2018)	2	10
	Only VAS/ NRS	(Andersen et al., 2008) (Keyserling et al., 2005) (Linton et al., 1996) (Mankovsky-Arnold et al., 2017) (Sullivan et al., 2010) (Wittink et al., 2001) (Kalezic et al., 2010) (Woznowski-Vu et al., 2019a)	8	

Design	Thesis (search included relevant studies)	(Karlsson 2017) (Kroll 2018; Micalos 2012; Vægter 2014)	5	39
	Abstract (no full text)	(Demirel et al., 2015) (Salter et al., 2017)	2	
	Study design not observational	(Winter and McCauley-Callagy 2002) (Andersen et al., 2008) (Bialosky et al., 2009) (Bobos et al., 2016) (Bodes Pardo et al., 2018) (Celenay et al., 2016) (Dissanayaka et al., 2016) (Galindez-Ibarbengoetxea et al., 2018) (Gallego Izquierdo et al., 2016) (Jeong et al., 2016) (Joseph et al., 2018) (Kashyap et al., 2018) (Kroll et al., 2018) (Lima et al., 2018) (Linton et al., 1996) (Lluch et al., 2014a; Lluch et al., 2014b) (Marshall and Murphy 2008) (Moseley 2005; Murray et al., 2017) (O'Leary et al., 2007) (Paungmali et al., 2018; Paungmali et al., 2017) (Petersen et al., 2015) (Trampas et al., 2015) (Waling et al., 2000) (Yeung et al., 2003) (Deering et al., 2019) (Fernandez-Carnero et al., 2019) (Hughes and Patterson 2020) (Perez-Cabezas et al., 2020) (Suso-Marti et al., 2019)	32	
				110

References

Andersen LL, Kjaer M, Sogaard K, Hansen L, Kryger AI, Sjogaard G. Effect of two contrasting types of physical exercise on chronic neck muscle pain. Arthritis Rheum 2008;59: 84-91.

Balaguier R, Madeleine P, Rose-Dulcina K, Vuillerme N. Effects of a Worksite Supervised Adapted Physical Activity Program on Trunk Muscle Endurance, Flexibility, and Pain Sensitivity Among Vineyard Workers. Journal of agromedicine 2017a;22: 200-214.

Balaguier R, Madeleine P, Rose-Dulcina K, Vuillerme N. Trunk kinematics and low back pain during pruning among vineyard workers-A field study at the Chateau Larose-Trintaudon. PLoS One 2017b;12: e0175126.

Bialosky JE, Bishop MD, Robinson ME, Zeppieri G, Jr., George SZ. Spinal manipulative therapy has an immediate effect on thermal pain sensitivity in people with low back pain: a randomized controlled trial. Phys Ther 2009;89: 1292-1303.

Binderup AT, Arendt-Nielsen L, Madeleine P. Pressure pain threshold mapping of the trapezius muscle reveals heterogeneity in the distribution of muscular hyperalgesia after eccentric exercise. European journal of pain (London, England) 2010;14: 705-712.

Bishop MD, George SZ, Robinson ME. Dynamic, but not static, pain sensitivity predicts exercise-induced muscle pain: covariation of temporal sensory summation and pain intensity. Neurosci Lett 2012;526: 1-4.

Bobos P, Billis E, Papanikolaou DT, Koutsojannis C, Macdermid JC. Does Deep Cervical Flexor Muscle Training Affect Pain Pressure Thresholds of Myofascial Trigger Points in Patients with Chronic Neck Pain? A Prospective Randomized Controlled Trial. Rehabilitation Research and Practice 2016;2016 (no pagination).

Bodes Pardo G, Lluch Girbes E, Roussel NA, Gallego Izquierdo T, Jimenez Penick V, Pecos Martin D. Pain Neurophysiology Education and Therapeutic Exercise for Patients With Chronic Low Back Pain: A Single-Blind Randomized Controlled Trial. Arch Phys Med Rehab 2018;99: 338-347.

Bruehl S, Burns JW, Chung OY, Ward P, Johnson B. Anger and pain sensitivity in chronic low back pain patients and pain-free controls: the role of endogenous opioids. Pain 2002;99: 223-233.

Bruehl S, Burns JW, Gupta R, Buvanendran A, Chont M, Kinner E, Schuster E, Passik S, France CR. Endogenous opioid function mediates the association between laboratory-evoked pain sensitivity and morphine analgesic responses. Pain 2013;154: 1856-1864.

Bruehl S and Chung OY. Parental history of chronic pain may be associated with impairments in endogenous opioid analgesic systems. Pain 2006;124: 287-294.

Bruehl S, Chung OY, Burns JW, Biridepalli S. The association between anger expression and chronic pain intensity: evidence for partial mediation by endogenous opioid dysfunction. Pain 2003;106: 317-324.

Bruehl S, Chung OY, Ward P, Johnson B. Endogenous opioids and chronic pain intensity: interactions with level of disability. The Clinical journal of pain 2004;20: 283-292.

Calixtre LB, Gruninger BL, Haik MN, Alburquerque-Sendin F, Oliveira AB. Effects of cervical mobilization and exercise on pain, movement and function in subjects with temporomandibular disorders: a single group pre-post test. J Appl Oral Sci 2016;24: 188-197.

Celenay ST, Kaya DO, Akbayrak T. Cervical and scapulothoracic stabilization exercises with and without connective tissue massage for chronic mechanical neck pain: A prospective, randomised controlled trial. Man Ther 2016;21: 144-150.

Cichon D, Ignasiak Z, Fugiel J, Kochan K, Ignasiak T. Efficacy of Physiotherapy in Reducing Back Pain and Improve Joint Mobility in Older Women. Ortopedia, traumatologia, rehabilitacja 2019;21: 45-55.

Cook DB, Stegner AJ, Ellingson LD. Exercise alters pain sensitivity in Gulf War veterans with chronic musculoskeletal pain. The journal of pain : official journal of the American Pain Society 2010;11: 764-772.

Daenen L, Nijs J, Roussel N, Wouters K, Cras P. Altered perception of distorted visual feedback occurs soon after whiplash injury: an experimental study of central nervous system processing. Pain Physician 2012;15: 405-413.

Danneels L, Cagnie B, D'Hooge R, De Deene Y, Crombez G, Vanderstraeten G, Parlevliet T, Van Oosterwijck J. The effect of experimental low back pain on lumbar muscle activity in people with a history of clinical low back pain: a muscle functional MRI study. J Neurophysiol 2016;115: 851-857.

de-la-Puente-Ranea L, Garcia-Calvo B, La Touche R, Fernandez-Carnero J, Gil-Martinez A. Influence of the actions observed on cervical motion in patients with chronic neck pain: a pilot study. J Exerc Rehabil 2016;12: 346-354.

Deering R, Pashibin T, Cruz M, Hunter SK, Hoeger Bement M. Fatiguing Trunk Flexor Exercise Decreases Pain Sensitivity in Postpartum Women. Front Physiol 2019;10: 315.

Demirel A, Oz M, Ulger O. Effect of deep friction massage and cervical stabilization exercise on pain thresholds in cervical disc herniation. Fizyoterapi Rehabilitasyon 2015;26 (3): S52.

Dissanayaka TD, Pallegama RW, Suraweera HJ, Johnson MI, Kariyawasam AP. Comparison of the Effectiveness of Transcutaneous Electrical Nerve Stimulation and Interferential Therapy on the Upper Trapezius in Myofascial Pain Syndrome: A Randomized Controlled Study. Am J Phys Med Rehabil 2016;95: 663-672.

Do JH, Yoon IJ, Cho YK, Ahn JS, Kim JK, Jeon J. Comparison of hospital based and home based exercise on quality of life, and neck and shoulder function in patients with spinal accessary nerve injury after head and neck cancer surgery. Oral Oncol 2018;86: 100-104.

Fernandez-Carnero J, Sierra-Silvestre E, Beltran-Alacreu H, Gil-Martinez A, La Touche R. Neural Tension Technique Improves Immediate Conditioned Pain Modulation in Patients with Chronic Neck Pain: A Randomized Clinical Trial. Pain Med 2019;20: 1227-1235.

Flor H, Furst M, Birbaumer N. Deficient discrimination of EMG levels and overestimation of perceived tension in chronic pain patients. Appl Psychophysiol Biofeedback 1999;24: 55-66.

Foxen-Craft E and Dahlquist LM. Brief submaximal isometric exercise improves cold pressor pain tolerance. J Behav Med 2017;40: 760-771.

Franco YRS, Franco KFM, Silva LA, Silva MO, Rodrigues MN, Liebano RE, Cabral CMN. Does the use of interferential current prior to pilates exercises accelerate improvement of chronic nonspecific low back pain? Pain Management 2018;8: 465-474.

Fuller AK and Robinson ME. Perceptual differences between patients with chronic low back pain and healthy volunteers using magnitude matching and clinically relevant stimuli. Behavior Therapy 1995;26: 241-253.

Gajsar H, Nahrwold K, Titze C, Hasenbring MI, Vaegter HB. Exercise does not produce hypoalgesia when performed immediately after a painful stimulus. Scand J Pain 2018;18: 311-320.

Galindez-Ibarbengoetxea X, Setuain I, Ramirez-Velez R, Andersen LL, Gonzalez-Izal M, Jauregi A, Izquierdo M. Immediate Effects of Osteopathic Treatment Versus Therapeutic Exercise on Patients With Chronic Cervical Pain. Altern Ther Health Med 2018;24: 24-32.

Gallego Izquierdo T, Pecos-Martin D, Lluch Girbes E, Plaza-Manzano G, Rodriguez Caldentey R, Mayor Melus R, Blanco Mariscal D, Falla D. Comparison of cranio-cervical flexion training versus cervical proprioception training in patients with chronic neck pain: A randomized controlled clinical trial. J Rehabil Med 2016;48: 48-55.

Goudman L, Mouraux A, Daenen L, Nijs J, Cras P, Roussel N, Moens M, Lenoir D, Coppieters I, Huysmans E, De Kooning M. Does Motor Cortex Engagement During Movement Preparation Differentially Inhibit Nociceptive Processing in Patients with Chronic Whiplash Associated Disorders, Chronic Fatigue Syndrome and Healthy Controls? An Experimental Study. J Clin Med 2020;9.

Gross DP, Bhambhani Y, Haykowsky MJ, Rashiq S. Acute opioid administration improves work-related exercise performance in patients with chronic back pain. The journal of pain : official journal of the American Pain Society 2008;9: 856-862.
Harvie DS, Smith RT, Moseley GL, Meulders A, Michiels B, Sterling M. Illusion-enhanced Virtual Reality Exercise for Neck Pain: A Replicated Single Case Series. The Clinical journal of pain 2020;36: 101-109.
Hughes L and 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 (Bethesda, Md : 1985) 2020;128: 914-924.
Ibrahim A, E. W. Mahmoud, Mohamed Raafat Mohamed Atteya. comparative-study-between-supervised-and-unsupervised-exercise-program-for-cervical-spondylosis. International Journal of Medical Research & Health Sciences 2018.
Jeong UC, Kim CY, Park YH, Hwang-Bo G, Nam CW. The effects of self-mobilization techniques for the sciatic nerves on physical functions and health of low back pain patients with lower limb radiating pain. J Phys Ther Sci 2016;28: 46-50.
Jones SA, Cooke HE, Wilson AC, Nagel BJ, Holley AL. A Pilot Study Examining Neural Response to Pain in Adolescents With and Without Chronic Pain. Frontiers in Neurology 2020;10 (no pagination).
Joseph LH, Benjamaporn H, Patraporn S, Ubon P, Aatit P. 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. Int J Ther Massage Bodywork 2018;11: 16-22.
Kalezic N, Noborisaka Y, Nakata M, Crenshaw AG, Karlsson S, Lyskov E, Eriksson PO. Cardiovascular and muscle activity during chewing in whiplash-associated disorders (WAD). Arch Oral Biol 2010;55: 447-453.
Karlsson L.Chronic Pain and Exercise
Studies on pain intensity, biochemistry, adherence and attitudes. 2017.
Karlsson L, Gerdle B, Ghafouri B, Backryd E, Olausson P, Ghafouri N, Larsson B. Intramuscular pain modulatory substances before and after exercise in women with chronic neck pain. Eur J Pain 2015;19: 1075-1085.
Kashyap R, Iqbal A, Alghadir AH. Controlled intervention to compare the efficacies of manual pressure release and the muscle energy technique for treating mechanical neck pain due to upper trapezius trigger points. J Pain Res 2018;11: 3151-3160.
Keyserling WM, Sudarsan SP, Martin BJ, Haig AJ, Armstrong TJ. Effects of low back disability status on lower back discomfort during sustained and cyclical trunk flexion. Ergonomics 2005;48: 219-233.
Knost B, Flor H, Birbaumer N, Schugens MM. Learned maintenance of pain: muscle tension reduces central nervous system processing of painful stimulation in chronic and subchronic pain patients. Psychophysiology 1999;36: 755-764.
Koltyn KF, Knauf MT, Brellenthin AG. Temporal summation of heat pain modulated by isometric exercise. European journal of pain (London, England) 2013;17: 1005-1011.
Kroll LE.The effects of aerobic exercise and the impact of migraine and coexisting tension-type headache and neck pain. 2018.
Kroll LS, Sjodahl Hammarlund C, Gard G, Jensen RH, Bendtsen L. Has aerobic exercise effect on pain perception in persons with migraine and coexisting tension-type headache

and neck pain? A randomized, controlled, clinical trial. European Journal of Pain (United Kingdom) 2018;22: 1399-1408.
Kumar S and Prasad N. Cervical EMG profile differences between patients of neck pain and control. Disabil Rehabil 2010;32: 2078-2087.
Lackner JM and Carosella AM. The relative influence of perceived pain control, anxiety, and functional self efficacy on spinal function among patients with chronic low back pain. Spine (Phila Pa 1976) 1999;24: 2254-2260; discussion 2260-2251.
Lemley KJ, Drewek B, Hunter SK, Hoeger Bement MK. Pain relief after isometric exercise is not task-dependent in older men and women. Med Sci Sport Exer 2014;46: 185-191.
Lima VP, de Alkmim Moreira Nunes R, da Silva JB, Paz GA, Jesus M, de Castro JBP, Dantas EHM, de Souza Vale RG. Pain perception and low back pain functional disability after a 10-week core and mobility training program: A pilot study. J Back Musculoskelet Rehabil 2018;31: 637-643.
Linton SJ, Hellsing AL, Bergstrom G. Exercise for workers with musculoskeletal pain: Does enhancing compliance decrease pain? J Occup Rehabil 1996;6: 177-190.
Ljungquist T, Nygren A, Jensen I, Harms-Ringdahl K. Physical performance tests for people with spinal pain--sensitivity to change. Disabil Rehabil 2003;25: 856-866.
Lluch E, Arguisuelas MD, Calvente Quesada O, Martinez Noguera E, Peiro Puchades M, Perez Rodriguez JA, Falla D. Immediate effects of active versus passive scapular correction on pain and pressure pain threshold in patients with chronic neck pain. J Manipulative Physiol Ther 2014a;37: 660-666.
Lluch E, Schomacher J, Gizzi L, Petzke F, Seegar D, Falla D. Immediate effects of active cranio-cervical flexion exercise versus passive mobilisation of the upper cervical spine on pain and performance on the cranio-cervical flexion test. Man Ther 2014b;19: 25-31.
Mankovsky-Arnold T, Wideman TH, Thibault P, Lariviere C, Rainville P, Sullivan MJL. Sensitivity to Movement-Evoked Pain and Multi-Site Pain are Associated with Work-Disability Following Whiplash Injury: A Cross-Sectional Study. J Occup Rehabil 2017;27: 413-421.
Marshall P and Murphy B. Self-report measures best explain changes in disability compared with physical measures after exercise rehabilitation for chronic low back pain. Spine (Phila Pa 1976) 2008;33: 326-338.
McCracken LM, Goetsch VL, Semenchuk EM. Coping with pain produced by physical activity in persons with chronic low back pain: immediate assessment following a specific pain event. Behav Med 1998;24: 29-34.
Micalos PS.The effect of aerobic exercise on pain and neurosensory modulation in healthy participants and with chronic pain disorder. 2012.
Moseley GL. Widespread brain activity during an abdominal task markedly reduced after pain physiology education: fMRI evaluation of a single patient with chronic low back pain. Aust J Physiother 2005;51: 49-52.
Murray M, Lange B, Nornberg BR, Sogaard K, Sjogaard G. Self-administered physical exercise training as treatment of neck and shoulder pain among military helicopter pilots and crew: a randomized controlled trial. BMC Musculoskelet Disord 2017;18: 147.
O'Leary S, Falla D, Hodges PW, Jull G, Vicenzino B. Specific therapeutic exercise of the neck induces immediate local hypoalgesia. The journal of pain : official journal of the American Pain Society 2007;8: 832-839.

Park SY and Yoo WG. Effect of sustained typing work on changes in scapular position, pressure pain sensitivity and upper trapezius activity. J Occup Health 2013;55: 167-172.
Paungmali A, Joseph LH, Punturee K, Sitilertpisan P, Pirunsan U, Uthaikhup S. Immediate Effects of Core Stabilization Exercise on beta-Endorphin and Cortisol Levels Among Patients With Chronic Nonspecific Low Back Pain: A Randomized Crossover Design. J Manipulative Physiol Ther 2018;41: 181-188.
Paungmali A, Joseph LH, Sitilertpisan P, Pirunsan U, Uthaikhup S. Lumbopelvic Core Stabilization Exercise and Pain Modulation Among Individuals with Chronic Nonspecific Low Back Pain. Pain practice : the official journal of World Institute of Pain 2017;17: 1008-1014.
Perez-Cabezas V, Ruiz-Molinero C, Jimenez-Rejano JJ, Chamorro-Moriana G, Gonzalez-Medina G, Chillon-Martinez R. Effectiveness of an Eye-Cervical Re-Education Program in Chronic Neck Pain: A Randomized Clinical Trial. Evidence-based complementary and alternative medicine : eCAM 2020;2020: 2760413.
Petersen SB, Cook C, Donaldson M, Hassen A, Ellis A, Learman K. The effect of manual therapy with augmentative exercises for neck pain: a randomised clinical trial. The Journal of manual & manipulative therapy 2015;23: 264-275.
Qu N, Graven-Nielsen T, Lindstrom R, Blogg Andersen Dc V, Hirata RP. Recurrent neck pain patients exhibit altered joint motion pattern during cervical flexion and extension movements. Clin Biomech (Bristol, Avon) 2020;71: 125-132.
Rabey M, Smith A, Beales D, Slater H, O'Sullivan P. Pain provocation following sagittal plane repeated movements in people with chronic low back pain: Associations with pain sensitivity and psychological profiles. Scand J Pain 2017;16: 22-28.
Saha FJ, Brummer G, Lauche R, Ostermann T, Choi KE, Rampp T, Dobos G, Cramer H. Gua Sha therapy for chronic low back pain: A randomized controlled trial. Complementary therapies in clinical practice 2019;34: 64-69.
Salter E, Bair M, Hauger R, Rasmusson A. Neuropeptide y as a potential neurobiological mediator of exercise benefits for pain sensitivity in patients with chronic pain and PTSD. Journal of Pain 2017;18 (4 Supplement 1): S87.
Schreiber KL, Campbell C, Martel MO, Greenbaum S, Wasan AD, Borsook D, Jamison RN, Edwards RR. Distraction analgesia in chronic pain patients: the impact of catastrophizing. Anesthesiology 2014;121: 1292-1301.
Scioli-Salter E, Forman DE, Otis JD, Tun C, Allsup K, Marx CE, Hauger RL, Shipherd JC, Higgins D, Tyzik A, Rasmusson AM. Potential neurobiological benefits of exercise in chronic pain and posttraumatic stress disorder: Pilot study. J Rehabil Res Dev 2016;53: 95-106.
Smith SM, Amtmann D, Askew RL, Gewandter JS, Hunsinger M, Jensen MP, McDermott MP, Patel KV, Williams M, Bacci ED, Burke LB, Chambers CT, Cooper SA, Cowan P, Desjardins P, Etropolski M, Farrar JT, Gilron I, Huang IZ, Katz M, Kerns RD, Kopecky EA, Rappaport BA, Resnick M, Strand V, Vanhove GF, Veasley C, Versavel M, Wasan AD, Turk DC, Dworkin RH. Pain intensity rating training: results from an exploratory study of the ACTTION PROTECCT system. Pain 2016;157: 1056-1064.
Sullivan AB, Covington E, Scheman J. Immediate benefits of a brief 10-minute exercise protocol in a chronic pain population: a pilot study. Pain Med 2010;11: 524-529.

Suso-Marti L, Leon-Hernandez JV, La Touche R, Paris-Alemany A, Cuenca-Martinez F. Motor Imagery and Action Observation of Specific Neck Therapeutic Exercises Induced Hypoalgesia in Patients with Chronic Neck Pain: A Randomized Single-Blind Placebo Trial. J Clin Med 2019;8.

Tang NKY, Salkovskis PM, Hodges A, Wright KJ, Hanna M, Hester J. Effects of mood on pain responses and pain tolerance: an experimental study in chronic back pain patients. Pain 2008;138: 392-401.

Trampas A, Mpeneka A, Malliou V, Godolias G, Vlachakis P. Immediate Effects of Core-Stability Exercises and Clinical Massage on Dynamic-Balance Performance of Patients With Chronic Specific Low Back Pain. J Sport Rehabil 2015;24: 373-383.

Tsauo JY, Lee HY, Hsu JH, Chen CY, Chen CJ. Physical exercise and health education for neck and shoulder complaints among sedentary workers. J Rehabil Med 2004;36: 253-257.

Vægter HB.Temporal and Spatial Manifestations of Exercise-induced Hypoalgesia and Conditioned Pain Modulation. 2014.

Vincent HK, Seay AN, Montero C, Conrad BP, Hurley RW, Vincent KR. Kinesiophobia and fear-avoidance beliefs in overweight older adults with chronic low-back pain: relationship to walking endurance--part II. Am J Phys Med Rehabil 2013;92: 439-445.

Waling K, Sundelin G, Ahlgren C, Jarvholm B. Perceived pain before and after three exercise programs--a controlled clinical trial of women with work-related trapezius myalgia. Pain 2000;85: 201-207.

Winter SV and McCauley-Callagy S. Effects of aquatic lumbar stablization and strengthening exercise protocol on chronic low back pain patients. Journal of Aquatic Physical Therapy 2002;10: 11-20.

Wittink H, Rogers W, Gascon C, Sukiennik A, Cynn D, Carr DB. Relative contribution of mental health and exercise-related pain increment to treadmill test intolerance in patients with chronic low back pain. Spine (Phila Pa 1976) 2001;26: 2368-2374.

Woznowski-Vu A, Uddin Z, Flegg D, Aternali A, Wickens R, Sullivan MJL, Sweet SN, Skou So T, Wideman TH. Comparing Novel and Existing Measures of Sensitivity to Physical Activity Among People With Chronic Musculoskeletal Pain: The Importance of Tailoring Activity to Pain. Clinical Journal of Pain 2019a;35: 656-667.

Woznowski-Vu A, Uddin Z, Flegg D, Aternali A, Wickens R, Sullivan MJL, Sweet SN, Skou ST, Wideman TH. Comparing Novel and Existing Measures of Sensitivity to Physical Activity Among People With Chronic Musculoskeletal Pain: The Importance of Tailoring Activity to Pain. The Clinical journal of pain 2019b;35: 656-667.

Yeung CK, Leung MC, Chow DH. The use of electro-acupuncture in conjunction with exercise for the treatment of chronic low-back pain. Journal of alternative and complementary medicine (New York, NY) 2003;9: 479-490.

Yoon S, Lefrancois-Daignault T, Cote JN. Effects of cycling while typing on upper limb and performance characteristics. Appl Ergon 2019;80: 161-167.

Appendix 11 Data Extraction Table Chapter three

Results of all included studies and study characteristics for local, remote, and regional tasks

Data extraction for **local tasks**

Author & Year Country **Spinal Complaint** Setting	**Population**		**Exercise** (Type, duration, intensity, perceived exertion)	**Outcome measurement** (test, device, unit, test sites, time point post-test)		**Results** (% change, diff., or pre/ post) significant changes only 1 Local, 2 Remote (1+2= pooled), 3 CON/comparison		**Summarised findings**
	Sample, Age (yrs), Gender	Participants' characteristics		Mechanical	Thermal	Mechanical	Thermal	
Falla et al., 2014 Germany **CLBP** Laboratory	**CLBP:** N=19, Age 32.2 ±9.5, 58% women **Con:** N=17, Age 29.4±7.4 47% women	ODI= 13.8+7.0%; D(mos)= 31.6+28.2; VAS avg= 3.1+ 2.0; SF-36= 67.6 ± 11.8; SF36-PCS=61.3 ±13.9; SF36-MCS = 68.3 ±13.7; TSK= 32.1 ± 6.8; PCS= 14.5 ± 8.7; STAI= 40.1 ± 7.2 Pain pre=1.9 ±1.5	25 cycles of **lifting** a 5kg box up and down on an adjusted shelf, 1s moving 3s resting (~200s) Pain post 160s=2.6±2.5	PPT (Somedic, kPA) over 8 Lx test sites, after the task	N/A	1)PPT ↓in CLBP, ↑ pain sensitivity (pre: 268.0±165.9 kPa; post: 242.0±166.7 kPa) 3)No change in PPT in CON	N/A	Impaired EIH in people with CLBP tested locally after lifting showing decreased PPT after a short lifting task. No change occurred in CON.
Kuithan et al., 2019, UK	**CLBP:** N=21, Age 31.7±13.3,	ODI= 16.0±6.8; DASS= 19.3±22.5; FABQ=27.2±11.6; PCS= 14.9±9.2;	Repetitive rotational **lifting** task 5kg box, 10 cycles ~7 min,	PPT (Somedic, kPA) **16** Lx test	Thermal detection & pain thres-hold	1)No significant change (2.10% ±18.4; CI: [-	1)No sig. changes 2)↑ CPT CLBP	Impaired EIH over local test sites for people with

CLBP Laboratory/ University setting	12 women **Con:** N=18, Age 28.2±12.5, 10 women	SF36-PCS= 49.36± 5.3; SF36-MCS= 46.51±13.0; IPAQ= 18 high, 4 medium NRS: 24hrs =3.9±2.1, pre= 3.1±2.0, episode= 4.9±1.9	2s moving 2s resting, or till pain toler-ance/ exhaustion Borg Scale CLBP=13.1±1.7 /Con= 11.1±2.2; Peak lifting NRS= 4.8 ± 2.0	sites, hand, within 5 min of completion of the task QST started PPT measured first	(cold & warm), Medoc TSA-II, °C, Hand & Lx TS: Series of 10 heat stimuli (VAS 0-100)	10.7, 6.5]) over Lx PPT in CLBP group 2)No change over thenar 3)↑ in CON over Lx region (9.43% ±13.4; CI: [2.8, 16.1]) pre 341.39±116.9/ 371.16±130.4	increase of +2.5 ±4.9°C, safety limit of the device n=18 3)No group differences ↑ CPT +1.6 ±5.6°C (hand, n=16), indicates thermal algesia but safety limit	CLBP (PPT) after lifting showing no change, but CON showed increased PPTs. No remote changes in both groups.

Legend: yrs= years; CLBP= chronic non-specific low back pain; CON= Control group; D= Duration; mos=months; avg= average; Mean ± = SD, or (range); ODI= Oswestry Disability Index; VAS= Visual Analog Pain Scale; NRS= Numeric Rating Scale; SF-36= Short Form Survey; Quality of life; PCS= Pain Catastrophising Scale; STAI= The State-Trait Anxiety Inventory; DASS= Depression, Anxiety and Stress Scale; MCS= Mental Component Scale; SF-36-PCS= Physical Component Scale; TSK= Tampa Scale of Kinesiophobia; FABQ= Fear Avoidance Believe questionnaire; IPAQ= International Physical Activity Questionnaire; s= seconds; PPT= Pressure Pain Thresholds; Lx= Lumbar; CPT= Cold Pain Threshold; ↓= decrease/decreased;↑= increase/ increased; CI= Confidence Interval EIH = Exercise Induced Hypoalgesia; Data which could not be obtained from the authors and had to be estimated were marked as italic and were described as such in the tables

Data extraction for **remote tasks**

Author & Year Country **Spinal complaint** Setting	**Population**		**Exercise** (Type, duration, intensity, perceived exertion)	**Outcome measurement** (test, device, unit, test sites, time point post-test))		**Results** (% change, diff., pre/post, significant changes only) 1 Local, 2 Remote (1+2= pooled), 3 CON/ comparison 4) during exercise		**Summarised findings**
	Sample, Age (yrs), Gender	Participants' characteristic		Mechanical	Thermal/ blood test	Mechanical	Thermal/ blood test	
Hoffman et al., 2005, USA **CLBP** Laboratory	**CLBP** N=8, Age 40±10, 4 women **Con** N=10, Age 34±8, no exercise	ODI= 23±16; D(yrs)= 7±4	**Cycling** at 50% of VO2 max for 5 min then 70% for 20 min; graded continuous 2 min stage protocol to 50W	Pressure Pain stimulator (Lucite) constant force (9.8N) over index finger: pain rating 0-100 2 min post task	N/A	1)No local test sites 2)Pain rating (mm) ↓ with exercise 79±12/ 57±26 (=28%) 3)No comparison as CON did not exercise	N/A	Remote Pressure Pain stimulation showed EIH after cycling in people with CLBP, no control group
Meeus et al., 2010, Belgium **CLBP**	**CLBP** N=21, Age 41.55± 12.40, 11 women	ODI= 18.57 (15.09); sedentary VAS= 3.63 (2.50); SF-36=	Max of 6 bouts on cycle **ergometer** (1min for each of two plateau phases of ↑ WL, incl. warm-up &cool down) each followed by 90s	PPT (Fisher Force Dial FDK 40 Push Pull Force Gage, Wagner, kg/ cm3), Lateral of L3, skin web finger	Blood test Nitric oxide levels, directly post	Authors provided data 1)Lx CLBP ↑pre: 8.67 ± 2.85 / post: 9.43±3.57 Diff: 0.76 ±2.04 [-0.16; 1.69] % Change 9.64± 29.36 [-1.29; 20.58] 2)% Change ↑ Deltoid: +9.05± 25.83 [-2.71; 20.81]; ↑Calf:	No significant change	EIH as CON However, based on obtained data PPT in CLBP significantly increased over local, but only

Laboratory	**CON** N=31, Age 39.88±12.63, 21 women	540.74 (129.60)	rest, 130W (final boost) D 1000s CLBP n=1, 1348s CLBP n=3/ CON n=2 1741s CLBP n=17/ CON n= 29	(thumb & index finger), calf, deltoid, directly after task		10.76±29.36 [-2.61; 24.12]; ↓Thumb -12.69± 20.46 [-22.01; -3.38] 3)↑ Mean PPT in Con & CLBP CON= 7.11±2.74/ 7.56±3.17 CLBP=8.10±3.02/8.28±3.49		over 2/3 of remote test sites (deltoid and calf)
Kemppainen et al., 1998, Finland **CNP** Laboratory	**CNP** N=8 **Con** N=8 Age 22-35 All male fighter pilots	History of acute in-flight neck pain attacks	**Cycle ergometer** WL 50, 100, 150, 200 W/ 60rpm, Steady state 3-4 min, stepwise ↑5-8 min, no exact D; Power CNP= 325W, CON= 315W	N/A	Cold pressor test, hand submerged in 4°C water, time (s) to pain, sensory intensity (SI) & unpleasantness (UR) (both%); after exercise at 200W, (1hr not reported here)	No further details obtained 1)No local test sites 2)Cold pressor test (s) ↑ in NP but not in CON (*all post values estimated*) Time Pre: 26.8 ±9.8/ *Post 45.66±23.6*; SI Pre: 46.0±14.6/ *10.73± 3.4*; UR: 44.8±13.4 / *1.63±2.2* 3)Time Con 28.2 ±4.4s */31.09±7.4*; SI: 43.3±11.2 / *27.66±15.8*; UR: 49.8±14.6 / *27.92±14.6*		After cycling remote Cold Pressure Test time ↑, pain intensity & unpleasantness rating ↓ in pilots with NP but time did not ↑ in CON
Ickmans et al., 2017, Belgium **WAD** University Hospital Laboratory	**WAD** N=26, Age 43.5 (IQR 30.8–47.3), 15 women **Con** N= 26, Age 37.0 (25.8– 53),	D(mos) = Med 28.5 (IQR 6.8-77.3) VAS pre = 57 (IQR 21.5 – 73.8) Unemployed N=10	Submaximal aerobic **cycling** Aerobic Power Index Test & age-predicted heartrate (75%), ↑25Watt /min, ~ 60rpm D: Median 5min (IQR WAD 4-6/ CON 5-6) Workload:125W	PPT (Fisher, Force Dial, Wagner kg/m²) traps & calf Occlusion Cuff Pressure arm, PT & VAS 3/10 TS 10 PPT over Traps & Calf CPM arm cuff 3/10 VAS, TS	N/A	1)No changes in PPT 2)No changes in PPT, Cuff Pressure, TS and CPM; TS (calf) ↓ pre:1(0 - 2.3)/ 0(0 – 2) 3)TS calf 1(0-2)/ 1 (0-1.3) no group difference PPT calf Difference (post-pre exercise) higher in CON 0.3(-0.3-0.7) compared to WAD -0.1(-0.4 – 0)		Study reported EIH as impaired, but no sign. change in PPT pre/post were found in both groups. Therefore, we consider that EIH was not

	15 women		(WAD 100-150/ CON 125-150)	directly after task				produced in both groups.
Smith et al., 2017, Australia **WAD** Laboratory	**WAD** N=21, Age 44.5±10.5, 55% women **CON** N=19, Age 37.4± 10.8, 74% women	NDI=20% Med (IQR 16,31); Grade II WAD; D =66% > 2yrs; Med 5yrs (4,6); TSK= 41 (34,44); PCS =12 (2,19); PDS SSS =10 (5,16); VAS (wk) = 3.4±1.8; 24hrs VAS= 2.9±1.8; CON: sedentary	**Aerobic Bicycle Exercise** Start at 25W, ↑ by 25W/ min to 75%of predicted HR, N=17; D= 30 min, Avg power output (W) WAD 62.8 (47.3,76.8), CON 81.7 (70.8,99.2) **Isometric Wall squat**, 3 min or fatigue, 100° knee flexion, WAD/ CON n=18/17 Peak RPE WAD= 5(3,9) CON= 6(5,8) Time (s) WAD= 106(43,180), CON= 152(122,180)	PPT (Somedic AB, kPa), C5, tibialis anterior; directly after task	CPM Test stimulus heat over Cx (VAS), Conditioning stimulus: cold pressor test	1)No change in PPTs in both groups 2)No change in PPT 3)No difference *All data estimated (Median only)* No further details obtained. *1) PPT neck ↑ 222.92/ 305.21* *2)PPT Tib ant ↑ 351.44/ 492.01* *3) no group differences, ↑ in both groups, both locally and remote Con: neck 315.95/ 401.84; Tib ant 415.34/ 584.66*	Post-test not reported	No changes after cycling in both groups over both local and remote test sites (PPT). Normal EIH (PPT) in people with WAD after Wall squat exercise over local and remote test sites

Van Oosterwijck et al., 2012, Belgium **WAD** Laboratory	**WAD** N=22, Age 38.4±9.2, all women **Con** N=22, Age 37.1±14.6, all women	D (mos) =82.1±90.7 (6-396); 31.8% widespread pain; Session 1: SF 36 bodily =44.2±21.6 ; General health= 32.8 ±19.7; Pain= 50.7± 26.7; Fatigue= 54.2± 25.3; SSS= 42.0 ±20.5	**Ergo-spirometry, Aerobic Power Index test**, ↑ 25W /min to 75% HR WAD= 4.3±.92 min; 116±25W max Con: 4.2±.1.1 min; 115±29W max	PPT (Fisher, Wagner) FDK 40 for control group. FDK 10 in WAD group/ kg) skin web between thumb and index finger, calf, L3, bilateral; directly after task, 1 week between tasks	N/A	1)No local test sites 2)WAD ↓ in PPT over all test sites. Hand: 4.31±1.69/ 3.97±2.03; Lx: 4.67±2.20/ 4.48±2.14, Calf: 4.24±1.52/ 3.94±1.51 3)Group diff as CON ↑ Hand: 5.09±1.72 / 5.32±1.71; Lx: 6.06±2.42/ 6.45±2.48; Calf: 5.57±1.5 /5.77±1.67	WAD group shows a ↓ in all remote test sites after cycling, whereas healthy people showed an ↑ in PPT Self-paced cycling WAD showed PPT ↑ over the calf as CON, but other test sites a ↓ differing from CON
			Self-Paced and physiologically limited **ergometer** test, based on D, HR, and WL WAD WL=41±16W/ D (min)=10.3±6.1 CON: WL= 48±15W/ D=12.7±4.3			1)No local test sites 2)PPT hand/back ↓; calf ↑ Hand: 4.02±1.77/ 3.78±1.95, Back: 4.70±2.20 / 4.60±1.97, Calf: 3.74±1.49 / 3.94±1.70 3)Group diff for Lx/ hand, calf ↑ in both Hand: 4.56±1.59/ 4.78±1.77; Lx: 5.41±2.05 /5.98±2.29; Calf: 5.42±1.78 / 5.80±1.94	
Smith et al. 2020, Australia **WAD** Laboratory	**WAD** N=40, Age 37.3±13.6, 70% women	NDI= 37 CI (33,41); VAS (100mm) =50 CI[43, 56]; D=28 mos (3,120);	**Aerobic Treadmill Walking** based on Aerobic Power Index 75% age-predicted HR, 4min 5-7km/h, ↑2% incline/ 2min D=30 min, Peak power output (W) WAD=306 CI	PPT (Somedic, kPa) Articular pillar C5/6, tibialis anterior pre and directly after exercise	N/A	Authors provided data 1)Cx no changes 268.53±146.13/ 258.93±143.36 =-2.03±18.90% 2)Tib ant no change 377.78± 208.51/ 384.38±217.47 = 3.39±25.45% 3)CON neck: pre: 303.47±110.01/ 317.33±135.18 = 7.78%±30.66 Tib Ant 494.17±203.06/ 550.27±230.56 = 13.31±25.67%	Impaired EIH compared to CON over local and remote test sites after isometric and aerobic exercise in

	CON N=30, Age 40.4±14.3, 78% female	PCL-5= 23 (18,37); TSK= 38(30,44); PCS 12(7,22) all Median (IQR) IPAQ 7 low, 18 mod, 14 high	[229,384], CON= 597[497,697]; RPE (0/10) WAD=4 (IQR 3,5), CON=5(3,6)	4) dorsum right hand (2nd and 3rd metacarpal) Tested pre and **during** exercise at 90 and 180 s for both exercise groups. There was a 15 min rest period between tasks		4)During exercise: Hand WAD 249.56±109.40/during 303.25±113.85 /post 291.75± 138.14 = 22.69±39.39% CON:298.63±104.98/during 387.80±116.01 /post 373.53±111.24 =30.42±28.38%	participants with WAD. For changes during exercise PPT over the hand increased during the exercise for both groups but greater increase in CON
			Isometric Quad-riceps contraction (Biodex) 90°knee flexion MVC 15s (best of 3), 10min rest, till exhaustion /3min at 20-25% of MVC. Peak MVC WAD= 119 [105,134] CON=158 [135,180]; RPE (0/10) WAD& CON=5(IQR 3,7)			Authors provided data 1)Cx 256.60±143.96/ 250.28±149.40 = -.063±30.34% 2)Tib ant 383.88±192.24/ 397.15±193.44 = 6.08±21.17% 3)CON Cx 299.63±106.46/ 335.33±109.21 =14.33±21.84%; Tib ant 501.07± 209.90/ 573.37±225.85 =16.8±21.77% 4) Hand: WAD 264.53±127.78/ during 298.87±118.78/ post 267.78±120.43 = 4.33±30.00%; CON: Hand 315.83±93.29/ during 387.77±113.25/ post 377.20±110.41 =22.98±29.90%	
Vaegter et al., 2016 & 2018 Denmark	**Mixed** N=61, Age 45.4±11.2, 42 women	Primary source of pain: CLBP=37, NP=16 **LS:** D(y)= 5.0 (2-53);	**Bicycling** exercise 15 min 70 rpm, 2 min warm up, resistance ↑ up to 75% Vo2max over 3 min, 10 min at 75%	PPT (Somedic, kPA), traps, quadriceps, biceps brachii	N/A	Authors provided data **PPTs** ↑, but less in people with HS; Cuff PT (kPa) ↑ in LS; Cuff PTOL (kPa) ↑ PTOL limit (cm)↓ in LS; Cuff PTOL↑ in HS; TS↑ only in HS **PPT** Dom. Quadriceps: pre493.82±392.02 /post 574.22±416.92 %=22.38±30.33	Both cycling and isometric exercises led to an increase in PPT indicating EIH in people with chronic msk

