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Publication date:
2020

Document Version
Publisher's PDF, also known as Version of record

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BY
MEGAN ELIZABETH MCPHEE CHRISTENSEN

DISSERTATION SUBMITTED 2020

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Dissertation submitted 08/10/2020

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Dissertation submitted: 8th October 2020

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Department: Department of Health Science and Technology

ISSN (online): 2246-1302
ISBN (online): 978-87-7210-821-6

Published by:
Aalborg University Press
Kroghstræde 3
DK – 9220 Aalborg Ø
Phone: +45 99407140
aauf@forlag.aau.dk
forlag.aau.dk

Printed in Denmark by Rosendahls, 2020

CV

Megan began her academic career in late 2013 as a Summer Research Scholar and then Honours student at the CCRE Spine, while obtaining her Bachelor of Physiotherapy (Honours, Class I) from the University of Queensland, Australia. With a spark for research well and truly ignited, after just a few months of clinical work as a physiotherapist at QEII Jubilee Hospital, Megan transitioned part-time into a research assistant role, helping primarily with a large multi-centre project investigating musculoskeletal pain assessment and management in the Emergency Department.

In 2016, Megan completed a Master of Science in Medicine (Pain Management) through the University of Sydney, Australia, and has since contributed to this education by revising and writing new modules on musculoskeletal pain pathophysiology and non-pharmacological management. In early 2017, Megan obtained a PhD-stipend from the Center for Neuroplasticity and Pain (CNAP) and subsequently began work on the studies included in the present dissertation. During the PhD period, Megan has been involved in student project supervision, co-ordination of research stays for international collaborators, reviewing papers for various international peer-reviewed journals, reviewing grant applications for EGG, writing and interviewing for IASP's Pain Research Forum as a Virtual PRF Correspondent, and has had the opportunity to speak and present posters at several international pain conferences.

After a brief hiatus in late 2019 to mid-2020 to take on the new full-time role of mum to Olivia, Megan completed this thesis on the basis of one submitted and three published articles.

PREFACE

This PhD thesis provides an extended summary of work performed at the Center for Neuroplasticity and Pain (CNAP), Department of Health Science and Technology, Aalborg University, Denmark, in the period from February 2017 to August 2020. It has been financially supported by Aalborg University and the Danish National Research Foundation (DNRF121).

The purpose of the thesis was to investigate temporal changes in pain processing mechanisms, specifically pressure pain sensitivity, temporal summation of pain and conditioned pain modulation, in relation to the experience of low back pain. This was achieved through the combined use of meta-analytic, experimental, observational, and interventional approaches. The thesis is organised primarily as an overview and discussion of the background, methodology, and findings for each of the measures investigated. It synthesises content from four journal articles, three of which are already published in international peer-reviewed journals and the fourth of which has been submitted.

Throughout the thesis, these articles are referred to as:

Systematic Review: **ME McPhee**, HB Vaegter & T Graven-Nielsen. (2020) Alterations in pro-nociceptive and anti-nociceptive mechanisms in patients with low back pain: A systematic review with meta-analysis. PAIN, 161: 464-475. DOI: 10.1097/j.pain.0000000000001737

Study I: **ME McPhee** & T Graven-Nielsen. (2019) Alterations in Temporal Summation of Pain and Conditioned Pain Modulation across an Episode of Experimental Exercise-Induced Low Back Pain. The Journal of Pain, 20(3):264-276. DOI: 10.1016/j.jpain.2018.08.010

Study II: **ME McPhee** & T Graven-Nielsen. (2019) Recurrent low back pain patients demonstrate facilitated pro-nociceptive mechanisms when in pain, and impaired anti-nociceptive mechanisms with and without pain. PAIN, 160: 2866-2876. DOI: 10.1097/j.pain.0000000000001679

Study III: **ME McPhee** & T Graven-Nielsen. (Submitted) Medial Prefrontal High-Definition Transcranial Direct Current Stimulation to Improve Pain Modulation in Chronic Low Back Pain: A Pilot Randomized Double-blind Crossover Trial

ENGLISH SUMMARY

Low back pain (LBP) has afflicted humans for thousands of years and today remains a leading cause of disability globally. The vast majority of LBP cases are classified as non-specific, meaning no clear pathophysiology has been identified. With this in mind, increased focus has been on illuminating some of the underlying mechanisms and drivers of LBP. During the past decades, measures of pain sensitivity, such as local and widespread hypersensitivity to pressure, temporal summation of pain (TSP), and conditioned pain modulation (CPM), have gained special interest and may reflect mechanisms that are now commonly acknowledged to play an important role in LBP. On this basis, a plethora of studies have been published in the past two decades looking either at cross-sectional differences in pain sensitivity measures between LBP patients and controls, or at the utility of these measures in predicting longer-term prognosis. Unfortunately, results of such studies have been highly inconsistent, hence it has remained unclear to what extent alterations in these mechanisms are present among LBP populations. In addition, many existing studies have reported pain sensitivity measures at only one timepoint, when patients were already in pain, making it unclear as to how these measures change over time in relation to the development and/or resolution of LBP.

The present thesis set out to further investigate this temporal relationship between central pain processing mechanisms and LBP experience. To do so, a systematic review and meta-analysis along with three experimental studies were planned and conducted to approach this relationship from four different angles. A meta-analysis of existing studies was performed to quantify the magnitude of alterations in TSP and CPM among LBP patients compared to controls, as well as to explore potential associations between these measures and pain severity/duration. Study I took healthy pain-free individuals and induced experimental LBP, by having participants perform fatiguing exercise, allowing for investigation of both pain-free baseline predictors of LBP development and changes in pressure pain sensitivity, TSP and CPM across a short-lasting experimental episode of LBP. Study II recruited patients with recurrent LBP, along with matched controls, and assessed pressure pain sensitivity, CPM and TSP both during a painful episode and when naturally recovered to pain-free. Finally, Study III took patients with chronic LBP and used a transcranial direct current stimulation (tDCS) paradigm to target cortical regions involved in pain-modulatory circuitry, and sham comparator, allowing for assessment of changes in pressure pain sensitivity, TSP and CPM in relation to changes in pain.

In addition to the primary outcomes, various factors that could influence both pain experience and central pain processing, namely age, gender, body mass index, sleep, mood, menstruation, anxiety, pain catastrophizing and physical activity, were captured across experimental studies (I-III). However, these factors rarely differed significantly between patient and control groups or between painful and pain-free sessions. A range of clinical variables were also recorded for LBP patient groups over the study periods, including the intensity, unpleasantness, duration, quality, and distribution of pain, as well as related disability (Study I-III). Of course, pain durations and disability levels were higher in LBP patients with increasing duration of pain than

for participants with experimental LBP, but the intensity, unpleasantness, and distribution of LBP was similar between experimental, recurrent, and chronic LBP groups during painful testing sessions (Study I-III).

The meta-analysis demonstrated that clear differences in TSP and CPM exist overall between LBP patients and controls, though the magnitude of these differences was small. Further, alterations in TSP were weakly related to pain severity, while CPM impairment showed relation to both pain duration and severity. Study I highlighted that mild experimental LBP provoked reductions in local and distant hypersensitivity to pressure but was not sufficient in intensity or duration to significantly affect TSP or CPM. Baseline pain-free TSP did, however, show some relation to the severity of LBP developed. Study II showed that, during a recurrent LBP episode, patients demonstrated local and widespread pressure hyperalgesia and facilitated TSP compared to controls, but this resolved when pain-free. On the contrary, CPM was impaired in recurrent LBP patients compared to controls overall regardless of pain status. Finally, Study III demonstrated similar patterns of change in pressure pain sensitivity and TSP in relation to pain status as Study I-II, though CPM did not appear to be impaired in this group and remained unchanged across the study period. Unfortunately, the tDCS paradigm selected was largely ineffective though, perhaps due to the already functioning descending inhibition in this group.

When taken together, findings from the present work would suggest that local and widespread hyperalgesia to pressure is primarily a consequence of the presence of LBP. Similarly, though TSP may have a small degree of predictive value for prognosis when assessed in a pain-free state, it seems that the facilitation observed in patients is also consequential to ongoing pain. CPM, on the other hand, seemed less impacted by pain presence per se and instead may deteriorate over time in LBP patients. The strength and generalisability of these conclusions are, however, limited by the considerable inter- and intra-individual variation in pain sensitivity measures, the selectivity of recruitment and the small experimental samples included. Nonetheless, this work has provided a comprehensive approach to understanding the influence of LBP presence on pain sensitivity measures, which can easily be applied to various other outcomes and conditions. This work has also clarified certain aspects of the relationship between measures of pain sensitivity and LBP presence, suggesting these measures may be important in tracking fluctuations in LBP conditions and/or predicting pain and treatment prognosis, though future work is required to explore these potential utilities.

DANSK RESUME

Lænderygsmerter har plaget mennesker i tusinde år og er i dag fortsat den største grund til nedsat funktionsevne blandt den globale befolkning. Den største andel af lænderygsmerter er kategoriseret som uspecifikke, dvs. at der ikke er en tydelig forklaring på hvorfor at smerterne opstår. På grund af dette har der været et øget fokus på at belyse nogle af de underliggende mekanismer, der om muligt kan bidrage til at lænderygsmerter udvikles. Gennem de seneste årtier har målinger af smertesensitivitet, såsom lokalt og udbredt smerteoverfølsomhed over for tryk (trykhypersensitivitet), ændringer i opfattelsen af faciliteret smertepåvirkning (Temporal summation of pain/TSP) og konditioneret smertemodulering (Conditioned pain modulation/CPM), fået særlig opmærksomhed, da disse afspejler mekanismer, der nu anderkendes at spille en vigtig rolle i lænderygsmerter. Et væld af studier er blevet offentliggjort inden for de sidste to årtier. Disse undersøger enten forskelle i smertemekanismerne mellem patienter med lænderygsmerter og kontrol deltagere eller hvorvidt, disse målinger kan bruges til at forudse en prognose på længere sigt. Desværre har resultaterne af disse studier været modstridende, og det er dermed fortsat uklart i hvilken grad sådanne ændringer i disse mekanismer er til stede hos patienter med lænderygsmerter. Desuden, rapporterer mange af studierne kun målinger af smertemekanismer på et enkelt tidspunkt når deltagerne allerede har smerte, hvilket gør det uklart, om målingerne ændrer sig over tid i forhold til udviklingen og/eller forbedringen af rygsmerten.

Formålet med denne tese er derfor yderligere at undersøge den tidsmæssige sammenhæng mellem de central-medierede smertemekanismer og lænderygsmerter. Til dette formål blev der planlagt en systematisk litteraturgennemgang med tilhørende meta-analyse samt tre eksperimentelle studier planlagt og udført for netop at belyse denne sammenhæng ud fra fire forskellige vinkler. Meta-analysen af eksisterende studier var udført for at identificere forskelle i ændringer af TSP- og CPM-målinger blandt patienter med lænderygsmerter i forhold til kontrol deltagere, samt for at udforske potentielle sammenhænge mellem disse smertemekanismer og smerteintensitet eller varighed. I studie I blev lænderygsmerter induceret i raske og smertefrie deltagere via hjælp af en trænings-induceret smertemodel, der fremkaldte træningsømhed i lænden. Dette gjorde det muligt at undersøge både hvordan smertefrie målinger kunne bruges til at forudse lænderygsmerternes udvikling og hvordan tryksmertetærskler (PPTs), TSP og CPM ændrer sig over en kortvarigt eksperimentel episode af lænderygsmerter. I studie II blev patienter med tilbagevendende lænderygsmerter rekrutteret sammen med matchede kontrol-deltagere. PPTs, CPM og TSP blev derefter målt både under en smertefuld episode og når de naturligt blev smertefrie igen. Endeligt, studie III involverede patienter med kroniske lænderygsmerter og her blev det forsøgt at mindske deres smerter ved hjælp af et trans-kranie jævnstrømsstimulerings protokol (tDCS), der var målrettet de hjerneregioner, der er involveret i smertemodulering og derved gør det muligt at vurdere ændringer i PPTs, TSP og CPM i forbindelse med ændringer i smerten.

Foruden de primære udfald blev en række faktorer, der kunne påvirke både smerte oplevelsen og målingen af smertemekanismer (heraf alder, køn, kropsmasse indeks (BMI), søvn, humør, menstruation, angst, smertekatastrofetænkning og fysisk aktivitet) registreret over tid i alle eksperimentelle studier (I-III). Disse faktorer viste dog sjældent signifikante forskelle mellem de to

grupper (patient og kontrol) eller mellem de smertefulde og smertefrie episoder. En række kliniske variabler blev også registreret for patienterne med lænderygsmerter over studieperioderne. Disse inkluderede intensiteter, ubehagelighed, varighed, kvalitet, og område af smerte og relateret funktionsniveau (Studier I-III). Som forventet varede smerter over længere tid og forårsagede en større grad af funktionsnedsættelse blandt patienterne med kliniske lænderygsmerter i forhold til de kontrol-deltagere med eksperimentelt-induceret lænderygsmerter. Dog var smerte-intensitet, -ubehag og -område forholdsvis sammenlignelige mellem grupperne under de smertefulde episoder (Studie I-III).

Meta-analysen demonstrerede overordnede tydelige forskelle i TSP og CPM mellem patienter med lænderygsmerter og kontrol deltagere, selvom størrelsen af disse forskelle var forholdsvis små. Desuden var ændringer i TSP svagt relateret til smerteintensitet, mens reduceret var relateret til både smertevarighed og smerteintensitet. Studie I viste, at mild eksperimentelt-induceret lænderygsmerter fremkaldte både en lokal og udbredt trykhypersensitivitet, men disse var ikke intense eller langvarige nok til at forårsage væsentlige ændringer i TSP eller CPM væsentlig. Dog viste TSP ved start, uden smerte, nogen sammenhæng med intensiteten af de udviklede lænderygsmerter. Studie II viste, at patienter under en episode af tilbagevendende lænderygsmerter også udviste lokalt og udbredt trykhypersensitivitet samt øget TSP sammenlignet med kontrol-deltagerne, men at dette normaliseret i en smertefri periode. I modsætning til dette var CPM generelt reduceret hos dem med tilbagevendende lænderygsmerter uanset smertestatus når disse blev sammenlignet med kontrol-deltagere. Endeligt, viste studie III lignende ændringsmønstrer i både tryksensitivitet og TSP i forhold til smerte status som i studier I-II. Dog forblev CPM uændret blandt denne patientgruppe under hele undersøgelsesperioden. Desværre var den valgte tDCS protokol ineffektiv, hvilket måske kan skyldes en allerede fungerende smerteinhiberende mekanisme (CPM) blandt denne gruppe.

Samlet set antyder resultaterne fra denne tese, at både en lokal og udbredt trykhypersensitivitet primært er en konsekvens af lænderygsmerternes tilstedeværelse. På trods af at TSP, til en vis grad, kan bruges som prædiktiv faktor i forhold til prognosen, når denne måles/vurderes under en smertefri tilstand/episode, ser det ud til, at den observerede facilitering hos patienterne er en følge af de vedvarende smerter. CPM virkede derimod mindre påvirket af smerternes tilstedeværelse og syntes i stedet at forværres over tid hos patienterne med lænderygsmerter. Styrken og generaliserbarheden af disse konklusioner er dog begrænset af den betydelige inter- og intra-individuelle variation i målingerne, selektiviteten af rekruttering og de få deltagere inkluderet. Ikke desto mindre har dette arbejde betydeligt øget forståelse af, hvordan lænderygsmerters tilstedeværelse kan påvirke eller influere på forskellige målinger, der på lignede vis let kan overføres og anvendes til at undersøge andre målinger eller andre sygdomstilstande. Denne tese har således afklaret visse aspekter af forholdet mellem forskellige målinger af smertemekanismer og det tidsmæssige perspektiv af lænderygsmerternes tilstedeværelse, hvilket tyder på, at disse målinger kan være vigtige for at spore ændringer og/eller forudsige smerte og behandlingsprognose. Yderligere forskning er dog nødvendigt for netop at undersøge disse potentielle anvendelser.

ACKNOWLEDGEMENTS

Albeit unconventional, the first acknowledgements here must go to the European Pain Federation and Rogerio Pessoto Hirata, as without venturing all the way from Australia to Austria to attend the EFIC congress in Vienna back in 2015 and fatefully asking to share a breakfast table with Rogerio, this PhD journey and my Danish life may never have begun. Not to mention that I would be sans iPad mini.

Of course, I must then acknowledge the incredible supervision I have received from Prof. Thomas Graven-Nielsen over the past 3 years. I can safely say, without his mentoring, my work would have been much less inspired, organized and methodologically sound, though perhaps there would have been a few more colours on my figures. Thanks also to the Danish National Research Foundation for financially supporting my work.

Next, a special thanks must go to Henrik Bjarke Vægter for jumping at the chance to be involved in the Systematic Review, and for providing insightful comments on my work. As we never managed to tie down a co-supervisor, I think the rest of my Research Interest Group (Pain and Motor Systems Plasticity) and all other staff at the Center for Neuroplasticity and Pain also deserve acknowledgement; not least for asking critical questions of my work at group meetings, expanding my perception and understanding of pain science, volunteering (in the loosest definition of the word) to participate in my pilot studies, and just generally being there to challenge and support me along the way. As well, thanks to all the participants and patients who volunteered to join my studies, without whom this thesis would not have been possible, and to the administrative staff at HST for their help with various practical aspects of PhD life.

To my comrades, Line and Dennis, thank you for the infinite discussions about pain, science, and the big questions in life – without you guys this journey would certainly have been much less enjoyable. To my mum, thanks for always listening to my endless rants over Skype, for taking every opportunity to visit me on the other side of the world, and for just generally always being in my corner. To my dad, thanks for inspiring me *not* to be a doctor, but for managing to pass along enough curiosity, passion, and empathy to push me down a career path almost equally as unforgiving. To the old Australian friends and family whom I had to leave down under, and to the new international network I have gained along the way, thanks for hanging around and making life more pleasant.

Of course, this acknowledgements section would not be complete without saying thanks to my lovely little family. To our beautiful daughter, Olivia, thanks for teaching me to make the most of every single second, both those spent watching you grow and develop, and those few you spent napping each day allowing me to write this thesis. Finally, to my wonderful husband, Steffan, without you I would never have made it through this whole journey so smoothly. Thank you for your unending support, for always reminding me of what is really important in life, and for keeping me calm – or you know, as calm as I ever am.

I think it takes a village to raise a PhD, so thank you all.

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TABLE OF ABBREVIATIONS & TERMS

BMI – Body mass index
CPM – Conditioned pain modulation
DOMS – Delayed onset muscle soreness
ECR – Extensor carpi radialis brevis (muscle)
eVAS – electronic Visual Analogue Scale
GAS – Gastrocnemius (muscle)
LBP – Low back pain (RLBP = recurrent, CLBP = chronic)
cPDT – Pain detection threshold (cuff)
PPT – Pressure pain threshold (handheld)
cPTT – Pain tolerance threshold (cuff)
QST – Quantitative sensory testing
TSP – Temporal summation of pain
UT – Upper trapezius (muscle)

'Pain sensitivity' is used throughout the thesis as an umbrella term to refer to pressure pain detection and tolerance thresholds, suprathreshold simulation ratings, temporal summation of pain and conditioned pain modulation.

'Pressure pain sensitivity' is used throughout the thesis to indicate only basal measures of pressure pain detection and tolerance thresholds, and ratings to individual suprathreshold pressure stimuli.

'Hypersensitivity' is used to throughout the thesis to indicate that either, a stimulus of the same intensity is now perceived to be more painful, or the point at which a stimulus becomes uncomfortable or painful is now lower than it was previously.

'Central pain processing mechanisms' is used throughout the thesis to cover mechanisms including, but not limited to, wind-up processes underlying temporal summation of pain and descending inhibitory processes underlying conditioned pain modulation.

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CHAPTER 1. A BRIEF INTRODUCTION TO PAIN SENSITIVITY IN LOW BACK PAIN

Low back pain (LBP) has been plaguing humans for thousands of years, with back pain management guidelines being discovered in Ancient Egypt from as early as 1600BC[336]. However, it is only in relatively recent times that a concerted research effort has been made to quantify the extent and impact of this condition. In 2017, the Global Burden of Diseases study[67,359] estimated the global point prevalence of disabling LBP at 8.5%, making it the world's leading cause of Years Lived with Disability. As a condition, it represents a significant source of economic burden, on the basis of increased health-care utilisation and lost productivity[186,189], even when best-practice guidelines are followed[177], not to mention obvious negative personal consequences.

1.1. DEFINING & CLASSIFYING LOW BACK PAIN

For many years, researchers have debated how to best define and classify the heterogeneous population reporting pain in the lower back region[35,66,167,244]. In its simplest form, one defines LBP as the presence of pain in the lower portion of the posterior trunk, demarcated superiorly by the inferior costal margin and inferiorly by the gluteal fold[66]. However, LBP can often be accompanied by pain radiating down into the legs, by pain from the thoracic and cervical regions, or by widespread pain symptoms. Beyond spatial extent, LBP conditions are also often classified based on their temporal pattern. Like most painful disorders, the usual distinction between acute and chronic LBP is three months, but the commonly recurring nature of LBP[123] has led to more nuanced classifications on the basis of episode frequency, severity, duration and care-seeking behaviour[135,227,306].

LBP may also be classified on the basis of presumed source or cause, potential underlying mechanisms, or symptom clustering[210,238,261,264,285]. However, even with the advent of advanced imaging techniques and diagnostic testing, there is often unclear correlation between symptomatology and identified structural and biochemical abnormalities[40]. In rare cases (<1%), a serious underlying pathology exists[119], and LBP is thus attributed to a diagnosis of cancer, vertebral fracture, infection or neurological compromise. The majority of remaining cases, however, are generally termed non-specific, meaning that a definite source or pathophysiological mechanism remains elusive[187]; and hence, classification is instead based on movement patterns, patient history or other clinical testing.

1.2. UNDERSTANDING THE ROLE OF HYPERSENSITIVITY

One avenue of interest among pain researchers in recent decades, following the discovery of a 'plastic' central component in pain[163,357], has been the quantification of sensitisation, especially in central pain processing mechanisms in patients with painful conditions. This sensitisation is often used to explain the discordance between clinical pain reports and

observable injury severity, especially in chronic pain conditions. As a result of the lack of clear pathophysiological explanation for most patients with LBP, researchers in this field have also moved focus away from biomechanical or structural explanations and instead started exploring the role of sensitisation, by way of sensory testing. As such, alterations in central pain processing mechanisms underlying hypersensitivity, in conjunction with psychosocial factors, are now commonly speculated to contribute to LBP development and/or maintenance[114], though empirical support for this is lacking.

Sensory testing has been implemented for over a century now[326]. Nonetheless, the advent of standardised testing batteries and development of measures to assess 'dynamic' central pain processing mechanisms (e.g. temporal summation of pain (TSP) and conditioned pain modulation (CPM)) have produced a surge in publications looking at potential diagnostic, discriminative and prognostic value. In particular, many cross-sectional studies have been performed, generally showing some degree of hypersensitivity (enhanced TSP or impaired CPM) in patients with pain when compared to pain-free control participants[173,230]. At the outset of this thesis, however, there was little consensus on whether these mechanisms were actually altered in LBP patients specifically. As well, the temporal relationship between LBP experiences and possible alterations observed in TSP and CPM was not established. It could be that some individuals are at greater susceptibility to developing recurring or persisting LBP due to inherent differences in these mechanisms, opening up for predictive and preventative utility, or it could be that the alterations observed are a consequence of ongoing pain.

1.3. AIMS AND HYPOTHESES OF THIS THESIS

This thesis aimed to clarify the relationship between LBP presence and alterations in pain sensitivity measures, with the hope of elucidating whether these alterations are consequential to LBP or are maintained despite pain recovery or reduction. More specific objectives were to:

I) Clarify the existence and magnitude of alterations in pain sensitivity (i.e. TSP and CPM) among LBP patient populations in comparison to pain-free controls or reference data (Systematic Review & Study II).
II) Examine the effect of inducing LBP experimentally on pain sensitivity measures (i.e. pressure pain thresholds, TSP and CPM) within-individuals (Study I).
III) Examine the impact of clinical LBP resolution (Study II) or reduction (Study III) on pain sensitivity measures within-individuals.
IV) Compare pain sensitivity between LBP patients and control participants when clinical pain is absent (Study II).

It was hypothesised that when LBP of any kind was present and/or more severe, patients would show hypersensitivity to pressure, enhanced TSP and impaired CPM compared to measures taken when individuals were pain-free, as well as compared to pain-free control participants.

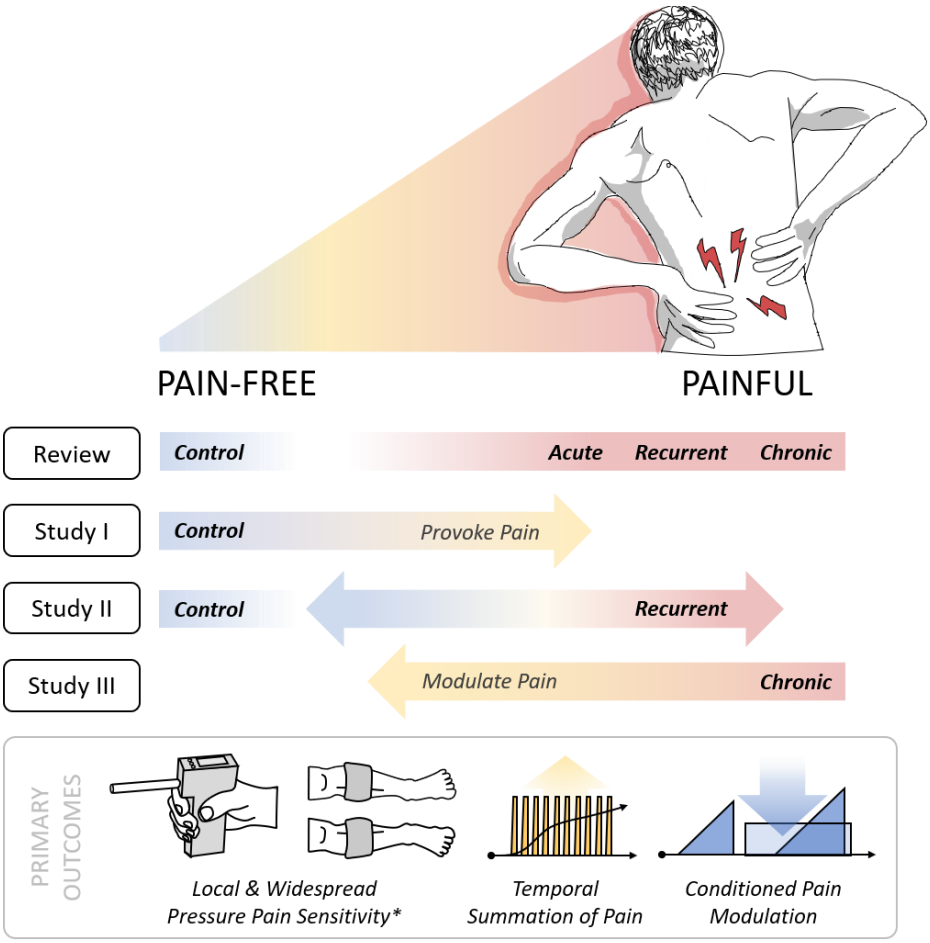

Figure 1-1 Conceptual schematic of the work contained in the present thesis. *A systematic review and meta-analyses was used to identify if alterations in central pain processing measures were present in patients with LBP, then the temporal relation of these alterations to the presence of LBP was probed using experimental provocation of LBP (Study I), observation of naturally fluctuating recurrent LBP (Study II) and experimental modulation of chronic LBP (Study III). Note: *indicates that these outcomes were only included in experimental studies, not the Systematic Review.*

CHAPTER 2. PROBING TEMPORAL ASPECTS OF HYPERSENSITIVITY

2.1. APPROACHING TEMPORAL RELATIONSHIPS BETWEEN PAIN AND HYPERSENSITIVITY

The current thesis takes four different approaches to investigating how pain sensitivity measures and the experience of LBP relate over time. This includes cross-sectional, forward provocatory, observational, and backward modulatory methods (Fig 1-1). In theory, this should then provide a comprehensive depiction of how alterations in pain processing mechanisms relate to state (the presence and characteristics of pain during testing) and/or trait (the clinical characteristics of the condition) features of LBP.

2.1.1. COMPARING CROSS-SECTIONAL DATA

In the past decade, many studies have emerged comparing patients with LBP to pain-free individuals across various measures of pain sensitivity. Surprisingly, however, prior to 2019 no large-scale collation and comparison of these studies had been performed. In the first instance, meta-analysis of case-control data can provide an indication as to whether pain sensitivity measures are altered in patients with LBP and to what extent. Further, when data is available for patients in different temporal classifications (i.e. acute, recurrent, chronic) or with differing pain durations, the existing literature provides the possibility to perform sub-group and correlational analysis, allowing greater insight into theoretical temporal alterations. Although this type of analysis comes with many limitations, such as: differing methodologies and definitions used between studies, the need to transform variables for comparison, missing or unavailable data, and use of group-level outcomes; it still allows broad conclusions to be drawn. This approach was used in this thesis as part of a systematic review and meta-analysis on TSP and CPM in LBP patients.

2.1.2. INDUCING EXPERIMENTAL LOW BACK PAIN

Without large-scale long-term prospective cohort studies of initially pain-free individuals, it is challenging to capture patients before they develop a painful condition. However, gaining insight into how patients appeared before they had pain is critical to understanding what aspects of altered pain sensitivity may precede, coincide with and/or be a consequence of the condition. In this way, experimental models of pain offer a unique possibility to track individuals before, during and following an 'episode', allowing one to test both the impact of pain presence on different measures of pain sensitivity, as well as the impact of baseline variation in sensitivity on the extent of pain developed.

