Pain Sensitization and Exercise-Induced
Hypoalgesia in People with Knee
Osteoarthritis

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Publications and Presentations

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Oral Presentations


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Knee osteoarthritis (OA) is estimated to affect approximately 20% of adults aged ≥ 45 years in Europe and the United States. Pain presentations of people with knee OA have been shown to vary and recent evidence has demonstrated alterations in nociceptive processing in the peripheral and central nervous system of people with knee OA, referred to as pain sensitization; a greater understanding of pain sensitization in knee OA could be integral to the designation and development of appropriate treatment interventions.

The overall aim of the thesis was to investigate pain sensitization in people with knee OA using clinically reproducible measures. The aims of the studies were to review the existing evidence for pain sensitization in knee osteoarthritis (OA) (study 1), to further investigate the presence of pain sensitization and to investigate the presence of neural mechanosensitivity (NM) in people with knee OA (study 2 & 3), to investigate potential differences in pain sensitization between subgroups of people with knee OA with high and low pressure pain sensitivity (PPS) (study 4) and to investigate the presence of exercise-induced hypoalgesia (EIH) in response to aerobic and isometric lower limb exercise in people with knee OA with varying degrees of pain sensitization (study 5 & 6).

Results from the systematic review and meta-analysis (study 1) indicated that pain sensitization is present in people with knee OA and may be associated with symptom severity. The reliability of lower limb nerve palpation (a measure of NM) was demonstrated (study 2) and case-control studies on knee OA patients with moderate to high symptom severity demonstrated signs of NM using nerve palpation and neurodynamic testing in people with knee OA which had not previously been reported (study 3). In addition, signs of pain sensitization using quantitative sensory testing were demonstrated in people with knee OA, including novel findings of contralateral pain sensitization signs and cold hyperalgesia (study 3); further analysis of results also suggested the presence of higher levels of pain sensitization in a knee OA subgroup with high PPS (study 4). In the first study to
investigate EIH in response to aerobic exercise in people with knee OA (study 5), results demonstrated no significant differences between knee OA patients and controls, or between knee OA subgroups with high and low PPS, for EIH in response to aerobic or isometric exercise. However, within-group results suggested a lesser efficiency of EIH in knee OA patients, particularly in those with high PPS, which had not previously been demonstrated. A further study investigated for the first time the effects of isometric and aerobic exercise on EIH in people with knee OA with normal and abnormal conditioned pain modulation (CPM) and demonstrated a dysfunctional EIH response in knee OA patients who had abnormal CPM at baseline (study 6).

This thesis provides novel contributions to the body of research regarding pain sensitization in people with knee OA, including findings of NM and signs of contralateral sensitization in knee OA patients. In addition, we demonstrated a greater degree of pain sensitization and decreased efficiency of EIH in knee OA patients with high PPS, and dysfunction of EIH in knee OA patients who exhibit abnormal CPM. These findings have clinical implications regarding the identification of knee OA patients who are pain-sensitized using QST and NM measures, and the appropriate selection of treatment pathways for these patients, including the potential role of an individualised approach to exercise prescription. Further investigation is warranted in relation to identifying knee OA patients with a high degree of pain sensitization; the clinical utility of pain sensitization and NM measures; and the effect of exercise interventions on pain sensitivity in knee OA patients with differing degrees of pain sensitization.
Statement of Original Authorship

I hereby certify that the submitted work is my own work, was completed while registered as a candidate for the degree of Doctor of Philosophy, and I have not obtained a degree elsewhere on the basis of the research presented in this submitted work.

Signed: __________________________________________________

Date: _____________________________________________________
Chapter 1

Introduction

This chapter will provide a description of the burden, pathology, symptoms and pain pathophysiology in knee osteoarthritis (OA), with a particular focus on the phenomenon of pain sensitization in knee OA, as well as an overview of exercise-induced hypoalgesia (EIH) and how this may be altered in chronic pain populations including knee OA cohorts. Finally, the chapter includes a description of the overall thesis aims, the relationship between the constituent studies and the specific aims of the six individual studies that comprise the body of the thesis.
1.1 Knee Osteoarthritis

1.1.1 Burden

Knee osteoarthritis (OA) is estimated to affect approximately 20% of adults aged ≥ 45 years in Europe and the United States (US)\textsuperscript{1-3}, with this number projected to rise significantly in coming years\textsuperscript{1}. Knee and hip OA are ranked as the 11\textsuperscript{th} highest contributor to global disability\textsuperscript{4} and have been shown to be associated with an increased risk of all-cause mortality, with walking disability and a history of cancer, diabetes, and cardiovascular disease reported to be the main risk factors of increased mortality in people with hip and knee OA\textsuperscript{5}. A diagnosis of knee OA is also reportedly associated with a two-fold increased risk of sick leave and 40–50% increased risk of disability pension\textsuperscript{6}, and is estimated to account for $185.5 billion of aggregate annual medical care expenditure in the US\textsuperscript{7}.

1.1.2 Pathology

Osteoarthritis is a degenerative joint disease characterised by damage to articular cartilage\textsuperscript{8}, changes in subchondral bone and synovial tissue\textsuperscript{9}, and chronic synovitis\textsuperscript{10}. Degeneration occurs secondary to failure of the repair response of damaged cartilage. This involves increased formation and apoptotic death of chondrocytes\textsuperscript{8, 11} and increased synthesis of tissue-destructive proteinases\textsuperscript{12}. Additionally, the process involves inadequate synthesis of components of the extracellular matrix making the matrix unable to withstand normal mechanical stresses\textsuperscript{8} and an increased production of pro-inflammatory mediators in the synovium\textsuperscript{9}.

1.1.3 Symptoms

The primary symptom of people with knee OA is pain that worsens during and after weight-bearing activities\textsuperscript{13}, and which may be present at rest in more severe cases\textsuperscript{14}. People with knee OA report functional limitations\textsuperscript{14}, knee instability and giving way\textsuperscript{15} as well as inactivity-related stiffness\textsuperscript{8}. Osteoarthritis is also associated with depression\textsuperscript{16} and sleep disturbances\textsuperscript{17}, and symptoms of OA can lead to a diminished quality of life\textsuperscript{8, 18}. 
1.1.4 Pain pathophysiology

The pathophysiology of pain in knee OA is poorly understood. Nociceptive input in knee OA is speculated to arise primarily from synovitis\(^\text{19-21}\) and bone marrow lesions\(^\text{22, 23}\) and may also be related to other features such as osteophytes, sclerosis and subchondral bone cysts\(^\text{19, 22}\), and the action of pro-inflammatory mediators in the knee joint\(^\text{23}\). However, the relationship between radiographic evidence of knee joint degeneration and pain severity is weak\(^\text{24-26}\) and recent evidence suggests the contribution of non-nociceptive neurophysiological pain mechanisms\(^\text{23, 27}\), as described below.

1.2 Pain Sensitization

According to the International Association for the Study of Pain (IASP)\(^\text{28}\), pain sensitization is defined as “increased responsiveness of nociceptive neurons to their normal input, and/or recruitment of a response to normally subthreshold inputs”.

1.2.1 Peripheral sensitization

Peripheral sensitization is defined as an increased response and reduced thresholds of nociceptive neurons in the periphery\(^\text{28}\). In people with knee OA, this encompasses an increased responsiveness of nociceptors in the deep somatic tissues local to the site of pathology which may be driven peripherally by inflammatory mediators such as prostaglandins, cytokines, and other mediators such as nerve growth factor\(^\text{29, 30}\).

1.2.2 Central sensitization

Central sensitization has been defined as an increased response of nociceptive neurons to normal or subthreshold afferent input within the central nervous system\(^\text{28}\) and is thought to involve a number of different mechanisms including the following:

a) Hyperexcitability of spinal cord neurons (spinal hyperexcitability) which involves increased responsiveness to innocuous and noxious stimulation of the knee joint, a decrease in the excitation threshold of high threshold
neurons and an expansion of the receptive field, resulting in primary and secondary hyperalgesia, greater summation of pain on repeated stimulation (increased temporal summation)\textsuperscript{30, 31} and increased flexor withdrawal response of the lower limb\textsuperscript{32}

b) Long term potentiation of synaptic input which is a persistent increase in the strength of neuronal synapses secondary to high frequency input\textsuperscript{31, 33}

c) A dysfunction of descending inhibitory pathways including inefficiency of the diffuse noxious inhibitory control mechanism (‘pain inhibits pain’) and of supraspinal opioidergic and serotonergic inhibition\textsuperscript{34-36}

d) Activation of descending facilitatory pathways characterised by the contribution of emotions, attention and stress to sensitization (‘cognitive-emotional sensitization’)\textsuperscript{37, 38}.

A further in-depth exploration of the existing evidence for pain sensitization in knee OA will be described in Chapter 2*.

1.2.3 Sensitization of Neural Tissue - Neural mechanosensitivity

Neural mechanosensitivity (NM) is an increased sensitivity of nerve trunks without interruption of normal nerve conduction\textsuperscript{39} which has been demonstrated in a number of chronic pain cohorts\textsuperscript{40-42}. It is thought to reflect sensitization of neural tissue which may be peripherally or centrally-mediated\textsuperscript{39, 43}. People with non-specific arm pain and whiplash-associated disorders (WAD) have demonstrated NM in response to palpation of nerve trunks and neurodynamic testing (NDT)\textsuperscript{40, 41}, and NM has also been shown in WAD patients in response to pressure pain threshold (PPT) testing over nerve sites\textsuperscript{42}.

Peripheral neural tissue is capable of becoming sensitized via local chemical and mechanical stimulation\(^39, 43, 44\). A source of chemical stimulation may be inflammation of structures adjacent to the neural tissue\(^39\), while mechanical stimulation could be associated with longitudinal stretch and movement-induced friction\(^39, 44\). Chronic irritation of these nerve afferents could potentially lead to an ongoing discharge that may contribute to the maintenance of pain and sensitization in people with knee OA and requires further empirical study\(^39\). Positive identification of NM, in conjunction with other somatosensory measures, may be indicative of the presence of pain sensitization, and may offer additional treatment targets in the form of nerve mobilisation and neural desensitization techniques\(^45, 46\). The presence of NM in knee OA has not been investigated to date.

### 1.3 Pain Sensitization and Exercise-Induced Hypoalgesia

Exercise-induced hypoalgesia is a form of endogenous pain inhibition that has been shown to be dysfunctional in several chronic pain cohorts\(^47, 50\). Research suggests that dysfunctional EIH during exercise is not characteristic for all chronic pain patients but rather appears to be limited to those with clear evidence of a high level of pain sensitization e.g. fibromyalgia, chronic fatigue syndrome (CFS) and WAD\(^51, 52\). People with fibromyalgia, CFS and WAD have demonstrated hyperalgesic responses to exercise\(^47, 49, 53, 56\), while normal EIH has been demonstrated in people with chronic low back pain\(^47, 54, 57\), rheumatoid arthritis\(^54\), shoulder myalgia\(^55\), hip OA\(^58\) and knee OA\(^58, 59\).

#### 1.3.1 Exercise-induced hypoalgesia in knee osteoarthritis

In relation to people with knee OA, only two studies to date have investigated the effect of resistance exercise on pain sensitivity \(^58, 59\). Kosek et al\(^58\) demonstrated a significant increase in PPTs suggestive of normal EIH response in knee OA patients in response to isometric knee extension and Burrows et al\(^59\) demonstrated a significant increase in PPTs suggestive of normal EIH in response to dynamic resistance exercise of the upper body, but not of the lower body, in people with knee OA. No study to date has investigated the effect of aerobic exercise on
measures of pain sensitivity in knee OA or the effect of exercise on pain sensitivity in a subgroup of people with knee OA with a higher level of pain sensitization.

1.3.2 Mechanisms of exercise-induced hypoalgesia

The EIH response is speculated to be caused by activation of endogenous opioid and non-opioid systems and dysfunction of these systems is associated with the presence of pain sensitization. The action of opioids, plasma b-endorphins, enkephalins as well as serotoninergic and norepinephrine neurotransmitters have been implicated. Cardiovascular changes are also speculated to be involved in EIH as exercise induces an increase in blood pressure that activates arterial baroreceptors which have been shown to cause CNS inhibition. Another mechanism thought to contribute to the EIH response is DNIC, which causes inhibition of wide-dynamic-range neurons in the dorsal horn of the spinal cord via a spinal-bulbo-spinal loop. Improvements in pain sensitivity in response to exercise have been shown to be multisegmental, occurring both local to the exercising muscle and at remote body sites.

1.3.3 Methods of measuring exercise-induced hypoalgesia

The modes of exercise investigated in studies of EIH have differed in terms of type, intensity, and duration. Aerobic, isometric and dynamic resistance exercise protocols have been employed and all have been shown to result in decreases in pain sensitivity measures in healthy cohorts. In healthy cohorts, hypoalgesic effects of resistance exercises tend to be larger for low to moderate intensity contractions held for longer durations (5 minutes), while the EIH effect for aerobic exercise appears to increase with higher intensities in a dose-response manner. The latter has been shown not to apply however in the case of certain chronic pain cohorts such as fibromyalgia and WAD patients, in whom self-paced exercise has been shown to produce a more favourable impact on pain sensitivity.

The mode of measuring pain sensitivity has differed across studies also. The majority of studies have used PPTs to measure pain sensitivity. Cold and heat stimuli, temporal summation of heat and mechanical stimuli in addition to
have also been employed as pain sensitivity measures. In certain studies, muscle contractions performed in the area of pain did not produce EIH, while exercise performed remote from the painful site did produce an EIH response, attenuation of pain sensitivity occurred in response to moderate isometric contractions performed remotely at the quadriceps but not locally at the infraspinatus muscle in shoulder myalgia patients and in response to upper limb dynamic resistance exercise, but not lower limb exercise in people with knee OA.

1.4 Thesis Overview
Pain presentations of people with knee OA have been shown to vary and recent evidence has demonstrated the presence of pain sensitization in this cohort. A greater understanding of pain sensitization in knee OA could be integral to the designation and development of appropriate treatment interventions. Therefore, the overall aim of the thesis was to investigate pain sensitization in people with knee OA using clinically reproducible measures. The aim of study 1 was to review the existing evidence for pain sensitization in knee OA. Study 2 was conducted to examine the reliability of a measure of neural mechanosensitivity (NM), which we would go on to use in study 3 and 4. The aim of study 3 was to further investigate the presence of pain sensitization and to investigate the presence of NM in people with knee OA. No study had previously examined sensitization of peripheral neural tissue (manifested by NM) in people with knee OA, despite a large body of evidence suggestive of sensitization of the nervous system. In study 4, we investigated potential differences in pain sensitization between subgroups of people with knee OA with high and low pressure pain sensitivity (PPS). This was a secondary analysis of the data from study 3. The aim of study 5 was to investigate the presence of another pain mechanism linked to pain sensitization, known as exercise-induced hypoalgesia (EIH). This mechanism was investigated in response to aerobic and isometric lower limb exercise in people with knee OA with high and low PPS. Finally, in study 6, we investigated EIH in people with knee OA with normal and abnormal conditioned pain modulation (a secondary analysis of data from study 5). The overview of this thesis and the relationship between the constituent studies are depicted in Figure 1.
Study 1. Pain sensitization in people with knee osteoarthritis: A systematic review and meta-analysis

Study 3. Neural mechanosensitivity and pain sensitization in people with knee osteoarthritis

Study 4. A greater degree of pain sensitization is present in people with knee osteoarthritis with high versus low pressure pain sensitivity

Study 2. Intraexaminer and interexaminer reliability of manual palpation and pressure algometry of the lower limb nerves in asymptomatic subjects

Study 5. Exercise-induced hypoalgesia in people with knee osteoarthritis with high versus low pressure pain sensitivity

Study 6. Exercise-induced hypoalgesia in people with knee osteoarthritis with normal and abnormal conditioned pain modulation

Figure 1.1 Overview of Thesis and Relationship Between Studies
1.4.1 Specific study aims

The specific aims of each of the 6 thesis studies are outlined below:

**Study 1:** Pain sensitization in people with knee osteoarthritis: a systematic review and meta-analysis

The aims of the first study were:
- To conduct a meta-analytic review of the evidence for pain sensitization as measured by quantitative sensory testing (QST) in people with knee OA
- To investigate, using meta-analysis, the presence of pain sensitization in people with knee OA who have high symptom severity versus those with low symptom severity

**Study 2:** Intraexaminer and interexaminer reliability of manual palpation and pressure algometry of the lower limb nerves in asymptomatic subjects

The aims of the second study were:
- To investigate the reliability of femoral nerve palpation in an asymptomatic group using manual palpation and pressure algometry
- To provide further evidence of the reliability of manual palpation and pressure algometry of the sciatic, common peroneal, and tibial nerves by means of alternate unilateral palpation
- To provide normative data for pressure algometry of the femoral nerve

**Study 3:** Neural mechanosensitivity and pain sensitization in people with knee osteoarthritis

The aims of the third study were:
- To investigate for signs of neural mechanosensitivity in people with knee OA by means of manual nerve palpation and neurodynamic testing
- To investigate for signs of pain sensitization using QST in people with knee OA compared to pain-free controls
**Study 4:** A greater degree of pain sensitization is present in people with knee osteoarthritis with high versus low pressure pain sensitivity

The aims of the fourth study were:
- To investigate potential differences between pain sensitization signs in knee OA subgroups with higher and lower PPS and pain-free controls
- To investigate potential differences in patient-reported outcome measures between knee OA participants with high and low PPS

**Study 5:** Exercise-induced analgesia in people with knee osteoarthritis with high and low pressure pain sensitivity

The aims of the fifth study were:
- To investigate changes in PPTs and TS in response to acute aerobic and isometric exercise in people with knee OA compared to healthy controls
- To investigate exercise-induced changes in PPTs and TS in knee OA patients with varying degrees of pain sensitization as determined by high and low PPS

**Study 6:** Exercise-induced hypoalgesia in people with knee osteoarthritis and healthy controls with normal and abnormal conditioned pain modulation

The aims of the sixth study were:
- To investigate changes in PPTs in response to acute aerobic and isometric exercise in knee OA patients with varying degrees of sensitization by comparing people with knee OA with abnormal CPM to those with normal CPM and pain-free controls
- To investigate for differences in the EIH response between knee OA patients with normal and abnormal CPM and between controls with normal and abnormal CPM
1.4.2 Methodological Overview

Study 1 involved a systematic review of 15 observational studies, including a meta-analysis using random effects of 9 studies on pain sensitization in knee OA. In study 2, intra-rater and inter-rater reliability of nerve palpation in 39 asymptomatic people were examined using intra-class correlation coefficients and Kappa correlation coefficients. Studies 3 and 4 were case-control studies assessing QST and NM measures in 52 people with knee OA and 38 healthy controls. In study 3, between-group comparisons were carried out using Mann Whitney U and Chi-Square tests. In study 4, the 52 knee OA patients were subdivided into 2 even-sized groups using a median split of PPT values. Comparisons between the 3 groups were carried out using Kruskal-Wallis tests and post-hoc Mann Whitney U and Chi Square tests. Studies 5 and 6 were case-control studies assessing EIH in 40 people with knee OA and 20 healthy controls as measured by changes in QST before, during, and after aerobic and isometric exercise. Between-group differences were assessed using repeated measures ANOVAs and within-group differences were tested using Wilcoxon signed rank tests. In study 5, knee OA patients were subdivided using a median split of PPTs and in study 6, knee OA patients were subdivided based on the presence of normal or abnormal CPM.

1.5 References


28. IASP. IASP Taxonomy. 2014.


Chapter 2

Study 1. Pain sensitization in people with knee osteoarthritis: A systematic review and meta-analysis

Fingleton C, Smart K, Moloney N, Fullen BM, Doody C
Osteoarthritis and Cartilage 2015 Jul; 23(7): 1043-1056
Study 1. Pain sensitization in people with knee osteoarthritis: A systematic review and meta-analysis

Study 2. Intraexaminer and interexaminer reliability of manual palpation and pressure algometry of the lower limb nerves in asymptomatic subjects

Study 3. Neural mechanosensitivity and pain sensitization in people with knee osteoarthritis

Study 4. A greater degree of pain sensitization is present in people with knee osteoarthritis with high versus low pressure pain sensitivity

Study 5. Exercise-induced hypoalgesia in people with knee osteoarthritis with high versus low pressure pain sensitivity

Study 6. Exercise-induced hypoalgesia in people with knee osteoarthritis with normal and abnormal conditioned pain modulation

Figure 2.1. Overview of Thesis and Relationship Between Studies
2.1 Abstract

**Objectives:** Emerging evidence suggests that pain sensitization plays an important role in pain associated with knee osteoarthritis (OA). This systematic review and meta-analysis examined the evidence for pain sensitization in people with knee OA and the relationship between pain sensitization and symptom severity.

**Methods:** A search of electronic databases and reference lists was carried out. All full text observational studies published between 2000 and 2014 with the aim of investigating pain sensitization in humans with knee OA using quantitative sensory testing (QST) measures of hyperalgesia and central hyperexcitability were eligible for inclusion. Meta-analysis of data was carried out where possible using a random effects model, which included results comparing knee OA participants to controls, and results comparing high symptom severity to low symptom severity. Other results were summarized in narrative format.

**Results:** Fifteen studies were identified following screening and quality appraisal. For the meta-analysis, pressure pain threshold (PPT) and heat pain threshold (HPT) means and standard deviations were pooled using random effects models. The point estimate was large for differences in PPTs between knee OA participants and controls \([-0.85; \text{ confidence interval (CI): } -1.1 \text{ to } -0.6]\), and moderate for PPT differences between knee OA participants with high symptom severity versus those with low symptom severity \([-0.51; \text{ CI: } -0.73 \text{ to } -0.30]\). A small point estimate was found for differences in HPTs between knee OA participants and controls \([-0.42; \text{ CI: } -0.87 \text{ to } 0.02]\). When sub-grouped into local and remote sites, a large point estimate was found for differences in remote HPTs between groups \([-0.86; \text{ CI: } -1.36 \text{ to } -0.36]\). Results summarized in narrative format were suggestive of widespread hyperalgesia, heightened spinal excitability and dysfunctional conditioned pain modulation in people with knee OA. Results were also suggestive of a possible association between symptom severity and sensitization, as measured by PPTs and temporal summation.

**Conclusions:** Evidence from this systematic review and meta-analysis suggests that pain sensitization is present in people with knee OA and may be associated with knee OA symptom severity. Implications for future research are discussed.
2.2 Introduction

Osteoarthritis (OA) of the knee is traditionally considered a progressive disorder of articular cartilage in the knee joint\(^1\). Pain presentations associated with knee OA vary considerably and often do not correlate with the severity of joint changes observed radiographically\(^2\). However, emerging evidence suggests that alterations in nociceptive processing within the peripheral and/or central nervous system may be an important factor in accounting for such variations in clinical presentations of pain associated with knee OA. A number of recent studies have investigated the presence of altered pain processing in knee OA but the precise mechanisms underlying pain sensitization in OA remain elusive\(^1\). Both peripheral and central neurophysiological mechanisms contribute to the pain of OA. Pain may result from nociceptors of the deep somatic tissue local to the knee becoming sensitized during inflammation (peripheral sensitization) and/or pathological neural signals from the joint causing central nervous system changes (central sensitization)\(^3\). A greater understanding of, and ability to clinically identify, pain mechanisms in knee OA could be integral to the designation and development of appropriate treatment interventions aimed at optimising pain relief.

There is currently no gold standard measure with which to assess for and identify the presence of pain sensitization in humans\(^4\). A number of different measures have been used to assess pain sensitization in people with knee OA. A commonly used method of assessment is quantitative sensory testing (QST), which involves the assessment of sensitivity to noxious or innocuous stimuli using standardised mechanical, thermal and/or electrical test modalities\(^5\), \(^6\). Studies have also employed tests of central pain augmentation processes believed to be involved in pain sensitization\(^1\), \(^4\), \(^7\) such as temporal summation, conditioned pain modulation and the flexor withdrawal reflex. Methods of assessing these mechanisms are described below. A recent systematic literature review considered evidence for the presence of sensitization in people with OA of the hip, knee, first carpometacarpal joint and lower limb\(^8\), and reported that the majority of the literature suggests that the central nervous system becomes hypersensitized in people with OA pain, while another systematic review presented a meta-analysis of pressure pain threshold
(PPT) data in people with osteoarthritis compared to healthy controls and reported that people with OA had lower PPTs at affected and remote anatomical test sites, suggesting pain sensitization\(^6\). No study to date has provided a meta-analysis of the evidence for pain sensitization specifically in people with OA of the knee. Therefore, to advance and expand upon the work of previous reviews, the aim of the current study was to conduct a meta-analytic review of the evidence for pain sensitization as measured by QST in people with knee OA specifically - with the secondary aim of meta-analytically investigating the presence of pain sensitization in people with knee OA who have high symptom severity versus those with low symptom severity.

2.3 Methods

2.3.1 Search Strategy

The study is reported in accordance with the PRISMA guidelines for the reporting of systematic reviews. Systematic searches of the following databases were conducted in June 2014: Pubmed 1950-2014, Web of Science 1970-2014, Medline 1948-2014, EMBASE 1980-2014, CINAHL Plus 1937-2014 and The Cochrane Library. Each database was searched using key word combinations. Three groups of keywords were compiled and combined (Figure 2.2). Search terms relating to pain sensitization, features of pain sensitization and knee osteoarthritis were included for identification of relevant articles. Titles were screened by CF and abstracts of potentially relevant articles were reviewed independently by two researchers (CF and CD). Full text articles of relevant abstracts were retrieved for further review by CF and CD. The two researchers then met to discuss which articles were suitable for inclusion and exclusion. Citations were imported into Endnote x5.

<table>
<thead>
<tr>
<th>Group 1 keywords</th>
<th>Group 2 keywords</th>
<th>MeSH terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Central/peripheral/pain) sensitization, hyperalgesia, central hypersensitivity, central hyperexcitability, allodynia, pain processing, pain modulation, pain threshold, pain pathophysiology, somatosensory, neuropathic pain, neuropathic-like pain</td>
<td>Knee osteoarthritis, knee OA, osteoarthritis of the knee, OA of the knee, knee arthritis, arthritis of the knee, knee arthralgia, arthralgia of the knee, degeneration of the knee</td>
<td>“Central nervous system sensitization”, “hyperalgesia” and “knee osteoarthritis”</td>
</tr>
</tbody>
</table>

Figure 2.2 Search Strategy
2.3.2 **Inclusion/Exclusion Criteria**

The main aim of potentially relevant studies had to be the investigation of pain sensitization using QST measures of hyperalgesia and central hyperexcitability in adult human participants, diagnosed with knee osteoarthritis via the American College of Rheumatology classification, radiographic evidence or people on a waiting list for total knee replacement (TKR). Papers had to be full text observational studies published in the English language in peer-reviewed academic journals, between 2000 and June 2014. A time limit was implemented in order to identify recent evidence. The exclusion criteria ruled out studies in which QST was not the primary testing method, experimental studies i.e. where an intervention was being evaluated, studies that did not assess measures of pain processing, review papers, and studies that included non-knee OA participants in the analysis. A flow diagram of study selection is detailed in Figure 2.3.

2.3.3 **Data Extraction**

Data extraction and analysis was carried out according to QST measures of pain sensitization utilised - only measures relating to pain processing were extracted and analysed. These included QST measures of hyperalgesia i.e pressure hyperalgesia, thermal hyperalgesia, and hyperalgesia to punctate and electrical stimuli, as well as QST measures of central hyperexcitability i.e temporal summation (TS), conditioned pain modulation (CPM) and flexor withdrawal response (FWR). For meta-analysis of data, means and standard deviations were sourced from the original papers when available, or by contacting the authors. Data that could not be retrieved was interpreted from graphs using digital ruler software (Pascal Free Ruler Version 1.7b5). Studies were classified by study design (case-control, cross sectional or cohort) for the purpose of quality appraisal.