Mixed Laboratory	Study subgrouped participants in low (LS) and high pain sensitivity (HS) based on PPTs No CON group Note: local and remote test sites not possible to distinguish	NRS peak 24hrs= 7(3-10); Pain sites N=4 (1-11); Depres-sion HADS 0-21= 8 (0-13); Anxiety HADS= 11(0-15); PCS=22.1 (8.8) **HS:** D (y)= 8.0 (2-40); NRS = 8 (3-10); Pain sites N=5(1-14); Depression = 9 (0-13) Anxiety = 10 (0-16); PCS=27.7 (12.9)	W LS= 97.5(50-210)/ HS=95 (40-185) HR LS= 151(135-167)/ HS= 153(137-170) RPE LS= 15 (11-19)/ HS= 15 (13-18)	Computer controlled cuff algometry (Noci-tech) over lower leg: cuff pressure PT (kPa), Cuff pressure PTOL (kPa), VAS Cuff PTOL limit (cm) TS 10 cuff pressure (2 min) 3 scores (VAS I – III); directly after task		[14.77; 29.99]; <u>Non-dom.:</u> 544.82±421.85 / 621.21 ±419.67 %=23.26±35.93 [14.24;32.27]; <u>Biceps:</u> 297.86± 245.64/ 342.53±270.24 %=25.36±41.60 [14.92;35.80]; <u>Traps</u>: 347.82±244.40/ 388.67±267.76 %=15.43±23.57 [9.51;21.34] **Cuff pressure** PT: 20.70±12.57/ 21.10±13.92 %=6.07 ±40.64 [-4.13; 16.27]; PTOL 53.77±18.70/ 56.14±1942 %=5.26±14.29 [1.68;8.85]; PTOL limit: 7.26±2.84/ 7.33±2.87 %=1.36±32.47 [-6.79; 9.51] **HS: TS** pre: 3.2±2.1/ 4.5±2.3/ 5.2±2.4 post: 4.0±2.3/ 5.6±2.1/6.4±2.3	pain. However, people with a higher pain sensitivity based on their PPT seem to respond with reduced EIH. Findings supported by response to cuff pressure and pain tolerance.
			Isometric exercise dom. quadriceps Based on MVC (different day) 90° knee flexion, 30% MVC for 90s MVC LS= 25.8(11.5) HS= 21.3(9.8)			Authors provided data PPTs ↑, but less in HS; Cuff PT and PTOL, and PTOL limit ↑ in LS; Cuff pressure PTOL ↑ in HS **PPT** <u>Dom. Quadriceps</u>: pre 507.25±402.04/ 558.08±408.22 %=14.23±28.36 [7.11; 21.34]; <u>Non-dom.</u> 544.27±397.06 / 591.55 ±414.82 %=12.44±24.25 [6.26;18.53]; <u>Biceps:</u> 308.73±248.11/ 330.35±267.44 %=10.22±23.46 [4.33;16.11]; <u>Traps</u>:	

						348.35±242.92/ 377.02±248.33 %=10.32±19.35 [5.47;15.18] **Cuff pressure** PT: 20.79±14.16/ 21.63±15.09 %=5.99 ±29.20 [-1.34; 1.34]; PTOL 53.44±18.98/ 56.84±18.52 %=7.74±14.97 [3.98;11.50]; PTOL limit: 7.36±2.75/ 7.04±2.95 %=-5.15±18.86 [-9.88; -0.42]	

Legend: CLBP= chronic non-specific low back pain, CON= Control group; CNP= Chronic non-specific Neck Pain; WAD= Whiplash Associated Disorders; CMSK= chronic Musculoskeletal Pain; LS= Low sensitivity, HS= High sensitivity, D= Duration, yrs=years, mos=months, Med = Median, ± = SD, (range), CI= Confidence interval, SSS= Symptom Severity Score, ODI= Oswestry Disability Index, VAS= Visual Analog Pain Scale, SF-36 = Short Form Survey, HADS= Hospital Anxiety and Depression Scale , PCS= Pain Catastrophizing Scale; NDI= Neck Disability Index, PCL-5=Posttraumatic Stress Disorder Checklist for DSM-5, IPAQ= International Physical Activity Questionnaire, WL= workload, W= Watt, HR = Heart rate, PPT= Pressure Pain Thresholds, CPT= Cold Pain Threshold, PT= Pain threshold, PTOL= Pain tolerance, TS=Temporal Summation, Traps= trapezius, Cx= cervical spine, Lx = lumbar spine, Dom= dominant, SI= Sensory Intensity response, UR= Unpleasantness Response, ↓= decrease/decreased, ↑= increase/ increased; Data which could not be obtained from the authors and had to be estimated were marked as italic and were described as such in the tables

Data extraction for **regional tasks**

Author & Year Country **Spinal Complaint** Setting	**Population**		**Exercise** (Type, duration, intensity, perceived exertion)	**Outcome measurement** (test, device, unit, test sites, time point post-test)		**Results** (**% change**, diff., or pre/post) **significant changes only** 1 Local, 2 Remote (1+2= pooled), 3 CON / comparison		**Summarised findings**
	Sample, Age (yrs) Gender	Participants' characteristics		Mechanical	Blood test/ MDs/ others	Mechanical	Blood test/ MD/ others	
Strom et al. 2012, Strom et al., 2009 a+b Norway, **CNP** Laboratory	**CNP** N=24, Age 39±6 14 women **Con** N=28, Age 33±6 16 women	VAS pre-start 10 ± 7 mm; MCSS= 2.5 (0.3-4.1); Pain D= <12 mos =3; 1-4 yrs =13; 5-10 yrs= 3, >10 yrs= 5 Pain pre active side =10.5(8), inactive 9(7)	**Computer based task** correction of typo-graphical errors 90 min + financial reward, CNP =10±2pages/15 min, 90±19s per page, CON= 11±2/ 82±15s Pain post task active/ inactive side: CNP 57±25/ 46±46 CON 43±28/ 33±27	PPT (Somedic, kPA), Traps & ECRB, active (expos) & inactive side, Sternum. Post-test 15 min after task (30 min not reported here)	N/A	1)↓Traps exposed; pre 343±170/ change β2= -32[-61; -3]; inactive 365±182/ β2= -39[-78; -2] 2)Changes not significant after 15 min 3)No group differences, CON exp Traps 350±154/ β2= -30[-59; -10]] Full analysis based on 30 min, no further data could be obtained N/A		↓ of local PPT, but no change in remote PPT 15 min after a 90 min computer task in CON & CNP

Persson et al., 2000, 2003, & 2009 Sweden **CNP** Univeristy laboratory	**CNP** N=17, Age 47 (24-62) **Con** N=25, Age 44 (21-61) All female hospital cleaners	D(yrs)=7 (range 1.5 - 25); pain drawing; 15/17 palpation traps painful; pain on the day; VAS (0-100mm) pre =42 (range 4-68)	**Endurance test** 1kg belt on wrist, lifting arm to 90°**abduction** till exertion CNP=209 s (124-391s), VAS (mm)= 74 (range 42-97) CON=330s (210-616s) Al RPE=19/20	PPT (Somedic, kPA), 3 sites over Traps, 4 Deltoid, bilateral=14 sites, & 3 Quads (CNP = 20 sites), directly after task (+10 &+20 min not reported here)	N/A	Normalised data 1)Traps exp 230±88=/↑15% CI [1-30] 2)Deltoid exp 261± 102 ↑ 13% CI [0-26] 3)No group comparison, but ↑ over all 4 test sites in CON PPT Exp Trap 273±83/ ↑13% CI [7-19], left Trap 271±77/ ↑6% CI [0-12], exp Deltoid 277±98/ ↑23% CI [11-34], left Deltoid 315±105/ ↑6% CI [2-11] N/A		↑ PPTs over both local and remote sites of the exposed test side only after shoulder endurance task. However, CON group showed an increase on both exposed and un-exposed sites
Christensen et al., 2017 Denmark **CNP** **WAD** Laboratory	**CNP:** N=16, Age 27.6 ±1.8, 10 women	NDI= 18.8 ±1.9; D(yrs)= 5.5 ±1.1; VAS(wk) =3.3±0.9	**Shoulder abduction** 6 series with 8min rest after each of first 3 slow series / break 10min/ 42s after each of last 3 fast series CNP= 25%/ WAD =67% > mini-mally difficult; VAS CNP =4.3± 1.8; WAD=4.8±18	PPT (Somedic, kPA) over Splenius capiti (Cx) Temporalis , ECRB bilateral PPT after task completion reported not after 1st movement series	Pain drawing (quantified area in arbitrary units)	Authors provided data 1)PPT Cx ↓ 179.6±93.9/ 151.0±73.0 2)↓ Temporalis (195.2±84.5/ 172.0± 82.9); ECRB (235.2±112.0/ 195.7±91.7)	Not reported	PPTs after arm abduction showed • Hyper-algesia in CNP • no changes in WAD • EIH in CON
	WAD N=9, Age 33.8±2.5, 7 Women	NDI= 41.3 ±3.8; D(yrs)= 4.5 ±1.1; VAS(wk)= 4.4±0.4				No sign. change		
	Con N=25, Age 29.9±1.6, 17 women					3)Con ↑ over Cx & Temporalis, whereas CNP ↓, no change in WAD CON: Cx: 227.0±80.7/ 253.8±94.9, Temporalis 341.0±82.8/ 374.7±95.2		

Grimby - Ekman et al. 2020, & 2017; Stensson & Grimby, 2019 Sweden **CNP** Laboratroy	**CNP** N= 26, Age 51±5.12, 19 women **Con** N=12, Age 34.6±16 7 women	HADS-Anxiety (n=25) =1.2(0.40); work percentage= 54% (47.2); SMBQ (n=25) =1.6(0.37); Sleep Quality= 3.8(1.3); Pain sites = 10(6.26)	**Arm cycling** 25 laps/min for 30 min with load 100g (women)/200 g (men) ↑ by 200g every 10 min to 500/600g RPE median=14 CNP; CON=10, Model based mean VAS=2.37/4.7 3	PPT (Somedic, kPa) three test sites over Traps, tested 15 min after task (+105 min and next morning not reported here)		Blood test 60 min post task a)DHEA-S (µmol/L) (CNP n=12, Con= 8) b) Anandamid e, OEA, PEA ,SEA,2-AG (all nM), Glutamate (µM) (CNP n=21, CON=11)	Authors provided data 1)Local PPT did not change directly after the task 355.13±202.01/ 338.14±188.73 3)CON did not change 355.94±138.93 / 384.86±145.03, no group difference present *based on RM-ANOVA of data provided	a) DHEA-S showed no significant time & group interaction; a decrease was observed in Con (3.6/2.9 µmol/L). No change in the CNP group (2.2/2.3 µmol/L) b)1+2) No significant diff between pre and post-test 3) Anandamide decreased in CON 0.85(0.14)/ 0.63(0.13) but no between group difference	For PPT pre and post exercise showed no significant difference (CNP & CON) after arm cycling. For Blood tests there was no clear response. Analysis showed altered 24h response considering all test points.
Ghafouri et al., 2013; Gerdle et al 2010 Sweden **CNP** Laboratory	**CNP** N=34, Age 45 (29-60), all women **Con:** N=24, Age 44 (27-56) All women	Inclusion criteria: > 6months, neck pain on the day & tightness in trap. region *Estimated NRS pre 4±1*	**Peg board exercise**, 30 cm apart, moving PEG (11.8g) back and forth 30 cm at 1.3Hz, seated, for 20 min. *Estimated data: NRS post 6±2*	N/A	Micro dialysis traps, NAE: both SEA, PEA levels as antinociceptive markers, 20 min after task		The levels of PEA & SEA in CNP significantly ↑ both pre & post exercise compared with CON. Pre-post diff. within group not significant. 1)PEA 1.75 (0.10–8.60) /2.25 (0.10–6.80); SEA 2.00 (0.10–18)/ 1.45 (0.10–20); 3)CON: PEA 0.65 (0.00–3.37/ 0.50 (0.10–2.30); SEA 0.60 (0.00–2.7)/ 0.55 (0.10–1.8)		Microdialysis showed no difference after a peg board task in CNP and CON. CNP had higher anti-nociceptive parameters.

Larsson et al., 2008 Denmark/ Sweden **CNP** Workplace	**CNP** N= 20, Age 43.8±9.8 **Con** N=20, Age 45.2±11.3 All women with repetitive work	Inclusion criteria: 4/10 NP, 90 days within last yr., but pain < 5/11 body regions. Pain avg working day (mm) = 34.8 CI [20.9]	A **working day** (8hrs) assessed with task exposure based on a score VAS after 1h recovery CNP= 17.2 ± 21.7 mm CON= 4.6 ± 8.3 mm	N/A	Microdialysis traps, Serotonin Glutamate (lmol), Pyruvate (lmol), Lactate, Potassium, Bradykinin (BKN) (pg/ml), Serotonin (5-HT) (nM), Cyto-kine (pg/mL): IL-1b, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IFN—g, GM, CSF, TNF-α. Sample taken pre (120 min), during (every 60min), &60 min post	All mean throughout day; no further details could be obtained. CNP ↑ of glutamate, CNP = 71.28± 42.39 CON 35.60±15.35 (*Estimated data pre/post work* CNP*: 68± 13/ 49±6 CON:42±6 / 36±3*) time effect both groups Pyruvate CNP=186.53 ±88.66/CON= 125.23±62.51; BKN CNP =12759±8717/CON=12165±8904, time effect both groups Cytokine overall time effect both groups, IL-1b ↓ CNP = 303± 184, CON= 380± 247 and IL-8 ↑ CNP =966±739, CON=1053±751 5-HT ↑for CNP, not accounted for work. CNP = 10.58±10.80. CON= 2.19±1.19/ post recovery CNP = 9.24± 8.32 CON=1.45±2.87.	Microdialysis study over a working day ↑ [5-HT], glutamate, & pyruvate in CNP could indicate activated peripheral muscle nociceptive processes. Analysis does not answer EIH question.
Gerdle et al., 2008a+b; Rosendal et al., 2004 & 2005 Sweden **CNP & WAD** Laboratory	**CNP** N=19, Age 41(21-61), all women	Start CNP after start of work task (mos)= 66(7-216) Baseline VAS(mm) =29±5	20 min repetitive low-force arm work **(Peg board)** (moving short wooden pegs (23g) 1Hz, 30cm, seated, Perceived exertion rate (0-9) *estimated data*	N/A	Microdialysis traps: Bradykinin (BKN) (pg/ml), Kallidin (pg/ml), Potassium (K+) (mmol/l), LDH (U/ml), Collagen Turnover (%), Plasma Creatine Kinase, RR (%)and Interstitial Lactate (mmol/L), Lactate dehydrogenase (LDH) (U/ml)Pyruvate	Data represent baseline/ exercise/1st recovery, no further details could be obtained. ↑BKN *estimated 3312.25±770.8/8039.53±2569.17/6857.71± 2877.5* Kallidin ↑ *estimated 385.35±121.4/ 800.20±242.8/ 563.79±202.3* Interstitial lactate ↑ *estimated 4.42±0.3/ 5.06±0.4/ 4.75±0.3* Pyruvate ↑ *estimated 180.83±14.4/216.53±20.2/200.30±16.4* ↑Glutamate] *estimated 47.37±3.7/ 64.25±5.2/ 49.14±3.4*	Microdialysis study. After Peg Board task CNP showed metabolic alterations: Increase in lactate, pyruvate, and potassium and

			CNP=6.39±0.6 *CON =1.54±0.3* *WAD: no data provided* Pain VAS (mm) post exercise CNP =70±5; WAD =71±24; CON =7±2		(µmol/L), Glutamate (µmol/L), serotonin (5-HT), Interleukin-6 (IL-6) (pg/ml), WAD only: BKN (pg/ml), Kallidin (pg/ml), Lactate (mmol/L), Pyruvate (µmol/L), K+ (mmol/l), Interleukin-6 (IL-6) (pg/ml), Glutamate (µmol/L), Serotonin (5-HT) Data sample every 20 min at baseline (140-160 min after catheter insertion), during the task (160-180 min), and 10 min after task / 1st recovery (180-200 min) & 2nd recovery (280-300 min, not reported here)	K+ *estimated 4.14±02/* 4.82±0.52/ *estimated 4.55± 0.1* IL-6 ↑ *estimated 1530.16±203.5/ 3115.68±570.0/ 2096.55±393.4* RR Lactate ↑ pre 20.8±.8 /post 22.0±1.0	increased levels of algesic substances (glutamate) compared to CON. Higher increase in BKN after exercise. However, baseline differences existed & the mechanism of EIH is not clearly evaluated. For WAD peripheral nociceptive processes are activated. Higher IL-6, and lower Pyruvate with different responses in
	WAD N=22, Age 36(24-45), all women	Inclusion criteria ≥WAD Grade II, and 6mos, Baseline VAS(mm)= 53±4				BKN ↑*estimated 3106.72±392.5/ 4545.45±822.1/ 3569.17± 719.4* Kallidin ↑ *estimated 186.71± 55.2/ 778.10±143.5/ 309.97±92.0* K+ 4.18 ± 0.11/4.48 ± 0.11/4.27±0.10 Pyruvate 91.7±10.0/ 108.8±10.6/ 140.6±16.3 Interstitial Lactate: 2.83±0.24/ 3.03±0.42/2.81±0.31 RR [3H]- collagen 47±9.0%	
	Con N=20, Age 36(26-56), all women	CON Baseline VAS= 0±0				BKN ↑ *estimated 2130.43±411.1/ 3569.17±822.1/ 2849.80±668.0* Kallidin ↑ *estimated212.46±55.2/ 347.65±55.2/ 214.31± 40.5* ↑[K+] 4.17 ± 0.05/ 4.46 ± 0.07 /4.23±0.23 or 4.14±0.07¶ ↑[IL-6] (pg/ml) 1760 ± 258/2920 ± 497/2677±460 ↑Glutamate 36.7 ± 4.1/45.9 ± 4.2/ 44.3±5.9 Pyruvate: 135.7±11.8/ 155.4±13.9/ 132.1±12.6 RR Lactate ↑ CON=19.4±1.0/21.5± 0.9; interstitial Lactate 3.11±0.29/ 3.39±0.36/ 3.12±032 No group diff between CNP & CON in RR Lactate, but in interstitial lactate	

						↑LDH only combined CNP & CON 0.99±0.66 / 1.84±2.23 RR [3H]- collagen 62± 8.7%, significantly higher than in WAD	Lactate, Kallidin, and Pyruvate compared with CON were found

Legend: CNP= chronic non-specific neck pain, CON= Control group; WAD= Whiplash Associated Disorders, ± = SD, (range), SMBQ=shirom-Melamed Burnout Questionnaire, NDI= Neck Disability Index, MCSS= musculoskeletal Complaint Severity Scale, , D= Duration, yrs=years, mos= months, RR= relative recovery, NAE=N-Acylethanolamine, PEA=N-Acylethanolamine, SEA=Nstearoylethanolamine, OEA= oleoylethanolamide; PEA= palmitoylethanolamide; SEA= stearoylethanolamide; AG= arachidonoylglycerol, DHEA-S Dehydroepiandrosterone, sulphated form, ECRB= Extensor Carpi Radialis Brevis, Traps=trapezius, Quads= quadriceps, exp= exposed, Diff= Difference, ↓= decrease/decreased, ↑= increase/ increased, β2= Estimated regression coefficients and 95% confidence intervals (CI) based on the fitted linear models of pressure pain threshold (PPT, kPa) changes from before starting the computer work to 15min after, ¶reported equivocal in publication, exp= exposed test side; Data which could not be obtained from the authors and had to be estimated were marked as italic and were described as such in the tables

Appendix 12 Risk of Bias Results Chapter three

Author & Year, Self-reported study design	Selection ****					Comparability **			Exposure/ Outcome ***				**Overall Risk of Bias**
	Case definition adequate	Representativeness of the cases	Same selection of controls and cases	Definition of controls	*	Controlled for Age	Controlled for gender	*	Description of EIH outcome measurement	Identical for outcome and intervention	Description of task	*	
Christensen et al., 2017 Cross-sectional	* Yes, NDI, VAS, duration	* Yes, chart provided	Not reported, matched for gender/ age	*Yes, healthy and questionnaire	3	* Age matched	*Gender matched	2	* Yes, reference for further details	* Yes	* Yes, standardised protocol, well described	3	GOOD Questionable to produce EIH as short task & long breaks
Falla et al., 2014 Not stated	* Yes, duration, ODI, VAS	GP, PTs and advertisement in popular press	Not stated	* Yes, questionnaire	2	* Age matched	*Gender matched	2	*Yes, PPT	*Yes	*Yes, lifting task 5kg	3	FAIR Fairly short task
Gerdle et al.,2008a,b Rosendal et al. 2004 Rosendal et al., 2005 A micro dialysis study/ in-vivo	Only for TM: sick-leave, NMCQ, WAD: VAS only	TM and WAD from same register, no further details given	Local pain & rehabilitation centre (TM and WAD), but adverts for controls, time point unclear	*Yes, but not able to match for work	1	Not stated, control group before WAD	*Only female	1	*Yes, micro dialysis following protocol	*Yes	*Yes, Peg board	3	POOR Questionable to produce EIH as minimal task and outcome

Ghafouri et al., 2013 Gerdle et al., 2010 Pilot com-parative cross-sectional	No, screening & examination but not reported	Recruited via local daily newspaper	*Yes, recruited via local daily newspaper, no further description	*Yes, no further description	2	Yes, but not prior to study?	* Only female	1	*Yes, microdialysis	*Yes	Peg board exercise, not stated in pilot, no further reference	2	FAIR Questionable to produce EIH? severity/ outcome?
Grimby-Ekman et al., 2020; Grimby-Ekman et al., 2017; Stensson & Grimby-Ekman, 2019 Not stated, except pilot	*Yes, NRS, pain sites, HADS, Sleep and Burn Out Symptoms	Recruited from physiotherapy clinics and university hospital	No university, but also friends and family of the symptomatic group	*Yes, no more than 3 days with pain in last 12 months	2	No	No	0	*Yes, PPT as in Persson blood test as well (1hr after task)	* Yes	*Yes, arm cycling	3	FAIR Recruitment and case definition only
Hoffman et al. 2005 Not stated	*Yes, duration, ODI	Not stated, n=8	Not stated	*Yes, no previous history	2	Not stated 40(10)/ control 34(8)	Not stated LBP 4 male/4 female /control 7/3	0	*Yes, tested for repro-ducibility	**No**, baseline assessment for Control only	*Yes, maximal cycling text	2	FAIR Unclear on cases, no exercise for control
Ickmans et al., 2017, Case-control/ cross-sectional	*Yes, WAD, VAS, duration	Hospital, adverts in patient support group	No, some matched with patients, and similar adverts	*Yes, pain free, inactive, no chronic disease	2	* Age matched	*Gender matched	2	*Yes, reproducible PPT, CPM, TS, Occlusion cuff Pressure	* Yes	* Yes, ergometer, submaximal aerobic exercise	3	FAIR Lack in reporting recruitment only

Kemppainen et al., 1998, Not stated	No, only in-flight (neck) pain attacks	no further details given, same air force	*Yes, same air force	*Yes, no experience	2	Age likely, not provided	*Only male	1	*Yes, cold pressor test	*Yes	No, unclear on exact times	2	FAIR, Severity unknown, poorly reported
Kuithan et al., 2019 Cross-sectional observa-tional	*Yes ODI, VAS, PCS, FABQ, SF-36, DASS	University population, self-reporting only	* Yes, same population and advertising	*Yes, no history	3	Yes, but not prior to study	Yes, but not prior to study	0	*Yes, reproducible for PPT & Thermal tests, location of TS?	*Yes (3/21 LBP could not finish task)	*Yes, reproducible, rotational lifting task	3	GOOD, University population
Larsson et al, 2008 Not stated	Yes, clinical examination and more assessed, not reported	Four industrial companies contacted	*Yes, corresponding work	*Currently no reporting of symptoms only	2	No test TM 43.8(9.8)/ control 45.2(11.3)	*Only female	1	*Yes, micro dialysis	Unsure, but corresponding tasks	No, 8h as regular working day	1	POOR Questionable to produce EIH as measured pre/post workday
Meeus et al., 2010 Experimental	*Yes, ODI, Vas, SF-36	University hospital and Physiotherapists	Similar, but two different cities	*Yes, no current confirmed questionnaire	2	Yes, tested, but not prior to study	Yes, tested, but not prior to study	0	*Yes, NO and PPT	*Yes (some could not finish the task Control=2, LBP=4)	Yes, cycle ergometer, but limitation stated difficulty to standardize	2	FAIR Lack in reporting recruitment only

Persson et al., 2009, Persson et al., 2003, Persson et al., 2000 Before-after trial/ corre-lative	*Yes, duration, pain drawing, VAS	No, contacted participants based on prior study 1 year ago, hospital cleaners 19/25 accepted	Unclear, different professions for control	*Yes, no pain last three months	2	Control group first, not matched	*Only female	1	*Yes, PPT	No, slight modification in outcome (PPT) CNP + PPT Quadriceps, and additional follow up	*Yes, static endurance task	2	FAIR Fairly short task was ~209 (Pain)/330 seconds (Con), confusing reports between papers (outcome)
Smith et al., 2017 Cross-sectional pre-post-	*Yes, NDI, duration, VAS, TSK, PCS	Whiplash Grade II no further information	Not mentioned	*Yes, no history and questionnaire	2	Control significantly younger	Yes, but not prior to study	0	*Yes, clear for local pain sensitivity and over leg, thermal pain thresholds	*Yes	*Yes, ergometer, standardised submaximal test & wall squat	3	FAIR Lack in reporting recruitment only
Smith et al. 2020 Pre-post study	*Yes, NDI, PCS, TSK, VAS, PCL-5, duration, TSK, PCS	Healthcare practitioners, advertisement, patient database	No, local university, word-of-mouth, and advertising	*Yes, no history in last 12 months	2	Not prior to study	Not prior to study	0	* Yes, clear description	*Yes	* Yes, standardised treadmill & isometric programme	3	FAIR Lack in reporting recruitment only
Strom et al., 2012,	*Yes, muscle	Advertising in local	*Yes, advertisem	*Yes, working	3	Not tested,	Recruit-ment	0	PPT location	*Yes	*Yes, standardi	2	GOOD

Strom et al.,2009a, b Not stated	complain severity score, VAS, duration	papers and the internet	ent local papers and internet PC workers	and healthy		control significant younger, covariate included	unclear not prior, not tested		only as muscle, not direct location		sed computer office task.		Questionable to produce EIH as computer task
Van Oosterwijck et al., 2012 Controlled experi-mental	*Yes, duration, CWP, SF-36, SSS	Red cross emergency unit over 6 months, all contacted, but no numbers	*Yes, friends and relatives of cases for control	*Yes, questionnaire and no relevant recent Hx	3	*Yes, age matched	*Only female	2	Different algo-meters to adjust for group changes	*Yes	*Yes, submaximal exercise stress test and self-paced well described and references	2	GOOD Lack in reporting recruitment
Vaegter et al., 2016, Vaegter et al., 2018, Experi-mental pre-post within-subject	*Yes, chronic MSK pain, duration, VAS, pain sites	recruited from multidisciplinary pain clinic, no numbers	No control group. However, they report of previously published similar study in healthy		1	No control group. However, they report of previously published similar study in healthy		0	*Yes, PPT, CPT, Cuff algometry	No control group	*Yes, both ergo-meter & isometric contraction of Quadriceps muscle	2	POOR Mixed chronic MSK pain, mainly lack of control group & recruitment

Abbreviations: *NDI= Neck Disability Index; VAS= Visual Analog Scale; EIH= Exercise Induced Hypoalgesia; ODI= Oswestry Disability Index; LBP= Low back pain; GP= General Practitioner; PT= Physiotherapy; PPT= Pressure Pain Threshold; TM= Trapezius Myalgia; NMCQ= Nordic Ministry Council Questionnaire; WAD= Whiplash Associated Disorders; HADS= Hospital Anxiety and Depression Scale; CPM= Conditioning Pain Modulation; FABQ= Fear Avoidance Beliefs Questionnaire; PCS= Pain Catastrophizing Scale; DASS= Depression Anxiety Stress Scales; SF-36= Short Form Health Survey; TS= Temporal Summation; CNP= Chronic neck pain; TSK= Tampa Scale of Kinesiophobia; PCL-5= The Posttraumatic Stress Disorder Checklist; CWP; SSS= Symptom Severity Score; MSK= musculoskeletal; CPT= Cold Pain Threshold*

** highlights that the criteria is fulfilled.*

PK and NHR were part of the publication Kuithan et al (2019), as the other reviewer (AD) was not involved in this publication, it was decided against another neutral reviewer, as internal bias

Appendix 13 Ethical Review, Risk assessment, Consent Form, Patient Information Chapters four, five, and six

UNIVERSITY OF BIRMINGHAM
APPLICATION FOR ETHICAL REVIEW

Who should use this form:

This form is to be completed by PIs or supervisors (for PGR student research) who have completed the University of Birmingham's Ethical Review of Research Self Assessment Form (SAF) and have decided that further ethical review and approval is required before the commencement of a given Research Project.

Please be aware that all new research projects undertaken by postgraduate research (PGR) students first registered as from 1st September 2008 will be subject to the University's Ethical Review Process. PGR students first registered before 1st September 2008 should refer to their Department/School/College for further advice.

Researchers in the following categories are to use this form:

3. The project is to be conducted by:
    - staff of the University of Birmingham; or
    - postgraduate research (PGR) students enrolled at the University of Birmingham (to be completed by the student's supervisor);
4. The project is to be conducted at the University of Birmingham by visiting researchers.

Students undertaking undergraduate projects and taught postgraduate (PGT) students should refer to their Department/School for advice.

NOTES:

- An electronic version of the completed form should be submitted to the Research Ethics Officer, at the following email address: aer-ethics@contacts.bham.ac.uk. Please **do not** submit paper copies.
- If, in any section, you find that you have insufficient space, or you wish to supply additional material not specifically requested by the form, please it in a separate file, clearly marked and attached to the submission email.
- If you have any queries about the form, please address them to the Research Ethics Team.

☐ **Before submitting, please tick this box to confirm that you have consulted and understood the following information and guidance and that you have taken it**

into account when completing your application:

- **The information and guidance provided on the University's ethics webpages (https://intranet.birmingham.ac.uk/finance/accounting/Research-Support-Group/Research-Ethics/Ethical-Review-of-Research.aspx)**

- **The University's Code of Practice for Research (http://www.as.bham.ac.uk/legislation/docs/COP_Research.pdf)**

UNIVERSITY OF BIRMINGHAM APPLICATION FOR ETHICAL REVIEW	*OFFICE USE ONLY:* Application No: Date Received:

24. TITLE OF PROJECT

Investigating the analgesic effect of walking and resistance exercise in healthy adults

25. THIS PROJECT IS:

University of Birmingham Staff Research project ☐
University of Birmingham Postgraduate Research (PGR) Student project ☒
Other ☐ (Please specify):

26. INVESTIGATORS

g) PLEASE GIVE DETAILS OF THE PRINCIPAL INVESTIGATORS OR SUPERVISORS (FOR PGR STUDENT PROJECTS)

Name: Title / first name / family name	Professor Deborah Falla
Highest qualification & position held:	Chair in Rehabilitation Science and
School/Department	School of Sport, Exercise and Rehabilitation
Telephone:	[redacted]
Email address:	[redacted]

Name: Title / first name / family name	Dr. Alison Rushton
Highest qualification & position held:	Senior Lecturer
School/Department	School of Sport, Exercise and Rehabilitation
Telephone:	[redacted]
Email address:	[redacted]

Name: Title / first name / family name	Dr. Nicola Heneghan
Highest qualification & position held:	Lecturer
School/Department	School of Sport, Exercise and Rehabilitation
Telephone:	[redacted]
Email address:	[redacted]

h) PLEASE GIVE DETAILS OF ANY CO-INVESTIGATORS OR CO-SUPERVISORS (FOR PGR STUDENT PROJECTS)

Name: Title / first name / family name	
Highest qualification & position held:	

School/Department	
Telephone:	
Email address:	

i) In the case of PGR student projects, please give details of the student

Name of	Pauline Kuithan	Student No:
Course of	PhD	Email
Principal	Prof. Deborah Falla	

Name of student:		Student No:	
Course of study:		Email address:	
Principal supervisor:			

27. ESTIMATED START OF PROJECT Date: 01/07/2018

ESTIMATED END OF PROJECT Date: 31/01/2020

28. FUNDING

List the funding sources (including internal sources) and give the status of each source.

Funding Body	*Approved/Pending /To be submitted*
Nil	

If you are requesting a quick turnaround on your application, please explain the reasons below (including funding-related deadlines). You should be aware that whilst effort will be made in cases of genuine urgency, it will not always be possible for the Ethics Committees to meet such requests.

29. SUMMARY OF PROJECT

Describe the purpose, background rationale for the proposed project, as well as the hypotheses/research questions to be examined and expected outcomes. This description should be in everyday language that is free from jargon. Please explain any technical terms or discipline-specific phrases.

The purpose of this project is to firstly investigate the feasibility of conducting a trial with six exercise sessions to investigate changes in pain sensitivity in healthy individuals.
The secondary purpose is to assess the reliability of the effects of endurance or resistance exercise on pain processing, known as exercise induced hypoalgesia (EIH).

Background rationale

- Pain processing

Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such

damage"(Pain, 2017). If pain persists, both peripheral and central sensitisation can occur. These terms refer either to local or central changes in the pain processing pathways, leading, amongst other effects, to reduced pain thresholds and/or higher pain intensities (hyperalgesia) (Pain, 2017). This can be caused by reduced endogenous activity of descending inhibitory pathways as for example the release of endorphin- and opioid-like substances affecting pain sensitivity and perception. However, factors influencing pain modulation are still not fully understood in healthy individuals. The findings can then contribute to improve care for patients with chronic musculoskeletal pain.

- Quantitative Sensory testing (QST)

Pain processing can be assessed using Quantitative Sensory Testing (QST), a relatively new approach, which is well established to evaluate EIH and sufficient reliability has been shown (Balaguier et al., 2016; Costa et al., 2017; Graven-Nielsen et al., 2015; Marcuzzi et al., 2017; Moloney et al., 2012; Potter et al., 2006). QST involves different stimuli, such as thermal or pressure stimuli, applied to the participant, who then indicates the point at which their pain threshold or tolerance is met. Another more dynamic measurement is temporal summation, where a series of moderately painful stimuli are applied and changes over time are evaluated. QST can help to distinguish between different impairments of pain processing as different stimuli are transmitted via different pathways (Rabey et al., 2015; Rolke et al., 2006b; Vaegter and Graven-Nielsen, 2016). Another certified measurement which is established in pain research, but not yet in EIH, is the pain withdrawal reflex (von Dincklage et al., 2009; von Dincklage et al., 2013). The test provides an objective measurement of a muscular response to a small electric stimulus applied to the skin.

- Exercise induced hypoalgesia (EIH)

Exercise leads to temporary hypoalgesic changes (lower) in pain sensitivity, which has been demonstrated in the form of increased pain thresholds following exercise (Naugle et al., 2012). That means for example, that more pressure can be applied before the pressure turns into pain. The decreased pain sensitivity could be explained by activated central inhibitory pathways, also known as endogenous pain inhibition (Lima et al., 2017). Research has shown equivocal results, but has indicated that the extent of EIH depends on physical activity status, with greater activity facilitating EIH; psychological state; and ethnicity (Brellenthin et al., 2017; Naugle et al., 2014a; Stolzman et al., 2015; Umeda et al., 2016). In healthy people, the effect of various intensities of aerobic and strength exercise, i.e. isometric exercise, demonstrated an extended period of increased thresholds. This endogenous pain inhibition could be used for people with chronic pain, as pain processing is affected in some of those. However, research to date has shown varying effects for EIH and the exact type and intensity of exercise to best induce EIH in healthy individuals remains unclear. Some evidence suggests a greater effect following isometric and high intensity exercises (Black et al., 2017; Gajsar et al., 2017; Koltyn, 2002; Micalos and Arendt-Nielsen, 2016; Naugle et al., 2012; Vaegter et al., 2015). Other research supports a dose-response relationship (Naugle et al., 2014b), but whether only local or additional remote changes after moderate activity occur remains open.

Reliability and reproducibility of EIH

No previous study has evaluated the reproducibility of EIH over multiple sessions with the same intervention. Therefore, it is important to investigate if the effects of EIH remain stable over sessions, or if the effects will adapt over time due to habituation. As the effect of EIH could be used for rehabilitation of chronic musculoskeletal disorders, we first need to understand how healthy people respond to an exercise programme of either strength or endurance over several weeks.
So far only two studies have conducted two identical sessions and analysed the effects of EIH (Vaegter et al., 2018a; Vaegter et al., 2018b) showing a trend for an even greater amount of EIH in the second session. However, a clinical setting usually involves an average of around 6 sessions as for example for people with low back pain (Hill et al., 2011). We chose 3 weeks to avoid any training effects as well as additional confounders (Baumgartner, 2000). In addition, this task mimics exercise and could contribute to implementation of exercise to change pain sensitivity in daily life and could be feasible to lead to behavioural changes in the future referring to the first objective of the study. Analysis of data will allow a power analysis and further repeated measures analysis might detect if fewer than six sessions would be sufficient for the second objective. However, to our best knowledge no previous literature can inform this decision.

Aims and objectives
Aim 1: To investigate the feasibility of conducting a trial with six exercise sessions to investigate changes in pain sensitivity in healthy individuals.

Objectives:

- to evaluate if exercise interventions and outcome measurements are appropriate (acceptance and appropriateness)
- to examine the distribution of QST scores and their standard deviation as a base to inform sample sizes for a future adequately powered RCT
- to find indicators for possible correlation and relationship in the results

Aim 2: To assess the reliability and stability of the effects of EIH with a repeated endurance or a resistance exercise protocol on pain processing
Objectives:

- to investigate if the effects of EIH are reproducible and stable over multiple sessions
- to evaluate if there is a difference between each sessions and if habituation occurs over time

Expected outcomes

If the study is feasible we will take this study to the next stage, a definitive trial in healthy participants, and the aim to adapt this design to a symptomatic population in the future.
Furthermore, the results from the current study may inform further research to shape treatment programs for participants with musculoskeletal disorders and

chronic pain. I.e. we expect that the results of the feasibility study, independent from the results of the reliability study, will allow us to better interpret the data and inform and justify adaptation to the programme.

30. CONDUCT OF PROJECT

Please give a description of the research methodology that will be used

Design

Feasibility trial with two intervention arms following the CONSORT guidelines (Eldridge et al., 2016) with an embedded reliability study using a test-retest design following the GRRAS guidelines (Kottner et al., 2011). This is in line with the UK Medical Research Council framework for complex interventions, where feasibility trials will be conducted before a randomised control trial.

Location

CPR Spine laboratories of the School of Sport, Exercise and Rehabilitation Sciences.

Allocation

Participants will be randomly allocated via a computer generated sequence to either an endurance or a resistance exercise training intervention. Participants and researchers will be aware of the allocation and cannot be blinded.

Overview of intervention

Participants will attend 6 sessions spread over 3 weeks with a minimum of 48 hrs rest in between each session to provide rest and recovery time and to minimise learning effects (see figure1). The first session will be used to familiarise participant with the test procedures and to design each participants' individually adjusted intervention based on their individual heart rate or maximum voluntary contraction strength. The following sessions will be identical to each other and will be calibrated to the functional capacity of each participant using results from their first session.