A number of experimental pain models exist, some of which involve injection or application of different chemical substances[18,102,115,209,342] like hypertonic saline, serotonin, bradykinin, capsaicin cream or nerve-growth factor, and some of which involve endogenous production of noxious substances through ischemia or over-exertion[9,98,104,272,325]. Each model has advantages and disadvantages in terms of administration complexity, location and/or tissue specificity, duration of pain induced, and concurrent elicitation of clinical features. In the present work, the desire was to mimic an episode of acute LBP, thus the model needed to produce deep-tissue pain, preferably exacerbated by movement, that could be maintained for several days. For this reason, delayed onset muscle soreness/pain (DOMS) as is induced by performing unaccustomed eccentric exercise to fatigue, was the obvious choice. Prior studies have used this approach to produce DOMS in the lower back[162,180] and have shown it to mimic mild LBP producing some degree of LBP-related disability[30]. This was employed in Study I of this thesis (Fig 2-1, summarised in Appendix A).

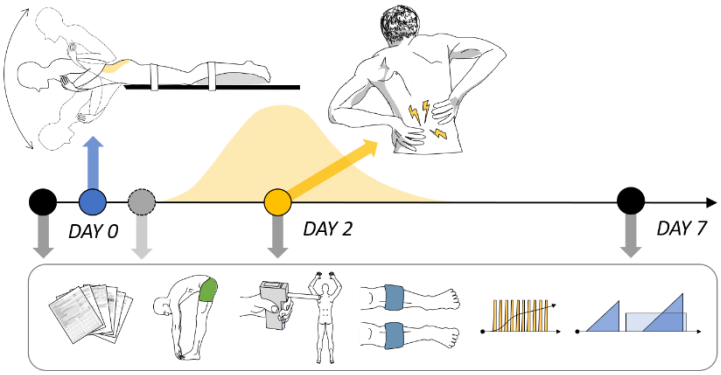

Figure 2-1 Illustration of Study I design with fatiguing exercise performed on Day 0 aiming to induce experimental LBP (shown as yellow curve) by the session on Day 2 and full recovery by Day 7

2.1.3. USING RECURRENCE AS A PAIN MODEL

Another way to probe temporal relations between LBP and pain sensitivity, or at least to probe the impact of pain presence on measures of pain sensitivity, is to select patients who present with defined painful and pain-free periods. This allows one to study the effect of clinical pain within-individuals over time. Naturally, recurrent LBP patients represent a perfect population for this type of investigation, with these patients commonly experiencing pain lasting for several days to weeks, followed by weeks to months of near-complete recovery. Several challenges with this approach are apparent; namely the difficulty of standardising testing intervals due to varying painful episode lengths, the inability to randomise painful and pain-free sessions due to the unpredictable nature of recurrent pain, and the general heterogeneity of LBP conditions. However, in part these challenges can be overcome by highly selective recruitment of patients with estimable pain episode trajectory and the use of age- and gender-matched control participants over a comparable time interval. As such, this study design is clearly advantageous in allowing for both within- and between-individual comparisons to determine the effect of an authentic clinical pain experience on measures of pain sensitivity. This approach was used in Study II of the current work (Fig 2-2, summarised in Appendix A).

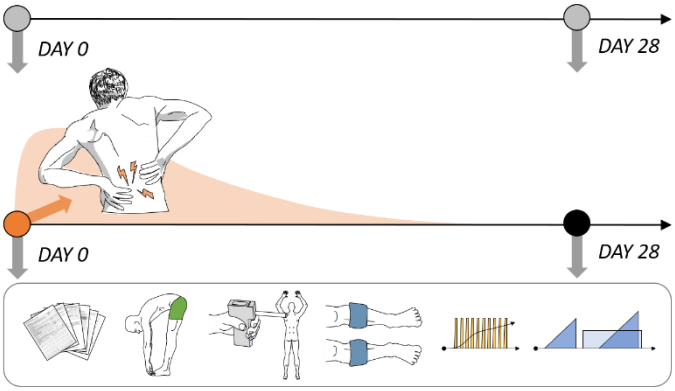

Figure 2-2 Illustration of Study II design with control participants (top) compared to RLBP patients (bottom) during a painful episode (Day 0, pain represented by orange curve) and once recovered to pain-free (Day 28)

2.1.4. MODULATING CHRONIC PAIN

Another approach to investigating temporal relationships between LBP and pain sensitivity is to take a relatively stable chronic pain condition and attempt to modulate it. This would allow one to track changes in both pain and hypersensitivity simultaneously over time, and thus gain insight into their possible co-variation. As such, in Study III of the current work, CLBP patients were recruited and tracked over an extended period during the application of an active and a sham high-definition transcranial direct current stimulation (HD-tDCS) paradigm, aimed at improving anti-nociceptive pain mechanisms and thus potentially reducing pain. By using a crossover design, sample size requirements are minimised and changes in clinical and pain sensitivity measures between conditions and over time can be compared without the added influence of between-group variation (Fig 2-3, summarised in Appendix A).

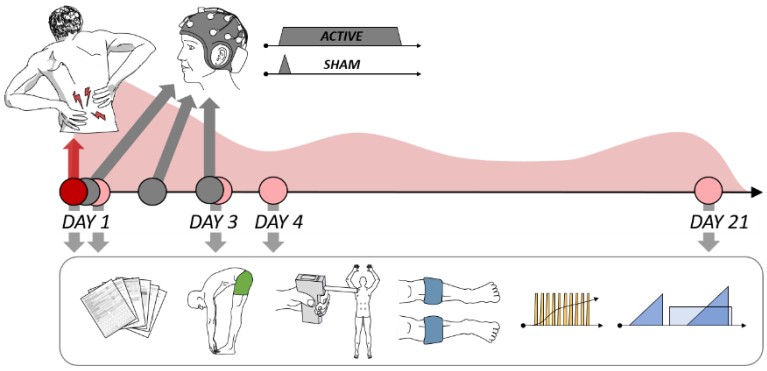

Figure 2-3 Illustration of Study III with CLBP patients receiving both Active and Sham tDCS targeted to the PFC/ACC, with the aim to improve pain modulation (Day 1-21 repeated in randomised cross-over)

2.2. SUMMARY

The present thesis details four approaches to understanding the effect of LBP on measures of pain sensitivity, including: meta-analysis of existing cross-sectional data, induction of experimental LBP in pain-free individuals, comparing painful and pain-free periods in RLBP patients and modulating CLBP symptomatology. In order to have an overview of these approaches and see the broader effect of present LBP on clinical and pain sensitivity measures across the experimental studies (I-III), throughout the thesis, a representative painful and pain-free or pain-reduced session has been selected for each LBP group. This is summarised in Figure 2-4, where an overall visual depiction of the different experimental timelines is shown, and the representative sessions included in the primary outcome analyses throughout the remainder of the thesis are highlighted.

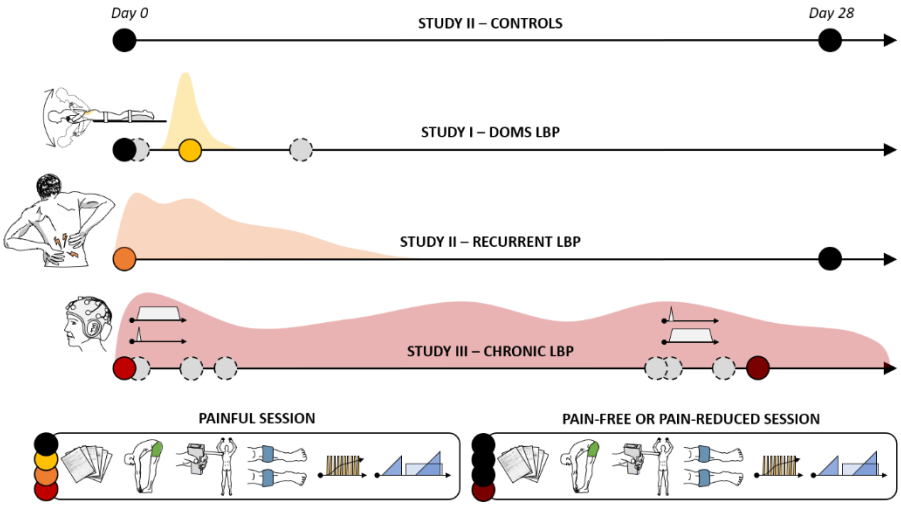

Figure 2-4 Study designs, split into participant groups, are overlayed to indicate temporal differences in painful and pain-free (Studies I-II) or pain-reduced (Study III) assessment sessions, as used for comparison throughout the present thesis. *Note: Coloured curves represent pain profiles, coloured dots represent painful sessions, black dots indicate pain-free sessions, grey dots with dashed borders indicate sessions in which a full assessment was conducted, for which data can be seen in the individual study manuscripts and/or their supplementary materials.*

CHAPTER 3. INDIVIDUAL & CLINICAL CHARACTERISTICS AND CONFOUNDERS

To accurately interpret the findings from the present experimental studies, it is imperative to understand both the characteristics of the included participants and the features of the LBP conditions being assessed. Hence, demographic information was collected from all included participants, and various measures were used to capture the severity, distribution and type of pain, as well as the impact it had on participants, both in terms of disability and care-seeking behaviour, among those with LBP conditions. As several contextual factors have also been shown to influence both LBP and pain sensitivity, these potential confounders were captured using various questionnaires. This chapter presents an overview of these characteristics.

3.1. GENERAL SAMPLE CHARACTERISTICS

3.1.1. PARTICIPANT SCREENING

To be able to draw conclusions about the relationship between pain sensitivity and LBP, it is essential to select suitable experimental participants both with and without clinical pain. Although seemingly simple, the quality assessment of the Systematic Review highlighted that many prior cross-sectional studies did not use adequate screening procedures to exclude individuals with prior histories of LBP in control groups, nor provide complete definitions or characterisations of LBP on testing in LBP groups. For this reason, strict inclusion and exclusion criteria were used in all present experimental studies (I-III, Table 3-1). All criteria were screened on recruitment and reconfirmed via clinical anamnesis and physical exam in the first session. While these strict criteria aid the strength of conclusions on effects of pain presence for the studied populations, they do notably also introduce potential generalisability issues.

Table 3-1 Inclusion and exclusion criteria for Studies I-III

	Study I & Study II (Healthy)	Study II (Recurrent LBP)	Study III (Chronic LBP)
General	Aged 18-60 years; Able to read, write and understand English		
Location	No history of significant LBP No history of chronic or recurrent pain conditions No recent acute lower limb pain	Primary complaint of pain in low back (defined as between inferior costal margin and inferior gluteal fold) No history of other chronic or recurrent pain conditions No recent acute lower limb pain	
Duration	No LBP lasting >24 hours not due to unaccustomed exercise No other injuries past 6 months	LBP for >24 hours, <3 months Present in first session but expected to resolve <4 weeks >1 previous episode past year	LBP for >3 months Continuously present (>3 days/week) since onset Present in first session
Intensity	VAS = 0	VAS>1/10 on testing	VAS>3/10 on average
Impact	No activity limitation	Pain sufficient to impact daily activity	
Other	No neurological, musculoskeletal, cardiorespiratory or mental disorders; Not currently or planning to be pregnant; No substance abuse; No regular medication use (Inclusive analgesics, exclusive contraceptives); No analgesic use in 24 hours prior to testing; Not currently seeking treatment for any condition (Inclusive LBP)		

3.1.2. DEMOGRAPHIC DETAILS

Much of the literature reports variation in pain sensitivity measures and incidence of pain conditions based on inherent individual factors, such as age, gender and body mass index. Typically advancing age[173,215], female gender[276,289,299] and high BMI[124,311,360] are associated with increased rates of pain complaints and altered pain sensitivity. As a result, it seemed pertinent to record and report these factors in all studies and to try to control for them in Study II as potential between-group confounders (Table 3-2). It is noteworthy, however, that in the present experimental studies all participants were relatively young (18-45 years). Perhaps even younger than expected for typical RLBP and/or CLBP patient populations, which may suggest this sample represents an earlier stage of LBP with milder symptomatology than much of the existing literature. As well, despite slightly higher average weight in LBP groups, BMI was within normal limits in most participants with no statistical group differences observed (Appendix C).

Table 3-2 Demographic Characteristics of All Participants in Experimental Studies

	Study I (Healthy)	Study II (Healthy)	Study II (RLBP)	Study III (CLBP)
Recruited & tested	30	30	30	12
Age	24.5 ± 4.5	27.3 ± 5.5	27.3 ± 5.4	28.6 ± 5.9
Height	173.8 ± 11.8	170.9 ± 9.9	175.6 ± 11.2	172.6 ± 9.4
Weight	72.1 ± 15.6	68.1 ± 12.3	75.2 ± 16.3	75.4 ± 16.1
Gender	14 men: 16 women	16 men: 14 women	16 men: 14 women	3 men: 9 women
Included in main analysis (reason for exclusions)	24 (excl. 6 due to no pain on Day-2)	30	26 (1 drop-out, excl. 3 with ongoing pain at Day-28)	12 (1 missing final follow-up session)

3.2. LOW BACK PAIN CHARACTERISTICS

3.2.1. PAIN RATINGS

The International Association for the Study of Pain (IASP) definition of pain states that it is both a "*sensory* and *emotional* experience…" As such, many have used subscales of intensity and unpleasantness, to capture and quantify these distinct aspects of the pain experience. In the present work, participants were instructed using a sound analogy adapted from Price[258], in which pain intensity is analogous with volume, whereas unpleasantness becomes dependent on other personal or preferential and evaluative factors. These features were evaluated on two separate Visual Analogue Scales (VAS) anchored at 0cm as 'no pain/unpleasantness' and 10cm as the 'worst pain/most unpleasant sensation imaginable'. The VAS as a numerically anchored ratio scale was initially validated in both healthy and chronic pain populations[45,256,258], and has since been used extensively to quickly capture pain severity. In Studies I-III, current pain intensity and unpleasantness ratings were recorded at every assessment session, while an overall pain severity score was collected in home diary measures. Interestingly, when comparing LBP rating data across studies (Appendix C), mean current pain intensity ratings were surprisingly similar, at around 2.5-3/10, though considerable inter- and intra-individual variability in LBP over time was observed in pain diaries (Studies I-III, Figure 3-1, Table 3-3).

3.2.2. PAIN DISTRIBUTION

Body schematics from the Navigate Pain application (Algance Solutions & Aalborg University) were used to capture the spatial extent of LBP. Participants were instructed to draw in different ways depending on the study purpose. In study I, participants were instructed to draw the areas in which they felt pain or soreness during tasks involving back muscle activity, such as forward bending and lifting (as DOMS rarely causes resting pain). In study II, RLBP patients were asked to draw their pain area both relaxed at rest and during provocative back movement. In study III, CLBP patients were asked to draw their pain area sitting at rest in a chair during each session. Due to these slight variations in instruction, direct comparison of pain areas between studies is not possible, though overlays of individual participants' pain areas for each study are shown in Figure 3-1. From these diagrams, it is readily apparent that pain in the DOMS model extended beyond the lower back, with some participants also reporting pain in e.g. the hamstrings and calves, which was rarely the case in the clinical populations. This is unsurprising given that the movement performed to fatigue also places a large amount of strain on the gluteal and posterior leg muscles. On the contrary, especially female participants in the RLBP and CLBP groups commonly drew pain extending upward into the shoulders and neck, which may be a protective consequence of clinical LBP, due to stiffening of the trunk in order to reduce movement[128].

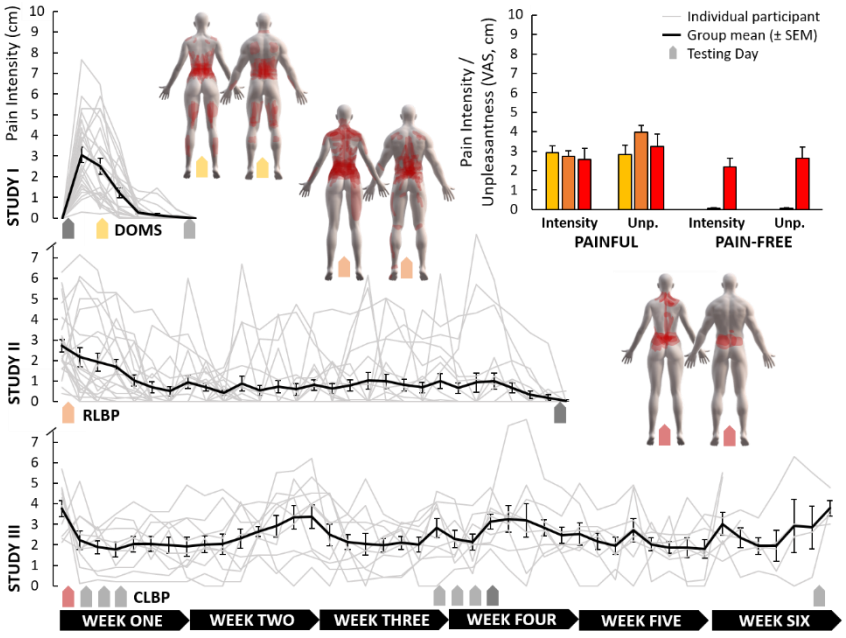

Figure 3-1 Pain diaries from each experimental study (I-III) illustrating individual participant reports (grey) and group mean (± SEM, black) data over the study period, mean (+SEM) pain intensity and unpleasantness ratings for each LBP group in a selected painful and pain-free session, and overlays of all participant's pain distributions from the first painful session for each LBP group (colour-coded). *Note: Painful session data is from Study I Day 2, Study II Day 0, and Study III Day 1; non-painful or pain-reduced data is from Study I Day 1, Study II Day 28, and Study III Day 24. Not all participants represented at all time-points due to missing or partially completed diaries.*

3.2.3. PAIN QUALITY

As pain is a highly individual and thus variable experience, in all studies, the 72-word table of the McGill Pain Questionnaire was used to record a depiction of each individual's pain. Among these words are descriptors of sensory (e.g. pulsing, hot, sharp), affective (e.g. tiring, terrifying), and evaluative features (e.g. annoying). Developed in 1975, the McGill Pain questionnaire[199] has been widely used both to capture pain types among different patient groups and to monitor changes in pain in response to intervention. In the present work, overall scores were similar between clinical LBP groups, though much lower in experimental LBP and generally highly variable between individuals. Interestingly, 'annoying' came out as one of the most common descriptors in all LBP conditions, despite being from the evaluative subdomain which is typically more associated with persistent pain states[270]. Other common descriptors across LBP conditions were primarily for sensory features of pain (e.g. tight, pressing), with only CLBP patients commonly using affective descriptors (i.e. tiring, Table 3-3).

Pain quality assessment is thought to be able to give an indication of potential underlying mechanisms. As such, in 2006 the Pain-DETECT questionnaire[83] was developed as a quick screening tool to identify neuropathic pain components among LBP patients. Based on the initial validation, this questionnaire was deemed to be reliable with high specificity, sensitivity, and positive predictive value in identifying these features, and was hence quickly adopted in further research. In studies II and III, the Pain-DETECT questionnaire was used to characterise neuropathic features among patients with RLBP and CLBP. The original cut-off values were used to interpret Pain-DETECT responses, with scores above or equal to 19 indicating predominantly neuropathic pain features and scores below or equal to 12 indicating predominantly nociceptive components. In the present studies, most participants had scores suggesting primarily nociceptive components, with only two RLBP patients and one CLBP patient scoring above the threshold to indicate presence of neuropathic features (Table 3-3).

3.2.4. PAIN-RELATED DISABILITY

The Roland-Morris Disability Questionnaire was originally developed and deemed reliable to assess LBP-related disability in 1983[280]. It consists of 24 statements that describe daily activities or functions that may be negatively impacted by LBP. Generally, participants included in the present work demonstrated very low levels of disability on this scale, suggesting they may represent a mild patient group. Disability was, however, slightly higher in RLBP patients than that provoked by the DOMS model, and slightly higher again in CLBP patients than RLBP patients (Table 3-3, Appendix C). It should be noted that it was intended only to include LBP patients who did not have comorbidities or concurrent pain conditions in other body regions, which may explain why the present sample were only mildly disabled by their pain.

The STarT-Back Screening Questionnaire (Short form) was developed as a prognostic screening tool to be used in primary care decision-making[126]. It has since had cut-off scores validated in external LBP populations[126] and has shown similar utility to other prognostic screening questionnaires[127]. In the present work, this measure indicated mild trajectories among the included LBP populations with majority low risk categorisations (Table 3-3).

3.2.5. CARE-SEEKING BEHAVIOURS

Participants with clinical LBP were asked a range of typical medical history questions regarding aggravating and easing factors, along with prior care sought (Table 3-3). All patients displayed mechanical aggravation of LBP on either specific movements or prolonged positioning, and most reported improvement with rest. Every participant with CLBP had sought some form of care previously (either medical or allied health), whereas only half of RLBP patients had done so. Further, a greater proportion of CLBP patients had obtained medical imaging of the spine (typically with plain x-ray or MRI) and trialled analgesic medication than RLBP patients. Although quality of life was not assessed in the current work, these reports naturally suggest a greater negative impact of pain and higher medicalisation of CLBP than RLBP.

Table 3-3 Clinical Characterisation of Low Back Pain in Experimental Studies based on Patient History and Questionnaire data collected in First Painful Session

		Study I (DOMS) *Day 2 (n = 24)*	Study II (RLBP) *Day 0 (n = 26)*	Study III (CLBP) *Day 0 (n = 12)*
PAIN RATINGS	**Pain Intensity (VAS, cm)**:			
	- Current at time of testing	2.9 ± 1.8	2.7 ± 1.5	2.6 ± 2.0
	- Maximum*	4.1 ± 2.0	5.8 ± 2.2	3.8 ± 1.3
	Pain Unpleasantness (VAS, cm):			
	- Current at time of testing	2.9 ± 2.4	4.0 ± 1.8	3.2 ± 2.3
	- Maximum*	-	6.6 ± 2.0	4.0 ± 1.6
CLINICAL FEATURES	**Pain Duration**:			
	- Current episode duration	3.3 ± 1.2 days	12.3 ± 15.9# days	5.3 ± 2.6#¤ years
	- Age at initial onset (years)	NA	19.7 ± 5.4	23.3 ± 6.6
	Aggravating Factors:			
	- Prolonged sitting/standing	-	73% (19)	50% (6)
	- Flexion		23% (6)	50% (6)
	- Extension		58% (15)	50% (6)
	Easing Factors:			
	- Exercise	-	46% (12)	40% (5)
	- Rest		100% (26)	67% (8)
	- Simple analgesics		19% (5)	33% (4)
	Prior Care/Treatment:			
	- General Practitioner	-	23% (6)	67% (8)
	- Physiotherapist/Chiropractor		46% (12)	50% (6)
	- Imaging		19% (5)	58% (7)
	- Massage		12% (3)	25% (3)
	- Medication		23% (6)	50% (6)
	STarT-Back Screening Tool:			
	- Total Score (/9)	1 (2)	2 (2)	3 (2)
	- Categorisation (Low/Med/High)	23 / 1 / 0	22 / 4 / 0	7 / 4 / 1
	McGill Pain Quality Descriptors:			
	- Total score	9.1 ± 6.4	20.2 ± 10.3#	18.2 ± 8.7#
	- Most common descriptors (n)	Annoying (13), sore (11), tight (9)	Annoying (13), sharp / shooting / pressing (10)	Tight (7), annoying / tiring (6)
	Pain-DETECT:			
	- Total score	-	10.5 (9)	9 (2.5)
	- Category (Noci/Unclear/Neuro)		15 / 9 / 2	10 / 1 / 1
	Roland-Morris Disability Questionnaire:	1.5 (1.5)	3.5 (3.5)	5 (3)

**DOMS and RLBP current episode, CLBP in past 24 hours; Difference between-groups to DOMS# or RLBP¤ (P<0.05)*

3.3. CAPTURING CONFOUNDERS

All observations of psychophysical outcomes, including pain sensitivity measures, come with a range of possible confounding influences. It is well-known that various factors, such as sleep[77,116,143,269,296], hormonal cycles[117,273,277,350], mood[72,339], anxiety[96,202,331], pain catastrophizing[353] and physical activity levels[118,216,275], can impact an individual's experience of pain. As such, it was not the intention of the present thesis to explore neither the effect of these factors on clinical pain, nor their association to pain sensitivity, hence the individual studies are not appropriately powered for this type of analysis. Instead, these factors were captured primarily to allow for better attribution of observed pain sensitivity findings to changes in LBP condition; i.e. to exclude the possibility that differences in pain sensitivity measures between sessions were due to changes in these factors and not to pain. A brief summary of relevant findings is provided here for context, but more detailed descriptions of the rationale for assessing these factors, the specific measures used, an overview of the validity of those measures and the general findings are provided in Appendix B. In addition, details of analyses conducted between studies are provided in Appendix C.

Generally, no differences were noted for mood between sessions or groups, and females were approximately randomly distributed between menstrual phases in each session. For CLBP patients, slightly shorter sleep duration was reported prior to the reduced pain session (Table 3-4) but no differences were noted overall between groups. Although no significant group differences were noted in number of nightly awakenings, a greater proportion of RLBP patients reported at least one awakening (Table 3-4). Sleep disturbance is commonly reported among LBP populations[116,143,192] and may even be a risk factor for LBP development[341], though objective sleep measures (e.g. actigraphy) have shown less clear differences[233,335].

For RLBP patients (Study II), positive affect, state anxiety and pain catastrophizing were slightly higher during the first painful session compared to when pain-free, though not different to control participants in either session (Table 3-4). On the contrary, for experimental LBP (Study I) pain catastrophizing scores were lower during the painful session compared to when pain-free (Table 3-4). As pain catastrophizing scores were not different between controls and the different clinical LBP populations overall, this contrasting finding between LBP conditions might indicate that participants, who had temporary pain present at the time of testing, related cognitions directly to that specific pain (i.e. experimental or recurrent LBP) rather than to pain in general, as the scale instructs. These findings would then aptly reflect that RLBP episodes are unpredictable and threatening by nature, whereas DOMS is familiar (to most) and thus of predictable severity, provocation (i.e. on movement), and time course.

Of note, healthy participants in Studies I and II tended to report lower physical activity levels than RLBP and CLBP patients from Studies II & III, and RLBP patients had higher mean activity prior to the painful session than the pain-free session (Table 3-4). This could reflect two scenarios: firstly, it could indicate that LBP was present and/or exacerbated by periods of high physical activity and resolved with reductions in this factor. However, this seems unlikely given most patients did not report exercise or activity as an aggravating factor (on the contrary many

reported prolonged static postures to be most aggravating), and when interviewing patients very few described undertaking laborious work or frequent exercise training. Alternatively, this could be an overestimation reflective of perceptual differences about effort when in pain versus not, whereby patients categorise more activities as more vigorous when in pain. The latter would be consistent with prior studies showing LBP patients to be more inaccurate at reporting physical behaviour[286], and showing associations between subjective, but not objective, physical activity levels and musculoskeletal pain[220].

Table 3-4 Baseline Questionnaire Characterisation of Participants across all experimental studies from one painful and one pain-free (or less painful) session presented as mean ± standard deviation or median (interquartile range).

		Study I (Healthy)		Study II (Healthy)		Study II (RLBP)		Study III (CLBP)	
		N = 24		N = 30		N = 26		N = 12	
		Pain (Day2)	NP (Day0)	NP (Day0)	NP (Day28)	Pain (Day-0)	NP (Day28)	Pain (Day1)	LP (Day24)
SLEEP	**Sleep time** (Hours slept on night prior to testing)	6.7±1.4	7.2±1.0	7.3±0.9	6.9±0.8	7.5±1.2	7.3±1.6	6.7±1.2	7.7±1.1*
SLEEP	**Awakenings** (Number of nightly awakenings on night prior to testing, and %>0)	0 (1.25) 42%	0 (1) 42%	0 (1) 43%	0 (1) 40%	1 (1) 62%	1 (2) 70%	1 (1.25) 58%	0 (1) 33%
MOOD	**Face scale** (Mood at time of testing)	3 (4)	2.5 (3)	3 (2.75)	4 (4)	4 (3.75)	3.5 (3.75)	3.5 (4.25)	5.5 (4)
MOOD	**Faces scale** (Mood week prior to test session)	3.5 (4)	3 (4)	4 (4)	3 (5)	3.5 (4.75)	3.5 (4.75)	5 (3.5)	4.5 (3.25)
MOOD	**PANAS** (Positive affect score)	NA	NA	30.1±6.4	29.1±7.2	30.8±5.9*	27.7±7.7	26.5±7.8	22.8±10.4
MOOD	**PANAS** (Negative affect score)	NA	NA	12.7 ± 3.2	13.0 ± 3.2	14.2 ± 4.9	12.9 ± 2.8	12.9 ± 3.1	11.9 ± 2.5
MOOD	**BDI** (Total Score)	NA	NA	NA	NA	NA	NA	8.1 ± 3.8	NA
ANXIETY	**STAI** (State anxiety score)	NA	NA	30.8±7.9	32.4±9.6	34.2±8.6*	31.3±7.2	34.9±8.4	39.7±11.2
ANXIETY	**STAI** (Trait anxiety score)	NA	NA	36.6±8.3	36.2±7.9	37.9±8.2	37.3±8.7	41.2±6.1	41.6±7.8
ANXIETY	**PCS** (Total score)	8.8±7.3	13.5±8.8*	12.9±8.6	13.5±9.6	15.5 ±9.0*#	11.8±8.0	13.9±8.2	13.5±10.7
ACTIVITY	**IPAQ** (Sitting time, estimated on a normal weekday)	NA	387.5 ± 143.7	451.2 ± 182.1	454.2 ± 167.5	360.2 ± 207.3	405.4 ± 224.5	385.0 ± 206.6	NA
ACTIVITY	**IPAQ** (Activity, MET-minutes/ week, estimated for week prior to testing)	NA	3985± 3438	4218 ± 3885	4002 ± 3667	5996 ± 5494	4908 ± 5095	6100 ± 4399	NA

*Note: NP = no pain, LP = less pain, NA = not assessed. *denotes significant between-sessions difference, #denotes difference from DOMS group, details of outcome measures provided in Appendix B and analysis in Appendix C.*

3.4. SUMMARY

Clinical characteristics, including pain intensity, unpleasantness, duration, related disability, quality, and distribution, were captured among both experimental and clinical LBP groups using validated self-report scales and applications. All LBP groups reported similar pain intensity and unpleasantness within the painful session, with pain mostly localised to the lower back region. Pain duration was obviously different between LBP conditions, as would be expected from inclusion requirements, and pain quality scores were higher for clinical LBP groups. Disability levels were generally very low but followed the expected trend with experimental LBP less impactful than RLBP, and CLBP patients showing most impact. Similarly, care-seeking behaviour, along with prior imaging and analgesic use, was higher in CLBP than RLBP patients.