2.3.4 **Quality Appraisal**

The methodological quality of case-control and cohort studies was assessed by two independent reviewers using the Newcastle Ottawa Quality Assessment Scale (NOS). The NOS is an appraisal tool for assessing the quality of non-randomised studies. The NOS is validated⁹ and has been recommended by the Cochrane Non-
Randomised Studies Methods Working Group\textsuperscript{10}. The scale uses a star rating system to judge quality based on three aspects of the study: selection of groups, comparability, and ascertainment of the outcomes of interest. A maximum of 9 stars can be awarded. Studies scoring $\geq 7/9$ are considered good quality; those scoring $\geq 5/9$ are fair quality and studies scoring 0-2/9 are poor quality\textsuperscript{11}. For cross-sectional studies, quality appraisal was carried out using the relevant criteria of the NOS checklist for cohort studies, as has previously been reported by Meeus et al\textsuperscript{10}. For the purpose of this review, 3/3 was considered a good quality cross sectional study, 2/3 was fair and 1/3 was considered poor quality. Studies scoring less than 40\% on methodological appraisal were excluded from the review\textsuperscript{8} i.e. studies with $< 4/9$ stars and studies with $< 2/3$ stars.

2.3.5 Data Analysis

The analysis was undertaken using Review Manager Software Package RevMan 5.1 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). Meta-analysis of data comparing knee OA participants to healthy controls was performed. In addition, meta-analysis was carried out on data comparing knee OA participants with high symptom severity to those with low symptom severity. Point estimates on the left side of the forest plots indicated increased features of pain sensitization in knee OA participants and were labelled ‘Sensitized’, while point estimates on the right side represented the opposite situation and were labelled ‘Non-sensitized’. Data that could not be pooled were summarised in narrative format. For continuous data where different scales were utilized for the assessment of the same outcome e.g. PPTs, the standardised mean differences (SMD) with 95\% confidence intervals (CI) were calculated\textsuperscript{12}. For continuous data where assessments were made on the same scale e.g. heat pain thresholds (HPTs), the mean differences (MD) with 95\% confidence interval were calculated\textsuperscript{12}. Meta-analyses were performed using a random effects model for analyses and pooled point estimate and 95\% confidence intervals were calculated with tests of heterogeneity\textsuperscript{12}. A funnel plot was conducted for visual inspection of publication bias in the primary meta-analysis (Figure 2.7). Point estimates of 0.20 were considered “small”, 0.50 was “medium” and 0.80 was considered “large”\textsuperscript{13}. The
level of significance was set at $p < 0.05$. Measurement areas of hyperalgesia were categorised into (i) local or (ii) remote. Local was defined as the area over the knee joint or adjacent to the knee joint. When multiple sites around the knee were tested, the site closest to the medial knee was chosen, as this is reported to be the most symptomatic area in people with OA knee\textsuperscript{14} and is the area of the knee most affected by radiographic change\textsuperscript{15}. Remote was defined as a site that was anatomically distant from the primary area of pain. When QST was measured at several remote sites, the furthest site from the knee was chosen.

![PRISMA Flow Chart]

**Figure 2.3 PRISMA Flow Chart**
2.4 Results

2.4.1 Search Strategy

The study selection process is presented in Figure 2.2. The screening process was carried out by two reviewers. Disagreement between authors was resolved by review of the full paper and further discussion. Fifteen studies were included in the final review (Table 2.1).

2.4.2 Study Characteristics

Seven case-control studies16-22, three cohort studies23-25 and five cross sectional studies26-30 were included in the review. Details of study characteristics are outlined in Table 2.1. A flow diagram of study selection is presented in figure 2.3.

2.4.3 Methodological Quality

Quality assessment was carried out by two researchers independently. There was an initial 86% agreement between researchers. Any disagreements were resolved by further review of papers until a consensus was reached. Six of the case-control/cohort studies were awarded 5/9 stars (fair quality)16, 18, 19, 22, 23, 25, while four case-control/cohort studies were awarded 4/9 stars (poor – fair quality)17, 20, 21, 24. Two cross-sectional studies were awarded 3/3 stars (good quality)26, 29 and 3 were awarded 2/3 stars (fair quality)27, 28, 30. All studies exceeded the 40% threshold for inclusion in the review. Methodological quality was compromised most commonly due to insufficiencies in the representativeness of the knee OA group and appropriate selection of controls (Table 2.2 & 2.3).
**Table 2.1 Summary of Study characteristics and Main Findings**

<table>
<thead>
<tr>
<th>Article</th>
<th>Participants</th>
<th>Hyperalgesia measures (hyperalgesia to pressure, thermal, punctate and electrical stimulation)</th>
<th>Measures of central hyperexcitability (CPM, TS, FWR)</th>
<th>Results summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arendt-nielsen 2010</td>
<td>A. 24 moderate/severe (VAS&gt;6) Knee OA participants (50% female) Mean age: 63.6 Mean pain duration: 95.6 months B. 24 mild/moderate (VAS&lt;6) knee OA participants (50% female) Mean age: 61.7 Mean pain duration: 78.7 months C. 24 healthy controls (50% female) Mean age: 61.6 Diagnosis: ACR classification</td>
<td>1. PPTs using pressure algometry on 8 sites in peripatellar region, tibialis anterior &amp; extensor carpi radialis longus bilaterally</td>
<td>1. Temporal summation of pressure pain using repeated stimuli from computer controlled pressure algometer 2. CPM provocation with cuff compression on arm. PPTs at the knee measured during and 5 minutes after test.</td>
<td>Group A PPTs were greater than control PPTs, Group A &amp; B TS was higher than control TS. Group A &amp; B CPM was greater than control CPM.</td>
</tr>
<tr>
<td>Courtney 2009</td>
<td>A. 20 knee OA participants Mean age: 61 Mean pain duration: 12.5 yrs B. 20 controls Mean age: 60 (60% female) Diagnosis: Kellgren-Lawrence Scale</td>
<td>No hyperalgesia measure used</td>
<td>1. Flexor withdrawal response using electrocutaneous stimulation at medial arch of foot</td>
<td>Significantly reduced FWR threshold in OA affected limb versus control group.</td>
</tr>
<tr>
<td>Finan 2012</td>
<td>113 participants with knee OA (66.7% female) 4 subgroups: A. low pain/low knee OA grade=24 B. high pain/high knee OA grade=32 C. low pain/high knee OA grade=27 D. high pain/low knee OA grade=30 Mean pain duration: 6.53yrs Diagnosis: ACR classification, &gt;2 Kellgren-Lawrence Scale, pain &gt;2/10 on NRS &gt;4 days/week</td>
<td>1. PPTs (handheld algometry) at upper trapezius bilaterally &amp; quadriceps insertion on index knee</td>
<td>1. Temporal summation assessed by repeated punctate stimulation at dorsal aspect middle finger &amp; patella of index knee 2. Temporal summation assessed by VAS response to repeated heat pulses (51 degrees) to dorsal forearm 3. CPM provocation by cold pressor test. PPTs measured at trapezius before &amp; after test.</td>
<td>Significantly heightened pain sensitivity in the high pain/low knee OA grade group, while the low pain/high knee OA grade group was less pain-sensitive.</td>
</tr>
<tr>
<td>Graven-nielson 2012</td>
<td>48 knee OA patients (75% female) Mean age: 65 Mean pain duration: 80 months (20 of these underwent TKR) B. 21 age and sex matched controls Mean age: 60 Diagnosis: radiographic</td>
<td>1. PPTs (handheld pressure algometry) at 7 sites in peripatellar region, lower leg &amp; forearm bilaterally 2. PPT (Cuff pressure algometry) at lower leg</td>
<td>1. CPM was provoked by cuff compression of arm with ischaemic arm exercise. PPTs at 2 knee sites &amp; lower leg cuff algometry was carried out during the test</td>
<td>Significantly reduced PPTs in knee, lower leg and forearm muscle in OA participants compared to controls. Dysfunctional CPM present in OA participants. Normalization of PPTs and CPM post TKR</td>
</tr>
<tr>
<td>Article</td>
<td>Participants</td>
<td>Hyperalgesia measures <em>(hyperalgesia to pressure, thermal, punctate and electrical stimulation)</em></td>
<td>Measures of central hyperexcitability <em>(CPM, TS, FWR)</em></td>
<td>Results summary</td>
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</tbody>
</table>
| Imamura 2008 | A. 62 female knee OA participants  
Mean age: 71.1  
Mean pain duration: 99.8 months  
B. 22 healthy controls  
Mean age: 68.95  
Diagnosis: ACR classification, 2-4 on Kellgren-Lawrence scale, VAS >=4 | 1. PPTs with handheld algometry: Subcutaneous hyperalgesia on dermatome levels L1-S2; Myotomal hyperalgesia on 9 Lower limb muscles; Sclerotomal hyperalgesia on supraspinal ligaments L1-S2, patellar tendon, pes anserinus bursae bilaterally | No measure of central hyperexcitability used | Significantly reduced PPTs at subcutaneous dermatomes *(p<0.001)*, myotomal structures *(p<0.001)* & sclerotomal structures compared to controls. |
| Kavchak 2012 | A. 16 knee OA participants  
(81.25% female)  
Mean age: 52  
Mean pain duration: 4.09yrs  
B. 16 healthy controls  
Mean age: 51  
Diagnosis: by orthopaedic physician, Kellgren-Lawrence scale >=2 | 1. PPTs using handheld algometry at MJL & lower leg unilaterally | No measure of central hyperexcitability used | Significantly reduced PPTs at MJL in knee OA participants |
| King 2013 | A. 113 with low symptom severity  
(73% female)  
Mean pain duration: 24.7 months  
B. 96 with high symptom severity  
(67% female)  
Mean pain duration: 57.8 months  
C. 107 healthy controls (66.7% female)  
Diagnosis: ACR classification, including self-reported knee pain | 1. PPTs at medial and lateral joint lines of the knee unilaterally, middle portion of quadriceps, forearm, trapezius  
2. HPT at forearm using a computer-controlled Medoc Pathway  
3. Cutaneous sensitivity at back of hand & patella using monofilaments | 1. Temporal summation using repeated thermal pulses at forearm  
2. Temporal summation using repeated punctate stimulation  
3. CPM using by cold pressor test. HPTs tested before and after | Significantly reduced PPTs in knee OA participants compared to controls.  
Significantly reduced PPTs in high symptom severity group compared to low symptom severity group.  
Greater facilitation of TS in high symptom severity group compared to low symptom severity group  
No significant difference for HPT between groups. |
| Lee 2011 | A. 26 knee OA participants (76.9% female)  
Mean age: 59  
Mean pain duration: not reported  
B. 33 healthy controls (69.7% female)  
Mean age: 57.7  
Diagnosis: documented in medical record | 1. PPTs using handheld pressure algometry locally at quadriceps and remotely at trapezius, first metacarpophalangeal joint  
2. HPTs with medoc thermal sensory analyser at ventral forearm  
3. Heat pain rating with medoc thermal sensory analyser at ventral forearm & NRS  
4. Cold pain rating with cold pressor test & NRS | No measure of central hyperexcitability used | Significantly reduced PPTs locally & remotely in knee OA group compared to controls.  
Significantly higher heat pain ratings in knee OA group compared to controls.  
Non-significant trend for lower HPTs in knee OA group versus controls.  
No significant difference in cold pain ratings between knee OA group & controls. |
<table>
<thead>
<tr>
<th>Article</th>
<th>Participants</th>
<th>Hyperalgesia measures (hyperalgesia to pressure, thermal, punctate and electrical stimulation)</th>
<th>Measures of central hyperexcitability (CPM, TS, FWR)</th>
<th>Results summary</th>
</tr>
</thead>
</table>
| Lundblad 2008 | A. 69 knee OA participants for TKR (51% female)  
Mean age: 68  
Mean pain duration: 8.5yrs  
B. 24 controls  
Mean age not reported  
Diagnosis: on TKR waiting list | 1. Pain threshold with pain matcher (electrical stimulus at finger) | No measure of central hyperexcitability used | Significantly reduced pain threshold remotely at the hand compared to controls. |
| Neogi 2013 | 2,126 participants with/at risk of knee OA (61% female)  
Mean age: 68  
Mean pain duration: not reported  
Diagnosis: radiographic | 1. PPTs with handheld algometer at patella bilaterally & at radioulnar joint | 1. TS with weighted monofilament | PPT and TS were significantly associated with pain severity. Knee OA duration and radiographic severity were not associated with PPT or TS. |
| Skou 2013a | 40 people post revision TKR  
A. 20 with pain (70% female)  
Mean age: 61.5  
Mean pain duration: 167 months  
B. 20 without pain (40% female)  
Mean age: 65.7  
Mean pain duration: 64.3 months  
Diagnosis: end stage knee OA patients who underwent TKR & revision TKR | 1. PPTs at 8 sites in peripatellar area & lower leg with handheld pressure algometry bilaterally  
2. PPT using cuff algometry at heads of gastrocnemius | 1. TS with computer-controlled pressure algometry at lower leg  
2. CPM was provoked by cuff compression of arm. PPT sites assessed before, during & 5 minutes after | Significantly decreased cuff PPTs at the lower leg in the group with pain post revision TKR compared to the group without pain post revision TKR. Dysfunctional CPM and significantly greater facilitation of TS were present in the group with pain post revision TKR compared to the group without pain post revision TKR. |
| Skou 2013b | 17 knee OA participants (24% female)  
8/17 had undergone TKR  
Mean age: 65.1  
Mean pain duration: 115.1 months  
Diagnosis: radiological & symptomatic knee OA | 1. PPTs at 8 sites in peripatellar area & lower leg with handheld pressure algometry unilaterally  
2. PPTs using computer-controlled pressure algometry on most sensitive peripatellar site & lower leg  
3. PPT using cuff algometry at heads of gastrocnemius | 1. TS with computer-controlled pressure algometry at most sensitive site & lower leg  
2. CPM was provoked by cuff compression of arm. PPT sites assessed before, during & 5 minutes after. | PPTs at the lower leg and TS accounted for 55% of the variance in perceived maximal pain intensity in people with knee OA |
<table>
<thead>
<tr>
<th>Article</th>
<th>Participants</th>
<th>Hyperalgesia measures (hyperalgesia to pressure, thermal, punctate and electrical stimulation)</th>
<th>Measures of central hyperexcitability (CPM, TS, FWR)</th>
<th>Results summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skou 2013c</td>
<td>73 knee OA/revision TKR participants</td>
<td>1. PPTs at lower leg and forearm using pressure algometry unilaterally</td>
<td>1. TS with computer-controlled pressure algometry at most knee &amp; lower leg</td>
<td>PPTs at lower leg &amp; forearm in Group 4 significantly lower than groups 1-3.</td>
</tr>
<tr>
<td></td>
<td>A. 26 knee OA participants with high local PPTs (38% female)</td>
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<td>TS significantly facilitated in groups 3-4 compared to groups 1-2.</td>
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<tr>
<td></td>
<td>Mean age: 64</td>
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<td></td>
<td>Mean pain duration: 86.6 months</td>
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<td>B. 27 knee OA participants with low local PPTs (56% female)</td>
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<td></td>
<td>Mean age: 61</td>
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<td>Mean pain duration: 152.2 months</td>
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<td>C. 10 revision TKR participants with high local PPTs (70% female)</td>
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<td>Mean age: 61</td>
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<td>Mean pain duration: 130.9 months</td>
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<td>D. 10 revision TKR participants with low local PPTs (70% female)</td>
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<td></td>
<td>Mean age: 61.5</td>
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<tr>
<td></td>
<td>Mean pain duration: 130.9 months</td>
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<td></td>
<td>Diagnosis: ACR classification</td>
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<tr>
<td>Wylde et al. 2011</td>
<td>A. 107 knee OA participants (48% female)</td>
<td>1. PPTs with handheld algometry at forearm &amp; medial knee unilaterally</td>
<td></td>
<td>Significantly lower median PPTs in knee OA patients compared to controls</td>
</tr>
<tr>
<td></td>
<td>Mean age: 69</td>
<td>2. Warm/cold detection &amp; hot/cold PPTs using a QST analyser at forearm &amp; medial knee</td>
<td></td>
<td>32% had local pressure hyperalgesia &amp; 20% had distant pressure hyperalgesia.</td>
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<td></td>
<td>Mean pain duration: 6 years</td>
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<td>No significant difference in HPTs between groups</td>
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<td></td>
<td>B. 50 healthy controls</td>
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<td></td>
<td>Mean age: 68</td>
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<td></td>
<td>Diagnosis: on waiting list for TKR</td>
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<tr>
<td>Wylde et al. 2013</td>
<td>A. 51 knee OA patients (57% female)</td>
<td>1. PPTs with handheld algometry at forearm &amp; medial knee unilaterally</td>
<td></td>
<td>Significantly lower PPTs in knee OA group at knee &amp; forearm compared to controls</td>
</tr>
<tr>
<td></td>
<td>Mean age: 68</td>
<td>2. HPTs using a QST analyser at forearm &amp; medial knee</td>
<td></td>
<td>Statistically significant correlation between pre-op forearm PPTs and WOMAC pain 1 year post TKR.No significant difference in HPTs between groups &amp; no significant correlation between HPTs and post op WOMAC pain.</td>
</tr>
<tr>
<td></td>
<td>Mean pain duration: not reported</td>
<td></td>
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<tr>
<td></td>
<td>All underwent TKR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B. 50 healthy controls (42% female)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean age: 69</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diagnosis: on waiting list for TKR</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TS = temporal summation; CPM = conditioned pain modulation; FWR = flexor withdrawal response; ACR = American College of Rheumatology; OA = osteoarthritis; CPM = conditioned pain modulation; PPT = pressure pain threshold; QST = quantitative sensory testing; HPT = heat pain threshold; MJL = medial joint line; TKR = total knee replacement; *Other Non QST or non pain processing outcome measures were not included in the analysis
### Table 2.2 Quality Appraisal Case-control Studies

<table>
<thead>
<tr>
<th>Case-control studies</th>
<th>S1: Adequate Case Definition</th>
<th>S2: Representativeness of cases</th>
<th>S3: Selection of Controls</th>
<th>S4: Definition of Controls</th>
<th>Ca: Controlled for age/gender</th>
<th>Cb: Controlled for additional factor</th>
<th>E1: Ascertainment of Exposure</th>
<th>E2: Same method for cases &amp; controls</th>
<th>E3: Non-response rate</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arendt-Nielsen 2010</td>
<td>★</td>
<td></td>
<td></td>
<td></td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>5/9 stars</td>
</tr>
<tr>
<td>Courtney 2009</td>
<td>★</td>
<td></td>
<td></td>
<td></td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>4/9 stars</td>
</tr>
<tr>
<td>Imamura 2008</td>
<td>★</td>
<td></td>
<td></td>
<td></td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>4/9 stars</td>
</tr>
<tr>
<td>Kaychak 2012</td>
<td>★</td>
<td></td>
<td></td>
<td></td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>5/9 stars</td>
</tr>
<tr>
<td>Wylde 2012</td>
<td>★</td>
<td></td>
<td></td>
<td></td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>4/9 stars</td>
</tr>
<tr>
<td>King 2013</td>
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<td></td>
<td></td>
<td></td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>5/9 stars</td>
</tr>
<tr>
<td>Lee 2011</td>
<td>★</td>
<td></td>
<td></td>
<td></td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>5/9 stars</td>
</tr>
</tbody>
</table>

S = selection; C = comparability; E = exposure
Table 2.3 Quality Appraisal Cohort/Cross-sectional Studies

<table>
<thead>
<tr>
<th>Cohort/Cross-sectional studies</th>
<th>S1: Representativeness of exposed cohort</th>
<th>S2: Selection of non-exposed cohort</th>
<th>S3: Ascertainment of exposure</th>
<th>S4: Outcome of interest not present at start</th>
<th>Ca: Study controls for age/gender</th>
<th>Cb: Study controls for additional factor</th>
<th>O1: Ax of outcome</th>
<th>O2: Long enough follow-up</th>
<th>O3: Adequate follow up</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finan 2012</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td></td>
<td>3/3 stars</td>
</tr>
<tr>
<td>Graven-Nielsen 2012</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
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<td>★</td>
<td>★</td>
<td>★</td>
<td></td>
<td>5/9 stars</td>
</tr>
<tr>
<td>Lundblad 2008</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td></td>
<td></td>
<td>4/9 stars</td>
</tr>
<tr>
<td>Neogi 2013</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td></td>
<td>3/3 stars</td>
</tr>
<tr>
<td>Skou 2013a</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td></td>
<td></td>
<td>2/3 stars</td>
</tr>
<tr>
<td>Skou 2013b</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td></td>
<td></td>
<td>2/3 stars</td>
</tr>
<tr>
<td>Skou 2013c</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td></td>
<td></td>
<td>2/3 stars</td>
</tr>
<tr>
<td>Wylde 2013</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td></td>
<td></td>
<td>5/9 stars</td>
</tr>
</tbody>
</table>

S = selection; C = comparability; O = outcome
Cohort studies marked out of 9 stars, cross-sectional studies marked out of 3 stars
2.4.4 Evidence for Pain Sensitization

Results are presented under headings according to the measures of pain sensitization employed. Meta-analyses of pressure hyperalgesia and heat hyperalgesia are reported below. Results that could not be pooled are summarised in narrative format. Table 2.1 outlines the characteristics of included studies.

a) Pressure Hyperalgesia

Eleven studies evaluated the presence of hyperalgesia in people with knee OA using measures of PPT\textsuperscript{16-19, 21-23, 25-28}. Eight studies compared PPTs in knee OA participants to healthy controls using handheld pressure algometry and were included in the meta-analysis\textsuperscript{16-19, 21-23, 25} (Figure 2.4). From a total of 1003 participants: from whom one local and one remote PPT were included (total assessments n = 2006), the point estimate for differences in PPTs between knee OA participants and controls was -0.86 (-1.09 to -0.62), indicating greater pressure pain sensitivity in people with knee OA (p < 0.001). A high level of heterogeneity was present ($I^2 = 82\%$, p < 0.001). The funnel plot was symmetrical indicating no significant publication bias (Figure 2.7). A meta-analysis comparing Local PPTs between participants with knee OA and controls found that, from 1003 participants, the point difference was -0.97 (-1.38 to -0.56) indicating greater local pressure pain sensitivity in people with knee OA (p < 0.001). Again, a high level of heterogeneity was present ($I^2 = 88\%$, p < 0.001). Similarly, a meta-analysis of Remote PPTs from 1003 participants demonstrated a point prevalence of -0.74 (-0.99 to -0.49) in favour of greater remote pressure pain sensitivity in the knee OA group (p < 0.001). Heterogeneity was high ($I^2 = 69\%$, p < 0.01).

Results from three studies comparing knee OA participants with high symptom severity to knee OA participants with low symptom severity\textsuperscript{18,19,26} were pooled in a meta-analysis (Figure 2.5). From a total of 316 participants: from whom one local and one remote PPT were included (total assessments n = 632), the point estimate was -0.51 (-0.73 to -0.30), indicating greater pressure pain sensitivity in the high symptom severity group (p < 0.001). Heterogeneity was low ($I^2 = 36\%$, p = 0.16). A meta-analysis of Local PPTs in knee OA participants with high versus low symptom
severity found that, from 316 participants, the point difference was -0.57 (-0.80 to -0.34), in favour of greater local pressure pain sensitivity in those with high symptom severity (p < 0.001). There was no evidence of heterogeneity found (I² = 0%, p < 0.58). Similarly, a meta-analysis of Remote PPTs from 316 participants demonstrated a point prevalence of -0.48 (-0.91 to -0.06) in favour of greater remote pressure pain sensitivity in the high symptom severity group (p < 0.05). Heterogeneity was moderate (I² = 62%, p = 0.07).

Three additional studies²³,²⁷,²⁹, including one large cross-sectional study of 2,126 people with knee OA²⁹, found a significant correlation between pressure pain sensitivity and symptom severity. Neogi et al²⁹ also reported that knee OA duration and radiographic severity were not significantly associated with pressure pain sensitivity (p>0.05). Similarly, Skou et al²⁷ found no correlation between knee OA pain duration and pressure pain sensitivity (p = 0.17).

In relation to studies which measured PPTs pre- and post-total knee replacement (TKR), Graven-Nielsen et al²³ showed that at 5 – 28 weeks post TKR, pressure pain sensitivity significantly reduced at all sites (p < 0.04). However, Skou et al²⁷ identified increased pressure pain sensitivity in people who had pain post revision-TKR compared to those who were pain-free post revision-TKR. A further study by Skou et al³⁰ demonstrated that people with high pressure pain sensitivity at the knee post revision-TKR had greater levels of widespread pressure pain sensitivity than people with knee OA (who had not undergone TKR). Wylde et al²⁵ investigated predictors of persistent pain post TKR and found that people with pressure pain sensitivity at the forearm (remote site) prior to TKR had significantly worse 1 year WOMAC pain scores than people with less pressure pain sensitivity at the forearm preoperatively (p = 0.031).
**Figure 2.4** Meta-analysis of Pressure Pain Thresholds: Knee OA Group Vs Controls

*Note data from Arendt-Nielsen & Graven-Nielsen are interpreted from graphed results*
Figure 2.5 Meta-analysis of Pressure Pain Thresholds: High Vs Low Symptom Severity

*Note data from Arendt-Nielsen are interpreted from graphed results
b) Thermal Hyperalgesia

The presence of hyperalgesia to hot and cold stimuli has been found in people with chronic musculoskeletal pain\textsuperscript{31, 32}. The response of participants with knee OA to thermal stimuli was investigated in five studies\textsuperscript{16-18, 25, 26}.

Heat Hyperalgesia

Four studies comparing heat pain thresholds (HPTs) in people with knee OA to healthy controls were pooled in a meta-analysis\textsuperscript{16-18, 25} (Figure 2.6). From a total of 740 participants: from whom one local and one remote HPT were included (total assessments n = 1421 – one study measured remote HPT only\textsuperscript{16}), the point estimate for differences in HPTs between people with knee OA and controls was -0.42 (-0.87 to 0.02), suggesting no significant difference in heat pain sensitivity between knee OA participants and controls (p = 0.06). There was a low level of heterogeneity ($I^2 = 30\%$, $p = 0.18$). A meta-analysis comparing Local HPTs between participants with knee OA and controls found that, from a total of 681 participants, the point difference was 0.04 (-0.58 to 0.66), indicating no significant difference between the knee OA group and controls ($p = 0.90$) and a low level of heterogeneity was present ($I^2 = 27\%$, $p = 0.25$). A meta-analysis of Remote HPTs from a total of 740 participants demonstrated a point prevalence of -0.86 (-1.36 to -0.36) indicating significantly greater remote heat pain sensitivity in people with knee OA ($p < 0.001$). There was no evidence for heterogeneity ($I^2 = 0\%$, $p = 0.79$).