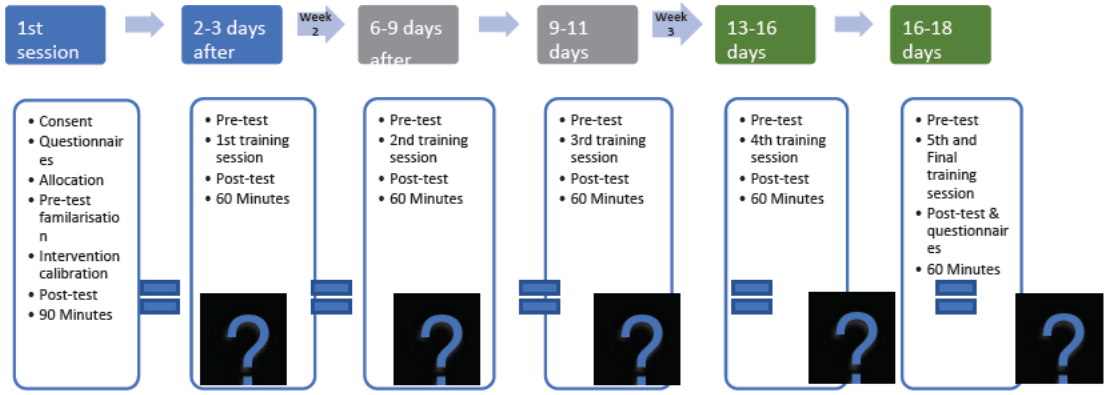


Figure 1 Three-week overview

Exercise Intervention

A. Endurance exercise intervention

All endurance components will be conducted on the same treadmill (The Biodex Gait Trainer 3) and will be controlled with a heart rate monitor.

Adjusting walking intensity (1st session)

The participant will begin walking on the treadmill at their preferred speed. The speed will be increased every 2 minutes, initially to the nearest whole or half km then consequently by 0.5 km/h. If brisk walking cannot be maintained (expected above 7km/h) an additional increase in treadmill gradient will be added every 2 minutes by 2.0%. The test will be terminated when the participant wants to stop or when >70% of heart rate is constantly maintained for a minimum of 2 minutes. Using the Karvonen equation (Camarda et al., 2008) we have selected to use moderate-to-high intensity of 75% ± 5% since we aim for the subject to partake in brisk walking for 15 minutes.

Training session (2nd – 6th session)

Participants will start with a two-minute warm-up at their preferred speed. According to the protocol above, participants will walk for 15 minutes at their designated speed, identified within the first session. The speed will be in- or decreased if their heart rate is not within the targeted interval (75% ±5% for more than 30 seconds).

B. Resistance exercise intervention

A functional dynamometer (Primus, BTE Technologies, US) will be used to implement the resistance exercise. Reliability of the isokinetic function of this device has been established (Torpel et al., 2017). In this protocol we use participants' individual data and adapt this to a standardised, but individually tailored exercise protocol.

Adjusting resistance training (first session)

Measurements to adjust the device to each individual will be taken such as height, hip width to adjust the starting position and trunk range of motion.

The task starts at knee level on the left side and ends at chest level on the right hand side or vice versa. The participant returns to the start position in the same way. The pictures demonstrate the start, mid and end positions. To detect maximal isometric strength the maximum of 3 consecutive readings from the mid position will be used.

Picture 1: Start, middle and end position of the task with the Primus RS

Resistance will be produced by the device. Participants will be familiarised with the protocol to ensure correct performance with emphasis on the trunk muscles.

Training session (2nd – 6th session)

During each session the participant will start with a two-minute warm-up simulating the movement as shown in the picture above without any resistance.
The 15-minute exercise will be divided into four sets (alternating two on each side) with a small break to change settings on the device in between.
The movement will be based on individual maximal trunk strength and consist of 8 cycles of the movement pattern above consisting of the following phases:
1) concentric lifting to the middle
2) isometric (hold) in the middle position
3) concentric lifting to the end position
4) isometric (hold) in the end position
5) eccentric return to middle position
6) isometric (hold) in the middle position
7) eccentric return to start position
8) rest

Measurements

Tests will be conducted by the same researcher during each session, Pauline Kuithan, M.Sc. Sport Physiotherapy and Master in Manual Therapy, who is an experienced physiotherapist with over ten years of clinical experience and expertise in quantitative sensory testing.
All measurements will be done as follows:

Questionnaires

- Demographic details (ethnicity, age, height, weight, resting heart rate, education level and occupation).
- SF-36 v2 Health Survey for the general health status of the participant (Brazier et al., 1992; Jenkinson et al., 1999).
- International Physical Activity Questionnaires (IPAQ) (Booth, 2000).
- Mood questionnaire (attachment 4).
- Questionnaire on expectations of exercise - pre- and post-study adapted from Resnick et al. (Resnick et al., 2000) (attachment 5).
- A printed Borg Scale (BS) to rate their level of perceived exhaustion will be provided (Borg, 1982).

Quantitative sensory testing

These tests or variations thereof have been used and reviewed in previous projects within the school without any complications (ERN_16-1389) and (ERN_17-0893). The conducting researcher and physiotherapist is experienced in the test procedures, and is in constant communication with the participant. Both the researcher and participant are able to stop each test at any time.

Thermal pain threshold testing (heat and cold)
For thermal testing (heat and cold) the TSA-II NeuroSensory Analyzer thermal stimulator and accompanying software (Medoc Ltd, Israel) will be used utilising a 30 x 30mm Peltier thermode. For heat pain threshold, temperature will be gradually increased from a baseline temperature of 32^0C until the maximum temperature of 50^0C. For cold pain threshold, temperature will be gradually reduced from the baseline temperature of 32^0C to a minimum temperature of 0^0C. Two measurements each will be conducted in a randomised order over the lumbar area on the right side and at the thenar eminence on the right side. To avoid interaction with the thermal temporal summation (described below), thermal thresholds will be taken first.

Pressure pain threshold (PPT) and pressure pain tolerance
PPT will be tested with a pressure algometer based on previous established and approved protocols. The algometer will be applied statically and dynamically perpendicular to the skin at a constant rate of pressure increase. Once pain threshold has been identified via the participant pushing a button, the device will be removed. Two consecutive measurements will be taken at the same site.
The following sites will be tested on the right site or bilaterally in a randomised order:

- 8 points over the lumbar erector spinae muscle (bilaterally over lower back)
- Mid-point of the muscle belly of tibialis anterior (lower leg)
- Mid-point of the muscle belly of extensor carpi radialis (forearm)
- Mid-point of the upper trapezius (upper back/ neck)

In addition, another two consecutive readings on each side over the lower back and one over the right forearm will be conducted to assess pressure pain tolerance. The participant identifies the maximum level of discomfort that can be tolerated and the device will be removed immediately. In contrast to thresholds this modality has been proofed to better detect changes in pain sensitivity after

exercise (Baiamonte et al., 2017). The same procedure will be conducted on a remote site. We will refrain from further pain tolerance testing so as not to interfere with the effects of EIH (Gajsar et al., 2018).
Final selection of equipment will be based on equipment availability at the point of testing.

Temporal summation (thermal)
After familiarisation consisting of a pre-test of five stimuli on the contralateral side, ten consecutive heat pulses will be applied on the right forearm and the lumbar region. For each pulse completed a verbal pain rating score from 0-100 will be taken. This is a similar protocol to that which we have used previously, adapted from (Owens et al., 2016). This test might interfere with the other results, this test will always be conducted last.

Temporal summation (pressure)
Ten consecutive pressure pulses will be applied unilaterally over the lumbar area. We will use a previous established protocol with a self-developed software. For each pulse completed, the pressure will be gradually increased at a rate of $2N/Cm^2/s$ to the peak value and maintained at this value for one second before being released at the same rate. There will be a 1 second interval between each pulse. Pain intensity will be taken using the numerical rating scale (0 being no pain to 10 being pain as bad as could be) for each pulse.

Pain Withdrawal Reflex
A surface electrode on the foot will produce a series of short and low intensity electrical impulses. If a physiological threshold is reached within the participant a muscular 'twitch' response will be detected via a different surface electrode placed on a muscle belly on the lower leg. The stimulus is a similar intensity to a static shock from touching a door, and the muscular response is more akin to a twitch than a big movement. The procedure has been successfully tested in multiple studies both in healthy and symptomatic people, and does not cause any damage to the skin. Participants will rate the intensity of each stimulus. The researcher is experienced in applying this test and patients can stop the test any time during the procedure.

Data Analysis
Data will be analysed with IBM SPSS Statistics 23.
1. For descriptive statistics we will present a flow chart for recruitment, and baseline demographics of both groups. For results we will report the mean or median, standard deviation and 95% confidence interval of each measure for each session. We will report data from the questionnaires and correlate those with the QST results (difference pre/post-test of one session) and with the exercise questionnaires for each session, and perceived exhaustion (Borg Scale) using non-parametric correlation. We will explore willingness, adherence and experience in a qualitative approach.
2. For reliability and stability of the results, data will be check for normality and a repeated measures ANOVA will be performed for each measurement method for the six sessions using a 95% confidence interval (CI). Considered factors for

each test will be intervention (endurance/ strength), session (1-6), pre/post, and location (local/remote). Squared partial eta will be calculated for effect size. This will be followed by a post hoc analysis. Furthermore, we will calculate intra-class correlation coefficients (ICC) for intra-tester reliability and limits of agreement for between test day reliability (Bland and Altman, 1999). Pearson's correlation coefficients will be conducted for the relationship between QST outcomes and questionnaires. Level of statistical significance will be set as $p<0.05$.

31. DOES THE PROJECT INVOLVE PARTICIPATION OF PEOPLE OTHER THAN THE RESEARCHERS AND SUPERVISORS?

Yes ☒ No ☐

Note: 'Participation' includes both active participation (such as when participants take part in an interview) and cases where participants take part in the study without their knowledge and consent at the time (for example, in crowd behaviour research).

If you have answered NO please go to Section 18. If you have answered YES to this question please complete all the following sections.

32. PARTICIPANTS AS THE SUBJECTS OF THE RESEARCH

Describe the number of participants and important characteristics (such as age, gender, location, affiliation, level of fitness, intellectual ability etc.). Specify any inclusion/exclusion criteria to be used.

40 healthy participants will be recruited for this study, aiming for 20 in each group. This is based on the reliability study rather than the feasibility aspect of the study (Walter et al., 1998).

Inclusion criteria:

- Both men and women are eligible for the study.
- The age range will be restricted to 18 - 55 years to limit age effects on physical performance
- Participants must have the capacity to give the consent at his/her own will.
- Participants will be considered as pain-free and included if they have no relevant history over the last two years of back or limb pain or injury that limited their function and/or required treatment from a health professional.

Exclusion criteria:

- Concurrent systemic, rheumatic or neuro-musculoskeletal disorders which may confound testing or are currently pregnant.
- Current musculoskeletal pain or pain related to trauma or history of musculoskeletal pain in the last 12 months that required treatment from a health care practitioner
- On average more than 90 minutes of vigorous physical activity per day or professional high-level competitive athletes.
- Cardiorespiratory disorders such as severe asthma or exacerbation, which affects exercise performance, as well as cardiac problems. This includes medications to control the blood pressure.

33. RECRUITMENT

Please state clearly how the participants will be identified, approached and recruited. Include any relationship between the investigator(s) and participant(s) (e.g. instructor-student).

Note: Attach a copy of any poster(s), advertisement(s) or letter(s) to be used for recruitment.

Healthy subjects will be recruited via poster advertisement (attachment 1) at the University of Birmingham, affiliated social media, and from the community and population of staff and students at the University of Birmingham.
Interested volunteers will be asked to contact Pauline Kuithan through email / telephone or face to face.
All information regarding the experiment will be provided in the 'Participant Information Leaflet', which will be sent or given to volunteers who indicated their interest.
An investigator (PK) involved in this project will explain the experimental measures and the exercise intervention to the participants and answer any questions they may have.
The investigators' telephone and e-mail references will be provided on the 'Participant Information Leaflet' (attachment 2). This leaflet summarises the protocol and requirements of the study. Following an expression of interest, the participant will be screened by one of the research team to assess eligibility and answer any questions the participant may have about the study.

Both documents have been reviewed by a 'Patient and Public Involvement' group in March 2018 and changes made. Data collection will take place in the School of Sport, Exercise and Rehabilitation Sciences.

34. CONSENT

a) Describe the process that the investigator(s) will be using to obtain valid consent. If consent is not to be obtained explain why**.** If the participants are minors or for other reasons are not competent to consent, describe the proposed alternate source of consent, including any permission / information letter to be provided to the person(s) providing the consent.

Prior to participating in the study, the 'Participant Information Leaflet' will be handed out again, summarised and discussed. Then a written consent form (attachment 3) will be read and signed by all participants. This includes information about data storage and that data will only be used for the purpose of research, statistical and audit purposes by the University of Birmingham in accordance with the provisions of the EU General Data Protection Regulation 2016/679.

Note: Attach a copy of the Participant Information Sheet (if applicable), the Consent Form (if applicable), the content of any telephone script (if applicable) and any other material that will be used in the consent process.

b) Will the participants be deceived in any way about the purpose of the study? **Yes** ☐ **No** ☒

If yes, please describe the nature and extent of the deception involved. Include how and when the deception will be revealed, and who will administer this feedback.

35. PARTICIPANT FEEDBACK

Explain what feedback/ information will be provided to the participants after participation in the research. (For example, a more complete description of the purpose of the research, or

access to the results of the research).

A summary of the study will be offered to participants via email after the completion of the entire study and data analysis.

36. PARTICIPANT WITHDRAWAL

b) Describe how the participants will be informed of their right to withdraw from the project.

Participants will have the opportunity to withdraw from the study at any point and up to two weeks following completion of data collection (6th session), without having to give a reason. This will be stated on the participant information sheet and written consent form with contact details provided.

b) Explain any consequences for the participant of withdrawing from the study and indicate what will be done with the participant's data if they withdraw.

There will be no consequences if a participant chooses to withdraw from the study. Participants will be informed that all data collected up to point of withdrawal will be included in data analysis unless the participant specifies otherwise.

37. COMPENSATION

Will participants receive compensation for participation?

i) Financial **Yes** ☒ **No** ☐

ii) Non-financial **Yes** ☐ **No** ☒

If **Yes** to **either** i) or ii) above, please provide details.

i) Participants will be reimbursed £35 for completion of the study

If participants choose to withdraw, how will you deal with compensation?

Participants will not be reimbursed for the time they contributed to the experiment on an hourly basis.

38. CONFIDENTIALITY

a) Will all participants be anonymous? **Yes** ☐ **No** ☒

b) Will all data be treated as confidential? **Yes** ☒ **No** ☐

Note: Participants' identity/data will be confidential if an assigned ID code or number is used, but it will not be anonymous. Anonymous data cannot be traced back to an individual participant.

Describe the procedures to be used to ensure anonymity of participants and/or confidentiality of data both during the conduct of the research and in the release of its findings.

All participants will be allocated an ID number to enable pseudo-anonymisation. Only necessary personal data will be collected during the study. All the data will be kept securely locked in a cabinet or saved on a University of Birmingham secured network and remains strictly confidential throughout. The data will only be shared with the participant, investigator and research team. It will not be given to a third party, and it will be stored for 10 years in line with University of Birmingham Research Governance guidelines. All data will be collected and stored under the identification number allocated at the point of recruitment.

If participant anonymity or confidentiality is not appropriate to this research project, explain, providing details of how all participants will be advised of the fact that data will not be anonymous or confidential

39. STORAGE, ACCESS AND DISPOSAL OF DATA

Describe what research data will be stored, where, for what period of time, the measures that will be put in place to ensure security of the data, who will have access to the data, and the method and timing of disposal of the data.

All data will be stored securely in electronic format. Access to data will required a password and all data will be managed in accordance with the EU General Data Protection Regulation 2016/679.
The investigators, Pauline Kuithan, and supervisor team will have access to the anonymised data.
Consent forms will be securely stored in a locked filing cabinet in Centre of Precision Rehabilitation for Spinal Pain (CPR Spine) at the University of Birmingham. Data will be kept for a minimum of 10 years under the University's Code of Practice for Research.

40. OTHER APPROVALS REQUIRED? e.g. Criminal Records Bureau (CRB) checks or NHS R&D approvals.

41.

☐ YES ☐ NO ☒ NOT APPLICABLE

If yes, please specify.

42. SIGNIFICANCE/BENEFITS

Outline the potential significance and/or benefits of the research

This research will contribute to the basic understanding and short-term mechanisms of pain relief with exercise. It will be shown if it is feasible to conduct this trail in a bigger study and moreover transfer it to symptomatic populations if indicated. In the future, it can then help to tailor intervention for chronic (low back pain) pain in the future. Reliability and stability of the benefits of exercise on pain sensitivity will be assessed in a high-quality methodological study and providing a robust protocol for testing. This is important for further understanding of the mechanisms behind EIH and potential differences between healthy people and those with chronic pain.
However, there is no immediate benefit to the participants of the study others than the effects of the exercise sessions. If participants are interested in their test results, these can be handed out to the participants after the study is completed.

43. RISKS

a) Outline any potential risks to **INDIVIDUALS**, including research staff, research participants, other individuals not involved in the research and the measures that will be taken to minimise any risks and the procedures to be adopted in the event of mishap

Please see attached risk assessment form for further details. Quantitative sensory testing have been successfully used in previous projects after receiving ethical approval.

Quantitative sensory testing

The TSA-II device has a high safety level to protect the participant that high (51°C) or low temperature (0°C) can only last for a very short time. As our participants, don't present sensory loss and qualified assessors are conducting the test and reviewing the temperature and the participants' response, it is unlikely that damage to the skin can be caused.

For Pressure Pain Thresholds and Pressure Pain Tolerance blunt pressure will be applied till the participant indicates pain threshold (the point at which the sensation goes from pressure to a sensation of discomfort) or pain tolerances (the point at which the sensation of discomfort cannot be tolerated anymore). The pressure will be applied by an experienced researcher and physiotherapist and the participants can stop the test any time they want to and it is unlikely that the skin can be damaged.

The Pain Withdrawal Reflex can be stopped any time if the participant cannot tolerate the stimulus any longer. However, usually the pain ratings are very low for the short stimulus. Preparation of the skin involves application of an abrasive paste or sandpaper to the superficial skin layer, which has been used in multiple studies within the school, and rarely causes minor skin irritations.

Exercise

The exercise will be supervised throughout by an experienced researcher and physiotherapist, PK. Participants will have sufficient time for familiarisation with the procedure. The researcher is also familiar with each device and its set-up and will instruct the participant how to use the emergency stop functions. Participants will be advised that they may experience muscle soreness for short periods of time, similar to what they would experience following a session of unaccustomed exercise at the gym. However, the entire tests and protocols are individually established and thus persistence soreness is not expected.

b) Outline any potential risks to **THE ENVIRONMENT and/or SOCIETY** and the measures that will be taken to minimise any risks and the procedures to be adopted in the event of mishap.

No expected risks

44. ARE THERE ANY OTHER ETHICAL ISSUES RAISED BY THE RESEARCH?

Yes ☐ **No** ☒

If yes, please specify

45. EXPERT REVIEWER/OPINION

You may be asked to nominate an expert reviewer for certain types of project, including those of an interventional nature or those involving significant risks. If you anticipate that this may apply to your work and you would like to nominate an expert reviewer at this stage, please provide details below.

Name
Contact details (including email address)
Brief explanation of reasons for nominating and/or nominee's suitability

46. CHECKLIST

Please mark if the study involves any of the following:

- Vulnerable groups, such as children and young people aged under 18 years, those with learning disability, or cognitive impairments ☐
- Research that induces or results in or causes anxiety, stress, pain or physical discomfort, or poses a risk of harm to participants (which is more than is expected from everyday life) ☒
- Risk to the personal safety of the researcher ☐
- Deception or research that is conducted without full and informed consent of the participants at time study is carried out ☐
- Administration of a chemical agent or vaccines or other substances (including vitamins or food substances) to human participants. ☐
- Production and/or use of genetically modified plants or microbes ☐
- Results that may have an adverse impact on the environment or food safety ☐
- Results that may be used to develop chemical or biological weapons ☐

Please check that the following documents are attached to your application.

	ATTACHED	NOT APPLICABLE
Recruitment advertisement: Attachment 1	☒	☐
Participant information sheet: Attachment 2	☒	☐
Consent form: Attachment 3	☒	☐
Questionnaires: Attachment 4-5	☒	☐
Interview Schedule	☐	☒

47. DECLARATION BY APPLICANTS

I submit this application on the basis that the information it contains is confidential and will be used by the University of Birmingham for the purposes of ethical review and monitoring of the research project described herein, and to satisfy reporting requirements to regulatory bodies. The information will not be used for any other purpose without my prior consent.

I declare that:

- The information in this form together with any accompanying information is complete and correct to the best of my knowledge and belief and I take full responsibility for it.
- I undertake to abide by University Code of Practice for Research (http://www.as.bham.ac.uk/legislation/docs/COP_Research.pdf) alongside any other relevant

professional bodies' codes of conduct and/or ethical guidelines.

- I will report any changes affecting the ethical aspects of the project to the University of Birmingham Research Ethics Officer.
- I will report any adverse or unforeseen events which occur to the relevant Ethics Committee via the University of Birmingham Research Ethics Officer.

Name of principal investigator/project supervisor:	Deborah Falla
Date:	23/10/18

Please now save your completed form, print a copy for your records, and then email a copy to the Research Ethics Officer, at aer-ethics@contacts.bham.ac.uk. As noted above, please do not submit a paper copy.

References

1. Pain IAftSo. Taxonomy 2017 [Available from: https://www.iasp-pain.org/Taxonomy.
2. Costa YM, Morita-Neto O, de Araujo-Junior EN, Sampaio FA, Conti PC, Bonjardim LR. Test-retest reliability of quantitative sensory testing for mechanical somatosensory and pain modulation assessment of masticatory structures. J Oral Rehabil. 2017;44(3):197-204.
3. Graven-Nielsen T, Vaegter HB, Finocchietti S, Handberg G, Arendt-Nielsen L. Assessment of musculoskeletal pain sensitivity and temporal summation by cuff pressure algometry: a reliability study. Pain. 2015;156(11):2193-202.
4. Potter L, McCarthy C, Oldham J. Algometer reliability in measuring pain pressure threshold over normal spinal muscles to allow quantification of anti-nociceptive treatment effects. International Journal of Osteopathic Medicine. 2006;9(4):113-9.
5. Balaguier R, Madeleine P, Vuillerme N. Is One Trial Sufficient to Obtain Excellent Pressure Pain Threshold Reliability in the Low Back of Asymptomatic Individuals? A Test-Retest Study. PLoS One. 2016;11(8):e0160866.
6. Moloney NA, Hall TM, Doody CM. Reliability of thermal quantitative sensory testing: a systematic review. J Rehabil Res Dev. 2012;49(2):191-207.
7. Marcuzzi A, Wrigley PJ, Dean CM, Adams R, Hush JM. The long-term reliability of static and dynamic quantitative sensory testing in healthy individuals. Pain. 2017;158(7):1217-23.
8. Rabey M, Slater H, O'Sullivan P, Beales D, Smith A. Somatosensory nociceptive characteristics differentiate subgroups in people with chronic low back pain: a cluster analysis. Pain. 2015;156(10):1874-84.
9. Vaegter HB, Graven-Nielsen T. Pain modulatory phenotypes differentiate subgroups with different clinical and experimental pain sensitivity. Pain. 2016;157(7):1480-8.
10. Rolke R, Magerl W, Campbell KA, Schalber C, Caspari S, Birklein F, et al. Quantitative sensory testing: a comprehensive protocol for clinical trials. Eur J Pain. 2006;10(1):77-88.
11. von Dincklage F, Olbrich H, Baars JH, Rehberg B. Habituation of the nociceptive flexion reflex is dependent on inter-stimulus interval and stimulus intensity. J Clin Neurosci. 2013;20(6):848-50.
12. von Dincklage F, Hackbarth M, Schneider M, Baars JH, Rehberg B. Introduction of a continual RIII reflex threshold tracking algorithm. Brain Res. 2009;1260:24-9.
13. Naugle KM, Fillingim RB, Riley JL. A meta-analytic review of the hypoalgesic effects of exercise. J Pain. 2012;13(12):1139-50.
14. Lima LV, Abner TSS, Sluka KA. Does exercise increase or decrease pain? Central mechanisms underlying these two phenomena. J Physiol. 2017;595(13):4141-50.
15. Brellenthin AG, Crombie KM, Cook DB, Sehgal N, Koltyn KF. Psychosocial Influences on Exercise-Induced Hypoalgesia. Pain Med. 2017;18(3):538-50.
16. Naugle KM, Naugle KE, Fillingim RB, Riley JL. Isometric exercise as a test of pain modulation: effects of experimental pain test, psychological variables, and sex. Pain Med. 2014;15(4):692-701.
17. Stolzman S, Danduran M, Hunter SK, Bement MH. Pain Response after Maximal Aerobic Exercise in Adolescents across Weight Status. Med Sci Sports Exerc. 2015;47(11):2431-40.
18. Umeda M, Kempka LE, Greenlee BT, Weatherby AC. A smaller magnitude of exercise-induced hypoalgesia in African Americans compared to non-Hispanic Whites: A potential influence of physical activity. Biol Psychol. 2016;113:46-51.
19. Black CD, Huber JK, Ellingson LD, Ade CJ, Taylor EL, Griffeth EM, et al. Exercise-Induced

Hypoalgesia Is Not Influenced by Physical Activity Type and Amount. Med Sci Sports Exerc. 2017;49(5):975-82.
20. Gajsar H, Titze C, Hasenbring MI, Vaegter HB. Isometric Back Exercise Has Different Effect on Pressure Pain Thresholds in Healthy Men and Women. Pain Med. 2017;18(5):917-23.
21. Koltyn KF. Exercise-induced hypoalgesia and intensity of exercise. Sports Med. 2002;32(8):477-87.
22. Micalos PS, Arendt-Nielsen L. Differential pain response at local and remote muscle sites following aerobic cycling exercise at mild and moderate intensity. Springerplus. 2016;5:91.
23. Vaegter HB, Handberg G, Graven-Nielsen T. Isometric exercises reduce temporal summation of pressure pain in humans. Eur J Pain. 2015;19(7):973-83.
24. Naugle KM, Naugle KE, Fillingim RB, Samuels B, Riley JL. Intensity thresholds for aerobic exercise-induced hypoalgesia. Med Sci Sports Exerc. 2014;46(4):817-25.
25. Vaegter HB, Lyng KD, Yttereng FW, Christensen MH, Sorensen MB, Graven-Nielsen T. Exercise-Induced Hypoalgesia After Isometric Wall Squat Exercise: A Test-Retest Reliabilty Study. Pain Med. 2018.
26. Vaegter HB, Dorge DB, Schmidt KS, Jensen AH, Graven-Nielsen T. Test-Retest Reliabilty of Exercise-Induced Hypoalgesia After Aerobic Exercise. Pain Med. 2018.
27. Hill JC, Whitehurst DG, Lewis M, Bryan S, Dunn KM, Foster NE, 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.
28. Baumgartner TA. Estimating the Stability Reliability of a Score. Measurement in Physical Education and Exercise Science. 2000;4(3):175-8.
29. Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. Pilot Feasibility Stud. 2016;2:64.
30. Kottner J, Audige L, Brorson S, Donner A, Gajewski BJ, Hrobjartsson A, et al. Guidelines for Reporting Reliability and Agreement Studies (GRRAS) were proposed. Int J Nurs Stud. 2011;48(6):661-71.
31. Camarda SR, Tebexreni AS, Pafaro CN, Sasai FB, Tambeiro VL, Juliano Y, et al. Comparison of maximal heart rate using the prediction equations proposed by Karvonen and Tanaka. Arq Bras Cardiol. 2008;91(5):311-4.
32. Torpel A, Becker T, Thiers A, Hamacher D, Schega L. Inter-session Reliability of Isokinetic Strength Testing in Knee and Elbow Extension and Flexion Using the BTE PrimusRS. J Sport Rehabil. 2017:1-14.
33. Brazier JE, Harper R, Jones NM, O'Cathain A, Thomas KJ, Usherwood T, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. BMJ. 1992;305(6846):160-4.
34. Jenkinson C, Stewart-Brown S, Petersen S, Paice C. Assessment of the SF-36 version 2 in the United Kingdom. J Epidemiol Community Health. 1999;53(1):46-50.
35. Booth M. Assessment of physical activity: An international perspective. (vol 71, pg 114, 2000). Res Q Exercise Sport. 2000;71(3):312-.
36. Resnick B, Zimmerman SI, Orwig D, Furstenberg AL, Magaziner J. Outcome expectations for exercise scale: utility and psychometrics. J Gerontol B Psychol Sci Soc Sci. 2000;55(6):S352-6.
37. Borg GAV. Psychophysical bases of perceived exertion. Medicine & Science in Sports & Exercise. 1982;14(5):377-81.
38. Baiamonte BA, Kraemer RR, Chabreck CN, Reynolds ML, McCaleb KM, Shaheen GL, et al. Exercise-induced hypoalgesia: Pain tolerance, preference and tolerance for exercise intensity, and physiological correlates following dynamic circuit resistance exercise. J Sports Sci. 2017;35(18):1-7.
39. Gajsar H, Nahrwold K, Titze C, Hasenbring MI, Vaegter HB. Exercise does not produce hypoalgesia when performed immediately after a painful stimulus. Scandinavian Journal of Pain. 2018;18(2):311-20.
40. Owens MA, Bulls HW, Trost Z, Terry SC, Gossett EW, Wesson-Sides KM, et al. An Examination of Pain Catastrophizing and Endogenous Pain Modulatory Processes in Adults with Chronic Low Back Pain. Pain Med. 2016;17(8):1452-64.
41. Bland JM, Altman DG. Measuring agreement in method comparison studies. Stat Methods Med Res. 1999;8(2):135-60.
42. Walter S, Eliasziw M, Donner A. Sample size and optimal designs for reliability studies. Statistics in medicine. 1998;17(1):101-10.

Pauline Kuithan (PhD School of Sprt+Ex Scie FT)

From: [redacted] (Research Support Group)
Sent: 01 November 2018 12:02
To: Deborah Falla (School of Sport Exercise and Rehabilitation Sciences); Alison Rushton (Physiotherapy); Nicola Heneghan (Physiotherapy)
Cc: Pauline Kuithan (PhD School of Sprt+Ex Scie FT)
Subject: Application for Ethical Review ERN_18-0833

Follow Up Flag: Follow up
Flag Status: Completed

Dear Professor Falla, Dr Rushton and Dr Heneghan

Re: "Investigating the analgesic effect of walking and resistance exercise in healthy adults"
Application for Ethical Review ERN_18-0833

Thank you for your application for ethical review for the above project, which was reviewed by the Science, Technology, Engineering and Mathematics Ethical Review Committee.

On behalf of the Committee, I confirm that this study now has full ethical approval.

I would like to remind you that any substantive changes to the nature of the study as described in the Application for Ethical Review, and/or any adverse events occurring during the study should be promptly bought to the Committee's attention by the Principal Investigator and may necessitate further ethical review.

Please also ensure that the relevant requirements within the University's Code of Practice for Research and the information and guidance provided on the University's ethics webpages (available at https://intranet.birmingham.ac.uk/finance/accounting/Research-Support-Group/Research-Ethics/Links-and-Resources.aspx) are adhered to and referred to in any future applications for ethical review. It is now a requirement on the revised application form (https://intranet.birmingham.ac.uk/finance/accounting/Research-Support-Group/Research-Ethics/Ethical-Review-Forms.aspx) to confirm that this guidance has been consulted and is understood, and that it has been taken into account when completing your application for ethical review.

Please be aware that whilst Health and Safety (H&S) issues may be considered during the ethical review process, you are still required to follow the University's guidance on H&S and to ensure that H&S risk assessments have been carried out as appropriate. For further information about this, please contact your School H&S representative or the University's H&S Unit at healthandsafety@contacts.bham.ac.uk.

Kind regards

[redacted]
Research Ethics Officer
Research Support Group
C Block Dome
Aston Webb Building
University of Birmingham
Edgbaston B15 2TT
Tel: [redacted]
Email: [redacted]
Web: https://intranet.birmingham.ac.uk/finance/RSS/Research-Support-Group/Research-Ethics/index.aspx

Please remember to submit a new Self-Assessment Form for each new project.

Amendment A

UNIVERSITY OF BIRMINGHAM
APPLICATION FOR ETHICAL REVIEW – REQUEST FOR AMENDMENTS

Who should use this form:

- This form is to be completed by PIs or supervisors (for PGR student research) who are requesting ethical approval for amendments to research projects that have previously received ethical approval from the University of Birmingham.

  Please be aware that all new research projects undertaken by postgraduate research (PGR) students first registered as from 1st September 2008 will be subject to the University's Ethical Review Process. PGR students first registered before 1st September 2008 should refer to their Department/School/College for further advice.

- What constitutes an amendment?

  Amendments requiring approval may include, but are not limited to, additions to the research protocol, study population, recruitment of participants, access to personal records, research instruments, or participant information and consent documentation. Amendments must be approved before they are implemented.

NOTES:

- Answers to questions must be entered in the space provided
- An electronic version of the completed form should be submitted to the Research Ethics Officer, at the following email address: aer-ethics@contacts.bham.ac.uk. Please **do not** submit paper copies.
- If, in any section, you find that you have insufficient space, or you wish to supply additional material not specifically requested by the form, please submit it in a separate file, clearly marked and attached to the submission email.
- If you have any queries about the form, please address them to the Research Ethics Team

UNIVERSITY OF BIRMINGHAM APPLICATION FOR ETHICAL REVIEW - REQUEST FOR AMENDMENTS	*OFFICE USE ONLY:* Application No: Date Received:

10. **TITLE OF PROJECT**

Investigating the analgesic effect of walking and resistance exercise in healthy adults

11. **APPROVAL DETAILS**

What is the Ethical Review Number (ERN) for the project?

ERN_18-0833

12. **THIS PROJECT IS:**

University of Birmingham Staff Research project ☐
University of Birmingham Postgraduate Research (PGR) student project ☒
Other ☐ (Please specify):

13. **INVESTIGATORS**

j) PLEASE GIVE DETAILS OF THE PRINCIPAL INVESTIGATORS OR SUPERVISORS (FOR PGR STUDENT PROJECTS)

Name: Title / first name / family name	Professor Deborah Falla
Highest qualification & position held:	Chair in Rehabilitation Science and Physiotherapy
School/Department	School of Sport, Exercise and Rehabilitation Sciences
Telephone:	[redacted]
Email address:	[redacted]

Name: Title / first name / family name	Dr. Alison Rushton
Highest qualification & position held:	Senior Lecturer
School/Department	School of Sport, Exercise and Rehabilitation Sciences
Telephone:	[redacted]
Email address:	[redacted]
Name: Title / first name / family name	Dr. Nicola Heneghan
Highest qualification & position held:	Lecturer
School/Department	School of Sport, Exercise and Rehabilitation Sciences
Telephone:	[redacted]
Email address:	[redacted]

k) PLEASE GIVE DETAILS OF ANY CO-INVESTIGATORS OR CO-SUPERVISORS (FOR PGR STUDENT PROJECTS)

l) In the case of PGR student projects, please give details of the student

Name of student:	Pauline Kuithan	Student No:	[redacted]
Course of study:	PhD		
Principal supervisor:	Prof. Deborah Falla		

14. **ESTIMATED START OF PROJECT** Date: 01/07/2018
ESTIMATED END OF PROJECT Date: 31/01/2020

15. **ORIGINAL APPLICATION FOR ETHICAL REVIEW AND ANY SUBSEQUENT APPROVED AMENDMENTS:**

Please complete the table below for the original application and any subsequent amendments submitted

Title and reference number of application or amendment	**Key points of application and/or changes made by amendment (include: aims of study, participant details, how participants were recruited and methodology)**	**Ethical considerations arising from these key points (e.g. gaining consent, risks to participants and/or researcher, points raised by Ethical Review Committee during review)**	**How were the ethical considerations addressed? (e.g. consent form, participant information, adhering to relevant procedures/clearance required)**
Original application	Aims: A feasibility study with a reliability and stability aspect on changes in pain sensitivity after exercise Participants: Healthy subjects will be recruited via poster advertisement on campus and via intranet. Methods: Quantitative Sensory Testing (Pressure and thermal pain threshold and tolerance, nociceptive reflex) will be analysed before and after an exercise intervention.	Consent: Written consent is gained before the start of the study. Risks: Only remote risks are considered. Testing pain sensitivity entitles the application of painful stimuli. However, this will not lead to any tissue damage. Committee points: 1. Clarification for six sessions 2. Information on pain perceived during the study (participant information leaflet) 3. Exclusion criteria 4. Amount of pain tolerance	Changes were made as outlined below and approved. Amendment does not affect these changes. 1. Further reference to justify 6 sessions is provided 2. Information leaflet changed 3. Exclusion criteria described in more details 4. Reference for no more pain tolerance is provided
Amendment 1	Minor changes in methods (time and details of protocols) and reimbursement	Committee points: Reimbursement	Changes made: reimbursement of participants pro rata

16. **DETAILS OF PROPOSED NEW AMENDMENT**
Provide details of the proposed new amendment, and clearly and explicitly state how the proposed new amendment will differ from the details of the study as already approved (see Q6 above).

This amendment will **expand the current project to include a new group of people with chronic low back pain**. The **same methods**, pain sensitivity testing before and after an exercise intervention over 6 sessions we used previously, **will be applied**.

Proposed title change: **Investigating the analgesic effect of walking and resistance exercise**

Because this is an extension of the project we would like to change the title as it better represents the study.

Why is amendment needed?
Chronic low back pain is the most common cause of years lived with disability (Vos et al., 2012). Moreover, it leads to a high financial burden with both direct and indirect costs for the health care system (Hill et al., 2011; Hong et al., 2013). Exercise is the management of choice (Falla and Hodges, 2017). However, the underlying mechanisms of effect of exercise are still not explored sufficiently. In the originally approved study, we examined temporal changes in pain sensitivity directly after exercise in healthy people. Preliminary data support the observation, that changes in pain sensitivity are stable over multiple sessions. The exercise interventions chosen for this project were tolerated well by the participants and there were no adverse reactions or events.

In people with chronic low back pain, dysfunction of this endogenous pain inhibition (exercise induced hypoalgesia) has been shown in our previous project (ERN_16-1389B) and supports the aim for further research. These results could contribute to the prediction of the outcome of exercise programmes for people with low back pain.

1. Population
Inclusion criteria: People with chronic non-specific low back pain
The following definition for non-specific chronic low back pain is pain in the region of the lower back which is not related to serious pathology and/or does not have a specific cause (also known as mechanical low back pain). Chronic refers to a sub type where back pain has persisted at least 3 months and has resulted in pain on at least half the days in the past 6 months. If possible, participants should be willing to refrain from analgesic medication during the testing episode.
Exclusion criteria:

- Concurrent systemic, rheumatic or neuro-musculoskeletal disorders which may confound testing or are currently pregnant.
- Acute radicular low back pain or pain related to acute trauma, fractures, or spinal stenosis.
  - Participants under active management of LBP through specific medications prescribed by a GP, consultant or therapists (physiotherapist, osteopath, chiropractor) less than 3 months before the possible enrolment others than PRN (per necessary).
  - Exercising for more than 90 minutes of vigorous intensity per day or competing in professional or high-level sport

2. **Compensation**
Reimbursement of back pain participants will be £7.50/h

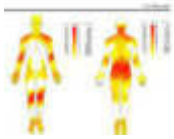
3. **Recruitment**
We will recruit via posters displayed at the University of Birmingham (Attachment 1), the CPR Spine register and social media affiliated with the centre or researcher.