Various factors could potentially contribute to the differences seen in the primary outcomes of this thesis. Individual characteristics, including age, gender, BMI, sleep, menstruation, mood, anxiety, pain catastrophizing, and physical activity, were captured in the present work using common validated self-report measures. All participants, including patients with LBP, were young with predominantly normal BMI. Most factors did not differ significantly between experimental groups, suggesting they are unlikely to confound between-group findings presented throughout the thesis. Small differences were noted, between sessions for the RLBP group, in positive affect, state anxiety and pain-related catastrophizing, indicating that this may play some role in identified between-session differences, which is discussed where relevant in subsequent chapters.

CHAPTER 4. LOCAL AND WIDESPREAD PRESSURE PAIN SENSITIVITY

To assess whether experimental LBP (Study I), RLBP (Study II) and CLBP (Study III) presence was associated with local and widespread hypersensitivity to pressure, the present work assessed pressure pain thresholds using both handheld and computerised-cuff methods at an array of body locations. This chapter discusses conceptual aspects of pain threshold assessment, methodological considerations, and findings from the experimental studies (I-III) for these measures.

4.1. ASSESSING BASAL PRESSURE PAIN SENSITIVITY

Pain thresholds have long been used as a probe to investigate sensitivity to sensory stimuli, allowing for comparison between body sites and tissues, between individuals and over time in response to interventions. As early as 1959 researchers were questioning whether such pain thresholds would ever be of clinical value[218]. Despite this, investigations have continued for more than six decades now across a broad range of stimuli and are beginning to show potential[11,92]. In chronic pain populations, reduced pain thresholds at both local and remote sites to the painful region, i.e. local and widespread pressure hypersensitivity, are commonly demonstrated in cross-sectional studies[11]. In patients with LBP[190,235] and other painful conditions[42,300], these alterations have generally been considered consequential to ongoing pain, though there is also evidence that high pain sensitivity may have predictive[110,291,348] and prognostic value[92] in some circumstances.

With regard to stimulus type, mechanical stimuli have been of particular interest in LBP populations, with pressure hypersensitivity consistently demonstrated in comparison to pain-free populations at both local and remote sites[62]. In fact, in this thesis, the focus has been exclusively on sensitivity to painful pressure for several reasons. Firstly, this was deemed to be the most relevant to LBP, as both handheld and cuff pressure algometry can better assess sensitivity of the deep musculoskeletal structures[78,188] thought to be involved in pain generation. Especially cuff compression has been shown to produce considerable strain in deep tissues, and evoke pain even in the absence of cutaneous nociception[255]. Pressure pain thresholds have also previously been reported to have high discriminative ability for identifying hypersensitivity in CLBP patients[221].

4.1.1. PAIN DETECTION VERSUS PAIN TOLERANCE

Pain detection thresholds, in this thesis, were defined as the lowest intensity at which a stimulus was first perceived to be painful. Pain tolerance thresholds, on the contrary, were defined as the intensity at which the participant could no longer tolerate further increases in stimulus intensity. These perceptual thresholds are well-known to be influenced by a range of individual state and trait factors[149,194,198]. They also intuitively seem to represent different constructs,

whereby detection thresholds may be more reflective of nociception and sensory factors, and tolerance thresholds more reflective of cognitive and evaluative processes[87]. In the present work, detection thresholds were assessed using handheld algometry bilaterally at five sites and using cuff algometry bilaterally on the lower legs. Tolerance thresholds were then only assessed with cuff algometry on the lower legs.

4.1.2. METHODOLOGICAL CONSIDERATIONS

When assessing pressure pain sensitivity, the main methodological considerations are body site and thus underlying tissues assessed, application characteristics (such as rate of stimulus increase, contact area, manual versus automated application), and instructions to participants. In the present work these features were standardised, as per the overview in Table 4-1, across all experimental studies. Such parameters were selected to be consistent with prior work[105].

Table 4-1 Overview of pressure pain sensitivity methods used in all studies

Method	Device	Body Location/s	Application	Instruction
Pressure Pain Thresholds (PPTs)	Handheld pressure algometer (Somedic, Sösdala, Sweden) with 1cm^2 rounded rubber tipped probe	Extensor Carpi Radialis Brevis (ECR): 3cm distal to lateral epicondyle; Upper Trapezius (UT): halfway between acromion & 7th cervical spinous process; L1/5: 3.5cm lateral to 1st/5th lumbar spinous processes; Gastrocnemius (GAS): halfway between popliteal line & calcaneus	Manually applied perpendicular to target muscle belly at 30kPa/s until participant pressed 'stop' button. Repeated two (Study III) or three (Study I-II) times.	Press the stop button as soon as the pressure first becomes uncomfortable or painful
Cuff Pain Detection Threshold (cPDT)	Computer-controlled cuff algometer system (NociTech & AAU, Aalborg, Denmark) paired with 2 x 10cm-wide tourniquet cuffs (VBM Medizintechnik GmbH, Sulz am Neckar, Germany) and an electronic Visual Analogue Scale (eVAS).	Cuffs positioned bilaterally over the widest portion of each lower leg, roughly 5cm below the tibial tuberosity. Sensitivity assessed separately for each leg.	Increased at 1kPa/s to a maximum of 100kPa (device safety limit) or until tolerance threshold obtained.	As soon as the pressure becomes uncomfortable or painful, start sliding the electronic Visual Analogue Scale (eVAS) dial to rate pain intensity (eVAS=1cm).
Cuff Pain Tolerance Threshold (cPTT)				When the pressure is so painful that you cannot tolerate anymore, press the button to stop (peak pressure).
Cuff Supra-Threshold Rating (cSTR)		As above but only assessed on dominant leg.	Increased at 100kPa/s to cPTT pressure, maintained for 1s, then released for 10s, repeated three times.	Immediately following each stimulus rate how painful it was by sliding the eVAS up, then return it to zero.

4.1.3. VALIDITY & RELIABILITY OF ASSESSMENT

Pressure pain sensitivity was of interest due to the ability to assess deep structures. Combined computer modelling with experimental and MRI approaches have shown handheld[78] and especially cuff[188] algometry to increase strain in muscle and deep tissues and cause pain, even

when cutaneous nociceptive fibers are anaesthetized[153,255], suggesting that these modalities are valid to assess deep tissue sensitivity.

In the supplementary material of Study II, the reliability of all measures was assessed within- and between-sessions where possible. Control participants from Study II provide a clean estimate of test-retest reliability for the measures included in the present thesis, as precisely the same methodology was repeated in each session with no intermediary provocations and no expected change in condition. Results of this reliability analysis can be seen in Table 4-2 (adapted from Study II supplementary material). Generally, pressure pain thresholds (PPTs), cuff detection and tolerance thresholds, and supra-threshold ratings were highly reliable (ICC>0.9) within a session. Reliability was lower between-sessions, but still high (ICC>0.8) for PPTs and cuff tolerance, and moderate (ICC>0.6) for cuff detection thresholds and supra-threshold ratings (Table 4-2). This is consistent with prior work in which both handheld[20,228,347] and cuff[103,105] pressure algometry have shown very good reliability.

Table 4-2 Intra-class correlation coefficients ($ICC_{3,k}$) with 95% confidence intervals [95%CI] for handheld and cuff pressure pain thresholds within and between sessions for control participants in Study II

	Within-session 1	Within-session 2	Between-sessions
PPT – ECR	0.969 [0.948, 0.984]	0.970 [0.950, 0.984]	0.849 [0.682, 0.928]
PPT – UT	0.977 [0.962, 0.988]	0.979 [0.964, 0.989]	0.864 [0.714, 0.935]
PPT – L1	0.971 [0.951, 0.984]	0.985 [0.975, 0.992]	0.863 [0.712, 0.935]
PPT – L5	0.979 [0.965, 0.989]	0.987 [0.979, 0.993]	0.891 [0.771, 0.948]
PPT – GAS	0.985 [0.975, 0.992]	0.987 [0.978, 0.993]	0.876 [0.740, 0.941]
cPDT	0.946 [0.909, 0.971]	0.975 [0.958, 0.987]	0.716 [0.403, 0.865]
cPTT	0.980 [0.966, 0.989]	0.989 [0.981, 0.994]	0.865 [0.716, 0.936]
Supra-threshold Ratings (eVAS)	0.952 [0.913, 0.976]	0.945 [0.894, 0.973]	0.616 [0.194, 0.817]

4.2. PRESSURE HYPERSENSITIVITY IN LOW BACK PAIN

4.2.1. HANDHELD PRESSURE ALGOMETRY

Pressure pain thresholds were very clearly affected by the presence of pain in the region being tested (L1 and L5 sites), indicating that local hypersensitivity to pressure was a feature of both experimental and clinical LBP (Figure 4-1). This was true both when PPTs were compared between-groups to an independent control population (Study II) and when compared within-groups to the same individuals when not in pain (Study I and II). Albeit not the main purpose of Study III, when looking at data from CLBP patients, the same trend is observed with higher PPTs in the least than most painful session. Further, on re-analysis across all studies, PPTs, especially at the L1 site, were reduced when LBP was present across all experimental studies

(Study I-III, Fig 4-1, Appendix C). No differences were noted, however, between LBP groups. This fits with much of the existing literature on the topic showing lowered PPTs, likely reflective of peripheral sensitisation, to be maintained by ongoing nociception[302,309] and to fluctuate with clinical pain intensity[62,190,235,300]. Thus, local pressure hypersensitivity observed here seems merely consequential to experimental and clinical LBP.

Intriguingly, remote assessment sites were also impacted by the presence of LBP, with reduced PPTs demonstrated both between RLBP and control participants (Study II) and within-groups between painful and pain-free sessions in participants with DOMS (Study I) and RLBP (Study II). This was also reflected when data were reanalysed across all studies (Figure 4-1, Appendix C), with increased PPTs observed during pain-free sessions for DOMS and CLBP participants, and reduced PPTs during painful sessions compared to controls for at least one external site in all LBP groups. For CLBP patients, there appears to be no change in remote sites between more and less painful sessions, though given the design of Study III, it is difficult to attribute changes or lack thereof to pain alone.

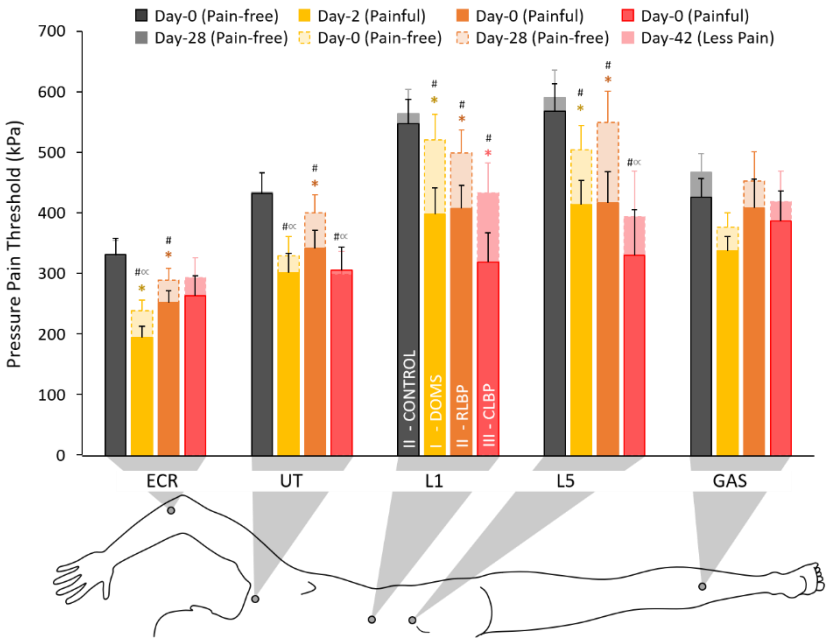

Figure 4-1 Mean (+SEM) pressure pain thresholds across all sites for all experimental studies from a representative session with low back pain present and absent. *Note: *denotes within-group difference between-sessions, #denotes difference from controls in painful session, ¤denotes difference from controls in pain-free/pain-reduced session. Details of analysis are shown in Appendix C.*

The Systematic Review conducted as part of this thesis did not include PPTs as an outcome. However, a recent meta-analysis[62] showed overall enhanced sensitivity to pressure at local sites (gluteal), regionally-related sites (scapula), and some remote sites (leg and arm, though not hand) in patients with LBP, suggesting pressure pain hypersensitivity to be present at both

local and distant sites. It should be noted though, that the magnitude of difference was variable across sites like that observed here, and conclusions from individual studies were often contradictory possibly due to differences in sample characteristics. Although widespread hyperalgesia has been reported among some LBP populations[6,205,221,236], it is not commonly reported in experimental pain models like DOMS. In this case, it is possible that widespread differences instead result from: peripheral sensitisation due to repeated testing over relatively short intervals[228,301], recruitment of additional muscles beyond the agonists at sufficient intensities to cause discrete muscle soreness, low-grade systemic inflammatory responses elicited by the intense and exhausting exercise[315], or perceptual alterations due to present pain state; though this requires further investigation.

4.2.2. CUFF PRESSURE ALGOMETRY

Cuff thresholds were not consistently altered by LBP presence. As shown in Figure 4-2 below, cPDT was significantly higher in RLBP patients when pain-free than when in pain (Study II). However, cPTT was unchanged by RLBP presence (Study II), and neither cPDT nor cPTT were altered by the presence of experimental LBP (Study I). In CLBP patients, both cPDT and cPTT were clearly increased in the less painful session, but due to the study design and repeated stimulus exposure (see Chapter 7, Figure 7-3) this cannot be solely attributed to changes in LBP severity and may more so reflect temporal habituation. On reanalysis of cPDTs and cPTTs across studies, no differences were observed between LBP groups and controls regardless of LBP presence (Appendix C).

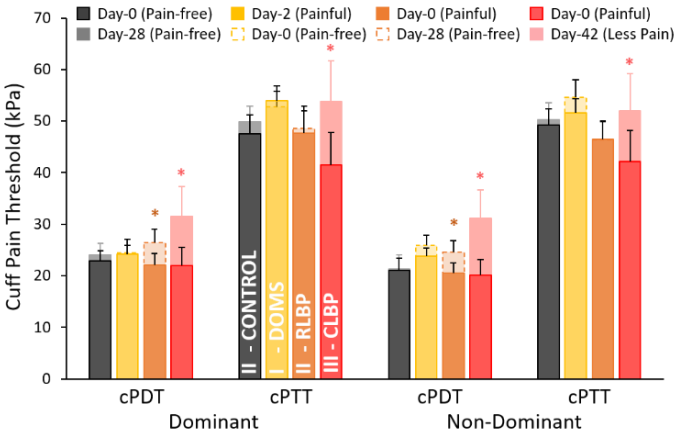

Figure 4-2 Mean (+SEM) Cuff pain detection (cPDT) and tolerance (cPTT) thresholds for the dominant and non-dominant legs of participants in each of the experimental studies. *Note: Data is presented from one painful and one pain-free (Studies I & II) or pain-reduced (Study III) session. *denotes a significant difference between-session within the RLBP or CLBP group (P<0.05)*

Cuff compression was theorised to provide a better characterisation of pain sensitivity in more relevant deeper structures than even handheld algometry, hence it is odd that few differences were observed. However, this was also the case for handheld algometry at the gastrocnemius site. The lower leg was deemed to be the best location for the cuffs as it: is easy to access,

allows for concurrent intensity rating with the upper limbs, provides reliable results while reducing ceiling effects due to the cuff device's safety limit[178], and is innervated by spinal levels that also innervate some regions of the lower back (L4-S2)[219]. However, deep tissue pressure hypersensitivity may remain localised, especially in the experimental LBP condition, making this remote assessment site inadequate to capture changes in muscle sensitivity.

In terms of tolerance thresholds, it is interesting that no differences were observed with regard to present LBP state (with the exception of in CLBP patients where effects are more likely time and/or exposure related) nor on reanalysis between groups. Generally, cuff pain tolerance thresholds have been less well studied among LBP populations. Prior studies using handheld algometry in CLBP patients have demonstrated lowered tolerance thresholds over the lower back[2,221] and other[344] assessment sites, but a single study using cuff algometry observed reduced tolerance only in those with severe CLBP[100]. The lack of findings here may, in part, be due to the remote assessment site or due to the mild symptomatology of the patients included.

4.2.3. SUPRA-THRESHOLD PRESSURE STIMULATION

In all studies, pain intensity ratings of three brief stimuli applied at cPTT intensity were collected. This was primarily as a manipulation check to make sure that this pressure level and thus TSP stimuli were considered painful. Nevertheless, as tolerance threshold assessment was based on a button press and not anchored to the eVAS ratings (i.e. participants did not need to reach 10/10 prior to stopping), it is interesting to look at these results alongside those ratings at tolerance. On reanalysis across studies, ratings of suprathreshold stimuli were lower overall in the pain-free or pain-reduced sessions, which seems to be an effect driven by the clinical LBP groups (Figure 4-3, Appendix C). As neither pressure nor perceived pain intensity at cPTT was different between sessions in most cases, this would imply that participant's appraisal of this stimulus may have changed[144]. This could be due to decreases in both stimulus and contextual novelty and hence increased predictability which is known to interfere with pain perception[247].

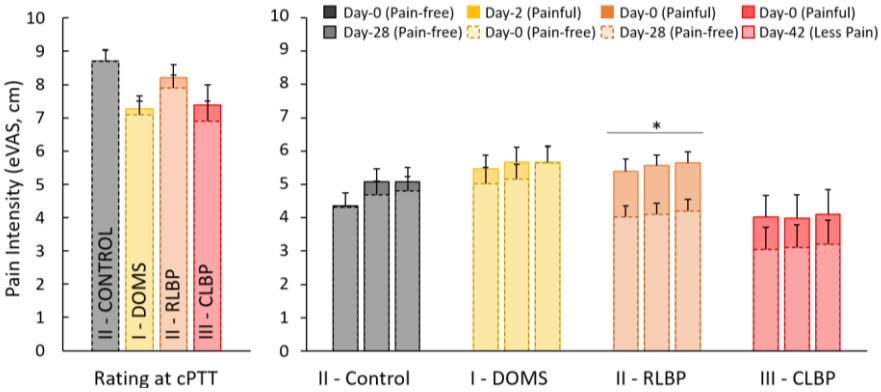

Figure 4-3 Mean (+SEM) pain intensity ratings at cPTT on threshold assessment (left) and of three 1-second stimuli at cPTT intensity (STR, right) in each of the studied populations for one painful and one pain-free or pain-reduced session. *Note: *denotes significant difference between-sessions within RLBP group (P<0.05). Details of between-studies analysis presented in Appendix C.*

4.3. SUMMARY

The present work evaluated pressure pain sensitivity using reliable methods at standardised assessment sites across all experimental studies. Local hypersensitivity to pressure was clearly present in all LBP populations compared to pain-free controls, but this largely resolved when LBP was not present. Widespread reductions in PPTs were also noted in both experimental and clinical LBP conditions, though reasons for this apparent widespread pressure hypersensitivity may differ between the DOMS model and clinical LBP. In experimental and RLBP, these widespread changes were not present when pain-free, but no significant differences between sessions were noted in CLBP patients. Pain detection and tolerance thresholds, along with ratings of supra-threshold stimuli, were also evaluated in all experimental groups using valid and reliable user-independent cuff algometry. This was theorised to provide better characterisation of deep tissue sensitivity but did not capture many differences between groups or sessions, with the exception of higher pain detection thresholds and lower supra-threshold ratings shown in Study II within RLBP patients when pain-free, and higher pain tolerance thresholds in CLBP patients when pain was reduced. The lack of between-group findings for cuff algometry was attributed to the remote assessment site and mild symptomatology of included LBP patients. Overall, the present findings would suggest pressure hypersensitivity to be a consequence of ongoing LBP.

CHAPTER 5. PRO-NOCICEPTIVE ASCENDING PATHWAYS

This chapter describes the conceptual underpinnings of dorsal horn wind-up, methodological considerations of TSP assessment in humans, and discusses findings from the present work on the impact of LBP on this measure (Systematic Review, and Studies I-III).

5.1. ASSESSING ASCENDING FACILITATORY PATHWAYS

5.1.1. MECHANISMS BEHIND TEMPORAL SUMMATION OF PAIN

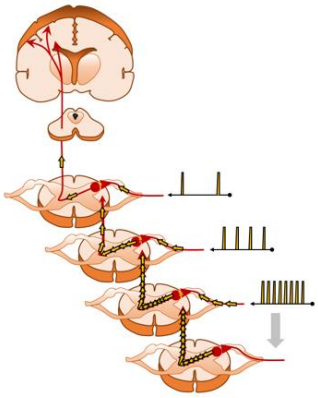

Figure 5-1 Diagram of ascending nociceptive pathways with illustration showing frequency-dependent increase in dorsal horn excitability and thus enhanced and prolonged neuronal firing after repeated C-fibre stimulation

Temporal summation of pain (TSP) is thought to measure at least the initial phase of 'wind-up'; a frequency-dependent C-fibre mediated enhancement of neuronal excitability in response to repeated noxious stimulation, first described in 1965[200,268]. Mechanistically, noxious stimulation at 0.5-2Hz[297] leads to release of various peptides from C-fibres, producing prolonged membrane depolarisation, removal of magnesium ion plugs, and activation of NMDA receptor channels in the dorsal horn[64]. This means that the same peripheral noxious stimuli and C-fibre activation will result in enhanced and prolonged activity in ascending nociceptive pathways; a mechanism which can potentially explain disparities between objective injury and perceived pain[358]. As direct recordings from dorsal horn neurones, like those performed in animals, are not possible in humans, TSP measures instead rely on perceived pain reports or spinal reflex assessment. Although these surrogate measures result in the same phenomenon of frequency-dependent increases in pain and reflex activity following repeated noxious stimulation, further validation and confirmation of precise mechanisms underlying TSP in humans is needed.

5.1.2. METHODOLOGICAL CONSIDERATIONS

Methods of assessing TSP vary considerably, with identified studies in LBP populations alone (as per the Systematic Review and updated searches) using everything from sural nerve stimulation to evoke withdrawal reflexes, von Frey hairs or pin prick devices to evoke mechanical pain, automated thermodes to evoke heat pain and handheld or cuff algometry systems to evoke deep tissue pain. Stimulation frequency and duration also varies considerably, not to mention stimulus intensity and location of testing. An overview of the various paradigms used in papers investigating LBP patients can be seen in Figure 5-2.

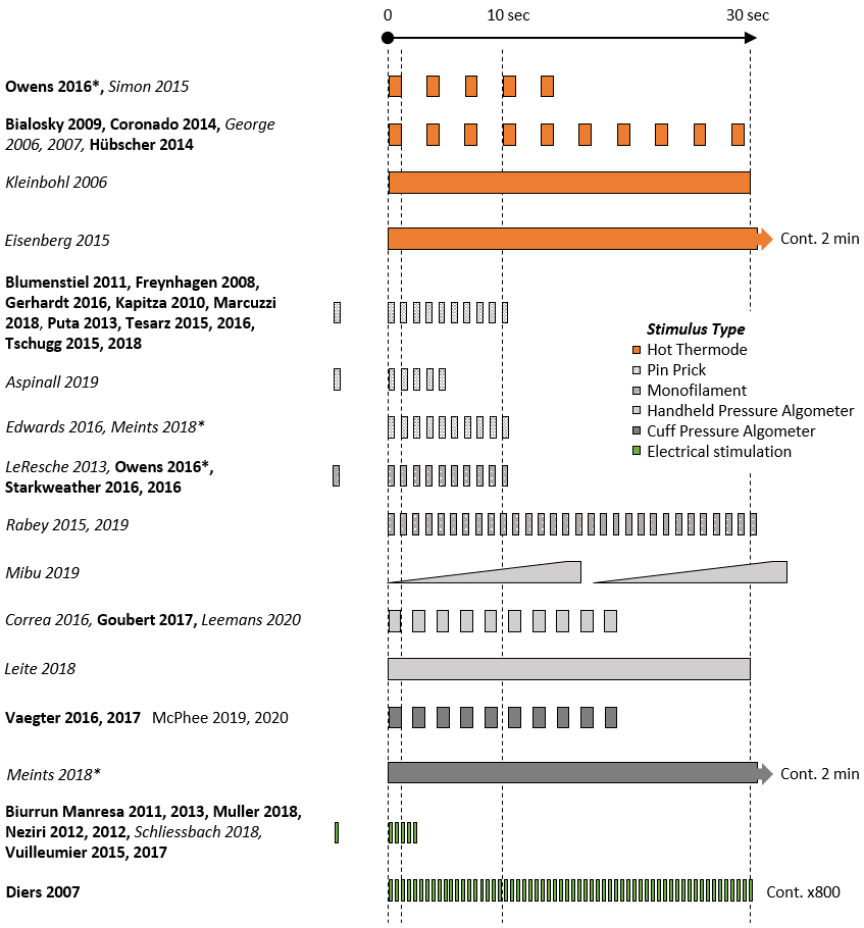

Figure 5-2 Variation in Temporal Summation of Pain Paradigms applied in studies of LBP patients[16,28,32-34,53,55,65,71,74,84,88,91,93,100,137,142,148,169-171,190,196,197,203,211,221,222,243,260,263,265,287,295,307,308,319,320,327,328,332,334,344,345]
*(Updated from Systematic Review Supplementary Material to include present studies, articles without healthy comparators in LBP populations and articles published after meta-analysis searches were complete). Note: depictions are based on manuscript descriptions and hence accuracy is dependent on reporting quality, *denotes that study contains more than 1 method, bold indicates inclusion in the Systematic Review and Meta-analysis.*

As yet, it is not entirely clear what relevance the modality has to findings, though mechanical stimuli have previously been suggested to be most convincingly affected in LBP[243]. It is further well established that the frequency and duration of stimuli can influence the magnitude of facilitation observed[223,224,257]. Another important consideration is how TSP is quantified, with different calculation methods (i.e. ratios, raw changes or normalized values) producing different results[4,313]. Typically, TSP should be reported as a relative measure to remove between-group differences in initial thresholds or painfulness of single stimuli, but as there are no consensus statements on best-practice of this measure, this is not performed uniformly across studies.

Theoretically, the wind-up mechanism TSP intends to assess is a segmental phenomenon, meaning the body site tested in relation to the location of pain or injury should also be considered highly influential. In the case of some modalities, such as the pin-prick, it is common practice to assess both the site of most pain and an unaffected hand or foot[281]. However, with other approaches, including spinal reflexes and cuff algometry, assessment sites are limited by practical accessibility. One could argue that testing a non-painful site, innervated by the same spinal segments as the painful site (such as the leg in LBP or the arm in neck pain conditions), would provide the cleanest measure of TSP by avoiding influences of peripherally sensitized tissues; however, this remains purely speculation.

5.1.3. VALIDITY & RELIABILITY OF TSP

In terms of validity, early human studies used heat stimuli and showed frequency-dependent summation of 'second pain' responses, assumed to be from C-fibre activation, consistent with animal models of wind-up[257]. Further, parallel use of simultaneous electrophysiological and psychophysical outcomes has shown concurrent summation of pain and reflex withdrawals, suggesting perceptual ratings do reflect the spinal component to some extent[8]. Beyond these parallel perceptual and reflex findings, the understanding of precise chemical mechanisms underlying wind-up from animal work has allowed for further validation of the perceptual correlate in humans. Namely, NMDA-antagonists have been shown to reduce TSP in several human trials[13,109,158]. More recently, studies using fMRI in the cervical spinal cord and brainstem have demonstrated increased activity in dorsal horn regions following repeated stimulation[36,37], consistent with observations of wind-up in animals. However, these studies also naturally observed activation in regions involved in descending inhibitory pathways during the TSP paradigm. In combination, these findings suggest that TSP paradigms may reflect changes in dorsal horn excitability to some extent, though should be interpreted as a net facilitatory response in humans due to the inseparable effect of cognitive-evaluative factors and descending controls. Further validation of precise mechanisms in humans is needed, especially for TSP from deep structures, which may be achieved with more direct comparisons of methods and modalities between animal and human models.

As in Chapter 4, the control participants in Study II allowed for analysis of reliability between-sessions. For TSP, this gave an $ICC_{3,k}$ of 0.652 [0.268, 0.834], meaning the method was moderately reliable over the study timeframe, and of similar reliability to that reported over shorter-intervals in the literature[105].

5.2. FINDINGS ON THE RELATIONSHIP BETWEEN LOW BACK PAIN & TSP

5.2.1. PAIN VERSUS PAIN-FREE

Temporal summation of pain seemed to be impacted by the presence a RLBP episode at the time of testing, both compared between-groups to controls and within-group to the pain-free session (Study II, Figure 5-3). This parallels findings from two prior small prospective cohort studies, showing trends for TSP to increase in LBP patients with ongoing pain at 2-4 months,

compared to either those whose pain reduced[251] or to pain-free control data[190]. However, pain-related fluctuation in TSP was unable to be replicated in the DOMS model (Study I) with no significant differences noted between sessions, nor in the CLBP group (Study III) where no changes in TSP were observed throughout the entire study period. On statistical comparison across all studies (I-III), no significant group differences were observed (Appendix C). This may, however, be due to the small magnitude of these differences, higher inter-individual variability in outcomes and mild LBP symptomatology; as in the Systematic Review, TSP was significantly facilitated in both acute and chronic LBP patients compared to controls (Fig 5-3). In addition, differences between the present and previous findings may also be due to the remote assessment site used here, as wind-up is considered a segmental phenomenon and thus greater alterations may have been seen if TSP was assessed over the lower back. This is, however, difficult to perform reliably using a deep-tissue stimulus, and in the Systematic Review no differences in effect size were observed dependent on test site using other modalities.