With regard to verbal heat pain ratings, Lee et al\textsuperscript{16} found that people with knee OA had higher remote heat pain ratings than healthy controls ($P < 0.05$), while King et al\textsuperscript{18} found that participants with high symptomatic knee OA reported greater pain upon reaching their HPT at the knee and forearm compared to the control and low symptomatic OA group ($P < .05$), after controlling for the temperature. Similarly, Finan et al\textsuperscript{26} found that a knee OA group with high pain intensity/low disease severity had significantly more thermal phasic pain in the forearm than other knee OA groups.
### Figure 2.6 Meta-analysis of Heat Pain Thresholds: Knee OA Group Vs Controls

#### 1.2.1 Local

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>People with Knee OA</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>King 2013 High</td>
<td>41.6</td>
<td>3.5</td>
</tr>
<tr>
<td>King 2013 Low</td>
<td>42.1</td>
<td>2.98</td>
</tr>
<tr>
<td>Wylde 2011</td>
<td>44.07</td>
<td>3.75</td>
</tr>
<tr>
<td>Wylde 2013</td>
<td>43.77</td>
<td>3.91</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>367</strong></td>
<td><strong>314</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.11; Chi² = 4.13, df = 3 (P = 0.25); I² = 27%
Test for overall effect: Z = 0.12 (P = 0.90)

#### 1.2.2 Remote

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>People with Knee OA</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>King 2013 High</td>
<td>41.4</td>
<td>3.25</td>
</tr>
<tr>
<td>King 2013 Low</td>
<td>42.1</td>
<td>2.98</td>
</tr>
<tr>
<td>Lee 2011</td>
<td>43.7</td>
<td>3.5</td>
</tr>
<tr>
<td>Wylde 2011</td>
<td>43.03</td>
<td>4.31</td>
</tr>
<tr>
<td>Wylde 2013</td>
<td>42.57</td>
<td>4.08</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>393</strong></td>
<td><strong>347</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 1.70, df = 4 (P = 0.79); I² = 0%
Test for overall effect: Z = 3.39 (P = 0.0007)

**Total (95% CI)**

<table>
<thead>
<tr>
<th>Mean Difference</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.42</td>
<td>[-0.87, 0.02]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.13; Chi² = 11.35, df = 8 (P = 0.18); I² = 30%
Test for overall effect: Z = 1.88 (P = 0.06)
Test for subgroup differences: Chi² = 4.95, df = 1 (P = 0.03), I² = 79.8%

Figure 2.6 Meta-analysis of Heat Pain Thresholds: Knee OA Group Vs Controls
Cold Hyperalgesia
It was not possible to perform meta-analysis on the cold pain threshold (CPT) data because of heterogeneity of measures and absence of control data. Overall, no evidence of cold pain sensitivity was evident in the review. King et al\textsuperscript{18} found no significant difference in cold pain thresholds (CPT) between knee OA participants and controls (p>0.05). Similarly, Lee et al\textsuperscript{16} found no significant difference between knee OA participants and controls for cold pain measured by the cold pressor test, while Finan et al\textsuperscript{26} also identified no significant difference between groups of knee OA participants for cold pressor test pain ratings. Cold pain thresholds were also measured in Wylde et al\textsuperscript{17} but were excluded from analysis, as a large number of participants did not perceive cold pain before the safety cut-off temperature of 5 degrees Celsius.

c) Hyperalgesia to Punctate & Electrical Stimulation
King et al\textsuperscript{18} demonstrated the presence of hyperalgesia to punctate stimulation in people with knee OA compared to controls (p<0.01). Similarly, Lundblad et al\textsuperscript{24} demonstrated that people with knee OA had significantly lower pain thresholds in response to an electrical stimulus delivered remotely at the hand than controls (p = 0.012).
d) **Temporal Summation**

Increased temporal summation (TS) or wind-up is a measure of spinal hyperexcitability in which the summation of repeated C-fibre input produces an augmented response\(^{33}\) and is tested by means of repeated noxious stimulation. Four studies demonstrated increased facilitation of TS in knee OA participants\(^{18,19,26,27}\). Both Arendt-Nielsen et al\(^{19}\) and King et al\(^{18}\) demonstrated greater facilitation of TS at local (knee) and remote (forearm) sites in a knee OA group compared to a non-knee OA group. Arendt-Nielsen et al\(^{19}\) and King et al\(^{18}\) demonstrated greater facilitation of TS in participants with knee OA with higher levels of symptom severity than in participants with less symptom severity and controls. Similarly, in the study by Finan et al\(^{26}\), participants with high pain intensity/low OA severity had a greater TS response at a remote site (finger), than other knee OA participants; however, no significant differences were found between groups for TS measures taken locally at the knee. In a large cross-sectional study of 2126 knee OA participants, Neogi et al\(^{29}\) found a significant correlation between TS and pain severity (\(p < 0.05\)). Neogi et al\(^{29}\) also found TS was not associated with radiographic changes or knee OA duration; conversely, Arendt-Nielsen et al\(^{19}\) and Skou et al\(^{27}\) both demonstrated a statistically significant correlation between TS and knee OA pain duration (\(p < 0.05\)).

In relation to TS pre and post TKR, Skou et al\(^{28}\) showed that increased TS was present in participants with pain post revision TKR compared to participants without pain post revision TKR when measured remotely at the tibialis anterior muscle. A further report by Skou et al\(^{30}\) indicated that TS was facilitated in people with and without high pressure pain sensitivity post revision-TKR compared to people with knee OA (who had not undergone TKR).

e) **Flexor Withdrawal Reflex**

The flexor withdrawal reflex (FWR) is a measure of spinal excitability\(^{1}\) and has been used to demonstrate sensitization in other chronic pain conditions, including chronic whiplash and fibromyalgia\(^{34}\). Courtney et al\(^{20}\) found people with knee OA to have significantly lower FWR threshold than healthy controls (\(P = 0.001\), with
specific differences between the more affected limb in the knee OA participants (P < .001).

f) Conditioned Pain Modulation
Conditioned pain modulation (CPM) is an endogenous pain inhibitory mechanism, which has been found to be impaired in many chronic pain populations\textsuperscript{35, 36}. Assessment of CPM involves the evaluation of a painful test stimulus in the absence and presence of a second painful (conditioning) stimulus applied to a remote site\textsuperscript{37}.

Two studies demonstrated a dysfunctional CPM response in people with knee OA\textsuperscript{19, 23}. Both Arendt-Nielsen et al\textsuperscript{19} and Graven-Nielsen et al\textsuperscript{24} showed dysfunctional CPM at local (knee) sites in a knee OA group compared to a non-knee OA group; however results differed in relation to remote sites. Graven-Nielsen et al\textsuperscript{23} reported CPM dysfunction at the tibialis anterior (TA), while Arendt-Nielsen et al\textsuperscript{19} found a normal CPM response at the TA, but an abnormal response at the forearm – both studies evoked CPM using cuff pressure and used handheld pressure algometry as the test stimulus. Using the cold pressor test as the conditioning stimulus with the test stimulus being handheld pressure algometry, Finan et al\textsuperscript{26} found a normal CPM response at the trapezius muscle in four groups of knee OA participants with varying levels of symptom and disease severity. In relation to CPM pre and post TKR, Graven-Nielsen et al\textsuperscript{23} found that a CPM stimulus caused a reduction in pressure sensitivity at the knee and a non-significant trend for reduced pressure sensitivity at the lower leg in knee OA participants after TKR. In contrast, Skou et al\textsuperscript{27} found that participants who still had pain post revision-TKR demonstrated a dysfunctional CPM response, but a normal CPM response was found in those without pain post revision-TKR. In King et al\textsuperscript{38}, CPM, provoked by the cold pressor test and tested using HPTs, showed no significant pain inhibiting effect on knee OA or control participants.
2.5 Discussion

2.5.1 Findings

Large standardised mean differences in pressure pain sensitivity between people with knee OA and healthy controls are suggestive of nervous system sensitization in this population. This evidence is supported by additional findings of widespread hyperalgesia in response to pressure, punctate and electrical stimuli and by findings from a previous meta-analysis of PPTs. While local findings may indicate peripheral nervous system changes due to prolonged inflammatory processes, findings of hyperalgesia remote to the knee suggest the involvement of the central nervous system. These central changes are thought to be initiated by ongoing pathological neuronal signals from the joint. Spinal hyperexcitability was demonstrated in knee OA participants in 5 studies in this review, exhibited via increased temporal summation and an exaggerated flexor withdrawal reflex. Results from this review also suggest that endogenous pain inhibitory mechanisms such as conditioned pain modulation are dysfunctional in people with knee OA. These findings of sensitization in people with knee OA indicate the potential for additional treatment targets in this cohort where treatment options are generally limited.

Results reported in this review are largely in keeping with sensitization characteristics that have been reported in other chronic pain conditions. As such, these conditions appear to share similar pain mechanisms; though, the degree to which this altered processing drives pain appears to vary between conditions and from person to person. While central mechanisms seem to be the driving force behind chronic pain conditions such as chronic whiplash and fibromyalgia, it appears to be a subgroup of people with knee OA whose pain is dominated by sensitization. For example, in Finan et al, features of pain sensitization were especially apparent in participants with high pain intensity and low disease severity. Additionally, in contrast to findings from other chronic pain populations, results from the current review suggest that cold hyperalgesia may not be a dominant feature in knee OA pain, with three studies showing no difference in cold pain sensitivity between knee OA participants and controls.
In relation to heat hyperalgesia, the meta-analysis indicated no significant difference in HPTs between people with knee OA and controls. Though, interestingly, when HPTs were sub-grouped into local and remote sites, people with knee OA were found to have significantly greater heat pain sensitivity at remote sites compared to controls, but not at local sites. It is possible that the lack of a significant difference locally between knee OA participants and controls may be linked to the presence of local hypoaesthesia, another sensory abnormality which has been found in people with knee OA\textsuperscript{16} and other pain conditions\textsuperscript{31, 42}, and which could potentially influence sensitivity to heat pain. However, such analysis is beyond the scope of this review and warrants further investigation.

The comparison between knee OA participants and healthy controls, while invaluable for determining the presence of altered pain processing in people with knee OA, is limited in terms of deciphering the role that peripheral disease state and pain severity play in pain sensitization. Comparing knee OA participants to each other (e.g. high symptom severity versus low symptom severity; pre-surgery versus post surgery etc.) provides additional information regarding factors that influence pain sensitization in people with knee OA. A relationship between symptom severity and pain sensitization, as measured by widespread hyperalgesia and temporal summation, is suggested by results from this review. Meta-analysis of data demonstrated significantly greater widespread hyperalgesia in knee OA participants with high symptom severity compared to those with low symptom severity (SMD = -0.51). A cross-sectional study of 2,126 people with knee OA support this relationship and showed symptom severity to be significantly correlated with pressure pain sensitivity and TS\textsuperscript{29}. Three additional studies reported greater spinal hyperexcitability, via TS, in subjects with high symptom severity versus lower symptom severity\textsuperscript{18, 19, 26}. Furthermore, the large cross-sectional study by Neogi et al\textsuperscript{29} reported that pain sensitization was not associated with radiographic severity\textsuperscript{29} and Finan et al\textsuperscript{26} demonstrated significantly heightened pain sensitivity in a group with high pain severity and low disease severity. These results indicate a possible link between symptom severity and sensitization, which is independent of radiographic disease severity, and lend
support to the concept that peripheral pathology is not the sole driver of painful symptoms in knee OA. However, conflicting results in relation to sensitization and symptom severity have also been reported by studies that used alternative outcome measures. Courtney et al\textsuperscript{20} found no significant relationship between FWR threshold, another measure of spinal hyperexcitability, and resting pain. Drivers of spinal hyperexcitability are not fully understood\textsuperscript{1}; it is possible that FWR and TS are mediated by slightly different mechanisms. Additionally, Finan et al\textsuperscript{26} found no significant difference in CPM levels between 4 groups of knee OA participants with varying symptom severity; though CPM was within normal limits in all participants in this study. Further investigation is recommended to establish this possible association.

While there is some evidence suggesting that sensitization is linked to pain severity in knee OA, it is yet to be established whether pain sensitivity in this cohort is principally maintained by peripheral pathology. Indeed, the degree of sensitization in knee OA may differ from chronic pain conditions such as fibromyalgia and chronic whiplash due to the presence of an identifiable peripheral pathology in knee OA. Graven-Nielsen et al\textsuperscript{23} demonstrated normalisation of PPTs and CPM post joint replacement, and normalisation of pain sensitivity tests has also been reported post total hip replacement\textsuperscript{43}; these findings imply that central changes may be reversible after interventions directed towards peripheral pain generators. However, Skou et al\textsuperscript{27} demonstrated pain sensitivity in people with ongoing pain post revision-TKR. The existence of a cohort whose pain is unresolved post repeated surgical intervention suggests that sensitization post surgery may be associated with maintained changes in central pain processing and may be independent of peripheral drivers of pain.

For individuals whose disorder is characterised by sensitization, there is the possibility that central hyperexcitability may be present before knee OA develops, as suggested by Neogi et al\textsuperscript{29} in response to findings that duration and radiographic severity of knee OA were not associated with sensitization. The absence of a relationship between disease course and sensitization suggests that
there are individuals who may be predisposed to sensitization, and that this trait is uncovered in the presence of nociceptive input from knee OA pathology. Phenotypic and genetic markers associated with chronic pain have been identified\textsuperscript{44}. Phenotypic markers such as pain catastrophising and depression have been found to be significantly associated with QST measures of pain sensitization\textsuperscript{26, 45}, while genetic markers most commonly linked to musculoskeletal pain are those relating to adrenergic and serotonergic pathways\textsuperscript{46}. A recent review of genetic studies points to certain genes that contribute to increased pain sensitivity and that are also associated with an increased risk of developing chronic pain conditions\textsuperscript{47}. Identification of how these markers contribute to pain perception would enable more specific and personalised therapies for individuals with knee OA in whom sensitization is a primary feature.

2.5.2 Limitations
This review had a number of limitations. Heterogeneity was high for the meta-analysis of PPT data. The source of heterogeneity could not be explained by variations in testing site, as the $I^2$ value was high in the subgroup analysis also. A random effects model was used to help account for this. Results could not be pooled for all pain sensitization measures, as assessment methods for many of the outcomes were not homogenous. However results that could not be pooled are summarised and discussed in narrative format and are considered in relation to pooled results. Studies in this review did not rank as high quality on the Newcastle Ottawa Scale. Weakness in study quality was most often related to representation of the knee OA population. Most knee OA participants were sampled from an outpatient hospital population, therefore the extent to which these findings may be generalised to primary care is not known.

2.5.3 Implications for research and clinical practice
Investigation is needed regarding criteria to identify people with knee OA in whom sensitization plays a dominant role. Studies, thus far, have used a wide variety of assessment methods, which is likely to be responsible for some of the variation in results reported in this review. Greater standardisation of measures is
recommended to allow for replication and verification of findings on this topic. Based on this review, suggested methods for measuring sensitization are PPT measurement at a local and remote site to test for widespread hyperalgesia; conditioned pain modulation using PPT as the test stimulus to assess a descending inhibitory pathway; and temporal summation to assess spinal hyperexcitability. The FWR could also be used where feasible as an objective measure of spinal hyperexcitability alongside temporal summation. It is also recommended that average pain over the past month and radiographic severity be recorded. Assessment of a phenotypic marker such as pain catastrophising would also be beneficial in terms of recognising people who may be sensitized. Further investigation into the co-occurrence of thermal hyperalgesia and hypoalgesia is warranted. In addition, longitudinal research to investigate predictors of ongoing sensitization post TKR is needed. Identifying individuals at risk of persistent sensitization post TKR could allow for targeted pharmacological interventions aimed at reducing sensitization pre-operatively. Research is also needed to assess the impact of therapies such as physiotherapy, exercise and psychological interventions on people with knee OA with features of sensitization.

2.5.4 Conclusions
Evidence from this systematic review and meta-analysis of widespread hyperalgesia, spinal hyperexcitability and conditioned pain modulation suggests the presence of a degree of sensitization in people with knee OA. However, the mechanisms by which sensitization may occur in people with knee OA are still unclear. Of note, heat hyperalgesia was shown to be present at remote but not local sites, while there was no evidence for the presence of cold hyperalgesia. In addition, sensitization, as measured via pressure pain sensitivity and TS, was shown to be significantly associated with symptom severity, while results suggested no association between sensitization and radiographic severity. Reversibility of sensitization post TKR suggests an association between peripheral pathology and central changes. However, sensitization has also been demonstrated in people post revision TKR, suggesting the presence of a subgroup of people with knee OA whose condition is characterised by central
hyperexcitability. The lack of association between disease course and sensitization suggests that the hyperexcitability may, in some cases, pre-exist the knee OA pathology. Future research is needed to identify people with knee OA in whom sensitization is a dominant feature; to establish predictors of ongoing sensitization post TKR and to assess the response of sensitized knee OA groups to commonly used conservative treatments.

2.6 References


Chapter 3

Study 2. Intraexaminer and interexaminer reliability of manual palpation and pressure algometry of the lower limb nerves in asymptomatic subjects

Fingleton C, Dempsey L, Smart K, Doody C
Study 1. Pain sensitization in people with knee osteoarthritis: A systematic review and meta-analysis

Study 3. Neural mechanosensitivity and pain sensitization in people with knee osteoarthritis

Study 4. A greater degree of pain sensitization is present in people with knee osteoarthritis with high versus low pressure pain sensitivity

Study 5. Exercise-induced hypoalgesia in people with knee osteoarthritis with high versus low pressure pain sensitivity

Study 2. Intraexaminer and interexaminer reliability of manual palpation and pressure algometry of the lower limb nerves in asymptomatic subjects

Study 6. Exercise-induced hypoalgesia in people with knee osteoarthritis with normal and abnormal conditioned pain modulation

Figure 3.1 Overview of Thesis and Relationship Between Studies
3.1 Abstract

**Objectives:** Nerve palpation is a method of clinically identifying mechanosensitivity of neural tissue by means of pressure algometry and manual palpation. There are few investigations of the reliability of lower limb nerve palpation, and femoral nerve palpation has never been previously reported. The aim of this study was to investigate the reliability of nerve palpation of the femoral, sciatic, tibial and common peroneal nerves and to report normative values for the femoral nerve.

**Methods:** The 4 lower limb nerves were palpated in 39 healthy volunteers using pressure algometry and manual digital palpation. Measurements were taken twice by 1 rater (intra-rater reliability) and once by a 2nd rater (inter-rater reliability).

**Results:** Intraclass Correlation Coefficients for pressure pain thresholds (PPTs) via pressure algometry of the femoral, common peroneal, tibial and sciatic nerves were 0.69, 0.84, 0.64 and 0.9 for intra-rater reliability respectively and 0.82, 0.7, 0.56, and 0.75 for inter-rater reliability. Kappa values for manual palpation were 0.59, 0.55 0.42 and 0.60 for intra-rater reliability and 0.30, 0.49, 0.37 and 0.60 for inter-rater reliability. Males demonstrated significantly higher PPTs than females for the femoral, sciatic and tibial nerves, and differences in PPTs were present between right and left sides.

**Conclusions:** Nerve palpation of the femoral, common peroneal, and sciatic nerves using pressure algometry demonstrated good to excellent reliability, while the tibial nerve PPTs showed moderate to good reliability. Manual palpation measurements demonstrated fair to moderate reliability. Further investigation is warranted regarding the reliability of manual nerve palpation within a clinical population.
3.2 Introduction

Neural tissue mechanosensitivity may be assessed by neural tissue provocation tests such as nerve palpation. Mechanical palpation using pressure algometry and manual palpation with the thumb have a high degree of clinical utility as they may be performed as part of a standard bedside examination\(^1\), \(^2\).

Findings of localised and widespread hyperalgesia are suggestive of pain sensitization\(^3\). Increased sensitivity to nerve palpation has been observed in a number of chronic pain conditions for example non-specific arm pain\(^4\), low-back pain\(^5\) and work-related upper limb pain\(^6\). It has been suggested that nerve sensitivity may be explained by peripheral sensitization mechanisms\(^7\), in which neurogenic inflammation leads to the sensitization of neural mechanoreceptors (nervi-nervorum)\(^8\). In addition, central sensitization mechanisms may play a role in nerve sensitization whereby non-noxious stimuli from the nervi-nervorum are processed abnormally in the central nervous system\(^9\). There are reports of the reliability of nerve palpation in relation to nerves of the upper limb\(^10\), \(^6\), \(^1\) and very limited data exist in relation to the reliability of lower limb nerve palpation\(^5\), \(^11\), despite its use in a number of studies on clinical decision-making in relation to low back and leg pain disorders\(^12\), \(^2\), \(^13\).

Walsh et al\(^11\) investigated the reliability of mechanically palpating the sciatic, tibial and common peroneal nerves of the lower limb using a pressure algometer and provided normative pressure-pain threshold (PPT) values for these nerves. Walsh and Hall\(^5\) carried out digital (manual) palpation of lower limb nerves bilaterally and simultaneously in patients with low back and leg pain and rated pain or discomfort on the symptomatic side in relation to the symptomatic side. However, there are conflicting reports in relation to differences in PPT measurements between symptomatic and asymptomatic sides in subjects with chronic pain, with reports of no significant differences\(^3\) as well as reports of significant differences between sides\(^14\). A possible explanation is the presence or absence of peripheral and central sensitization of the nervous system in chronic pain states and it may therefore be important to carry out nerve palpation of right and left sides separately. In relation
to the femoral nerve, no studies have investigated the reliability of femoral nerve palpation, or reported normative PPT values. The femoral nerve crosses the hip joint, supplying muscles of the anterior thigh and innervating the knee joint\textsuperscript{15}, which may make it vulnerable to sensitization in patients with longstanding pain disorders of the lower limb. In addition, there have been no studies investigating the reliability of manual palpation of lower limb nerves which have reported separate right and left sided palpation.

This aim of this study was to investigate the reliability of femoral nerve palpation, using manual pressure and pressure algometry, in addition to further testing the reliability of manual palpation and pressure algometry of the sciatic, common peroneal and tibial nerves by means of alternate unilateral palpation. The study also sought to provide normative PPT data for the femoral nerve.

### 3.3 Methods

#### 3.3.1 Subjects

The Quality Appraisal Tool for Studies of Diagnostic Reliability (QUAREL) guidelines was used in the design of this study\textsuperscript{16}. Based on previous reliability studies, a sample of 39 participants was selected for the study\textsuperscript{1, 5, 6, 11}. A power calculation reported in a previous nerve palpation reliability study\textsuperscript{11} indicated that, based on an intraclass correlation coefficient (ICC) of 0.8 or above, 39 participants were needed to give a power of 80\% and significance level of 5\%. All subjects were students of University College Dublin (UCD) who were over 18 years, with no chronic pain or neurological disorders and no previous history of lumbar spine or lower limb pathologies. Ethical approval was obtained from the UCD Human Research Ethics Committee (Appendix A.1). Subjects were invited via email to take part in the study and provided written informed consent prior to participation (Appendix B.1).
3.3.2 Design

Procedure

Two raters palpated the participants’ femoral, sciatic, tibial and common peroneal nerves using manual pressure with the thumb in addition to pressure algometry (Figure 3.2 & 3.3). All testing was carried out in a laboratory in UCD. Both raters were Chartered Physiotherapists. Rater 1 (CF) had 6 months experience of nerve palpation techniques and Rater 2 (LD) underwent training in nerve palpation prior to the commencement of the study. Rater 1 (CF) tested subjects’ right and left lower limbs to gather normative data. Rater 2 (LD) performed the assessment on subjects’ left lower limb only, to determine inter-rater reliability. Rater 1 repeated the assessment on the right lower limb to establish intra-rater reliability. Randomisation software was used to determine a random order for testing, i.e. to determine which Rater went first, and whether Rater 1 tested the left or right side first, in order to minimise a potential order effect\textsuperscript{16}.

Participants wore shorts provided by the researchers and were positioned on a plinth in supine for palpation of the femoral and common peroneal nerves, and in prone for palpation of the tibial and sciatic nerves. The femoral nerve was palpated lateral to the femoral artery inferior to the inguinal ligament; the common peroneal nerve where it passes behind the head of the fibula as it winds forwards around the neck; the tibial nerve where it bisects the popliteal fossa, lateral to the popliteal artery; and the sciatic nerve midway between the ischial tuberosity and the greater trochanter, deep to the gluteas maximus muscle\textsuperscript{17, 18}. At each nerve site, palpation was performed first with manual pressure, and thereafter with the pressure algometer. An initial trial was carried out at the subject’s wrist to familiarise them with the testing protocol.

Manual Palpation

Digital pressure with the thumb was used to manually palpate each of the nerve sites using the standardised procedure established by the researchers, in which a similar mild-to-moderate steady pressure was applied by each examiner; the rate of pressure was established prior to the commencement of the study by means of
practice sessions on a blinded third party, who provided feedback on the consistency of the pressure applications; this was repeated until consistency in pressure application was reported at all nerve sites. The method described by Jepsen et al\textsuperscript{6} in a study on asymptomatic and symptomatic subjects was used, whereby mechanical allodynia was quantified according to none, mild, moderate or severe. As very few subjects were categorised as severe, these scores were subsequently collapsed into normal or abnormal (i.e. normal = none; abnormal = mild, moderate or severe), as described by Jepson et al\textsuperscript{6}.

Figure 3.2 Manual Nerve Palpation

Pressure Algometry
An electronic digital algometer (Somedic AB) was used for all test sites. The algometer consisted of a circular probe with a 2 cm\textsuperscript{2} round rubber tip at the end connected to a pressure transducer within the handle of the unit. The applied pressure was indicated on a digital display in kilopascals (kPa). Pressure was
applied at a rate of 30 kPa/s and subjects were instructed to press the button (terminating the pressure) as soon as the feeling of pressure began to change to that of pressure and pain. The application rate of 30 KPa/s, as used by Graven-Nielson et al\textsuperscript{14}, Skou et al\textsuperscript{19} and De-la-Llave-Rincon et al\textsuperscript{34}, was chosen to give participants sufficient time to respond to the stimulus, without maintaining pressure for an excessive time; which could lead to superficial tissue injury, and in addition may prevent the investigator from maintaining a constant rate of pressure\textsuperscript{10}, which is described as one of the most difficult aspects of pressure algometry\textsuperscript{20}. Three measures were obtained from each test site with a 10 second rest period between each measurement. The mean of the three measures was calculated. Raters were blinded to all measurements, which were stored in the memory of the algometer and retrieved when testing was completed.

\begin{figure}[ht]
\centering
\includegraphics[width=\textwidth]{Images/Figure3.3}
\caption{Nerve Palpation: Pressure Algometry}
\end{figure}
3.3.3 Data Analysis

Data analysis was carried out using the Statistical Package for Social Sciences (SPSS) version 20.

Reliability

For both manual palpation and pressure algometry, the right sided values of Rater 1 were compared to the retest values of Rater 1 to establish intra-rater reliability, and the left sided values of Rater 1 were compared to left sided values taken by Rater 2 to obtain interrater reliability.

Kappa correlation coefficients were used to determine intra-rater and inter-rater reliability of the manual nerve palpation data. Standard error and 95% CI were also calculated for each test site. The classification system proposed by Landis and Koch was used to determine the reliability level of the Kappas (≤0 = poor, 0.01-0.20 = slight, 0.21-0.40 = fair, 0.41-0.60 = moderate, 0.61-0.80 = substantial and 0.81-1 = almost perfect).

Intraclass correlation coefficients (ICCs) were calculated to assess reliability of the mechanical PPT data. A 2 way ANOVA (random effects model) was used to calculate inter-rater reliability, and a 1 way ANOVA (random effects model) was used to find intra-rater reliability. The classification system established by Shrout and Fleiss was used to determine the level of reliability (> 0.75 excellent, 0.6 - 0.75 good, 0.4 - 0.59 fair and < 0.4 poor).

The standard error of measurement (SEM) was calculated to assess the amount of variability between PPT measures attributable to measurement error. The formula used was SEM = S√1-ICC, where S is the pooled standard deviation. Mean differences with 95% confidence intervals were calculated to determine the level of agreement between PPT measurements. Bland-Altman plots were created for intra-rater and inter-rater reliability of the femoral nerve to examine for the presence of systematic bias and random error.
Normative PPT Data
The means and standard deviation (SD) at each site were calculated. Paired t-tests were used to identify whether there were significant differences between right and left sides at each site and independent t-tests were used to determine whether there were any differences between the PPTs of males and females\textsuperscript{11}.

3.4 Results
Twenty males and nineteen females between 18 and 33 years, with a mean age of 22 years (SD = 4 years) participated in the study.