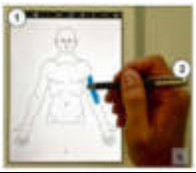
4. Patient reported Outcome measurements
Questionnaires (Attachment 7)
To better describe our population we will include frequently used standardised and validated questionnaires for people with low back pain such as the Oswestry Disability Index or the Fear Avoidance Beliefs Questionnaire (Brown et al., 1997; Fairbank and Pynsent, 2000;

Lame et al., 2008; Osman et al., 2000; Waddell et al., 1993). Furthermore, we will adapt questionnaires from this study with questions regarding their pain before, within and after each session. We will use a numeric rating scale to assess and monitor pain levels during the exercise (Breivik et al., 2008).

Pain drawing

In addition, we will ask participants to shade painful areas on a body chart using an iPad (see picture). Pain drawing have been used in previous projects and its method has been validated (Barbero et al., 2015).





17. **JUSTIFICATION FOR PROPOSED <u>NEW AMENDMENT</u>**

Based on preliminary testing, the study is feasible and can be extended to a population with chronic low back pain. This is supported by discussing this study in a local Patient and Public Involvement event and by comments from participants from the ongoing study.
As described above, chronic low back pain is a massive financial burden for the healthcare system and its management needs to be further improved. Chronic pain can lead to changes in pain sensitivity as earlier shown in a previous project. To make clinically relevant conclusions, we will take the preliminary findings from the original study, which will hopefully be completed in May 2019. If we know how healthy people respond, this will help to inform how people with chronic low back pain will respond and if those differ over six sessions.

Feedback form our current participants suggested that the exercise targets the right area, i.e. lumbar region for the resistance task, but as it is adjusted to individual levels, it seems to be feasible.

"Do you think this programme is feasible for people with low back pain and why?"

- Resistance group (4 sets of 8 repetitions, 50% of voluntary isometric maximum strength):
  "*possibly because it could help to strengthen their back and possibly relieve some of the pain*"
  "*yes they can do it*"
- Walking group (brisk walking for 15 minutes at ~70% of heart rate (220-age) on a treadmill)
  "*yes, it didn't aggravate my back at all*"
  "*yes, the walking programme is tailored to their heart rate so is achievable per any level of fitness and is functional*"

Findings will help to shape future management of low back pain. Based on previous results (ERN_16-1389B) pain sensitivity is impaired in people with chronic low back pain after a lifting task. If these results remain stable over multiple session has not been tested before. This could have potentially an impact on positive outcomes of exercise programmes.

18. **ETHICAL CONSIDERATIONS**

What ethical considerations, if any, are raised by the proposed <u>new amendment</u>?

Pilot testing and data collection up to now did not reveal any adverse effects or issues with the conduction of the study and participants accepted both testing and exercise without any issues. However, we are currently only testing in an asymptomatic population.

In this amendment we will expand the currently tested protocol to a different group which is more vulnerable and therefore it is to expect that this might cause adverse effects or reproduce/ increase the participants' symptoms.

In people with low back pain, the tasks (i.e. resistance exercise) might lead to a temporary increase

of symptoms, likely to be described as temporary stiffness, or soreness. Nevertheless, exercise is **safe** and **recommended** as the treatment of choice for management of low back pain (O'Sullivan et al., 2017; Smith et al., 2017; Werber and Schiltenwolf, 2016). Increase in symptoms would be similar if attending a gym. The aim of the study is not to provoke those symptoms, and for that reason the intensity will be adjusted to 50% of their maximum voluntary strength/ walking based on a comfortable pace and 70% of their maximal heart rate. Most exercise programmes will use higher intensities in a population, who is currently not undergoing any treatment. However, the intensity seems to be sufficient to produce temporary analgesic effects.
Furthermore, all sessions are supervised by a musculoskeletal physiotherapist, with more than 10 years of clinical experience in that area. Moreover, in our previous study (ERN_16-1389B), which comprised a more provocative rotational task, no lasting problems were reported. Pain perceived during the task settled quickly after the session (for most participants with ending of the task or during the post-test of pain sensitivity).
Furthermore, this task will be adjusted to each individual participant, they can stop anytime, and there will be a minimum of 2 days between each session to have adequate recovery time.

DECLARATION BY APPLICANTS

I make this application on the basis that the information it contains is confidential and will be used by the
University of Birmingham for the purposes of ethical review and monitoring of the research project described
herein, and to satisfy reporting requirements to regulatory bodies. The information will not be used for any
other purpose without my prior consent.

I declare that:

- The information in this form together with any accompanying information is complete and correct to the best of my knowledge and belief and I take full responsibility for it.
- I undertake to abide by University Code of Conduct for Research (http://www.birmingham.ac.uk/Documents/university/legal/research.pdf) alongside any other relevant professional bodies' codes of conduct and/or ethical guidelines.
- I will report any changes affecting the ethical aspects of the project to the University of Birmingham Research Ethics Officer.
- I will report any adverse or unforeseen events which occur to the relevant Ethics Committee project to the University of Birmingham Research Ethics Officer.

Signature of Principal investigator/project supervisor:	Deborah Falla
Date:	11/03/19

References

ALEXANDROV, A. V., FROLOV, A. A., HORAK, F. B., CARLSON-KUHTA, P. & PARK, S. 2005. Feedback equilibrium control during human standing. *Biol Cybern,* 93**,** 309-22.

ALSOUHIBANI, A., VAEGTER, H. B. & HOEGER BEMENT, M. 2019. Systemic Exercise-Induced Hypoalgesia Following Isometric Exercise Reduces Conditioned Pain Modulation. *Pain Med,* 20**,** 180-190.

BAIAMONTE, B. A., KRAEMER, R. R., CHABRECK, C. N., REYNOLDS, M. L., MCCALEB, K. M., SHAHEEN, G. L. & HOLLANDER, D. B. 2017. Exercise-induced hypoalgesia: Pain tolerance, preference and tolerance for exercise intensity, and physiological correlates following dynamic circuit resistance exercise. *J Sports Sci,* 35**,** 1-7.

BALAGUIER, R., MADELEINE, P. & VUILLERME, N. 2016. Is One Trial Sufficient to Obtain Excellent Pressure Pain Threshold Reliability in the Low Back of Asymptomatic Individuals? A Test-Retest Study. *PLoS One,* 11**,** e0160866.

BARATTO, L., MORASSO, P. G., RE, C. & SPADA, G. 2002. A new look at posturographic analysis in the clinical context: sway-density versus other parameterization techniques. *Motor Control,* 6**,** 246-70.
BARBERO, M., MORESI, F., LEONI, D., GATTI, R., EGLOFF, M. & FALLA, D. 2015. Test-retest reliability of pain extent and pain location using a novel method for pain drawing analysis. *Eur J Pain,* 19**,** 1129-38.
BARKER, S., CRAIK, R., FREEDMAN, W., HERRMANN, N. & HILLSTROM, H. 2006. Accuracy, reliability, and validity of a spatiotemporal gait analysis system. *Med Eng Phys,* 28**,** 460-7.
BAUMGARTNER, T. A. 2000. Estimating the Stability Reliability of a Score. *Measurement in Physical Education and Exercise Science,* 4**,** 175-178.
BIANCHI, L., ANGELINI, D., ORANI, G. P. & LACQUANITI, F. 1998. Kinematic coordination in human gait: relation to mechanical energy cost. *J Neurophysiol,* 79**,** 2155-70.
BLACK, C. D., HUBER, J. K., ELLINGSON, L. D., ADE, C. J., TAYLOR, E. L., GRIFFETH, E. M., JANZEN, N. R. & SUTTERFIELD, S. L. 2017. Exercise-Induced Hypoalgesia Is Not Influenced by Physical Activity Type and Amount. *Med Sci Sports Exerc,* 49**,** 975-982.
BLAND, J. M. & ALTMAN, D. G. 1999. Measuring agreement in method comparison studies. *Stat Methods Med Res,* 8**,** 135-60.
BLUMENSTIEL, K., GERHARDT, A., ROLKE, R., BIEBER, C., TESARZ, J., FRIEDERICH, H. C., EICH, W. & TREEDE, R. D. 2011. Quantitative Sensory Testing Profiles in Chronic Back Pain Are Distinct From Those in Fibromyalgia. *Clinical Journal of Pain,* 27**,** 682-690.
BOOTH, M. 2000. Assessment of physical activity: An international perspective. (vol 71, pg 114, 2000). *Research Quarterly for Exercise and Sport,* 71**,** 312-312.
BORG, G. A. V. 1982. Psychophysical bases of perceived exertion. *Medicine & Science in Sports & Exercise,* 14**,** 377-381.
BORGHESE, N. A., BIANCHI, L. & LACQUANITI, F. 1996. Kinematic determinants of human locomotion. *J Physiol,* 494 (Pt 3)**,** 863-79.
BRAZIER, J. E., HARPER, R., JONES, N. M., O'CATHAIN, A., THOMAS, K. J., USHERWOOD, T. & WESTLAKE, L. 1992. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ,* 305**,** 160-4.
BREIVIK, H., BORCHGREVINK, P. C., ALLEN, S. M., ROSSELAND, L. A., ROMUNDSTAD, L., HALS, E. K., KVARSTEIN, G. & STUBHAUG, A. 2008. Assessment of pain. *Br J Anaesth,* 101**,** 17-24.
BRELLENTHIN, A. G., CROMBIE, K. M., COOK, D. B., SEHGAL, N. & KOLTYN, K. F. 2017. Psychosocial Influences on Exercise-Induced Hypoalgesia. *Pain Med,* 18**,** 538-550.
BROWN, T. A., CHORPITA, B. F., KOROTITSCH, W. & BARLOW, D. H. 1997. Psychometric properties of the Depression Anxiety Stress Scales (DASS) in clinical samples. *Behav Res Ther,* 35**,** 79-89.
CAMARDA, S. R., TEBEXRENI, A. S., PAFARO, C. N., SASAI, F. B., TAMBEIRO, V. L., JULIANO, Y. & BARROS NETO, T. L. 2008. Comparison of maximal heart rate using the prediction equations proposed by Karvonen and Tanaka. *Arq Bras Cardiol,* 91**,** 311-4.
CAPPELLINI, G., IVANENKO, Y. P., POPPELE, R. E. & LACQUANITI, F. 2006. Motor patterns in human walking and running. *J Neurophysiol,* 95**,** 3426-37.
CAVAGNA, G. A. & MARGARIA, R. 1966. Mechanics of walking. *J Appl Physiol,* 21**,** 271-8.
CHOLEWICKI, J. & MCGILL, S. M. 1996. Mechanical stability of the in vivo lumbar spine: implications for injury and chronic low back pain. *Clin Biomech (Bristol, Avon),* 11**,** 1-15.
CLARK, D. J., TING, L. H., ZAJAC, F. E., NEPTUNE, R. R. & KAUTZ, S. A. 2010. Merging of healthy motor modules predicts reduced locomotor performance and muscle coordination complexity post-stroke. *J Neurophysiol,* 103**,** 844-57.
COSTA, Y. M., MORITA-NETO, O., DE ARAUJO-JUNIOR, E. N., SAMPAIO, F. A., CONTI, P. C. & BONJARDIM, L. R. 2017. Test-retest reliability of quantitative sensory testing for mechanical somatosensory and pain modulation assessment of masticatory structures. *J Oral Rehabil,* 44**,** 197-204.

COURTINE, G., DE NUNZIO, A. M., SCHMID, M., BERETTA, M. V. & SCHIEPPATI, M. 2007. Stance- and locomotion-dependent processing of vibration-induced proprioceptive inflow from multiple muscles in humans. *J Neurophysiol,* 97**,** 772-9.

COURTINE, G., PAPAXANTHIS, C. & SCHIEPPATI, M. 2006. Coordinated modulation of locomotor muscle synergies constructs straight-ahead and curvilinear walking in humans. *Exp Brain Res,* 170**,** 320-35.

COURTINE, G. & SCHIEPPATI, M. 2003a. Human walking along a curved path. I. Body trajectory, segment orientation and the effect of vision. *Eur J Neurosci,* 18**,** 177-90.

COURTINE, G. & SCHIEPPATI, M. 2003b. Human walking along a curved path. II. Gait features and EMG patterns. *Eur J Neurosci,* 18**,** 191-205.

COURTINE, G. & SCHIEPPATI, M. 2004. Tuning of a basic coordination pattern constructs straight-ahead and curved walking in humans. *J Neurophysiol,* 91**,** 1524-35.

COUTTS, F. 1999. Gait analysis in the therapeutic environment. *Man Ther,* 4**,** 2-10.

CREATH, R., KIEMEL, T., HORAK, F., PETERKA, R. & JEKA, J. 2005. A unified view of quiet and perturbed stance: simultaneous co-existing excitable modes. *Neurosci Lett,* 377**,** 75-80.

CRENNA, P. & FRIGO, C. 1991. A motor programme for the initiation of forward-oriented movements in humans. *J Physiol,* 437**,** 635-53.

DAVIS, B. L. & VAUGHAN, C. L. 1993. Phasic behavior of EMG signals during gait: Use of multivariate statistics. *J Electromyogr Kinesiol,* 3**,** 51-60.

DAVIS, R. B., OUNPUU, S., DENNIS, T. & GAGE, J. R. 1991. A gait analysis data collection and reduction technique. *Hum Mov Sci,* 10**,** 575-587.

DE NUNZIO, A. M., NARDONE, A., PICCO, D., NILSSON, J. & SCHIEPPATI, M. 2008. Alternate trains of postural muscle vibration promote cyclic body displacement in standing parkinsonian patients. *Mov Disord,* 23**,** 2186-93.

DE NUNZIO, A. M., NARDONE, A. & SCHIEPPATI, M. 2005. Head stabilization on a continuously oscillating platform: the effect of a proprioceptive disturbance on the balancing strategy. *Exp Brain Res,* 165**,** 261-72.

DOMENICI, P., JAMON, M. & CLARAC, F. 1998. Curve walking in freely moving crayfish (Procambarus clarkii). *J Exp Biol,* 201 (Pt 9)**,** 1315-29.

DREW, T., PRENTICE, S. & SCHEPENS, B. 2004. Cortical and brainstem control of locomotion. *Prog Brain Res,* 143**,** 251-61.

DWORKIN, R. H., TURK, D. C., FARRAR, J. T., HAYTHORNTHWAITE, J. A., JENSEN, M. P., KATZ, N. P., KERNS, R. D., STUCKI, G., ALLEN, R. R., BELLAMY, N., CARR, D. B., CHANDLER, J., COWAN, P., DIONNE, R., GALER, B. S., HERTZ, S., JADAD, A. R., KRAMER, L. D., MANNING, D. C., MARTIN, S., MCCORMICK, C. G., MCDERMOTT, M. P., MCGRATH, P., QUESSY, S., RAPPAPORT, B. A., ROBBINS, W., ROBINSON, J. P., ROTHMAN, M., ROYAL, M. A., SIMON, L., STAUFFER, J. W., STEIN, W., TOLLETT, J., WERNICKE, J., WITTER, J. & IMMPACT 2005. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain,* 113**,** 9-19.

ELDRIDGE, S. M., CHAN, C. L., CAMPBELL, M. J., BOND, C. M., HOPEWELL, S., THABANE, L., LANCASTER, G. A. & GROUP, P. C. 2016. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. *Pilot Feasibility Stud,* 2**,** 64.

FAIRBANK, J. C. & PYNSENT, P. B. 2000. The Oswestry Disability Index. *Spine (Phila Pa 1976),* 25**,** 2940-52; discussion 2952.

FALLA, D., ARENDT-NIELSEN, L. & FARINA, D. 2008. Gender-specific adaptations of upper trapezius muscle activity to acute nociceptive stimulation. *Pain,* 138**,** 217-25.

FALLA, D., GIZZI, L., TSCHAPEK, M., ERLENWEIN, J. & PETZKE, F. 2014. Reduced task-induced variations in the distribution of activity across back muscle regions in individuals with low back pain. *Pain,* 155**,** 944-953.

FALLA, D. & HODGES, P. W. 2017. Individualized Exercise Interventions for Spinal Pain. *Exerc Sport Sci Rev,* 45**,** 105-115.

GAJSAR, H., NAHRWOLD, K., TITZE, C., HASENBRING, M. I. & VAEGTER, H. B. 2018a. Exercise does not produce hypoalgesia when performed immediately after a painful stimulus. *Scand J Pain,* 18**,** 311-320.

GAJSAR, H., NAHRWOLD, K., TITZE, C., HASENBRING, M. I. & VAEGTER, H. B. 2018b. Exercise does not produce hypoalgesia when performed immediately after a painful stimulus. *Scandinavian Journal of Pain,* 18**,** 311-320.

GAJSAR, H., TITZE, C., HASENBRING, M. I. & VAEGTER, H. B. 2017. Isometric Back Exercise Has Different Effect on Pressure Pain Thresholds in Healthy Men and Women. *Pain Med,* 18**,** 917-923.

GALLAGHER, K. M. & CALLAGHAN, J. P. 2015. Early static standing is associated with prolonged standing induced low back pain. *Human Movement Science,* 44**,** 111-121.

GALLAGHER, K. M. & CALLAGHAN, J. P. 2016. Standing on a declining surface reduces transient prolonged standing induced low back pain development. *Appl Ergon,* 56**,** 76-83.

GEWANDTER, J. S., DWORKIN, R. H., TURK, D. C., MCDERMOTT, M. P., BARON, R., GASTONGUAY, M. R., GILRON, I., KATZ, N. P., MEHTA, C., RAJA, S. N., SENN, S., TAYLOR, C., COWAN, P., DESJARDINS, P., DIMITROVA, R., DIONNE, R., FARRAR, J. T., HEWITT, D. J., IYENGAR, S., JAY, G. W., KALSO, E., KERNS, R. D., LEFF, R., LEONG, M., PETERSEN, K. L., RAVINA, B. M., RAUSCHKOLB, C., RICE, A. S., ROWBOTHAM, M. C., SAMPAIO, C., SINDRUP, S. H., STAUFFER, J. W., STEIGERWALD, I., STEWART, J., TOBIAS, J., TREEDE, R. D., WALLACE, M. & WHITE, R. E. 2014. Research designs for proof-of-concept chronic pain clinical trials: IMMPACT recommendations. *Pain,* 155**,** 1683-95.

GIZZI, L., NIELSEN, J. F., FELICI, F., IVANENKO, Y. P. & FARINA, D. 2011. Impulses of activation but not motor modules are preserved in the locomotion of subacute stroke patients. *Journal of Neurophysiology,* 106**,** 202-210.

GODI, M., NARDONE, A. & SCHIEPPATI, M. 2010. Curved walking in hemiparetic patients. *J Rehabil Med,* 42**,** 858-65.

GRAVEN-NIELSEN, T., VAEGTER, H. B., FINOCCHIETTI, S., HANDBERG, G. & ARENDT-NIELSEN, L. 2015. Assessment of musculoskeletal pain sensitivity and temporal summation by cuff pressure algometry: a reliability study. *Pain,* 156**,** 2193-2202.

GRYFE, C. I., AMIES, A. & ASHLEY, M. J. 1977. A longitudinal study of falls in an elderly population: I. Incidence and morbidity. *Age Ageing,* 6**,** 201-10.

GUGLIELMETTI, S., NARDONE, A., DE NUNZIO, A. M., GODI, M. & SCHIEPPATI, M. 2009. Walking along circular trajectories in Parkinson's disease. *Mov Disord,* 24**,** 598-604.

HASE, K. & STEIN, R. B. 1998. Analysis of rapid stopping during human walking. *J Neurophysiol,* 80**,** 255-61.

HASE, K. & STEIN, R. B. 1999. Turning strategies during human walking. *J Neurophysiol,* 81**,** 2914-22.

HERMENS, H. J., FRERIKS, B., MERLETTI, R., HAGG, G. G., STEGEMAN, D., BLOK, J., RAU, G. & DISSELHORST-KLUG, C. 1999. European Recommendations for Surface Electro-MyoGraphy: Results of the SENIAM Project. Enschede, The Netherlands: Roessingh Research and Development.

HILL, J. C., WHITEHURST, D. G., LEWIS, M., BRYAN, S., DUNN, K. M., FOSTER, N. E., KONSTANTINOU, K., MAIN, C. J., MASON, E., SOMERVILLE, S., SOWDEN, G., VOHORA, K. & HAY, E. M. 2011. Comparison of stratified primary care management for low back pain with current best practice (STarT Back): a randomised controlled trial. *Lancet,* 378**,** 1560-71.

HODGES, P. W., GURFINKEL, V. S., BRUMAGNE, S., SMITH, T. C. & CORDO, P. C. 2002. Coexistence of stability and mobility in postural control: evidence from postural compensation for respiration. *Exp Brain Res,* 144**,** 293-302.

HOJEN-SORENSEN, P. A. D. F. R., WINTHER, O. & HANSEN, L. K. 2002. Mean-field approaches to independent component analysis. *Neural Computation,* 14**,** 889-918.

HONG, J., REED, C., NOVICK, D. & HAPPICH, M. 2013. Costs associated with treatment of chronic low back pain: an analysis of the UK General Practice Research Database. *Spine (Phila Pa 1976),* 38**,** 75-82.

HUBSCHER, M., MOLONEY, N., REBBECK, T., TRAEGER, A. & REFSHAUGE, K. M. 2014. 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,* 30**,** 886-893.

IVANENKO, Y. P., CAPPELLINI, G., DOMINICI, N., POPPELE, R. E. & LACQUANITI, F. 2005. Coordination of locomotion with voluntary movements in humans. *J Neurosci,* 25**,** 7238-53.

IVANENKO, Y. P., CAPPELLINI, G., POPPELE, R. E. & LACQUANITI, F. 2008a. Spatiotemporal organization of alpha-motoneuron activity in the human spinal cord during different gaits and gait transitions. *Eur J Neurosci,* 27**,** 3351-68.

IVANENKO, Y. P., D'AVELLA, A., POPPELE, R. E. & LACQUANITI, F. 2008b. On the origin of planar covariation of elevation angles during human locomotion. *J Neurophysiol,* 99**,** 1890-8.

IVANENKO, Y. P., POPPELE, R. E. & LACQUANITI, F. 2004. Five basic muscle activation patterns account for muscle activity during human locomotion. *J Physiol,* 556**,** 267-82.

IVANENKO, Y. P., POPPELE, R. E. & LACQUANITI, F. 2006. Motor control programs and walking. *Neuroscientist,* 12**,** 339-48.

JAKUSCHEIT, A., POSCH, M. J., GKAITATZIS, S., NEUMARK, L., HACKBARTH, M., SCHNEIDER, M., LICHTNER, G., BAARS, J. H. & VON DINCKLAGE, F. 2017. Utility of nociceptive flexion reflex threshold and bispectral index to predict movement responses under propofol anaesthesia. *Somatosens Mot Res,* 34**,** 139-144.

JENKINSON, C., STEWART-BROWN, S., PETERSEN, S. & PAICE, C. 1999. Assessment of the SF-36 version 2 in the United Kingdom. *J Epidemiol Community Health,* 53**,** 46-50.

KALICHMAN, L., KIM, D. H., LI, L., GUERMAZI, A. & HUNTER, D. J. 2010. Computed tomography-evaluated features of spinal degeneration: prevalence, intercorrelation, and association with self-reported low back pain. *Spine J,* 10**,** 200-8.

KAVOUNOUDIAS, A., GILHODES, J. C., ROLL, R. & ROLL, J. P. 1999. From balance regulation to body orientation: two goals for muscle proprioceptive information processing? *Exp Brain Res,* 124**,** 80-8.

KAVOUNOUDIAS, A., ROLL, R. & ROLL, J. P. 1998. The plantar sole is a 'dynamometric map' for human balance control. *Neuroreport,* 9**,** 3247-52.

KOLENDA, T., SIGURDSSON, S., WINTHER, O., HANSEN, L. K. & LARSEN, J. 2002. DTU: Toolbox. Lyngby, Denmark: ISP Group at Institute of Informatics and Mathematical Modeling at the Technical University of Denmark.

KOLTYN, K. F. 2002. Exercise-induced hypoalgesia and intensity of exercise. *Sports Med,* 32**,** 477-87.

KOTTNER, J., AUDIGE, L., BRORSON, S., DONNER, A., GAJEWSKI, B. J., HROBJARTSSON, A., ROBERTS, C., SHOUKRI, M. & STREINER, D. L. 2011. Guidelines for Reporting Reliability and Agreement Studies (GRRAS) were proposed. *Int J Nurs Stud,* 48**,** 661-71.

LABRUYERE, R. & VAN HEDEL, H. J. 2012. Curve walking is not better than straight walking in estimating ambulation-related domains after incomplete spinal cord injury. *Arch Phys Med Rehabil,* 93**,** 796-801.

LACQUANITI, F., GRASSO, R. & ZAGO, M. 1999. Motor Patterns in Walking. *News Physiol Sci,* 14**,** 168-174.

LAJOIE, Y. & GALLAGHER, S. P. 2004. Predicting falls within the elderly community: comparison of postural sway, reaction time, the Berg balance scale and the Activities-specific Balance Confidence (ABC) scale for comparing fallers and non-fallers. *Archives of Gerontology and Geriatrics,* 38**,** 11-26.

LAME, I. E., PETERS, M. L., KESSELS, A. G., VAN KLEEF, M. & PATIJN, J. 2008. Test--retest stability of the Pain Catastrophizing Scale and the Tampa Scale for Kinesiophobia in chronic pain over a longer period of time. *J Health Psychol,* 13**,** 820-6.

LIMA, L. V., ABNER, T. S. S. & SLUKA, K. A. 2017. Does exercise increase or decrease pain? Central mechanisms underlying these two phenomena. *J Physiol,* 595**,** 4141-4150.

LOVIBOND, S. H. & LOVIBOND, P. F. 1995. *Manual for the depression anxiety stress scales,* Sydney, N.S.W., Psychology Foundation of Australia.
MACKINNON, C. D., BISSIG, D., CHIUSANO, J., MILLER, E., RUDNICK, L., JAGER, C., ZHANG, Y., MILLE, M. L. & ROGERS, M. W. 2007. Preparation of anticipatory postural adjustments prior to stepping. *J Neurophysiol,* 97**,** 4368-79.
MARCUZZI, A., WRIGLEY, P. J., DEAN, C. M., ADAMS, R. & HUSH, J. M. 2017. The long-term reliability of static and dynamic quantitative sensory testing in healthy individuals. *Pain,* 158**,** 1217-1223.
MASSION, J. 1992. Movement, posture and equilibrium: interaction and coordination. *Prog Neurobiol,* 38**,** 35-56.
MASSION, J., ALEXANDROV, A. & FROLOV, A. 2004. Why and how are posture and movement coordinated? *Prog Brain Res,* 143**,** 13-27.
MASSION, J., IOFFE, M., SCHMITZ, C., VIALLET, F. & GANTCHEVA, R. 1999. Acquisition of anticipatory postural adjustments in a bimanual load-lifting task: normal and pathological aspects. *Exp Brain Res,* 128**,** 229-35.
MATSUYAMA, K. & DREW, T. 1997. Organization of the projections from the pericruciate cortex to the pontomedullary brainstem of the cat: a study using the anterograde tracer Phaseolus vulgaris-leucoagglutinin. *J Comp Neurol,* 389**,** 617-41.
MAURER, C., MERGNER, T. & PETERKA, R. J. 2006. Multisensory control of human upright stance. *Exp Brain Res,* 171**,** 231-50.
MAZAHERI, M., COENEN, P., PARNIANPOUR, M., KIERS, H. & VAN DIEEN, J. H. 2013. Low back pain and postural sway during quiet standing with and without sensory manipulation: a systematic review. *Gait Posture,* 37**,** 12-22.
MCCOLLUM, G. & LEEN, T. K. 1989. Form and exploration of mechanical stability limits in erect stance. *J Mot Behav,* 21**,** 225-44.
MCGOWAN, C. P., NEPTUNE, R. R., CLARK, D. J. & KAUTZ, S. A. 2010. Modular control of human walking: Adaptations to altered mechanical demands. *J Biomech,* 43**,** 412-9.
MCILROY, W. E. & MAKI, B. E. 1997. Preferred placement of the feet during quiet stance: development of a standardized foot placement for balance testing. *Clin Biomech (Bristol, Avon),* 12**,** 66-70.
MCPHEETERS, M. L., KRIPALANI, S., PETERSON, N. B., IDOWU, R. T., JEROME, R. N., POTTER, S. A. & ANDREWS, J. C. 2012. Closing the quality gap: revisiting the state of the science (vol. 3: quality improvement interventions to address health disparities). *Evid Rep Technol Assess (Full Rep)***,** 1-475.
MICALOS, P. S. & ARENDT-NIELSEN, L. 2016. Differential pain response at local and remote muscle sites following aerobic cycling exercise at mild and moderate intensity. *Springerplus,* 5**,** 91.
MIENTJES, M. I. & FRANK, J. S. 1999. Balance in chronic low back pain patients compared to healthy people under various conditions in upright standing. *Clin Biomech (Bristol, Avon),* 14**,** 710-6.
MOLONEY, N. A., HALL, T. M. & DOODY, C. M. 2012. Reliability of thermal quantitative sensory testing: a systematic review. *J Rehabil Res Dev,* 49**,** 191-207.
MORASSO, P. G. & SANGUINETI, V. 2002. Ankle muscle stiffness alone cannot stabilize balance during quiet standing. *J Neurophysiol,* 88**,** 2157-62.
MORASSO, P. G. & SCHIEPPATI, M. 1999. Can muscle stiffness alone stabilize upright standing? *J Neurophysiol,* 82**,** 1622-6.
NAUGLE, K. M., FILLINGIM, R. B. & RILEY, J. L. 2012. A meta-analytic review of the hypoalgesic effects of exercise. *J Pain,* 13**,** 1139-50.
NAUGLE, K. M., NAUGLE, K. E., FILLINGIM, R. B. & RILEY, J. L. 2014a. Isometric exercise as a test of pain modulation: effects of experimental pain test, psychological variables, and sex. *Pain Med,* 15**,** 692-701.
NAUGLE, K. M., NAUGLE, K. E., FILLINGIM, R. B., SAMUELS, B. & RILEY, J. L. 2014b. Intensity thresholds for aerobic exercise-induced hypoalgesia. *Med Sci Sports Exerc,* 46**,** 817-25.

NEZIRI, A. Y., HAESLER, S., PETERSEN-FELIX, S., MULLER, M., ARENDT-NIELSEN, L., MANRESA, J. B., ANDERSEN, O. K. & CURATOLO, M. 2010. Generalized expansion of nociceptive reflex receptive fields in chronic pain patients. *Pain,* 151**,** 798-805.

NIES, N. & SINNOTT, P. L. 1991. Variations in balance and body sway in middle-aged adults. Subjects with healthy backs compared with subjects with low-back dysfunction. *Spine (Phila Pa 1976),* 16**,** 325-30.

O'KANE, F. W., MCGIBBON, C. A. & KREBS, D. E. 2003. Kinetic analysis of planned gait termination in healthy subjects and patients with balance disorders. *Gait Posture,* 17**,** 170-9.

O'NEILL, S., KJAER, P., GRAVEN-NIELSEN, T., MANNICHE, C. & ARENDT-NIELSEN, L. 2011. Low pressure pain thresholds are associated with, but does not predispose for, low back pain. *Eur Spine J,* 20**,** 2120-5.

O'SULLIVAN, K., O'KEEFFE, M. & O'SULLIVAN, P. 2017. NICE low back pain guidelines: opportunities and obstacles to change practice. *Br J Sports Med*.

OATES, A. R., FRANK, J. S. & PATLA, A. E. 2010. Control of dynamic stability during adaptation to gait termination on a slippery surface. *Exp Brain Res,* 201**,** 47-57.

OKUBO, Y., SCHOENE, D. & LORD, S. R. 2016. Step training improves reaction time, gait and balance and reduces falls in older people: a systematic review and meta-analysis. *Br J Sports Med*.

OLREE, K. S. & VAUGHAN, C. L. 1995. Fundamental patterns of bilateral muscle activity in human locomotion. *Biol Cybern,* 73**,** 409-14.

OSMAN, A., BARRIOS, F. X., GUTIERREZ, P. M., KOPPER, B. A., MERRIFIELD, T. & GRITTMANN, L. 2000. The Pain Catastrophizing Scale: further psychometric evaluation with adult samples. *J Behav Med,* 23**,** 351-65.

OSMAN, A., BARRIOS, F. X., KOPPER, B. A., HAUPTMANN, W., JONES, J. & O'NEILL, E. 1997. Factor structure, reliability, and validity of the Pain Catastrophizing Scale. *J Behav Med,* 20**,** 589-605.

OULLIER, O., BARDY, B. G., STOFFREGEN, T. A. & BOOTSMA, R. J. 2002. Postural coordination in looking and tracking tasks. *Hum Mov Sci,* 21**,** 147-67.

OWENS, M. A., BULLS, H. W., TROST, Z., TERRY, S. C., GOSSETT, E. W., WESSON-SIDES, K. M. & GOODIN, B. R. 2016. An Examination of Pain Catastrophizing and Endogenous Pain Modulatory Processes in Adults with Chronic Low Back Pain. *Pain Med,* 17**,** 1452-64.

PAIN, I. A. F. T. S. O. 2017. *Taxonomy* [Online]. Available: https://www.iasp-pain.org/Taxonomy [Accessed last access 6.4.2018].

PANJABI, M. M. 1992. The stabilizing system of the spine. Part I. Function, dysfunction, adaptation, and enhancement. *J Spinal Disord,* 5**,** 383-9; discussion 397.

PARK, S., HORAK, F. B. & KUO, A. D. 2004. Postural feedback responses scale with biomechanical constraints in human standing. *Exp Brain Res,* 154**,** 417-27.

PARSONS, T. D. & COURTNEY, C. G. 2014. An initial validation of the Virtual Reality Paced Auditory Serial Addition Test in a college sample. *J Neurosci Methods,* 222**,** 15-23.

PATLA, A. E. 1985. Some characteristics of EMG patterns during locomotion: implications for the locomotor control process. *J Mot Behav,* 17**,** 443-61.

PEROTTO, A. O. 1994. Anatomical Guide for the Electromyographer.

PINSAULT, N. & VUILLERME, N. 2009. Test-retest reliability of centre of foot pressure measures to assess postural control during unperturbed stance. *Med Eng Phys,* 31**,** 276-86.

POTTER, L., MCCARTHY, C. & OLDHAM, J. 2006. Algometer reliability in measuring pain pressure threshold over normal spinal muscles to allow quantification of anti-nociceptive treatment effects. *International Journal of Osteopathic Medicine,* 9**,** 113-119.

POZZO, T., PAPAXANTHIS, C., STAPLEY, P. & BERTHOZ, A. 1998. The sensorimotor and cognitive integration of gravity. *Brain Res Brain Res Rev,* 28**,** 92-101.

RABEY, M., SLATER, H., O'SULLIVAN, P., BEALES, D. & SMITH, A. 2015. Somatosensory nociceptive characteristics differentiate subgroups in people with chronic low back pain: a cluster analysis. *Pain,* 156**,** 1874-1884.

RESNICK, B., ZIMMERMAN, S. I., ORWIG, D., FURSTENBERG, A. L. & MAGAZINER, J. 2000. Outcome expectations for exercise scale: utility and psychometrics. *J Gerontol B Psychol Sci Soc Sci,* 55**,** S352-6.

ROGERS, M. W., KUKULKA, C. G., BRUNT, D., CAIN, T. D. & HANKE, T. A. 2001. The influence of stimulus cue on the initiation of stepping in young and older adults. *Arch Phys Med Rehabil,* 82**,** 619-24.

ROLKE, R., BARON, R., MAIER, C., TOLLE, T. R., TREEDE, R. D., BEYER, A., BINDER, A., BIRBAUMER, N., BIRKLEIN, F., BOTEFUR, I. C., BRAUNE, S., FLOR, H., HUGE, V., KLUG, R., LANDWEHRMEYER, G. B., MAGERL, W., MAIHOFNER, C., ROLKO, C., SCHAUB, C., SCHERENS, A., SPRENGER, T., VALET, M. & WASSERKA, B. 2006a. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. *Pain,* 123**,** 231-43.

ROLKE, R., MAGERL, W., CAMPBELL, K. A., SCHALBER, C., CASPARI, S., BIRKLEIN, F. & TREEDE, R. D. 2006b. Quantitative sensory testing: a comprehensive protocol for clinical trials. *Eur J Pain,* 10**,** 77-88.

ROLL, J. P. & VEDEL, J. P. 1982. Kinaesthetic role of muscle afferents in man, studied by tendon vibration and microneurography. *Exp Brain Res,* 47**,** 177-90.

ROLL, J. P., VEDEL, J. P. & RIBOT, E. 1989a. Alteration of proprioceptive messages induced by tendon vibration in man: a microneurographic study. *Exp Brain Res,* 76**,** 213-22.

ROLL, J. P., VEDEL, J. P. & ROLL, R. 1989b. Eye, head and skeletal muscle spindle feedback in the elaboration of body references. *Prog Brain Res,* 80**,** 113-23; discussion 57-60.

ROSSIGNOL, S. 1996. Visuomotor regulation of locomotion. *Can J Physiol Pharmacol,* 74**,** 418-25.

ROSSIGNOL, S., CHAU, C., BRUSTEIN, E., BELANGER, M., BARBEAU, H. & DREW, T. 1996. Locomotor capacities after complete and partial lesions of the spinal cord. *Acta Neurobiol Exp (Wars),* 56**,** 449-63.

RUHE, A., FEJER, R. & WALKER, B. 2011. Center of pressure excursion as a measure of balance performance in patients with non-specific low back pain compared to healthy controls: a systematic review of the literature. *Eur Spine J,* 20**,** 358-68.

SCHEPENS, B. & DREW, T. 2003. Strategies for the integration of posture and movement during reaching in the cat. *J Neurophysiol,* 90**,** 3066-86.

SCHEPENS, B. & DREW, T. 2004. Independent and convergent signals from the pontomedullary reticular formation contribute to the control of posture and movement during reaching in the cat. *J Neurophysiol,* 92**,** 2217-38.

SCHIEPPATI, M., HUGON, M., GRASSO, M., NARDONE, A. & GALANTE, M. 1994. The limits of equilibrium in young and elderly normal subjects and in parkinsonians. *Electroencephalogr Clin Neurophysiol,* 93**,** 286-98.

SCHIEPPATI, M. & NARDONE, A. 1999. Group II spindle afferent fibers in humans: their possible role in the reflex control of stance. *Prog Brain Res,* 123**,** 461-72.

SCHMID, M., DE NUNZIO, A. M. & SCHIEPPATI, M. 2005. Trunk muscle proprioceptive input assists steering of locomotion. *Neurosci Lett,* 384**,** 127-32.

SCHWEIGART, G. & MERGNER, T. 2008. Human stance control beyond steady state response and inverted pendulum simplification. *Exp Brain Res,* 185**,** 635-53.

SMITH, B. E., HENDRICK, P., SMITH, T. O., BATEMAN, M., MOFFATT, F., RATHLEFF, M. S., SELFE, J. & LOGAN, P. 2017. Should exercises be painful in the management of chronic musculoskeletal pain? A systematic review and meta-analysis. *Br J Sports Med,* Available online 8 June 2017, ISSN 1473-0480, https.doi.org/10.1136/bjsports-2016-097383.

SOUSA, A. S. & TAVARES, J. M. 2015. Interlimb Coordination During Step-to-Step Transition and Gait Performance. *J Mot Behav,* 47**,** 563-74.

SPARROW, W. A. & TIROSH, O. 2005. Gait termination: a review of experimental methods and the effects of ageing and gait pathologies. *Gait Posture,* 22**,** 362-71.

STENHAGEN, M., EKSTROM, H., NORDELL, E. & ELMSTAHL, S. 2013. Falls in the general elderly population: a 3- and 6- year prospective study of risk factors using data from the longitudinal population study 'Good ageing in Skane'. *BMC Geriatr,* 13**,** 81.

STERKE, C. S., HUISMAN, S. L., VAN BEECK, E. F., LOOMAN, C. W. N. & VAN DER CAMMEN, T. J. M. 2010. Is the Tinetti Performance Oriented Mobility Assessment (POMA) a feasible and valid predictor of short-term fall risk in nursing home residents with dementia? *International Psychogeriatrics,* 22**,** 254-263.