It was suggested in the Systematic Review and Study II, that facilitation of TSP was likely to be the product of ongoing nociception, consistent with the measure's theoretical underpinnings. However, as discussed in Study II, the apparent effect of LBP on TSP may also reflect differences in perceptual or evaluative processes when individuals are in pain. Perceptually rated TSP has previously been reported to relate to anxiety[278], fear-avoidance beliefs[89] and pain catastrophizing[46,90,274], and given both anxiety and PCS scores were higher in RLBP patients when pain was present, it is difficult to disentangle which factor is driving these effects.

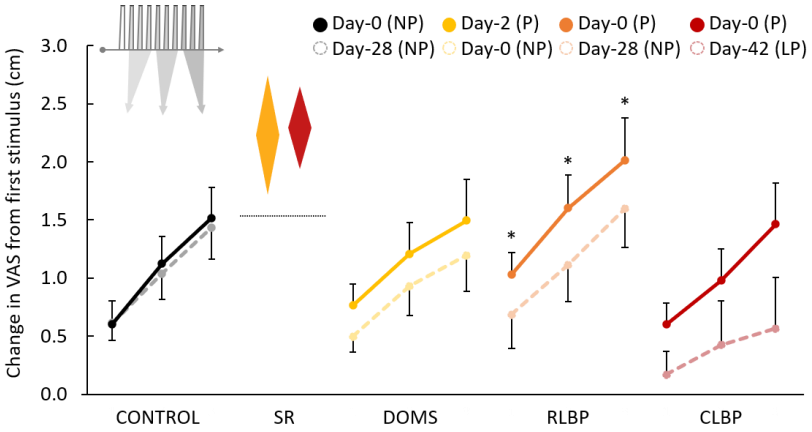

Figure 5-3 Pain intensity across TSP stimulation series as normalized VAS-epochs (i.e. normalized by subtraction to first stimulus rating, then presented as mean (+/-SEM) of stimuli 2-4, 5-7, and 8-10) for controls (Study II) and from a painful (P) and non-painful (NP, Study I-II) or less painful (LP, Study III) session for each LBP group. Standardised mean difference (SMD) and confidence intervals (CI) from Systematic Review (SR) presented as expected effect size from control groups 3rd VAS-epoch (dotted line). *Note: *denotes significant between-sessions difference within the RLBP group in Study II; Meta-analysis results from the Systematic Review shown as yellow (acute/recurrent; SMD = 0.51 [95% CI: 0.16, 0.85]) and red (chronic; SMD = 0.55 [95%CI: 0.30, 0.81]) diamonds; illustration of paradigm in top left corner.*

5.2.2. EFFECTS OF PAIN SEVERITY ON TSP

In the Systematic Review, a weak but significant positive correlation was found between pain severity and the standardized mean difference in TSP between-groups. Such a relationship was also replicated in Study I, whereby participants with increased TSP at baseline developed more severe pain following the fatiguing exercise. Further, when TSP data from the most painful session of all LBP conditions (Studies I-III) was collated, a weak positive correlation was also found between TSP (represented by VAS-epoch III) and maximum pain intensity ($R=0.258$, $P<0.05$). From a theoretical perspective, this makes sense, as increased excitability of dorsal horn neurons and thus enhanced transmission of nociceptive input, would lead to greater pain perception. In line with these findings, prior work has identified relationships between TSP and both chronic post-operative (e.g. post-arthroplasty[141,250] and post-thoracotomy[352]) pain severity and analgesic responses[108,253], though relationships among patients with spinal pain have been less clear[136]. There is some evidence from prior studies that TSP may co-vary with LBP intensity, both on experimental induction[29] and with changes in response to interventions[28], though these were relatively minor effects observed in small samples. However, it is also possible that this relationship between LBP and TSP is present instead due to concomitant effects of perceptual features, such as pain-related fear or pain catastrophizing, as these factors are not commonly accounted for in analyses. Nevertheless, the present work seems to suggest both that facilitated TSP co-occurs with pain and presumed nociception, possibly in a severity dependent manner (Study II), but also that variation in TSP among pain-free individuals may be predictive of future pain experiences (Study I). These suggestions require further study to refine and confirm, especially in idiopathic musculoskeletal pain conditions.

5.2.3. INSIGHTS FROM COMPARISON TO 'THE STANDARD'

Considerable variation in methodology was noted in the Systematic Review, however the pin-prick approach from the German Neuropathic Pain Network's (DFNS) QST battery was the modality reported most frequently. Although not a primary outcome, and thus not reported in the main analyses, this outcome was also assessed in Study II of the present work at both the spinal level of most LBP and at the ipsilateral hand dorsum. A problem was encountered, however, with this approach, as despite performing the assessment in accordance with the DFNS protocol[281] (i.e. 1 vs 10 stimuli at 1Hz with a 256mN pin-prick stimulator), there were 106/448 instances where participants reported an NRS of 0 that needed replacement for ratio calculations. Further, these ratios then showed no clear relation to cuff TSP, with within-session, group and site correlations varying from -0.3 to 0.6. This is not unprecedented, as DNRF reference papers also report considerable between-subject variability in pin-prick TSP making it difficult to demonstrate abnormalities in patients[281]. However, there is also reason to believe that true differences exist in the extent of hyperexcitability elicitable by muscle and cutaneous nociceptors; for example, on the basis of seminal animal works showing prolonged dorsal horn discharge after muscle versus cutaneous afferent stimulation[132,346]. These different modalities may offer insight into distinct phenomena related to the different tissue-types assessed, though this requires further investigation to establish. On this note, the Systematic Review highlighted differences between modalities, with reflex withdrawals to electrical stimuli showing the largest between-group alterations, consistent with claims that this modality may

have discriminative value for chronic LBP[221]. Different modalities may, therefore, also be best suited for differing purposes, for example these electrical approaches may be most useful in diagnostics, whereas mechanical modalities including cuff pressure algometry, with their increased inter-individual variation, may have more utility in prognostics.

5.3. SUMMARY

There is substantial variation in TSP methodology, and as yet, the relevance of different paradigms to outcome and condition remains poorly studied. Nevertheless, meta-analysis showed differences in TSP between LBP patients and pain-free controls, with greater facilitation of TSP being associated with higher pain severity. The effect of LBP on TSP was, however, not consistent between the present experimental studies, with facilitation only shown in the presence of a RLBP episode and not from experimental nor mild chronic LBP in the small sample studied here. It was suggested that TSP may reflect current pain status to some degree, but also that variation among pain-free individuals may be of predictive value in determining the severity of future pain experiences.

CHAPTER 6. ANTI-NOCICEPTIVE DESCENDING PATHWAYS

In this chapter, conceptual development of conditioned pain modulation (CPM) assessment in humans, methodological considerations, and findings from the present work on the impact of LBP on this measure (Systematic Review and Studies I-III) are presented and discussed.

6.1. ASSESSING DESCENDING INHIBITORY PATHWAYS

6.1.1. DIFFUSE NOXIOUS INHIBITORY CONTROL

'Diffuse noxious inhibitory control' (DNIC) was first coined by Le Bars and colleagues[165] in 1979 to describe an inhibitory spino-bulbar-spinal loop. This was originally established in animals as a global inhibitory mechanism activated by strong noxious stimulation of an extremity site (typically nose or tail), leading to dramatically reduced firing in wide-dynamic range neurons of the dorsal horn in response to concurrent stimulation of heterotopic sites[165,166]. A significant amount of work has been done to corroborate this DNIC mechanism in humans[355] and elaborate on the precise descending pathways involved[38,61,279,338,354]. At present, it is understood that these descending pathways originate in the locus coeruleus (inhibitory) and rostral ventromedial medulla (inhibitory and excitatory) and project downward to the dorsal horn, with noradrenaline being the primary neurotransmitter involved in generating inhibition[21-23]. The periaqueductal gray (PAG) in the midbrain is also considered an important origin of descending inhibitory pathways, though more so in inhibition due to cortical influences (as this region integrates input from e.g. hypothalamus, amygdala, rostral anterior cingulate cortex) rather than specifically due to counterirritation[22,242,339].

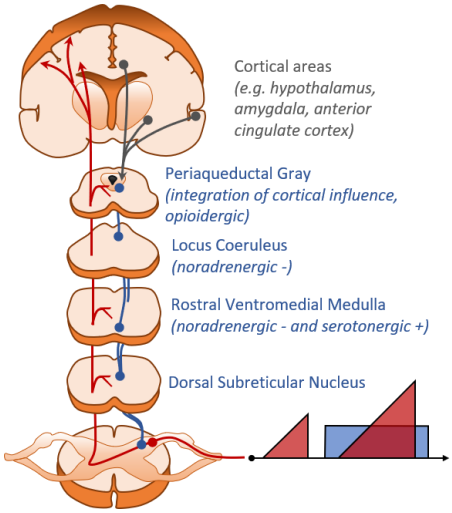

Figure 6-1 Illustration of DNIC/CPM paradigm including ascending nociceptive and descending inhibitory pathways, along with relevant cortical and subcortical regions involved

6.1.2. CPM – THE PERCEPTUAL CORRELATE OF DNIC

Initial papers in humans used much the same stimulation methodology as in animals; meaning a test stimulus (e.g. pain threshold) was applied before and during a painful heterotopic conditioning stimulus (e.g. cold water bath or nasal septum clamp)[355]. Similar to TSP, this had to be done sans invasive recordings, which again meant adopting outcomes of nociceptive

withdrawal reflexes, perceptual ratings, or both. In fact, early studies using both measures demonstrated highly consistent results[355], and subsequent work has confirmed good correlations between reflex and perceptual pain thresholds[204]; so many human test paradigms now rely on perceptual outcomes alone[361]. In exploratory studies, CPM measurement has shown some value in predicting future disability in LBP patients[68], and predicting prognostic and treatment outcomes in other painful musculoskeletal conditions[69,92,234].

6.1.3. METHODOLOGICAL CONSIDERATIONS

The use of non-invasive testing methods in a conscious person introduces several methodological issues, due to the involvement of pain evaluative cortical processes. This means the measure is no longer likely to be a sole reflection of the classic 'DNIC' spino-bulbar-spinal loop. Especially for methods using pain ratings or thresholds, CPM may be more representative of perceptual features than spinal nociception[176]; though even reflex responses are not immune to cognitive interference[63], and, as mentioned, have previously been shown to correlate with perception anyway[355]. Prior studies have demonstrated expectation[82], distraction[131,207,208], pain catastrophizing[52,324,353] and affective state[70,213] to impact the magnitude of CPM recorded. Mechanistically, these psychological influences are unsurprising due to ongoing communication between cortical regions and brainstem origins of descending controls[181]. Other personal factors, such as age[112], gender[299], menstrual cycles[273], sleep[303,305], alcohol consumption[149] and physical activity[95,217,293,330] have also been purported to be influential[121,201]; which seems rational mechanistically given the central role of monoamines (e.g. dopamine, noradrenaline, serotonin) in these modulatory pathways[22]. In the present work, most of these factors were either recorded and shown to be consistent between sessions (Appendix C) or were controlled for with standardised instructions and use of within-participant or matched-control designs. Nevertheless, it is important to remember that psychophysical CPM assessment reflects a net response of the whole system, not just that of the intended descending pathways.

Beyond these influences, another general issue with CPM testing is that precise test methodology varies considerably between research groups and studies[75,145]. As demonstrated in Figure 6-2 below (updated from supplementary material of Systematic Review), in papers looking at LBP alone there are at least 23 different test paradigms using combinations of 8 different test modalities with 6 different conditioning modalities. This is not to mention additional variation in test and conditioning stimulus intensities, stimulus timing and application sites between studies, which can also influence outcomes. Although consensus papers have emerged recommending ways to standardise testing, few articles follow these recommendations[361], not least because there is ongoing debate on the relevance of stimulus combination and temporo-spatial array to outcome[139,214]. As a result, methodology selection in the present work was based on prior studies showing good reliability with cuff measures[105,140,252], available equipment and theoretical rationales of modality relevance to LBP. In addition, the CPM method used here was extended, compared to prior work using cuff algometry, to include an extra ramp to assess pain thresholds prior to conditioning, to observe habituation to repeated cuff stimuli. As well, ramped assessments both during and following

conditioning were collected to look at both parallel and sequential CPM effects, as there is still debate around which is most reflective of descending inhibitory function (Fig 6-2).

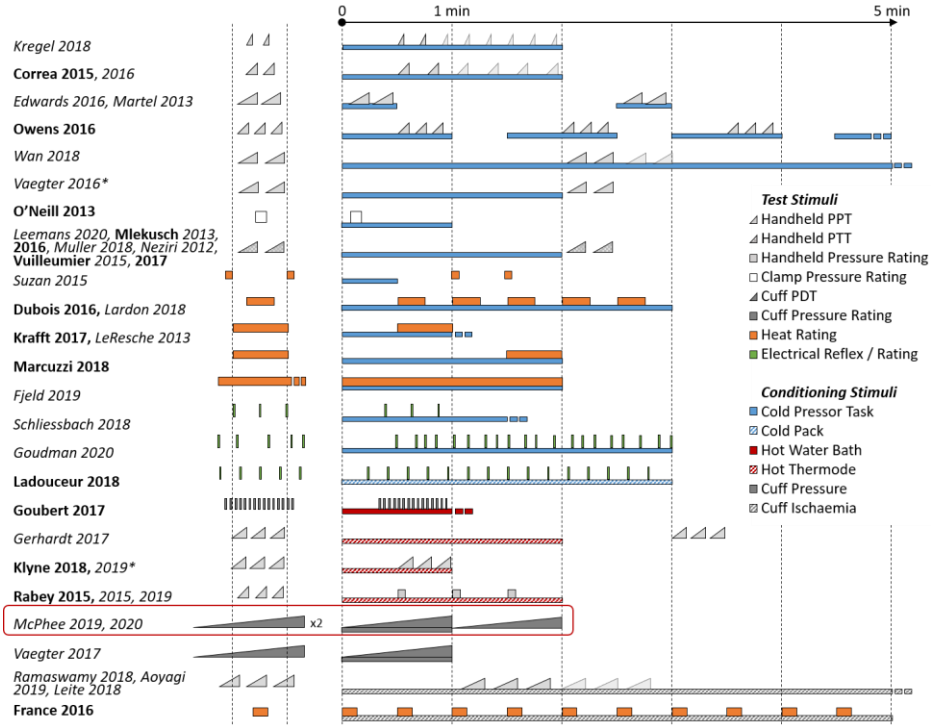

Figure 6-2 Variation in Conditioned Pain Modulation Paradigms applied in studies of LBP patients[6,54,55,68,71,79,82,94,100,101,149,150,155,157,160,161,169-171,190,193,196,205,206,211,222,237,243,262,263,265,267,287,314,333,334,344,345,349]
*(Updated from Systematic Review Supplementary Material to include present studies, articles without healthy comparators in LBP populations and articles published after meta-analysis searches were complete). Note: depictions are based on manuscript descriptions and hence accuracy is dependent on reporting quality, *denotes that study contains more than 1 method, bold indicates inclusion in Systematic Review and Meta-analysis, Red rectangle indicates paradigm used in Study I-III.*

6.1.4. VALIDITY & RELIABILITY

In the present work, a computerized cuff algometer was used to assess CPM. This system is user-independent and hence allows for standardisation of stimulus application and timing, as well as allowing for individualisation of test and conditioning stimulus intensities based on participant pain thresholds or ratings[103]. It was again assumed that this stimulation type is of most relevance to musculoskeletal pain, due to the compression of deep tissues, though this remains speculative.

Recently, this cuff methodology was back-translated and validated as an appropriate stimulus type and configuration to activate DNIC, with findings in rodents paralleling psychophysical responses in humans[58]. Prior human studies have also shown this or similar cuff methodology to be able to produce consistent CPM responses when repeated in quick succession[130], along with being highly reliable over short retest intervals (hours)[50] and moderately reliable when repeated over longer intervals (weeks)[103]. Although not yet a diagnostic or discriminative tool, this method has also demonstrated some relation to clinical features[332] including prognosis. It can be debated whether applying both the test stimulus and the conditioning stimulus within the same spinal segmental innervation is wise, as this may introduce additional intra-spinal inhibitory processes. However, such an approach has recently been shown to produce some of the most reliable results[229] and generally CPM magnitude does not vary significantly regardless of test stimulus site, so long as it is not immediately adjacent to conditioning[140,151].

As for all prior measures, CPM reliability across the study timeframe in the present work was tested in control participants from Study II. This demonstrated an ICC (3, k) of 0.567 [0.091, 0.794] for the parallel-CPM measure, and 0.605 [0.170, 0.812] for the sequential-CPM measure, which is consistent with prior reports of reliability for this modality[103]. Among other CPM reliability studies, reports have varied dependent on the testing timeframe, CPM paradigm and statistical methodology used[140,145], with some reporting good to excellent reliability[7,31,50,172] and others poor reliability[239,356]. As is evident from the literature, presented statistics, and the later findings (Figure 6-3), reliability with the present methodology is acceptable, but inter- and intra-individual variability in CPM is generally high. This remains a critical issue for researchers and clinicians looking to use CPM for diagnostic and/or prognostic purposes.

6.2. FINDINGS ON THE RELATIONSHIP BETWEEN LOW BACK PAIN & CPM

6.2.1. EFFECTS OF PAIN PRESENCE & SEVERITY

The Systematic Review identified impaired CPM in patients with LBP compared to control participants overall. Similarly, an overall group difference in CPM between RLBP patients and controls was demonstrated in Study II. However, no statistically significant alterations in CPM were identified between-sessions within experimental (Study I) or clinical (Study II & III) LBP groups, suggesting pain presence on the day of testing did not have a clear impact on CPM magnitude. To some extent, this would support the concept of CPM efficacy as a trait measure, potentially reflecting a mechanism that contributes to, or enhances susceptibility to pain maintenance and thus allowing for predictive value in prognostics. In line, CPM has been reported as a predictor of prognosis and treatment response in numerous studies[69,92,108,133,284], though the degree of relation between CPM and outcome is variable. As well, prognostic capacity in spinal pain conditions specifically has so far been lacking, with most large-scale prospective cohort studies showing limited to no utility in predicting treatment response or long-term changes in pain[68,79,161,171,206,211,287], though a possible relation to disability[68]. Difficulties in demonstrating prognostic utility could, however, be a result of methodological issues like high variability and the confounding influences of various individual and contextual characteristics.

A relationship between pain severity and CPM impairment was also observed in the Systematic Review. As there was a lack of effect of pain presence in the present experimental studies (Study I-II), this may instead suggest that the intensity of LBP was simply not sufficient here to acutely impair CPM, but that more severe LBP could have. In line, prior experimental work using more painful provocations, such as hypertonic saline[14] and capsaicin[129], have been able to demonstrate acute impairment of CPM, and clinical studies in populations with more severe pain have also shown normalization of CPM following pain-relieving procedures[106,154]. Interestingly, a relationship between LBP severity and impaired CPM has also been evident within some individual studies[100,332], though more commonly reported is a relationship between CPM impairment and the spatial extent of pain[6,94,101,334]. The present work did not investigate this question, as included patients primarily reported localized LBP. However, as widespread pain is often associated with greater disability, this warrants further study to determine whether impaired CPM prior to or soon after pain-onset can predict spread of LBP, or alternatively if the mechanism becomes more impaired with expanding pain areas.

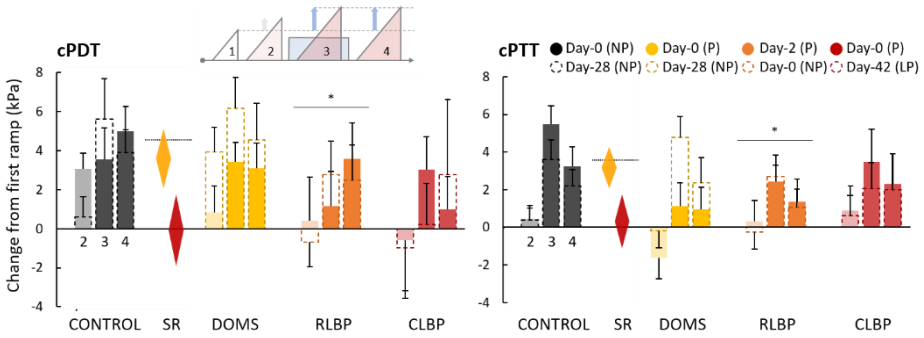

Figure 6-3 Mean (+SEM) CPM effect, as increase in cuff pain detection (cPDT) and tolerance (cPTT) thresholds from the first ramp to the 2nd (faded, prior to conditioning), 3rd (during conditioning) and 4th (immediately following conditioning) ramps, for controls (Study II) and from a painful (P) and non-painful (NP, Study I-II) or less painful (LP, Study III) session for each LBP group. Standardised mean difference (SMD) and confidence intervals (CI) from Systematic Review (SR) are presented as expected effect size from control group mean of ramps 3-4 (dotted line). *Note: *denotes significant main effect of Group within Study II where RLBP patients showed reduced CPM compared to controls. Meta-analysis results from the Systematic Review shown as yellow (acute or recurrent; SMD = -0.11 [95%CI: -0.30, 0.08]) and red (chronic; SMD = -0.57 [95%CI: -0.82, -0.33]) diamonds; illustration of paradigm provided in top left corner.*

6.2.2. RELATIONSHIPS BETWEEN PAIN DURATION & CPM

When data in the Systematic Review was sub-grouped into acute and chronic, only chronic LBP patients showed significantly lower CPM compared to controls (Figure 6-3). On a group level, mean pain duration also significantly correlated with CPM. Such a relationship was not clearly demonstrable in the experimental studies of this thesis, though this may have been due to the small samples of comparatively mild recurrent and chronic LBP patients included. Some prior studies have shown a relationship between pain duration and CPM impairment in patients with knee osteoarthritis[10,81], though not consistently[12,298], and this relationship has not been replicable in various other painful musculoskeletal conditions[107,120,240,323]. Nevertheless, if this

relationship truly exists in LBP, it suggests either that there is a temporal degradation in pain inhibitory mechanisms due to ongoing nociception and pain, or that inefficient CPM prior to or in the acute phase of pain contributes to pain recurrence and/or persistence. Consistent with the former, a recent small longitudinal study following patients after spinal cord injury showed reductions in CPM over time as neuropathic pain was maintained[85]. However, this was not the case for musculoskeletal pain in this patient group, suggesting interactions between CPM efficacy and pain persistence may depend on underlying mechanisms. When instead looking at musculoskeletal pain populations, there is some preliminary evidence to suggest impaired CPM may precede development of chronic neck pain[290], but this requires replication in larger samples and other painful musculoskeletal conditions.

6.2.3. INSIGHTS FROM CPM TESTING

The reason for the lack of differences observed between painful and pain-free sessions in the present work could very well be primarily due to variability. As well, based on the present studies, pain detection thresholds do not appear to be an ideal test stimulus, despite their frequent use (Figure 6-2). This is because some degree of habituation occurs on repetition of the stimulus alone (i.e. Ramp 2 in Figure 6-3) especially in control participants, followed by highly variable findings for the two subsequent ramps (i.e. ramps during and following conditioning, though these do correlate significantly). On the contrary, pain tolerance thresholds appear to be more stable, showing less habituation on reapplication and more consistent inhibition during and following conditioning. This is in line with the initial papers on CPM in humans, where intolerable pain was demonstrated to be more sensitive to the conditioning stimuli tested than threshold pain[355]. It also parallels recent animal findings showing the direction of modulation to be dependent on test stimulus intensity, with only the more noxious test stimuli demonstrating inhibition[316].

On the matter of habituation to repeated threshold testing, it is noteworthy that this was most problematic in controls and less evident in LBP populations (Studies I-III). It was also the case that experimental LBP appeared to reduce habituation in controls, albeit non-significantly on post-hoc testing (Study I). Early QST studies in LBP patients highlighted this phenomenon of lacking habituation to repeated stimuli as a discriminative feature of chronic LBP[248,249], and posited that it may be mechanistically linked to chronic LBP development and/or LBP persistence[39]. Recent work has further shown lacking habituation in cortical responses to painful stimuli among CLBP patients compared to controls, again suggesting this to underlie pain persistence[343]. The present work would instead tend to support this being a consequence of LBP presence (Study I), but it is still open for further investigation. In reality, the results seen here are probably explained by a combination of: lacking capacity to habituate due to hyperexcitability e.g. in ascending nociceptive pathways, reduced descending inhibitory function, hyperawareness of sensory stimuli producing more accurate and thus consistent ratings, and persistent anxious or catastrophic thoughts despite lack of stimulus novelty; though this is merely speculation.

Although this was not the focus of the present work, two alternative CPM paradigms were tested in some of the study populations (Study I-II). This was primarily to develop test methodology

that was able to be used concurrently with affective and attentional manipulations (unpublished supplementary work), but also to develop a cuff pressure-based approach that was more consistent in timing and outcome with typical thermal paradigms (i.e. where a brief noxious test stimulus is applied and evaluated with pain ratings before and following a period of conditioning[259]). Unfortunately, the first of these approaches using two 5-second test stimuli prior to and following conditioning was ineffective (Study I), producing no measurable inhibition in healthy controls. However, the second approach using three 1-second test stimuli prior to and after 75-seconds with ongoing conditioning seemed to produce inhibition and demonstrate results consistent with the ramped approach for RLBP patients and controls (Study II). Further work is needed to elaborate on these findings and determine the relevance of different stimulus arrangements; but, perhaps with significant methodological refinement, and open publication of large normative datasets for reference, CPM may eventually be of clinical use.

6.3. SUMMARY

In papers on LBP alone, there is considerable variation in stimulus parameters used to assess CPM. Even when using the same paradigm, there is high inter- and intra-individual variability, which greatly hinders the comparability and interpretation of results. Nevertheless, impaired CPM was shown on meta-analysis, driven by changes observed in CLBP patients. In the present experimental studies, a recently back translated and validated method was used. This method identified impaired CPM among RLBP patients compared to controls within Study II but could not elucidate other differences between groups or sessions. Additional relationships between CPM degradation and both pain duration and severity were observed in the meta-analysis but could not directly be replicated in the present experimental work. It remains unclear as to whether impairments in CPM are consequential or contributory to pain persistence, as there is evidence consistent with both possibilities.

CHAPTER 7. ATTEMPTS TO MODULATE PAIN SENSITIVITY

From the present work, there appeared to be a relationship between LBP and impaired CPM (Systematic Review & Study II). In the Systematic Review, this manifested as an overall group impairment in especially chronic LBP patients compared to controls, the magnitude of which was moderately correlated to pain duration. Then in Study II, a similar group level impairment was observed without normalisation in the pain-free period, unlike the other measures. If CPM impairment were to represent a relevant pathophysiological feature of LBP, it would seem pertinent to attempt to modulate this mechanism and examine the resultant impact on the pain experience. In clinical populations showing impaired CPM, such as patients with painful diabetic neuropathy, duloxetine (a serotonin and noradrenaline reuptake inhibitor) and Tapentadol (a combined opioid and noradrenaline reuptake inhibitor) have shown some efficacy in restoring inhibitory function[225,362]. This has been mechanistically corroborated in animals[25,363] though has proven difficult to reliably replicate in other patient groups[147]. Other strategies addressing known influential factors (such as attempting to increase physical activity, improve sleep or enhance mood), could also improve CPM in patients with those specific factor-related problems. However, this introduces difficulties in disentangling effects, as these factors also interplay heavily with both one another and the clinical pain experience. An arguably cleaner and/or simpler approach would be to intervene by stimulating cortical or sub-cortical regions involved in controlling descending noxious inhibitory pathways, which also allows for a sham comparison to check efficacy. This approach was used in Study III and is also currently being trialled in larger scale work elsewhere[49,317].

7.1. NON-INVASIVE BRAIN STIMULATION

7.1.1. TRANSCRANIAL DIRECT CURRENT STIMULATION

Transcranial direct current stimulation (tDCS) is a form of non-invasive brain stimulation, where weak electrical direct currents are applied to the scalp through specifically placed electrodes in order to alter cortical excitability in particular brain regions. Over the years, tDCS has been studied as a way to cure numerous ailments[5,366], including pain. In contrast to other forms of stimulation and pharmacological management, the technique offers the advantages of being non-invasive, more tolerable, accessible, relatively low cost and easy to apply. Thus far, efficacy has been shown among patients with post-surgical and chronic neuropathic pain conditions[59,152,232,254], though effects on experimental pain sensitivity are inconsistent[97,212].

7.1.2. TARGETING STIMULATION

Various stimulation targets have been trialled with tDCS to address pain and related symptoms in patients[152,254]. The motor cortex is most commonly used[184], perhaps foremost because of its definitive localisation, along with the promise shown in studies of repetitive transcranial magnetic stimulation applied to this region. Motor cortex tDCS has also been used to acutely

improve descending inhibitory processes in healthy individuals[80]; however, no acute changes in QST parameters were provoked after a single session in CLBP patients[183].

Regarding descending inhibitory processes, various cortical regions are thought to have influential connections with descending inhibitory pathways, allowing for the pain-modulating effects of cognitive engagement and affective manipulation[339]. As the main source of cortical projections to the periaqueductal gray (PAG) are from the medial prefrontal cortex (mPFC)[24,364], and as this region is also heavily involved in affective processing[266], this was considered an ideal location to target[159]. This region was additionally of interest since both impaired CPM and affective symptoms are commonly present in LBP patients and are suggested to influence pain progression. As well, fMRI and electrophysiological investigations in LBP patients have shown: altered functional connectivity within and between the mPFC and PAG during LBP exacerbation[195,329,365], altered activity in these same regions in response to noxious experimental stimuli[65,99,175,195] and morphological alterations generally in prefrontal areas[156].

Stimulation targeting was based on a previous HD-tDCS study, which had used a high-definition array to target an mPFC subregion, namely the anterior cingulate cortex (ACC)[322]. Based on the computer modelling in this study, the HD-tDCS array appeared to generally target the medial prefrontal region, so was deemed appropriate for use here. The electrode arrangement (see Figure 7-1 below) includes with one central anode over the frontal vertex (Fz) and four surrounding cathodes at FP1, FP2, F7 and F8. Modelling was independently repeated in MatLab using SimNIBS software[321] (Figure 7-1) with appropriate tissue impedances, electrode properties (i.e. as specified by Neuroelectrics®) and stimulation parameters (2mA anodal direct current) for the present work, again showing current flow generally through the mPFC.