3.4.1 Reliability
Pressure Algometry
Intraclass correlation coefficients (ICCs) of the femoral, common peroneal, tibial and sciatic nerves were 0.69, 0.84, 0.64 and 0.90 respectively for intra-rater reliability, while those for inter-rater reliability were 0.82, 0.7, 0.56, and 0.75. The SEM values and 95% confidence intervals are reported in Tables 3.1 and 3.2. These scores demonstrate good to excellent reliability for PPTs of the femoral, common peroneal and sciatic nerves, and moderate to good reliability for tibial nerve PPTs. Mean differences between PPT measures ranged from -17 to 12 indicating a good level of agreement as both measures were close to zero\textsuperscript{27}. The limits of agreement for femoral nerve intra-rater and inter-rater reliability are shown in Bland Altman plots (Figure 3.4 & 3.5). For intraexaminer and interexaminer reliability, values were evenly scattered above and below zero and approximately 95% of values were within the limits of agreement suggesting there was no significant systematic bias or random error\textsuperscript{26}. The SEM values of 16-39 kPa for pairs of PPT readings give an indication as to the differences in 2 PPT readings that may be considered a result of measurement error.
### Table 3.1 Pressure Algometry: Intra-rater reliability

<table>
<thead>
<tr>
<th>Site</th>
<th>Rater 1A KPa Mean (SD)</th>
<th>Rater 1B KPa Mean (SD)</th>
<th>ICC (95% CI)</th>
<th>SEM</th>
<th>Mean Diff.(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral</td>
<td>168(51)</td>
<td>163(41)</td>
<td>0.69 (.41, .84)</td>
<td>26</td>
<td>5 (-16,26)</td>
</tr>
<tr>
<td>Peroneal</td>
<td>125(41)</td>
<td>114(37)</td>
<td>0.84 (.69, .91)</td>
<td>16</td>
<td>11 (-7,29)</td>
</tr>
<tr>
<td>Tibial</td>
<td>141(45)</td>
<td>140(38)</td>
<td>0.64 (.32, .81)</td>
<td>25</td>
<td>1(-18,20)</td>
</tr>
<tr>
<td>Sciatic</td>
<td>244(89)</td>
<td>233(82)</td>
<td>0.90 (.81, .95)</td>
<td>27</td>
<td>11(-28,50)</td>
</tr>
</tbody>
</table>

SD, standard deviation; CI, confidence interval; SEM, standard error of measurement; ICC, intraclass correlation coefficient

### Table 3.2 Pressure Algometry: Inter-rater reliability

<table>
<thead>
<tr>
<th>Site</th>
<th>Rater 1 KPa Mean (SD)</th>
<th>Rater 2 KPa Mean (SD)</th>
<th>ICC (95% CI)</th>
<th>SEM</th>
<th>Mean Diff.(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral</td>
<td>158(55)</td>
<td>176(53)</td>
<td>0.82 (.65, .9)</td>
<td>23</td>
<td>-17(-41,7)</td>
</tr>
<tr>
<td>Peroneal</td>
<td>127(38)</td>
<td>136(35)</td>
<td>0.70 (.43, .84)</td>
<td>20</td>
<td>-10(-26,7)</td>
</tr>
<tr>
<td>Tibial</td>
<td>136(35)</td>
<td>124(34)</td>
<td>0.56 (.16, .77)</td>
<td>23</td>
<td>12(-3,28)</td>
</tr>
<tr>
<td>Sciatic</td>
<td>244(86)</td>
<td>256(69)</td>
<td>0.75 (.53, .87)</td>
<td>39</td>
<td>-13(-48,23)</td>
</tr>
</tbody>
</table>

SD, standard deviation; CI, confidence interval; SEM, standard error of measurement; ICC, intraclass correlation coefficient

### Manual Palpation

Manual palpation measurements showed Kappa scores of 0.59, 0.55, 0.42 and 0.60 for intra-rater reliability of the femoral, common peroneal, tibial and sciatic nerves and Kappa scores of 0.30, 0.49, 0.37 and 0.60 respectively for inter-rater reliability (Tables 3.3 & 3.4). Inter-rater reliability was classified as fair for the femoral nerve and tibial nerve and moderate for the common peroneal and sciatic nerve. Intra-rater reliability was classified as moderate for all nerves\(^1\). The number of intraexaminer and interexaminer agreements are shown in Tables 3.7 and 3.8.

### Table 3.3 Manual Palpation: Intra-rater reliability

<table>
<thead>
<tr>
<th>Site</th>
<th>Kappa</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral</td>
<td>0.59</td>
<td>0.17</td>
</tr>
<tr>
<td>Peroneal</td>
<td>0.55</td>
<td>0.15</td>
</tr>
<tr>
<td>Tibial</td>
<td>0.42</td>
<td>0.18</td>
</tr>
<tr>
<td>Sciatic</td>
<td>0.60</td>
<td>0.14</td>
</tr>
</tbody>
</table>

SE, standard error

### Table 3.4 Manual Palpation: Inter-rater reliability

<table>
<thead>
<tr>
<th>Site</th>
<th>Kappa</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral</td>
<td>0.30</td>
<td>0.13</td>
</tr>
<tr>
<td>Peroneal</td>
<td>0.49</td>
<td>0.15</td>
</tr>
<tr>
<td>Tibial</td>
<td>0.37</td>
<td>0.18</td>
</tr>
<tr>
<td>Sciatic</td>
<td>0.60</td>
<td>0.13</td>
</tr>
</tbody>
</table>

SE, standard error
3.4.2 Preliminary Normative Values

Means (SD) for all tests sites, males and females and for left and right sides are shown in Tables 3.5 and 3.6. There were significant differences between left and right sides for PPTs measures of the common peroneal and tibial nerves (p = 0.007, p = 0.003), with no significant differences between sides for the femoral or sciatic nerve. Males demonstrated significantly higher PPTs than females for the femoral, sciatic and tibial nerves (p < 0.01), and showed no difference for the common peroneal nerve on either the left (P = 0.07) or right sides (p = 0.93).

### Table 3.5 Pressure Pain Thresholds: Males Vs Females

<table>
<thead>
<tr>
<th>Site</th>
<th>Side</th>
<th>Males KPa Mean (SD)</th>
<th>Females KPa Mean (SD)</th>
<th>Mean Diff.</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral</td>
<td>L</td>
<td>187(58)</td>
<td>148(42)</td>
<td>39</td>
<td>(16, 61)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>181(50)</td>
<td>150(36)</td>
<td>31</td>
<td>(11, 51)</td>
<td>0.002</td>
</tr>
<tr>
<td>Peroneal</td>
<td>L</td>
<td>139(36)</td>
<td>125(36)</td>
<td>14</td>
<td>(-2, 31)</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>120(35)</td>
<td>119(43)</td>
<td>0.83</td>
<td>(-17, 19)</td>
<td>0.93</td>
</tr>
<tr>
<td>Tibial</td>
<td>L</td>
<td>148(29)</td>
<td>113(32)</td>
<td>35</td>
<td>(22, 49)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>162(36)</td>
<td>121(37)</td>
<td>41</td>
<td>(25, 57)</td>
<td>0</td>
</tr>
<tr>
<td>Sciatic</td>
<td>L</td>
<td>290(74)</td>
<td>212(61)</td>
<td>77</td>
<td>(47, 108)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>208(85)</td>
<td>199(65)</td>
<td>81</td>
<td>(47, 115)</td>
<td>0</td>
</tr>
</tbody>
</table>

SD, standard deviation; CI, confidence interval

### Table 3.6 Pressure Pain Thresholds: Left Vs Right

<table>
<thead>
<tr>
<th>Site</th>
<th>Left KPa Mean (SD)</th>
<th>Right KPa Mean (SD)</th>
<th>Mean Diff.</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral</td>
<td>167(54)</td>
<td>165(46)</td>
<td>2</td>
<td>(-8, 11)</td>
<td>0.73</td>
</tr>
<tr>
<td>Peroneal</td>
<td>132(37)</td>
<td>120(39)</td>
<td>12</td>
<td>(4, 20)</td>
<td>0.003</td>
</tr>
<tr>
<td>Tibial</td>
<td>130(35)</td>
<td>141(42)</td>
<td>-11</td>
<td>(-19, -3)</td>
<td>0.007</td>
</tr>
<tr>
<td>Sciatic</td>
<td>250(78)</td>
<td>238(85)</td>
<td>12</td>
<td>(-3, 26)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

SD, standard deviation; CI, confidence interval
Figure 3.4 Bland Altman Plot: Femoral nerve intra-rater reliability

Figure 3.5 Bland Altman Plot: Femoral nerve inter-rater reliability
3.5 Discussion

3.5.1 Findings

This is the first study to report on reliability of femoral nerve palpation and results demonstrated good to excellent reliability for palpation via pressure algometry of the femoral nerve, in addition to the sciatic and common peroneal nerves, and moderate reliability for the tibial nerve. Manual palpation of nerve trunks demonstrated fair to moderate reliability for all measures.

For PPT measurements via pressure algometry, ICCs of the femoral, common peroneal and sciatic nerves demonstrated good to excellent reliability (ICC = 0.69-0.9), and moderate to good reliability for the tibial nerve (ICC = 0.56-0.64); these ICCs were lower than those reported in previous investigations. Walsh and Hall\textsuperscript{5} and Walsh et al\textsuperscript{11} reported ICCs for lower limb nerve PPTs via pressure algometry which ranged from 0.83 to 0.96 and Sterling et al\textsuperscript{10} reported ICCs of 0.92-0.97 in a study on upper limb nerve palpation. This discrepancy may be in part due to the

| Table 3.7 Number of Intraexaminer Agreements for Manual Palpation: Rater 1A Vs 1B |
|------------------|------------------|------------------|------------------|
| Femoral Kappa: 0.59 |
|                | Normal | Abnormal | Total |
| Rater 1A Normal | 5      | 2        | 7     |
| Abnormal        | 3      | 29       | 32    |
| Total           | 8      | 31       | 39    |

| Table 3.8 Number of Intrexaminer Agreements for Manual Palpation: Rater 1 Vs 2 |
|------------------|------------------|------------------|------------------|
| Femoral Kappa: 0.30 |
|                | Normal | Abnormal | Total |
| Rater 1 Normal  | 5      | 1        | 6     |
| Abnormal        | 11     | 22       | 33    |
| Total           | 16     | 23       | 39    |

| Table 3.7 Number of Intraexaminer Agreements for Manual Palpation: Rater 1A Vs 1B |
|------------------|------------------|------------------|------------------|
| Femoral Kappa: 0.59 |
|                | Normal | Abnormal | Total |
| Rater 1A Normal | 7      | 2        | 9     |
| Abnormal        | 12     | 27       | 39    |

| Table 3.8 Number of Intrexaminer Agreements for Manual Palpation: Rater 1 Vs 2 |
|------------------|------------------|------------------|------------------|
| Femoral Kappa: 0.49 |
|                | Normal | Abnormal | Total |
| Rater 1 Normal  | 9      | 4        | 13    |
| Abnormal        | 5      | 21       | 26    |
| Total           | 14     | 25       | 39    |

| Table 3.7 Number of Intraexaminer Agreements for Manual Palpation: Rater 1A Vs 1B |
|------------------|------------------|------------------|------------------|
| Femoral Kappa: 0.42 |
|                | Normal | Abnormal | Total |
| Rater 1A Normal | 4      | 4        | 8     |
| Abnormal        | 3      | 28       | 31    |
| Total           | 7      | 32       | 39    |

| Table 3.8 Number of Intrexaminer Agreements for Manual Palpation: Rater 1 Vs 2 |
|------------------|------------------|------------------|------------------|
| Femoral Kappa: 0.37 |
|                | Normal | Abnormal | Total |
| Rater 1 Normal  | 7      | 2        | 9     |
| Abnormal        | 3      | 27       | 30    |
| Total           | 12     | 27       | 39    |

| Table 3.7 Number of Intraexaminer Agreements for Manual Palpation: Rater 1A Vs 1B |
|------------------|------------------|------------------|------------------|
| Femoral Kappa: 0.59 |
|                | Normal | Abnormal | Total |
| Rater 1A Normal | 7      | 5        | 12    |
| Abnormal        | 1      | 26       | 27    |
| Total           | 8      | 31       | 39    |

| Table 3.8 Number of Intrexaminer Agreements for Manual Palpation: Rater 1 Vs 2 |
|------------------|------------------|------------------|------------------|
| Femoral Kappa: 0.60 |
|                | Normal | Abnormal | Total |
| Rater 1 Normal  | 10     | 3        | 13    |
| Abnormal        | 4      | 22       | 26    |
| Total           | 14     | 25       | 39    |
experience of the two raters in the current study in palpating these anatomical landmarks and in the practice of pressure algometry. Stubhaug et al.\textsuperscript{28} suggest that hand-held pressure algometry only works well in examiners with extensive training; however this concept is disputed by other authors\textsuperscript{29}.

The ICC should be considered along with the SEM to provide an estimate of measurement precision\textsuperscript{25}. The SEM scores for PPT measurements in this study ranged from 16-39 KPa, indicating that changes in PPTs must be over 16-39 KPa before an examiner can be confident that a clinical change has occurred\textsuperscript{25}.

In the current study, sciatic nerve PPTs showed excellent reliability according to the ICC scores (0.75, 0.9), but were also found to have the lowest level of measurement precision (SEM = 27-39). Changes in sciatic nerve PPT scores of up to 27-39 KPa may be entirely due to measurement error, which needs to be considered by examiners when interpreting the clinical importance of a change in PPT scores. Lower precision of sciatic nerve palpation may be due to the deeper anatomical location of the nerve.

It is unclear as to why the tibial nerve ICCs showed lower reliability (0.56, 0.64) than other nerves. One contributing factor to the lower ICC values could be the superficial position of the tibial nerve which may have made the nerve more inclined to move upon pressure application; leading to a higher level of measurement error by raters in this study. This concept is supported by the higher SEM values in this study (23-25 KPa).

ICCs for the femoral nerve (0.69, 0.82), which have not previously been reported, demonstrated good to excellent reliability, and were comparable to those of the common peroneal (0.7, 0.84) and sciatic nerve (0.75, 0.9). The Bland-Altman plot for femoral nerve intra-rater reliability demonstrated a small trend for differences to become greater with higher PPT measurements. This finding suggests that measurements may be less precise in the higher range of PPT values and could be an inherent feature of pressure algometry. This trend corresponds with the lower
ICC (0.69) and higher SEM (26 KPa) for femoral nerve intra-rater reliability compared to inter-rater reliability (ICC = 0.82; SEM = 23). Despite this, both intra-rater and inter-rater reliability Bland-Altman plots for the femoral nerve showed that there was no significant level of random error or systematic bias.

It was found that PPTs differed between individual nerve trunks of the lower limb. Of note, the sciatic nerve had the highest PPT mean values (233-256 KPa), followed by the femoral nerve (158-176 KPa). The lowest PPT mean values were shared by the common peroneal and tibial nerves (114-140 KPa). These findings were in keeping with previous reports. It is suggested that such variations in nerve PPTs are related to differences in the anatomical position and accessibility of nerve trunks.

Significant differences between left and right-sided PPTs were found in the current study and are in contrast with previous reports. It is unclear whether differences observed in this study are inherent or secondary to measurement error. However, researchers attempted to reduce the potential for measurement error due to an order effect by randomising the order of testing between sides. The finding that males had significantly higher PPTs than females was in keeping with the literature reporting differences in pain perception between men and women. Racine et al., in a systematic review of the literature over 10 years on sex differences in pain perception, reported that females demonstrate lower pressure pain measurements than males. In a meta-analysis of sex differences in the perception of noxious experimental stimuli, Riley et al. reported the largest effect sizes were for pressure pain and tolerance measures. Differences in pain perception between males and females may be influenced by many factors including gonadal hormones, genetics and psychosocial factors.

Manual digital palpation of nerve trunks was found to have fair to moderate reliability (Kappa = 0.30-0.60) while palpation via pressure algometry was found to have moderate to excellent reliability (ICC = 0.56-0.90). These Kappa scores differed from those in a previous investigation by Walsh et al., which
demonstrated excellent reliability for manual palpation of lower limb nerves (Kappa = 0.7-0.8). However, these discrepancies may be partially explained by methodological differences between the 2 studies. Participants in the study by Walsh and Hall had low back-related leg pain and in addition, examiners palpated both sides simultaneously and asked patients to compare sides; this method appears to assume normal responses in the unaffected side and does not take into account the possible presence of mechanosensitivity on the unaffected side due to secondary hyperalgesia and peripheral and central sensitization processes. Higher levels of intra-rater (Kappa 0.83) and lower levels of inter-rater reliability (Kappa 0.14) of lower limb palpation-based neural tissue pain provocation tests in patient populations with low-back and leg pain have also been found; findings which may also be due to differences in methodology and testing procedures. Of note, Kappa scores from this study were consistent with those from a previous investigation of upper limb manual nerve palpation in another asymptomatic group (Kappa = 0.29-0.69) suggesting that this technique may have greater reliability in a clinical population, however this requires further investigation.

3.5.2 Limitations
One limitation of this study was that the order of manual palpation techniques and pressure algometry was not randomised which may have created an order effect; authors attempted to minimise this by randomising the order of testing between sides and between raters. A 4-point rating scale (none, mild, moderate, severe) was used in this study for manual palpation based on previous study, and a lack of published research in relation to palpation of the femoral nerve. However very few subjects reported severe responses and the scale was subsequently dichotomised in the reliability analysis. The use of a dichotomous scale for recording responses as normal or abnormal from the outset would have simplified the study design. Additionally, the limited experience of raters in this study in the practice of pressure algometry could have affected the level of measurement error in this study, though this concept has been disputed by other authors. Accurate palpation of nerve sites, particularly in relation to the sciatic nerve which lies deep to other sensitive structures, is another limitation of the study. Raters attempted
to ensure accuracy of palpation by carefully locating nerve sites in relation to standardised anatomical landmarks\textsuperscript{17,18}.

3.5.3 \textit{Conclusions}

In this study, nerve palpation using pressure algometry showed a good to excellent level of reliability for the femoral, sciatic and common peroneal nerves, while manual nerve palpation showed a fair to moderate level of reliability. Further investigation of the reliability of nerve palpation of the femoral nerve, in addition to the tibial nerve, is warranted given the limited empirical study to date which has shown some discrepancies between findings. In particular, future studies could investigate the reliability of manual nerve palpation in both normal and clinical populations by means of separate right and left sided palpation. Further study of manual palpation is pertinent as the technique requires no equipment making it accessible to clinicians.

3.6 \textit{References}


Chapter 4

Study 3. Neural mechanosensitivity and pain sensitization in people with osteoarthritis of the knee

Fingleton C, Smart K, O’ Leary H, Doody C
Under Review, Manual Therapy
Figure 4.1 Overview of Thesis and Relationship Between Studies
4.1 Abstract

Objectives: Sensitization of the nervous system in people with knee osteoarthritis (OA) has been widely reported in the literature, but no study to date has investigated the pain-sensitivity of peripheral neural tissue in this cohort. The aims of this study were to investigate for signs of neural mechanosensitivity (NM) by means of manual nerve palpation and neurodynamic testing and for signs of pain sensitization using quantitative sensory testing (QST) in people with knee OA compared to pain-free controls.

Methods: 52 people diagnosed with knee OA according to American College of Rheumatology classification and 38 age and sex-matched pain-free controls underwent assessment of NM via palpation of the sciatic, femoral, tibial and common peroneal nerves and straight-leg raise (SLR) testing. QST testing measured pressure pain thresholds, vibration and mechanical detection sense, dynamic touch and thermal sensitivity and temporal summation (TS). Between-group differences were assessed using Mann-Whitney U and Chi-Square tests.

Results: Knee OA participants showed a significantly greater frequency of sensitivity to nerve palpation at the sciatic (30.8%; P = 0.009), femoral (34.6%; P = 0.009), tibial (34.6%; P = 0.009) and peroneal (50%; P < 0.001) nerves compared to controls (7.9-10.5%) and significantly decreased SLR range of motion compared to controls (P < 0.001). Significant differences were also found between knee OA and controls groups for QST measures (P = 0.000-0.024).

Conclusion: Findings of sensitivity to nerve palpation and decreased ROM on SLR are suggestive of the presence of NM in people with knee OA and warrant further investigation. Findings of significant differences between knee OA participants and controls for QST measures were suggestive of a degree of pain sensitization in the knee OA group.
4.2 Introduction

Evidence has pointed to the presence of altered pain processing in the peripheral and central nervous system in people with knee osteoarthritis (OA)\(^1\). This altered state, which has been referred to as pain sensitization, has been attributed to a number of underlying mechanisms including a peripheral inflammatory-driven increase in responsiveness of nociceptors in the deep somatic tissues local to the knee in osteoarthritis (e.g. joint capsule, ligaments, menisci, periosteum and subchondral bone)\(^2\), together with centrally-mediated nociceptive dysfunction reflecting spinal hyperexcitability\(^3\), long term potentiation of neuronal synapses\(^4\), dysfunction of descending inhibitory pathways \(^5\) and activation of descending facilitatory pathways\(^6\).

Several studies have reported signs of pain sensitization in people with knee OA measured using quantitative sensory testing (QST) protocols\(^1,7\), which involves the assessment of sensitivity to noxious or innocuous stimuli using standardised mechanical, thermal and/or electrical test modalities\(^8,9\). These studies have reported widespread pressure hyperalgesia\(^10,11\), as well as both increased and decreased responses to noxious and innocuous mechanical\(^12,13\) and thermal stimuli\(^14,15\). Signs of central nervous system hyperexcitability, including temporal summation (TS), have also been identified in people with knee OA\(^16,11\).

No study to date has investigated the presence of pain sensitivity of peripheral neural tissue in people with knee OA. It has been suggested that minor nerve damage or inflammation alone may be sufficient to induce sensitivity over structurally normal nerve trunks (neural mechanosensitivity)\(^17,18\), potentially contributing to neuropathic-like symptoms and sensitization in people with chronic musculoskeletal conditions\(^19,20\). Signs of neural mechanosensitivity (NM) have been demonstrated in response to pressure and stretch in individuals with chronic musculoskeletal disorders in the absence of detectable nerve damage\(^21,22,23\). It is yet to be established whether NM is present in people with painful knee OA. The aim of this study was to investigate for signs of NM by means of manual nerve
palpation and neurodynamic testing and for signs of pain sensitization using QST in people with knee OA compared to pain-free controls.

4.3 Methods

4.3.1 Participants

Fifty-two people with knee OA took part in the study. Inclusion criteria included a diagnosis of knee OA according to American College of Rheumatology classification and pain > 3/10 on a numerical rating scale. Pain due to knee OA had to be the participants’ main pain. Thirty-eight age and sex-matched pain-free volunteers were included as a control group. Control group participants were ineligible if they had experienced a pain episode, caused by musculoskeletal injury or otherwise, in the previous three months. Exclusion criteria for both the knee OA group and control group were rheumatologic (e.g. rheumatoid arthritis, fibromyalgia or ankylosing spondylitis); a neurological disorder (e.g. Parkinson’s disease, shingles, multiple sclerosis or stroke); diabetic neuropathy, cognitive impairment and current use of antidepressant or anticonvulsant medication and in the knee OA group total knee replacement (TKR).

For this multi-centre study, knee OA participants were recruited from musculoskeletal triage clinics and physiotherapy departments in three hospital sites in Dublin, Ireland: St Vincent’s University Hospital; Cappagh National Orthopaedic Hospital; and Beaumont Hospital. Control participants were recruited from poster advertisement in University College Dublin (UCD) and local community centres, and from university staff and associates. The study was approved by the research ethics committees of UCD (Reference: LS-12-119-Fingleton-Doody) St Vincent’s Healthcare Group (Reference: 03/10/12), Cappagh Hospital (Reference: 11/06/14) and Beaumont Hospital (Reference: 14/68) (Appendices A.2 – A.9). Written informed consent was given by all participants prior to taking part in the study (Appendices B.2 – B.3).

The sample size was based on a power calculation from a systematic review by Suokas et al9, in which the minimum standardised mean difference (SMD) from the
study meta-analysis (SMD = -0.68) was used to estimate the sample size required to detect differences between two groups of osteoarthritis participants for local PPTs and indicated that 34 people per group were needed to give a power of 80% and false positive error of less than 5%.

4.3.2 Protocol
Potential participants were initially invited to take part in the study by physiotherapists in the musculoskeletal triage clinics and outpatient physiotherapy departments at the different hospital sites. Potential participants were screened for eligibility by the clinic physiotherapists and consent was sought from eligible individuals to receive a phone call from the study researcher. Potential participants were also given an information leaflet on this initial encounter. A total of 93 people consented to be contacted via phone call by the study researcher. Thirty-three people subsequently decided not to take part due to change of mind (n = 22), travel restraints (n = 4) or time burden (n = 6). An additional 8 participants were excluded following a further screening over the phone by the study researcher, with the main reasons for exclusion being diabetic neuropathy (n = 2) and knee pain not being their main pain (n = 7).

Fifty-two knee OA participants and 38 healthy controls consented to take part in the study and attended a single session of testing which included completion of measures of NM and QST. A subgroup of 40 knee OA participants and 35 controls underwent a measure of TS.

Demographic information was collected and patient-reported clinical pain, stiffness and physical function were assessed in knee OA participants only using the Western Ontario & McMaster Universities Osteoarthritis Index (WOMAC) v3.0 VAS (Appendix C.1). The WOMAC is an established questionnaire that has been shown to be reliable and valid.24
Neural mechanosensitivity was assessed using: a) nerve palpation; and b) neurodynamic testing:

a) Nerve Palpation

Neural tissue mechanosensitivity was assessed via manual nerve palpation (MNP) of the sciatic, femoral, tibial and common peroneal nerves. Manual palpation of the lower limb nerves has been found to have moderate intra-rater reliability ($k = 0.50-0.82$) and fair to moderate inter-rater reliability ($k = 0.30-0.60$) in an asymptomatic group$^{25}$. An additional study on a group with low back related leg pain demonstrated excellent inter-rater reliability for sciatic, tibial and peroneal nerve palpation ($k = 0.70-0.80$)$^{26}$. The femoral nerve was palpated lateral to the femoral artery inferior to the inguinal ligament; the common peroneal nerve where it passes behind the head of the fibula as it winds forwards around the neck; the tibial nerve where it bisects the popliteal fossa, lateral to the popliteal artery; and the sciatic nerve midway between the ischial tuberosity and the greater trochanter, deep to the gluteus maximus muscle$^{27, 28}$. Mild-to-moderate digital pressure was applied with the thumb, and the participant indicated whether the stimulus was painful or non-painful. If the participant reported that the stimulus was painful, the test was considered positive.

b) Neurodynamic Testing – Straight Leg Raise

A passive straight leg raise test was carried out bilaterally to assess NM in the sciatic nerve and its terminal branches. The passive SLR has been found to be a reliable test for the assessment of neural tissue mechanosensitivity ($r > 0.75$)$^{29, 30}$. The participant was positioned in supine with a single pillow under the head and arms by sides. Dorsiflexion was applied at the ankle to initiate tension on the tibial branch of the sciatic nerve – this step allowed for discrimination between neural tension and muscle tightness. The lower limb was then lifted into hip flexion, with the ankle maintained in dorsiflexion and the knee in extension, in accordance with the sequence described by Boyd et al$^{29}$. The test was performed to the initial onset of symptoms, at which point an assessment of hip flexion angle was made from a visual estimate based on $5^\circ$ increments as described by Holm et al$^{30}$ who found a
high level of agreement between goniometer measurements and visual estimates for assessment of hip flexion (r = 0.80). The ankle was then put into plantarflexion to differentiate between involvement of neural versus non-neural tissue; relief of symptoms on plantarflexion was interpreted as confirmation of neural tissue involvement.