STOLZMAN, S., DANDURAN, M., HUNTER, S. K. & BEMENT, M. H. 2015. Pain Response after Maximal Aerobic Exercise in Adolescents across Weight Status. *Med Sci Sports Exerc,* 47**,** 2431-40.

THIGPEN, M. T., LIGHT, K. E., CREEL, G. L. & FLYNN, S. M. 2000. Turning difficulty characteristics of adults aged 65 years or older. *Phys Ther,* 80**,** 1174-87.

THOMAS, J. I. & LANE, J. V. 2005. A pilot study to explore the predictive validity of 4 measures of falls risk in frail elderly patients. *Archives of Physical Medicine and Rehabilitation,* 86**,** 1636-1640.

TISSERAND, R., ROBERT, T., CHABAUD, P., LIVET, P., BONNEFOY, M. & CHEZE, L. 2015. Comparison between investigations of induced stepping postural responses and voluntary steps to better detect community-dwelling elderly fallers. *Neurophysiologie Clinique-Clinical Neurophysiology,* 45**,** 269-284.

TORPEL, A., BECKER, T., THIERS, A., HAMACHER, D. & SCHEGA, L. 2017. Inter-session Reliability of Isokinetic Strength Testing in Knee and Elbow Extension and Flexion Using the BTE PrimusRS. *J Sport Rehabil***,** 1-14.

TURCATO, A. M., GODI, M., GIORDANO, A., SCHIEPPATI, M. & NARDONE, A. 2015. The generation of centripetal force when walking in a circle: insight from the distribution of ground reaction forces recorded by plantar insoles. *Journal of Neuroengineering and Rehabilitation,* 12.

UMEDA, M., KEMPKA, L. E., GREENLEE, B. T. & WEATHERBY, A. C. 2016. A smaller magnitude of exercise-induced hypoalgesia in African Americans compared to non-Hispanic Whites: A potential influence of physical activity. *Biol Psychol,* 113**,** 46-51.

VAEGTER, H. B., DORGE, D. B., SCHMIDT, K. S., JENSEN, A. H. & GRAVEN-NIELSEN, T. 2018a. Test-Retest Reliabilty of Exercise-Induced Hypoalgesia After Aerobic Exercise. *Pain Med*.

VAEGTER, H. B. & GRAVEN-NIELSEN, T. 2016. Pain modulatory phenotypes differentiate subgroups with different clinical and experimental pain sensitivity. *Pain,* 157**,** 1480-1488.

VAEGTER, H. B., HANDBERG, G. & GRAVEN-NIELSEN, T. 2015. Isometric exercises reduce temporal summation of pressure pain in humans. *Eur J Pain,* 19**,** 973-83.

VAEGTER, H. B., LYNG, K. D., YTTERENG, F. W., CHRISTENSEN, M. H., SORENSEN, M. B. & GRAVEN-NIELSEN, T. 2018b. Exercise-Induced Hypoalgesia After Isometric Wall Squat Exercise: A Test-Retest Reliabilty Study. *Pain Med*.

VITON, J. M., TIMSIT, M., MESURE, S., MASSION, J., FRANCESCHI, J. P. & DELARQUE, A. 2000. Asymmetry of gait initiation in patients with unilateral knee arthritis. *Arch Phys Med Rehabil,* 81**,** 194-200.

VON DINCKLAGE, F., HACKBARTH, M., SCHNEIDER, M., BAARS, J. H. & REHBERG, B. 2009. Introduction of a continual RIII reflex threshold tracking algorithm. *Brain Res,* 1260**,** 24-9.

VON DINCKLAGE, F., OLBRICH, H., BAARS, J. H. & REHBERG, B. 2013. Habituation of the nociceptive flexion reflex is dependent on inter-stimulus interval and stimulus intensity. *J Clin Neurosci,* 20**,** 848-50.

VON KORFF, M., ORMEL, J., KEEFE, F. J. & DWORKIN, S. F. 1992. Grading the severity of chronic pain. *Pain,* 50**,** 133-49.

VOS, T., et al. 2012. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet,* 380**,** 2163-96.

WADDELL, G., NEWTON, M., HENDERSON, I., SOMERVILLE, D. & MAIN, C. J. 1993. A Fear-Avoidance Beliefs Questionnaire (FABQ) and the role of fear-avoidance beliefs in chronic low back pain and disability. *Pain,* 52**,** 157-168.

WAGNER, J., MAKEIG, S., GOLA, M., NEUPER, C. & MULLER-PUTZ, G. 2016. Distinct beta Band Oscillatory Networks Subserving Motor and Cognitive Control during Gait Adaptation. *J Neurosci,* 36**,** 2212-26.

WALTER, S., ELIASZIW, M. & DONNER, A. 1998. Sample size and optimal designs for reliability studies. *Statistics in medicine,* 17**,** 101-110.

WELLS, G. A., SHEA, B., O'CONNEL, D. ET AL. . 2009. *The Newcastle-Ottawa scale (NOS) for assessing the quailty of nonrandomised studies in meta-analyses.* [Online]. Available: http://www.ohri.ca/programs/clinical_epidemiology/nosgen.pdf [Accessed].

WERBER, A. & SCHILTENWOLF, M. 2016. Treatment of Lower Back Pain-The Gap between Guideline-Based Treatment and Medical Care Reality. *Healthcare (Basel),* 4.

WINTER, D. A. 1991. *The Biomechanics and Motor Control of Human Gait: Normal, Elderly and Pathological.,* Waterloo. Ontario, Waterloo Biomechanics.

WINTER, D. A., PATLA, A. E., PRINCE, F., ISHAC, M. & GIELO-PERCZAK, K. 1998. Stiffness control of balance in quiet standing. *J Neurophysiol,* 80**,** 1211-21.

From: [redacted] Research Support Group) [redacted]
Sent: 17 January 2019 15:24
To: Deborah Falla (School of Sport Exercise and Rehabilitation Sciences) [redacted]; Alison Rushton (Physiotherapy) [redacted]; Nicola Heneghan (Physiotherapy) [redacted]
Subject: Application for amendment ERN_18-0831A

Dear Professor Falla, Dr Rushton and Dr Heneghan

Re: "Investigating the analgesic effect of walking and resistance exercise in healthy adults"
Application for amendment ERN_18-0831A

Thank you for the above application for amendment, which was reviewed by the Science, Technology, Engineering and Mathematics Ethical Review Committee.

On behalf of the Committee, I can confirm that this amendment now has full ethical approval.

I would like to remind you that any substantive changes to the nature of the study as now amended, and/or any adverse events occurring during the study should be promptly brought to the Committee's attention by the Principal Investigator and may necessitate further ethical review. A revised amendment application form is now available at https://intranet.birmingham.ac.uk/finance/accounting/Research-Support-Group/Research-Ethics/Ethical-Review-Forms.aspx . Please ensure this form is submitted for any further amendments.

Please also ensure that the relevant requirements within the University's Code of Practice for Research and the information and guidance provided on the University's ethics webpages (available at https://intranet.birmingham.ac.uk/finance/accounting/Research-Support-Group/Research-Ethics/Links-and-Resources.aspx) are adhered to and referred to in any future applications for ethical review. It is now a requirement on the revised application form (https://intranet.birmingham.ac.uk/finance/accounting/Research-Support-Group/Research-Ethics/Ethical-Review-Forms.aspx) to confirm that this guidance has been consulted and is understood, and that it has been taken into account when completing your application for ethical review.

Please be aware that whilst Health and Safety (H&S) issues may be considered during the ethical review process, you are still required to follow the University's guidance on H&S and to ensure that H&S risk assessments have been carried out as appropriate. For further information about this, please contact your School H&S representative or the University's H&S Unit at healthandsafety@contacts.bham.ac.uk.

If you require a hard copy of this correspondence, please let me know.

Kind regards

[redacted]
Research Ethics Officer
Research Support Group
C Block Dome
Aston Webb Building
University of Birmingham
Edgbaston B15 2TT

Amendment B

UNIVERSITY OF BIRMINGHAM
APPLICATION FOR ETHICAL REVIEW – REQUEST FOR AMENDMENTS

Who should use this form:

- This form is to be completed by PIs or supervisors (for PGR student research) who are requesting ethical approval for amendments to research projects that have previously received ethical approval from the University of Birmingham.

  Please be aware that all new research projects undertaken by postgraduate research (PGR) students first registered as from 1st September 2008 will be subject to the University's Ethical Review Process. PGR students first registered before 1st September 2008 should refer to their Department/School/College for further advice.

- What constitutes an amendment?

  Amendments requiring approval may include, but are not limited to, additions to the research protocol, study population, recruitment of participants, access to personal records, research instruments, or participant information and consent documentation. Amendments must be approved before they are implemented.

NOTES:

- Answers to questions must be entered in the space provided
- An electronic version of the completed form should be submitted to the Research Ethics Officer, at the following email address: aer-ethics@contacts.bham.ac.uk. Please **do not** submit paper copies.
- If, in any section, you find that you have insufficient space, or you wish to supply additional material not specifically requested by the form, please submit it in a separate file, clearly marked and attached to the submission email.
- If you have any queries about the form, please address them to the Research Ethics Team.

UNIVERSITY OF BIRMINGHAM APPLICATION FOR ETHICAL REVIEW - REQUEST FOR AMENDMENTS	*OFFICE USE ONLY:* Application No: Date Received:

19. **TITLE OF PROJECT**

Investigating the analgesic effect of walking and resistance exercise in healthy adults

20. **APPROVAL DETAILS**

What is the Ethical Review Number (ERN) for the project?

ERN_18-0833

21. **THIS PROJECT IS:**

University of Birmingham Staff Research project ☐

University of Birmingham Postgraduate Research (PGR) student project ☒

Other ☐ (Please specify):

22. **INVESTIGATORS**

m) PLEASE GIVE DETAILS OF THE PRINCIPAL INVESTIGATORS OR SUPERVISORS (FOR PGR STUDENT PROJECTS)

Name: Title / first name / family name	Professor Deborah Falla
Highest qualification & position held:	Chair in Rehabilitation Science and Physiotherapy
School/Department	School of Sport, Exercise and Rehabilitation Sciences
Telephone:	[redacted]
Email address:	[redacted]

Name: Title / first name / family name	Dr. Alison Rushton
Highest qualification & position held:	Senior Lecturer
School/Department	School of Sport, Exercise and Rehabilitation Sciences
Telephone:	[redacted]
Email address:	[redacted]
Name: Title / first name / family name	Dr. Nicola Heneghan
Highest qualification & position held:	Lecturer
School/Department	School of Sport, Exercise and Rehabilitation Sciences
Telephone:	[redacted]
Email address:	[redacted]

n) PLEASE GIVE DETAILS OF ANY CO-INVESTIGATORS OR CO-SUPERVISORS (FOR PGR STUDENT PROJECTS)

o) In the case of PGR student projects, please give details of the student

Name of student:	Pauline Kuithan	Student No:	[redacted]
Course of study:	PhD		
Principal supervisor:	Prof. Deborah Falla		

23. **ESTIMATED START OF PROJECT** Date: 01/07/2018

ESTIMATED END OF PROJECT Date: 31/01/2020

24. **ORIGINAL APPLICATION FOR ETHICAL REVIEW AND ANY SUBSEQUENT APPROVED AMENDMENTS:**

Please complete the table below for the original application and any subsequent amendments submitted

Title and reference number of application or amendment	**Key points of application and/or changes made by amendment (include: aims of study, participant details, how participants were recruited and methodology)**	**Ethical considerations arising from these key points (e.g. gaining consent, risks to participants and/or researcher, points raised by Ethical Review Committee during review)**	**How were the ethical considerations addressed? (e.g. consent form, participant information, adhering to relevant procedures/clearance required)**
Original application	Aims: A feasibility study with a reliability and stability aspect on changes in pain sensitivity after exercise Participants: Healthy subjects will be recruited via poster advertisement on campus and via intranet. Methods: Quantitative Sensory Testing (Pressure and thermal pain threshold and tolerance, nociceptive reflex) will be analysed before and after an exercise intervention.	Consent: Written consent is gained before the start of the study. Risks: Only remote risks are considered. Testing pain sensitivity entitles the application of painful stimuli. However, this will not lead to any tissue damage. Committee points: 5. Clarification for six sessions 6. Information on pain perceived during the study (participant information leaflet) 7. Exclusion criteria 8. Amount of pain tolerance	Changes were made as outlined below and approved. Amendment does not affect these changes. 5. Further reference to justify 6 sessions is provided 6. Information leaflet changed 7. Exclusion criteria described in more details 8. Reference for no more pain tolerance is provided
Amendment 1	Minor changes in methods (time and details of protocols) and reimbursement	Committee points: Reimbursement	Changes made: reimbursement of participants pro rata

25. **DETAILS OF PROPOSED NEW AMENDMENT**
Provide details of the proposed new amendment, and clearly and explicitly state how the proposed new amendment will differ from the details of the study as already approved (see Q6 above).

This amendment will **expand the current project to include a new group of people with chronic low back pain**. The **same methods**, pain sensitivity testing before and after an exercise intervention over 6 sessions we used previously, **will be applied**.

Proposed title change: **Investigating the analgesic effect of walking and resistance exercise**

Because this is an extension of the project we would like to change the title as it better represents the study.

Why is amendment needed?
Chronic low back pain is the most common cause of years lived with disability (Vos et al., 2012). Moreover, it leads to a high financial burden with both direct and indirect costs for the health care system (Hill et al., 2011; Hong et al., 2013). Exercise is the management of choice (Falla and Hodges, 2017). However, the underlying mechanisms of effect of exercise are still not explored sufficiently. In the originally approved study, we examined temporal changes in pain sensitivity directly after exercise in healthy people. Preliminary data support the observation, that changes in pain sensitivity are stable over multiple sessions. The exercise interventions chosen for this project were tolerated well by the participants and there were no adverse reactions or events.

In people with chronic low back pain, dysfunction of this endogenous pain inhibition (exercise induced hypoalgesia) has been shown in our previous project (ERN_16-1389B) and supports the aim for further research. These results could contribute to the prediction of the outcome of exercise programmes for people with low back pain.

5. Population
Inclusion criteria: People with chronic non-specific low back pain
The following definition for non-specific chronic low back pain is pain in the region of the lower back which is not related to serious pathology and/or does not have a specific cause (also known as mechanical low back pain). Chronic refers to a sub type where back pain has persisted at least 3 months and has resulted in pain on at least half the days in the past 6 months. If possible, participants should be willing to refrain from analgesic medication during the testing episode.
Exclusion criteria:

- Concurrent systemic, rheumatic or neuro-musculoskeletal disorders which may confound testing or are currently pregnant.
- Acute radicular low back pain or pain related to acute trauma, fractures, or spinal stenosis.
  - Participants under active management of LBP through specific medications prescribed by a GP, consultant or therapists (physiotherapist, osteopath, chiropractor) less than 3 months before the possible enrolment others than PRN (per necessary).
  - Exercising for more than 90 minutes of vigorous intensity per day or competing in professional or high-level sport

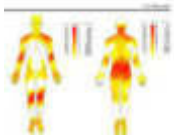
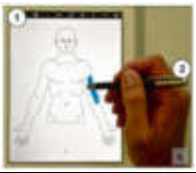
6. **Compensation**
Reimbursement of back pain participants will be £7.50/h

7. **Recruitment**
We will recruit via posters displayed at the University of Birmingham (Attachment 1), the CPR Spine register and social media affiliated with the centre or researcher.

8. Patient reported Outcome measurements
Questionnaires (Attachment 7)
To better describe our population we will include frequently used standardised and validated questionnaires for people with low back pain such as the Oswestry Disability Index or the Fear Avoidance Beliefs Questionnaire (Brown et al., 1997; Fairbank and Pynsent, 2000;

Lame et al., 2008; Osman et al., 2000; Waddell et al., 1993). Furthermore, we will adapt questionnaires from this study with questions regarding their pain before, within and after each session. We will use a numeric rating scale to assess and monitor pain levels during the exercise (Breivik et al., 2008).

Pain drawing
In addition, we will ask participants to shade painful areas on a body chart using an iPad (see picture). Pain drawing have been used in previous projects and its method has been validated (Barbero et al., 2015).

26. **JUSTIFICATION FOR PROPOSED <u>NEW AMENDMENT</u>**

Based on preliminary testing, the study is feasible and can be extended to a population with chronic low back pain. This is supported by discussing this study in a local Patient and Public Involvement event and by comments from participants from the ongoing study.
As described above, chronic low back pain is a massive financial burden for the healthcare system and its management needs to be further improved. Chronic pain can lead to changes in pain sensitivity as earlier shown in a previous project. To make clinically relevant conclusions, we will take the preliminary findings from the original study, which will hopefully be completed in May 2019. If we know how healthy people respond, this will help to inform how people with chronic low back pain will respond and if those differ over six sessions.

Feedback form our current participants suggested that the exercise targets the right area, i.e. lumbar region for the resistance task, but as it is adjusted to individual levels, it seems to be feasible.

"Do you think this programme is feasible for people with low back pain and why?"

- Resistance group (4 sets of 8 repetitions, 50% of voluntary isometric maximum strength):
  "*possibly because it could help to strengthen their back and possibly relieve some of the pain*"
  "*yes they can do it*"
- Walking group (brisk walking for 15 minutes at ~70% of heart rate (220-age) on a treadmill)
  "*yes, it didn't aggravate my back at all*"
  "*yes, the walking programme is tailored to their heart rate so is achievable per any level of fitness and is functional*"

Findings will help to shape future management of low back pain. Based on previous results (ERN_16-1389B) pain sensitivity is impaired in people with chronic low back pain after a lifting task. If these results remain stable over multiple session has not been tested before. This could have potentially an impact on positive outcomes of exercise programmes.

27. **ETHICAL CONSIDERATIONS**

What ethical considerations, if any, are raised by the proposed <u>new amendment</u>?

Pilot testing and data collection up to now did not reveal any adverse effects or issues with the conduction of the study and participants accepted both testing and exercise without any issues. However, we are currently only testing in an asymptomatic population.

In this amendment we will expand the currently tested protocol to a different group which is more vulnerable and therefore it is to expect that this might cause adverse effects or reproduce/ increase the participants' symptoms.

In people with low back pain, the tasks (i.e. resistance exercise) might lead to a temporary increase of symptoms, likely to be described as temporary stiffness, or soreness. Nevertheless, exercise is **safe** and **recommended** as the treatment of choice for management of low back pain (O'Sullivan et al., 2017; Smith et al., 2017; Werber and Schiltenwolf, 2016). Increase in symptoms would be similar if attending a gym. The aim of the study is not to provoke those symptoms, and for that reason the intensity will be adjusted to 50% of their maximum voluntary strength/ walking based on a comfortable pace and 70% of their maximal heart rate. Most exercise programmes will use higher intensities in a population, who is currently not undergoing any treatment. However, the intensity seems to be sufficient to produce temporary analgesic effects.
Furthermore, all sessions are supervised by a musculoskeletal physiotherapist, with more than 10 years of clinical experience in that area. Moreover, in our previous study (ERN_16-1389B), which comprised a more provocative rotational task, no lasting problems were reported. Pain perceived during the task settled quickly after the session (for most participants with ending of the task or during the post-test of pain sensitivity).
Furthermore, this task will be adjusted to each individual participant, they can stop anytime, and there will be a minimum of 2 days between each session to have adequate recovery time.

28.

29. **DECLARATION BY APPLICANTS**

I make this application on the basis that the information it contains is confidential and will be used by the University of Birmingham for the purposes of ethical review and monitoring of the research project described herein, and to satisfy reporting requirements to regulatory bodies. The information will not be used for any other purpose without my prior consent.

I declare that:

- The information in this form together with any accompanying information is complete and correct to the best of my knowledge and belief and I take full responsibility for it.
- I undertake to abide by University Code of Conduct for Research (http://www.birmingham.ac.uk/Documents/university/legal/research.pdf) alongside any other relevant professional bodies' codes of conduct and/or ethical guidelines.
- I will report any changes affecting the ethical aspects of the project to the University of Birmingham Research Ethics Officer.
- I will report any adverse or unforeseen events which occur to the relevant Ethics Committee project to the University of Birmingham Research Ethics Officer.

Signature of Principal investigator/project supervisor:	Deborah Falla
Date:	11/03/19

ALEXANDROV, A. V., FROLOV, A. A., HORAK, F. B., CARLSON-KUHTA, P. & PARK, S. 2005. Feedback equilibrium control during human standing. *Biol Cybern,* 93**,** 309-22.

BAIAMONTE, B. A., KRAEMER, R. R., CHABRECK, C. N., REYNOLDS, M. L., MCCALEB, K. M., SHAHEEN, G. L. & HOLLANDER, D. B. 2017. Exercise-induced hypoalgesia: Pain tolerance, preference and tolerance for exercise intensity, and physiological correlates following dynamic circuit resistance exercise. *J Sports Sci,* 35**,** 1-7.

BALAGUIER, R., MADELEINE, P. & VUILLERME, N. 2016. Is One Trial Sufficient to Obtain Excellent Pressure Pain Threshold Reliability in the Low Back of Asymptomatic Individuals? A Test-Retest Study. *PLoS One,* 11**,** e0160866.

BARATTO, L., MORASSO, P. G., RE, C. & SPADA, G. 2002. A new look at posturographic analysis in the clinical context: sway-density versus other parameterization techniques. *Motor Control,* 6**,** 246-70.

BARBERO, M., MORESI, F., LEONI, D., GATTI, R., EGLOFF, M. & FALLA, D. 2015. Test-retest reliability of pain extent and pain location using a novel method for pain drawing analysis. *Eur J Pain,* 19**,** 1129-38.

BARKER, S., CRAIK, R., FREEDMAN, W., HERRMANN, N. & HILLSTROM, H. 2006. Accuracy, reliability, and validity of a spatiotemporal gait analysis system. *Med Eng Phys,* 28**,** 460-7.

BASQUES, B. A., ESPINOZA ORIAS, A. A., SHIFFLETT, G. D., FICE, M. P., ANDERSSON, G. B., AN, H. S. & INOUE, N. 2016. The Kinematics and Spondylosis of the Lumbar Spine Vary Depending on the Levels of Motion Segments in Individuals with Low Back Pain. *Spine (Phila Pa 1976)*.

BAUMGARTNER, T. A. 2000. Estimating the Stability Reliability of a Score. *Measurement in Physical Education and Exercise Science,* 4**,** 175-178.

BIANCHI, L., ANGELINI, D., ORANI, G. P. & LACQUANITI, F. 1998. Kinematic coordination in human gait: relation to mechanical energy cost. *J Neurophysiol,* 79**,** 2155-70.

BLACK, C. D., HUBER, J. K., ELLINGSON, L. D., ADE, C. J., TAYLOR, E. L., GRIFFETH, E. M., JANZEN, N. R. & SUTTERFIELD, S. L. 2017. Exercise-Induced Hypoalgesia Is Not Influenced by Physical Activity Type and Amount. *Med Sci Sports Exerc,* 49**,** 975-982.

BLAND, J. M. & ALTMAN, D. G. 1999. Measuring agreement in method comparison studies. *Stat Methods Med Res,* 8**,** 135-60.

BLUMENSTIEL, K., GERHARDT, A., ROLKE, R., BIEBER, C., TESARZ, J., FRIEDERICH, H. C., EICH, W. & TREEDE, R. D. 2011. Quantitative Sensory Testing Profiles in Chronic Back Pain Are Distinct From Those in Fibromyalgia. *Clinical Journal of Pain,* 27**,** 682-690.

BOOTH, M. 2000. Assessment of physical activity: An international perspective. (vol 71, pg 114, 2000). *Research Quarterly for Exercise and Sport,* 71**,** 312-312.

BORG, G. A. V. 1982. Psychophysical bases of perceived exertion. *Medicine & Science in Sports & Exercise,* 14**,** 377-381.

BORGHESE, N. A., BIANCHI, L. & LACQUANITI, F. 1996. Kinematic determinants of human locomotion. *J Physiol,* 494 (Pt 3)**,** 863-79.

BRAZIER, J. E., HARPER, R., JONES, N. M., O'CATHAIN, A., THOMAS, K. J., USHERWOOD, T. & WESTLAKE, L. 1992. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ,* 305**,** 160-4.

BREIVIK, H., BORCHGREVINK, P. C., ALLEN, S. M., ROSSELAND, L. A., ROMUNDSTAD, L., HALS, E. K., KVARSTEIN, G. & STUBHAUG, A. 2008. Assessment of pain. *Br J Anaesth,* 101**,** 17-24.

BRELLENTHIN, A. G., CROMBIE, K. M., COOK, D. B., SEHGAL, N. & KOLTYN, K. F. 2017. Psychosocial Influences on Exercise-Induced Hypoalgesia. *Pain Med,* 18**,** 538-550.

BROWN, T. A., CHORPITA, B. F., KOROTITSCH, W. & BARLOW, D. H. 1997. Psychometric properties of the Depression Anxiety Stress Scales (DASS) in clinical samples. *Behav Res Ther,* 35**,** 79-89.

CAMARDA, S. R., TEBEXRENI, A. S., PAFARO, C. N., SASAI, F. B., TAMBEIRO, V. L., JULIANO, Y. & BARROS NETO, T. L. 2008. Comparison of maximal heart rate using the prediction equations proposed by Karvonen and Tanaka. *Arq Bras Cardiol,* 91**,** 311-4.

CAPPELLINI, G., IVANENKO, Y. P., POPPELE, R. E. & LACQUANITI, F. 2006. Motor patterns in human walking and running. *J Neurophysiol,* 95**,** 3426-37.

CAVAGNA, G. A. & MARGARIA, R. 1966. Mechanics of walking. *J Appl Physiol,* 21**,** 271-8.

CHOLEWICKI, J. & MCGILL, S. M. 1996. Mechanical stability of the in vivo lumbar spine: implications for injury and chronic low back pain. *Clin Biomech (Bristol, Avon),* 11**,** 1-15.

CLARK, D. J., TING, L. H., ZAJAC, F. E., NEPTUNE, R. R. & KAUTZ, S. A. 2010. Merging of healthy motor modules predicts reduced locomotor performance and muscle coordination complexity post-stroke. *J Neurophysiol,* 103**,** 844-57.

COSTA, Y. M., MORITA-NETO, O., DE ARAUJO-JUNIOR, E. N., SAMPAIO, F. A., CONTI, P. C. & BONJARDIM, L. R. 2017. Test-retest reliability of quantitative sensory testing for mechanical somatosensory and pain modulation assessment of masticatory structures. *J Oral Rehabil,* 44**,** 197-204.

COURTINE, G., DE NUNZIO, A. M., SCHMID, M., BERETTA, M. V. & SCHIEPPATI, M. 2007. Stance- and locomotion-dependent processing of vibration-induced proprioceptive inflow from multiple muscles in humans. *J Neurophysiol,* 97**,** 772-9.

COURTINE, G., PAPAXANTHIS, C. & SCHIEPPATI, M. 2006. Coordinated modulation of locomotor muscle synergies constructs straight-ahead and curvilinear walking in humans. *Exp Brain Res,* 170**,** 320-35.

COURTINE, G. & SCHIEPPATI, M. 2003a. Human walking along a curved path. I. Body trajectory, segment orientation and the effect of vision. *Eur J Neurosci,* 18**,** 177-90.

COURTINE, G. & SCHIEPPATI, M. 2003b. Human walking along a curved path. II. Gait features and EMG patterns. *Eur J Neurosci,* 18**,** 191-205.

COURTINE, G. & SCHIEPPATI, M. 2004. Tuning of a basic coordination pattern constructs straight-ahead and curved walking in humans. *J Neurophysiol,* 91**,** 1524-35.

COUTTS, F. 1999. Gait analysis in the therapeutic environment. *Man Ther,* 4**,** 2-10.

CREATH, R., KIEMEL, T., HORAK, F., PETERKA, R. & JEKA, J. 2005. A unified view of quiet and perturbed stance: simultaneous co-existing excitable modes. *Neurosci Lett,* 377**,** 75-80.

CRENNA, P. & FRIGO, C. 1991. A motor programme for the initiation of forward-oriented movements in humans. *J Physiol,* 437**,** 635-53.

CUMMINS, T. M., KUCHARCZYK, M. M., GRAVEN-NIELSEN, T. & BANNISTER, K. 2020. Activation of the descending pain modulatory system using cuff pressure algometry: Back translation from man to rat. *Eur J Pain,* 24**,** 1330-1338.

DAVIS, B. L. & VAUGHAN, C. L. 1993. Phasic behavior of EMG signals during gait: Use of multivariate statistics. *J Electromyogr Kinesiol,* 3**,** 51-60.

DAVIS, R. B., OUNPUU, S., DENNIS, T. & GAGE, J. R. 1991. A gait analysis data collection and reduction technique. *Hum Mov Sci,* 10**,** 575-587.

DE NUNZIO, A. M., NARDONE, A., PICCO, D., NILSSON, J. & SCHIEPPATI, M. 2008. Alternate trains of postural muscle vibration promote cyclic body displacement in standing parkinsonian patients. *Mov Disord,* 23**,** 2186-93.

DE NUNZIO, A. M., NARDONE, A. & SCHIEPPATI, M. 2005. Head stabilization on a continuously oscillating platform: the effect of a proprioceptive disturbance on the balancing strategy. *Exp Brain Res,* 165**,** 261-72.

DOMENICI, P., JAMON, M. & CLARAC, F. 1998. Curve walking in freely moving crayfish (Procambarus clarkii). *J Exp Biol,* 201 (Pt 9)**,** 1315-29.

DREW, T., PRENTICE, S. & SCHEPENS, B. 2004. Cortical and brainstem control of locomotion. *Prog Brain Res,* 143**,** 251-61.

DWORKIN, R. H., TURK, D. C., FARRAR, J. T., HAYTHORNTHWAITE, J. A., JENSEN, M. P., KATZ, N. P., KERNS, R. D., STUCKI, G., ALLEN, R. R., BELLAMY, N., CARR, D. B., CHANDLER, J., COWAN, P., DIONNE, R., GALER, B. S., HERTZ, S., JADAD, A. R., KRAMER, L. D., MANNING, D. C., MARTIN, S., MCCORMICK, C. G., MCDERMOTT, M. P., MCGRATH, P., QUESSY, S., RAPPAPORT, B. A., ROBBINS, W., ROBINSON, J. P., ROTHMAN, M., ROYAL, M. A., SIMON, L., STAUFFER, J. W., STEIN, W., TOLLETT, J., WERNICKE, J., WITTER, J. & IMMPACT 2005. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain,* 113**,** 9-19.

ELDRIDGE, S. M., CHAN, C. L., CAMPBELL, M. J., BOND, C. M., HOPEWELL, S., THABANE, L., LANCASTER, G. A. & GROUP, P. C. 2016. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. *Pilot Feasibility Stud,* 2**,** 64.

FAIRBANK, J. C. & PYNSENT, P. B. 2000. The Oswestry Disability Index. *Spine (Phila Pa 1976),* 25**,** 2940-52; discussion 2952.

FALLA, D., ARENDT-NIELSEN, L. & FARINA, D. 2008. Gender-specific adaptations of upper trapezius muscle activity to acute nociceptive stimulation. *Pain,* 138**,** 217-25.

FALLA, D., GIZZI, L., TSCHAPEK, M., ERLENWEIN, J. & PETZKE, F. 2014. Reduced task-induced variations in the distribution of activity across back muscle regions in individuals with low back pain. *Pain,* 155**,** 944-953.

FALLA, D. & HODGES, P. W. 2017. Individualized Exercise Interventions for Spinal Pain. *Exerc Sport Sci Rev,* 45**,** 105-115.

GAJSAR, H., NAHRWOLD, K., TITZE, C., HASENBRING, M. I. & VAEGTER, H. B. 2018. Exercise does not produce hypoalgesia when performed immediately after a painful stimulus. *Scandinavian Journal of Pain,* 18**,** 311-320.

GAJSAR, H., TITZE, C., HASENBRING, M. I. & VAEGTER, H. B. 2017. Isometric Back Exercise Has Different Effect on Pressure Pain Thresholds in Healthy Men and Women. *Pain Med,* 18**,** 917-923.

GALLAGHER, K. M. & CALLAGHAN, J. P. 2015. Early static standing is associated with prolonged standing induced low back pain. *Human Movement Science,* 44**,** 111-121.

GALLAGHER, K. M. & CALLAGHAN, J. P. 2016. Standing on a declining surface reduces transient prolonged standing induced low back pain development. *Appl Ergon,* 56**,** 76-83.

GEWANDTER, J. S., DWORKIN, R. H., TURK, D. C., MCDERMOTT, M. P., BARON, R., GASTONGUAY, M. R., GILRON, I., KATZ, N. P., MEHTA, C., RAJA, S. N., SENN, S., TAYLOR, C., COWAN, P., DESJARDINS, P., DIMITROVA, R., DIONNE, R., FARRAR, J. T., HEWITT, D. J., IYENGAR, S., JAY, G. W., KALSO, E., KERNS, R. D., LEFF, R., LEONG, M., PETERSEN, K. L., RAVINA, B. M., RAUSCHKOLB, C., RICE, A. S., ROWBOTHAM, M. C., SAMPAIO, C., SINDRUP, S. H., STAUFFER, J. W., STEIGERWALD, I., STEWART, J., TOBIAS, J., TREEDE, R. D., WALLACE, M. & WHITE, R. E. 2014. Research designs for proof-of-concept chronic pain clinical trials: IMMPACT recommendations. *Pain,* 155**,** 1683-95.

GIZZI, L., NIELSEN, J. F., FELICI, F., IVANENKO, Y. P. & FARINA, D. 2011. Impulses of activation but not motor modules are preserved in the locomotion of subacute stroke patients. *Journal of Neurophysiology,* 106**,** 202-210.

GODI, M., NARDONE, A. & SCHIEPPATI, M. 2010. Curved walking in hemiparetic patients. *J Rehabil Med,* 42**,** 858-65.

GRAVEN-NIELSEN, T., VAEGTER, H. B., FINOCCHIETTI, S., HANDBERG, G. & ARENDT-NIELSEN, L. 2015. Assessment of musculoskeletal pain sensitivity and temporal summation by cuff pressure algometry: a reliability study. *Pain,* 156**,** 2193-2202.

GRYFE, C. I., AMIES, A. & ASHLEY, M. J. 1977. A longitudinal study of falls in an elderly population: I. Incidence and morbidity. *Age Ageing,* 6**,** 201-10.

GUGLIELMETTI, S., NARDONE, A., DE NUNZIO, A. M., GODI, M. & SCHIEPPATI, M. 2009. Walking along circular trajectories in Parkinson's disease. *Mov Disord,* 24**,** 598-604.

HASE, K. & STEIN, R. B. 1998. Analysis of rapid stopping during human walking. *J Neurophysiol,* 80**,** 255-61.

HASE, K. & STEIN, R. B. 1999. Turning strategies during human walking. *J Neurophysiol,* 81**,** 2914-22.

HERMENS, H. J., FRERIKS, B., MERLETTI, R., HAGG, G. G., STEGEMAN, D., BLOK, J., RAU, G. & DISSELHORST-KLUG, C. 1999. European Recommendations for Surface Electro-MyoGraphy: Results of the SENIAM Project. Enschede, The Netherlands: Roessingh Research and Development.

HILL, J. C., WHITEHURST, D. G., LEWIS, M., BRYAN, S., DUNN, K. M., FOSTER, N. E., KONSTANTINOU, K., MAIN, C. J., MASON, E., SOMERVILLE, S., SOWDEN, G., VOHORA, K. & HAY, E. M. 2011.

Comparison of stratified primary care management for low back pain with current best practice (STarT Back): a randomised controlled trial. *Lancet,* 378**,** 1560-71.
HODGES, P. W., GURFINKEL, V. S., BRUMAGNE, S., SMITH, T. C. & CORDO, P. C. 2002. Coexistence of stability and mobility in postural control: evidence from postural compensation for respiration. *Exp Brain Res,* 144**,** 293-302.
HODSON-TOLE, E. F. & WAKELING, J. M. 2009. Motor unit recruitment for dynamic tasks: current understanding and future directions. *J Comp Physiol B,* 179**,** 57-66.
HOJEN-SORENSEN, P. A. D. F. R., WINTHER, O. & HANSEN, L. K. 2002. Mean-field approaches to independent component analysis. *Neural Computation,* 14**,** 889-918.
HONG, J., REED, C., NOVICK, D. & HAPPICH, M. 2013. Costs associated with treatment of chronic low back pain: an analysis of the UK General Practice Research Database. *Spine (Phila Pa 1976),* 38**,** 75-82.
HOOGENDOORN, W. E., BONGERS, P. M., DE VET, H. C., DOUWES, M., KOES, B. W., MIEDEMA, M. C., ARIENS, G. A. & BOUTER, L. M. 2000. Flexion and rotation of the trunk and lifting at work are risk factors for low back pain: results of a prospective cohort study. *Spine (Phila Pa 1976),* 25**,** 3087-92.
HUBSCHER, M., MOLONEY, N., REBBECK, T., TRAEGER, A. & REFSHAUGE, K. M. 2014. 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,* 30**,** 886-893.
ICKMANS, K., MALFLIET, A., DE KOONING, M., GOUDMAN, L., HUBLOUE, I., SCHMITZ, T., GOUBERT, D. & AGUILAR-FERRANDIZ, M. E. 2017. Lack of Gender and Age Differences in Pain Measurements Following Exercise in People with Chronic Whiplash-Associated Disorders. *Pain Physician,* 20**,** E829-E840.
IVANENKO, Y. P., CAPPELLINI, G., DOMINICI, N., POPPELE, R. E. & LACQUANITI, F. 2005. Coordination of locomotion with voluntary movements in humans. *J Neurosci,* 25**,** 7238-53.
IVANENKO, Y. P., CAPPELLINI, G., POPPELE, R. E. & LACQUANITI, F. 2008a. Spatiotemporal organization of alpha-motoneuron activity in the human spinal cord during different gaits and gait transitions. *Eur J Neurosci,* 27**,** 3351-68.
IVANENKO, Y. P., D'AVELLA, A., POPPELE, R. E. & LACQUANITI, F. 2008b. On the origin of planar covariation of elevation angles during human locomotion. *J Neurophysiol,* 99**,** 1890-8.
IVANENKO, Y. P., POPPELE, R. E. & LACQUANITI, F. 2004. Five basic muscle activation patterns account for muscle activity during human locomotion. *J Physiol,* 556**,** 267-82.
IVANENKO, Y. P., POPPELE, R. E. & LACQUANITI, F. 2006. Motor control programs and walking. *Neuroscientist,* 12**,** 339-48.
JENKINSON, C., STEWART-BROWN, S., PETERSEN, S. & PAICE, C. 1999. Assessment of the SF-36 version 2 in the United Kingdom. *J Epidemiol Community Health,* 53**,** 46-50.
KALICHMAN, L., KIM, D. H., LI, L., GUERMAZI, A. & HUNTER, D. J. 2010. Computed tomography-evaluated features of spinal degeneration: prevalence, intercorrelation, and association with self-reported low back pain. *Spine J,* 10**,** 200-8.
KAVOUNOUDIAS, A., GILHODES, J. C., ROLL, R. & ROLL, J. P. 1999. From balance regulation to body orientation: two goals for muscle proprioceptive information processing? *Exp Brain Res,* 124**,** 80-8.
KAVOUNOUDIAS, A., ROLL, R. & ROLL, J. P. 1998. The plantar sole is a 'dynamometric map' for human balance control. *Neuroreport,* 9**,** 3247-52.
KHATRI, C., CHAPMAN, S. J., GLASBEY, J., KELLY, M., NEPOGODIEV, D., BHANGU, A., FITZGERALD, J. E. & ON BEHALF OF THE, S. C. 2015. Social Media and Internet Driven Study Recruitment: Evaluating a New Model for Promoting Collaborator Engagement and Participation. *PLOS ONE,* 10**,** e0118899.
KOES, B. W., VAN TULDER, M. W. & THOMAS, S. 2006. Diagnosis and treatment of low back pain. *BMJ,* 332**,** 1430-4.

KOLENDA, T., SIGURDSSON, S., WINTHER, O., HANSEN, L. K. & LARSEN, J. 2002. DTU: Toolbox. Lyngby, Denmark: ISP Group at Institute of Informatics and Mathematical Modeling at the Technical University of Denmark.