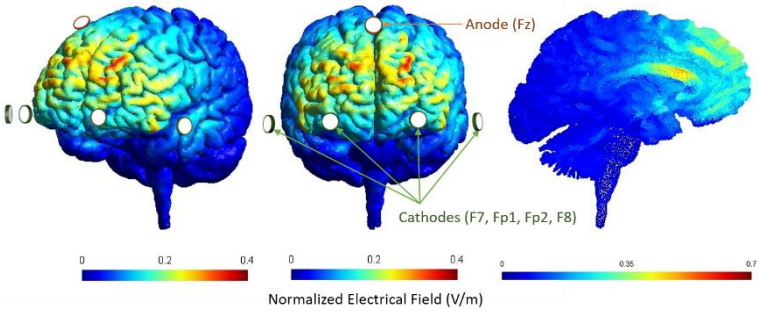

Figure 7-1 Electrical field modelling of active 2mA mPFC HD-tDCS used in Study III. *Note: images generated with SimNIBS[321] using 'Ernie' dataset and Study III electrode parameters).*

7.1.3. CONTROLLING FOR CONTEXT VIA SHAM TDCS

To attribute changes in symptomatology and pain sensitivity measures to active tDCS, a sham-comparator was essential. Much debate has arisen regarding sham paradigms, especially regarding their efficacy in crossover trials, as there are perceptible differences in the sensations produced[146,231,283]. In the present work, a long (60s) ramp on and off was used in both conditions to better mimic the duration of sensations at the beginning of the active paradigm. Participants were also given no specific details regarding differences in timing or intensity between

paradigms. Instead, they were informed of the expected sensations from stimulation, such as that they may feel itching, tingling and warmth, and were told that these sensations would be strongest in the first few minutes, then slowly fade away irrespective of the paradigm. These decisions were based on recommendations from prior literature suggesting that longer sham stimulation duration and managing expectations could improve blinding success[41,245,271].

Despite the fact this was a crossover trial, with participants acting as their own controls, blinding failure did not appear to be a major issue in the present work. Only 58.3% of participants correctly guessed which protocol they received, which was not statistically different from chance, and only reported a median certainty of 2-3 (on a 5 point-Likert scale from not at all to completely certain, Study III). Participants typically reported guessing the active protocol based on either more intense sensation during stimulation or reduced back pain, but these guesses were frequently wrong. Side effects were also commonly reported in both conditions further aiding blinding maintenance for both participants and experimenter. This strengthens study conclusions, and suggests that cross-over designs are appropriate, at least for pilot testing. In future studies with larger samples, it would be interesting to look at differential effects based on believed treatment, but this was not possible in the present work.

7.2. FINDINGS ON THE EFFECTS OF TDCS

An overview of the design of Study III can be seen in Figure 2-3 and a summary in Appendix A. In short, Active and Sham tDCS were applied to the mPFC of CLBP patients each on three consecutive days, separated by at least two weeks. Self-report data was collected at the start of each session and pre- and post-stimulation, while pain sensitivity measures were assessed pre- and post the first day of stimulation, immediately and 24-hours following the third day of stimulation, and on Day 21 in each phase. Overall, the active and sham tDCS both reduced current pain intensity in the immediate post-stimulation period of the first session, but no long-term changes (on Day 4 or 21) in pain ratings were noted (Figure 7-2).

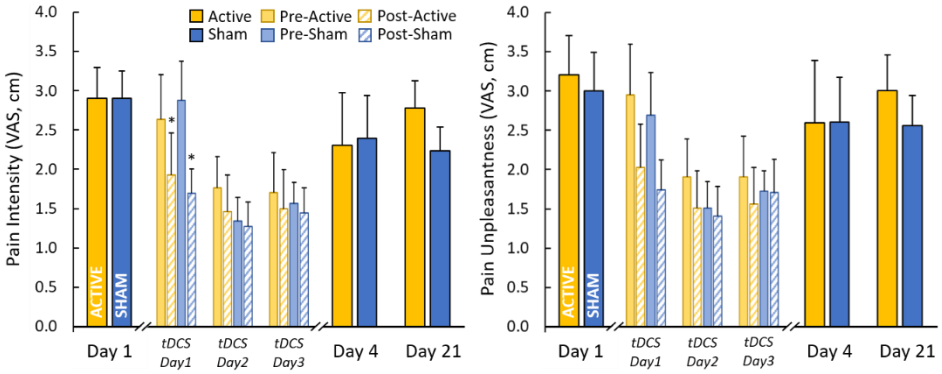

Figure 7-2 Intensity (left) and unpleasantness (right) of pain both on average over the preceding 24 hours (Day 1, 4, 21) and immediately prior to and following tDCS (Day 1-3) for the active (yellow) and sham (blue) HD-tDCS paradigms. *Note: *denotes a significantly larger reduction in pain ratings on Day 1 than Day 2-3 as demonstrated on normalised data in Study III Supplementary Material.*

In terms of pain sensitivity measures, cuff pain tolerance thresholds were increased over time in both paradigms (Fig 7-3), suggesting general temporal habituation rather than a tDCS-related effect. Normal TSP and CPM responses were present (Fig 7-3) and of similar magnitude to healthy controls in Study I-II (Fig 5-3, 6-3, Appendix C), and these were unchanged by either tDCS paradigm. In the supplementary material of Study III, immediate effects of tDCS were also explored (greyed bars in Fig 7-3), in which there was a reduction in ECR PPTs following active compared to sham tDCS, likely related to generally higher PPTs on Day 1 in the active phase, but otherwise no differential effects were observed between tDCS paradigms.

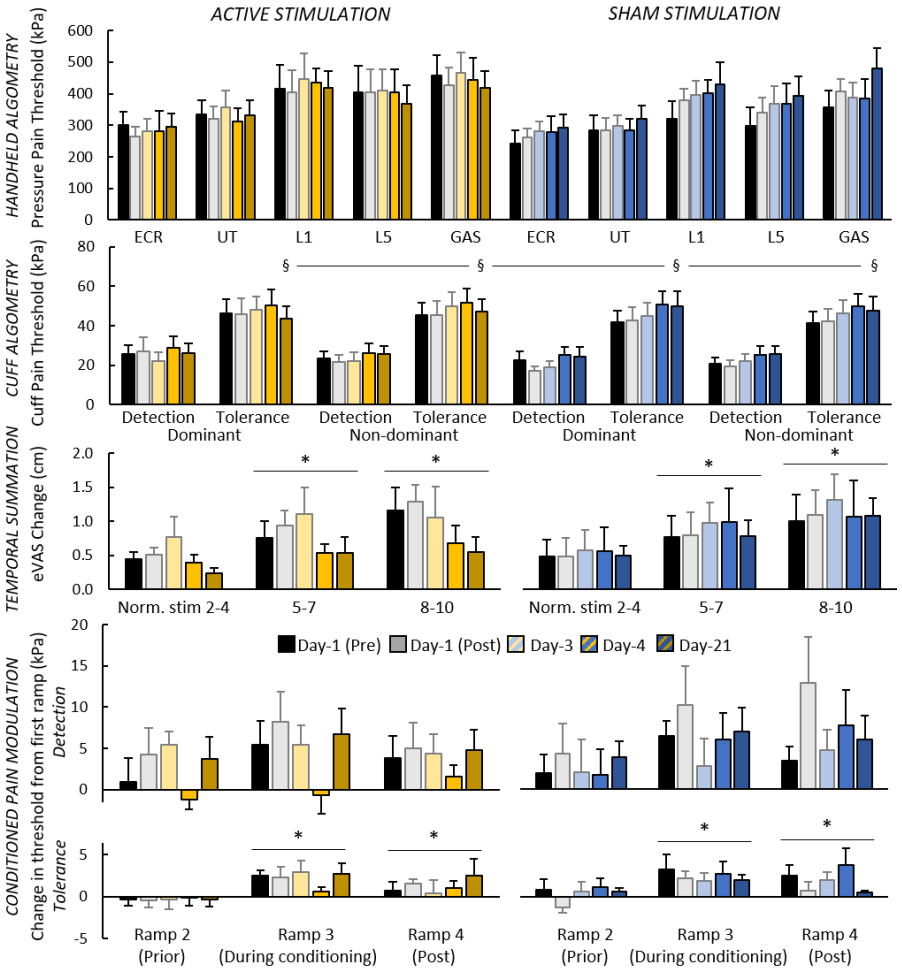

Figure 7-3 Overview of results for main psychophysical outcomes across testing sessions on Day 1 pre and post stimulation, Day 3 post stimulation, Day 4 and Day 21, for Active (yellow) and Sham (blue) HD-tDCS conditions. *Note: §denotes overall higher cuff thresholds at Day 21 than Day 1 Pre (pain tolerance), *denotes significant main effect of Epoch / Ramp showing TSP and CPM (on cPTT only) effects to be present overall.*

7.3. COMPLEXITIES OF MODULATING ANTI-NOCICEPTION

Although this HD-tDCS paradigm intended to target cortical projections to descending inhibitory pathways, and thus alter pain modulatory efficacy, it is safe to say that it did not produce major effects. There are many features of the present work that could explain this lack of efficacy, for example: (1) CLBP patients already demonstrated efficient CPM at baseline; (2) the modelling of penetration depth is based on an ideal situation with little electrode to scalp impedance, whereas in reality, some participants in the present study had long and/or thick hair making it difficult to achieve a low impedance; (3) A-priori sample size calculations were conducted but the sample remains small and heterogeneous; (4) included patients generally demonstrated mild LBP features at the time of testing and no clear affective disturbances; and (5) stimulation targets were based on functional connectivity findings, which may be problematic if these regions are not actually involved in the functions posited, or if their involvement is in processing present pain state rather than representing a feature relevant to the LBP condition[51,60]. In addition, a prior study aiming to intervene with affective features of CLBP by targeting the ACC (albeit with a different electrode type and array) showed greater promise in improving pain and disability[191], but also used many more sessions (10 versus 3 here) and did not assess CPM.

Generally, there has been ongoing debate about the efficacy of tDCS, with a recent review questioning whether it can produce *any* neurophysiological effects at all[134]. This large-scale meta-analysis showed significant effects on only 1/30 neurophysiological outcomes (motor-evoked potentials) and even that effect had been declining over the preceding decade[134]. In clinical trials, systematic review conclusions also vary widely with some suggesting great potential in pain management[97,179,254], and others suggesting limited to no efficacy[184,232], including for CLBP[3]. For QST measures, a recent review[97] was positive, showing 'homogenous' improvements in CPM across studies (following motor cortex stimulation), but effect sizes were still small. It may be the case that combined strategies (i.e. tDCS with concurrent exercise, psychological or pharmacological intervention) produce greater effects[44], by capitalizing on the post-tDCS window of enhanced excitability[254], but this requires further investigation in large-scale, well-controlled clinical trials.

Based on findings from the Systematic Review and Study II, the hope was that taking a group of CLBP patients would mean having a population with deficient CPM, which tDCS could then help to restore. It was thus problematic that the small sample of CLBP patients recruited here did not demonstrate deficiencies in CPM at baseline, as exploratory correlations within the study did actually support an improved effect of tDCS in those with most impaired CPM at baseline. The normal CPM responses observed in this sample may result from their relatively mild LBP symptoms, low disability, young age and high physical activity levels; suggesting that recruiting an older and more severely impacted CLBP population, or screening participants prior to inclusion, may have resulted in a different outcome. As also highlighted in a recent review[254], strict screening should be considered in future work. Beyond variation in CPM, it is important to consider that individual differences in brain state prior to stimulation[226], anatomical variation in brain architecture[174], and differences in pathophysiological mechanisms underlying an individuals' pain condition may all also contribute to differences in stimulation efficacy.

CHAPTER 8. CONCLUSIONS, IMPLICATIONS & FUTURE DIRECTIONS

8.1. SUMMARY OF MAIN FINDINGS

The present work has suggested that alterations in pressure pain sensitivity and TSP may be primarily reflective of present LBP state (Systematic Review, Studies I-III), while CPM may be prone to progressive impairment over time as pain transitions from acute to chronic (Systematic Review, Study II) and/or mild to severe. A summary of these findings is provided in Figure 8-1.

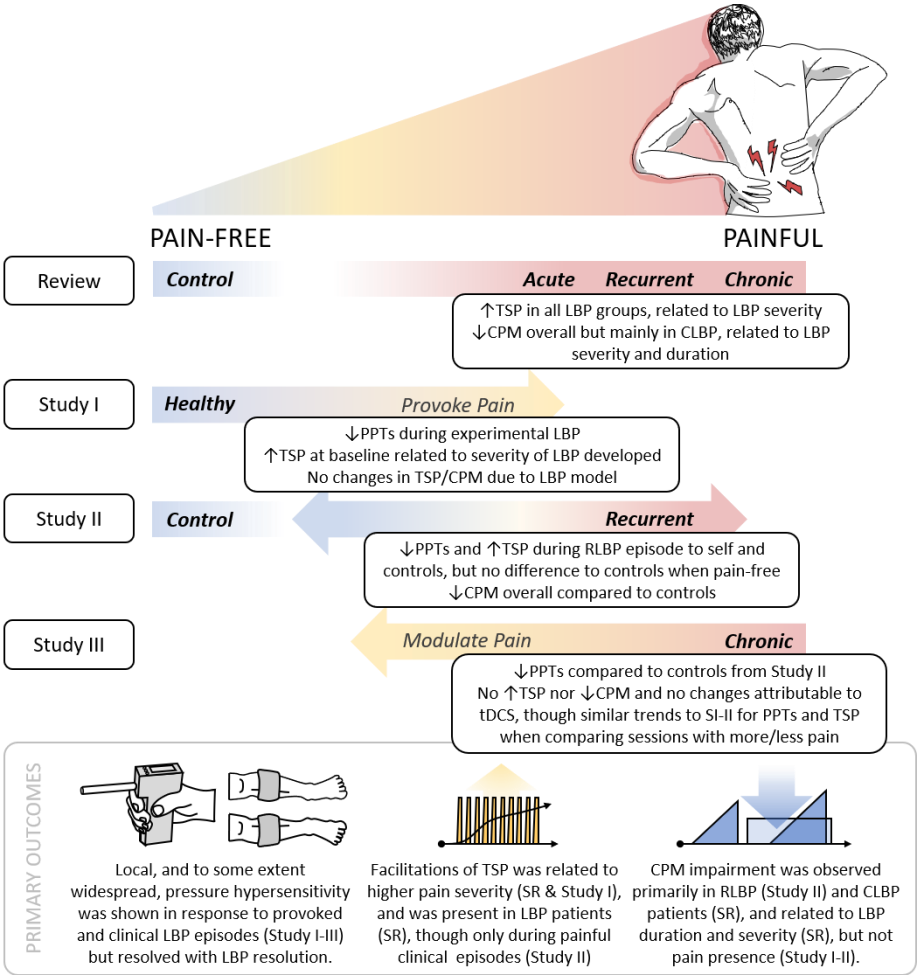

Figure 8-1 Brief summary of individual study conclusions, as well as summary of findings across studies for primary outcome measures overlayed onto conceptual schematic of thesis.

In response to the objectives described in Chapter 1, the present work has **(I)** clarified that alterations in both TSP and CPM do indeed exist among patients with LBP, at least on group level comparison with pain-free populations. The magnitude of these alterations was small, but showed some relation to pain severity and, in the case of CPM, to pain duration. **(II)** The effect of experimental LBP on pain sensitivity measures within-individuals (Study I) was examined; demonstrating that the DOMS model reduced PPTs over both local lower back and some remote sites, though was unable to alter TSP nor CPM. **(III)** The impact of clinical LBP resolution (Study II) or reduction (Study III) on pain sensitivity measures within-individuals was investigated; demonstrating that the presence of pain was associated with hypersensitivity to pressure and facilitated TSP at least for RLBP patients (Study II), though CPM remained unchanged between sessions (Study II & III). **(IV)** Pain sensitivity was compared between LBP patients and control participants when clinical pain was absent (Study II); showing that RLBP patients in remission do not appear different from controls in terms of pressure pain sensitivity nor TSP, though do continue to show impaired CPM.

8.2. CONCEPTUAL CONSIDERATIONS

Disentangling the effects of present LBP (state), versus having a LBP condition (trait), on pain sensitivity measures, and inevitably on other outcomes, is clearly a challenging endeavour. In Figure 8-2, a conceptual illustration of the overarching thesis design is shown, indicating the comparison possibilities that such an approach gives. This includes: Cross-sectional differences between participants with experimental or clinical pain and control participants, as performed in much of the existing literature (Fig 8-2, C); Reliability of measures in control participants, as is essential to understand if measures are to be of individual predictive utility (Fig 8-2, E); Stability of measures in populations with clinical pain to understand the influence of present pain state (Fig 8-2, G); And, the effect of having a clinical LBP diagnosis without present pain, potentially allowing for elucidation of pathophysiological mechanisms underlying the development or maintenance of the condition that could be highly relevant interventional or preventative targets (Fig 8-2, F). Each comparison is integral to the understanding of the relationship between LBP experience and pain sensitivity measures, and hence the potential utility of these measures. However, it is also important to note that attempts to disentangle state and trait effects of pain are limited by the variability of both the measures used and the LBP experience. It is clear from the present and prior work that significant variation exists between pain-free individuals alone, and it is possible that this variation could be useful in predicting future pain development, maintenance, or severity, but only if the measures used are valid and reliable (Fig 8-2, A). There is also significant variation in the experience of LBP both within- and between-individuals, and assessment sessions capture only a snapshot of this experience which may or may not accurately reflect the individual or their LBP more generally (Fig 8-2, B). As well, if pain presence and/or severity has a major confounding impact on outcome measures, then this variation in present pain experience will have ramifications for the measures' prognostic and diagnostic utility, as they may just become a reflection of pain state. In addition, various psychosocial and contextual factors can influence both pain perception and pain sensitivity, and while these can be assessed through questionnaires or activity trackers, it remains challenging to properly separate and control for their effects (Fig 8-2, D).

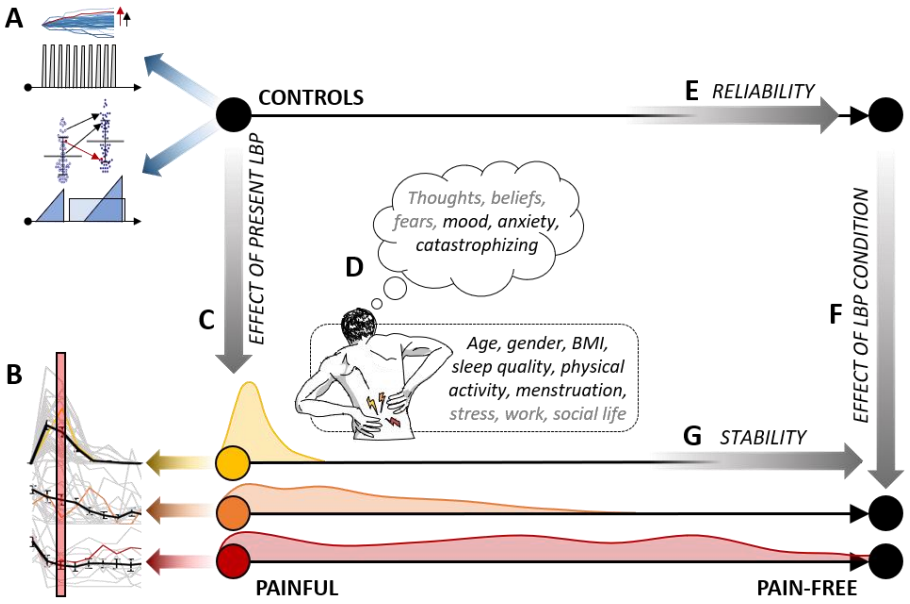

Figure 8-2 Illustration of comparison possibilities and interpretations from the present combination of study designs, and sources of variation within pain and pain sensitivity measures, demonstrated using excerpts of data from the present experimental works, that require elaboration in future work. *Note: A. Represents considerable inter-individual variation in TSP and CPM when pain-free, B. Shows high variability in pain perception across LBP conditions, C. Indicates cross-sectional comparison of pain-free population to patients with present LBP, D. Indicates potential influential individual and contextual factors which could be sources of additional variation, E. Indicates control comparisons over time provide valuable insight into reliability of outcome measures, F. Indicates comparison in which trait features of the LBP condition can be seen without confounding effects of present pain, and G. Indicates comparisons within LBP conditions over time provide*

8.3. IMPLICATIONS OF FINDINGS

Conceptual difficulties aside, the present work has made several observations that could have implications both for clinicians treating LBP patients and for future research. Firstly, pressure hypersensitivity was heavily impacted by fluctuations in present pain state. Hence pressure pain sensitivity measures may be useful to track changes in LBP condition over time and in response to treatment, as a supplement to self-reported and other clinical outcome measures. Thus far, the prognostic value of pressure pain thresholds has been limited[92,234], but it remains possible that they may be useful in informing treatment selection and/or understanding variation in treatment response. It may also be useful for clinicians to consider that enhanced sensitivity to pressure, observed in patients as diffuse tenderness on palpation or general soreness, may be more reflective of the present state of the patient (i.e. that they currently have acute pain from the presenting condition or other injuries, or maybe even simply because they are currently stressed, anxious or sleep deprived, etc.) rather than being indicative of either the severity of their pain condition or that there is tissue damage.

As with pressure pain sensitivity, it may be the case that TSP proves useful in tracking changes in pain state over time, as well as having potential for predicting prognosis or aiding treatment selection. On this note, this thesis brings an interesting conundrum to light, namely that TSP in a pain-free state predicted future pain severity but TSP itself was also altered in the presence of clinical pain, suggesting both trait and state properties. It therefore seems imperative to consider present pain state during TSP assessment in future work, as the variation observed in single homogeneous populations (i.e. patients with the same pain severity, or healthy individuals with no pain) may be highly informative of prognostic features, but this natural or inherent variance in TSP could be masked by the presence of pain. This is seemingly important to consider regardless of whether present pain is related to the condition being studied or not, as TSP over an unaffected site (the lower leg) was altered by LBP presence here (albeit within similar segmental innervation). As such, ongoing trials are investigating the utility of these measures in patient selection for more mechanism-based intervention, which, if successful, could improve treatment efficacy in clinical practice. From the present work, however, perhaps the key positive takeaway is that these features, especially pressure hypersensitivity and TSP, are not 'fixed' and should resolve with pain.

CPM showed some level of impairment generally among LBP patients that increased with pain duration. The present thesis could not disentangle whether this was a time-related reduction in descending inhibitory capacity, or a change in the proportion of people with dysfunctional CPM represented in more chronic populations. Nevertheless, it would seem that CPM impairments may reflect a trait feature of LBP conditions, becoming increasingly pronounced with greater chronicity. If this is the case, and CPM is actually a relevant feature with a role in LBP maintenance, then developing and refining methods to improve or restore CPM could be of great benefit in treating LBP conditions or even preventing the recurrence and/or persistence of LBP in the first place. This remains to be further explored. However, it is also important to remember that, although not significantly affected by pain presence in these studies, CPM is often greatly influenced by a range of other state and contextual factors, and has previously been acutely altered by more severe pain states, meaning on an individual level it still may not be an ideal trait-measure unless suitable control procedures are developed and implemented.

8.4. FUTURE DIRECTIONS

This thesis has highlighted methodological inconsistencies in TSP and CPM assessment that need to be addressed before significant progress can be made. In particular, understanding the relevance of stimulus modality and arrangement in TSP and CPM assessments to specific pain conditions, and how these factors affect the test outcome, is essential, both in obtaining a valid and useful measure and in allowing for meaningful comparison between trials. Fortunately, there are now ongoing global efforts to: compare methodologies from different research groups, create standardised testing batteries and generate large normative datasets, at least for CPM; which will no-doubt aid our understanding of this measure and its utility. Similar global efforts on TSP would also be highly valuable in refining and validating this measure and furthering the understanding of its potential predictive capabilities. Once better refined, standardised, and understood, if these measures continue to show predictive capacity,

future studies should attempt to define cut-off values and develop clinical prediction rules in the progression toward truly personalised mechanism-based treatment.

From a conceptual standpoint, it seems necessary to highlight that the measures of pain sensitivity investigated in the present thesis are all ultimately reflective of a net response from the individual participant. Although not explored in the present thesis, and while theoretically the different pain sensitivity measures intend to assess distinct mechanisms, there are also undeniably interactions and relationships between these measures. Prior literature has attempted to use this advantageously, by creating indices or phenotypic groups based on specific combinations of pain sensitivity measures, which may increase their diagnostic or prognostic value. However, much work remains to understand, refine, and forward validate these combined approaches.

The present work has provided a comprehensive approach to understanding the impact of LBP presence on pressure pain detection and tolerance thresholds, TSP and CPM. This strategy of using cross-sectional (Systematic Review), observational (Study II), forward (Study I) and backward (Study III) manipulations could be equally useful in assessing the impact of pain presence on other measures and in other disorders, both painful and otherwise, to help disentangle state and trait features of pain conditions as highlighted in recent work[60]. As only mild variants of LBP were investigated in this thesis, it is unclear if findings are replicable in other subgroups, for example, with greater severity of pain and disability, widespread pain features, comorbid conditions, or with neuropathic or radicular symptomatology. It is further unclear if the present findings are specific to LBP or musculoskeletal pain alone, or if pain in any location from any source could produce some of the same results. Future work is needed to expand upon the present studies, both specifically in LBP conditions and otherwise, by tracking patients over longer time spans, using more homogenous patient groups (e.g. with regard to pain onset and history, temporal profile of pain, disability level, and/or mechanistic classifications), and using different experimental pain provocations and clinical interventions with stronger effects. It is hoped that with continued work in this direction, a better understanding of both the effects of present pain state on measures of pain sensitivity and trait features that underlie LBP development and maintenance can be obtained.

LITERATURE LIST

1. Abdoli N, Farnia V, Salemi S, et al. Reliability and Validity of Persian Version of State-Trait Anxiety Inventory Among High School Students. *East Asian Arch Psychiatry* 2020; **30**(2): 44-7.

2. Alfieri FM, Lima ARS, Battistella LR, Silva N. Superficial temperature and pain tolerance in patients with chronic low back pain. *J Bodyw Mov Ther* 2019; **23**(3): 583-7.

3. Alwardat M, Pisani A, Etoom M, et al. Is transcranial direct current stimulation (tDCS) effective for chronic low back pain? A systematic review and meta-analysis. *J Neural Transm (Vienna)* 2020; **127**(9): 1257-70.

4. Anderson RJ, Craggs JG, Bialosky JE, et al. Temporal summation of second pain: variability in responses to a fixed protocol. *Eur J Pain* 2013; **17**(1): 67-74.

5. Antal A, Alekseichuk I, Bikson M, et al. Low intensity transcranial electric stimulation: Safety, ethical, legal regulatory and application guidelines. *Clin Neurophysiol* 2017; **128**(9): 1774-809.

6. Aoyagi K, He J, Nicol AL, et al. A Subgroup of Chronic Low Back Pain Patients With Central Sensitization. *Clin J Pain* 2019; **35**(11): 869-79.

7. Arendt-Nielsen L, Andresen T, Malver LP, Oksche A, Mansikka H, Drewes AM. A double-blind, placebo-controlled study on the effect of buprenorphine and fentanyl on descending pain modulation: a human experimental study. *Clin J Pain* 2012; **28**(7): 623-7.

8. Arendt-Nielsen L, Brennum J, Sindrup S, Bak P. Electrophysiological and psychophysical quantification of temporal summation in the human nociceptive system. *Eur J Appl Physiol Occup Physiol* 1994; **68**(3): 266-73.

9. Arendt-Nielsen L, Curatolo M, Drewes A. Human experimental pain models in drug development: translational pain research. *Curr Opin Investig Drugs* 2007; **8**(1): 41-53.

10. Arendt-Nielsen L, Egsgaard LL, Petersen KK, et al. A mechanism-based pain sensitivity index to characterize knee osteoarthritis patients with different disease stages and pain levels. *Eur J Pain* 2015; **19**(10): 1406-17.

11. Arendt-Nielsen L, Morlion B, Perrot S, et al. Assessment and manifestation of central sensitisation across different chronic pain conditions. *Eur J Pain* 2018; **22**(2): 216-41.

12. Arendt-Nielsen L, Nie H, Laursen MB, et al. Sensitization in patients with painful knee osteoarthritis. *Pain* 2010; **149**(3): 573-81.

13. Arendt-Nielsen L, Petersen-Felix S, Fischer M, Bak P, Bjerring P, Zbinden AM. The effect of N-methyl-D-aspartate antagonist (ketamine) on single and repeated nociceptive stimuli: a placebo-controlled experimental human study. *Anesth Analg* 1995; **81**(1): 63-8.

14. Arendt-Nielsen L, Sluka KA, Nie HL. Experimental muscle pain impairs descending inhibition. *Pain* 2008; **140**(3): 465-71.

15. Asmundson GJ, Katz J. Understanding the co-occurrence of anxiety disorders and chronic pain: state-of-the-art. *Depress Anxiety* 2009; **26**(10): 888-901.

16. Aspinall SL, Jacques A, Leboeuf-Yde C, Etherington SJ, Walker BF. No difference in pressure pain threshold and temporal summation after lumbar spinal manipulation compared to sham: A randomised controlled trial in adults with low back pain. *Musculoskelet Sci Pract* 2019; **43**: 18-25.

17. Axen I. Pain-related Sleep Disturbance: A Prospective Study With Repeated Measures. *Clin J Pain* 2016; **32**(3): 254-9.

18. Babenko VV, Graven-Nielsen T, Svensson P, Drewes AM, Jensen TS, Arendt-Nielsen L. Experimental human muscle pain induced by intramuscular injections of bradykinin, serotonin, and substance P. *Eur J Pain* 1999; **3**(2): 93-102.