Quantitative sensory testing included measurement of: a) pressure pain thresholds; b) vibration detection thresholds (VDTs); c) mechanical detection thresholds (MDTs); d) dynamic mechanical touch; e) heat and cold sensitivity; and f) temporal summation:

a) Pressure Pain Thresholds
Pressure pain thresholds were measured using a handheld pressure algometer (Somedic AB, Sweden). Handheld pressure algometry has been shown to have good intra and inter-rater reliability (r = 0.56-0.95)\textsuperscript{25,34}. Pressure was applied at a rate of thirty kilopascals (KPa) per second, perpendicular to the skin with a 2 cm\textsuperscript{2} probe. Pressure pain thresholds were assessed at four sites: locally at the medial joint line (3 cm medial to the mid point on the medial edge of patella) of the index knee (the knee that the participant identified as being their symptomatic or more symptomatic knee); contra-laterally at the medial joint line of the non-index knee; distally at the tibialis anterior muscle (5 cm distal to the tibial tuberosity); and remotely at the volar surface of the forearm (5 cm distal to the lateral epicondyle)\textsuperscript{35,14}. Participants pressed the button at the moment when the feeling of pressure changed to that of pressure and pain. The average of two PPT measurements was recorded for each site.

b) Vibration Detection Thresholds
Vibration detection threshold (VDT) was measured using the Rydel-Seiffer 128 Hz tuning fork (HCE Healthcare, UK). This device has been shown to have good intra and inter-rater reliability (k = 0.67-0.98)\textsuperscript{36}. The vibrating tuning fork was applied perpendicularly to the skin at a constant pressure. The following five sites were assessed: locally over the patella on the index side; contra-laterally over the patella.
on the non-index knee; distally over the medial malleolus of the index and non-index sides; and remotely over the ulnar styloid process. Vibration detection threshold was determined as a disappearance threshold. Participants, with their eyes closed, identified the moment when they could no longer feel the vibration. The two arms of the tuning fork bear calibrated weights at their extremities – a triangle and an arbitrary scale from 0 (minimum score) to 8 (maximum score) imprinted on the weights allowed assessment of VDT.

**c) Mechanical Detection thresholds**

Mechanical detection thresholds were tested using Von Frey monofilaments (Somedic, Sweden). This test has been shown to have good intra and inter-rater reliability \( r = 0.89-0.90 \). The test was performed bilaterally at the index and non-index MJLs. The ascending method of limits was used, whereby monofilaments of incremental diameters were applied to the participant’s skin until the MDT was reached, which was when the participant could feel three out of four touches. Participants had their eyes closed during testing.

**d) Sensitivity to dynamic mechanical touch**

Abnormal responses to dynamic mechanical touch were assessed using light brushstrokes on the skin (SENSELab Brush-05, Somedic, Sweden). The test was performed bilaterally at the knees. The brush was applied in horizontal brushstrokes across each knee, from 10 cm above the joint lines to 10 cm below the joint lines, and including the back of the knee. Participants were asked to indicate if they felt any pain such as stinging or burning, any numbness, or if the brushstrokes felt different in any area. Abnormal responses were mapped on a diagram in which the knee is divided into different sections. This diagram was adapted from the Knee Pain Map – a tool which was developed to allow for description of the location and pattern of knee pain. The same mapping method was also used for heat and cold sensitivity. Responses were recorded as either increased or decreased, depending on the descriptor the participant used to describe the sensation. An increased response was recorded for descriptors such as ‘sore’, ‘irritating’, ‘uncomfortable’ and was classified as mechanical allodynia. A
decreased response was recorded for descriptors such as ‘numb’ and ‘less feeling’ and was classified as mechanical hypoesthesia.

e) Heat and Cold Sensitivity
The presence of sensitivity to heat and cold was assessed using thermorollers (Rolltemp, Somedic, Sweden). This method has been recommended by guidelines from the European Federation of Neurological Societies (EFNS)\(^4^2\). The warm and cold rollers were calibrated to maintain temperatures of 40 and 25 degrees Celsius respectively. These temperatures are relevant for screening between normal and abnormal temperature sensibility\(^3^7\). The tests were performed bilaterally at the knees. The rollers were applied in horizontal movements across each knee, from 10 cm above the joint lines to 10 cm below the joint lines, and including the back of the knee. Participants were asked to report if the rollers felt particularly hot or cold in any area of if they felt any other abnormal sensations such as stinging, burning or numbness in response to the rollers. Abnormal responses were mapped on a diagram. An increased response was recorded for descriptors such as ‘very hot/cold’, ‘icy’ (for cold), ‘uncomfortable’ and was classified in this study as cold/heat hyperalgesia in the results. A decreased response was recorded for descriptors such as ‘numb’ and ‘less feeling’ and was classified as cold/heat hypoesthesia.

f) Temporal Summation
Temporal summation was assessed using repeated stimulation by weighted pinprick stimulus, a method that has been recommended by the German Research Network on Neuropathic Pain\(^3^7\). Pain ratings were gathered in response first to a single stimulus and then in response to a sequence of 10 stimuli of a weighted (256 mN) punctate noxious probe (MRC Systems, Germany) applied to the volar surface of the forearm and the patella of the index knee (1/s applied within an area of 1 cm\(^2\))\(^3^7\) \(^1^6\). Participants rated the stimuli from 0 (no pain) to 10 (worst pain imaginable). The absolute difference between the pain rating from repeated stimulation and the pain rating from the single stimulus was calculated\(^4^3\).
Prior to each QST test, standardised instructions were read out to participants, in line with those published by the German Research Network on Neuropathic Pain\textsuperscript{37}. See Appendix C.6 for standardised instructions.

Participants were classified as having either 1) mild to moderate or 2) severe radiographic knee OA based on their radiology report. The Kellgren-Lawrence (KL) grading criteria were used to aid dichotomisation of participants. The four point KL scale was not utilised because assessment of severity was based on the radiology reports rather than on a primary interpretation of the original radiographs.

4.3.3 Statistical Analysis

Data were analysed using SPSS v 20. Descriptive data are presented as means ± standard deviations (SDs) for parametric data and as medians with interquartile ranges (IQR) for non-parametric data. Differences between knee OA participants and controls were assessed using Mann-Whitney U tests for non-normally distributed continuous data and Chi squared tests for categorical data. Differences between the index (most symptomatic side) and non-index (least symptomatic/ non symptomatic) sides were assessed using Wilcoxon signed rank tests and McNemar tests for non-normally distributed continuous data and categorical data respectively. Spearman Rho correlations were used to assess relationships between continuous variables. For dynamic mechanical touch and heat and cold sensitivity frequencies, frequency data were calculated for each region and presented diagrammatically.
4.4 Results

4.4.1 Participant Characteristics

Participant characteristics are presented in Table 4.1. Fifty two knee OA participants and 38 pain-free controls participated in this study. A post-hoc sample size calculation confirmed that a study sample of n = 38 in the control group was capable of detecting a true difference of -0.70 in local PPTs between the knee OA participants and controls. There were no significant differences between knee OA participants and controls for age (P = 0.28) or gender (P = 0.72). Twenty three (44.2%) knee OA participants had unilateral knee pain symptoms and 29 (55.8%) had bilateral knee pain symptoms.

<table>
<thead>
<tr>
<th>Table 4.1 Participant characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Knee OA group</td>
</tr>
<tr>
<td>N=52</td>
</tr>
<tr>
<td>Female n(%)/Male n(%)</td>
</tr>
<tr>
<td>Age (years) Mean ± SD</td>
</tr>
<tr>
<td>Radiographic disease severity*</td>
</tr>
<tr>
<td>Strongest pain over last 4 weeks 0-10 mean±sd</td>
</tr>
<tr>
<td>WOMAC Pain 0-50</td>
</tr>
<tr>
<td>WOMAC Stiffness 0-20</td>
</tr>
<tr>
<td>WOMAC Activities of daily living 0-170</td>
</tr>
<tr>
<td>WOMAC Total 0-240</td>
</tr>
</tbody>
</table>

WOMAC, Western Ontario & McMaster Universities Osteoarthritis Index
* X-ray data missing for 3 participants

4.4.2 Neural Mechanosensitivity Measures

The participants with knee OA demonstrated a significantly greater frequency of sensitivity to nerve palpation at the sciatic (30.8%; P = 0.009), femoral (34.6%; P = 0.009), tibial (34.6%; P = 0.009) and peroneal (50%; P < 0.001) nerves compared to controls (7.9-10.5%). Similar significant differences were found for both the index side and for the non-index side compared to controls for the local sites of tibial (28.8%, P<0.035) and peroneal (42.3%, P< 0.001) nerves only (Table 4.2). Knee OA participants also demonstrated significantly decreased ROM in response to SLR (Median, 52.5°; IQR, 12.5°) compared to controls (Median, 65.0°; IQR, 21.25°) (P < 0.001) and for both index and non-index sides (Table 4.2).
4.4.3 Quantitative Sensory Testing Measures

Knee OA participants showed significantly greater overall pressure pain sensitivity compared to controls at all test sites (Average of 4 PPT sites: knee OA median 178.25 KPa (IQR 69.96 KPa); control median 241.19 KPa (IQR 175.38 KPa); P < 0.001) (Table 4.3). In addition knee OA participants showed significantly diminished vibration sense (Average of all 5 VDT sites: knee OA median 5.7 (IQR 1.39); control median 5.88 (IQR 1.15); P = 0.024) and mechanical detection sense (Average of both MDT sites: knee OA median 0.55g (IQR 0.41); control median 0.40g (IQR 0.29); P < 0.001) compared to controls (Table 4.3). Knee OA participants also demonstrated significantly higher levels of TS overall (Average of both TS sites: knee OA median 2.00 (IQR 2.19); control median 1.25 (IQR 2.00); P = 0.018) compared to controls (Table 4.3).

<table>
<thead>
<tr>
<th>Table 4.2 Neural Mechanoosensitivity Comparisons</th>
<th>Knee OA</th>
<th>Controls</th>
<th>Knee OA Vs controls</th>
<th>Knee OA index Vs non-index sides (paired differences)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity to Nerve Palpation</td>
<td>% (n)</td>
<td>% (n)</td>
<td>Pearson Chi-Square</td>
<td>McNemar</td>
</tr>
<tr>
<td>Index side</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sciatic</td>
<td>26.9% (14)</td>
<td>7.9% (3)</td>
<td>0.023*</td>
<td>0.022*</td>
</tr>
<tr>
<td>Femoral</td>
<td>30.8% (16)</td>
<td>10.5% (4)</td>
<td>0.023*</td>
<td>0.065</td>
</tr>
<tr>
<td>Tibial</td>
<td>28.8% (15)</td>
<td>10.5% (4)</td>
<td>0.035*</td>
<td>0.508</td>
</tr>
<tr>
<td>Peroneal</td>
<td>42.3% (22)</td>
<td>7.9% (3)</td>
<td>0.000*</td>
<td>0.049*</td>
</tr>
<tr>
<td>Non-index side</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sciatic</td>
<td>9.6% (5)</td>
<td>7.9% (3)</td>
<td>0.777</td>
<td></td>
</tr>
<tr>
<td>Femoral</td>
<td>17.3% (9)</td>
<td>10.5% (4)</td>
<td>0.366</td>
<td></td>
</tr>
<tr>
<td>Tibial</td>
<td>23.1% (12)</td>
<td>10.5% (4)</td>
<td>0.021*</td>
<td></td>
</tr>
<tr>
<td>Peroneal</td>
<td>25.0% (13)</td>
<td>7.9% (3)</td>
<td>0.013*</td>
<td></td>
</tr>
<tr>
<td>Straight Leg Raise</td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td>Mann-Whitney U</td>
<td>Wilcoxon signed rank</td>
</tr>
<tr>
<td>Index side</td>
<td></td>
<td></td>
<td></td>
<td>Index Vs. non-index SLR</td>
</tr>
<tr>
<td>Sciatic</td>
<td>50° (15°)</td>
<td>65° (21°)</td>
<td>&lt;0.001*</td>
<td>0.007*</td>
</tr>
<tr>
<td>Femoral</td>
<td>50° (15°)</td>
<td>65° (21°)</td>
<td>&lt;0.001*</td>
<td></td>
</tr>
<tr>
<td>Tibial</td>
<td>50° (15°)</td>
<td>65° (21°)</td>
<td>&lt;0.001*</td>
<td></td>
</tr>
<tr>
<td>Peroneal</td>
<td>50° (15°)</td>
<td>65° (21°)</td>
<td>&lt;0.001*</td>
<td></td>
</tr>
<tr>
<td>Non-index side</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sciatic</td>
<td>60° (20°)</td>
<td>65° (21°)</td>
<td>&lt;0.001*</td>
<td></td>
</tr>
<tr>
<td>Femoral</td>
<td>60° (20°)</td>
<td>65° (21°)</td>
<td>&lt;0.001*</td>
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</tr>
<tr>
<td>Tibial</td>
<td>60° (20°)</td>
<td>65° (21°)</td>
<td>&lt;0.001*</td>
<td></td>
</tr>
<tr>
<td>Peroneal</td>
<td>60° (20°)</td>
<td>65° (21°)</td>
<td>&lt;0.001*</td>
<td></td>
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</tbody>
</table>

*Significant, P < 0.05
### Table 4.3 Quantitative Sensory Testing Comparisons

<table>
<thead>
<tr>
<th></th>
<th>Knee OA N = 52</th>
<th>Controls N = 38</th>
<th>Knee OA Vs Controls</th>
<th>Knee OA index Vs non-index</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pressure Pain Thresholds (kPa)</strong></td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td>Mann-Whitney U</td>
<td>Wilcoxon signed rank</td>
</tr>
<tr>
<td><strong>Index side</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local – medial joint line</td>
<td>155.00 (100.50)</td>
<td>266.00 (199.26)</td>
<td>&lt;0.001*</td>
<td>0.017*</td>
</tr>
<tr>
<td>Distal – tibialis anterior</td>
<td>189.00 (110.25)</td>
<td>264.42 (158.63)</td>
<td>0.002*</td>
<td></td>
</tr>
<tr>
<td><strong>Non-index side</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local – medial joint line</td>
<td>169.66 (65.17)</td>
<td>266.00 (199.26)</td>
<td>0.000*</td>
<td></td>
</tr>
<tr>
<td>Remote – forearm</td>
<td>165.00 (84.67)</td>
<td>181.50 (120.25)</td>
<td>0.042*</td>
<td></td>
</tr>
<tr>
<td><strong>Total (mean for all sites)</strong></td>
<td>178.25 (69.96)</td>
<td>241.19 (175.38)</td>
<td>&lt;0.001*</td>
<td></td>
</tr>
<tr>
<td><strong>Vibration Detection Threshold (0-8)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Index side</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local – patella</td>
<td>4.65 (1.53)</td>
<td>5.00 (0.98)</td>
<td>0.119</td>
<td>0.149</td>
</tr>
<tr>
<td>Distal – ankle</td>
<td>5.30 (1.94)</td>
<td>6.00 (1.65)</td>
<td>0.055</td>
<td>0.244</td>
</tr>
<tr>
<td><strong>Non-index side</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local – patella</td>
<td>5.00 (1.54)</td>
<td>5.00 (0.98)</td>
<td>0.601</td>
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</tr>
<tr>
<td>Distal – ankle</td>
<td>5.18 (1.75)</td>
<td>6.00 (1.65)</td>
<td>0.017*</td>
<td></td>
</tr>
<tr>
<td>Remote – forearm</td>
<td>7.23 (1.50)</td>
<td>7.70 (1.07)</td>
<td>0.089</td>
<td></td>
</tr>
<tr>
<td><strong>Total (mean for all sites)</strong></td>
<td>5.37 (1.39)</td>
<td>5.88 (1.15)</td>
<td>0.024*</td>
<td></td>
</tr>
<tr>
<td><strong>Mechanical Detection Threshold (Grams)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Index side</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local – medial joint line</td>
<td>0.60 (0.60)</td>
<td>0.40 (0.29)</td>
<td>&lt;0.001*</td>
<td>0.005*</td>
</tr>
<tr>
<td><strong>Non-index side</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local – medial joint line</td>
<td>0.40 (0.23)</td>
<td>0.40 (0.29)</td>
<td>0.005*</td>
<td></td>
</tr>
<tr>
<td><strong>Total (mean for all sites)</strong></td>
<td>0.55 (0.41)</td>
<td>0.40 (0.29)</td>
<td>&lt;0.001*</td>
<td></td>
</tr>
<tr>
<td><strong>Temporal Summation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local – patella</td>
<td>1.50 (2.88)</td>
<td>1.00 (2.00)</td>
<td>0.048*</td>
<td></td>
</tr>
<tr>
<td>Remote – forearm</td>
<td>2.25 (3.19)</td>
<td>1.00 (2.00)</td>
<td>0.022*</td>
<td></td>
</tr>
<tr>
<td><strong>Total (mean for all sites)</strong></td>
<td>2.00 (2.19)</td>
<td>1.25 (2.00)</td>
<td>0.018*</td>
<td></td>
</tr>
</tbody>
</table>

IQR, inter-quartile range; *Significant, P < 0.05
Abnormal responses to dynamic mechanical touch, cold and heat are illustrated in Figures 4.2, 4.3 and 4.4 respectively. Knee OA participants demonstrated a significantly higher overall frequency of abnormal responses to touch (allodynia, 44.2%, P < 0.001; hypoaesthesia, 15.4%, P = 0.011), cold (hyperalgesia, 50%, P < 0.001; hypoaesthesia, 11.5%, P = 0.030) and heat (hyperalgesia, 30.8%, P < 0.001; hypoaesthesia, 23.1%, P = 0.002) compared to controls (0% - 10.5%; P < 0.001). Further details on frequency of allodynic/hyperalgesic responses and hypoaesthetic responses to touch, cold and heat are provided in supplemental information (Appendix D).

Figure 4.2 Frequency of Abnormal Responses to Touch in Knee OA Group
Figure 4.3 Frequency of Abnormal Responses to Cold in Knee OA Group (Thermoroller test)

Figure 4.4 Frequency of Abnormal Responses to Heat in Knee OA Group (Thermoroller test)
4.5 Discussion

4.5.1 Findings

Results from this study demonstrate a greater frequency of sensitivity to nerve palpation and decreased ROM in response to SLR testing in knee OA participants compared to controls; this is the first study to report these signs of NM in people with knee OA. However, NM has previously been demonstrated in other chronic musculoskeletal pain conditions e.g. non-specific arm pain and WAD\textsuperscript{21, 22, 23}.

There are a number of possible explanations for our findings suggestive of NM over local and remote peripheral nerve trunks. From rat studies, it appears that the presence of inflammation is sufficient to induce widespread NM and neuropathic symptoms\textsuperscript{19, 20, 44, 45}. Eliav \textit{et al}\textsuperscript{19} demonstrated ectopic discharge and NM to pressure and stretch in rats in response to inflammatory stimulation of the saphenous nerve and, in another study, demonstrated widespread neuropathic pain following exposure of the sciatic nerve to inflammation\textsuperscript{45}; the authors argue that a disease process near a nerve may expose the nerve to an inflammatory milieu and thereby give rise to neuritis-evoked neuropathic pain.

A study by Dilley \textit{et al}\textsuperscript{20} demonstrated NM in response to inflammation of the sciatic and peroneal nerves of rats. Furthermore, the study reported expression of Activating Transcription Factor-3 (ATF3) in dorsal root ganglion (DRG) cells, suggesting an alteration in gene expression which could lead to widespread changes; these changes in the DRG cells may explain findings from the current study of sensitivity to nerve palpation remote from the site of injury. Simulation of knee OA in rats has also been shown to evoke expression of ATF3 in DRG cells, in addition to a decrease in intra-epidermal nerve fibre density within plantar epidermis and ipsilateral spinal cord microgliosis, suggestive of significant neural injury\textsuperscript{46}. Studies by Bove \textit{et al}\textsuperscript{18, 47, 48} suggest that sensitivity of nerve trunks may occur via the nervi nervorum (small filaments which constitute the intrinsic innervation of nerve sheaths). However, Schmid \textit{et al}\textsuperscript{49} suggest that intraneural inflammation may be involved. In a study investigating entrapment neuropathy in rats\textsuperscript{46}, mild compression without axonal damage was shown to cause loss of
myelin and compromise of small diameter axons in rats. Furthermore, T-lymphocytes and macrophages were shown to enter the nerve and DRG cells, and glia was proliferated in the DRG cells suggestive of an immune mediated response.

It is also possible that neural tissue may develop secondary hyperalgesia or allodynia via pain sensitization in the same manner as reported in muscle, fascia and skin. This concept of hyperalgesia presenting across different levels of tissue has previously been suggested by Imamura et al who demonstrated pressure pain sensitivity across myotomal, dermatomal and scleratomal areas in people with knee OA. Sensitivity to nerve palpation has also been demonstrated over nerve trunks at pain-free areas of the arm in people with WAD. In addition we speculate that chemical or mechanical stimulation of nervi nervorum along the nerve trunk may occur due to painful spasm of the muscles acting on the knee. Motor efferents serving muscles which act on the knee have been shown to carry afferent branches from the knee capsular elements (Hilton’s Law), suggesting that pain and inflammation at the knee joint may activate muscle contraction. Findings of decreased ROM in response to SLR testing in knee OA participants compared to controls are also suggestive of NM of the sciatic nerve and/or its branches, lending support to this concept. In a recent study, pulsed radiofrequency stimulation of the composite nerve supply of the knee resulted in muscle relaxation and associated sustained pain relief in people with knee OA. As such, irritation along the nerve trunks may occur secondary to inflammation or mild compression from adjacent hyperalgesic and hypertonic muscle tissue.

Findings of pressure pain sensitivity at local, distal and remote sites are in keeping with previous reports. Results of a recent meta-analysis demonstrating a large point estimate (standardised mean difference (SMD) = -0.97) for differences in local PPS between knee OA patients and controls, and a moderate-large point estimate of -0.74 for differences in remote PPS, are consistent with findings from the current study (SMD local PPS = -1.21; SMD remote PPS = -0.56). The presence of sensitization signs remote from the site of injury has been attributed to centrally – mediated nociceptive dysfunction. Evidence from this study of heightened
TS in knee OA participants compared to controls provides further evidence of centrally–mediated nociceptive dysfunction.

Increased pressure pain sensitivity and diminished mechanical detection sense were present on both index and non-index sides, as were decreased ROM on SLR and sensitivity on tibial and peroneal nerve palpation. Contralateral hyperalgesia has been reported previously in response to unilateral nociceptive stimulation in animals\textsuperscript{57-59} and in humans\textsuperscript{60} and spread of sensitization to the contralateral limb is well–documented in people with complex regional pain syndrome\textsuperscript{61}. Pressure pain sensitivity at the contralateral knee has been demonstrated in knee OA\textsuperscript{10, 35, 51}, but this is the first report of contralateral hypoesthesia in addition to NM in knee OA. Contralateral spread of sensitization is thought to involve activation of bilateral areas of the brain associated with descending control pathways\textsuperscript{60}, in addition to altered spinal processing\textsuperscript{61, 62} which may be mediated by neurons projecting across the spinal cord to their contralateral counterpart\textsuperscript{62, 63} and/or by nerve growth factors via commissural interneurons in the spinal cord and brainstem\textsuperscript{64} and the possible involvement of spinal glia cells and pro-inflammatory cytokines\textsuperscript{65}.

In contrast with these bilateral findings, the presence of abnormal thermal processing appeared to largely be limited to the index knee. A recent systematic review found no evidence for cold hyperalgesia in knee OA and found differences between knee OA and control groups for remote but not local HPTs\textsuperscript{1} which are contrary to the current study. A possible reason for this discrepancy may be that these previous studies used CPTs/cold pressor test and HPTs as opposed to the thermoroller test employed in the current study. The temperature of the thermorollers (25 and 40 degrees Celcius) lies between reference values for detection and pain thresholds\textsuperscript{37} and, as such, the presence of normal or abnormal sensation rather than pain threshold is documented, likely resulting in a larger number of positive responses.
4.5.2 Limitations

One limitation of the study was that testing was carried out by an unblinded assessor, introducing the potential for measurement bias. Independent, assessor-blinded replication is required to corroborate our findings. A further limitation is that sensitivity to nerve palpation could potentially have arisen from hyperalgesia of the tissue overlying the nerves. Future studies would benefit from using a control condition involving palpation of non-neural tissue sites to verify that sensitivity over nerve sites is due to NM rather than generalised hyperalgesia.

4.5.3 Conclusions

This is the first study to demonstrate pain sensitivity to nerve palpation and decreased ROM on neurodynamic testing in people with knee OA, findings which are suggestive of neural mechanosensitivity in this cohort. The presence of NM may be clinically important as identification of NM could potentially create additional treatment targets in the form of nerve mobilisation and desensitization techniques. Findings of abnormal responses to thermal stimuli at the knee in people with knee OA are contrary to previous reports and further investigation of thermal processing in knee OA may be warranted, with emphasis on accounting for the presence of hyperalgesic and hypoesthesia abnormalities. Additionally, findings of pressure pain sensitivity, diminished mechanical detection sense and NM on the non-index knee may be suggestive of a contralateral spread of sensitization, and is another potential area for further investigation.

4.6 References


19. Eliav E, Benoliel R and Tal M. Inflammation with no axonal damage of the rat saphenous nerve trunk induces ectopic discharge and mechanosensitivity in myelinated axons. 2001; 311: 49-52


25. Fingleton CP, Dempsey L, Smart K and Doody CM. Intraexaminer and interexaminer reliability of manual palpation and pressure algometry of the


Chapter 5

Study 4. A greater degree of pain sensitization is present in people with knee osteoarthritis with high versus low pressure pain sensitivity

Fingleton C, Smart K, O’ Leary H, Doody C
Study 1. Pain sensitization in people with knee osteoarthritis: A systematic review and meta-analysis

Study 2. Intraexaminer and interexaminer reliability of manual palpation and pressure algometry of the lower limb nerves in asymptomatic subjects

Study 3. Neural mechanosensitivity and pain sensitization in people with knee osteoarthritis

Study 4. A greater degree of pain sensitization is present in people with knee osteoarthritis with high versus low pressure pain sensitivity

Study 5. Exercise-induced hypoalgesia in people with knee osteoarthritis with high versus low pressure pain sensitivity

Study 6. Exercise-induced hypoalgesia in people with knee osteoarthritis with normal and abnormal conditioned pain modulation

Figure 5.1 Overview of Thesis and Relationship Between Studies
5.1 Abstract

**Objectives:** The presence of pain sensitization has been demonstrated in people with knee osteoarthritis (OA); it is speculated to exist on a spectrum and play a dominant role in a subgroup of knee OA patient. The aim of the current study was to investigate potential differences in pain sensitization signs between knee OA subgroups with high and low pressure pain sensitivity (PPS).

**Methods:** 52 knee OA patients were subdivided into high PPS and low PPS groups, as determined by a median split of pressure pain thresholds (PPTs). High PPS (n=26), low PPS (n=26) and control groups (n =38) underwent quantitative sensory testing (QST) involving measurement of pressure-pain thresholds (PPTs), vibration and mechanical-detection thresholds (VDT, MDT), dynamic touch and thermal sensitivity, temporal summation (TS) and lower limb nerve palpation. Between-group differences were assessed using Kruskal-Wallis tests and post-hoc Mann-Whitney U and Chi-Square tests.

**Results:** A greater frequency of dynamic mechanical allodynia and increased VDTs were demonstrated in the high PPS group compared to the low PPS and control groups (P < 0.05). Additionally, results demonstrated increased TS and mechanosensitivity of the femoral and peroneal nerves in the high PPS group, but not in the low PPS group, compared to controls (P < 0.05).

**Conclusion:** Results are suggestive of a high degree of pain sensitization in people with knee OA with high PPS compared to those with low PPS.
5.2 Introduction

Pain presentations associated with knee osteoarthritis (OA) vary considerably and may not be associated with the level of radiographic disease severity\textsuperscript{1-3}. A growing body of evidence suggests alterations in nociceptive processing within the peripheral and central nervous system in people with knee OA\textsuperscript{4} which may account for some of the variations in clinical pain presentations. These alterations have been attributed to a number of mechanisms including an inflammatory-driven hyperexcitability of nociceptors in the deep somatic tissues local to the knee\textsuperscript{5} together with nociceptive dysfunction within the central nervous system (CNS) encompassing heightened responsiveness of spinal cord neurons\textsuperscript{6}, long term potentiation of neuronal synapses\textsuperscript{7} and dysfunction of descending modulatory pathways\textsuperscript{8, 9}.