KOLTYN, K. F. 2002. Exercise-induced hypoalgesia and intensity of exercise. *Sports Med,* 32**,** 477-87.

KONG, J. T., JOHNSON, K. A., BALISE, R. R. & MACKEY, S. 2013. Test-retest reliability of thermal temporal summation using an individualized protocol. *J Pain,* 14**,** 79-88.

KOTTNER, J., AUDIGE, L., BRORSON, S., DONNER, A., GAJEWSKI, B. J., HROBJARTSSON, A., ROBERTS, C., SHOUKRI, M. & STREINER, D. L. 2011. Guidelines for Reporting Reliability and Agreement Studies (GRRAS) were proposed. *Int J Nurs Stud,* 48**,** 661-71.

LABRUYERE, R. & VAN HEDEL, H. J. 2012. Curve walking is not better than straight walking in estimating ambulation-related domains after incomplete spinal cord injury. *Arch Phys Med Rehabil,* 93**,** 796-801.

LACQUANITI, F., GRASSO, R. & ZAGO, M. 1999. Motor Patterns in Walking. *News Physiol Sci,* 14**,** 168-174.

LAJOIE, Y. & GALLAGHER, S. P. 2004. Predicting falls within the elderly community: comparison of postural sway, reaction time, the Berg balance scale and the Activities-specific Balance Confidence (ABC) scale for comparing fallers and non-fallers. *Archives of Gerontology and Geriatrics,* 38**,** 11-26.

LAME, I. E., PETERS, M. L., KESSELS, A. G., VAN KLEEF, M. & PATIJN, J. 2008. Test--retest stability of the Pain Catastrophizing Scale and the Tampa Scale for Kinesiophobia in chronic pain over a longer period of time. *J Health Psychol,* 13**,** 820-6.

LIMA, L. V., ABNER, T. S. S. & SLUKA, K. A. 2017. Does exercise increase or decrease pain? Central mechanisms underlying these two phenomena. *J Physiol,* 595**,** 4141-4150.

LOVIBOND, S. H. & LOVIBOND, P. F. 1995. *Manual for the depression anxiety stress scales,* Sydney, N.S.W., Psychology Foundation of Australia.

MACKINNON, C. D., BISSIG, D., CHIUSANO, J., MILLER, E., RUDNICK, L., JAGER, C., ZHANG, Y., MILLE, M. L. & ROGERS, M. W. 2007. Preparation of anticipatory postural adjustments prior to stepping. *J Neurophysiol,* 97**,** 4368-79.

MARCUZZI, A., WRIGLEY, P. J., DEAN, C. M., ADAMS, R. & HUSH, J. M. 2017. The long-term reliability of static and dynamic quantitative sensory testing in healthy individuals. *Pain,* 158**,** 1217-1223.

MARTINEZ-VALDES, E., LAINE, C. M., FALLA, D., MAYER, F. & FARINA, D. 2016. High-density surface electromyography provides reliable estimates of motor unit behavior. *Clin Neurophysiol,* 127**,** 2534-41.

MASSION, J. 1992. Movement, posture and equilibrium: interaction and coordination. *Prog Neurobiol,* 38**,** 35-56.

MASSION, J., ALEXANDROV, A. & FROLOV, A. 2004. Why and how are posture and movement coordinated? *Prog Brain Res,* 143**,** 13-27.

MASSION, J., IOFFE, M., SCHMITZ, C., VIALLET, F. & GANTCHEVA, R. 1999. Acquisition of anticipatory postural adjustments in a bimanual load-lifting task: normal and pathological aspects. *Exp Brain Res,* 128**,** 229-35.

MATSUYAMA, K. & DREW, T. 1997. Organization of the projections from the pericruciate cortex to the pontomedullary brainstem of the cat: a study using the anterograde tracer Phaseolus vulgaris-leucoagglutinin. *J Comp Neurol,* 389**,** 617-41.

MAURER, C., MERGNER, T. & PETERKA, R. J. 2006. Multisensory control of human upright stance. *Exp Brain Res,* 171**,** 231-50.

MAZAHERI, M., COENEN, P., PARNIANPOUR, M., KIERS, H. & VAN DIEEN, J. H. 2013. Low back pain and postural sway during quiet standing with and without sensory manipulation: a systematic review. *Gait Posture,* 37**,** 12-22.

MCCOLLUM, G. & LEEN, T. K. 1989. Form and exploration of mechanical stability limits in erect stance. *J Mot Behav,* 21**,** 225-44.

MCGOWAN, C. P., NEPTUNE, R. R., CLARK, D. J. & KAUTZ, S. A. 2010. Modular control of human walking: Adaptations to altered mechanical demands. *J Biomech,* 43**,** 412-9.
MCILROY, W. E. & MAKI, B. E. 1997. Preferred placement of the feet during quiet stance: development of a standardized foot placement for balance testing. *Clin Biomech (Bristol, Avon),* 12**,** 66-70.
MCPHEETERS, M. L., KRIPALANI, S., PETERSON, N. B., IDOWU, R. T., JEROME, R. N., POTTER, S. A. & ANDREWS, J. C. 2012. Closing the quality gap: revisiting the state of the science (vol. 3: quality improvement interventions to address health disparities). *Evid Rep Technol Assess (Full Rep)***,** 1-475.
MICALOS, P. S. & ARENDT-NIELSEN, L. 2016. Differential pain response at local and remote muscle sites following aerobic cycling exercise at mild and moderate intensity. *Springerplus,* 5**,** 91.
MIDDLEBROOK, N., HENEGHAN, N. R., EVANS, D. W., RUSHTON, A. & FALLA, D. 2020. Reliability of temporal summation, thermal and pressure pain thresholds in a healthy cohort and musculoskeletal trauma population. *PLoS One,* 15**,** e0233521.
MIENTJES, M. I. & FRANK, J. S. 1999. Balance in chronic low back pain patients compared to healthy people under various conditions in upright standing. *Clin Biomech (Bristol, Avon),* 14**,** 710-6.
MOLONEY, N. A., HALL, T. M. & DOODY, C. M. 2012. Reliability of thermal quantitative sensory testing: a systematic review. *J Rehabil Res Dev,* 49**,** 191-207.
MORASSO, P. G. & SANGUINETI, V. 2002. Ankle muscle stiffness alone cannot stabilize balance during quiet standing. *J Neurophysiol,* 88**,** 2157-62.
MORASSO, P. G. & SCHIEPPATI, M. 1999. Can muscle stiffness alone stabilize upright standing? *J Neurophysiol,* 82**,** 1622-6.
MULLER, J., MULLER, S., ENGEL, T., RESCHKE, A., BAUR, H. & MAYER, F. 2016. Stumbling reactions during perturbed walking: Neuromuscular reflex activity and 3-D kinematics of the trunk - A pilot study. *J Biomech,* 49**,** 933-8.
NAUGLE, K. M., FILLINGIM, R. B. & RILEY, J. L.2012. A meta-analytic review of the hypoalgesic effects of exercise. *J Pain,* 13**,** 1139-50.
NAUGLE, K. M., NAUGLE, K. E., FILLINGIM, R. B. & RILEY, J. L. 2014a. Isometric exercise as a test of pain modulation: effects of experimental pain test, psychological variables, and sex. *Pain Med,* 15**,** 692-701.
NAUGLE, K. M., NAUGLE, K. E., FILLINGIM, R. B., SAMUELS, B. & RILEY, J. L. 2014b. Intensity thresholds for aerobic exercise-induced hypoalgesia. *Med Sci Sports Exerc,* 46**,** 817-25.
NIE, H., ARENDT-NIELSEN, L., ANDERSEN, H. & GRAVEN-NIELSEN, T. 2005. Temporal summation of pain evoked by mechanical stimulation in deep and superficial tissue. *J Pain,* 6**,** 348-55.
NIE, H., ARENDT-NIELSEN, L., MADELEINE, P. & GRAVEN-NIELSEN, T. 2006. Enhanced temporal summation of pressure pain in the trapezius muscle after delayed onset muscle soreness. *Exp Brain Res,* 170**,** 182-90.
NIE, H., GRAVEN-NIELSEN, T. & ARENDT-NIELSEN, L. 2009. Spatial and temporal summation of pain evoked by mechanical pressure stimulation. *Eur J Pain,* 13**,** 592-9.
NIES, N. & SINNOTT, P. L. 1991. Variations in balance and body sway in middle-aged adults. Subjects with healthy backs compared with subjects with low-back dysfunction. *Spine (Phila Pa 1976),* 16**,** 325-30.
NIJS, J., APELDOORN, A., HALLEGRAEFF, H., CLARK, J., SMEETS, R., MALFLIET, A., GIRBES, E. L., DE KOONING, M. & ICKMANS, K. 2015. Low back pain: guidelines for the clinical classification of predominant neuropathic, nociceptive, or central sensitization pain. *Pain Physician,* 18**,** E333-46.
O' CONAIRE, E., RUSHTON, A. & WRIGHT, C. 2011. The assessment of vibration sense in the musculoskeletal examination: Moving towards a valid and reliable quantitative approach to vibration testing in clinical practice. *Man Ther,* 16**,** 296-300.
O'KANE, F. W., MCGIBBON, C. A. & KREBS, D. E. 2003. Kinetic analysis of planned gait termination in healthy subjects and patients with balance disorders. *Gait Posture,* 17**,** 170-9.

O'NEILL, S., KJAER, P., GRAVEN-NIELSEN, T., MANNICHE, C. & ARENDT-NIELSEN, L. 2011. Low pressure pain thresholds are associated with, but does not predispose for, low back pain. *Eur Spine J,* 20**,** 2120-5.
O'SULLIVAN, K., O'KEEFFE, M. & O'SULLIVAN, P. 2017. NICE low back pain guidelines: opportunities and obstacles to change practice. *Br J Sports Med*.
OATES, A. R., FRANK, J. S. & PATLA, A. E. 2010. Control of dynamic stability during adaptation to gait termination on a slippery surface. *Exp Brain Res,* 201**,** 47-57.
OKUBO, Y., SCHOENE, D. & LORD, S. R. 2016. Step training improves reaction time, gait and balance and reduces falls in older people: a systematic review and meta-analysis. *Br J Sports Med*.
OLREE, K. S. & VAUGHAN, C. L. 1995. Fundamental patterns of bilateral muscle activity in human locomotion. *Biol Cybern,* 73**,** 409-14.
OSMAN, A., BARRIOS, F. X., GUTIERREZ, P. M., KOPPER, B. A., MERRIFIELD, T. & GRITTMANN, L. 2000. The Pain Catastrophizing Scale: further psychometric evaluation with adult samples. *J Behav Med,* 23**,** 351-65.
OSMAN, A., BARRIOS, F. X., KOPPER, B. A., HAUPTMANN, W., JONES, J. & O'NEILL, E. 1997. Factor structure, reliability, and validity of the Pain Catastrophizing Scale. *J Behav Med,* 20**,** 589-605.
OULLIER, O., BARDY, B. G., STOFFREGEN, T. A. & BOOTSMA, R. J. 2002. Postural coordination in looking and tracking tasks. *Hum Mov Sci,* 21**,** 147-67.
OWENS, M. A., BULLS, H. W., TROST, Z., TERRY, S. C., GOSSETT, E. W., WESSON-SIDES, K. M. & GOODIN, B. R. 2016. An Examination of Pain Catastrophizing and Endogenous Pain Modulatory Processes in Adults with Chronic Low Back Pain. *Pain Med,* 17**,** 1452-64.
PAIN, I. A. F. T. S. O. 2017. *Taxonomy* [Online]. Available: https://www.iasp-pain.org/Taxonomy [Accessed last access 6.4.2018].
PANJABI, M. M. 1992. The stabilizing system of the spine. Part I. Function, dysfunction, adaptation, and enhancement. *J Spinal Disord,* 5**,** 383-9; discussion 397.
PARK, S., HORAK, F. B. & KUO, A. D. 2004. Postural feedback responses scale with biomechanical constraints in human standing. *Exp Brain Res,* 154**,** 417-27.
PARSONS, T. D. & COURTNEY, C. G. 2014. An initial validation of the Virtual Reality Paced Auditory Serial Addition Test in a college sample. *J Neurosci Methods,* 222**,** 15-23.
PATLA, A. E. 1985. Some characteristics of EMG patterns during locomotion: implications for the locomotor control process. *J Mot Behav,* 17**,** 443-61.
PEROTTO, A. O. 1994. Anatomical Guide for the Electromyographer.
PINSAULT, N. & VUILLERME, N. 2009. Test-retest reliability of centre of foot pressure measures to assess postural control during unperturbed stance. *Med Eng Phys,* 31**,** 276-86.
POTTER, L., MCCARTHY, C. & OLDHAM, J. 2006. Algometer reliability in measuring pain pressure threshold over normal spinal muscles to allow quantification of anti-nociceptive treatment effects. *International Journal of Osteopathic Medicine,* 9**,** 113-119.
POZZO, T., PAPAXANTHIS, C., STAPLEY, P. & BERTHOZ, A. 1998. The sensorimotor and cognitive integration of gravity. *Brain Res Brain Res Rev,* 28**,** 92-101.
RABEY, M., SLATER, H., O'SULLIVAN, P., BEALES, D. & SMITH, A. 2015. Somatosensory nociceptive characteristics differentiate subgroups in people with chronic low back pain: a cluster analysis. *Pain,* 156**,** 1874-1884.
RESNICK, B., ZIMMERMAN, S. I., ORWIG, D., FURSTENBERG, A. L. & MAGAZINER, J. 2000. Outcome expectations for exercise scale: utility and psychometrics. *J Gerontol B Psychol Sci Soc Sci,* 55**,** S352-6.
ROGERS, M. W., KUKULKA, C. G., BRUNT, D., CAIN, T. D. & HANKE, T. A. 2001. The influence of stimulus cue on the initiation of stepping in young and older adults. *Arch Phys Med Rehabil,* 82**,** 619-24.
ROLKE, R., BARON, R., MAIER, C., TOLLE, T. R., TREEDE, R. D., BEYER, A., BINDER, A., BIRBAUMER, N., BIRKLEIN, F., BOTEFUR, I. C., BRAUNE, S., FLOR, H., HUGE, V., KLUG, R., LANDWEHRMEYER, G. B.,

MAGERL, W., MAIHOFNER, C., ROLKO, C., SCHAUB, C., SCHERENS, A., SPRENGER, T., VALET, M. & WASSERKA, B. 2006a. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. *Pain,* 123**,** 231-43.

ROLKE, R., MAGERL, W., CAMPBELL, K. A., SCHALBER, C., CASPARI, S., BIRKLEIN, F. & TREEDE, R. D. 2006b. Quantitative sensory testing: a comprehensive protocol for clinical trials. *Eur J Pain,* 10**,** 77-88.

ROLL, J. P. & VEDEL, J. P. 1982. Kinaesthetic role of muscle afferents in man, studied by tendon vibration and microneurography. *Exp Brain Res,* 47**,** 177-90.

ROLL, J. P., VEDEL, J. P. & RIBOT, E. 1989a. Alteration of proprioceptive messages induced by tendon vibration in man: a microneurographic study. *Exp Brain Res,* 76**,** 213-22.

ROLL, J. P., VEDEL, J. P. & ROLL, R. 1989b. Eye, head and skeletal muscle spindle feedback in the elaboration of body references. *Prog Brain Res,* 80**,** 113-23; discussion 57-60.

ROSSIGNOL, S. 1996. Visuomotor regulation of locomotion. *Can J Physiol Pharmacol,* 74**,** 418-25.

ROSSIGNOL, S., CHAU, C., BRUSTEIN, E., BELANGER, M., BARBEAU, H. & DREW, T. 1996. Locomotor capacities after complete and partial lesions of the spinal cord. *Acta Neurobiol Exp (Wars),* 56**,** 449-63.

ROUSSEL, N. A., NIJS, J., MEEUS, M., MYLIUS, V., FAYT, C. & OOSTENDORP, R. 2013. Central sensitization and altered central pain processing in chronic low back pain: fact or myth? *Clin J Pain,* 29**,** 625-38.

RUHE, A., FEJER, R. & WALKER, B. 2011. Center of pressure excursion as a measure of balance performance in patients with non-specific low back pain compared to healthy controls: a systematic review of the literature. *Eur Spine J,* 20**,** 358-68.

SCHEPENS, B. & DREW, T. 2003. Strategies for the integration of posture and movement during reaching in the cat. *J Neurophysiol,* 90**,** 3066-86.

SCHEPENS, B. & DREW, T. 2004. Independent and convergent signals from the pontomedullary reticular formation contribute to the control of posture and movement during reaching in the cat. *J Neurophysiol,* 92**,** 2217-38.

SCHIEPPATI, M., HUGON, M., GRASSO, M., NARDONE, A. & GALANTE, M. 1994. The limits of equilibrium in young and elderly normal subjects and in parkinsonians. *Electroencephalogr Clin Neurophysiol,* 93**,** 286-98.

SCHIEPPATI, M. & NARDONE, A. 1999. Group II spindle afferent fibers in humans: their possible role in the reflex control of stance. *Prog Brain Res,* 123**,** 461-72.

SCHMID, M., DE NUNZIO, A. M. & SCHIEPPATI, M. 2005. Trunk muscle proprioceptive input assists steering of locomotion. *Neurosci Lett,* 384**,** 127-32.

SCHWEIGART, G. & MERGNER, T. 2008. Human stance control beyond steady state response and inverted pendulum simplification. *Exp Brain Res,* 185**,** 635-53.

SHOJAEI, I., SALT, E. G., HOOKER, Q., VAN DILLEN, L. R. & BAZRGARI, B. 2017a. Comparison of lumbo-pelvic kinematics during trunk forward bending and backward return between patients with acute low back pain and asymptomatic controls. *Clin Biomech (Bristol, Avon),* 41**,** 66-71.

SHOJAEI, I., VAZIRIAN, M., SALT, E. G., VAN DILLEN, L. R. & BAZRGARI, B. 2017b. Timing and magnitude of lumbar spine contribution to trunk forward bending and backward return in patients with acute low back pain. *J Biomech,* 53**,** 71-77.

SMITH, B. E., HENDRICK, P., SMITH, T. O., BATEMAN, M., MOFFATT, F., RATHLEFF, M. S., SELFE, J. & LOGAN, P. 2017. Should exercises be painful in the management of chronic musculoskeletal pain? A systematic review and meta-analysis. *Br J Sports Med,* Available online 8 June 2017, ISSN 1473-0480, https.doi.org/10.1136/bjsports-2016-097383.

SOUSA, A. S. & TAVARES, J. M. 2015. Interlimb Coordination During Step-to-Step Transition and Gait Performance. *J Mot Behav,* 47**,** 563-74.

SPARROW, W. A. & TIROSH, O. 2005. Gait termination: a review of experimental methods and the effects of ageing and gait pathologies. *Gait Posture,* 22**,** 362-71.

STENHAGEN, M., EKSTROM, H., NORDELL, E. & ELMSTAHL, S. 2013. Falls in the general elderly population: a 3- and 6- year prospective study of risk factors using data from the longitudinal population study 'Good ageing in Skane'. *BMC Geriatr,* 13**,** 81.

STERKE, C. S., HUISMAN, S. L., VAN BEECK, E. F., LOOMAN, C. W. N. & VAN DER CAMMEN, T. J. M. 2010. Is the Tinetti Performance Oriented Mobility Assessment (POMA) a feasible and valid predictor of short-term fall risk in nursing home residents with dementia? *International Psychogeriatrics,* 22**,** 254-263.

STOLZMAN, S., DANDURAN, M., HUNTER, S. K. & BEMENT, M. H. 2015. Pain Response after Maximal Aerobic Exercise in Adolescents across Weight Status. *Med Sci Sports Exerc,* 47**,** 2431-40.

SUNG, P. S. 2014. A kinematic analysis for shoulder and pelvis coordination during axial trunk rotation in subjects with and without recurrent low back pain. *Gait Posture,* 40**,** 493-8.

THIGPEN, M. T., LIGHT, K. E., CREEL, G. L. & FLYNN, S. M. 2000. Turning difficulty characteristics of adults aged 65 years or older. *Phys Ther,* 80**,** 1174-87.

THOMAS, J. I. & LANE, J. V. 2005. A pilot study to explore the predictive validity of 4 measures of falls risk in frail elderly patients. *Archives of Physical Medicine and Rehabilitation,* 86**,** 1636-1640.

TISSERAND, R., ROBERT, T., CHABAUD, P., LIVET, P., BONNEFOY, M. & CHEZE, L. 2015. Comparison between investigations of induced stepping postural responses and voluntary steps to better detect community-dwelling elderly fallers. *Neurophysiologie Clinique-Clinical Neurophysiology,* 45**,** 269-284.

TORPEL, A., BECKER, T., THIERS, A., HAMACHER, D. & SCHEGA, L. 2017. Inter-session Reliability of Isokinetic Strength Testing in Knee and Elbow Extension and Flexion Using the BTE PrimusRS. *J Sport Rehabil***,** 1-14.

TUCKER, K., BUTLER, J., GRAVEN-NIELSEN, T., RIEK, S. & HODGES, P. 2009. Motor unit recruitment strategies are altered during deep-tissue pain. *J Neurosci,* 29**,** 10820-6.

TURCATO, A. M., GODI, M., GIORDANO, A., SCHIEPPATI, M. & NARDONE, A. 2015. The generation of centripetal force when walking in a circle: insight from the distribution of ground reaction forces recorded by plantar insoles. *Journal of Neuroengineering and Rehabilitation,* 12.

UMEDA, M., KEMPKA, L. E., GREENLEE, B. T. & WEATHERBY, A. C. 2016. A smaller magnitude of exercise-induced hypoalgesia in African Americans compared to non-Hispanic Whites: A potential influence of physical activity. *Biol Psychol,* 113**,** 46-51.

VAEGTER, H. B., DORGE, D. B., SCHMIDT, K. S., JENSEN, A. H. & GRAVEN-NIELSEN, T. 2018a. Test-Retest Reliabilty of Exercise-Induced Hypoalgesia After Aerobic Exercise. *Pain Med*.

VAEGTER, H. B. & GRAVEN-NIELSEN, T. 2016. Pain modulatory phenotypes differentiate subgroups with different clinical and experimental pain sensitivity. *Pain,* 157**,** 1480-1488.

VAEGTER, H. B., HANDBERG, G. & GRAVEN-NIELSEN, T. 2015. Isometric exercises reduce temporal summation of pressure pain in humans. *Eur J Pain,* 19**,** 973-83.

VAEGTER, H. B., LYNG, K. D., YTTERENG, F. W., CHRISTENSEN, M. H., SORENSEN, M. B. & GRAVEN-NIELSEN, T. 2018b. Exercise-Induced Hypoalgesia After Isometric Wall Squat Exercise: A Test-Retest Reliabilty Study. *Pain Med*.

VAN TULDER, M. & KOES, B. 2006. Chronic low back pain. *Am Fam Physician,* 74**,** 1577-9.

VITON, J. M., TIMSIT, M., MESURE, S., MASSION, J., FRANCESCHI, J. P. & DELARQUE, A. 2000. Asymmetry of gait initiation in patients with unilateral knee arthritis. *Arch Phys Med Rehabil,* 81**,** 194-200.

VON DINCKLAGE, F., HACKBARTH, M., SCHNEIDER, M., BAARS, J. H. & REHBERG, B. 2009. Introduction of a continual RIII reflex threshold tracking algorithm. *Brain Res,* 1260**,** 24-9.

VON DINCKLAGE, F., OLBRICH, H., BAARS, J. H. & REHBERG, B. 2013. Habituation of the nociceptive flexion reflex is dependent on inter-stimulus interval and stimulus intensity. *J Clin Neurosci,* 20**,** 848-50.

VON KORFF, M., ORMEL, J., KEEFE, F. J. & DWORKIN, S. F. 1992. Grading the severity of chronic pain. *Pain,* 50**,** 133-49.

VOS, T et al. 2012. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet,* 380**,** 2163-96.

WADDELL, G., NEWTON, M., HENDERSON, I., SOMERVILLE, D. & MAIN, C. J. 1993. A Fear-Avoidance Beliefs Questionnaire (FABQ) and the role of fear-avoidance beliefs in chronic low back pain and disability. *Pain,* 52**,** 157-168.

WAGNER, J., MAKEIG, S., GOLA, M., NEUPER, C. & MULLER-PUTZ, G. 2016. Distinct beta Band Oscillatory Networks Subserving Motor and Cognitive Control during Gait Adaptation. *J Neurosci,* 36**,** 2212-26.

WALTER, S., ELIASZIW, M. & DONNER, A. 1998. Sample size and optimal designs for reliability studies. *Statistics in medicine,* 17**,** 101-110.

WELLS, G. A., SHEA, B., O'CONNEL, D. ET AL. . 2009. *The Newcastle-Ottawa scale (NOS) for assessing the quailty of nonrandomised studies in meta-analyses.* [Online]. Available: http://www.ohri.ca/programs/clinical_epidemiology/nosgen.pdf [Accessed].

WERBER, A. & SCHILTENWOLF, M. 2016. Treatment of Lower Back Pain-The Gap between Guideline-Based Treatment and Medical Care Reality. *Healthcare (Basel),* 4.

WINTER, D. A. 1991. *The Biomechanics and Motor Control of Human Gait: Normal, Elderly and Pathological.,* Waterloo. Ontario, Waterloo Biomechanics.

WINTER, D. A., PATLA, A. E., PRINCE, F., ISHAC, M. & GIELO-PERCZAK, K. 1998. Stiffness control of balance in quiet standing. *J Neurophysiol,* 80**,** 1211-21.

Application for amendment 18-0833B

[redacted]

To: Deborah Falla (School of Sport Exercise and Rehabilitation Sciences); Alison Rushton (Physiotherapy); Nicola Heneghan (Physiotherapy)
Cc: Pauline Kudhan (PhD School of Sprt+Ex Scie FT)

FollowUp. Start by 17 June 2019. Due by 24 June 2019.

Reply | Reply All | Forward | ...

Mon 17/06/2019 13:40

Dear Professor Falla, Dr Rushton and Dr Heneghan

Re: "Investigating the analgesic effect of walking and resistance exercise in healthy adults"
Application for amendment 18-0833B

Thank you for the above application for amendment, which was reviewed by the Science, Technology, Engineering and Mathematics Ethical Review Committee.

On behalf of the Committee, I can confirm that this amendment now has full ethical approval.

I would like to remind you that any substantive changes to the nature of the study as now amended, and/or any adverse events occurring during the study should be promptly brought to the Committee's attention by the Principal Investigator and may necessitate further ethical review. A revised amendment application form is now available at https://intranet.birmingham.ac.uk/finance/accounting/Research-Support-Group/Research-Ethics/Ethical-Review-Forms.aspx . Please ensure this form is submitted for any further amendments.

Please also ensure that the relevant requirements within the University's Code of Practice for Research and the information and guidance provided on the University's ethics webpages (available at https://intranet.birmingham.ac.uk/finance/accounting/Research-Support-Group/Research-Ethics/Links-and-Resources.aspx) are adhered to and referred to in any future applications for ethical review. It is now a requirement on the revised application form (https://intranet.birmingham.ac.uk/finance/accounting/Research-Support-Group/Research-Ethics/Ethical-Review-Forms.aspx) to confirm that this guidance has been consulted and is understood, and that it has been taken into account when completing your application for ethical review.

Please be aware that whilst Health and Safety (H&S) issues may be considered during the ethical review process, you are still required to follow the University's guidance on H&S and to ensure that H&S risk assessments have been carried out as appropriate. For further information about this, please contact your School H&S representative or the University's H&S Unit at healthandsafety@contacts.bham.ac.uk.

If you require a hard copy of this correspondence, please let me know.

Kind regards

[redacted]
Research Ethics Officer
Research Support Group
C Block Dome
Aston Webb Building
University of Birmingham
Edgbaston B15 2TT
Tel: [redacted]
Email: [redacted]
Web: https://intranet.birmingham.ac.uk/finance/RSS/Research-Support-Group/Research-Ethics/index.aspx

Please remember to submit a new Self-Assessment Form for each new project.

Click Research Governance for further details regarding the University's Research Governance and Clinical Trials Insurance processes, or email researchgovernance@contacts.bham.ac.uk with any queries relating to research governance.

School of Sport, Exercise & Rehabilitation Sciences

Summary Assessment Number

Hazard and Risk Assessment Summary (for research work)

Assessor	Pauline Kuithan	Location of Activity (list all locations)	CPR Spine Laboratory	Date of Assessment	21/02/19
Supervisor (if not above)	Prof. Deborah Falla	Activity/Experiment Assessed (attach protocols)	Investigating the analgesic effect of walking and resistance exercise TSA-II – NeuroSensory Analyzer (Medoc, CE)		

ASSESSMENT OF HAZARD AND RISK														ACTION REQUIRED
ACTIVITY/HAZARD (List only hazards from which there is a significant risk of harm under foreseeable conditions)	**PERSONS AT RISK** (See key)	**ACTIVITY INVOLVES…** (See key)					**RISK RATING** (See key)			**LIKELIHOOD of HARM** (See key)				(For example: Is chemical/biological/manual handling/equipme risk assessment required; Is code of practice(COP)/standard operating procedures(SOP) required. Where risk assessments/COP/SOP exists please attach them)
		C	B	M	E	R	H	M	L	Y	Pr	Po	R	
Moving equipment in the lab leading to injury	S/Pg			x					x				x	Equipment to tidied between activities
False application of thermode/ unexpected failure	Pa			x	x				x				x	The TSA-II device has a high safety level to protect the participant that h (51°C) or low temperature (0°C) can only last for a very short time. For whatever reason this system fails, the thermode can be easily removed the trained researcher from the skin as soon as the participant asks for it any other potential risk factor occurs. As our participants, don't present sensory loss and qualified assessors are conducting the test and reviewi the temperature and the patients' response, it is unlikely that damage to the skin can be caused. This does not add any risk or hazards for people with low back pain.

Key

PERSONS AT RISK	
Ug	Undergraduate
Pg	Postgraduate
S	Staff
C	Contractor
V	Visitor
Pa	Patient/Experimental subject
Pu	General Public
Yp	Young Person
Nm	New/Expectant Mother

ACTIVITY INVOLVES…	
C	Chemicals
B	Biological fluids/material
M	Manual Hazard e.g. trip
E	Equipment hazard
R	Radioisotope

RISK RATING	
H	High
M	Medium
L	Low

LIKELIHOOD	
Y	Yes/ Very High
Pr	Probable
Po	Possible
R	Remote

RISK SIGNIFICANCE	Y	Pr	Po	R	
H	✓	✓	✓	✓	✓ = Significant risk
M	✓	✓	✓	✓	
L	✓	✓	X	X	X = Insignificant risk

Date for Review

GUIDANCE FOR WRITING THIS ASSESSMENT CAN BE FOUND HERE

School of Sport, Exercise & Rehabilitation Sciences

Summary Assessment Number

Hazard and Risk Assessment Summary (for research work)

Assessor	Pauline Kuithan	Location of Activity (list all locations)	CPR Spine Laboratory	Date of Assessment	21/02/2019
Supervisor (if not above)	Prof. Deborah Falla	Activity/Experiment Assessed (attach protocols)	Investigating the analgesic effect of walking and resistance **Algometer**		

ASSESSMENT OF HAZARD AND RISK														ACTION REQUIRED
ACTIVITY/HAZARD (List only hazards from which there is a significant risk of harm under foreseeable conditions)	**PERSONS AT RISK** (See key)	**ACTIVITY INVOLVES…** (See key)					**RISK RATING** (See key)			**LIKELIHOOD of HARM** (See key)				(For example: Is chemical/biological/manual handling/equipme risk assessment required; Is code of practice(COP)/standard operating procedures(SOP) required. Where risk assessments/COP/SOP exists please attach them)
		C	B	M	E	R	H	M	L	Y	Pr	Po	R	
Moving equipment in the lab leading to injury	S/Pg			x					x				x	Equipment to tidied between activities
False application of algometer / unexpected failure	Pa			x	x				x				x	Blunt pressure will be applied till the patient indicates pain threshold or tolerance. For whatever reason the device does not indicate the stop the trained researcher will stop immediately in communication with the participant. This is not adding extra risk or hazards to a population with low back pai Even though lower thresholds are expected, the participant indicates the individual threshold by clicking the button.

Key

PERSONS AT RISK	
Ug	Undergraduate
Pg	Postgraduate
S	Staff
C	Contractor
V	Visitor
Pa	Patient/Experimental subject
Pu	General Public
Yp	Young Person

ACTIVITY INVOLVES…	
C	Chemicals
B	Biological fluids/material
M	Manual Hazard e.g. trip
E	Equipment hazard
R	Radioisotope

RISK RATING	
H	High
M	Medium
L	Low

LIKELIHOOD	
Y	Yes/ Very High
Pr	Probable
Po	Possible
R	Remote

RISK SIGNIFICANCE					
	Y	Pr	Po	R	
H	✓	✓	✓	✓	✓ = Significant risk
M	✓	✓	✓	✓	
L	✓	✓	X	X	X = Insignificant risk

Date for Review

GUIDANCE FOR WRITING THIS ASSESSMENT CAN BE FOUND HERE

School of Sport, Exercise & Rehabilitation Sciences

Summary Assessment Number

Hazard and Risk Assessment Summary (for research work)

Assessor	Pauline Kuithan	Location of Activity (list all locations)	CPR Spine Laboratory	Date of Assessment	21.02.2019
Supervisor (if not above)	Prof. Deborah Falla	Activity/Experiment Assessed (attach protocols)	Investigating the analgesic effect of walking and resistance exercise **BTe Primus RS** The Primus is intended to be used for musculoskeletal testing and treatment. BTE has issued the EC Declaration of Conformity declaring that the Primus meets the provisions of the European Medical Device regulations and applicable directives.		

ASSESSMENT OF HAZARD AND RISK														ACTION REQUIRED
ACTIVITY/HAZARD (List only hazards from which there is a significant risk of harm under foreseeable conditions)	**PERSONS AT RISK** (See key)	**ACTIVITY INVOLVES…** (See key)					**RISK RATING** (See key)			**LIKELIHOOD of HARM** (See key)				(For example: Is chemical/biological/manual handling/equipme risk assessment required; Is code of practice(COP)/standard operating procedures(SOP) required. Where risk assessments/COP/SOP exists please attach them)
		C	B	M	E	R	H	M	L	Y	Pr	Po	R	
Starting/ running the machine	S/Pg			x					x				x	Potential risk when starting or setting up the device, as when done wron equipment can move and become loose. When set up correctly, there is risk.
Unexpected failure of Primus, false use of the Primus	Pa			x	x				x			x		The exercise is supervised by a researcher, who is familiar with the devi and participant and researcher are aware of the emergency stop functio and how to use it in case of potential risk or failure of the device. This task might produce some slight discomfort in patient with low back pain. However, based on our previous research from a similar lifting task we could not observe any exacerbation of symptoms after the session. Both researcher and participant can stop the task any time, for example discomfort increases or persistence of symptoms is expected. Moreover the exercise is supervised by an experienced physiotherapist and adjust to the individual capacity of each participant for each session.

Key

PERSONS AT RISK	
Ug	Undergraduate
Pg	Postgraduate
S	Staff
C	Contractor
V	Visitor
Pa	Patient/Experimental subject
Pu	General Public
Yp	Young Person

ACTIVITY INVOLVES…	
C	Chemicals
B	Biological fluids/material
M	Manual Hazard e.g. trip
E	Equipment hazard
R	Radioisotope

RISK RATING	
H	High
M	Medium
L	Low

LIKELIHOOD	
Y	Yes/ Very High
Pr	Probable
Po	Possible
R	Remote

RISK SIGNIFICANCE	Y	Pr	Po	R
H	✓	✓	✓	✓
M	✓	✓	✓	✓
L	✓	✓	X	X

✓ = Significant risk

X = Insignificant risk

Date for Review

GUIDANCE FOR WRITING THIS ASSESSMENT CAN BE FOUND HERE

School of Sport, Exercise & Rehabilitation Sciences

Summary Assessment Number

Hazard and Risk Assessment Summary (for research work)

Assessor	Pauline Kuithan	Location of Activity (list all locations)	CPR Spine Laboratory	Date of Assessment	21.02.2019
Supervisor (if not above)	Prof. Deborah Falla	Activity/Experiment Assessed (attach protocols)	Investigating the analgesic effect of walking and resistance exercise **Treadmill** - **Biodex Gait Trainer 3**		

ASSESSMENT OF HAZARD AND RISK														ACTION REQUIRED
ACTIVITY/HAZARD (List only hazards from which there is a significant risk of harm under foreseeable conditions)	**PERSONS AT RISK** (See key)	**ACTIVITY INVOLVES…** (See key)					**RISK RATING** (See key)			**LIKELIHOOD of HARM** (See key)				(For example: Is chemical/biological/manual handling/equipme risk assessment required; Is code of practice(COP)/standard operating procedures(SOP) required. Where risk assessments/COP/SOP exists please attach them)
		C	B	M	E	R	H	M	L	Y	Pr	Po	R	
Falling on treadmill/ trip hazard	Pa			x	x			x				x		The treadmill has an emergency stop which both participants and researcher are aware of. In case of a fall the treadmill will stop to stop ar further potential damage. However, walking on a constant speed without perturbation is unlikely to cause falls.
Unexpected failure of the treadmill, false usage of the device	Pa			x	x				x				x	In case of malfunction of the device, the emergency stop can be activat or the participants can get of it. Both participant and researchers will be familiarised with the procedure and how to walk on the treadmill. The walking task is adapted to the individual heart rate for each participa I.e. the walking pace and incline of the treadmill will be adjusted, so that the participant can walk comfortably. The session is supervised by an experienced physiotherapist, who monitors the exercise. Both participan and therapist can stop the exercise at any point when for example the pa intensity increases and is likely to persist till after the session or exacerbation of symptoms is expected.

Key

PERSONS AT RISK	
Ug	Undergraduate
Pg	Postgraduate
S	Staff
C	Contractor
V	Visitor
Pa	Patient/Experimental subject
Pu	General Public
Yp	Young Person

ACTIVITY INVOLVES…	
C	Chemicals
B	Biological fluids/material
M	Manual Hazard e.g. trip
E	Equipment hazard
R	Radioisotope

RISK RATING	
H	High
M	Medium
L	Low

LIKELIHOOD	
Y	Yes/ Very High
Pr	Probable
Po	Possible
R	Remote

RISK SIGNIFICANCE				
	Y	Pr	Po	R
H	✓	✓	✓	✓
M	✓	✓	✓	✓
L	✓	✓	X	X

✓ = Significant risk

X = Insignificant risk

Date for Review

GUIDANCE FOR WRITING THIS ASSESSMENT CAN BE FOUND HERE

Hazard and Risk Assessment Summary (for research work)

Assessor	Pauline Kuithan	Location of Activity (list all locations)	CPR Spine Laboratory	Date of Assessment	21.02.2019
Supervisor (if not above)	Prof. Deborah Falla	Activity/Experiment Assessed (attach protocols)	Investigating the analgesic effect of walking and resistance exercise **Paintracker,** Dolosys, Berlin, Germany certified and tested for medical use (DIN EN ISO 13485:2012)		

ASSESSMENT OF HAZARD AND RISK														ACTION REQUIRED
ACTIVITY/HAZARD (List only hazards from which there is a significant risk of harm under foreseeable conditions)	**PERSONS AT RISK** (See key)	**ACTIVITY INVOLVES…** (See key)					**RISK RATING** (See key)			**LIKELIHOOD of HARM** (See key)				(For example: Is chemical/biological/manual handling/equipme risk assessment required; Is code of practice(COP)/standard operating procedures(SOP) required. Where risk assessments/COP/SOP exists please attach them)
		C	B	M	E	R	H	M	L	Y	Pr	Po	R	
Preparation of skin	Pa			x	x				x				x	For good conduction the skin needs to be prepared in the same manner for electromyography, a well-established procedure within the centre. No damage to the skin is expected, but minor skin irritation might occur at a level comparable to that expected due to shaving or exfoliating.
Unexpected failure of the device	Pa			x	x				x				x	The device is tested and approved for medical use, therefore it is unlikel that a failure of the device can lead to any tissue damage. However, the researcher is observing the test and can interact and remove the device case of emergency. This is not adding extra risk or hazards to a population with low back pai

Key

PERSONS AT RISK	
Ug	Undergraduate
Pg	Postgraduate
S	Staff
C	Contractor
V	Visitor
Pa	Patient/Experimental subject
Pu	General Public
Yp	Young Person

ACTIVITY INVOLVES…	
C	Chemicals
B	Biological fluids/material
M	Manual Hazard e.g. trip
E	Equipment hazard
R	Radioisotope

RISK RATING	
H	High
M	Medium
L	Low

LIKELIHOOD	
Y	Yes/ Very High
Pr	Probable
Po	Possible
R	Remote

RISK SIGNIFICANCE	Y	Pr	Po	R
H	✓	✓	✓	✓
M	✓	✓	✓	✓
L	✓	✓	X	X

✓ = Significant risk

X = Insignificant risk

Date for Review

GUIDANCE FOR WRITING THIS ASSESSMENT CAN BE FOUND HERE

Consent Form

Study ID:

Hypoalgesic changes and their stability in pain processing due to walking or resistance exercise in healthy adults

This information is being collected as part of a research project concerned with the investigation of changes in pain sensitivity due to repeated exercise sessions by the Centre of Precision Rehabilitation of Spinal Pain within the School of Sport, Exercise and Rehabilitation Sciences at the University of Birmingham. The information which you supply and that which may be collected as part of the research project will be entered into a filing system or database and will only be accessed by authorised personnel involved in the project. The information will be retained by the University of Birmingham and will only be used for the purpose of research and statistical and audit purposes. By supplying this information you are consenting to the University storing your information for the purposes stated above. The information will be processed by the University of Birmingham in accordance with the provisions of the EU General Data Protection Regulation 2016/679. No identifiable personal data will be published.