19. Bahammam MA. Validity and reliability of an Arabic version of the state-trait anxiety inventory in a Saudi dental setting. *Saudi Med J* 2016; **37**(6): 668-74.

20. 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.

21. Bannister K, Bee LA, Dickenson AH. Preclinical and early clinical investigations related to monoaminergic pain modulation. *Neurotherapeutics* 2009; **6**(4): 703-12.

22. Bannister K, Dickenson AH. What do monoamines do in pain modulation? *Curr Opin Support Palliat Care* 2016; **10**(2): 143-8.

23. Bannister K, Dickenson AH. The plasticity of descending controls in pain: translational probing. *J Physiol* 2017; **595**(13): 4159-66.

24. Bannister K, Dickenson AH. Central Nervous System Targets: Supraspinal Mechanisms of Analgesia. *Neurotherapeutics* 2020.

25. Bannister K, Patel R, Goncalves L, Townson L, Dickenson AH. Diffuse noxious inhibitory controls and nerve injury: restoring an imbalance between descending monoamine inhibitions and facilitations. *Pain* 2015; **156**(9): 1803-11.

26. Bartley EJ, Rhudy JL. Endogenous inhibition of the nociceptive flexion reflex (NFR) and pain ratings during the menstrual cycle in healthy women. *Annals of behavioral medicine : a publication of the Society of Behavioral Medicine* 2012; **43**(3): 343-51.

27. Beck AT, Guth D, Steer RA, Ball R. Screening for major depression disorders in medical inpatients with the Beck Depression Inventory for Primary Care. *Behav Res Ther* 1997; **35**(8): 785-91.

28. 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. *Physical therapy* 2009; **89**(12): 1292-303.

29. 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): 1-4.

30. Bishop MD, Horn ME, George SZ, Robinson ME. Self-reported pain and disability outcomes from an endogenous model of muscular back pain. *BMC Musculoskelet Disord* 2011; **12**: 35.

31. Biurrun Manresa JA, Fritsche R, Vuilleumier PH, et al. Is the conditioned pain modulation paradigm reliable? A test-retest assessment using the nociceptive withdrawal reflex. *PLoS One* 2014; **9**(6): e100241.

32. Biurrun Manresa JA, Neziri AY, Curatolo M, Arendt-Nielsen L, Andersen OK. Test-retest reliability of the nociceptive withdrawal reflex and electrical pain thresholds after single and repeated stimulation in patients with chronic low back pain. *European Journal of Applied Physiology* 2011; **111**(1): 83-92.

33. Biurrun Manresa JA, Neziri AY, Curatolo M, Arendt-Nielsen L, Andersen OK. Reflex receptive fields are enlarged in patients with musculoskeletal low back and neck pain. *Pain* 2013; **154**(8): 1318-24.

34. Blumenstiel K, Gerhardt A, Rolke R, et al. Quantitative sensory testing profiles in chronic back pain are distinct from those in fibromyalgia. *Clinical Journal of Pain* 2011; **27**(8): 682-90.

35. Borkan JM, Cherkin DC. An agenda for primary care research on low back pain. *Spine (Phila Pa 1976)* 1996; **21**(24): 2880-4.

36. Bosma RL, Ameli Mojarad E, Leung L, Pukall C, Staud R, Stroman PW. Neural correlates of temporal summation of second pain in the human brainstem and spinal cord. *Hum Brain Mapp* 2015; **36**(12): 5038-50.

37. Bosma RL, Mojarad EA, Leung L, Pukall C, Staud R, Stroman PW. FMRI of spinal and supra-spinal correlates of temporal pain summation in fibromyalgia patients. *Hum Brain Mapp* 2016; **37**(4): 1349-60.

38. Bouhassira D, Le Bars D, Bolgert F, Laplane D, Willer JC. Diffuse noxious inhibitory controls in humans: a neurophysiological investigation of a patient with a form of Brown-Sequard syndrome. *Ann Neurol* 1993; **34**(4): 536-43.

39. Brands AM, Schmidt AJ. Learning processes in the persistence behavior of chronic low back pain patients with repeated acute pain stimulation. *Pain* 1987; **30**(3): 329-37.

40. Brinjikji W, Luetmer PH, Comstock B, et al. Systematic literature review of imaging features of spinal degeneration in asymptomatic populations. *AJNR Am J Neuroradiol* 2015; **36**(4): 811-6.

41. Brunoni AR, Schestatsky P, Lotufo PA, Bensenor IM, Fregni F. Comparison of blinding effectiveness between sham tDCS and placebo sertraline in a 6-week major depression randomized clinical trial. *Clin Neurophysiol* 2014; **125**(2): 298-305.

42. Buchgreitz L, Lyngberg AC, Bendtsen L, Jensen R. Increased pain sensitivity is not a risk factor but a consequence of frequent headache: a population-based follow-up study. *Pain* 2008; **137**(3): 623-30.

43. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989; **28**(2): 193-213.

44. Cardenas-Rojas A, Pacheco-Barrios K, Giannoni-Luza S, Rivera-Torrejon O, Fregni F. Noninvasive brain stimulation combined with exercise in chronic pain: a systematic review and meta-analysis. *Expert Rev Neurother* 2020; **20**(4): 401-12.

45. Carlsson AM. Assessment of chronic pain. I. Aspects of the reliability and validity of the visual analogue scale. *Pain* 1983; **16**(1): 87-101.

46. Carriere JS, Martel MO, Meints SM, Cornelius MC, Edwards RR. What do you expect? Catastrophizing mediates associations between expectancies and pain-facilitatory processes. *Eur J Pain* 2019; **23**(4): 800-11.

47. Carvalho FA, Morelhao PK, Franco MR, et al. Reliability and validity of two multidimensional self-reported physical activity questionnaires in people with chronic low back pain. *Musculoskelet Sci Pract* 2017; **27**: 65-70.

48. Carvalho HW, Andreoli SB, Lara DR, et al. Structural validity and reliability of the Positive and Negative Affect Schedule (PANAS): evidence from a large Brazilian community sample. *Braz J Psychiatry* 2013; **35**(2): 169-72.

49. Castelo-Branco L, Uygur Kucukseymen E, Duarte D, et al. Optimised transcranial direct current stimulation (tDCS) for fibromyalgia-targeting the endogenous pain control system: a randomised, double-blind, factorial clinical trial protocol. *BMJ Open* 2019; **9**(10): e032710.

50. Cathcart S, Winefield AH, Rolan P, Lushington K. Reliability of temporal summation and diffuse noxious inhibitory control. *Pain Res Manag* 2009; **14**(6): 433-8.

51. Ceko M, Frangos E, Gracely J, et al. Default mode network changes in fibromyalgia patients are largely dependent on current clinical pain. *Neuroimage* 2020; **216**: 116877.

52. Christensen KS, O'Sullivan K, Palsson TS. Conditioned Pain Modulation Efficiency is Associated with Pain Catastrophizing in Patients with Chronic Low Back Pain. *Clin J Pain* 2020.

53. Coronado RA, Bialosky JE, Robinson ME, George SZ. Pain sensitivity subgroups in individuals with spine pain: potential relevance to short-term clinical outcome. *Physical therapy* 2014; **94**(8): 1111-22.

54. Correa JB, Costa LO, de Oliveira NT, Sluka KA, Liebano RE. Central sensitization and changes in conditioned pain modulation in people with chronic nonspecific low back pain: a case-control study. *Exp Brain Res* 2015; **233**(8): 2391-9.

55. Correa JB, Costa LO, Oliveira NT, Lima WP, Sluka KA, Liebano RE. Effects of the carrier frequency of interferential current on pain modulation and central hypersensitivity in people with chronic nonspecific low back pain: A randomized placebo-controlled trial. *Eur J Pain* 2016; **20**(10): 1653-66.

56. Craig CL, Marshall AL, Sjostrom M, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc* 2003; **35**(8): 1381-95.

57. Crawford JR, Henry JD. The positive and negative affect schedule (PANAS): construct validity, measurement properties and normative data in a large non-clinical sample. *Br J Clin Psychol* 2004; **43**(Pt 3): 245-65.

58. Cummins TM, Kucharczyk MM, Graven-Nielsen T, Bannister K. Activation of the descending pain modulatory system using cuff pressure algometry: Back translation from man to rat. *Eur J Pain* 2020.

59. David M, Moraes AA, Costa MLD, Franco CIF. Transcranial direct current stimulation in the modulation of neuropathic pain: a systematic review. *Neurol Res* 2018; **40**(7): 555-63.

60. Davis KD, Cheng JC. Differentiating trait pain from state pain: a window into brain mechanisms underlying how we experience and cope with pain. *Pain Rep* 2019; **4**(4): e735.

61. De Broucker T, Cesaro P, Willer JC, Le Bars D. Diffuse noxious inhibitory controls in man. Involvement of the spinoreticular tract. *Brain* 1990; **113 (Pt 4)**: 1223-34.

62. den Bandt HL, Paulis WD, Beckwee D, Ickmans K, Nijs J, Voogt L. 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. *J Orthop Sports Phys Ther* 2019; **49**(10): 698-715.

63. Dhondt E, Van Oosterwijck S, Coppieters I, Danneels L, Van Oosterwijck J. Effects of Conditioned Pain Modulation on the Nociceptive Flexion Reflex in Healthy People: A Systematic Review. *Clin J Pain* 2019; **35**(9): 794-807.

64. Dickenson AH, Sullivan AF. Evidence for a role of the NMDA receptor in the frequency dependent potentiation of deep rat dorsal horn nociceptive neurones following C fibre stimulation. *Neuropharmacology* 1987; **26**(8): 1235-8.

65. Diers M, Koeppe C, Diesch E, et al. Central processing of acute muscle pain in chronic low back pain patients: an EEG mapping study. *J Clin Neurophysiol* 2007; **24**(1): 76-83.

66. Dionne CE, Dunn KM, Croft PR, et al. A consensus approach toward the standardization of back pain definitions for use in prevalence studies. *Spine (Phila Pa 1976)* 2008; **33**(1): 95-103.

67. Disease GBD, Injury I, Prevalence C. 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. *Lancet* 2016; **388**(10053): 1545-602.

68. Dubois JD, Cantin V, Piche M, Descarreaux M. Physiological and Psychological Predictors of Short-Term Disability in Workers with a History of Low Back Pain: A Longitudinal Study. *PLoS One* 2016; **11**(10): e0165478.

69. Edwards RR, Dolman AJ, Martel MO, et al. Variability in conditioned pain modulation predicts response to NSAID treatment in patients with knee osteoarthritis. *BMC Musculoskelet Disord* 2016; **17**: 284.

70. Edwards RR, Dolman AJ, Michna E, et al. Changes in Pain Sensitivity and Pain Modulation During Oral Opioid Treatment: The Impact of Negative Affect. *Pain Med* 2016; **17**(10): 1882-91.

71. Edwards RR, Dolman AJ, Michna E, et al. Changes in pain sensitivity and pain modulation during oral opioid treatment: The impact of negative affect. *Pain Medicine (United States)* 2016; **17**(10): 1882-91.

72. Edwards RR, Dworkin RH, Sullivan MD, Turk DC, Wasan AD. The Role of Psychosocial Processes in the Development and Maintenance of Chronic Pain. *J Pain* 2016; **17**(9 Suppl): T70-92.

73. Eichhorn N, Treede RD, Schuh-Hofer S. The Role of Sex in Sleep Deprivation Related Changes of Nociception and Conditioned Pain Modulation. *Neuroscience* 2018; **387**: 191-200.

74. Eisenberg E, Burstein Y, Suzan E, Treister R, Aviram J. Spinal cord stimulation attenuates temporal summation in patients with neuropathic pain. *Pain* 2015; **156**(3): 381-5.

75. Fernandes C, Pidal-Miranda M, Samartin-Veiga N, Carrillo-de-la-Pena MT. Conditioned pain modulation as a biomarker of chronic pain: a systematic review of its concurrent validity. *Pain* 2019; **160**(12): 2679-90.

76. Fernandez-Blazquez MA, Avila-Villanueva M, Lopez-Pina JA, Zea-Sevilla MA, Frades-Payo B. Psychometric properties of a new short version of the State-Trait Anxiety Inventory (STAI) for the assessment of anxiety in the elderly. *Neurologia* 2015; **30**(6): 352-8.

77. Finan PH, Goodin BR, Smith MT. The association of sleep and pain: an update and a path forward. *J Pain* 2013; **14**(12): 1539-52.

78. Finocchietti S, Nielsen M, Morch CD, Arendt-Nielsen L, Graven-Nielsen T. Pressure-induced muscle pain and tissue biomechanics: a computational and experimental study. *Eur J Pain* 2011; **15**(1): 36-44.

79. Fjeld OR, Grotle M, Matre D, et al. Predicting the outcome of persistent sciatica using conditioned pain modulation: 1-year results from a prospective cohort study. *Scand J Pain* 2019; **20**(1): 69-75.

80. Flood A, Waddington G, Cathcart S. High-Definition Transcranial Direct Current Stimulation Enhances Conditioned Pain Modulation in Healthy Volunteers: A Randomized Trial. *J Pain* 2016; **17**(5): 600-5.

81. Foucher KC, Chmell SJ, Courtney CA. Duration of symptoms is associated with conditioned pain modulation and somatosensory measures in knee osteoarthritis. *J Orthop Res* 2019; **37**(1): 136-42.

82. France CR, Burns JW, Gupta RK, et al. Expectancy Effects on Conditioned Pain Modulation Are Not Influenced by Naloxone or Morphine. *Annals of behavioral medicine : a publication of the Society of Behavioral Medicine* 2016; **50**(4): 497-505.

83. Freynhagen R, Baron R, Gockel U, Tolle TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. *Curr Med Res Opin* 2006; **22**(10): 1911-20.

84. Freynhagen R, Rolke R, Baron R, et al. Pseudoradicular and radicular low-back pain--a disease continuum rather than different entities? Answers from quantitative sensory testing. *Pain* 2008; **135**(1-2): 65-74.

85. Gagne M, Cote I, Boulet M, Jutzeler CR, Kramer JLK, Mercier C. Conditioned Pain Modulation Decreases Over Time in Patients With Neuropathic Pain Following a Spinal Cord Injury. *Neurorehabil Neural Repair* 2020: 1545968320962497.

86. Gaudry E, Vagg P, Spielberger CD. Validation of the State-Trait Distinction in Anxiety Research. *Multivariate Behav Res* 1975; **10**(3): 331-41.

87. Gelfand S. The Relationship of Experimental Pain Tolerance to Pain Threshold. *Can J Psychol* 1964; **18**: 36-42.

88. George SZ, Wittmer VT, Fillingim RB, Robinson ME. Fear-avoidance beliefs and temporal summation of evoked thermal pain influence self-report of disability in patients with chronic low back pain. *Journal of Occupational Rehabilitation* 2006; **16**(1): 95-108.

89. George SZ, Wittmer VT, Fillingim RB, Robinson ME. Fear-avoidance beliefs and temporal summation of evoked thermal pain influence self-report of disability in patients with chronic low back pain. *J Occup Rehabil* 2006; **16**(1): 95-108.

90. George SZ, Wittmer VT, Fillingim RB, Robinson ME. Sex and pain-related psychological variables are associated with thermal pain sensitivity for patients with chronic low back pain. *J Pain* 2007; **8**(1): 2-10.

91. George SZ, Wittmer VT, Fillingim RB, Robinson ME. Sex and Pain-Related Psychological Variables Are Associated With Thermal Pain Sensitivity for Patients With Chronic Low Back Pain. *Journal of Pain* 2007; **8**(1): 2-10.

92. Georgopoulos V, Akin-Akinyosoye K, Zhang W, McWilliams DF, Hendrick P, Walsh DA. Quantitative sensory testing and predicting outcomes for musculoskeletal pain, disability, and negative affect: a systematic review and meta-analysis. *Pain* 2019; **160**(9): 1920-32.

93. Gerhardt A, Eich W, Janke S, Leisner S, Treede RD, Tesarz J. Chronic Widespread Back Pain is Distinct from Chronic Local Back Pain. *Clinical Journal of Pain* 2016; **32**(7): 568-79.

94. Gerhardt A, Eich W, Treede RD, Tesarz J. Conditioned pain modulation in patients with nonspecific chronic back pain with chronic local pain, chronic widespread pain, and fibromyalgia. *Pain* 2017; **158**(3): 430-9.

95. Geva N, Defrin R. Enhanced pain modulation among triathletes: a possible explanation for their exceptional capabilities. *Pain* 2013; **154**(11): 2317-23.

96. Geva N, Defrin R. Opposite Effects of Stress on Pain Modulation Depend on the Magnitude of Individual Stress Response. *J Pain* 2018; **19**(4): 360-71.

97. Giannoni-Luza S, Pacheco-Barrios K, Cardenas-Rojas A, et al. Non-invasive motor cortex stimulation effects on quantitative sensory testing (QST) in healthy and chronic pain subjects: a systematic review and meta-analysis. *Pain* 2020.

98. Gibson W, Arendt-Nielsen L, Graven-Nielsen T. Delayed onset muscle soreness at tendon-bone junction and muscle tissue is associated with facilitated referred pain. *Exp Brain Res* 2006; **174**(2): 351-60.

99. Giesecke T, Gracely RH, Grant MA, et al. Evidence of augmented central pain processing in idiopathic chronic low back pain. *Arthritis Rheum* 2004; **50**(2): 613-23.

100. Goubert D, Danneels L, Graven-Nielsen T, Descheemaeker F, Meeus M. Differences in pain processing between patients with chronic low back pain, recurrent low back pain, and fibromyalgia. *Pain Physician* 2017; **20**(4): 307-18.

101. Goudman L, Huysmans E, Coppieters I, et al. Electrical (Pain) Thresholds and Conditioned Pain Modulation in Patients with Low Back-Related Leg Pain and Patients with Failed Back Surgery Syndrome: A Cross-Sectional Pilot Study. *Pain Med* 2020; **21**(3): 538-47.

102. Graven-Nielsen T, Arendt-Nielsen L. Induction and assessment of muscle pain, referred pain, and muscular hyperalgesia. *Curr Pain Headache Rep* 2003; **7**(6): 443-51.

103. Graven-Nielsen T, Izumi M, Petersen KK, Arendt-Nielsen L. User-independent assessment of conditioning pain modulation by cuff pressure algometry. *Eur J Pain* 2017; **21**(3): 552-61.

104. Graven-Nielsen T, Jansson Y, Segerdahl M, et al. Experimental pain by ischaemic contractions compared with pain by intramuscular infusions of adenosine and hypertonic saline. *Eur J Pain* 2003; **7**(1): 93-102.

105. 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.

106. Graven-Nielsen T, Wodehouse T, Langford RM, Arendt-Nielsen L, Kidd BL. Normalization of widespread hyperesthesia and facilitated spatial summation of deep-tissue pain in knee osteoarthritis patients after knee replacement. *Arthritis Rheum* 2012; **64**(9): 2907-16.

107. Grinberg K, Granot M, Lowenstein L, Abramov L, Weissman-Fogel I. A common pronociceptive pain modulation profile typifying subgroups of chronic pelvic pain syndromes is interrelated with enhanced clinical pain. *Pain* 2017; **158**(6): 1021-9.

108. Grosen K, Fischer IW, Olesen AE, Drewes AM. Can quantitative sensory testing predict responses to analgesic treatment? *Eur J Pain* 2013; **17**(9): 1267-80.

109. Guirimand F, Dupont X, Brasseur L, Chauvin M, Bouhassira D. The effects of ketamine on the temporal summation (wind-up) of the R(III) nociceptive flexion reflex and pain in humans. *Anesth Analg* 2000; **90**(2): 408-14.

110. Gupta A, McBeth J, Macfarlane GJ, et al. Pressure pain thresholds and tender point counts as predictors of new chronic widespread pain in somatising subjects. *Ann Rheum Dis* 2007; **66**(4): 517-21.

111. Gustafson LW, Gabel P, Hammer A, et al. Validity and reliability of State-Trait Anxiety Inventory in Danish women aged 45 years and older with abnormal cervical screening results. *BMC Med Res Methodol* 2020; **20**(1): 89.

112. Hackett J, Naugle KE, Naugle KM. The Decline of Endogenous Pain Modulation With Aging: A Meta-Analysis of Temporal Summation and Conditioned Pain Modulation. *J Pain* 2019.

113. Hanna F, Daas RN, El-Shareif TJ, Al-Marridi HH, Al-Rojoub ZM, Adegboye OA. The Relationship Between Sedentary Behavior, Back Pain, and Psychosocial Correlates Among University Employees. *Front Public Health* 2019; **7**: 80.

114. Hartvigsen J, Hancock MJ, Kongsted A, et al. What low back pain is and why we need to pay attention. *Lancet* 2018; **391**(10137): 2356-67.

115. Hayashi K, Shiozawa S, Ozaki N, Mizumura K, Graven-Nielsen T. Repeated intramuscular injections of nerve growth factor induced progressive muscle hyperalgesia, facilitated temporal summation, and expanded pain areas. *Pain* 2013; **154**(11): 2344-52.

116. Heffner KL, France CR, Trost Z, Ng HM, Pigeon WR. Chronic low back pain, sleep disturbance, and interleukin-6. *Clin J Pain* 2011; **27**(1): 35-41.

117. Hellstrom B, Anderberg UM. Pain perception across the menstrual cycle phases in women with chronic pain. *Percept Mot Skills* 2003; **96**(1): 201-11.

118. Heneweer H, Vanhees L, Picavet HS. Physical activity and low back pain: a U-shaped relation? *Pain* 2009; **143**(1-2): 21-5.

119. Henschke N, Maher CG, Refshauge KM, et al. Prevalence of and screening for serious spinal pathology in patients presenting to primary care settings with acute low back pain. *Arthritis Rheum* 2009; **60**(10): 3072-80.

120. Heredia-Rizo AM, Petersen KK, Madeleine P, Arendt-Nielsen L. Clinical Outcomes and Central Pain Mechanisms are Improved After Upper Trapezius Eccentric Training in Female Computer Users With Chronic Neck/Shoulder Pain. *Clin J Pain* 2019; **35**(1): 65-76.

121. Hermans L, Van Oosterwijck J, Goubert D, et al. Inventory of Personal Factors Influencing Conditioned Pain Modulation in Healthy People: A Systematic Literature Review. *Pain Pract* 2016; **16**(6): 758-69.

122. Hermesdorf M, Berger K, Baune BT, Wellmann J, Ruscheweyh R, Wersching H. Pain Sensitivity in Patients With Major Depression: Differential Effect of Pain Sensitivity Measures, Somatic Cofactors, and Disease Characteristics. *J Pain* 2016; **17**(5): 606-16.

123. Hestbaek L, Leboeuf-Yde C, Engberg M, Lauritzen T, Bruun NH, Manniche C. The course of low back pain in a general population. Results from a 5-year prospective study. *J Manipulative Physiol Ther* 2003; **26**(4): 213-9.

124. Heuch I, Hagen K, Heuch I, Nygaard O, Zwart JA. The impact of body mass index on the prevalence of low back pain: the HUNT study. *Spine (Phila Pa 1976)* 2010; **35**(7): 764-8.

125. Heuch I, Heuch I, Hagen K, Zwart JA. Is there a U-shaped relationship between physical activity in leisure time and risk of chronic low back pain? A follow-up in the HUNT Study. *BMC Public Health* 2016; **16**: 306.

126. Hill JC, Dunn KM, Lewis M, et al. A primary care back pain screening tool: identifying patient subgroups for initial treatment. *Arthritis Rheum* 2008; **59**(5): 632-41.

127. Hill JC, Dunn KM, Main CJ, Hay EM. Subgrouping low back pain: a comparison of the STarT Back Tool with the Orebro Musculoskeletal Pain Screening Questionnaire. *Eur J Pain* 2010; **14**(1): 83-9.

128. Hodges P, van den Hoorn W, Dawson A, Cholewicki J. Changes in the mechanical properties of the trunk in low back pain may be associated with recurrence. *J Biomech* 2009; **42**(1): 61-6.

129. Hoeger Bement M, Petersen KK, Sorensen LB, Andersen HH, Graven-Nielsen T. Temporal aspects of endogenous pain modulation during a noxious stimulus prolonged for 1 day. *Eur J Pain* 2020; **24**(4): 752-60.

130. Hoegh M, Petersen KK, Graven-Nielsen T. Effects of repeated conditioning pain modulation in healthy volunteers. *Eur J Pain* 2018; **22**(10): 1833-43.

131. Hoegh M, Seminowicz DA, Graven-Nielsen T. Delayed effects of attention on pain sensitivity and conditioned pain modulation. *Eur J Pain* 2019; **23**(10): 1850-62.

132. Hoheisel U, Mense S. Long-term changes in discharge behaviour of cat dorsal horn neurones following noxious stimulation of deep tissues. *Pain* 1989; **36**(2): 239-47.

133. Holley AL, Wilson AC, Palermo TM. Predictors of the transition from acute to persistent musculoskeletal pain in children and adolescents: a prospective study. *Pain* 2017; **158**(5): 794-801.

134. Horvath JC, Forte JD, Carter O. Evidence that transcranial direct current stimulation (tDCS) generates little-to-no reliable neurophysiologic effect beyond MEP amplitude modulation in healthy human subjects: A systematic review. *Neuropsychologia* 2015; **66**: 213-36.

135. Hoy D, March L, Brooks P, et al. Measuring the global burden of low back pain. *Best Pract Res Clin Rheumatol* 2010; **24**(2): 155-65.

136. Hubscher M, Moloney N, Leaver A, Rebbeck T, McAuley JH, Refshauge KM. Relationship between quantitative sensory testing and pain or disability in people with spinal pain-a systematic review and meta-analysis. *Pain* 2013; **154**(9): 1497-504.

137. Hübscher 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. *Clinical Journal of Pain* 2014; **30**(10): 886-93.

138. Iacovides S, Avidon I, Baker FC. Does pain vary across the menstrual cycle? A review. *Eur J Pain* 2015; **19**(10): 1389-405.

139. Ibancos-Losada MDR, Osuna-Perez MC, Castellote-Caballero MY, Diaz-Fernandez A. Conditioned Pain Modulation Effectiveness: An Experimental Study Comparing Test Paradigms and Analyzing Potential Predictors in a Healthy Population. *Brain Sci* 2020; **10**(9).

140. Imai Y, Petersen KK, Morch CD, Arendt Nielsen L. Comparing test-retest reliability and magnitude of conditioned pain modulation using different combinations of test and conditioning stimuli. *Somatosens Mot Res* 2016; **33**(3-4): 169-77.

141. Izumi M, Petersen KK, Laursen MB, Arendt-Nielsen L, Graven-Nielsen T. Facilitated temporal summation of pain correlates with clinical pain intensity after hip arthroplasty. *Pain* 2017; **158**(2): 323-32.

142. Kapitza KP, Passie T, Bernateck M, Karst M. First non-contingent respiratory biofeedback placebo versus contingent biofeedback in patients with chronic low back pain: a randomized, controlled, double-blind trial. *Appl Psychophysiol Biofeedback* 2010; **35**(3): 207-17.

143. Kelly GA, Blake C, Power CK, O'Keeffe D, Fullen BM. The association between chronic low back pain and sleep: a systematic review. *Clin J Pain* 2011; **27**(2): 169-81.

144. Kemp J, Despres O, Dufour A. Unreliability of the visual analog scale in experimental pain assessment: a sensitivity and evoked potentials study. *Pain Physician* 2012; **15**(5): E693-9.

145. Kennedy DL, Kemp HI, Ridout D, Yarnitsky D, Rice AS. Reliability of conditioned pain modulation: a systematic review. *Pain* 2016; **157**(11): 2410-9.

146. Kessler SK, Turkeltaub PE, Benson JG, Hamilton RH. Differences in the experience of active and sham transcranial direct current stimulation. *Brain Stimul* 2012; **5**(2): 155-62.

147. Kisler LB, Weissman-Fogel I, Coghill RC, Sprecher E, Yarnitsky D, Granovsky Y. Individualization of Migraine Prevention: A Randomized Controlled Trial of Psychophysical-based Prediction of Duloxetine Efficacy. *Clin J Pain* 2019; **35**(9): 753-65.

148. Kleinböhl D, Görtelmeyer R, Bender HJ, Hölzl R. Amantadine sulfate reduces experimental sensitization and pain in chronic back pain patients. *Anesthesia and Analgesia* 2006; **102**(3): 840-7.

149. Klyne DM, Moseley GL, Sterling M, Barbe MF, Hodges PW. Individual Variation in Pain Sensitivity and Conditioned Pain Modulation in Acute Low Back Pain: Effect of Stimulus Type, Sleep, and Psychological and Lifestyle Factors. *Journal of Pain* 2018; **19**(8): 942.e1-.e18.

150. Klyne DM, Moseley GL, Sterling M, Barbe MF, Hodges PW. Are Signs of Central Sensitization in Acute Low Back Pain a Precursor to Poor Outcome? *J Pain* 2019; **20**(8): 994-1009.

151. Klyne DM, Schmid AB, Moseley GL, Sterling M, Hodges PW. Effect of types and anatomic arrangement of painful stimuli on conditioned pain modulation. *J Pain* 2015; **16**(2): 176-85.

152. Knotkova H, Borckardt JJ, Riggs A, DaSilva AF. Transcranial Direct Current Stimulation Potential for Pain Management. In: Knotkova H, Nitsche MA, Bikson M, Woods AJ, eds. Practical Guide to Transcranial Direct Current Stimulation: Principles, Procedures and Applications. Cham: Springer International Publishing; 2019: 541-67.

153. Kosek E, Ekholm J, Hansson P. Pressure pain thresholds in different tissues in one body region. The influence of skin sensitivity in pressure algometry. *Scand J Rehabil Med* 1999; **31**(2): 89-93.

154. Kosek E, Ordeberg G. Lack of pressure pain modulation by heterotopic noxious conditioning stimulation in patients with painful osteoarthritis before, but not following, surgical pain relief. *Pain* 2000; **88**(1): 69-78.

155. Krafft S, Göhmann HD, Sommer J, Straube A, Ruscheweyh R. Learned control over spinal nociception in patients with chronic back pain. *European journal of pain (london, england)* 2017; **21**(9): 1538-49.