Signs of pain sensitization have been demonstrated in people with knee OA including widespread pressure hyperalgesia\textsuperscript{10, 11}, abnormal responses to both noxious and innocuous mechanical and thermal stimuli\textsuperscript{12-15} and increased temporal summation (TS) suggestive of spinal hyperexcitability\textsuperscript{11, 16, 17}. Preliminary evidence is also suggestive of the presence of pain-sensitivity of peripheral neural tissue (neural mechanosensitivity (NM)) in people with knee OA\textsuperscript{18}. Pain sensitization is speculated to exist on a spectrum in people with knee OA, but play a dominant role in the presentations of a subgroup of knee OA patients\textsuperscript{4, 19}.

Studies have attempted to identify knee OA subgroups with higher levels of pain sensitization by subdividing participants using: a median split of the WOMAC total score\textsuperscript{15}; a split based on a numerical rating scale of pain severity in the previous 24 hours\textsuperscript{16}; and a combination of WOMAC pain sub-scale median split and subdivision of Kellgren-Lawrence disease severity score\textsuperscript{20}. These studies were included in a recent meta-analysis, which demonstrated greater pressure pain sensitivity at local and remote sites in people with knee OA versus controls, and greater pressure pain sensitivity in those with high versus low symptom severity\textsuperscript{4}. The presence of widespread pressure pain sensitivity is thought to be an indicator of pain sensitization as it reflects the spread of hyperalgesia to areas distal to and remote
from the primary injury or pathology\textsuperscript{10, 16}; a process which is widely held to be mediated by nociceptive dysfunction within the peripheral and central nervous system respectively\textsuperscript{6}. No study to date has examined potential differences in the somatosensory processing of people with knee OA with varying degrees of pressure pain sensitivity.

The primary aim of the current study was to identify a knee OA subgroup with a high degree of pain sensitization by investigating potential differences in the somatosensory processing of people with knee OA with higher and lower pressure pain sensitivity (PPS) and pain-free controls. A secondary aim was to investigate potential differences in patient-reported outcome measures between the high and low PPS groups. Individuals were classified as having high or low pressure pain sensitivity based on a median split of PPT values. We hypothesised that the group with higher PPS would show greater somatosensory abnormalities consistent with pain sensitization and would report significantly greater self-reported pain and disability compared to those with lower PPS.

5.3 Methods

5.3.1 Participants

Fifty-two people with knee OA took part in the study. Inclusion criteria included a diagnosis of knee OA according to American College of Rheumatology classification and pain > 3/10 (≥ 4/10) on a numerical rating scale. Pain due to knee OA had to be participants’ main pain. Thirty-eight age and sex-matched pain-free volunteers were included as a control group. Control group participants were ineligible if they had experienced a pain episode, caused by musculoskeletal injury or otherwise, in the previous three months. Exclusion criteria for both the knee OA group and control group were rheumatologic disease such as rheumatoid arthritis, fibromyalgia or ankylosing spondylitis; a neurological disorder such as Parkinson’s disease, shingles, multiple sclerosis or stroke; cognitive impairment; and current use of antidepressant or anticonvulsant medication. In addition, knee OA group participants were excluded if they had undergone a total knee replacement (TKR).
Knee OA participants were recruited from outpatient musculoskeletal physiotherapy clinics in three hospital sites in Dublin, Ireland. Control participants were recruited from poster advertisement in University College Dublin (UCD) and local community centres, and from university staff and associates. The study was approved by the research ethics committees of UCD and the three hospital research ethics committees (Appendices A2 – A9). Written informed consent was obtained from all participants prior to taking part (Appendices B.2 – B.3).

5.3.2 Protocol
Potential participants were initially invited to take part in the study by the clinical Physiotherapists at the different hospital sites. Potential participants were screened for eligibility by the physiotherapists and participants were also given a study information leaflet. Initial consent was sought from potential participants to receive a phone call from the study researcher and 93 people consented. Thirty-three people subsequently decided not to take part due to change of mind (n = 22), travel restraints (n = 4) or time burden (n = 6). An additional 8 participants were excluded following a further screening, with the main reasons for exclusion being diabetic neuropathy (n = 2) and knee pain not being their main pain (n = 7).

Fifty-two knee OA participants and 38 healthy controls consented to take part in the study and attended a single session of testing which included completion of patient-reported validated outcome measures (knee OA group only), measures of neural tissue sensitization and QST. A subgroup of 40 knee OA participants and 35 controls underwent a measure of TS.

Demographic information was collected and patient-reported clinical pain, stiffness and physical function were assessed with the WOMAC v3.0 VAS. The WOMAC is an established questionnaire that has been shown to be reliable and valid21. Quality of life (QOL) was assessed using the EQ-5D-5L, which consists of a descriptive system, comprising five dimensions (mobility, self care, usual activities, pain/discomfort, anxiety/depression) and a visual analogue scale (VAS) for self-
reported health. Sensory and affective pain symptoms were assessed with the Short Form McGill Pain Questionnaire (SF-MPQ), which has been shown to have good test-retest reliability with in people with musculoskeletal pain. PainDETECT was used to assess neuropathic-like pain and has been widely used to assess pain phenotype in people with OA knee. The Pain Catastrophising Scale (PCS) is a 13-item instrument with three subscale scores assessing rumination, magnification and helplessness. It has been used in cohorts with a knee OA and shown to be associated with neuropathic-like symptoms. See Appendix C for questionnaires and standardised instructions. Participants were classified as having either 1) mild to moderate or 2) severe radiographic knee OA based on their radiology report. The Kellgren-Lawrence (KL) grading criteria were used to aid dichotomisation of participants. The four point KL scale was not utilised because assessment of severity was based on the radiology reports rather than on a primary interpretation of the original radiographs.

Testing included measurement of: a) pressure pain thresholds; b) vibration detection thresholds (VDTs); c) mechanical detection thresholds (MDTs); d) dynamic mechanical touch; e) heat and cold sensitivity; f) temporal summation; and g) manual nerve palpation.

a) Pressure Pain Thresholds
Pressure pain thresholds were measured using a handheld pressure algometer (Somedic AB, Sweden). Pressure was applied at a rate of thirty kilopascals (KPa) per second, perpendicular to the skin with a 2 cm² probe. Pressure pain thresholds were assessed at 4 sites: locally at the medial joint line of the index (the knee that the participant identified as being their symptomatic or more symptomatic knee) and non-index (asymptomatic or less symptomatic) knee (3 cm medial to the midpoint on the medial edge of patella); distally at the tibialis anterior muscle (5 cm distal to the tibial tuberosity); and remotely at the volar surface of the forearm (5 cm distal to the lateral epicondyle). Participants pressed the button at the moment when the feeling of pressure changed to that of pressure and pain. The average of two PPT measurements was recorded for each site.
b) Vibration Detection Thresholds

Vibration detection threshold (VDT) was measured using the Rydel-Seiffer 128 Hz tuning fork (HCE Healthcare, UK). The vibrating tuning fork was applied perpendicularly to the skin at a constant pressure. The following three sites were assessed: locally over the patella on the index side; distally over the medial malleolus of the index sides; and remotely over the ulnar styloid process. Vibration detection threshold was determined as a disappearance threshold\textsuperscript{30}. Participants, with their eyes closed, identified the moment when they could no longer feel the vibration. The two arms of the tuning fork bear calibrated weights at their extremities – a triangle and an arbitrary scale from 0 (minimum score) to 8 (maximum score) imprinted on the weights allowed assessment of VDT\textsuperscript{31}.

c) Mechanical Detection thresholds

Mechanical detection thresholds were tested using Von Frey monofilaments (Somedic, Sweden)\textsuperscript{32}. The test was performed at the index MJL. The ascending method of limits was used, whereby monofilaments of incremental diameters were applied to the participant’s skin until the MDT was reached, which was when the participant could feel three out of four touches\textsuperscript{14,33}. Participants had their eyes closed during testing.

d) Dynamic Mechanical Allodynia & Hypoaesthesia

Abnormal responses to dynamic mechanical touch were assessed at the index knee using light brushstrokes on the skin (SENSELab Brush-05, Somedic, Sweden). The brush was applied in horizontal brushstrokes across front and back of the knee, from 10 cm above the joint lines to 10 cm below the joint lines. Participants were asked to indicate if they felt any pain such as stinging or burning as well as any numbness, or difference of sensation in any area. Responses were recorded as either increased or decreased. An increased response was recorded for descriptors such as ‘sore’, ‘irritating’, ‘burning’, ‘stinging’, ‘uncomfortable’ and was classified in the results as mechanical allodynia. A decreased response was recorded for descriptors such as ‘numb’ and ‘less feeling’ and was classified as mechanical hypoaesthesia. Abnormal responses were mapped on a Knee Pain Map\textsuperscript{34}.
e) **Heat/Cold Hyperalgesia & Hypoaesthesia**

Sensitivity to heat and cold was assessed using thermorollers (Rolltemp, Somedic, Sweden)\textsuperscript{35}. The warm and cold rollers were calibrated to maintain temperatures of 40 and 25 degrees Celsius respectively. These temperatures each lie between the reference values for detection threshold and pain threshold\textsuperscript{30}. The tests were performed bilaterally at the knees using the same method as for sensitivity to dynamic mechanical touch. Participants were asked to report if the rollers felt particularly hot or cold in any area or if they felt any other abnormal sensations such as stinging, burning or numbness. An increased response was recorded for descriptors such as ‘very hot/cold’, ‘icy’ (for cold), ‘uncomfortable’ and was classified as cold/heat hyperalgesia in the results. A decreased response was recorded for descriptors such as ‘numb’ and ‘less feeling’ was classified as cold/heat hypoaesthesia.

f) **Temporal Summation**

Temporal summation was assessed using repeated stimulation by weighted pinprick stimulus. Pain ratings were gathered in response first to a single stimulus and then to a sequence of 10 stimuli of a weighted (256 mN) punctate noxious probe (MRC Systems, Germany) applied to the volar surface of the forearm and the patella of the index knee (1/s applied within an area of 1 cm\textsuperscript{2})\textsuperscript{20,30}. Participants rated the stimuli from 0 (no pain) to 10 (worst pain imaginable). The absolute difference between the pain rating from repeated stimulation and the pain rating from the single stimulus was calculated\textsuperscript{36}.

g) **Manual Nerve Palpation (MNP)**

Sensitization of peripheral neural tissue (neural mechanosensitivity) was assessed via nerve palpation of the sciatic, femoral, tibial and common peroneal nerves. Manual palpation of the lower limb nerves has been found to have moderate to excellent intra-rater reliability\textsuperscript{37,38}. The femoral nerve was palpated lateral to the femoral artery inferior to the inguinal ligament; the common peroneal nerve where it passes behind the head of the fibula as it winds forwards around the neck; the tibial nerve where it bisects the popliteal fossa, lateral to the popliteal
artery; and the sciatic nerve midway between the ischial tuberosity and the
greater trochanter, deep to the gluteus maximus muscle\textsuperscript{39, 40}. Mild-to-moderate
digital pressure was applied, and the participant indicated whether the stimulus
was painful or non painful. If the participant reported that the stimulus was
painful, the test was considered positive.

5.3.3 Subgrouping
Knee OA participants were subdivided into two groups – high pressure pain
sensitivity (High PPS) and low pressure pain sensitivity (Low PPS) based on their
widespread pressure pain thresholds (PPTs). A median split of the averaged PPTs
for men and women respectively were used to create the subgroups. Participants
for the high PPS group had an averaged PPT score less than the median averaged
PPT, while participants from the low PPS had an averaged PPT score greater than
or equal to the median averaged PPT. An averaged PPT score was chosen to
subgroup knee OA participants as widespread pressure hyperalgesia at local and
remote sites is a feature of pain sensitization which has been repeatedly identified
in people with knee OA\textsuperscript{4, 10}. A median split of PPTs was used to achieve equal sized
subgroups with differing degrees of pain sensitivity. This method has previously
been used in people with chronic musculoskeletal pain\textsuperscript{41}.

5.3.4 Statistical Analysis
Data were analysed using SPSS v 20. Data were analysed for normal distribution
using Shapiro Wilk tests and normality plots. Descriptive data are presented as
means ± standard deviations (SDs) for parametric data and as medians with
interquartile ranges (IQR) for non-parametric data. Differences between the high
and low PPS and control groups were analysed using the non-parametric Kruskal–
Wallis test. Primary and post hoc analysis of subgroups was carried using Mann-
Whitney U tests. Mann-Whitney U tests were used to investigate associations
between categorical and continuous variables and Spearman Rho tests were used
to investigate correlations between continuous variables. The level of significance
was set at $P < 0.05$. No adjustment of the $P$ value was made for multiple
comparisons as all tests were planned and reasonable.
5.4 Results

5.4.1 Participant Characteristics

Participant characteristics are presented in Table 5.1. High and low PPS groups were determined by a gender-adjusted median split of the averaged PPT score, as described above, resulting in an equal number (n = 26) of female (n = 12) and male (n = 14) participants in either group. There were no significant differences between high and low PPS groups and controls for age (P = 0.100) or sex (P = 0.937). 56% of the high PPS group had severe radiographic disease severity, compared to 44% in the low PPS group (P = 0.401), and 62% of the high PPS group had self-reported bilateral pain symptoms compared to 50% of the low PPS group (P = 0.407).

Comparisons of somatosensory abnormalities between the high and low PPS participants and controls are shown in Table 5.2. Results are presented below as positive sensory signs (TS, increased responses to dynamic touch, cold and heat).

<table>
<thead>
<tr>
<th>Table 5.1 Participant Characteristics</th>
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</thead>
<tbody>
<tr>
<td><strong>Knee OA-high pressure pain sensitivity N=26</strong></td>
</tr>
<tr>
<td>Female (%)/Male (%)</td>
</tr>
<tr>
<td>Age (years) mean ± SD</td>
</tr>
<tr>
<td>Unilateral (%)/Bilateral pain (%)</td>
</tr>
<tr>
<td>Radiographic disease severity Mild-moderate (%)/severe (%)</td>
</tr>
<tr>
<td>Average pain last 4 weeks 0-10</td>
</tr>
<tr>
<td>Strongest pain last 4 weeks 0-10</td>
</tr>
<tr>
<td>PainDETECT total 0-35</td>
</tr>
<tr>
<td>PainDETECT final score 0-37</td>
</tr>
<tr>
<td>WOMAC pain 0-50</td>
</tr>
<tr>
<td>WOMAC stiffness 0-20</td>
</tr>
<tr>
<td>WOMAC ADLs 0-170</td>
</tr>
<tr>
<td>WOMAC total 0-240</td>
</tr>
<tr>
<td>EuroQOL mobility 1-5</td>
</tr>
<tr>
<td>EuroQOL selfcare 1-5</td>
</tr>
<tr>
<td>EuroQOL activity 1-5</td>
</tr>
<tr>
<td>EuroQOL pain 1-5</td>
</tr>
<tr>
<td>EuroQOL anxiety 1-5</td>
</tr>
<tr>
<td>EuroQOL health VAS 0-100</td>
</tr>
<tr>
<td>SF-MPQ sensory 0-33</td>
</tr>
<tr>
<td>SF-MPQ affective 0-12</td>
</tr>
<tr>
<td>SF-MPQ total 0-45</td>
</tr>
<tr>
<td>PCS rumination 0-16</td>
</tr>
<tr>
<td>PCS magnification 0-12</td>
</tr>
<tr>
<td>PCS helplessness 0-24</td>
</tr>
<tr>
<td>PCS total 0-52</td>
</tr>
</tbody>
</table>

WOMAC, Western Ontario & McMaster Universities Osteoarthritis Index; ADLs; activities of daily living; SF-MPQ, Short Form McGill Pain Questionnaire; PCS, Pain Catastrophising Scale.
MNP) and negative sensory signs (VDT, MDT, decreased response to dynamic touch, cold and heat). Positive and negative sensory signs represented gains and losses in sensory function respectively\textsuperscript{30}.

### 5.4.2 Positive Sensory Signs

There were significant differences between the high PPS, low PPS and control groups for TS (P = 0.033) (Table 5.2). Post hoc tests demonstrated no significant difference between high and low PPS groups (P = 0.396). Overall TS score was significantly increased in the high PPS group compared to controls (P = 0.007), while there was no significant difference in TS between the low PPS group and controls (P = 0.190).

Significant differences were found between the three groups for mechanical allodynia (Figure 5.2A), and hyperalgesia to cold and heat (Figure 5.2B & C) (P < 0.001) (Table 5.2). Post hoc tests demonstrated a significantly higher frequency of mechanical allodynia in the high PPS group compared to the low PPS group (P = 0.001) and controls (P < 0.001). There was no significant difference between the low PPS group and controls (P = 0.079). There was also no significant difference between the high and low PPS groups for cold hyperalgesia (P = 0.165) or heat hyperalgesia (P = 0.126). A significantly greater frequency of cold and heat hyperalgesia was shown in both the high PPS group (P < 0.001) and low PPS group (P < 0.01) compared to controls. There were significant differences between the high and low PPS and control groups for frequency of mechanosensitivity at the femoral (P = 0.030), tibial (P = 0.026) and peroneal (P < 0.001) nerves, but not at the sciatic nerve (P = 0.058) (Table 5.2). Post hoc tests showed no significant differences between high and low PPS groups (P > 0.05). A significantly higher frequency of sensitivity to nerve palpation was found at all nerve sites in the high PPS group compared to controls (P < 0.02), and at the peroneal nerve only in the low PPS group compared to controls (P = 0.017).
5.4.3 Negative Sensory Signs

Significant differences were found between the three groups for VDTs ($P = 0.005$) (Figure 5.3) (Table 5.2). Post hoc tests demonstrated significantly diminished vibration sense overall in the high PPS group compared to the low PPS group and controls ($P < 0.05$) and no significant difference between low PPS group and controls ($P = 0.452$) for vibration sense.

Figure 5.2 Frequency of Abnormal Responses to Touch, Cold and Heat: A) Mechanical Allodynia & Hypoaesthesia and B) Cold Hyperalgesia & Hypoaesthesia and C) Heat hyperalgesia & Hypoaesthesia

Figure 5.3 Vibration Detection Threshold (VDT) Scores
A significant difference was found between the three groups for MDTs (P < 0.001) (Table 5.2). There was no significant difference between the high and low PPS groups for MDTs (P = 0.742), and both the high (P = 0.001) and low (P = 0.001) PPS groups demonstrated significantly decreased mechanical detection sense compared to controls.

There were significant differences between the three groups for frequency of mechanical hypoesthesia (P = 0.025) (Figure 5.2a) and heat hypoesthesia (P = 0.006) (Figure 5.2c), but not for cold hypoesthesia (P = 0.095) (Figure 5.2b) (Table 5.2). There were no significant differences between the high and low PPS groups for mechanical (P = 0.442) or heat (P = 0.126) hypoesthesia. The high and low PPS groups both demonstrated a higher frequency of mechanical hypoesthesia (P < 0.04), and heat hypoesthesia (P = 0.002) compared to controls.

5.4.4 Patient-reported Outcome Measures

There were no significant differences between high and low PPS groups for self-reported clinical pain, stiffness or physical function (WOMAC), quality of life (EuroQOL), neuropathic-like pain (PainDETECT), sensory/affective pain dimensions (SF-MPQ) or pain catastrophizing (PCS) (P = 0.100 – 0.848) (Table 5.1). Positive and negative sensory signs were further investigated for associations with patient-reported measures. None of these measures (TS, MNP, mechanical allodynia, cold or heat hyperalgesia, mechanical, cold or heat hypoesthesia, VDT or MDT) were found to be associated with clinical pain severity, stiffness or physical function (WOMAC) (P > 0.05). There was a significant positive association between pain catastrophising (PCS) and the presence of mechanical allodynia (P= 0.019) and heat hypoesthesia (P = 0.038), and between neuropathic-like pain symptoms (PainDETECT) and the presence of mechanical allodynia (P = 0.032), mechanical hypoesthesia (P = 0.040) and heat hypoesthesia (P = 0.043). Mechanical hypoesthesia was also significantly associated with increased sensory/affective pain (SF-MPQ) (P = 0.049) and peroneal nerve sensitivity was significantly associated with increased self-reported problems with mobility (P = 0.045) and daily activities (P = 0.024).
Table 5.2 Knee OA High and Low Pressure Pain Sensitivity Groups and Healthy Controls Comparisons

<table>
<thead>
<tr>
<th></th>
<th>Knee OA-High Pressure Pain Sensitivity N=26</th>
<th>Knee OA-Low Pressure Pain Sensitivity N=26</th>
<th>Controls N=38</th>
<th>High Vs Low Vs Controls</th>
<th>High Vs Controls</th>
<th>Low Vs Controls</th>
<th>High Vs Low</th>
</tr>
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<tbody>
<tr>
<td><strong>Vibration Detection Threshold</strong></td>
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<td></td>
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<tr>
<td>0-8 Median (IQR)</td>
<td></td>
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<tr>
<td>Local – patella</td>
<td>4.28 (1.75)</td>
<td>4.83 (1.71)</td>
<td>5.00 (0.98)</td>
<td>0.032*</td>
<td>0.012*</td>
<td>0.913</td>
<td>0.043*</td>
</tr>
<tr>
<td>Distal – ankle</td>
<td>4.73 (2.18)</td>
<td>5.95 (1.69)</td>
<td>6.00 (1.65)</td>
<td>0.008*</td>
<td>0.004*</td>
<td>0.759</td>
<td>0.012*</td>
</tr>
<tr>
<td>Remote – forearm</td>
<td>7.00 (1.61)</td>
<td>7.25 (1.28)</td>
<td>7.70 (1.07)</td>
<td>0.225</td>
<td>0.115</td>
<td>0.203</td>
<td>0.748</td>
</tr>
<tr>
<td><strong>Total (mean for all sites)</strong></td>
<td>5.35 (1.34)</td>
<td>5.82 (1.05)</td>
<td>6.20 (1.15)</td>
<td>0.005*</td>
<td>0.002*</td>
<td>0.452</td>
<td>0.018*</td>
</tr>
<tr>
<td><strong>Mechanical Detection Threshold</strong></td>
<td></td>
<td></td>
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<td>Grams, Median (IQR)</td>
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<tr>
<td>Local – medial joint line</td>
<td>0.60 (0.60)</td>
<td>0.60 (0.60)</td>
<td>0.40 (0.29)</td>
<td>&lt;0.001*</td>
<td>0.001*</td>
<td>0.001*</td>
<td>0.742</td>
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<tr>
<td><strong>Temporal Summation</strong></td>
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<tr>
<td><strong>Absolute difference</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local – patella</td>
<td>2.00 (2.06)</td>
<td>2.50 (4.00)</td>
<td>1.00 (2.00)</td>
<td>0.069</td>
<td>0.029*</td>
<td>0.100</td>
<td>0.989</td>
</tr>
<tr>
<td>Remote – forearm</td>
<td>1.88 (2.19)</td>
<td>1.25 (2.63)</td>
<td>1.00 (2.00)</td>
<td>0.034*</td>
<td>0.007*</td>
<td>0.490</td>
<td>0.147</td>
</tr>
<tr>
<td><strong>Total (mean for all sites)</strong></td>
<td>2.19 (1.84)</td>
<td>1.88 (2.63)</td>
<td>1.25 (2.00)</td>
<td>0.033*</td>
<td>0.007*</td>
<td>0.190</td>
<td>0.396</td>
</tr>
<tr>
<td><strong>Dynamic touch</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased (alldynia)</td>
<td>65.4%</td>
<td>19.2%</td>
<td>5.3%</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>0.079</td>
<td>0.001*</td>
</tr>
<tr>
<td>Decreased (hypoesthesia)</td>
<td>11.5%</td>
<td>19.2%</td>
<td>0.0%</td>
<td>0.025*</td>
<td>0.032*</td>
<td>0.005*</td>
<td>0.442</td>
</tr>
<tr>
<td><strong>Cold Frequency</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased (hyperalgesia)</td>
<td>57.7%</td>
<td>38.5%</td>
<td>10.5%</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>0.008*</td>
<td>0.165</td>
</tr>
<tr>
<td>Decreased (hypoesthesia)</td>
<td>11.5%</td>
<td>11.5%</td>
<td>0.0%</td>
<td>0.095</td>
<td>0.032*</td>
<td>0.032*</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>Heat Frequency</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased (hyperalgesia)</td>
<td>38.5%</td>
<td>19.2%</td>
<td>0.0%</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>0.005*</td>
<td>0.126</td>
</tr>
<tr>
<td>Decreased (hypoesthesia)</td>
<td>23.1%</td>
<td>23.1%</td>
<td>0.0%</td>
<td>0.006*</td>
<td>0.002*</td>
<td>0.002*</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>Sensitivity to Nerve Palpation Frequency</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Sciatic</td>
<td>30.8%</td>
<td>23.1%</td>
<td>7.9%</td>
<td>0.058</td>
<td>0.017*</td>
<td>0.086</td>
<td>0.532</td>
</tr>
<tr>
<td>Femoral</td>
<td>38.5%</td>
<td>23.1%</td>
<td>10.5%</td>
<td>0.030*</td>
<td>0.008*</td>
<td>0.174</td>
<td>0.229</td>
</tr>
<tr>
<td>Tibial</td>
<td>38.5%</td>
<td>19.2%</td>
<td>10.5%</td>
<td>0.026*</td>
<td>0.008*</td>
<td>0.325</td>
<td>0.126</td>
</tr>
<tr>
<td>Peroneal</td>
<td>53.8%</td>
<td>30.8%</td>
<td>7.9%</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>0.017*</td>
<td>0.092</td>
</tr>
</tbody>
</table>

*P < 0.05, no correction; IQR, inter-quartile range; See supplemental information (Appendix D) for further details on frequency of allodynic/hyperalgesic responses & hypoesthetic responses to touch, cold & heat.
5.5 Discussion

The current study demonstrated greater somatosensory abnormalities in people with knee OA with high PPS compared to those with low PPS and pain-free controls. Findings of a greater frequency of mechanical allodynia and decreased vibration detection sense in the high PPS group compared to the low PPS and control groups are suggestive of a higher degree of pain sensitization in people with knee OA with high PPS. Additionally, results demonstrating the presence of increased TS and mechanosensitivity of the femoral and peroneal nerves in the high PPS group, but not in the low PPS group, compared to controls add support to the concept that those with high PPS may have a higher degree of sensitization.

5.5.1 Positive Sensory Signs

Gains in sensory function such as increased TS, allodynia and hyperalgesia were classified as positive sensory signs. Results from the current study demonstrating a significantly greater frequency of dynamic mechanical allodynia in the high PPS group compared to the low PPS group and controls are suggestive that knee OA participants with high PPS may have a higher degree of pain sensitization. Few studies have identified allodynia in people with knee OA\textsuperscript{13} and the presence of allodynia is thought to indicate an increase in synaptic function triggered within the CNS\textsuperscript{7}.

Though there was no significant difference between the high and low PPS groups for TS, results from this study showing significantly increased TS in the high PPS group, but not in the low PPS group, compared to controls may suggest a higher level of abnormal central nociceptive processing via spinal hyperexcitability in those with high PPS. Increased TS has been reported previously in knee OA cohorts\textsuperscript{11,16,20}. Findings from the current report extend upon existing evidence by identifying two subgroups of knee OA participants with potentially differing levels of TS compared to controls. Similarly, sensitivity to nerve palpation of the femoral and peroneal nerves was found in the high PPS group, and not the low PPS group, compared to controls, possibly suggesting a higher degree of neural mechanosensitivity in the high PPS group. It has been postulated that the presence
of neural mechanosensitivity remote from the site of injury may reflect hypersensitivity of primary nerve afferents (nervi nervorum) along the nerve trunk due to abnormal CNS processing of non-nociceptive input\textsuperscript{42}.

A high frequency of hyperalgesia to cold and heat at the knee was demonstrated across both the high PPS group and the low PPS group compared to controls, with no significant differences between high and low PPS groups for these measures. In contrast to the central processes believed to be involved in allodynia\textsuperscript{7}, increased TS\textsuperscript{36} and remote neural mechanosensitivity\textsuperscript{43}, findings of local hyperalgesia to cold and heat are thought to be primarily caused by peripheral sensitization of A\(\delta\) and C fibres surrounding the area of pain\textsuperscript{44}, which may explain why these particular abnormalities were present in the low PPS group, who are hypothesized to have a lower degree of pain sensitization.