Please initialise each box if you agree with the statement and sign the form

I confirm that I have read and understand the participant information leaflet for this study. I have had the opportunity to ask questions if necessary and have had these answered satisfactorily.	
I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason as I will have the right to withdraw my data from the study up to two weeks following completion of data collection. If I withdraw my data will be removed from the study and will be destroyed. Participants will be free to withdraw at any time during the experimental session.	
I understand that my personal data will be processed for the purposes detailed above, in accordance with the EU General Data Protection Regulation 2016/679.	
Based upon the above, I agree to take part in this study.	

Name of participant……	Date……	Signature……..
Name of researcher/		
individual obtaining consent……	Date……	Signature……..

Contact details of participant

Contact number: | Email address:

UNIVERSITY OF BIRMINGHAM | CENTRE OF PRECISION REHABILITATION FOR SPINAL PAIN

Did you know that exercise can temporarily change your pain perception?

Healthy participants (aged 18 - 65) wanted

What we already know: Exercise can temporarily activate your pain inhibitory system, which means reduced sensitivity to pain. For example after exercise a higher temperature needs to be reached before you perceive a warm stimulus as painful.

What we don't know: If you will get the same changes in pain sensitivity for each of the six repeated exercise sessions.

What do you have to do?

You have to attend to the School of Sport and Exercise Science for **6 sessions** within **three weeks**. Each visit will last about 90 - 120 minutes.

- We will test the point where you feel that different stimuli such as pressure or temperature turn into discomfort (pain thresholds) over different body sites including your back, arm and leg before and after the exercise.
- Individually designed exercise sessions of either treadmill based brisk walking **or** a resistance programme for about 15 minutes per session.

Participants will be compensated £5 per hour upon completion of the study (7 to 12 hours) or participation counts for research hours

Interested? Please contact Pauline [redacted]
PhD student supervised by Professor Deborah Falla

[redacted]

UNIVERSITY OF BIRMINGHAM | CENTRE OF PRECISION REHABILITATION FOR SPINAL PAIN

Participant Information Leaflet

Did you know that exercise can temporarily change your pain perception?

Study title: Investigating the analgesic effect of walking and resistance exercise in healthy adults

Before you decide to participate it is important you understand why the research is being done and what it will involve. Please take time to read the following information sheet carefully and discuss it with the researcher or others if you wish. Please be aware that we will use tests to detect pain thresholds which may cause pain as further outlined under Quantitative Sensory Testing below.

1. What is the purpose of the study?

Next to several long-term benefits from exercise, it has been shown that exercise leads to a temporary decrease in pain sensitivity. That means that pain thresholds are higher after exercise, for example more pressure can be applied before you feel that the pressure turns into pain. Yet it remains to be established if those results remain stable over a number of six sessions.

2. Why have I been chosen?

You have been chosen because we understand you have not previously experienced **musculoskeletal or cardiorespiratory** disorders:
Inclusion criteria:

- Females or males between 18 - 65 years
- No relevant history over the last two years of back or limb pain or injury that limited your function and/or required treatment from a health professional and will affect your performance

Exclusion criteria:

- Ongoing systemic, rheumatic or neuro-musculoskeletal disorders, such as back or neck pain, requiring treatment from a health care practitioner within the last 12 months
- Any condition such as severe asthma or heart condition which requires ongoing treatment or medication such as corticosteroids which may confound testing
- Currently pregnant
- You are exercising for more than 90 minutes of vigorous intensity per day or competing in professional or high-level sport

3. Do I have to take part?

You are free to decide whether you participate or not. If you agree to take part you are free to withdraw at any time during the experimental sessions and you can withdraw your data up to two weeks following data collection without giving a reason by contacting Pauline Kuithan using the email or contact number stated below. Any decision to withdraw will not in any way affect you and has no effect on future healthcare.

4. What do I have to do?

You will be asked to visit the Laboratory in the School of Sport, Exercise and Rehabilitation Sciences **six times** over a period of **three weeks** from the baseline testing. For example if you started on a Monday, then tests could be arranged on a similar time on Thursdays and Mondays for three weeks.

The first and the final sessions take about 120 minutes, sessions 2-5 last approximately 90 minutes. You will be asked to do the following:

- Complete **questionnaires** where eligibility will be confirmed and to evaluate your health condition and activity levels. Complete some clinical measures to rate and evaluate your health condition as height and weight, strength or heartrate when walking (primarily in the 1st session).
- **Quantitative Sensory Testing:** as pre- and post-test conducted every session
- **Pressure Pain Thresholds**: A hand-held probe (algometer) is pushed on the skin and by pushing a button you stop when the pressure turns into pain or pain tolerance is reached.
- **Thermal Threshold**: A probe, which can increase/decrease its temperature, is placed on your skin. You indicate when the cold or warm feeling turns into pain.
- **Temporal Summation**: Ten consecutive heat or pressure stimuli will be applied on your arm, and for each you rate pain intensity. Stimuli are of very short duration and cannot cause damage.
- **Withdrawal Reflex**: A small electric stimulus will be applied to produce a muscular 'twitch' response on the leg. The stimulus will be a similar intensity to a static shock from touching a door. This might require shaving of a small area over the lower leg to attach the electrodes.

Pressure Test

Thermal Test

Withdrawal Reflex

- **Exercise:** You will be randomised to **either an endurance** or **strength** programme. In the first session we individually define your exercise intensity and for the following five sessions you will conduct the same **individual adjusted** exercise programme of either
- **Treadmill** based brisk walking for ~15 minutes.
- **Strength training** with a Primus BTE device (see picture) in form of a turning, bending and lifting exercise to target trunk muscles for ~15 minutes.

BTE PRIMUS

5. Will my taking part in this study be kept confidential?

All information collected on you will be kept strictly confidential. The consent form containing your allocated ID will never be present in electronic form, and only available to the researchers. All data will be managed in accordance with the EU General Data Protection Regulation 2016/679.

6. What will happen to the results of the research study?

All data for presentation will be anonymised, that means your identity will not be revealed in any way. The findings from this study will be presented, or shared with other researchers in the form of presentations and scientific papers as appropriate.

7. What do I get out of participating?

After completion we can provide you with an overview of your results. However, this study aim is not to improve your physical fitness level. For completion of the study you will receive a reimbursement of £5 per hour (study participation will range from 7 to 12 hours) upon completition of the study. Participation can also be used for research hours. The results of this study will contribute to shape future treatment for musculoskeletal disorders.

8. Does the study follow Ethics prescriptions?

This study underwent the ethical review processes of the University of Birmingham and received official approval from the University Ethics Committee.

9. Who is organising and funding the research?

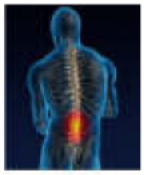
The study has been designed and organised by Professor Deborah Falla, Chair in Rehabilitation Science and Physiotherapy ([redacted] or [redacted] and the CPR Spine team.

For further information please contact Pauline Kuithan

Pauline Kuithan, PhD Student & registered Physiotherapist School of Sport, Exercise and Rehabilitation Sciences University of Birmingham	[redacted]

Thank you for taking time to read this and considering taking part in the study!

UNIVERSITY OF BIRMINGHAM | CENTRE OF PRECISION REHABILITATION FOR SPINAL PAIN



Did you know that exercise can temporarily change your pain perception?

Participants with **low back pain** (aged 18 - 65) wanted

What we already know: Exercise can temporarily activate your pain inhibitory system, which means reduced sensitivity to pain. For example after exercise a higher temperature needs to be reached before you perceive a warm stimulus as painful.

What we don't know: If you will get the same changes in pain sensitivity for each of the six repeated exercise sessions.

Am I eligible?

- Low back pain for more than 3 of the past 6 months
- Not currently seeking treatment
- No spread of the pain into your leg or pain related to trauma or fracture

What do you have to do?

You have to attend to the School of Sport and Exercise Science for **6 sessions** within **three weeks**. Each visit will last about 1.5 - 2 hours.

- We will test the point where you feel that different stimuli such as pressure or temperature turn into discomfort (pain thresholds) over different body sites including your back, arm and leg before and after the exercise.
- Individually designed exercise sessions of either treadmill based brisk walking **or** a resistance programme for about 15 minutes per session.

You will be compensated £7.5 per hour upon completion of the study (7 to 12 hours)

Interested? Please contact Pauline [redacted]
PhD student supervised by Professor Deborah Falla

[redacted]

UNIVERSITY OF BIRMINGHAM | CENTRE OF PRECISION REHABILITATION FOR SPINAL PAIN

Participant Information Leaflet

Did you know that exercise can temporarily change your pain perception?

Title: Investigating the analgesic effect of walking and resistance exercise

Before you decide to participate it is important you understand why the research is being done and what it will involve. Please take time to read the following information sheet carefully and discuss it with the researcher or others if you wish.
Please be aware that we will use tests to detect pain thresholds which may cause pain as further outlined under Quantitative Sensory Testing below. Furthermore, it is possible that the exercise temporarily increases your symptoms. However, the exercise will be adjusted to your individual characteristics and you can stop any time. All tests will be supervised by an experienced physiotherapist.

1. What is the purpose of the study?

Next to several long-term benefits from exercise, it has been shown that exercise leads to a temporary decrease in pain sensitivity. That means that pain thresholds are higher after exercise, for example more pressure can be applied before you feel that the pressure turns into pain. Yet it remains to be established if those results remain stable over a number of six sessions.

2. Why have I been chosen?

You have been chosen because we understand you have previously experienced a back pain problem that has the following characteristics:

- It has lasted more than 3 months
- You have experienced pain on more than 90 days out of the past 6 months

While exclusion criteria include:

- Under 18 years or over 66 years old
- Concurrent systemic, rheumatic or neuro-musculoskeletal disorders which may confound testing or if you are currently pregnant.
- Cardiorespiratory disorders such as severe asthma or exacerbation, which affects exercise performance, as well as cardiac problems. This includes medications to control the blood pressure.
- Radiating leg pain, or low back pain related to trauma, fractures, spinal stenosis.
- Being under active management of LBP through specific medications prescribed by a GP or receiving therapies e.g. physiotherapy others than PRN/ as needed.
- You are exercising for more than 90 minutes of vigorous intensity per day or competing in professional or high-level sport

3. Do I have to take part?

You are free to decide whether you participate or not. If you agree to take part you are free to withdraw at any time during the experimental sessions and you can withdraw your data up to two weeks following data collection without giving a reason by contacting Pauline Kuithan using the email or contact number stated below. Any decision to withdraw will not in any way affect you and has no effect on future healthcare.

4. What do I have to do?

You will be asked to visit the Laboratory in the School of Sport, Exercise and Rehabilitation Sciences six times over a period of three weeks from the baseline testing. For example if you started on a Monday, then tests could be arranged on a similar time on Thursdays and Mondays for three weeks.

The first session will take about 120 minutes, sessions 2-6 last approximately 90 minutes.

- Complete **questionnaires** where eligibility will be confirmed and to evaluate your health condition, low back pain, and activity levels. Complete some clinical measures to rate and evaluate your health condition as height and weight, strength or heartrate when walking (primarily in the 1st session).

Pressure Test

- **Quantitative Sensory Testing:** as pre- and post-test conducted every session
  - **Pressure Pain Thresholds**: A hand-held probe (algometer) is pushed on the skin and by pushing a button you stop when the pressure turns into pain or pain tolerance is reached.

Thermal Test

  - **Thermal Threshold**: A probe, which can increase/decrease its temperature, is placed on your skin. You indicate when the cold or warm feeling turns into pain.
  - **Withdrawal Reflex**: A small electric stimulus will be applied to produce a muscular 'twitch' response on the leg. The stimulus will be a similar intensity to a static shock from touching a door. This might require shaving of a small area over the lower leg to attach the electrodes.
- **Exercise:** You will be randomised to **either** an **endurance** or **strength** programme. In the first session we individually define your exercise intensity and for the following five sessions you will conduct the same **individual adjusted** exercise programme of either
  - **Treadmill** based brisk walking for ~15 minutes.
  - **Strength training** with a Primus BTE device (see picture) in form of a turning, bending and lifting exercise to target trunk muscles for ~15 minutes.

BTE PRIMUS

5. Will my taking part in this study be kept confidential?

All information collected on you will be kept strictly confidential. The consent form containing your allocated ID will never be present in electronic form, and only available to the researchers. All data will be managed in accordance with the EU General Data Protection Regulation 2018.

6. What will happen to the results of the research study?

All data for presentation will be anonymised, that means your identity will not be revealed in any way. The findings from this study will be presented, or shared with other researchers in the form of presentations and scientific papers as appropriate.

7. What do I get out of participating?

After completion we can provide you with an overview of your results. However, this study aim is not to improve your physical fitness level. For completion of the study you will receive a **reimbursement** of £7.5 per hour (study participation will range from 7 to 12 hours). Participation can also be used for research hours. The results of this study will contribute to shape future treatment for musculoskeletal disorders.

8. Does the study follow Ethics prescriptions?

This study underwent the ethical review processes of the University of Birmingham and received official approval from the University Ethics Committee.

9. Who is organising and funding the research?

The study has been designed and organised by Professor Deborah Falla, Chair in Rehabilitation Science and Physiotherapy ([redacted] or [redacted]) and the CPR Spine team.

For further information please contact Pauline Kuithan

Pauline Kuithan, PhD Student & registered Physiotherapist School of Sport, Exercise and Rehabilitation Sciences University of Birmingham	[redacted]

Thank you for taking time to read this and considering taking part in the study!

UNIVERSITY OF BIRMINGHAM | CENTRE OF PRECISION REHABILITATION FOR SPINAL PAIN

Participant Information Leaflet

Did you know that exercise can temporarily change your pain perception?

Study title: Investigating the analgesic effect of walking and resistance exercise in healthy adults

Before you decide to participate it is important you understand why the research is being done and what it will involve. Please take time to read the following information sheet carefully and discuss it with the researcher or others if you wish. Please be aware that we will use tests to detect pain thresholds which may cause pain as further outlined under Quantitative Sensory Testing below.

1. What is the purpose of the study?

Next to several long-term benefits from exercise, it has been shown that exercise leads to a temporary decrease in pain sensitivity. That means that pain thresholds are higher after exercise, for example more pressure can be applied before you feel that the pressure turns into pain. Yet it remains to be established if those results remain stable over a number of six sessions.

2. Why have I been chosen?

You have been chosen because we understand you have not previously experienced **musculoskeletal or cardiorespiratory** disorders:
Inclusion criteria:

- Females or males between 18 - 65 years
- No relevant history over the last two years of back or limb pain or injury that limited your function and/or required treatment from a health professional and will affect your performance

Exclusion criteria:

- Ongoing systemic, rheumatic or neuro-musculoskeletal disorders, such as back or neck pain, requiring treatment from a health care practitioner within the last 12 months
- Any condition such as severe asthma or heart condition which requires ongoing treatment or medication such as blood pressure medication which may confound testing
- Currently pregnant
- You are exercising for more than 90 minutes of vigorous intensity per day or competing in professional or high-level sport

3. Do I have to take part?

You are free to decide whether you participate or not. If you agree to take part you are free to withdraw at any time during the experimental sessions and you can withdraw your data up to two weeks following data collection without giving a reason by contacting Pauline Kuithan using the email or contact number stated below. Any decision to withdraw will not in any way affect you and has no effect on future healthcare.

4. What do I have to do?

You will be asked to visit the Laboratory in the School of Sport, Exercise and Rehabilitation Sciences **six times** over a period of **three weeks** from the baseline testing. For example if you started on a Monday, then tests could be arranged on a similar time on Thursdays and Mondays for three weeks.

All sessions will take about 90 minutes. You will be asked to do the following:

- Complete **questionnaires** where eligibility will be confirmed and to evaluate your health condition and activity levels. Complete some clinical measures to rate and evaluate your health condition as height and weight, strength or heartrate when walking (primarily in the 1st session).
- **Quantitative Sensory Testing:** as pre- and post-test conducted every session
  - **Pressure Pain Thresholds**: A hand-held probe (algometer) is pushed on the skin and by pushing a button you stop when the pressure turns into pain or pain tolerance is reached.
  - **Thermal Threshold**: A probe, which can increase/decrease its temperature, is placed on your skin. You indicate when the cold or warm feeling turns into pain.
  - **Temporal Summation**: Ten consecutive heat or pressure stimuli will be applied on your arm, and for each you rate pain intensity. Stimuli are of very short duration and cannot cause damage.
  - **Withdrawal Reflex**: A small electric stimulus will be applied to produce a muscular 'twitch' response on the leg. The stimulus will be a similar intensity to a static shock from touching a door.

Pressure Test

Thermal Test

Withdrawal Reflex

After these tests you will rest for about 25 minutes. After the rest the same tests will be repeated. During the first session you will be asked to complete some questionnaires, for the following sessions you can read, study or relax.

5. Will my taking part in this study be kept confidential?

All information collected on you will be kept strictly confidential. The consent form containing your allocated ID will never be present in electronic form, and only available to the researchers. All data will be managed in accordance with the EU General Data Protection Regulation 2016/679.

6. What will happen to the results of the research study?

All data for presentation will be anonymised, that means your identity will not be revealed in any way. The findings from this study will be presented, or shared with other researchers in the form of presentations and scientific papers as appropriate.

7. What do I get out of participating?

After completion we can provide you with an overview of your results. However, this study aim is not to improve your physical fitness level. Time spent during the experiment can be used for research hours. The results of this study will contribute to shape future treatment for musculoskeletal disorders.

8. Does the study follow Ethics prescriptions?

This study underwent the ethical review processes of the University of Birmingham and received official approval from the University Ethics Committee.

9. Who is organising and funding the research?

The study has been designed and organised by Professor Deborah Falla, Chair in Rehabilitation Science and Physiotherapy (or and the CPR Spine team.

For further information please contact Pauline Kuithan

Pauline Kuithan, PhD Student & registered Physiotherapist School of Sport, Exercise and Rehabilitation Sciences University of Birmingham	

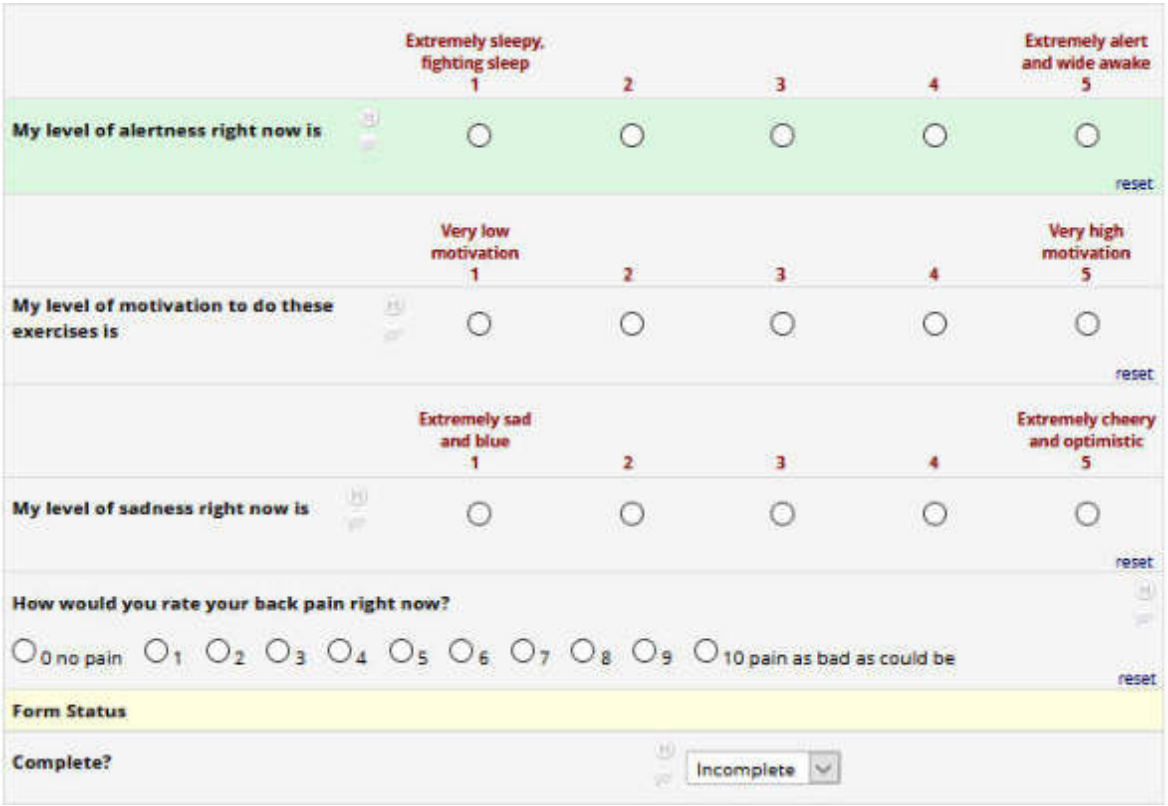
Thank you for taking time to read this and considering taking part in the study!

Appendix 14 Questionnaires Chapters four, five, and six

At each session, participants completed a custom-designed mood questionnaire and a modified Outcome Expectations for Exercise Scale (OEE) questionnaire on expectations of exercise pre-(first and final session) and post-(all sessions) exercise adapted from Resnick et al. (2000). This included perceived changes in pain sensitivity for thermal and pressure pain as well as activity undertaken between sessions. It is to note that for the asymptomatic group (CON) a non-electronic version of the questionnaires was used based on the same wording. Perceived pain was only evaluated in the CLBP group. Chapter six with the non-exercising control group filled in questionnaires at the beginning of the study and the mood questionnaire only.

Resnick, B., et al. (2000). "Outcome expectations for exercise scale: utility and psychometrics." J Gerontol B Psychol Sci Soc Sci 55(6): S352-356.

Mood Questionnaire first session



	Extremely sleepy, fighting sleep 1	2	3	4	Extremely alert and wide awake 5
My level of alertness right now is	○	○	○	○	○

reset

	Very low motivation 1	2	3	4	Very high motivation 5
My level of motivation to do these exercises is	○	○	○	○	○

reset

	Extremely sad and blue 1	2	3	4	Extremely cheery and optimistic 5
My level of sadness right now is	○	○	○	○	○

reset

How would you rate your back pain right now?

○ 0 no pain ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10 pain as bad as could be

reset

Form Status

Complete? Incomplete

OEE first session

Please rate each of the following statements:

Exercise....

	strongly agree	agree	neither agree nor disagree	disagree	strongly disagree	
Makes me feel better physically * must provide value	○	○	○	○	○	reset
Makes my mood better in general * must provide value	○	○	○	○	○	reset
Helps me feel less tired * must provide value	○	○	○	○	○	reset
Makes my muscles stronger * must provide value	○	○	○	○	○	reset
Is an activity I enjoy doing * must provide value	○	○	○	○	○	reset
Gives me a sense of personal accomplishment * must provide value	○	○	○	○	○	reset
Makes me more alert mentally * must provide value	○	○	○	○	○	reset
Improves my endurance in performing my daily activities * must provide value	○	○	○	○	○	reset
Helps to strengthen my bones * must provide value	○	○	○	○	○	reset

OEE Session post (Chapter four and five only)

Please rate each of the following statements:

The exercise....

	strongly agree	agree	neither agree nor disagree	disagree	strongly disagree
made me feel better physically * must provide value	○	○	○	○	○ reset
improved my general mood * must provide value	○	○	○	○	○ reset
made me feel more awake * must provide value	○	○	○	○	○ reset
made me feel stronger * must provide value	○	○	○	○	○ reset
I enjoyed doing the exercise session * must provide value	○	○	○	○	○ reset
gave me a sense of personal accomplishment * must provide value	○	○	○	○	○ reset
made me more alert mentally * must provide value	○	○	○	○	○ reset
mad me feel like I had improved my endurance * must provide value	○	○	○	○	○ reset
made me less sensitised to pressure * must provide value	○	○	○	○	○ reset
made me less sensitised to thermla stimuli	○	○	○	○	○ reset

Overall my sensitivty to pain felt

○ A lot less ○ less ○ the same ○ more ○ a lot more reset

Back Pain right now

no pain 5 pain as bad as it could be

Change the slider above to set a response

reset

Mood Questionnaire session two to six

	Extremely sleepy, fighting sleep 1	2	3	4	Extremely alert and wide awake 5
My level of alertness right now is	○	○	○	○	○

reset

	Very low motivation 1	2	3	4	Very high motivation 5
My level of motivation to do these exercises is	○	○	○	○	○

reset

	Extremely sad and blue 1	2	3	4	Extremely cheery and optimistic 5
My level of sadness right now is	○	○	○	○	○

reset

How would you rate your back pain right now?

○ 0 no pain ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10 pain as bad as could be

reset

How would you rate the average intensity of your back pain since the last session?

○ 0 no pain ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10 pain as bad as could be

reset

Have you taken any pain medication since last session? ○ Yes ○ No

reset

Did you have pain after the last session? ○ Yes ○ No

reset

Form Status

OEE Session 2-6 post (Chapter four and five only)

Please rate each of the following statements:

The exercise....

	strongly agree	agree	neither agree nor disagree	disagree	strongly disagree
made me feel better physically * must provide value	○	○	○	○	○
improved my general mood * must provide value	○	○	○	○	○
made me feel more awake * must provide value	○	○	○	○	○
made me feel stronger * must provide value	○	○	○	○	○
I enjoyed doing the exercise session * must provide value	○	○	○	○	○
gave me a sense of personal accomplishment * must provide value	○	○	○	○	○
made me more alert mentally * must provide value	○	○	○	○	○
made me feel like I had improved my endurance * must provide value	○	○	○	○	○
made me less sensitised to pressure * must provide value	○	○	○	○	○
made me less sensitised to thermal stimuli	○	○	○	○	○

reset

Comparison to the last session

	A lot less	less	the same	more	a lot more
Today's intensity felt	○	○	○	○	○
Overall my sensitivity to pain felt	○	○	○	○	○

reset

Exercise since last session (Type, Day, Time and Intensity (vigorous, moderate, easy)

Expand

Back Pain right now

0=no pain — 10=pain as bad as it could be

Change the slider above to set a response

reset

OEE end of study (Chapter four and five only)

Please rate each of the following statements:

Exercise....

	strongly agree	agree	neither agree nor disagree	disagree	strongly disagree
Makes me feel better physically * must provide value	○	○	○	○	○
Makes my mood better in general * must provide value	○	○	○	○	○
Helps me feel less tired * must provide value	○	○	○	○	○
Makes my muscles stronger * must provide value	○	○	○	○	○
Is an activity I enjoy doing * must provide value	○	○	○	○	○
Gives me a sense of personal accomplishment * must provide value	○	○	○	○	○
Makes me more alert mentally * must provide value	○	○	○	○	○
Improves my endurance in performing my daily activities * must provide value	○	○	○	○	○
Helps to strengthen my bones * must provide value	○	○	○	○	○

reset

How would you describe your experience over the six sessions?

Expand

Were you pleased with the allocation/ your exercise intervention?

Expand

Do you think you would have had a different outcome from the other exercise?

Expand

If you could change anything in this study, what would it be?

Expand

Do you think this programme is feasible for people with severe low back pain and why?

Expand

Low back Pain Questionnaire (participants CLBP Chapter four and five only)

Record ID	51
Has your pain persisted at least 3 months and resulted in pain on at least half the days in the past 6 months?	(●) Yes ( ) No reset
When was your first episode of back pain? **Year:**	
What caused it?	Expand
How often do you get episodes of low back pain?	( ) Constant pain ( ) Almost constant pain ( ) Weekly ( ) Monthly ( ) less than monthly reset
How long does your back pain usually last for?	( ) A few hours ( ) A few days ( ) Several weeks ( ) Several months ( ) Several years ( ) constant reset
Have you ever experienced any of these features with your back pain?	[ ] Numbness [ ] Weakness [ ] Tingling [ ] Pins and needles [ ] Burning [ ] Leg pain
Form Status	
Complete?	Incomplete
	Save & Exit Form Save & Exit Record
	-- Cancel --

When did this episode start?

Today

How would you rate the average intensity of your most recent episode of back pain?

No pain — Pain as bad as could be

Change the slider above to set a response

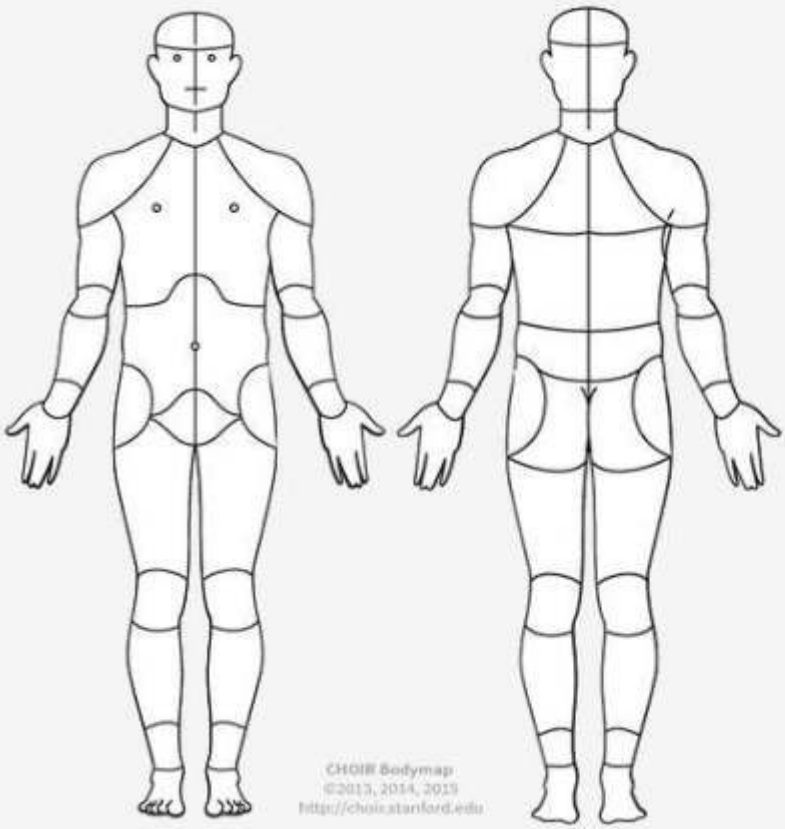
reset

What best describes your current low back pain state within the last 4 weeks?

- Stable
- Getting better
- Getting worse
- Fluctuant with pain free episodes
- Fluctuant without pain free episodes

reset

Where is your most painful area?



Which activities provoke your pain?

Do any of these activities make your pain worse?

- [ ] Sitting
- [ ] Standing
- [ ] Sitting from standing
- [ ] Standing from sitting
- [ ] Bending forwards
- [ ] Trunk Rotation (twisting)
- [ ] Lifting
- [ ] Carrying
- [ ] Picking up an object
- [ ] Overhead activity

Which activities or techniques do you use to alleviate your pain?

Expand

Have you taken any pain medication within the last 24 hours?

- ○ Yes
- ○ No

reset

How would you rate your pain <u>at the present time</u>, that is right now'?

No pain — Pain as bad as could be

Change the slider above to set a response

reset

In the past 4 weeks, how intense has your <u>worst</u> pain been?

No pain — Pain as bad as could be

Change the slider above to set a response

reset

In the last 24 hours, <u>on average</u>, how intense has your pain been?

(That is, your usual pain at times when you were experiencing pain)

No pain — Pain as bad as could be

Change the slider above to set a response

reset

reset

Treatment history

In the past, did you ever receive any of the following treatments and if so, did they contribute to your health?

	No	Yes, with success	Yes, with temporary success	Yes, but no improvement
Pain medication	○	○	○	○
Physiotherapy (passive interventions)	○	○	○	○
Physiotherapy (active interventions such as exercise)	○	○	○	○
Advice on bending	○	○	○	○
Advice on lifting	○	○	○	○

reset

Appendix 15 STROBE Guidelines Chapter four (representative of Chapters five and six)

Checklist of items that should be included in reports of ***cross-sectional studies.***
It should be noted this study had a randomised design.
Retrieved from https://www.strobe-statement.org/download/strobe-checklist-cross-sectional-studies-doc

	Item No	Recommendation	Section
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	4.1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4.1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4.2.1
Objectives	3	State specific objectives, including any prespecified hypotheses	4.2.2
Methods			
Study design	4	Present key elements of study design early in the paper	4.3.1
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4.3.2
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	4.3.2
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4.3.3 -5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4.3.8*
Bias	9	Describe any efforts to address potential sources of bias	4.3.6
Study size	10	Explain how the study size was arrived at	4.3.7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4.3.8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4.3.8
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	4.3.8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4.4.1
		(b) Give reasons for non-participation at each stage	4.4.1
		(c) Consider use of a flow diagram	4.4.1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	4.4.1-4.4.3

		(b) Indicate number of participants with missing data for each variable of interest	4.4
Outcome data	15*	Report numbers of outcome events or summary measures	4.4-7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	4.4-7
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	4.5
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	4.5.5
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	4.6
Generalisability	21	Discuss the generalisability (external validity) of the study results	4.5.5/ 4.6
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NA

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Appendix 16 Additional Results Chapter four

Results OEE and mood questionnaire are presented descriptively as the median score for both groups (CLBP, CON).

OEE pre and post study
Modified OEE before and after the study (median), values represent:
1= strongly agree; 2 = agree; 3= neither agree nor disagree; 4= disagree; 5= strongly disagree

Exercise…	CLBP pre	CLBP post	CON pre	CON post
Makes me feel better physically	2	2	1	2
Makes my mood better in general	2	2	1	2
Helps me feel less tired	2	2	2	2
Makes my muscles stronger	1	2	2	2
Is an activity I enjoy doing	2	2	2	1
Gives me a sense of personal accomplishment	2	2	1	2
Makes me more alert mentally	2	2	2	2
Improves my endurance in performing my daily activities	2	2	2	2
Helps to strengthen my bones	2	2	2	2

Mood

Mood was assessed at the beginning of each session with a modified Likert scale. The group median for alertness (1= Extremely sleepy, fighting sleep; 5= Extremely alert and wide awake); Motivation (1= Very low motivation; 5= Very high motivation); and Level of Sadness (1= extremely sad and blue; 5=extremely cheery and optimistic)

	Session 1	Session 2	Session 3	Session 4	Session 5	Session 6
Alertness						
CLBP	3	4	4	3	4	4
CON	4	4	4	4	4	4
Motivation						
CLBP	4	4	4	4	4	3
CON	4	4	4	4	4	4
Level of Sadness						
CLBP	4	4	4	4	4	4
CON	4	4	4	4	4	4

OEE

OEE results after each session are shown in the table (Median) based on a Likert-Scale 1= strongly agree; 2 = agree; 3= neither agree nor disagree; 4= disagree; 5= strongly disagree. Whereas the final two questions were on the intensity of the exercise with a modified Likert 5-item scale: 1= A lot less; 2= less; 3= the same; 4= more; 5= a lot more.

The exercise…	Group	Session 1	Session 2	Session 3	Session 4	Session 5	Session 6
made me feel better	CLBP	3	3	2	2	2	2
	CON	2	2	2	2	2	3
improved my general mood	CLBP	2	3	2	2	2	2
	CON	3	2	2	2	2	2
made me feel more awake	CLBP	2	2	2	3	2	2
	CON	2	2	2	2	3	3
made me feel stronger	CLBP	3	3	2	3	2	2
	CON	3	2	3	2	2	2
I enjoyed doing the exercise session	CLBP	2	2	2	2	2	2
	CON	2	2	2	2	2	2
gave me a sense of personal accomp-lishment	CLBP	3	2	2	2	2	2
	CON	2	2	2	2	2	2
made me more alert mentally	CLBP	2	2	2	2	3	2
	CON	2	3	2	2	3	3
made me feel like I had im-proved my endurance	CLBP	3	2	2	2	2	2
	CON	3	3	3	3	3	3
made me less sensitised to pressure	CLBP	3	3	3	3	3	2
	CON	2	3	2	2	2	2
made me less sensitised to thermal stimuli	CLBP	3	3	3	3	3	2
	CON	3	3	3	2	2	2
		Modified Likert-Scale					
Today's intensity felt	LBP	NA	3	3	3	2	3
	CON		3	4	2	3	3
Overall my sensitivity to pain felt	CLBP	NA	3	3	3	2	3
	CON	NA	2	3	3	3	3

Temporal Summation

Temporal Summation (TS) was conducted after the QST test battery. Ten consecutive heat pulses of 50°C were applied firstly over the right forearm and then over the lumbar region. Temperature increased with a rate of 8°C/sec from the baseline temperature of 40°C with an interstimulus interval of 2.5sec. For each pulse, a verbal pain rating score from 0-100 on a numeric rating scale (NRS) was taken based on a previous protocol (Chapter two). Due to initial findings, the length of the protocol, and further questionnaires with the CLBP group TS was not tested in participants with CLBP. For analysis, three NRS scores representing the ten stimuli (I= 1st-4th, II= 5th-7th, III=8th-10th stimuli) were considered and reported descriptively since no evidence of TS was found.

Data from the remaining participants (8/15) were excluded as full data sets were not obtained due to participants stopping the test due to pain or technical issues. However, this was not due to TS and occurred mainly during the first set of stimuli.

Temporal summation pain scores (NRS 0-100) for the CON group over both lumbar and thenar test sites pre and post the exercise averaged across six sessions are presented below.