156. Kregel J, Meeus M, Malfliet A, et al. Structural and functional brain abnormalities in chronic low back pain: A systematic review. *Semin Arthritis Rheum* 2015; **45**(2): 229-37.

157. Kregel J, Schumacher C, Dolphens M, et al. Convergent Validity of the Dutch Central Sensitization Inventory: Associations with Psychophysical Pain Measures, Quality of Life, Disability, and Pain Cognitions in Patients with Chronic Spinal Pain. *Pain Practice* 2018; **18**(6): 777-87.

158. Kristensen JD, Svensson B, Gordh T, Jr. The NMDA-receptor antagonist CPP abolishes neurogenic 'wind-up pain' after intrathecal administration in humans. *Pain* 1992; **51**(2): 249-53.

159. Kummer KK, Mitric M, Kalpachidou T, Kress M. The Medial Prefrontal Cortex as a Central Hub for Mental Comorbidities Associated with Chronic Pain. *Int J Mol Sci* 2020; **21**(10).

160. Ladouceur A, Rustamov N, Dubois JD, et al. Inhibition of Pain and Pain-Related Brain Activity by Heterotopic Noxious Counter-Stimulation and Selective Attention in Chronic Non-Specific Low Back Pain. *Neuroscience* 2018; **387**: 201-13.

161. Lardon A, Dubois JD, Cantin V, Piché M, Descarreaux M. Predictors of disability and absenteeism in workers with non-specific low back pain: A longitudinal 15-month study. *Applied Ergonomics* 2018; **68**: 176-85.

162. Larsen LH, Hirata RP, Graven-Nielsen T. Pain-evoked trunk muscle activity changes during fatigue and DOMS. *Eur J Pain* 2017.

163. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *J Pain* 2009; **10**(9): 895-926.

164. Lauderdale DS, Knutson KL, Yan LL, Liu K, Rathouz PJ. Self-reported and measured sleep duration: how similar are they? *Epidemiology* 2008; **19**(6): 838-45.

165. Le Bars D, Dickenson AH, Besson JM. Diffuse noxious inhibitory controls (DNIC). I. Effects on dorsal horn convergent neurones in the rat. *Pain* 1979; **6**(3): 283-304.

166. Le Bars D, Dickenson AH, Besson JM. Diffuse noxious inhibitory controls (DNIC). II. Lack of effect on non-convergent neurones, supraspinal involvement and theoretical implications. *Pain* 1979; **6**(3): 305-27.

167. Leboeuf-Yde C, Lauritsen JM, Lauritzen T. Why has the search for causes of low back pain largely been nonconclusive? *Spine (Phila Pa 1976)* 1997; **22**(8): 877-81.

168. Lee PH, Macfarlane DJ, Lam TH, Stewart SM. Validity of the International Physical Activity Questionnaire Short Form (IPAQ-SF): a systematic review. *Int J Behav Nutr Phys Act* 2011; **8**: 115.

169. Leemans L, Elma O, Nijs J, et al. Transcutaneous electrical nerve stimulation and heat to reduce pain in a chronic low back pain population: a randomized controlled clinical trial. *Braz J Phys Ther* 2020.

170. Leite PMS, Mendonca ARC, Maciel LYS, et al. Does Electroacupuncture Treatment Reduce Pain and Change Quantitative Sensory Testing Responses in Patients with Chronic Nonspecific Low Back Pain? A Randomized Controlled Clinical Trial. *Evid Based Complement Alternat Med* 2018; **2018**: 8586746.

171. Leresche L, Turner JA, Saunders K, Shortreed SM, Von Korff M. Psychophysical tests as predictors of back pain chronicity in primary care. *Journal of Pain* 2013; **14**(12): 1663-70.

172. Lewis GN, Heales L, Rice DA, Rome K, McNair PJ. Reliability of the conditioned pain modulation paradigm to assess endogenous inhibitory pain pathways. *Pain Res Manag* 2012; **17**(2): 98-102.

173. Lewis GN, Rice DA, McNair PJ. Conditioned pain modulation in populations with chronic pain: a systematic review and meta-analysis. *J Pain* 2012; **13**(10): 936-44.

174. Li LM, Uehara K, Hanakawa T. The contribution of interindividual factors to variability of response in transcranial direct current stimulation studies. *Front Cell Neurosci* 2015; **9**: 181.

175. Li T, Zhang S, Kurata J. Suppressed descending pain modulatory and enhanced sensorimotor networks in patients with chronic low back pain. *J Anesth* 2018; **32**(6): 831-43.

176. Lie MU, Petriu E, Matre D, et al. Psychophysical or spinal reflex measures when assessing conditioned pain modulation? *Eur J Pain* 2019; **23**(10): 1879-89.

177. Lin CC, Li Q, Williams CM, et al. The economic burden of guideline-recommended first line care for acute low back pain. *Eur Spine J* 2018; **27**(1): 109-16.

178. Lindskou TA, Christensen SW, Graven-Nielsen T. Cuff Algometry for Estimation of Hyperalgesia and Pain Summation. *Pain Med* 2017; **18**(3): 468-76.

179. Lloyd DM, Wittkopf PG, Arendsen LJ, Jones AKP. Is Transcranial Direct Current Stimulation (tDCS) Effective for the Treatment of Pain in Fibromyalgia? A Systematic Review and Meta-Analysis. *J Pain* 2020.

180. Lo Vecchio S, Petersen LJ, Finocchietti S, Gazerani P, Arendt-Nielsen L, Graven-Nielsen T. The Effect of Combined Skin and Deep Tissue Inflammatory Pain Models. *Pain Med* 2015; **16**(11): 2053-64.

181. Lockwood S, Dickenson AH. What goes up must come down: insights from studies on descending controls acting on spinal pain processing. *J Neural Transm (Vienna)* 2020; **127**(4): 541-9.

182. Lorish CD, Maisiak R. The Face Scale: a brief, nonverbal method for assessing patient mood. *Arthritis Rheum* 1986; **29**(7): 906-9.

183. Luedtke K, May A, Jurgens TP. No effect of a single session of transcranial direct current stimulation on experimentally induced pain in patients with chronic low back pain--an exploratory study. *PLoS One* 2012; **7**(11): e48857.

184. Luedtke K, Rushton A, Wright C, Geiss B, Juergens TP, May A. Transcranial direct current stimulation for the reduction of clinical and experimentally induced pain: a systematic review and meta-analysis. *Clin J Pain* 2012; **28**(5): 452-61.

185. Ma WF, Liu YC, Chen YF, Lane HY, Lai TJ, Huang LC. Evaluation of psychometric properties of the Chinese Mandarin version State-Trait Anxiety Inventory Y form in Taiwanese outpatients with anxiety disorders. *J Psychiatr Ment Health Nurs* 2013; **20**(6): 499-507.

186. Maetzel A, Li L. The economic burden of low back pain: a review of studies published between 1996 and 2001. *Best Pract Res Clin Rheumatol* 2002; **16**(1): 23-30.

187. Maher C, Underwood M, Buchbinder R. Non-specific low back pain. *Lancet* 2017; **389**(10070): 736-47.

188. Manafi-Khanian B, Arendt-Nielsen L, Frokjaer JB, Graven-Nielsen T. Deformation and pressure propagation in deep somatic tissue during painful cuff algometry. *Eur J Pain* 2015; **19**(10): 1456-66.

189. Maniadakis N, Gray A. The economic burden of back pain in the UK. *Pain* 2000; **84**(1): 95-103.

190. Marcuzzi A, Wrigley PJ, Dean CM, Graham PL, Hush JM. From acute to persistent low back pain: a longitudinal investigation of somatosensory changes using quantitative sensory testing-an exploratory study. *Pain Rep* 2018; **3**(2): e641.

191. Mariano TY, Burgess FW, Bowker M, et al. Transcranial Direct Current Stimulation for Affective Symptoms and Functioning in Chronic Low Back Pain: A Pilot Double-Blinded, Randomized, Placebo-Controlled Trial. *Pain Med* 2019; **20**(6): 1166-77.

192. Marin R, Cyhan T, Miklos W. Sleep disturbance in patients with chronic low back pain. *Am J Phys Med Rehabil* 2006; **85**(5): 430-5.

193. Martel MO, Wasan AD, Edwards RR. Sex differences in the stability of conditioned pain modulation (cpm) among patients with chronic pain. *Pain Medicine (United States)* 2013; **14**(11): 1757-68.

194. Martinez-Calderon J, Meeus M, Struyf F, et al. Psychological factors are associated with local and generalized pressure pain hypersensitivity, pain intensity, and function in people with chronic shoulder pain: A cross-sectional study. *Musculoskelet Sci Pract* 2019; **44**: 102064.

195. Matsuo Y, Kurata J, Sekiguchi M, Yoshida K, Nikaido T, Konno SI. Attenuation of cortical activity triggering descending pain inhibition in chronic low back pain patients: a functional magnetic resonance imaging study. *J Anesth* 2017; **31**(4): 523-30.

196. McPhee ME, Graven-Nielsen T. Recurrent low back pain patients demonstrate facilitated pronociceptive mechanisms when in pain, and impaired antinociceptive mechanisms with and without pain. *Pain* 2019; **160**(12): 2866-76.

197. Meints SM, Wang V, Edwards RR. Sex and Race Differences in Pain Sensitization among Patients with Chronic Low Back Pain. *Journal of Pain* 2018.

198. Meints SM, Wang V, Edwards RR. Sex and Race Differences in Pain Sensitization among Patients with Chronic Low Back Pain. *J Pain* 2018; **19**(12): 1461-70.

199. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. *Pain* 1975; **1**(3): 277-99.

200. Mendell LM, Wall PD. Responses of Single Dorsal Cord Cells to Peripheral Cutaneous Unmyelinated Fibres. *Nature* 1965; **206**: 97-9.

201. Mertens MG, Hermans L, Crombez G, et al. Comparison of five conditioned pain modulation paradigms and influencing personal factors in healthy adults. *Eur J Pain* 2020.

202. Metzger S, Poliakov B, Lautenbacher S. Differential effects of experimentally induced anxiety and fear on pain: the role of anxiety sensitivity. *J Pain Res* 2019; **12**: 1791-801.

203. Mibu A, Nishigami T, Tanaka K, Manfuku M, Yono S. Difference in the impact of central sensitization on pain-related symptoms between patients with chronic low back pain and knee osteoarthritis. *J Pain Res* 2019; **12**: 1757-65.

204. Micalos PS, Drinkwater EJ, Cannon J, Arendt-Nielsen L, Marino FE. Reliability of the nociceptive flexor reflex (RIII) threshold and association with Pain threshold. *Eur J Appl Physiol* 2009; **105**(1): 55-62.

205. Mlekusch S, Neziri AY, Limacher A, Juni P, Arendt-Nielsen L, Curatolo M. Conditioned pain modulation in patients with acute and chronic low back pain. *Clinical Journal of Pain* 2016; **32**(2): 116-21.

206. Mlekusch S, Schliessbach J, Camara RJ, Arendt-Nielsen L, Juni P, Curatolo M. Do central hypersensitivity and altered pain modulation predict the course of chronic low back and neck pain? *Clin J Pain* 2013; **29**(8): 673-80.

207. Moont R, Crispel Y, Lev R, Pud D, Yarnitsky D. Temporal changes in cortical activation during distraction from pain: a comparative LORETA study with conditioned pain modulation. *Brain Res* 2012; **1435**: 105-17.

208. Moont R, Pud D, Sprecher E, Sharvit G, Yarnitsky D. 'Pain inhibits pain' mechanisms: Is pain modulation simply due to distraction? *Pain* 2010; **150**(1): 113-20.

209. Mork H, Ashina M, Bendtsen L, Olesen J, Jensen R. Experimental muscle pain and tenderness following infusion of endogenous substances in humans. *Eur J Pain* 2003; **7**(2): 145-53.

210. Muller-Schwefe G, Morlion B, Ahlbeck K, et al. Treatment for chronic low back pain: the focus should change to multimodal management that reflects the underlying pain mechanisms. *Curr Med Res Opin* 2017; **33**(7): 1199-210.

211. Muller M, Curatolo M, Limacher A, et al. Predicting transition from acute to chronic low back pain with quantitative sensory tests - a prospective cohort study in the primary care setting. *Eur J Pain* 2018.

212. Mylius V, Borckardt JJ, Lefaucheur JP. Noninvasive cortical modulation of experimental pain. *Pain* 2012; **153**(7): 1350-63.

213. Nahman-Averbuch H, Nir RR, Sprecher E, Yarnitsky D. Psychological Factors and Conditioned Pain Modulation: A Meta-Analysis. *Clin J Pain* 2016; **32**(6): 541-54.

214. Nahman-Averbuch H, Yarnitsky D, Granovsky Y, Gerber E, Dagul P, Granot M. The role of stimulation parameters on the conditioned pain modulation response. *Scand J Pain* 2013; **4**(1): 10-4.

215. Naugle KM, Cruz-Almeida Y, Vierck CJ, Mauderli AP, Riley JL, 3rd. Age-related differences in conditioned pain modulation of sensitizing and desensitizing trends during response dependent stimulation. *Behav Brain Res* 2015; **289**: 61-8.

216. Naugle KM, Naugle KE, Fillingim RB, Samuels B, Riley JL, 3rd. Intensity thresholds for aerobic exercise-induced hypoalgesia. *Med Sci Sports Exerc* 2014; **46**(4): 817-25.

217. Naugle KM, Riley JL, 3rd. Self-reported physical activity predicts pain inhibitory and facilitatory function. *Med Sci Sports Exerc* 2014; **46**(3): 622-9.

218. Neisser U. Temperature thresholds for cutaneous pain. *J Appl Physiol* 1959; **14**(3): 368-72.

219. Netter FH. Atlas of Human Anatomy: Saunders/Elsevier; 2014.

220. Neupane S, Karstad K, Hallman DM, Rugulies R, Holtermann A. Objectively measured versus self-reported occupational physical activity and multisite musculoskeletal pain: a prospective follow-up study at 20 nursing homes in Denmark. *Int Arch Occup Environ Health* 2020; **93**(3): 381-9.

221. Neziri AY, Curatolo M, Limacher A, et al. Ranking of parameters of pain hypersensitivity according to their discriminative ability in chronic low back pain. *Pain* 2012; **153**(10): 2083-91.

222. Neziri AY, Dickenmann M, Scaramozzino P, et al. Effect of intravenous tropisetron on modulation of pain and central hypersensitivity in chronic low back pain patients. *Pain* 2012; **153**(2): 311-8.

223. Nie H, Arendt-Nielsen L, Andersen H, Graven-Nielsen T. Temporal summation of pain evoked by mechanical stimulation in deep and superficial tissue. *J Pain* 2005; **6**(6): 348-55.

224. Nie H, Graven-Nielsen T, Arendt-Nielsen L. Spatial and temporal summation of pain evoked by mechanical pressure stimulation. *Eur J Pain* 2009; **13**(6): 592-9.

225. Niesters M, Proto PL, Aarts L, Sarton EY, Drewes AM, Dahan A. Tapentadol potentiates descending pain inhibition in chronic pain patients with diabetic polyneuropathy. *Br J Anaesth* 2014; **113**(1): 148-56.

226. Nishida K, Koshikawa Y, Morishima Y, et al. Pre-stimulus Brain Activity Is Associated With State-Anxiety Changes During Single-Session Transcranial Direct Current Stimulation. *Front Hum Neurosci* 2019; **13**: 266.

227. Norton G, McDonough CM, Cabral HJ, Shwartz M, Burgess JF, Jr. Classification of patients with incident non-specific low back pain: implications for research. *Spine J* 2016; **16**(5): 567-76.

228. Nussbaum EL, Downes L. Reliability of clinical pressure-pain algometric measurements obtained on consecutive days. *Physical therapy* 1998; **78**(2): 160-9.

229. Nuwailati R, Curatolo M, LeResche L, Ramsay DS, Spiekerman C, Drangsholt M. Reliability of the conditioned pain modulation paradigm across three anatomical sites. *Scand J Pain* 2020; **20**(2): 283-96.

230. O'Brien AT, Deitos A, Trinanes Pego Y, Fregni F, Carrillo-de-la-Pena MT. Defective Endogenous Pain Modulation in Fibromyalgia: A Meta-Analysis of Temporal Summation and Conditioned Pain Modulation Paradigms. *J Pain* 2018; **19**(8): 819-36.

231. O'Connell NE, Cossar J, Marston L, et al. Rethinking clinical trials of transcranial direct current stimulation: participant and assessor blinding is inadequate at intensities of 2mA. *PLoS One* 2012; **7**(10): e47514.

232. O'Connell NE, Marston L, Spencer S, DeSouza LH, Wand BM. Non-invasive brain stimulation techniques for chronic pain. *Cochrane Database Syst Rev* 2018; **4**: CD008208.

233. O'Donoghue GM, Fox N, Heneghan C, Hurley DA. Objective and subjective assessment of sleep in chronic low back pain patients compared with healthy age and gender matched controls: a pilot study. *BMC Musculoskelet Disord* 2009; **10**: 122.

234. O'Leary H, Smart KM, Moloney NA, Doody CM. Nervous System Sensitization as a Predictor of Outcome in the Treatment of Peripheral Musculoskeletal Conditions: A Systematic Review. *Pain Pract* 2017; **17**(2): 249-66.

235. O'Neill S, Kjaer P, Graven-Nielsen T, Manniche C, Arendt-Nielsen L. Low pressure pain thresholds are associated with, but does not predispose for, low back pain. *Eur Spine J* 2011; **20**(12): 2120-5.

236. O'Neill S, Manniche C, Graven-Nielsen T, Arendt-Nielsen L. Generalized deep-tissue hyperalgesia in patients with chronic low-back pain. *Eur J Pain* 2007; **11**(4): 415-20.

237. O'Neill S, Manniche C, Graven-Nielsen T, Arendt-Nielsen L. Association between a composite score of pain sensitivity and clinical parameters in low-back pain. *Clin J Pain* 2014; **30**(10): 831-8.

238. O'Sullivan P. Diagnosis and classification of chronic low back pain disorders: maladaptive movement and motor control impairments as underlying mechanism. *Man Ther* 2005; **10**(4): 242-55.

239. Olesen SS, van Goor H, Bouwense SA, Wilder-Smith OH, Drewes AM. Reliability of static and dynamic quantitative sensory testing in patients with painful chronic pancreatitis. *Reg Anesth Pain Med* 2012; **37**(5): 530-6.

240. Oono Y, Wang K, Baad-Hansen L, et al. Conditioned pain modulation in temporomandibular disorders (TMD) pain patients. *Exp Brain Res* 2014; **232**(10): 3111-9.

241. Orr LC, George SZ, Simon CB. Association between physical activity and pain processing in adults with chronic low back pain compared to pain-free controls. *J Back Musculoskelet Rehabil* 2017; **30**(3): 575-81.

242. Ossipov MH, Dussor GO, Porreca F. Central modulation of pain. *J Clin Invest* 2010; **120**(11): 3779-87.

243. 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**(8): 1452-64.

244. Ozguler A, Leclerc A, Landre MF, Pietri-Taleb F, Niedhammer I. Individual and occupational determinants of low back pain according to various definitions of low back pain. *J Epidemiol Community Health* 2000; **54**(3): 215-20.

245. Palm U, Reisinger E, Keeser D, et al. Evaluation of sham transcranial direct current stimulation for randomized, placebo-controlled clinical trials. *Brain Stimul* 2013; **6**(4): 690-5.

246. Park SM, Kim HJ, Jeong H, et al. Longer sitting time and low physical activity are closely associated with chronic low back pain in population over 50 years of age: a cross-sectional study using the sixth Korea National Health and Nutrition Examination Survey. *Spine J* 2018; **18**(11): 2051-8.

247. Peng W, Huang X, Liu Y, Cui F. Predictability modulates the anticipation and perception of pain in both self and others. *Soc Cogn Affect Neurosci* 2019; **14**(7): 747-57.

248. Peters ML, Schmidt AJ. Psychophysiological responses to repeated acute pain stimulation in chronic low back pain patients. *J Psychosom Res* 1991; **35**(1): 59-74.

249. Peters ML, Schmidt AJ, Van den Hout MA. Chronic low back pain and the reaction to repeated acute pain stimulation. *Pain* 1989; **39**(1): 69-76.

250. Petersen KK, Arendt-Nielsen L, Simonsen O, Wilder-Smith O, Laursen MB. Presurgical assessment of temporal summation of pain predicts the development of chronic postoperative pain 12 months after total knee replacement. *Pain* 2015; **156**(1): 55-61.

251. Petersen KK, Jensen MB, Graven-Nielsen T, Hauerslev LV, Arendt-Nielsen L, Rathleff MS. Pain Catastrophizing, Self-reported Disability, and Temporal Summation of Pain Predict Self-reported Pain in Low Back Pain Patients 12 Weeks After General Practitioner Consultation: A Prospective Cohort Study. *Clin J Pain* 2020; **36**(10): 757-63.

252. Petersen KK, Vaegter HB, Arendt-Nielsen L. An updated view on the reliability of different protocols for the assessment of conditioned pain modulation. *Pain* 2017; **158**(5): 988.

253. Petersen KK, Vaegter HB, Stubhaug A, et al. The predictive value of quantitative sensory testing: a systematic review on chronic postoperative pain and the analgesic effect of pharmacological therapies in patients with chronic pain. *Pain* 2020.

254. Pinto CB, Teixeira Costa B, Duarte D, Fregni F. Transcranial Direct Current Stimulation as a Therapeutic Tool for Chronic Pain. *J ECT* 2018; **34**(3): e36-e50.

255. Polianskis R, Graven-Nielsen T, Arendt-Nielsen L. Pressure-pain function in desensitized and hypersensitized muscle and skin assessed by cuff algometry. *J Pain* 2002; **3**(1): 28-37.

256. Price DD, Bush FM, Long S, Harkins SW. A comparison of pain measurement characteristics of mechanical visual analogue and simple numerical rating scales. *Pain* 1994; **56**(2): 217-26.

257. Price DD, Hu JW, Dubner R, Gracely RH. Peripheral suppression of first pain and central summation of second pain evoked by noxious heat pulses. *Pain* 1977; **3**(1): 57-68.

258. Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. *Pain* 1983; **17**(1): 45-56.

259. Pud D, Granovsky Y, Yarnitsky D. The methodology of experimentally induced diffuse noxious inhibitory control (DNIC)-like effect in humans. *Pain* 2009; **144**(1-2): 16-9.

260. 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**(3): e58885.

261. Rabey M, Beales D, Slater H, O'Sullivan P. Multidimensional pain profiles in four cases of chronic non-specific axial low back pain: An examination of the limitations of contemporary classification systems. *Man Ther* 2015; **20**(1): 138-47.

262. Rabey M, Poon C, Wray J, Thamajaree C, East R, Slater H. Pro-nociceptive and anti-nociceptive effects of a conditioned pain modulation protocol in participants with chronic low back pain and healthy control subjects. *Manual Therapy* 2015; **20**(6): 763-8.

263. 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.

264. 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.

265. Rabey M, Smith A, Kent P, Beales D, Slater H, O'Sullivan P. Chronic low back pain is highly individualised: patterns of classification across three unidimensional subgrouping analyses. *Scand J Pain* 2019.

266. Rainville P, Duncan GH, Price DD, Carrier B, Bushnell MC. Pain affect encoded in human anterior cingulate but not somatosensory cortex. *Science* 1997; **277**(5328): 968-71.

267. Ramaswamy S, Wodehouse T, Langford R, Thomson S, Taylor R, Mehta V. Characterizing the Somatosensory Profile of Patients With Failed Back Surgery Syndrome With Unilateral Lumbar Radiculopathy Undergoing Spinal Cord Stimulation: A Single Center Prospective Pilot Study. *Neuromodulation : journal of the International Neuromodulation Society* 2018.

268. Randic M, Jiang MC, Cerne R. Long-term potentiation and long-term depression of primary afferent neurotransmission in the rat spinal cord. *J Neurosci* 1993; **13**(12): 5228-41.

269. Raymond I, Ancoli-Israel S, Choiniere M. Sleep disturbances, pain and analgesia in adults hospitalized for burn injuries. *Sleep Med* 2004; **5**(6): 551-9.

270. Reading AE. A comparison of the McGill Pain Questionnaire in chronic and acute pain. *Pain* 1982; **13**(2): 185-92.

271. Reckow J, Rahman-Filipiak A, Garcia S, et al. Tolerability and blinding of 4x1 high-definition transcranial direct current stimulation (HD-tDCS) at two and three milliamps. *Brain Stimul* 2018; **11**(5): 991-7.

272. Reddy KS, Naidu MU, Rani PU, Rao TR. Human experimental pain models: A review of standardized methods in drug development. *J Res Med Sci* 2012; **17**(6): 587-95.

273. Rezaii T, Hirschberg AL, Carlstrom K, Ernberg M. The influence of menstrual phases on pain modulation in healthy women. *J Pain* 2012; **13**(7): 646-55.

274. Rhudy JL, Martin SL, Terry EL, et al. Pain catastrophizing is related to temporal summation of pain but not temporal summation of the nociceptive flexion reflex. *Pain* 2011; **152**(4): 794-801.

275. Rice D, Nijs J, Kosek E, et al. Exercise-Induced Hypoalgesia in Pain-Free and Chronic Pain Populations: State of the Art and Future Directions. *J Pain* 2019; **20**(11): 1249-66.

276. Riley JL, 3rd, Cruz-Almeida Y, Staud R, Fillingim RB. Age does not affect sex effect of conditioned pain modulation of pressure and thermal pain across 2 conditioning stimuli. *Pain Rep* 2020; **5**(1): e796.

277. Riley JL, 3rd, Robinson ME, Wise EA, Price DD. A meta-analytic review of pain perception across the menstrual cycle. *Pain* 1999; **81**(3): 225-35.

278. Robinson ME, Bialosky JE, Bishop MD, Price DD, George SZ. Supra-threshold scaling, temporal summation, and after-sensation: relationships to each other and anxiety/fear. *J Pain Res* 2010; **3**: 25-32.

279. Roby-Brami A, Bussel B, Willer JC, Le Bars D. An electrophysiological investigation into the pain-relieving effects of heterotopic nociceptive stimuli. Probable involvement of a supraspinal loop. *Brain* 1987; **110 (Pt 6)**: 1497-508.

280. Roland M, Morris R. A study of the natural history of back pain. Part I: development of a reliable and sensitive measure of disability in low-back pain. *Spine (Phila Pa 1976)* 1983; **8**(2): 141-4.

281. Rolke R, Baron R, Maier C, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. *Pain* 2006; **123**(3): 231-43.

282. Rosseland R, Pallesen S, Nordhus IH, Matre D, Blagestad T. Effects of Sleep Fragmentation and Induced Mood on Pain Tolerance and Pain Sensitivity in Young Healthy Adults. *Front Psychol* 2018; **9**: 2089.

283. Russo R, Wallace D, Fitzgerald PB, Cooper NR. Perception of comfort during active and sham transcranial direct current stimulation: a double blind study. *Brain Stimul* 2013; **6**(6): 946-51.

284. Sangesland A, Storen C, Vaegter HB. Are preoperative experimental pain assessments correlated with clinical pain outcomes after surgery? A systematic review. *Scand J Pain* 2017; **15**: 44-52.

285. Schafer A, Hall T, Briffa K. Classification of low back-related leg pain--a proposed patho-mechanism-based approach. *Man Ther* 2009; **14**(2): 222-30.

286. Schaller A, Rudolf K, Dejonghe L, Grieben C, Froboese I. Influencing Factors on the Overestimation of Self-Reported Physical Activity: A Cross-Sectional Analysis of Low Back Pain Patients and Healthy Controls. *Biomed Res Int* 2016; **2016**: 1497213.

287. Schliessbach J, Siegenthaler A, Bütikofer L, et al. Predicting drug efficacy in chronic low back pain by quantitative sensory tests. *European Journal of Pain (United Kingdom)* 2018; **22**(5): 973-88.

288. Schuh-Hofer S, Wodarski R, Pfau DB, et al. One night of total sleep deprivation promotes a state of generalized hyperalgesia: a surrogate pain model to study the relationship of insomnia and pain. *Pain* 2013; **154**(9): 1613-21.

289. Schwertner DS, Oliveira R, Koerich M, Motta AF, Pimenta AL, Gioda FR. Prevalence of low back pain in young Brazilians and associated factors: Sex, physical activity, sedentary behavior, sleep and body mass index. *J Back Musculoskelet Rehabil* 2020; **33**(2): 233-44.

290. Shahidi B, Maluf KS. Adaptations in Evoked Pain Sensitivity and Conditioned Pain Modulation after Development of Chronic Neck Pain. *Biomed Res Int* 2017.

291. Sharma S, Ohrbach R, Fillingim RB, Greenspan JD, Slade G. Pain Sensitivity Modifies Risk of Injury-Related Temporomandibular Disorder. *J Dent Res* 2020; **99**(5): 530-6.

292. Shiri R, Coggon D, Falah-Hassani K. Exercise for the Prevention of Low Back Pain: Systematic Review and Meta-Analysis of Controlled Trials. *Am J Epidemiol* 2018; **187**(5): 1093-101.

293. Shiro Y, Ikemoto T, Terasawa Y, et al. Physical Activity May Be Associated with Conditioned Pain Modulation in Women but Not Men among Healthy Individuals. *Pain Res Manag* 2017; **2017**: 9059140.

294. Silsbury Z, Goldsmith R, Rushton A. Systematic review of the measurement properties of self-report physical activity questionnaires in healthy adult populations. *BMJ Open* 2015; **5**(9): e008430.

295. Simon CB, Riley JL, Fillingim RB, Bishop MD, George SZ. Age Group Comparisons of TENS Response among Individuals with Chronic Axial Low Back Pain. *Journal of Pain* 2015; **16**(12): 1268-79.

296. Sivertsen B, Lallukka T, Petrie KJ, Steingrimsdottir OA, Stubhaug A, Nielsen CS. Sleep and pain sensitivity in adults. *Pain* 2015; **156**(8): 1433-9.