5.5.2 Negative Sensory Signs

Loss of large fibre function such as diminished mechanical detection or vibration sense and loss of small fibre function such as thermal hypoaesthesia were classified as negative sensory signs\textsuperscript{30}. Previous studies have demonstrated negative sensory signs such as increased detection thresholds to light touch\textsuperscript{13, 14}, vibration\textsuperscript{12, 13, 45} and thermal stimuli in people with knee OA\textsuperscript{14, 46}. Mechanisms underlying hypoaesthesia in people with chronic musculoskeletal pain remain speculative; it may be caused by a peripherally-driven release of inflammatory mediators at the site of pathology\textsuperscript{33, 47}, by a centrally-driven activation of pre-synaptic inhibition or activation of descending inhibitory processes\textsuperscript{48, 49}.

In the current study, diminished mechanical detection sense at the knee and local hypoaesthesia to dynamic touch and heat were present in both high and low PPS groups compared to controls and there were no significant differences between high and low PPS groups, while vibration sense was significantly diminished in the high PPS group compared to the low PPS group and controls. A possible explanation for the presence of VDT in the high PPS group only is that light touch (MDT), innocuous thermal stimuli and high frequency vibration sense (VDT) are
perceived by distinct sensory receptors. Receptors for light touch (Meissner and Merkel endings) and innocuous thermal stimuli (cold and warm fibres) are located in the skin, while the receptors for high frequency vibration (Pacinian corpuscles) are found in deeper layers of skin, between layers of muscle, and in periosteum and it may be that dysfunction of vibration sense is reflective of a centrally-driven sensory inhibition, while other more superficial measures of hypoaesthesia may also involve a peripheral inflammatory component.

5.5.3 Patient-reported Outcome Measures

Higher levels of neuropathic-like pain and pain catastrophising were associated with the presence of mechanical allodynia. Neuropathic-like pain and pain catastrophising have previously been reported in people with knee OA and identification of these outcomes have been cited as possible clinical indicators of pain sensitization. Results from the current study are in keeping with findings from the few studies that have previously reported associations between pain sensitization and neuropathic-like pain and pain catastrophising in this cohort.

There was no significant difference between high and low PPS groups for patient-reported symptoms and our finding that pain severity was not associated with somatosensory abnormalities, in particular PPS, is contrary to some existing evidence. This is possibly due to our inclusion criterion specifying that participants in the current study were required to have an average pain rating of > 3/10 in order to be included in the study. Previous reports which demonstrated associations between pain severity and pressure pain sensitivity and TS included participants with greater variations in their level of pain. It is also possible that the presence of somatosensory abnormalities did not play a dominant role in reporting of symptoms for many participants in the current study. It is thought to be a subgroup of people with knee OA whose pain is primarily driven by pain sensitization and a recent meta-analysis of 40 studies relating to spinal pain found a weak relationship between pain threshold and reporting of pain and disability. The influence of pain sensitization on people’s experience of pain is an ongoing area for investigation.
Identification of a knee OA subgroup with a high degree of sensitization is clinically relevant with regard to choice of treatment pathways\textsuperscript{55}. In the current study, we demonstrated that knee OA patients with higher PPS showed a greater degree of pain sensitization suggesting that PPT measurement may be useful for identifying pain-sensitized patients in future research, as well as clinically. However, the dearth of standardised cut-off points for normal and abnormal PPTs is a barrier to PPT assessment in the clinical setting. Abnormalities that were present in the high PPS group, and not in the low PPS group, such as mechanical allodynia, decreased VDT, TS and femoral and peroneal nerve sensitivity, may also be valuable for assisting with the identification of pain-sensitized patients; for example, mechanical allodynia is simple to assess and was present in 65\% of the high PPS group compared to 19\% of the low PPS group. Further investigation is needed to establish the clinical utility of pain sensitization measures.

5.5.4 Limitations
A median split of PPT data was used to subgroup knee OA participants in the absence of normative values regarding high and low degrees of sensitization. One limitation of this method is that the size of between-group differences may have been underestimated due to similarity of participants whose scores were close to the median. Further investigation is warranted using a larger sample and more conservative cut-offs for high and low PPS rather than the median split used in the current study (e.g. high PPS cut off = 25\textsuperscript{th} percentile PPT; low PPS cutoff = 75\textsuperscript{th} percentile PPT). The sample size of our study did not facilitate such a design. In addition, this study carried a risk of measurement bias as testing was carried out by a single unblinded assessor. Replication is required using independent, blinded assessment to corroborate our findings.

5.5.5 Conclusions
This study demonstrated distinguishable differences between the somatosensory profiles of people with knee OA with high and low levels of widespread PPS in comparison to pain-free controls. Both high and low PPS groups exhibited
diminished mechanical detection sense, as well as hyperalgesia and hypoaesthesia to thermal stimuli and hypoaesthesia to dynamic touch. However high frequency of dynamic mechanical allodynia, diminished vibration sense, increased TS and high frequency of femoral and tibial nerve mechansosensitivity were unique to the high PPS group, suggesting that the high PPS group showed a higher degree of sensitization and that these measures may be especially useful for identifying people with knee OA who are pain-sensitized. Further research is warranted to confirm our findings and to establish the clinical utility of these measures.

5.6 References


40. Field D and Hutchinson J. *Field’s anatomy, palpation and surface markings.* Butterworth-Heinemann Medical, 2006


Study 5. Exercise-induced hypoalgesia in people with knee osteoarthritis with high versus low pressure pain sensitivity

Fingleton C, Smart K, Doody C
Under Review, Clinical Journal of Pain
Study 1. Pain sensitization in people with knee osteoarthritis: A systematic review and meta-analysis

Study 2. Intraexaminer and interexaminer reliability of manual palpation and pressure algometry of the lower limb nerves in asymptomatic subjects

Study 3. Neural mechanosensitivity and pain sensitization in people with knee osteoarthritis

Study 4. A greater degree of pain sensitization is present in people with knee osteoarthritis with high versus low pressure pain sensitivity

Study 5. Exercise-induced hypoalgesia in people with knee osteoarthritis with high versus low pressure pain sensitivity

Study 6. Exercise-induced hypoalgesia in people with knee osteoarthritis with normal and abnormal conditioned pain modulation

Figure 6.1 Overview of Thesis and Relationship Between Studies
6.1 Abstract

Objectives: Normal function of exercise-induced hypoalgesia (EIH) has been demonstrated in response to isometric and dynamic resistance exercise in people with knee osteoarthritis. The aim of the current study was to investigate EIH in response to aerobic exercise, in addition to isometric exercise, in people with knee OA, and to compare EIH in knee OA patients with varying degrees of pain sensitization, as determined by high and low pressure pain sensitivity (PPS).

Methods: 40 knee OA patients were subdivided into high PPS and low PPS groups via a median split of pressure pain thresholds (PPTs). High PPS (n = 20), low PPS (n = 20) and control participants (n = 20) underwent PPT testing before, during and after aerobic and isometric exercise protocols. Between-group differences were analysed using repeated measures ANOVAs and within-group differences were analysed using Wilcoxon signed-rank tests.

Results: No significant differences were demonstrated between knee OA and control groups, or between high PPS, low PPS and control groups, for changes in PPTs post-aerobic or isometric exercise (P > 0.05). A significant within-group increase in PPTs was demonstrated post-aerobic and isometric exercise in controls (and in the low PPS group post-isometric exercise) (P < 0.05), while no significant change in PPTs occurred in the full knee OA group (or high PPS group) (P > 0.05).

Conclusions: While no significant differences were demonstrated between groups for changes in pain sensitivity in response to exercise, results indicating attenuation of pain sensitivity in controls (and the low PPS group), but not in the full knee OA group (or high PPS group) are suggestive of a decreased EIH response in people with knee OA that may be related to baseline degree of pain sensitization.
6.2 Introduction

Sensory abnormalities have been demonstrated in people with knee osteoarthritis (OA). These abnormalities, consistent with the paradigm of pain sensitization, are thought to involve peripheral mechanisms including an inflammatory-driven hypersensitivity of tissue local to the knee, as well as central processes underpinned by spinal hyperexcitability and dysfunction of descending pain modulation. Signs of pain sensitization including widespread hyperalgesia and hypoesthesias, as well as spinal hyperexcitability, have demonstrated in people with knee OA. Pain sensitization is thought to exist on a spectrum in people with knee OA and speculated to be a dominant mechanism in a subgroup people with knee OA.

Recently, studies have demonstrated dysfunction of a process known as exercise-induced hypoalgesia (EIH) in people with chronic pain. The process of EIH is thought to be caused by activation of endogenous opioid and non-opioid systems. A normal EIH response is characterised by a decrease in pain sensitivity in response to exercise; EIH has been demonstrated in response to aerobic and resistance exercise in pain-free cohorts. In chronic pain populations, both hypoalgesic and hyperalgesic responses to exercise have been demonstrated. A hyperalgesic response to high intensity aerobic exercise has been demonstrated in people with fibromyalgia, chronic fatigue syndrome (CFS), and chronic whiplash, and in response to moderate isometric exercise in fibromyalgia.

However, a normal attenuation of widespread pain sensitivity has been reported in response to high intensity aerobic exercise in people with chronic low back pain and rheumatoid arthritis and in response to moderate isometric contractions performed remotely at the quadriceps, but not locally at the infraspinatus muscle, in people with shoulder myalgia. Isometric knee extension produced an EIH response in people with hip/knee OA, and resistance exercise performed remotely at the upper body, but not locally at the lower body, has also been shown to produce a normal EIH response in people with knee OA. Pain sensitivity in these studies was measured using a variety of measures including...
pressure pain thresholds (PPTs)\textsuperscript{11}, cold\textsuperscript{23, 24} and heat stimuli\textsuperscript{19, 25}, temporal summation (TS) of heat\textsuperscript{13} and mechanical\textsuperscript{14} stimuli and conditioned pain modulation\textsuperscript{11, 14}. Only two studies have investigated the effect of resistance exercise on pain sensitivity in people with knee OA\textsuperscript{21, 22} and no study to date has investigated the effect of aerobic exercise on pain sensitivity in people with knee OA.

In addition, no study has investigated EIH in knee OA patients with varying degrees of pain sensitization; a notable difference between conditions such as fibromyalgia and CFS that exhibit dysfunctional EIH and those such as knee OA which appear to have a more normal EIH response is that pain in fibromyalgia and CFS is thought to be driven by sensitization in the absence of specific musculoskeletal pathology\textsuperscript{26}, whereas in CLBP, RA and knee OA, pain may be linked to an identifiable peripheral pathology\textsuperscript{8, 27, 28}, with sensitization-driven pain existing to varying degrees in these latter cohorts\textsuperscript{1, 27-29}. We thus hypothesised that knee OA patients with a higher degree of pain sensitization as determined by the presence of high pressure pain sensitivity (high PPS)\textsuperscript{30} may demonstrate dysfunction of EIH compared to those with lower PPS and healthy controls. The aims of the current study were 1) to investigate EIH via changes in PPTs and TS in response to acute aerobic and isometric exercise in people with knee OA compared to healthy controls and 2) to investigate exercise-induced changes in PPTs and TS in knee OA patients with varying degrees of pain sensitization as determined by high and low PPS.

6.3 Methods

6.3.1 Participants

Forty people with knee OA took part in the study. Inclusion criteria included a diagnosis of knee OA according to American College of Rheumatology classification and pain > 3/10 (≥ 4/10) on a numerical rating scale. Pain due to knee OA had to be the participants’ main pain. Twenty age and sex-matched pain-free volunteers were included as a control group. Control group participants were ineligible if they had experienced a pain episode, caused by musculoskeletal injury or otherwise, in the previous three months. Exclusion criteria for both the knee OA group and
control group were rheumatologic disease such as rheumatoid arthritis, fibromyalgia or ankylosing spondylitis; a neurological disorder such as parkinson’s disease, shingles, multiple sclerosis or stroke; cognitive impairment; and current use of antidepressant or anticonvulsant medication. All participants were also screened for suitability to exercise using the PAR-Q\textsuperscript{31}. In addition, knee OA group participants were excluded if they had undergone a total knee replacement (TKR) and if they had < 90 degrees knee flexion.

Knee OA participants were recruited from outpatient musculoskeletal triage or physiotherapy clinics in three hospital sites in Dublin, Ireland. Control participants were recruited from poster advertisement in University College Dublin (UCD) and local community centres, and from university staff and associates. The study was approved by the research ethics committees of UCD and the three hospital research ethics committees (Appendices A.5 – A.9). Written informed consent was obtained from all participants prior to taking part (Appendices B.4 – B.5).

6.3.2 Protocol
Potential participants were initially invited to take part in the study by the clinical physiotherapists at the different hospital sites. Potential participants were screened for eligibility by the physiotherapists, and participants were also given a study information leaflet. Initial consent was sought from potential participants to receive a phone call from the study researcher and 71 people consented. Thirty one people subsequently decided not to take part due to change of mind (n = 15), travel restraints (n = 2) or time burden (n = 6). An additional 5 participants were excluded following a further screening, with the main reasons for exclusion being diabetic neuropathy (n = 1) and knee pain not being their main pain (n = 4).

Forty knee OA participants and twenty healthy controls consented to take part in the study and attended a single session of testing. Baseline measurements included demographic variables, patient-reported validated outcome measures (knee OA group only) and assessment of pressure pain thresholds (PPTs) and temporal summation (TS). See Appendix C.6 for standardised instructions.
Patient-Reported Outcome Measures

Patient-reported clinical pain, stiffness and physical function were assessed with the WOMAC v3.0 VAS. The WOMAC is an established questionnaire that has been shown to be reliable and valid \(^{32}\) (Appendix C.1).

Pressure Pain Thresholds

Pressure pain thresholds are a measure of pressure hyperalgesia \(^{33}\) and were measured in this study using a handheld pressure algometer (Somedic AB, Sweden). Pressure was applied at a rate of thirty kilopascals (KPa) per second, perpendicular to the skin with a 2cm\(^2\) probe. Pressure pain thresholds were assessed at 3 sites: at the medial joint line (MJL) (3 cm medial to the mid point on the medial edge of patella) \(^{34}\) of the index knee (the knee that the participant identified as being their symptomatic or more symptomatic knee); at the quadriceps femoris muscle (midway between the groin and the apex of the patella) \(^{35}\) on the index knee; and remotely at the volar surface of the forearm (5 cm distal to the lateral epicondyle) \(^6, 36\). Participants pressed the button at the moment when the feeling of pressure changed to that of pressure and pain. The average of two PPT measurements was recorded for each site.

Temporal Summation

Temporal summation is a measure of spinal hyperexcitability in which repeated C-fibre input produces an increased response \(^{37}\); this process was assessed using repeated stimulation by weighted pinprick stimulus, a method that has been recommended by the German Research Network on Neuropathic Pain \(^{33}\). Pain ratings were gathered in response first to a single stimulus and then to a sequence of 10 stimuli of a weighted (256 mN) punctate noxious probe (MRC Systems, Germany) applied to 2 sites, the volar surface of the forearm and the patella of the index knee (1/s applied within an area of 1 cm\(^2\)) \(^{33, 38}\). Participants rated the stimuli from 0 (no pain) to 10 (worst pain imaginable). The absolute difference between the pain rating from repeated stimulation and the pain rating from the single stimulus was calculated \(^{39}\).
Exercise-induced hypoalgesia

Participants subsequently underwent measurement of EIH in response to a) aerobic and b) isometric exercise protocols. These tests were performed in a random sequence with 15-minute rest periods between each test. The difference between pre- and post-exercise measurements of PPT scores and TS score were examined.

a) Aerobic Exercise Protocol

Participants carried out aerobic exercise in a sitting position on a cycle ergometer. The saddle and handlebars were positioned to suit each participant and adjustments were made if needed during a one-minute trial period to ensure that pedalling could be performed with < 3/10 knee rating. Exercise was adapted when necessary to limit aggravation of local knee pain, which could potentially alter results of post-exercise pain testing.

Participants underwent a submaximal exercise protocol called the Aerobic Power Index test\(^40\), which has been shown to be reliable in people with chronic pain \(^41\) and sedentary adults \(^42\). Participants were instructed to begin pedalling at 25 watts (W) per minute and the workload was increased by 25 W every minute. The test stopped at the end of the minute in which the participant reached the submaximal level, which was defined as 75% of the age-predicted maximum heart rate and was calculated by subtracting the participant’s age in years from 220\(^40\). A heart rate monitor (Polar FS3c) was strapped around the participant’s chest. Pain was measured on a numerical rating scale at the end of each minute. If local pain at the knee joint exceeded 3/10, the participant’s workload was reduced by 25 W by decreasing rate of pedalling and/or decreasing resistance. The test was discontinued if the participant reported knee pain of > 3/10 which persisted despite decreased workload. Two knee OA participants were unable to complete the aerobic exercise protocol due to pain > 3/10 and their data for this test were excluded from the analysis. Prior to testing, PPTs were tested at the MJL of the index knee and the forearm and TS was tested at the index patella and forearm.
Reassessment of PPTs and TS at the knee and forearm was performed immediately following exercise.

b) Isometric Exercise Protocol
Maximal isometric knee extension strength on the index leg was assessed in a sitting position with hips and knees in 90 degrees of flexion. A push-pull dynamometer (Baseline evaluation instruments, White Plains, USA) fixed to the chair was used to measure the maximum voluntary contraction (MVC)\textsuperscript{43}. Three measurements were taken, each trial lasting 5 seconds, with 30 seconds rest between trials. The greatest value was used to calculate 10% of the individual's MVC force. Exercise was adapted when necessary to limit aggravation of local knee pain which could potentially alter results of pain testing during and post-exercise.

A weight corresponding to 10% of the MVC was placed in an adjustable ankle weight cuff (Fitness Depot, Canada). In a sitting position with the ankle weight on the index leg, the participant was instructed to extend their knee as far as could be achieved without pain > 3/10. The participant was then instructed to hold an isometric knee extension contraction until exhaustion, up to a maximum of 5 minutes. Pain was measured on a numerical rating scale at the beginning of the exercise and at the end of each minute. If pain at the knee joint exceeded 3/10, the participant was instructed to decrease the angle of knee extension. If pain persisted, the weight of the ankle cuff was decreased by up to 20%. The test was discontinued if the participant reported pain of > 3/10 which persisted despite these decreases in knee angle and weight. Prior to testing, PPTs were assessed at the index MJL, forearm and index quadriceps muscle and TS was assessed at the patella and forearm. During exercise, PPTs were assessed at the contracting quadriceps femoris muscle and at the forearm 45 seconds after beginning the contraction and then every 60 seconds during the contraction. Reassessment of PPTs at the knee, forearm and quadriceps and of TS at the knee and forearm was performed immediately following exercise.
6.3.3 Subgrouping

Knee OA participants were subdivided into two groups – high pressure pain sensitivity (High PPS) and low pressure pain sensitivity (Low PPS) based on their widespread pressure pain thresholds (PPTs). A median split of the averaged local and remote (index MJL and forearm) PPTs for men and women respectively were used to create the subgroups. Participants for the high PPS group had an averaged PPT score less than the median averaged PPT, while participants from the low PPS had an averaged PPT score greater than or equal to the median averaged PPT. An averaged PPT score was chosen to subgroup knee OA participants as widespread pressure hyperalgesia at local and remote sites is a feature of pain sensitization which has been repeatedly identified in people with knee OA\textsuperscript{1,44}. A median split of PPTs was used to achieve equal sized subgroups with differing degrees of sensitivity. This method has previously been used in people with chronic musculoskeletal pain\textsuperscript{45}.

6.3.4 Statistical Analysis

Data were analysed using SPSS v 20. Sample size was calculated for a repeated measures ANOVA interaction effect, with 3 groups, and 2 time-points (pre and post). Based on an intraclass correlation coefficient of 0.08, it was determined that 17 participants in each of the 3 groups would be required in order to detect a small effect size (eta-squared of 0.02). Descriptive data are presented as means ± standard deviations (SDs) unless otherwise specified. Baseline differences between sub-groups of knee OA participants and controls were analysed using the non-parametric Kruskal–Wallis test for continuous data and the Chi-square test for categorical data. Post hoc analysis of subgroups at baseline was carried out using Mann Whitney U tests and Chi-square tests for continuous and categorical data respectively. Repeated measures ANOVAs were used to examine the effect of exercise tests on pain sensitivity as measured by PPTs and TS. Possible changes in pain sensitivity (as measured by PPT and TS) in response to aerobic exercise were compared between the groups using repeated measures ANOVAs examining time*group interaction effects, with between-subject factor ‘group’ (knee OA group and controls/ high PPS group, low PPS group and controls) and within-
subject factor ‘time’ (pre and post). The same method of repeated measures ANOVA was used for comparing changes in pain sensitivity during isometric exercise between groups, but the ‘time’ factor had 4 levels (pre, middle, end, post). A Greenhouse-Geisser Correction was used for data that violated the assumption of sphericity. Post hoc analysis of subgroups was also carried out using the same method of repeated measures ANOVA, but with 2 groups in the ‘group’ factor (i.e. knee OA group 1, knee OA group 2). Within-group changes in outcome measures between pre- and post-exercise measurements were analysed using Wilcoxon signed rank tests for paired comparisons as data were non-normally distributed. The level of significance was set at $P < 0.05$. No adjustment of the $P$ value was made for multiple comparisons as all tests were planned and reasonable.

6.4 Results

6.4.1 Participant Characteristics

The baseline participant characteristics are presented in Table 6.1. There was no significant difference between knee OA participants and controls for age ($P = 0.455$) or gender distribution ($P = 1.000$) and no significant difference between high and low PPS groups for age ($P = 0.341$), gender distribution ($P = 1.000$), radiographic disease severity ($P = 0.419$) or number of participants with bilateral knee pain ($P = 0.113$). There were no significant differences between high and low PPS groups for WOMAC pain ($P = 0.341$), stiffness ($P = 0.659$), activities of daily living ($P = 0.221$) or total score ($P = 0.277$).

Table 6.1 Participant Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Knee OA full group</th>
<th>Knee OA-high PPS</th>
<th>Knee OA-low PPS</th>
<th>Controls</th>
</tr>
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<tbody>
<tr>
<td>N</td>
<td>40</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Female (%) / Male (%)</td>
<td>18 (45%) / 22 (55%)</td>
<td>9 (45%) / 11 (55%)</td>
<td>9 (45%) / 11 (55%)</td>
<td>9 (45%) / 11 (55%)</td>
</tr>
<tr>
<td>Age (years), mean ± SD</td>
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<td>64.9 ± 9.65</td>
<td>62.4 ± 10.25</td>
<td>62.0 ± 7.90</td>
</tr>
<tr>
<td>Unilateral (%) / Bilateral pain (%)</td>
<td>21 (52.5%) / 19 (47.5%)</td>
<td>8 (40%) / 12 (60%)</td>
<td>13 (65%) / 7 (35%)</td>
<td></td>
</tr>
<tr>
<td>Radiographic disease severity*</td>
<td>Mild-moderate (%) / severe (%)</td>
<td>21 (56.8%) / 16 (43.2%)</td>
<td>9 (50%) / 9 (50%)</td>
<td>12 (60%) / 7 (40%)</td>
</tr>
<tr>
<td>WOMAC pain 0-50</td>
<td>22.66 ± 10.70</td>
<td>24.73 ± 9.98</td>
<td>20.59 ± 11.24</td>
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</tr>
<tr>
<td>WOMAC stiffness 0-20</td>
<td>11.09 ± 5.28</td>
<td>11.36 ± 4.65</td>
<td>10.81 ± 5.96</td>
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</tr>
<tr>
<td>WOMAC ADLs 0-170</td>
<td>79.06 ± 36.44</td>
<td>87.64 ± 36.40</td>
<td>70.49 ± 35.30</td>
<td></td>
</tr>
<tr>
<td>WOMAC total 0-240</td>
<td>112.80 ± 47.90</td>
<td>123.70 ± 47.97</td>
<td>101.90 ± 46.45</td>
<td></td>
</tr>
</tbody>
</table>

PPS, pressure pain sensitivity; WOMAC, Western Ontario & McMaster Universities Osteoarthritis Index; ADLs, activities of daily living; *Participants were classified as having either 1) mild-moderate or 2) severe radiographic knee OA based on their radiology report.
6.4.2 Knee OA Group Vs Healthy Controls

Baseline Pain Sensitivity

Knee OA participants had significantly decreased PPTs locally at the MJL (166.09 ± 62.13 KPa), but not remotely at the forearm (185.50 ± 55.20 KPa), compared to controls (MJL, 242.13 ± 122.32 KPa, P = 0.018; forearm, 193 ± 77 KPa; P = 0.956). TS score was also significantly increased in knee OA participants compared to controls when measured at the knee (knee OA, 2.31 ± 1.87; controls, 1.14 ± 1.16, P = 0.031) but not at the forearm (knee OA, 1.96 ± 1.64; controls, 1.24 ± 1.23, P = 0.091).

Between-Group Differences for Changes in Pain Sensitivity

There were no significant differences between knee OA participants and controls for changes in PPTs over time (interaction effect) pre- and post-aerobic (Figure 6.2) or isometric exercise (Figure 6.3) when measured locally at the knee, remotely at the forearm or overall (P > 0.05), or for changes in TS score over time pre- and post-aerobic or isometric exercise locally at the knee, remotely at the forearm or overall (P > 0.05) (Table 6.2). The quadriceps muscle (contracting muscle) and forearm were analysed at 4 time-points (pre, middle, end, post) for isometric exercise and no significant differences were found between knee OA participants and controls for changes in PPTs (P > 0.05) (Table 6.2).

Within-Group Changes in Pain Sensitivity

For the control group, there was a significant increase in PPTs between pre- and post measures locally at the knee for aerobic (P = 0.011) and isometric (P = 0.011) exercise, but not remotely at the forearm (Aerobic, P = 0.737; Isometric, P = 0.204) (Table 6.2). There were no significant changes in PPTs between pre- and post measures in knee OA participants at the knee (Aerobic, P = 0.180; Isometric, P = 0.111) or forearm (Aerobic, P = 0.468; Isometric, P = 0.164) (Table 6.2). During isometric exercise, both knee OA participants and controls showed a significant increase in PPTs of the forearm at the middle (knee OA, P = 0.009; controls, P = 0.009) and end (knee OA, P = 0.007; controls, P = 0.002) time-points, which was no longer significant post-exercise (knee OA, P = 0.164; controls, P = 0.204), while
there were no significant changes in PPTs at the contracting quadriceps muscle during or post-exercise in either group (P > 0.05) (Table 6.2). There were no significant differences between pre- and post-exercise TS scores in knee OA or control participants (P > 0.05) (Table 6.2).