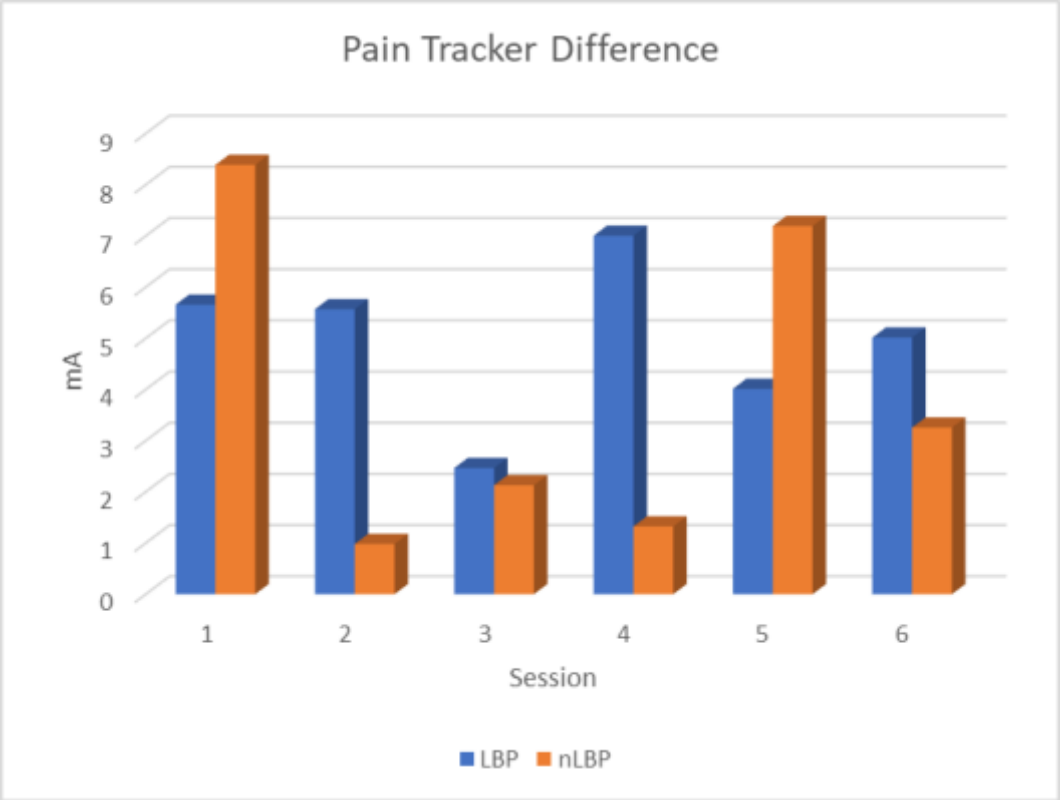
	N=	Lumbar I	Lumbar II	Lumbar III	N	Hand I	Hand II	Hand III
Pre	7/15	48.68 ±32.53	38.91 ±32.57	32.39 ±33.13	10/15	56.77 ±28.91	50.11 ±29.42	44.05 ±30.99
Post	7/15	46.77 ±32.52	35.44 ±31.35	28.71 ±31.20	10/15	57.42 ±30.97	47.79 ±30.89	40.56 ±31.93

Nociceptive Withdrawal Reflex

The final measurement was the nociceptive withdrawal reflex to avoid any interaction such as conditioning pain modulation or offset analgesia which can affect both QST measurements and EIH (Gajsar et al., 2018b, Alsouhibani et al., 2019). A Dolosys Pain Tracker (Dolosys GmbH, Germany) was used to assess the nociceptive withdrawal reflex of the tibialis anterior muscle as an objective and patient independent outcome on pain sensitivity (Neziri et al., 2010, Jakuscheit et al., 2017). Sitting on a plinth with legs hanging over the edge, two surface electrodes on the medial arch of the left foot produced a series of short low intensity electrical impulses (20-45 stimuli). If a physiological threshold was reached, a muscular 'twitch' response was detected via surface electrodes placed over the tibialis anterior. Electrodes were left attached to the skin during the exercise and positions marked with a surgical pen in between sessions. It was tested on the contralateral side to the PPT over the tibialis anterior muscle to avoid any interactions with the test side. For analysis, the mean intensity required to produce a reflex (minimum of three) was assessed a bespoke software provided by the company (Dolosys GmbH, Germany).

Analysis of the pain tracker was limited due to the fact that many participants did not tolerate the test and stopped early due to discomfort or unpleasantness, or no threshold could be obtained.

For three participants in the CON group the device was not available for all six sessions. Results below represent data of CLBP (n= 5,4,5,4,5,5) per session one to six) and for CON (n=7,7,9,8,9,11). In eight cases (CLBP) and seven cases (CON) only a pre or post score was obtained. No further analysis was conducted due to the inadequate sample size. The mean for the CON group was 7.06±0.59 mA across the pre-tests and 12.01±1.38mA for the post-tests. In the CLBP group the average pre score was 9.25±1.42 mA and 13.13±2.23 mA. No scores were obtained in nine participants of the CLBP group and three in the CON group. In the CON group the device was not available for the first sessions in four participants. Visual observation indicated higher thresholds after the exercise for both groups and all sessions as a potential sign for EIH.



Difference (Mean) of the nociceptive reflex in mA for each of the six session for both groups. Please note low numbers as outlined in text.

References

ALSOUHIBANI, A., VAEGTER, H. B. & HOEGER BEMENT, M. 2019. Systemic Exercise-Induced Hypoalgesia Following Isometric Exercise Reduces Conditioned Pain Modulation. Pain Med, 20, 180-190.

GAJSAR, H., NAHRWOLD, K., TITZE, C., HASENBRING, M. I. & VAEGTER, H. B. 2018. Exercise does not produce hypoalgesia when performed immediately after a painful stimulus. Scand J Pain, 18, 311-320.

JAKUSCHEIT, A., POSCH, M. J., GKAITATZIS, S., NEUMARK, L., HACKBARTH, M., SCHNEIDER, M., LICHTNER, G., BAARS, J. H. & VON DINCKLAGE, F. 2017. Utility of nociceptive flexion reflex threshold and bispectral index to predict movement responses under propofol anaesthesia. Somatosens Mot Res, 34, 139-144.

NEZIRI, A. Y., HAESLER, S., PETERSEN-FELIX, S., MULLER, M., ARENDT-NIELSEN, L., MANRESA, J. B., ANDERSEN, O. K. & CURATOLO, M. 2010. Generalized expansion of nociceptive reflex receptive fields in chronic pain patients. Pain, 151, 798-805.

Participants' perception of study participation

A five-item questionnaire as outlined in earlier was conducted at the end of the study. This was important to gain further insight of the participants point of view. The outcomes can help to contribute to the conduction of qualitative research in EIH. For example, this would be required for a feasibility study.

CLBP Group

Participants' quotes for CLBP group are presented for each of the five questions regarding their experience, the allocation, outcome, changes, and transfer of the study to a more severe CLBP group. Original quotes were modified for clarification of context.

How would you describe your experience over the six sessions?	**Were you pleased with the allocation/ your exercise intervention?**	**Do you think you would have had a different outcome from the other exercise?**	**If you could change anything in this study, what would it be?**	**Do you think this programme is feasible for people with severe low back pain and why?**
interesting! At first, I struggled with the exercises but after my 2nd visit, they were not so bad. Didn't enjoy the prodding into various parts of the body, but hopefully the results will be useful in the research	yes	possibly	nothing I can think of as everything was explained well and was efficient.	I think the exercise could cause issues with people with severe back pain as there is a little bit of twisting involved with can be uncomfortable.
Was challenging and I felt like I improved as time went on	Yes, I felt it improved my general fitness and strength in my back	May have made walking quicker and easier.	I think this study is good, to improve perhaps continuous sessions rather than break in between?	Yes, though at times I did want to not do the exercises I feel that people with low back pain should try exercising to help them as I always feel better afterwards though I don't always have time to exercise.
interesting, but no big effect on back pain	yes	no	no	yes, the exercise is not very intensive or damaging
Tiring and good	It hurt so I wasn't overall happy	I might have felt stronger rather than in pain	Instead of repeating pressure on the same area come back to it as my skin still hurt	No, the exercise was painful
was enjoyable and interesting	yes. preferred resistance over cardio	not sure	none	depends on pain. exercise was a way harder when my back pain was more severe. There would probably be days I would not be able to complete the programme
it was a great experience and made me realized my strengths over the period of time	yes, absolutely.	Maybe, but I am content with the same.	nothing, it seems perfect for me	yes, it will help them know about their pain tolerance and severity and further improve their overall endurance too.

I really enjoyed these exercises. I also feel very motivated to start exercising on a daily basis as I feel that my pain has decreased overall over the last few weeks (even though I have pain sometime after each session).	Yes, I am very pleased with the exercise intervention. They gave me a sense of accomplishme nt and gave me insight into my own physical strengths.	Not that I can think of. I am pleased with what I have done during the exercises.	No suggestions here, sorry.	I think this study can give a wider understanding of how pain is perceived by each individual, how different muscles interacts differently in pain perception in different positions (laying down, sitting etc.) and how exercises can help to improve pain for lower back.
it was quite interesting. I have never been part of an experiment. I felt very safe, and that I was taken care. It was a challenge to have to pay attention to the pain and try to rate it.	Yes, especially when she stopped with pain tracker, that was really annoying and hard.	I don`t know. I haven't done it to be able to compare.	I don`t think so.	No, I believe that people with severe back pain would feel a lot more the pressures, and they wouldn't be able to the resistance exercise as it requires a good deal of back muscle moving.
it is the thing which makes the pain less on my back.	Absolutely yes	I am not sure	I would use something like a machine, not a human hand, to perform the act of giving pain to the subject with the purpose of zero margin of error.	Partly agree, since it has made me feel better, but I am not sure whether I should describe my pain as severe.
Very positive, I feel I've become stronger and my back is less sensitive to pain.	Yes, it definitely helped my back pain.	No.	Increase the length of time spent doing the exercises.	Definitely, as the study tales into account contributing factors and physical capabilities each session so if there's any fluctuations in back pain, eg being more severe, it's recognised, and the intensity lowered.
good	yes	don't know	0	yes, it's not pretty easy but not that difficult either.
0	Yes	Yes	Nothing	Loads might need to be decreased
good	yes	yes	add more exercise	Yes, more stronger
Enjoyed the exercise, made me feel need to do more exercise in daily basis.	N/A	Encourage me to do regular exercise, perhaps.	N/A	Yes, the exercise relatively easy.

Interesting and different to what I usually do	yes	Not sure	0	Maybe not as it could be too painful for them to do the exercise.

Asymptomatic control group

Participants' quotes for CON group are presented for each of the five questions regarding their experience, the allocation, outcome, changes, and transfer of the study to a group with LBP. Original quotes were modified for clarification of context.

How would you describe your experience over the six sessions?	**Were you pleased with the allocation/ your exercise intervention?**	**Do you think you would have had a different outcome from the other exercise?**	**If you could change anything in this study, what would it be?**	**Do you think this programme is feasible for people with low back pain and why?**
decreased sensitivity after exercise	yes	yes	handle primus	Yes, they can do it
really good, very unique	yes	not sure	make the cold more cold (less than 0)	possibly because it could help to strengthen their back and possibly relieve some of the pain
calm but sometimes demanding	yes	no	nothing	no because my allo-cation mainly involved my back muscles, so would not be suitable for people with back pain
It was rewarding to see how my ability including strength, technique, pressure and pain tolerance and others improved over the past three weeks. I did enjoy the sessions as they were a mixture of relaxing and very active moments. I felt good when having to concentrate on my pain and pressure thresholds. Overall a fun and interesting experience	very pleased	I probably would have as I think the strength exercise focusses more on other things	I am no expert in the field to make any suggestions	Yes, though it could be difficult for the but could help them improve their awareness of pain tolerance
interesting	yes	no	the study took 20-30 minutes longer than what I was informed initially	No, the back and forth bending on the machine would probably cause pain
It was interesting to learn about the different activities that were being done and the rationale behind them. I found the exercise a bit tedious but didn't	I didn't mind	Maybe if I had done cardio and gotten my heart rate up, my body would be	the amount of pain test spots -> although it might be necessary	If someone has low back and had to do the exercise I did, they might find it painful -> so maybe not feasible

mind it some of the pain tests I didn't look forward to		warmer and less sensitive		depending on the exercise
all right	yes	NA	NA	yes, it is trying to find a solution to LBP
slightly painful but interesting to see changes before and after exercise	yes	yes	can think of any	no. back is a bit stiff after exercise
after six sessions I have experienced how pain can change after doing exercise	yes	maybe I would have had a lower decrease in pain	nothing	Yes, because exercise tasks are feasible to do by this population
my sensitivity to pain generally decreases	yes	no	variety of pain tolerance test	Yes, as the exercise are good for people with low back pain
It was overall pleasant and well-guided by the researcher. Everything was explained to me carefully and with attention, I've felt no pressure or anything negative during its conduction	yes	I couldn't say	nothing I guess	I couldn't say as I haven't experienced low back pain, but exercises weren't demanding
I really enjoyed the sessions and would happily be involved again	yes	can't be sure	nothing	I can't see why not.
Very good. It helped me to improve my memory and feel less tired. Also, I love doing exercise, so I enjoyed a lot these six sessions	Yes, I was	I don't know	I don't know. I enjoyed this study so I don't really think I'd change anything	Yes, because you are doing exercise and it helps to avoid back pain
I feel the sessions have helped to improve my physicality and be less sensitive to pain. I feel more adopt to take on strength exercises and resistant to pain.	yes	not particularly, I don't know what to expect	less resistance / strength exercises	Yes, as they could still take on the exercises, even though they might be more suspectable to the pains and pressures
felt desensitised to pain as the sessions increased felt the exercise was a bit too light to fell an impact	yes	no same outcome	heavier weights in the exercise reduce recovery time	Yes, exercises were easy and short duration so you can easily put it into daily routine

Appendix 17 Additional Results Chapter five

OEE and Mood Questionnaires

OEE pre and post study

Modified OEE before and after the study (median):
Values represent 1= strongly agree; 2 = agree; 3= neither agree nor disagree; 4= disagree; 5= strongly disagree

Exercise…	CLBP pre	CLBP post	CON pre	CON post
Makes me feel better physically	1	1	1	2
Makes my mood better in general	1	1	1	2
Helps me feel less tired	2	1	2	2
Makes my muscles stronger	1	1	1	2
Is an activity I enjoy doing	1	1	1	2
Gives me a sense of personal accomplishment	1	1	1	2
Makes me more alert mentally	1	1	1	2
Improves my endurance in performing my daily activities	1	2	1	2
Helps to strengthen my bones	1	2	2	2

Mood

Mood was assessed at the beginning of each session with a modified Likert scale. The group median for alertness (1= Extremely sleepy, fighting sleep; 5= Extremely alert and wide awake); Motivation (1= Very low motivation; 5= Very high motivation); and Level of Sadness (1= extremely sad and blue; 5=extremely cheery and optimistic)

	Session 1	Session 2	Session 3	Session 4	Session 5	Session 6
Alertness						
CLBP	4	3	3	3	4	4
CON	4	4	4	4	4	4
Motivation						
CLBP	4	4	4	4	4	4
CON	4	4	4	4	4	4
Level of Sadness						
CLBP	4	4	4	4	4	4
CON	4	4	4	4	4	4

OEE

OEE results after each session are shown in the table (Median) based on a Likert-Scale 1= strongly agree; 2 = agree; 3= neither agree nor disagree; 4= disagree; 5= strongly disagree. Whereas the final two questions were on the intensity of the exercise with a modified Likert 5-item scale: 1= A lot less; 2= less; 3= the same; 4= more; 5= a lot more.

The exercise…	Group	Session 1	Session 2	Session 3	Session 4	Session 5	Session 6
made me feel better	CLBP	2	2	2	2	2	1
	CON	2	2	2	2	2	2
improved my general mood	CLBP	2	2	2	2	1	2
	CON	2	2	2	2	2	2
made me feel more awake	CLBP	2	2	2	2	2	2
	CON	2	1	2	2	2	2
made me feel stronger	CLBP	2	2	3	2	2	2
	CON	3	3	3	3	3	3
I enjoyed doing the exercise session	CLBP	2	1	2	2	2	2
	CON	2	2	2	2	2	2
gave me a sense of personal accomplishment	CLBP	2	2	2	2	2	2
	CON	2	2	3	2	2	2
made me more alert mentally	CLBP	2	2	2	2	2	2
	CON	2	2	2	2	2	3
made me feel like I had im-proved my endurance	CLBP	3	2	2	2	2	2
	CON	3	3	3	3	3	3
made me less sensitised to pressure	CLBP	2	2	2	2	2	2
	CON	2	2	2	2	2	2
made me less sensitised to thermal stimuli	CLBP	3	2	2	2	2	2
	CON	2	3	2	2	3	2
		Modified Likert-Scale					
Today's intensity felt	LBP	NA	4	3	2	2	3
	CON	NA	3.5	2	2	2	3
Overall my sensitivity to pain felt	CLBP	NA	3	3	2	2	3
	CON	NA	3	2.5	3	3	3

TS

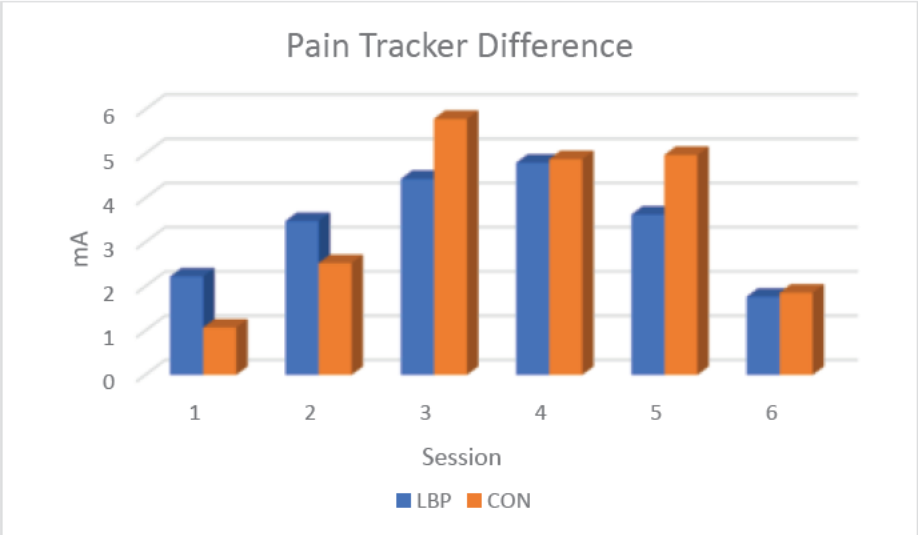
Only the CON was tested as the protocol could not show any signs of temporal summation (Appendix 16).

Temporal summation pain scores (NRS 0-100, Mean± SD) for the CON group after a treadmill task averaged for five sessions over two different test sites.
NRS= Numeric Rating Scale

CON		Hand I	Hand II	Hand III		Lumbar I	Lumbar II	Lumbar III
	N=	Mean± SD			N=	Mean± SD		
PRE	15	40.91±23.55	38.55±19.01	32.17±13.43	14	39.37±21.81	31.34±12.69	27.03±9.86
POST		40.83±23.42	33.99±13.69	28.49±10.61		36.73±17.91	28.24±10.06	21.64±10.12

Nociceptive withdrawal reflex

Data of eight participants of the CLBP group were considered, except for session two, for which nine data sets were available. In the CON group data sets of nine participants were included, except for session six, where eight sets were considered. For one participant in the CLBP group the device was only available for the last two sessions, and one participant was not tested due to blisters under both feet. The average pre score for the CLBP was 7.76±0.85mA and 7.97±1.90mA for the CON group; and respectively post scores were 11.14±1.52mA and 11.48±0.99mA. The difference for each session is displayed below.



Difference (Mean) of the nociceptive reflex in mA for each session It is to note that the first session was the set-up session so information of EIH is inconclusive due to variations in the duration of the set-up.

Participants' perception of study participation

CLBP Group

Participants' quotes for the CLBP group are presented for each of the five questions regarding their experience, the allocation, outcome, changes, and transfer of the study to a group with more severe LBP. Original quotes were modified for clarification of context.

How would you describe your experience over the six sessions?	**Were you pleased with the allocation/ your exercise intervention?**	**Do you think you would have had a different outcome from the other exercise?**	**If you could change anything in this study, what would it be?**	**Do you think this programme is feasible for people with severe low back pain and why?**
Very happy, it makes me more stronger.	YES	YES	Exercise time can be longer.	I am not sure.
Very enjoyable	neither yes or no, happy to be in either	Yes weights might have triggered my back pain differently	Ability to change playlist each session	Yes, its low intensity/ weight bearing exercise and should be accessible. No rotations involved,
Fun. Enjoyed the exercises involved	Yes	No	Nothing	Yes because it accurately measures back pain before and after exercise and that could help inform physio's as to what helps
Very positive, very friendly and professional	Yes, it felt effective but wasn't as vigorous as my usual exercise choice, but was still a challenge which surprised me	Potentially, I am unsure what other options were available but higher intensity would've provoked pain after finishing which walking didn't	Nothing :)	Possibly not, they may struggle with lying flat on front/back and moving between The exercise might be possible, but they could struggle doing it at an high enough intensity to reach the correct heart rate zone I think
quite unusual, exercise in general improves my mood, but being measure does not	absolutely	no	wearing headphone s while	no, pressure tolerance may be so low that it isn't even measurable

			listening to music	
Interesting study	yes	Yes	n/a	Yes as could study how their pain tolerance differ after exercising
I could feel my pain sensitivity reduced a lot over the time	yes	may be core strengthening would help more in back pain	nothing	yes as anyone can easily incorporate walking in their day to day life
Two words.... Hill Walking. Experience has been enjoyable and interesting.	Yes.	No.	n/a	Yes, depending on whether they can tolerate pressure on lower back.
Useful and motivating	Yes it is appropriate	No	Base on my understanding all is appropriate and adequate	To some degree yes.
Positive.	Neither pleased nor displeased.	Not sure.	I encountered no problems with the study so would not suggest changing anything.	Yes, it can help people realise what stimulates the back pain. In my case, it became clear that walking exercises do not aggravate my lower back pain. It highlighted to me that sitting is a major contribution to back pain instead.
It was reasonably enjoyable	I might have preferred being in the weight trained group as I already feel reasonably fit and the incline walking did trigger some back pain.	I feel it might have helped with strengthening the muscles of my lower back which I don't feel occurred from the walking	Reducing or removing the incline in the treadmill walking	I would be inclined to say no because the incline walking did flare up my lower back pain

good	yeas	yeas, improve my strength	0	yeas, simple activity everyone can do with no need for equipment
It was a great experience to take part in those sessions, as I am interested in physiotherapy-related topics, I am very happy I could help.	Yes, everything was great.	It was a good moderate activity which I really enjoyed, but more intense activities would in general have different outcomes.	Everything was good.	It is okay, but I think some people especially measuring the pain tolerance over their back might be very uncomfortable.
Overall pleasant, I usually manage my back pain with exercise, which I couldn't do for a couple of weeks due to an illness and my schedule, so these sessions helped to prevent / minimize the pain episodes I've had in the last month.	Yes, though I would prefer more intense exercising	Not regarding the pain - I think even these sessions helped to reduce pain	-	I think so, maybe with more severe pain a more gradual build-up would be needed, but overall exercise helps with pain management.
It was a good experience. I helped me to perform better in my work and reduce the lower back pain after long work sessions.	Yes, completely.	No.	Maybe, it could try with a different exercise routine. But, I think it worked very well.	Yes, because it does not require a high effort of your back to accomplish the tasks. Furthermore, you can stop if you feel uncomfortable.

Asymptomatic Control Group

Participants' quotes for the CON group are presented for each of the five questions regarding their experience, the allocation, outcome, changes, and transfer of the study to a group with LBP. Original quotes were modified for clarification of context.

How would you describe your experience over the six sessions?	Were you pleased with the allocation/ your exercise intervention ?	Do you think you would have had a different outcome from the other exercise?	If you could change anything in this study, what would it be?	Do you think this programme is feasible for people with low back pain and why?
at times walking challenging. Increase in tolerance of pain in cold/heat	yes	unsure	Machine that tests heat + cold needs to go lower temperatures I didn't like the pain tolerance	yes, the walking programme is tailored to their heart rate so is achievable per any level of fitness and is functional
painful but sense of accomplishment	yes	yes	more consistent way of measuring ppt & tolerance	no, cause the speed of walking might be difficult for people with clbp. People may find pain tolerance test difficult/ unwilling to take part
pressure pain hot and cold pain	yes	no	nothing	yes, it didn't aggravate my back at all
I feel that my tolerance to heat and pressure has increased between each session and each time before and after the exercise, particularly in the last three sessions	yes	no, I think it would have been very similar	NA	Not if they were given running exercise, I think that may aggravate a pre-existing condition such as low back pain
It was interesting and I felt in control of what was being done to me. For example, we didn't do the electric impulses test at all because I found it too painful	yes	perhaps, my shoulder strength is less good than my cardio, so the other test would have probably tired me out more	I'd prefer to have different music each session. It gets a bet repetitive always listening to the same tracks	No the pressure that is applied to the lower back would be likely to exacerbate their symptoms, should imagine
It's been a good time. I enjoyed the sessions, especially after the session I felt more concentrated in my studies	yes everything good	no I don't think so	nothing or maybe run instead of walk	yes because I think exercise is good for everything physical mental and emotional health

pretty the same. I enjoyed them. It was quite easy and not tired to be fair	more or less, not too bad to good normal	I don't know because I have never heard about the other exercise	I think I will feel more comfortable if the exercise was longer every session	Yes, I strongly do. Because it's not complicated to follow and the most important it's easy
The sessions have been really interesting and made enjoyable and relaxed by the researcher. Over the sessions I have become more confident in being able to identify the point at which pressure turned into pain. The sessions were very well organised and always run smoothly and on time	I would have preferred the resistance exercise interventio n. However, the treadmill exercise was fine	I am unsure	Have more even gaps between the sessions rather than 4 or 1 day in between	Yes I do because I feel they would still be able to complete the walking on the treadmill
I could feel how only 15 minutes of walking can improve my physical and mental status	yes	I think that the other exercise would be too challenging for me	It was difficult for me to last for 15 minutes on the treadmill not due to endurance but muscle strength. The inclination on the treadmill was really challenging my muscles	I believe that this programme is feasible for younger adults. It is based on realistic amount of exercise that people can perform during a week.
I feel less tired after the exercise	yes	yes	the pain tracker system	Yes, they usually not perform exercises because they are afraid to get pain
It's a good experience. It's hard to do only some parts	yes	maybe yes	It is ok in this way I couldn't change anything	Yes I think it is feasible because people with LBP could tolerate it
The whole protocol is quite interesting	I don't know	I don't know	I would not change anything	Yes, but the running part I think it should be slower and longer

I really enjoyed it excellent experience	yes	maybe the other type would be strength training	nothing everything was well organised	I think it is, since the parameters used are individualised accordingly. However, a lower intensity might be needed for them.
interesting and eye opening	yes	yes	nothing	yes, exercise on the treadmill didn't seem to affect my back, so may not cause people with LBP any further pain
I found the experience interesting and left feeling brighter mood	yes	I don't know for sure	I wouldn't change anything	I do think it is feasible

Appendix 18 Additional Results Chapter six

OEE

Modified OEE before the study (median)

Values represent 1= strongly agree; 2 = agree; 3= neither agree nor disagree; 4= disagree; 5= strongly disagree

Exercise…	
Makes me feel better physically	1
Makes my mood better in general	1
Helps me feel less tired	1.5
Makes my muscles stronger	1
Is an activity I enjoy doing	1
Gives me a sense of personal accomplishment	1
Makes me more alert mentally	1
Improves my endurance in performing my daily activities	1
Helps to strengthen my bones	1

Mood Questionnaire

Mood was assessed at the beginning of each session with a modified Likert scale. The group median for alertness (1= Extremely sleepy, fighting sleep; 5= Extremely alert and wide awake); Motivation (1= Very low motivation; 5= Very high motivation); and Level of Sadness (1= extremely sad and blue; 5=extremely cheery and optimistic)

	Session 1	Session 2	Session 3	Session 4	Session 5	Session 6
Alertness	4	4.5	4	4	4.5	5
Motivation	4.5	5	4	4	4	4.5
Level of Sadness	4	4.5	4	4	4	5

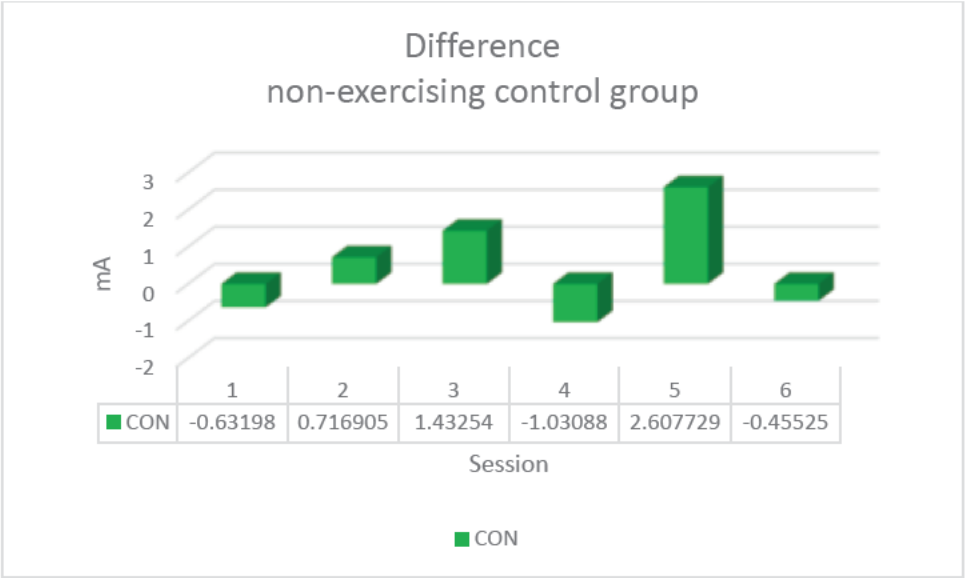
Temporal Summation

For consistency Temporal Summation (TS) was tested but was not found.

		Hand I	Hand II	Hand III		Lumbar I	Lumbar II	Lumbar III
	N	Mean± SD			N	Mean± SD		
Pre	10	61.89±23.86	50.04±29.50	41.42±29.35	9	52.56±26.61	38.52±29.43	33.20±28.53
Post		66.83±23.11	52.76±28.24	44.55±30.45		53.02±27.03	37.45±30.18	31.96±29.17

Nociceptive withdrawal reflex

For one participant the test side was on the left instead of the right due to on old injury and sensory deficit. Data of five participants (Session one to four) and four participants (session five and six) were considered. The average pre was 10.30±0.78 mA and post 10.74 ±1.10mA. The mean difference for each session is displayed in the Figure below.



Pain withdrawal reflex in the non-exercising control participants

Appendix 19 Discussion of Temporal Summation and Nociceptive Withdrawal Reflex

Temporal summation of pain (TS) of heat could not be shown in Chapter two, even though the applied protocol has been shown to produce TS before (Owens et al., 2016). Therefore, the protocol was modified to have shorter breaks and a higher intensity. Findings from the modified protocol did not lead to TS, and therefore are only presented in the Appendix of the relevant Chapters four to six. As alternatives to the TSA-II device, the CHEPS by the same company (Medoc, Israel) enables a higher frequency (Kong et al., 2013). However, this device was not available for the series of studies included in this thesis. The use of PPT or other mechanical pressure was specifically avoided, due to the already high numbers of PPT and PPTOL, even though this has been shown to be a useful alternative (Ickmans et al., 2017; Middlebrook et al., 2020; Nie et al., 2005; Nie et al., 2006; Nie et al., 2009). Alternatively cuff pressure could be used (Graven-Nielsen et al., 2015), which is now commercially available, but maybe not feasible for clinical practice in the near future. Cuff pressure testing has recently gained interest, potentially enhanced due to the problems from other test modalities (Cummins et al., 2020).

The nociceptive withdrawal reflex was applied in Chapter four to six (Appendices 16-18). Based on being one of the very few non-subjective measurements addressing an additional aspect of pain modulation. It is expected that thresholds are higher after the exercise, as demonstrated in a study by Guieu et al. (1992) after a 20-minute cycling protocol. In general, the procedure was not well tolerated by participants. In other cases, a reflex could not be produced even with high intensities above 30 mA. Due to these problems, the data set was insufficient even for descriptive analysis (data saturation commonly below 50%). Most

studies used a different test site, i.e., hamstrings, for the reflex (Linde et al., 2020). However, this protocol was established in agreement with the manufacturer. A recently published systematic review highlights the lack of standardisation and the inconsistency of results (Linde et al., 2020); although the nociceptive withdrawal reflex is a promising tool for objective pain measurement, further research needs to be conducted to validate the concept. Standardisation of electrodes was high within and between sessions, but conduction could be altered as skin might be warmer and moist after the exercise. In this study it was observed that more asymptomatic participants tolerated the testing procedure. Lower thresholds in participants with chronic musculoskeletal pain have been reported previously (low quality evidence) (Linde et al., 2020). Furthermore, participants might have been able to learn to control the reflex as it has been shown in other research in young asymptomatic participants (Ruscheweyh et al., 2015) and participants with CLBP (Krafft et al., 2017), potentially affecting the results over multiple sessions. For both TS and the nociceptive withdrawal reflex further research is required.

References

CUMMINS, T. M., KUCHARCZYK, M. M., GRAVEN-NIELSEN, T. & BANNISTER, K. 2020. Activation of the descending pain modulatory system using cuff pressure algometry: Back translation from man to rat. Eur J Pain, 24, 1330-1338.

GRAVEN-NIELSEN, T., VAEGTER, H. B., FINOCCHIETTI, S., HANDBERG, G. & ARENDT-NIELSEN, L. 2015. Assessment of musculoskeletal pain sensitivity and temporal summation by cuff pressure algometry: a reliability study. Pain, 156, 2193-2202.

GUIEU, R., BLIN, O., POUGET, J. & SERRATRICE, G. 1992. Nociceptive threshold and physical activity. Canadian Journal of Neurological Sciences, 19, 69-71.

ICKMANS, K., MALFLIET, A., DE KOONING, M., GOUDMAN, L., HUBLOUE, I., SCHMITZ, T., GOUBERT, D. & AGUILAR-FERRANDIZ, M. E. 2017. Lack of Gender and Age Differences in Pain Measurements Following Exercise in People with Chronic Whiplash-Associated Disorders. Pain Physician, 20, E829-E840.

KONG, J. T., JOHNSON, K. A., BALISE, R. R. & MACKEY, S. 2013. Test-retest reliability of thermal temporal summation using an individualized protocol. J Pain, 14, 79-88.

KRAFFT, S., GOHMANN, H. D., SOMMER, J., STRAUBE, A. & RUSCHEWEYH, R. 2017. Learned control over spinal nociception in patients with chronic back pain. European Journal of Pain (London, England), 21, 1538-1549. doi: 10.1002/ejp.1055

LINDE, L. D., DUARTE, F. C. K., ESMAEILI, H., HAMAD, A., MASANI, K. & KUMBHARE, D. A. 2020. The nociceptive flexion reflex: a scoping review and proposed standardized methodology for acquisition in those affected by chronic pain. British Journal of Pain, doi: 10.1177/2049463720913289

MIDDLEBROOK, N., HENEGHAN, N. R., EVANS, D. W., RUSHTON, A. & FALLA, D. 2020. Reliability of temporal summation, thermal and pressure pain thresholds in a healthy cohort and musculoskeletal trauma population. PLoS One, 15, e0233521.

NIE, H., ARENDT-NIELSEN, L., ANDERSEN, H. & GRAVEN-NIELSEN, T. 2005. Temporal summation of pain evoked by mechanical stimulation in deep and superficial tissue. J Pain, 6, 348-55.

NIE, H., ARENDT-NIELSEN, L., MADELEINE, P. & GRAVEN-NIELSEN, T. 2006. Enhanced temporal summation of pressure pain in the trapezius muscle after delayed onset muscle soreness. Exp Brain Res, 170, 182-90.

NIE, H., GRAVEN-NIELSEN, T. & ARENDT-NIELSEN, L. 2009. Spatial and temporal summation of pain evoked by mechanical pressure stimulation. Eur J Pain, 13, 592-9.

OWENS, M. A., BULLS, H. W., TROST, Z., TERRY, S. C., GOSSETT, E. W., WESSON-SIDES, K. M. & GOODIN, B. R. 2016. An Examination of Pain Catastrophizing and Endogenous Pain Modulatory Processes in Adults with Chronic Low Back Pain. Pain Med, 17, 1452-64.

RUSCHEWEYH, R., WEINGES, F., SCHIFFER, M., BAUMLER, M., FELLER, M., KRAFFT, S., STRAUBE, A., SOMMER, J. & MARZINIAK, M. 2015. Control over spinal nociception as quantified by the nociceptive flexor reflex (RIII reflex) can be achieved under feedback of the RIII reflex. European Journal of Pain (London, England), 19, 480-9. doi: 10.1002/ejp.570

Appendix 20 Copyright Permissions

Chapter one- Kuithan et al. 2022

CCC RightsLink

My Orders | My Library | My Profile | Welcome pxk634@student.bham.ac.uk | Log out | Help | FAQ

My Orders > Orders > All Orders

License Details

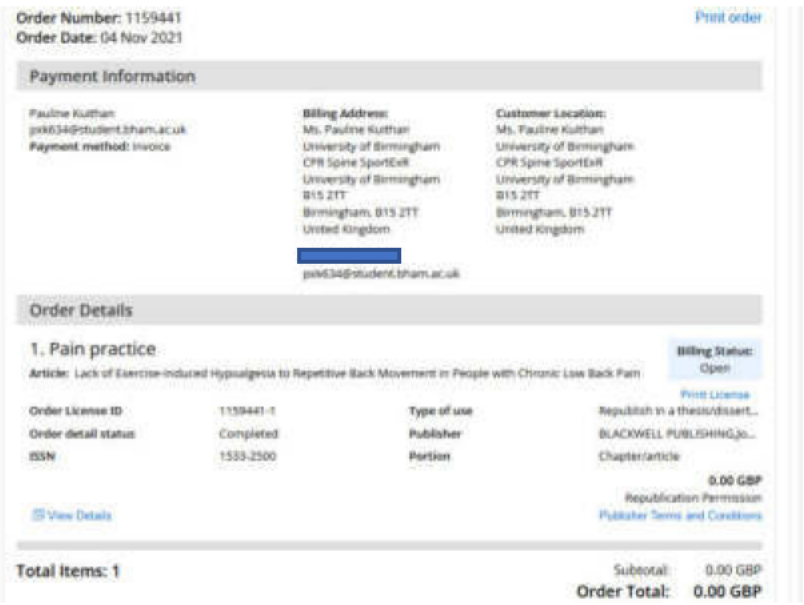
This Agreement between University of Birmingham -- Pauline Kuithan ("You") and Springer Nature ("Springer Nature") consists of your license details and the terms and conditions provided by Springer Nature and Copyright Clearance Center.

Print | Copy

License Number	5250370434739
License date	Feb 15, 2022
Licensed Content Publisher	Springer Nature
Licensed Content Publication	Der Schmerz
Licensed Content Title	Schmerzmodellierung durch Bewegung
Licensed Content Author	Pauline Kuithan et al
Licensed Content Date	Feb 15, 2022
Type of Use	Thesis/Dissertation
Requestor type	academic/university or research institute
Format	print and electronic
Portion	full article/chapter
Will you be translating?	yes, without original language
Number of languages	1
Circulation/distribution	1 - 29
Author of this Springer Nature content	no
Title	Exercise-induced Hypoalgesia in Chronic Low Back Pain
Institution name	University of Birmingham
Expected presentation date	Apr 2022
Specific Languages	Figure will be translated into English, no text
Requestor Location	University of Birmingham CPR Spine Sport/ExR [redacted]
Total	0.00 GBP

BACK

Chapter two - Kuithan et al. 2019



Order Number: 1159441
Order Date: 04 Nov 2021

Print order

Payment Information

Pauline Kuithan
pxk634@student.bham.ac.uk
Payment method: Invoice

Billing Address:
Ms. Pauline Kuithan
University of Birmingham
CPR Spine SportExR
University of Birmingham
B15 2TT
Birmingham, B15 2TT
United Kingdom
[redacted]
pxk634@student.bham.ac.uk

Customer Location:
Ms. Pauline Kuithan
University of Birmingham
CPR Spine SportExR
University of Birmingham
B15 2TT
Birmingham, B15 2TT
United Kingdom

Order Details

1. Pain practice

Billing Status: Open

Article: Lack of Exercise-induced Hypoalgesia to Repetitive Back Movement in People with Chronic Low Back Pain

Print License

Order License ID	1159441-1	**Type of use**	Republish in a thesis/dissert...
Order detail status	Completed	**Publisher**	BLACKWELL PUBLISHING,Jo...
ISSN	1533-2500	**Portion**	Chapter/article

0.00 GBP
Republication Permission

View Details | Publisher Terms and Conditions

Total items: 1

Subtotal: 0.00 GBP
Order Total: 0.00 GBP