297. Sivilotti LG, Thompson SW, Woolf CJ. Rate of rise of the cumulative depolarization evoked by repetitive stimulation of small-caliber afferents is a predictor of action potential windup in rat spinal neurons in vitro. *J Neurophysiol* 1993; **69**(5): 1621-31.

298. Skou ST, Graven-Nielsen T, Rasmussen S, Simonsen OH, Laursen MB, Arendt-Nielsen L. Widespread sensitization in patients with chronic pain after revision total knee arthroplasty. *Pain* 2013; **154**(9): 1588-94.

299. Skovbjerg S, Jorgensen T, Arendt-Nielsen L, Ebstrup JF, Carstensen T, Graven-Nielsen T. Conditioned Pain Modulation and Pressure Pain Sensitivity in the Adult Danish General Population: The DanFunD Study. *J Pain* 2017; **18**(3): 274-84.

300. Slade GD, Sanders AE, Ohrbach R, et al. Pressure pain thresholds fluctuate with, but do not usefully predict, the clinical course of painful temporomandibular disorder. *Pain* 2014; **155**(10): 2134-43.

301. Slater H, Arendt-Nielsen L, Wright A, Graven-Nielsen T. Experimental deep tissue pain in wrist extensors--a model of lateral epicondylalgia. *Eur J Pain* 2003; **7**(3): 277-88.

302. Smith AD, Jull G, Schneider GM, Frizzell B, Hooper RA, Sterling M. Modulation of Cervical Facet Joint Nociception and Pain Attenuates Physical and Psychological Features of Chronic Whiplash: A Prospective Study. *PM R* 2015; **7**(9): 913-21.

303. Smith MT, Edwards RR, McCann UD, Haythornthwaite JA. The effects of sleep deprivation on pain inhibition and spontaneous pain in women. *Sleep* 2007; **30**(4): 494-505.

304. Spielberger CD. Manual for the State-Trait Anxiety Inventory. Revised edition ed. Palo Alto (CA); 1983.

305. Staffe AT, Bech MW, Clemmensen SLK, Nielsen HT, Larsen DB, Petersen KK. Total sleep deprivation increases pain sensitivity, impairs conditioned pain modulation and facilitates temporal summation of pain in healthy participants. *PLoS One* 2019; **14**(12): e0225849.

306. Stanton TR, Latimer J, Maher CG, Hancock MJ. How do we define the condition 'recurrent low back pain'? A systematic review. *Eur Spine J* 2010; **19**(4): 533-9.

307. Starkweather AR, Lyon DE, Kinser P, et al. Comparison of Low Back Pain Recovery and Persistence: A Descriptive Study of Characteristics at Pain Onset. *Biol Res Nurs* 2016; **18**(4): 401-10.

308. Starkweather AR, Ramesh D, Lyon DE, et al. Acute low back pain: Differential somatosensory function and gene expression compared with healthy no-pain controls. *Clinical Journal of Pain* 2016; **32**(11): 933-9.

309. Staud R, Nagel S, Robinson ME, Price DD. Enhanced central pain processing of fibromyalgia patients is maintained by muscle afferent input: a randomized, double-blind, placebo-controlled study. *Pain* 2009; **145**(1-2): 96-104.

310. Steer RA, Ball R, Ranieri WF, Beck AT. Further evidence for the construct validity of the Beck depression Inventory-II with psychiatric outpatients. *Psychol Rep* 1997; **80**(2): 443-6.

311. Su CA, Kusin DJ, Li SQ, Ahn UM, Ahn NU. The Association Between Body Mass Index and the Prevalence, Severity, and Frequency of Low Back Pain: Data From the Osteoarthritis Initiative. *Spine (Phila Pa 1976)* 2018; **43**(12): 848-52.

312. Sullivan MJ, Bishop SR, Pivik J. The pain catastrophizing scale: development and validation. *Psychological assessment* 1995; **7**(4): 524.

313. Suzan E, Aviram J, Treister R, Eisenberg E, Pud D. Individually based measurement of temporal summation evoked by a noxious tonic heat paradigm. *J Pain Res* 2015; **8**: 409-15.

314. Suzan E, Treister R, Pud D, Haddad M, Eisenberg E. The effect of hydromorphone therapy on psychophysical measurements of the descending inhibitory pain systems in patients with chronic radicular pain. *Pain Med* 2015; **16**(1): 168-75.

315. Suzuki K, Nakaji S, Yamada M, Totsuka M, Sato K, Sugawara K. Systemic inflammatory response to exhaustive exercise. Cytokine kinetics. *Exerc Immunol Rev* 2002; **8**: 6-48.

316. Tansley SN, Macintyre LC, Diamond L, et al. Conditioned pain modulation in rodents can feature hyperalgesia or hypoalgesia depending on test stimulus intensity. *Pain* 2019; **160**(4): 784-92.

317. Tavares DRB, Okazaki JEF, Rocha AP, et al. Effects of Transcranial Direct Current Stimulation on Knee Osteoarthritis Pain in Elderly Subjects With Defective Endogenous Pain-Inhibitory Systems: Protocol for a Randomized Controlled Trial. *JMIR Res Protoc* 2018; **7**(10): e11660.

318. Terhaar J, Boettger MK, Schwier C, Wagner G, Israel AK, Bar KJ. Increased sensitivity to heat pain after sad mood induction in female patients with major depression. *Eur J Pain* 2010; **14**(5): 559-63.

319. Tesarz J, Eich W, Treede RD, Gerhardt A. Altered pressure pain thresholds and increased wind-up in adult patients with chronic back pain with a history of childhood maltreatment: A quantitative sensory testing study. *Pain* 2016; **157**(8): 1799-809.

320. Tesarz J, Gerhardt A, Leisner S, Janke S, Treede RD, Eich W. Distinct quantitative sensory testing profiles in nonspecific chronic back pain subjects with and without psychological trauma. *Pain* 2015; **156**(4): 577-86.

321. Thielscher A, Antunes A, Saturnino GB. Field modeling for transcranial magnetic stimulation: A useful tool to understand the physiological effects of TMS? *Conf Proc IEEE Eng Med Biol Soc* 2015; **2015**: 222-5.

322. To WT, Eroh J, Hart J, Jr., Vanneste S. Exploring the effects of anodal and cathodal high definition transcranial direct current stimulation targeting the dorsal anterior cingulate cortex. *Sci Rep* 2018; **8**(1): 4454.

323. Tompra N, van Dieen JH, Coppieters MW. Central pain processing is altered in people with Achilles tendinopathy. *Br J Sports Med* 2016; **50**(16): 1004-7.

324. Traxler J, Hanssen MM, Lautenbacher S, Ottawa F, Peters ML. General versus pain-specific cognitions: Pain catastrophizing but not optimism influences conditioned pain modulation. *Eur J Pain* 2019; **23**(1): 150-9.

325. Trost Z, France CR, Thomas JS. Pain-related fear and avoidance of physical exertion following delayed-onset muscle soreness. *Pain* 2011; **152**(7): 1540-7.

326. Trotter W, Davies HM. Experimental studies in the innervation of the skin. *J Physiol* 1909; **38**(2-3): 134-246 1.

327. Tschugg A, Lener S, Hartmann S, et al. Extraforaminal Lumbar Disk Herniations Lead To Neuroplastic Changes: a Study Using Quantitative Sensory Testing. *Muscle and Nerve* 2018.

328. Tschugg A, Loscher WN, Hartmann S, Neururer S, Wildauer M, Thome C. Gender Influences Radicular Pain Perception in Patients with Lumbar Disc Herniation. *Journal of women's health (2002)* 2015; **24**(9): 771-6.

329. Tu Y, Jung M, Gollub RL, et al. Abnormal medial prefrontal cortex functional connectivity and its association with clinical symptoms in chronic low back pain. *Pain* 2019; **160**(6): 1308-18.

330. Umeda M, Lee W, Marino CA, Hilliard SC. Influence of moderate intensity physical activity levels and gender on conditioned pain modulation. *J Sports Sci* 2016; **34**(5): 467-76.

331. Vachon-Presseau E, Martel MO, Roy M, et al. Acute stress contributes to individual differences in pain and pain-related brain activity in healthy and chronic pain patients. *J Neurosci* 2013; **33**(16): 6826-33.

332. Vaegter HB, Graven-Nielsen T. Pain modulatory phenotypes differentiate subgroups with different clinical and experimental pain sensitivity. *Pain* 2016; **157**(7): 1480-8.

333. 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. *Clinical Journal of Pain* 2016; **32**(1): 58-69.

334. Vaegter HB, Palsson TS, Graven-Nielsen T. Facilitated Pronociceptive Pain Mechanisms in Radiating Back Pain Compared With Localized Back Pain. *Journal of Pain* 2017; **18**(8): 973-83.

335. van de Water AT, Eadie J, Hurley DA. Investigation of sleep disturbance in chronic low back pain: an age- and gender-matched case-control study over a 7-night period. *Man Ther* 2011; **16**(6): 550-6.

336. van Middendorp JJ, Sanchez GM, Burridge AL. The Edwin Smith papyrus: a clinical reappraisal of the oldest known document on spinal injuries. *Eur Spine J* 2010; **19**(11): 1815-23.

337. van Poppel MN, Chinapaw MJ, Mokkink LB, van Mechelen W, Terwee CB. Physical activity questionnaires for adults: a systematic review of measurement properties. *Sports Med* 2010; **40**(7): 565-600.

338. Villanueva L, Le Bars D. The activation of bulbo-spinal controls by peripheral nociceptive inputs: diffuse noxious inhibitory controls. *Biol Res* 1995; **28**(1): 113-25.

339. Villemure C, Schweinhardt P. Supraspinal pain processing: distinct roles of emotion and attention. *Neuroscientist* 2010; **16**(3): 276-84.

340. Villemure C, Slotnick BM, Bushnell MC. Effects of odors on pain perception: deciphering the roles of emotion and attention. *Pain* 2003; **106**(1-2): 101-8.

341. Vinstrup J, Jakobsen MD, Andersen LL. Poor Sleep Is a Risk Factor for Low-Back Pain among Healthcare Workers: Prospective Cohort Study. *Int J Environ Res Public Health* 2020; **17**(3).

342. Vollert J, Magerl W, Baron R, et al. Pathophysiological mechanisms of neuropathic pain: comparison of sensory phenotypes in patients and human surrogate pain models. *Pain* 2018; **159**(6): 1090-102.

343. Vossen CJ, Vossen HG, Joosten EA, van Os J, Lousberg R. Does habituation differ in chronic low back pain subjects compared to pain-free controls? A cross-sectional pain rating ERP study reanalyzed with the ERFIA multilevel method. *Medicine (Baltimore)* 2015; **94**(19): e865.

344. Vuilleumier PH, Arguissain FG, Biurrun Manresa JA, et al. Psychophysical and Electrophysiological Evidence for Enhanced Pain Facilitation and Unaltered Pain Inhibition in Acute Low Back Pain Patients. *Journal of Pain* 2017; **18**(11): 1313-23.

345. Vuilleumier PH, Biurrun Manresa JA, Ghamri Y, et al. Reliability of quantitative sensory tests in a low back pain population. *Regional Anesthesia and Pain Medicine* 2015; **40**(6): 665-73.

346. Wall PD, Woolf CJ. Muscle but not cutaneous C-afferent input produces prolonged increases in the excitability of the flexion reflex in the rat. *J Physiol* 1984; **356**: 443-58.

347. Waller R, Straker L, O'Sullivan P, Sterling M, Smith A. Reliability of pressure pain threshold testing in healthy pain free young adults. *Scand J Pain* 2015; **9**(1): 38-41.

348. Walton DM, Macdermid JC, Nielson W, Teasell RW, Reese H, Levesque L. Pressure pain threshold testing demonstrates predictive ability in people with acute whiplash. *J Orthop Sports Phys Ther* 2011; **41**(9): 658-65.

349. Wan DWL, Arendt-Nielsen L, Wang K, Xue CC, Wang Y, Zheng Z. Pain Adaptability in Individuals With Chronic Musculoskeletal Pain Is Not Associated With Conditioned Pain Modulation. *Journal of Pain* 2018; **19**(8): 897-909.

350. Wang JV, Hattier G, Jhawar N, Mesinkovska N, Zachary CB, Saedi N. Variations in pain perception during the menstrual cycle: implications for esthetic procedures. *Clin Dermatol* 2019; **37**(6): 689-91.

351. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. *J Pers Soc Psychol* 1988; **54**(6): 1063-70.

352. Weissman-Fogel I, Granovsky Y, Crispel Y, et al. Enhanced presurgical pain temporal summation response predicts post-thoracotomy pain intensity during the acute postoperative phase. *J Pain* 2009; **10**(6): 628-36.

353. Weissman-Fogel I, Sprecher E, Pud D. Effects of catastrophizing on pain perception and pain modulation. *Exp Brain Res* 2008; **186**(1): 79-85.

354. Willer JC, Le Bars D, De Broucker T. Diffuse noxious inhibitory controls in man: involvement of an opioidergic link. *Eur J Pharmacol* 1990; **182**(2): 347-55.

355. Willer JC, Roby A, Le Bars D. Psychophysical and electrophysiological approaches to the pain-relieving effects of heterotopic nociceptive stimuli. *Brain* 1984; **107 (Pt 4)**: 1095-112.

356. Wilson H, Carvalho B, Granot M, Landau R. Temporal stability of conditioned pain modulation in healthy women over four menstrual cycles at the follicular and luteal phases. *Pain* 2013; **154**(12): 2633-8.

357. Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. *Nature* 1983; **306**(5944): 686-8.

358. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain* 2011; **152**(3 Suppl): S2-15.

359. Wu A, March L, Zheng X, et al. Global low back pain prevalence and years lived with disability from 1990 to 2017: estimates from the Global Burden of Disease Study 2017. *Ann Transl Med* 2020; **8**(6): 299.

360. Yamada K, Kubota Y, Iso H, Oka H, Katsuhira J, Matsudaira K. Association of body mass index with chronic pain prevalence: a large population-based cross-sectional study in Japan. *J Anesth* 2018; **32**(3): 360-7.

361. Yarnitsky D, Bouhassira D, Drewes AM, et al. Recommendations on practice of conditioned pain modulation (CPM) testing. *Eur J Pain* 2015; **19**(6): 805-6.

362. Yarnitsky D, Granot M, Nahman-Averbuch H, Khamaisi M, Granovsky Y. Conditioned pain modulation predicts duloxetine efficacy in painful diabetic neuropathy. *Pain* 2012; **153**(6): 1193-8.

363. Yoneda S, Kasai E, Matsuo M, et al. Duloxetine ameliorates the impairment of diffuse noxious inhibitory control in rat models of peripheral neuropathic pain and knee osteoarthritis pain. *Neurosci Lett* 2020; **729**: 134990.

364. Yu R, Gollub RL, Spaeth R, Napadow V, Wasan A, Kong J. Disrupted functional connectivity of the periaqueductal gray in chronic low back pain. *Neuroimage Clin* 2014; **6**: 100-8.

365. Yu S, Li W, Shen W, et al. Impaired mesocorticolimbic connectivity underlies increased pain sensitivity in chronic low back pain. *Neuroimage* 2020; **218**: 116969.

366. Zhao H, Qiao L, Fan D, et al. Modulation of Brain Activity with Noninvasive Transcranial Direct Current Stimulation (tDCS): Clinical Applications and Safety Concerns. *Front Psychol* 2017; **8**: 685.

APPENDICES

Appendix A. Article Overview

Overview of the three primary articles included in this thesis

	STUDY I	*STUDY II*	*STUDY III*
Title	Alterations in Temporal Summation of Pain and Conditioned Pain Modulation Across an Episode of Experimental Exercise-Induced Low Back Pain	Recurrent Low Back Pain Patients demonstrate Facilitated Pro-nociceptive Mechanisms when in Pain, and Impaired Anti-nociceptive Mechanisms with and without Pain	Medial Prefrontal High-Definition Transcranial Direct Current Stimulation to Improve Pain Modulation in Chronic Low Back Pain: A Pilot Randomized Double-blind Crossover Trial
Objective	To investigate predictive value of pain sensitivity for LBP development and changes in pain sensitivity consequential to LBP	To investigate whether pain sensitivity alterations are a consequence of LBP presence	To investigate changes in clinical pain and pain sensitivity induced by mPFC tDCS
Sample	30 Pain-free participants (6 excluded, no DOMS at Day-2)	30 Recurrent LBP patients (4 excluded, 1 withdrew and 3 with ongoing pain at Day-28) 30 Pain-free controls	12 Chronic LBP patients (1 missing final follow-up session)
Design	Data collected at baseline (Day-0), post-exercise (Day-0), with LBP (Day-2) and post-resolution (Day-7)	Data collected with RLBP present (Day-0) and resolved (Day-28), and over same timeframe in controls	Active/sham tDCS for 3 days separated by >2 weeks. Data collected pre/post 1st (Day-1) and post 3rd session (Day-3), at Day-4 and Day-21
Model	Delayed onset muscle soreness in lumbar erector spinae/gluteal muscles, induced by repeated prone trunk extensions to fatigue	Subclinical recurrent LBP present for >24 hours at time of recruitment and testing, that is expected to resolve completely in less than 4 weeks	Chronic LBP with average pain score ≥3/10. Stimulation applied using HD-tDCS with anode at Fz and cathodes at F7, F8, FP1 and FP2.
Materials	History, physical exam, sleep, menstruation, mood, IPAQ, PCS, Pain VAS intensity and unpleasantness, RMDQ, STarT-Back Screening Tool, (Pain-DETECT, BDI)		
Measures	Handheld pressure pain thresholds (PPTs), cuff pain detection (cPDT) and tolerance (cPTT) thresholds, supra-threshold ratings (STR), temporal summation of pain (TSP) and conditioned pain modulation (CPM)		
Results	Mild pain and disability provoked. PPTs reduced at L1, L5 and ECR compared to pain-free, UT and GAS reduced to Day-7. Cuff thresholds increased at Day-7. No significant changes over time in TSP or CPM. Baseline TSP (along with lumbar PPTs, number of exercise repetitions, mood, and gender) associated with peak LBP severity	Mild LBP and disability reported. PCS scores higher on Day-0 than Day-28 for RLBP patients. PPTs reduced at L1, L5, ECR and UT on Day-0 compared to Day-28 and controls. cPDT increased on Day-28 compared to Day-0 in RLBP. TSP increased on Day-0 compared to Day-28 and to controls. CPM reduced in RLBP patients compared to controls overall.	Mild LBP and disability reported. Immediate reduction in pain intensity observed after first tDCS session. No differences between Active and Sham for pain or questionnaire outcomes. No differences in pain sensitivity between Active and Sham protocols at Day-4 or Day-21. Negative correlation between baseline CPM and response to Active tDCS.
Conclusion	TSP assessed in a pain-free state may help explain variation in future pain severity. The DOMS LBP model produced local and widespread pressure hypersensitivity but was not sufficient to alter central pain processing mechanisms.	A RLBP episode was associated with increased pain catastrophizing, local and widespread pressure hypersensitivity and facilitated TSP, compared to when pain resolved and to controls. CPM was reduced overall and may represent a relevant feature contributing to RLBP development or maintenance.	This mPFC tDCS paradigm was unable to produce specific changes in pain, disability, PPTs, cuff thresholds, TSP or CPM, possibly due to issues with sample characteristics. Exploratory correlations may indicate potentially better effects in a selected sample with very inefficient CPM.

Appendix B. Confounding Factors

Additional details on material used to capture potential confounders

Factor:	*Rationale:*	*Measures used:*	*Description and validity:*
Sleep	Sleep is increasingly acknowledged to play a key role in painful disorders, with many studies implying close links between poor sleep and pain exacerbation[77,116,143,269,296]. In LBP patients specifically, sleep disturbance is common[17,116,143,192,233,335], with more than half of chronic patients in recent studies reporting insomnia symptoms[233,335]. Further, it has been shown previously that both reduced total sleep time and interruptions to sleep have a detrimental effect on pain thresholds[282,288,296], TSP and CPM[73,305].	- Number of hours slept night prior to testing session (Study I-III) - Number of awakenings in night prior to testing session (Study I-III)	These questions are asked in validated sleep quality questionnaires[43] and have adequate face validity. Participants tend to overestimate sleep duration, but this is done so systematically and reports still show moderate correlation to objective measures[164].
Menstruation	There is debate as to the influence of female hormonal cycles on pain sensitivity measures, with some studies showing differences between menstrual phases[273] and others showing no significant impact[26,138,356]. As all studies (I-III) involved more than one session, data was collected from female participants about menstruation in an effort to ensure avoidance of systematic bias.	- Current day of menstrual cycle (Study I-III) - Average cycle length (Study I-III) - Contraceptive use (yes/no, Study I-III)	These particular questions have not been validated but reflect factors that individuals can estimate based on their last menstrual period. Without hormone testing, it is not possible to determine precisely which phase females were in, but the present measures were deemed adequate to understand if female participants had normal cycles and were roughly evenly distributed between phases to exclude clear systematic bias.
Mood	Both experimental manipulation of affect and the presence of affective disorders have been shown to influence pain experiences[72,339], as well as pain sensitivity[122,318,340]. Hence, affective state during the session was thought to be important to assess, both to identify potential basal differences in affect between patients and controls, and to capture potentially influential changes between sessions.	- Face Scale[182] (Study I-III) - Positive and Negative Affective Schedule (PANAS[351], Study II-III) - Beck Depression Inventory-II (BDI[27], Study III)	The Face Scale provides a unidimensional 20-point picture scale of facial images ranging from very positive (1) to very negative (20) expressions. It is a simple measure that provides a quick unidimensional assessment of mood. The PANAS was used as a more nuanced classification of affect, as it asks participants to rate the extent to which they currently feel each of the 20-affective states listed. The PANAS has been validated to reliably capture two distinct affective components[48,57]. The BDI has been validated and used as a tool to screen for possible affective disorders in various settings[27,310].

Factor (cont.)	*Rationale (cont.)*	*Measures (cont.)*	*Description and validity (cont.)*
Anxiety	Similar to affective disorders, anxiety disorders also well known to commonly co-occur with pain conditions[15], and artificial manipulation of anxiety[202] or stress[96,331] can impact pain experiences.	- Spielberger State and Trait Anxiety Inventory (STAI[304], Study II-III)	The STAI is a 40-item scale, where participants rate the extent to which statements describe them now (state) or in general (trait), and which has been widely used in psychological research. It has been translated and validated into many languages[1,19,76,111,185] and provides useful distinct characterisation of state and trait anxiety[86].
Pain Catastrophizing	Along with anxiety and affective disorders, patients with chronic pain often have catastrophic thoughts about their condition. Such thoughts have been increasingly captured in research, for example, by using the Pain Catastrophizing Scale (PCS)[312].	- The Pain Catastrophizing Scale[312] (PCS, Study I-III)	The PCS is a 13-item scale of cognitions that may arise when one is in pain, on which participants rate how frequently they have such catastrophic thoughts. It has been used extensively in pain research and has been shown to have high construct validity.
Physical Activity	A u-shaped relationship is purported to exist between physical activity and clinical pain, suggesting that both too much and too little activity can be problematic[118]. Within normal limits, however, physical activity seems protective against LBP development[125,292]. In relation to pain sensitivity, physical activity also often seems protective and it is well-established that exercise can have acute positive effects on pain threshold measures[216,275]. Physical activity was thus captured to identify between-group differences.	- International Physical Activity Questionnaire[56] Short Form (IPAQ, Study I-III)	The IPAQ has been widely used and translated into several languages, offering a quick estimate of weekly exertion and daily sitting time[337]. Unfortunately, attempts to validate the IPAQ against objective activity data (e.g. with accelerometer or pedometer) have proven difficult, with very poor correlation between these measures, and studies commonly demonstrating over-estimation of activity levels by participants[168]. Reports of reliability for the IPAQ have also been variable with excellent reliability reported in healthy controls[294] but poor reliability in CLBP patients[47]. Despite this, IPAQ responses have previously been shown to correlate with TSP and CPM[217,241], along with LBP[113,246].

Appendix C. Additional Analyses Between-Studies

For the sake of completeness, an additional overall analysis was conducted to compare between study groups for the main outcomes, and where the same methodology was used in all participants. In some cases, these findings contradict the individual study findings, likely due to the small effect sizes and addition of variability. Nevertheless, they serve as an indication of potential differences and similarities between the populations and LBP models investigated.

Details of analytical methods and results for comparisons made on questionnaire data pooled from all studies

Characteristic	*Model*	*Omnibus Test*	*Post-hoc Comparisons*
Age	One-way ANOVA with: Group (4)	No difference between groups (P>0.25)	-
Body Mass Index (BMI)	One-way ANOVA with: Group (4)	No difference between groups (P>0.38)	*No differences were noted for height or weight either using the same analysis.*
Mood (Faces Scale, Past week / Now)	2-way ANOVA with: Group (4), Session (2) for each variable	No differences observed for either past week or now (P>0.05)	-
Sleep (Hours)	2-way ANOVA with: Group (4), Session (2)	Significant Group*Session interaction: $F_{3,88}$=3.73, P=0.014, η^2=0.11	No differences between groups. CLBP patients slept more hours prior to the representative less painful session than the more painful session (P=0.016).
Sleep (Awakenings)	Kruskal-Wallis Test with: Group (4) Wilcoxon with: Session (2)	No differences between Groups (P>0.09) or Sessions (P>0.74)	-
Pain Catastrophizing (PCS)	2-way ANOVA with: Group (4), Session (2)	Significant Group*Session interaction: $F_{3,88}$=9.25, P<0.001, η^2=0.24	In RLBP, PCS score was higher during the painful session than the non-painful session (P=0.001). In DOMS, PCS score was lower during the painful session than the non-painful session (P<0.001). In the painful session, RLBP patients showed higher PCS scores than participants with DOMS (P=0.035).
International Physical Activity Questionnaire (Sitting time / Score)	One-way ANOVA with: Group (4) for each variable	No difference between groups for either sitting time or activity (P>0.20)	-

Details of analytical methods and results for comparisons made on clinical characteristic data pooled from all studies

Characteristic	*Model*	*Omnibus Test*	*Post-hoc Comparisons*
Pain Intensity (VAS)	One-way ANOVA with: Group (3)	No differences between groups (P>0.84)	-
Pain Unpleasantness (VAS)	One-way ANOVA with: Group (3)	No differences between groups (P>0.16)	-
Pain Duration (years)	One-way ANOVA with: Group (3)	Significant main effect of Group: $F_{2,59}$=17.36, P<0.001	Pain duration was greater in RLBP (P<0.001) and CLBP (P=0.001) patients than provoked in the DOMS model.
McGill Pain Score	One-way ANOVA with: Group (3)	Significant main effect of Group: $F_{2,59}$=10.33, P<0.001	McGill scores were higher in RLBP (P<0.001) and CLBP (P=0.017) patients than provoked in the DOMS model.
Roland-Morris Disability Questionnaire (RMDQ)	One-way ANOVA with: Group (3)	Significant main effect of Group: $F_{2,59}$=4.43, P=0.016	Disability was higher in RLBP (P=0.049) and CLBP (P=0.042) patients than provoked in the DOMS model.
STarT-Back Screening Questionnaire (SBSQ)	Kruskal-Wallace H test with: Group (3)	Significant main effect of Group: H_2=17.18, P<0.001	STarT-Back Scores were higher in RLBP than DOMS (P=0.008) and in CLBP than both RLBP and DOMS (P<0.03)

Details of analytical methods and results for comparisons made on primary outcome data pooled from all studies

Outcome	*Model*	*Omnibus Test*	*Post-hoc Comparisons*
Pressure Pain Thresholds (PPTs)	RM-ANOVA with between-subjects factor: Group (4); and within-subject factors: Site (5) and Session (2)	Significant 3-way Group*Site*Session interaction: $F_{12,352}$=2.97, P=0.001, η^2=0.092	Compared to control group: ↓ ECR & UT in DOMS (P<0.03), ↓ L1 & L5 in CLBP (P<0.04) in painful session; no significant differences between-groups in pain-free session Compared between sessions: no differences in controls (P>0.06), ↓ during DOMS at ECR, L1 & L5 (P<0.02), ↓ during RLBP at ECR, UT, L1 & L5 (P<0.04); ↓ in more painful CLBP session at L1 (P<0.02)
Cuff Pain Detection Threshold (cPDT)	ANOVA with between-subjects factor: Group (4); and within-subjects factor: Session (2)	Significant Session*Group interaction: $F_{3,88}$=2.83, P=0.043, η^2=0.088	No differences between groups in either session Compared between sessions: ↓ cPDT during RLBP (P=0.04) and during more painful session in CLBP (P=0.001)
Cuff Pain Tolerance Threshold (cPTT)	ANOVA with between-subjects factor: Group (4); and within-subjects factor: Session (2)	Significant Session*Group interaction: $F_{3,88}$=3.02, P=0.034, η^2=0.094	No differences between groups in either session Compared between sessions: ↓ cPTT during more painful session in CLBP (P=0.001)
Supra-threshold Pressure Stimulation	ANOVA with between-subjects factor: Group (4); and within-subjects factor: Session (2)	Main effect of Session: $F_{3,88}$=12.52, P=0.001, η^2=0.125	Pain ratings of supra-threshold pressure were generally higher in the more painful session (P=0.001)
Temporal Summation of Pain (TSP)	RM-ANOVA with between-subjects factor: Group (4); and within-subjects factors: Epoch (3) and Session (2)	Main effect of Epoch: $F_{2,176}$=64.79, P<0.001, η^2=0.424	All epochs significantly different (first < second < third) indicating significant TSP demonstrated, but no differences observable between groups or sessions
Conditioned Pain Modulation (CPM)	RM-ANOVA with between-subjects factor: Group (4); and within-subjects factors: Ramp (3), Threshold (2) and Session (2)	Main effect of Ramp: $F_{2,176}$=17.72, P<0.001, η^2=0.168	Normalized change in cPDT and cPTT on ramps during and post conditioning stimulation were significantly higher overall than the repeated ramp prior to conditioning (P<0.001) indicating a normal inhibitory response to conditioning, but no differences observable between groups or sessions

ISSN (online): 2246-1302
ISBN (online): 978-87-7210-821-6

AALBORG UNIVERSITY PRESS