**Figure 6.2** Between-group Differences for Changes in Pressure Pain Thresholds Pre- and Post-aerobic Exercise

**Figure 6.3** Between-group Differences for Changes in Pressure Pain Thresholds Pre- and Post-isometric Exercise
Table 6.2 Knee OA Group and Healthy Controls: Changes in pain sensitivity

<table>
<thead>
<tr>
<th></th>
<th>Knee OA group</th>
<th>Healthy control group</th>
<th>Between-group comparisons: Interaction Effect (DF; F-value; P-value)</th>
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<tr>
<td></td>
<td>N=40</td>
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<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
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<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
</tr>
<tr>
<td>Aerobic exercise (EIH)</td>
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<td></td>
<td></td>
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<tr>
<td>Pressure pain thresholds (KPa)</td>
<td></td>
<td></td>
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<tr>
<td>Medial joint line</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Pre</td>
<td>186.30 ± 62.95</td>
<td>179.34 ± 73.80</td>
<td>242.13 ± 122.32</td>
</tr>
<tr>
<td>Post</td>
<td>184.71 ± 82.49</td>
<td>193.77 ± 76.48</td>
<td>217.95 ± 93.20</td>
</tr>
<tr>
<td>Forearm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>242.13 ± 122.32</td>
<td>278.49 ± 157.68</td>
<td>1, 56; 3.43; 0.069</td>
</tr>
<tr>
<td>Forearm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>184.71 ± 82.49</td>
<td>193.77 ± 76.48</td>
<td>217.95 ± 93.20</td>
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<tr>
<td>Forearm</td>
<td></td>
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<tr>
<td>Total (average of 2 sites)</td>
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<td>Temporal summation</td>
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<tr>
<td>Patella</td>
<td>2.32 ± 1.85</td>
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<td>1.14 ± 1.02</td>
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<td>Forearm</td>
<td>1.97 ± 1.64</td>
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<td>1.25 ± 1.26</td>
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<td>Total (average of 2 sites)</td>
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<td>2.04 ± 1.46</td>
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<tr>
<td>Medial joint line</td>
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</tr>
<tr>
<td>Pre</td>
<td>166.09 ± 62.13</td>
<td>184.52 ± 102.51</td>
<td>265.14 ± 127.38</td>
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<tr>
<td>Middle</td>
<td>184.71 ± 82.49</td>
<td>212.32</td>
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<td>End</td>
<td>242.13 ± 122.32</td>
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<tr>
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<td>384.09 ± 107.10</td>
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<td>Total (average of 2 sites: medial joint line &amp; forearm)</td>
<td>175.80 ± 51.13</td>
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<td>Temporal summation</td>
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<td>Patella</td>
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<td>1.14 ± 1.02</td>
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<td>Forearm</td>
<td>1.96 ± 1.64</td>
<td>2.39 ± 1.97</td>
<td>1.24 ± 1.23</td>
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<td>Total (average of 2 sites)</td>
<td>2.13 ± 1.60</td>
<td>2.44 ± 1.79</td>
<td>1.19 ± 1.04</td>
</tr>
</tbody>
</table>

*significant within-group increase in PPTs from baseline, Wilcoxon signed rank test, P < 0.05
+2 participants were unable to complete the aerobic exercise protocol
Table 6.3 Knee OA High and Low Pressure Pain Sensitivity Groups and Healthy Controls: Changes in Pain Sensitivity

<table>
<thead>
<tr>
<th></th>
<th>High pressure pain sensitivity</th>
<th>Low pressure pain sensitivity</th>
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<th>Between-group comparisons: Interaction Effect (DF; F-value; P-value)</th>
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<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
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<td>Pressure pain thresholds (KPa)</td>
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<tr>
<td>Medial joint line</td>
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<tr>
<td>Pre</td>
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<td>139.56 ± 58.56</td>
<td>206.47 ± 58.40</td>
<td>219.11 ± 66.54</td>
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<tr>
<td>Post</td>
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<td>193.77 ± 76.48</td>
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<td>214.97 ± 57.33</td>
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<tr>
<td>Patella</td>
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<tr>
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<tr>
<td>Patella</td>
<td>2.43 ± 1.97</td>
<td>2.72 ± 1.96</td>
<td>2.20 ± 1.77</td>
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<tr>
<td>Forearm</td>
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<td>2.04 ± 1.29</td>
<td>1.37 ± 1.32</td>
<td>1.64 ± 1.21</td>
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<tr>
<td>Total (average of 2 sites)</td>
<td>2.50 ± 1.69</td>
<td>2.38 ± 1.53</td>
<td>1.78 ± 1.40</td>
<td>1.70 ± 1.33</td>
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*significant within-group increase in PPTs from baseline, Wilcoxon signed ranked test, P < 0.05

2 participants were unable to complete the aerobic exercise protocol due to pain > 3/10
6.4.3  Knee OA High Pressure Pain Sensitivity (PPS) Vs Low PPS Group Vs Controls

Baseline Pain Sensitivity

The high PPS group showed significantly increased TS at the patella (2.54 ± 1.97) and the forearm (2.61 ± 1.70) compared to controls (patella, 1.14 ± 1.02, P = 0.024; forearm, 1.24 ± 1.23, P = 0.004) and there were no significant differences between the low PPS group (patella, 2.09 ± 1.79; forearm, 1.30 ± 1.32) and controls for TS at the knee (P = 0.157) or forearm (P = 0.355). Compared to the low PPS group, the high PPS group showed significantly increased TS at the forearm (P = 0.009) but not at the knee (P = 0.512).

Between-Group Differences for Changes in Pain Sensitivity

There were no significant differences between high and low PPS groups and controls for changes in PPTs over time pre- and post-aerobic or isometric exercise when measured locally at the knee, remotely at the forearm or overall (P > 0.05), or for changes in TS score over time pre- and post-aerobic or isometric exercise locally at the knee, remotely at the forearm or overall (P > 0.05) (Table 6.3). PPTs at the quadriceps muscle (contracting muscle) and forearm were analysed at 4 time-points (pre, middle, end, post) for isometric exercise and no significant differences were found between knee OA participants and controls for changes in PPTs (P > 0.05) (Table 6.3).

Within-Group Changes in Pain Sensitivity

There were no significant differences in PPTs between pre- and post-measures in the high PPS group at the knee (Aerobic, P = 0.469, Isometric, P = 1.000) or forearm (Aerobic, P = 0.587, Isometric, P = 0.271) (Table 6.3). High PPS participants showed a significant increase in forearm PPTs in the middle (P = 0.028) and at the end (P = 0.021) of isometric exercise, but not post-exercise (P = 0.271) and showed no significant change in quadriceps PPTs during or after isometric exercise (P > 0.05) (Table 6.3). In the low PPS group, there were no significant differences in PPTs post-aerobic exercise at the knee (P = 0.212) or forearm (P = 0.717), and increased PPTs were found post-isometric exercise at the knee (P = 0.028), but not the forearm (P = 0.411) (Table 6.3). Low PPS participants showed no significant
change in PPT scores at the forearm or quadriceps muscle during or after isometric exercise (P > 0.05) (Table 6.3). There were no significant differences between pre- and post-exercise TS scores, except for an increase in TS at the forearm post-isometric exercise in the low PPS group (P = 0.025) (Table 6.3).

6.5 Discussion

6.5.1 Findings

This is the first study to investigate EIH in response to aerobic exercise in people with knee OA, and to investigate EIH in people with knee with varying degrees of PPS. Results showing no significant differences between knee OA participants and controls for changes in PPTs post-aerobic and isometric exercise were suggestive of a normal function of EIH in people with knee OA, while findings of no significant differences between high PPS, low PPS and control groups for changes in PPTs post-exercise also suggested a normal EIH response. However within-group findings of a significant increase in PPTs post-aerobic and isometric exercise in controls (and in the low PPS group post-isometric exercise only), and no significant change in PPTs in the full knee OA group (or high PPS group), may be suggestive of decreased efficiency of the EIH response in people with knee OA that may be related to baseline degree of sensitization. Findings at baseline of significantly decreased PPTs and increased TS in the knee OA group compared to controls were suggestive of a degree of pain sensitization in knee OA participants.1,46

This was the first study to measure TS in people with knee OA pre- and post-exercise and no significant differences were found between groups. The lack of change between pre- and post-exercise TS scores in knee OA and control groups suggests that exercise did not significantly attenuate TS in the current study. This finding is in contrast with Vierck et al13 who demonstrated reduced TS in controls post-exercise. The shorter duration of exercise measured in the current study (aerobic: ≤ 10 minutes, isometric: ≤ 5 minutes) compared to Vierck et al (≥ 15 minutes) may not have been sufficient to decrease TS scores in our study participants. Vierck et al13 also used a different method of TS measurement, using a preheated thermode as opposed to pinprick stimulation used in the current
study, which may also account for differences in results between studies. Another report that used the same aerobic exercise protocol as our study demonstrated a normal decrease in TS measured using cuff occlusion at the shoulder but lack of TS attenuation at the finger in healthy controls\textsuperscript{14}.

Normal EIH in response to resistance exercise has previously been demonstrated in knee OA\textsuperscript{21, 22}. Kosek et al\textsuperscript{21} measured PPTs during isometric knee extension and showed significantly increased PPTs in the hip and knee OA participants, which were not significantly different from the control group. The current study also demonstrated an increase in PPTs (at the forearm only) in knee OA and control groups during isometric exercise, but post-exercise, the control group demonstrated a significant increase in MJL PPT score that was not present in the knee OA group. This finding of increased MJL PPT post-exercise in controls, but not in knee OA participants, was also demonstrated in response to our aerobic exercise protocol and may be suggestive of a lesser efficiency of EIH in people with knee OA. It is possible that gains in PPTs during exercise diminished faster in knee OA participants due to dysfunction of descending inhibition or that the increases in PPTs seen during exercise may have been partially caused by distraction (discussed below). However, a study by Burrows et al\textsuperscript{22} demonstrating increases in PPTs post-dynamic upper limb resistance exercise in knee OA participants provides support for normal function of EIH in people with knee OA; though, as with our study, lower limb resistance exercise did not significantly attenuate pain sensitivity.

We speculated that there may be a subgroup of people with knee OA who exhibit dysfunctional EIH. A group of knee OA participants with high PPS have been found to demonstrate greater signs of pain sensitization than those with low PPS or controls\textsuperscript{30}. Further to this, a recent study by Vaegter et al\textsuperscript{45} demonstrated significantly greater attenuation of pain sensitivity in response to exercise in people with chronic musculoskeletal pain with low PPS compared to those with high PPS suggesting that the presence of high PPS may be associated with dysfunction of EIH. However, our results demonstrated no significant differences between high and low PPS groups and controls. The discrepancy between studies
may be because the sample in the study by Vægter et al were attending a pain specialist (the majority with back or neck pain) and as such, may have had a higher baseline degree of sensitivity than participants in the current study who were recruited from musculoskeletal triage/physiotherapy clinics. In addition the study by Vaegter et al did not include a healthy control comparison group, but utilized a resting control condition, which may also account for differences between the studies. Despite the lack of significant differences between high and low PPS groups for changes in PPTs in the current study, the low PPS group, similar to the control group, tended to show an increase in PPTs post-exercise and demonstrated a significant increase in MJL PPTs post-isometric exercise, while there was no significant increase in PPTs in the high PPS group. These findings may be suggestive of a decreased EIH response in knee OA participants with high PPS and also suggest that EIH in people with knee OA may be related to the baseline degree of sensitization; though further research is warranted.

While activation of opioid and non-opioid supraspinal pathways are thought to be the primary mechanisms underlying EIH, other factors may have contributed to decreases in pain sensitivity related to exercise in this study. As mentioned above, measurement of pain sensitivity during exercise introduces the possibility that the exercise stimulus may distract the participant, altering their report of pain sensitivity. Findings from this study of changes in PPTs during isometric exercise must be interpreted cautiously in light of this. A second consideration is that significant increases in PPTs post-exercise were found at the MJL and not at the forearm in low PPS participants and controls, a surprising finding that may implicate the contribution of a local modulatory effect. Helmark et al demonstrated an increase in the anti-inflammatory cytokine interleukin-10 intra-articularly and peri-synovially in response to exercise in people with knee OA and the anti-inflammatory effects of exercise are well-described in the literature. As such, it is possible that a local anti-inflammatory response may have contributed to the local increase in PPTs observed in the current study.
Results from this study suggesting a possible decreased efficiency of EIH in people with knee OA compared to pain-free controls are clinically important as exercise is a central component of symptom management in knee OA\textsuperscript{53, 54}. Findings of increased PPTs post-isometric exercise in low PPS and control groups, but not in high PPS groups, suggest that EIH response may vary depending on a patient’s level of pain sensitization and warrant further research due to the potential detrimental effects of inappropriate exercise prescription for sensitized chronic pain patients\textsuperscript{55}. Future studies could attempt to identify people with knee OA with a high degree of sensitization using a more conservative cut-off for ‘high PPS’, for example selecting participants whose PPT score is in the 25\textsuperscript{th} percentile rather than a median split in PPT measurement, or by selecting those who show dysfunction of a direct measure of central hyperexcitability, such as increased TS which is suggestive of spinal hyperexcitability\textsuperscript{33} or lack of conditioned pain modulation (CPM) which is suggestive of abnormal endogenous pain modulation\textsuperscript{56}.

6.5.2 Limitations

A limitation of this study is that testing was carried out by an unblinded assessor and replication is required using independent, blinded assessment to corroborate our findings. Additionally, multiple measures of endogenous inhibition were carried out in the same session, creating a potential risk of carry-over effects. However, participants were given 15-minute breaks between each test, which has been deemed sufficient for effects to wear off due to the short duration of each protocol\textsuperscript{57, 58}. A median split was used to subgroup participants and a limitation of this method is that the size of between-group differences may have been underestimated due to similarity of participants whose scores were close to the median. Finally, the lack of a control condition meant that post-exercise pain sensitivity could potentially have been influenced by pre-exercise pain tests\textsuperscript{11}, however reliability testing has shown that the effects of repeated pain testing on measures of pain are small and trivial\textsuperscript{11}. 

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6.5.3 Conclusions

This was the first study to measure EIH in response to aerobic exercise in people with knee OA and the first to investigate EIH in knee OA participants with differing degrees of pain sensitization. Results demonstrating no significant difference between knee OA participants, including those with high and low PPS, and controls for changes in PPTs in response to aerobic and isometric exercise are suggestive of a normal function of EIH in people with knee OA. However, significant within-group increases in PPTs in the control group and a lack of significant increases in PPTs in knee OA participants may be suggestive of a lesser efficiency of EIH response in people with knee OA. Additionally, the significant increase in PPTs post-isometric exercise in those with low PPS, but not those with high PPS, suggests a variability of EIH response in people with knee OA that may be related to baseline degree of pain sensitization and warrants further investigation.

6.6 References


of deep-tissue pain in knee osteoarthritis patients after knee replacement. 


Chapter 7

Study 6. Exercise-induced hypoalgesia in people with knee osteoarthritis with normal and abnormal conditioned pain modulation

Fingleton C, Smart K, Doody C
Accepted Pending Revision, Clinical Journal of Pain
**Study 1.** Pain sensitization in people with knee osteoarthritis: A systematic review and meta-analysis

**Study 2.** Intraexaminer and interexaminer reliability of manual palpation and pressure algometry of the lower limb nerves in asymptomatic subjects

**Study 3.** Neural mechanosensitivity and pain sensitization in people with knee osteoarthritis

**Study 4.** A greater degree of pain sensitization is present in people with knee osteoarthritis with high versus low pressure pain sensitivity

**Study 5.** Exercise-induced hypoalgesia in people with knee osteoarthritis with high versus low pressure pain sensitivity

**Study 6.** Exercise-induced hypoalgesia in people with knee osteoarthritis with normal and abnormal conditioned pain modulation

*Figure 7.1 Overview of Thesis and Relationship Between Studies*
7.1 Abstract

Objectives: Recent evidence suggests that exercise-induced hypoalgesia (EIH) in people with knee OA may be associated with baseline degree of pain sensitization. The aim of this study was to investigate the effect of aerobic and isometric exercise in people with knee OA with varying degrees of pain sensitization by comparing knee OA patients with abnormal conditioned pain modulation (CPM) to those with normal CPM and pain-free controls.

Methods: 40 people with knee OA were subdivided into groups with abnormal and normal CPM, as determined by a decrease/increase in pressure pain thresholds (PPTs) following the cold pressor test. Abnormal CPM (n = 19), normal CPM (n = 21) and control participants (n = 20) underwent PPT testing before, during and after aerobic and isometric exercise protocols. Between-group differences were analysed using repeated measures ANOVAs and within-group differences were analysed using Wilcoxon signed-rank tests.

Results: Significant differences were demonstrated between groups for changes in PPTs post-aerobic ($F(2, 55) = 4.860, P = 0.011$) and isometric ($F(2, 57) = 4.727; P = 0.013$) exercise, with significant decreases in PPTs demonstrated during and post-exercise in the abnormal CPM group ($P < 0.05$), and significant increases in PPTs shown during and post-exercise in the normal CPM and control groups ($P < 0.05$).

Conclusions: Results are suggestive of dysfunctional EIH in response to aerobic and isometric exercise in knee OA patients with abnormal CPM, and normal function of EIH in knee OA patients with an efficient CPM response. Identification of people with knee OA with inefficient endogenous pain modulation may allow for more individualised and graded approach to exercise in these individuals.
7.2 Introduction

Sensitization of the nervous system has been demonstrated in people with osteoarthritis (OA) of the knee\(^1\) and is thought to exist on a spectrum in this cohort\(^1,2\), with pain sensitization acting as a more dominant mechanism in a subgroup of people with knee OA\(^3\). Features of pain sensitization including the presence of hyperalgesia and hypoaesthesia to mechanical/thermal stimuli have been identified in people with knee OA using QST testing\(^4-7\). Direct measures of central hyperexcitability, including increased temporal summation (TS), suggestive of spinal hyperexcitability\(^8\), and a lack of conditioned pain modulation (CPM), suggestive of abnormal endogenous pain modulation\(^9\), have also been demonstrated in people with knee OA\(^1,10,11\).

Exercise-induced hypoalgesia (EIH) is a process believed to be mediated by endogenous pain inhibitory pathways\(^12\). In healthy pain-free cohorts, acute bouts of exercise have been shown to attenuate pain sensitivity, as measured by pressure pain thresholds (PPTs)\(^13\), cold\(^14,15\) and heat stimuli\(^16,17\), TS of heat\(^18\) and mechanical\(^19\) stimuli or conditioned pain modulation (CPM)\(^13,19\). This process is speculated to be caused by activation of both endogenous opioid and non-opioid systems\(^12\). However, in chronic pain populations, exercise has been found to result in both increases and decreases in pain sensitivity\(^13\). People with chronic fatigue syndrome (CFS)\(^20,21\), fibromyalgia\(^19\) and whiplash-associated disorders (WADs)\(^22\) have demonstrated increases in pain sensitivity in response to moderate to high intensity exercise, while a normal attenuation of pain sensitivity has been demonstrated in people with chronic low back pain (CLBP)\(^21,23\), rheumatoid arthritis (RA)\(^19\) and knee OA\(^24,25\).

Normal EIH has been demonstrated in knee OA patients during isometric knee extension exercise\(^20\), as well as post-dynamic resistance exercise of the upper limb, but an inefficient EIH response was shown post-dynamic resistance exercise of the lower limb\(^25\). Increased clinical pain intensity during a walking task has also been reported people with knee OA\(^26\). Fingleton et al\(^27\) demonstrated inefficient EIH post-aerobic and isometric exercise in knee OA patients; in addition, knee OA patients
with low PPS were shown to have normal EIH post-isometric exercise, while those with high PPS showed inefficient EIH. As high PPS is thought to be a good indicator of pain sensitization\textsuperscript{28}, this finding was suggestive that EIH in knee OA patients may be related to the baseline degree of pain sensitization. Evidence to date suggests that dysfunctional EIH may be characteristic of chronic pain patients with clear evidence of a high level of pain sensitization\textsuperscript{29-31}.

An abnormal CPM response is reported to be a clinical indicator of pain sensitization\textsuperscript{32,33} and has been demonstrated in people with knee OA\textsuperscript{3,10,11}. Osgood et al\textsuperscript{3} demonstrated abnormal CPM in 40% of a knee OA cohort. In a normal CPM response, pain sensitivity (test stimulus) is reduced in response to the introduction of a second painful (conditioning) stimulus\textsuperscript{9}. Inefficiency of CPM has been shown to be predictive of the development of chronic pain following surgery in pain-free individuals\textsuperscript{34-38}. In addition, inefficiency of CPM is associated with the development of peripheral neuropathy post-chemotherapy\textsuperscript{39} and ongoing pain post-revision total knee replacement\textsuperscript{40} and is also predictive of an increased responsiveness to centrally-acting serotonin-noradrenalin reuptake inhibitors (SNRIs) in people with diabetic neuropathy\textsuperscript{41}. The CPM response, like EIH, is a process mediated by descending pain inhibition\textsuperscript{42}. While EIH is thought to be mediated primarily by activation of endogenous opioid systems\textsuperscript{12}, the CPM response thought to primarily reflect the functioning of the diffuse noxious inhibitory control (DNIC) system\textsuperscript{9}, which is proposed to inhibit ongoing pain in remote areas upon introduction of a new pain via a spinal-bulbo-spinal loop which inhibits wide-dynamic-range neurons in the dorsal horn of the spinal cord\textsuperscript{43,44}.

Currently no studies have investigated the efficacy of EIH in people with Knee OA with normal and abnormal CPM efficiency. The aim of the current study was to investigate whether knee OA patients with abnormal CPM exhibit dysfunctional EIH as measured by changes in PPTs in response to aerobic and isometric exercise compared to those with normal CPM and pain-free controls.
7.3 Methods

7.3.1 Participants

Forty people with knee OA took part in the study. Inclusion criteria included a diagnosis of knee OA according to American College of Rheumatology classification and pain > 3/10 (≥ 4/10) on a numerical rating scale. Pain due to knee OA had to be the participants’ main pain. Twenty age and sex-matched pain-free volunteers were included as a control group. Control group participants were ineligible if they had experienced a pain episode, caused by musculoskeletal injury or otherwise, in the previous three months. Exclusion criteria for both the knee OA group and control group were rheumatologic disease such as rheumatoid arthritis, fibromyalgia or ankylosing spondylitis; a neurological disorder such as parkinson’s disease, shingles, multiple sclerosis or stroke; cognitive impairment; and current use of antidepressant or anticonvulsant medication. All participants were also screened for suitability to exercise using the PAR-Q45. In addition, knee OA group participants were excluded if they had undergone a total knee replacement (TKR) and if they had < 90 degrees knee flexion.

Knee OA participants were recruited from outpatient musculoskeletal triage or physiotherapy clinics in three hospital sites in Dublin, Ireland. Control participants were recruited from poster advertisement in University College Dublin (UCD) and local community centres, and from university staff and associates. The study was approved by the research ethics committees of UCD and the three hospital research ethics committees (Appendices A.5 – A.9). Written informed consent was obtained from all participants prior to taking part (Appendices B.4 – B.5).

7.3.2 Protocol

Potential participants were initially invited to take part in the study by the clinical physiotherapists at the different hospital sites. Potential participants were screened for eligibility by the physiotherapists and participants were also given a study information leaflet. Initial consent was sought from potential participants to receive a phone call from the study researcher and 71 people consented. Thirty-one people
subsequently decided not to take part due to change of mind (n = 15), travel restraints (n = 2) or time burden (n = 6). An additional 5 participants were excluded following a further screening, with the main reasons for exclusion being diabetic neuropathy (n = 1) and knee pain not being their main pain (n = 4). Forty knee OA participants and twenty healthy controls consented to take part in the study and attended a single session of testing. Baseline measurements included demographic variables, patient-reported validated outcome measures (knee OA group only) and assessment of PPTs and CPM. See Appendix C.6 for standardised instructions.

Patient-Reported Outcome Measures
Patient-reported clinical pain, stiffness and physical function were assessed with the WOMAC v3.0 VAS. The WOMAC is an established questionnaire that has been shown to be reliable and valid \(^{(46)}\) (Appendix C.1). Pain catastrophising was assessed using the Pain Catastrophising Scale (PCS), which is a 13-item instrument with three subscale scores assessing rumination, magnification and helplessness \(^{(47)}\); it has been used in cohorts with knee OA \(^{(26,48)}\) and found to be associated with the presence of impaired CPM \(^{(49)}\) (Appendix C.5).

Pressure Pain Thresholds
Pressure pain thresholds are a measure of hyperalgesia \(^{(8)}\) and were assessed using a handheld pressure algometer (Somedic AB, Sweden). Pressure was applied at a rate of thirty kilopascals (KPa) per second, perpendicular to the skin with a 2cm\(^2\) probe. Pressure pain thresholds were assessed at 3 sites: at the medial joint line (3 cm medial to the mid point on the medial edge of patella) \(^{(50)}\) of the index knee (the knee that the participant identified as being their symptomatic or more symptomatic knee; at the quadriceps femoris muscle (midway between the groin and the apex of the patella) \(^{(51)}\) on the index knee; and remotely at the volar surface of the forearm (5 cm distal to the lateral epicondyle) \(^{(6,52)}\). Participants pressed the button at the moment when the feeling of pressure changed to that of pressure and pain. The average of two PPT measurements was recorded for each site \(^{(10,11,40)}\).
Conditioned Pain Modulation

For CPM measurement, PPT was used as the test stimulus, and immersion of the hand in cold water (cold pressor test) was the conditioning stimulus, a method which is shown to have excellent within-session reliability. The difference between pre- and post-cold pressor test measurements of PPT score (average of PPTs measured at the MJL and forearm) were examined. Participants immersed the hand (contralateral to the arm on which PPT was measured) in a water bath maintained at 4°C. The immersion lasted a maximum of 60 seconds. Participants were permitted to remove their hand prior to the completion of the trial if the pain became intolerable. Reassessment of PPTs at the knee and forearm was performed immediately following withdrawal of the hand from the water.

Exercise-induced Hypoalgesia

Participants subsequently underwent assessment of EIH in response to a) aerobic and b) isometric exercise protocols. These tests were performed in a random sequence with 15-minute rest periods between each test. The difference between pre- and post-exercise measurements of PPT score (average of PPTs measured at the MJL and forearm) were examined. An increase in PPTs during and post-exercise was interpreted as EIH, and a decrease or overall absence of change in PPTs was interpreted as inefficient EIH.

a) Aerobic Exercise Protocol

Participants carried out aerobic exercise in a sitting position on a cycle ergometer. The saddle and handlebars were positioned to suit each participant and adjustments were made if needed during a one-minute trial period to ensure that pedalling could be performed with < 3/10 pain rating. Exercise was adapted when necessary to limit aggravation of local knee pain, which could potentially alter results of post-exercise pain testing.

Participants underwent a submaximal exercise protocol known as the Aerobic Power Index test, which has been shown to be reliable in people with chronic pain and sedentary adults. The participant began pedaling at 25 watts (W) per minute and
the work-load was increased by 25 W every minute. The test stopped at the end of the minute in which the participant reached the submaximal level, which was defined as 75% of the age-predicted maximum heart rate and was calculated by subtracting the participant’s age in years from 220. A heart rate monitor (Polar FS3c) was strapped around the participant’s chest. Pain was measured on a numerical rating scale at the end of each minute. If pain at the knee joint exceeded 3/10, the participant’s workload was reduced by 25 W by decreasing rate of pedalling and/or decreasing resistance. The test was discontinued if the participant reported pain of > 3/10 which persisted despite decreased workload. Two knee OA participants were unable to complete the aerobic exercise protocol due to pain > 3/10 and their data for this test were excluded from the analysis. Prior to testing PPTs were tested at the MJL index knee and forearm and reassessment of PPTs at the knee and forearm was performed immediately following exercise.

b) Isometric Exercise Protocol
Maximal isometric knee extension strength on the index leg was assessed in a sitting position with hips and knees in 90 degrees of flexion. A push-pull dynamometer (Baseline evaluation instruments, White Plains, USA) fixed to the chair was used to measure the maximum voluntary contraction (MVC). Three measurements were taken, each trial lasting 5 seconds, with 30 seconds rest between trials. The greatest value was used to calculate 10% of the individual’s MVC force. Exercise was adapted when necessary to limit aggravation of local knee pain which could potentially alter results of post-exercise pain testing.

A weight corresponding to 10% of the MVC was placed in an adjustable ankle weight cuff (Fitness Depot, Canada). In a sitting position with the ankle weight on the index leg, the participant was instructed to extend their knee as far as could be achieved without pain > 3/10. The participant was then instructed to hold an isometric knee extension contraction until exhaustion, up to a maximum of 5 minutes. Pain was measured on a numerical rating scale at the beginning of the exercise and at the end of each minute. If pain at the knee joint exceeded 3/10, the participant was instructed to decrease the angle of knee extension. If pain persisted, the weight of
the ankle cuff resistance was decreased by up to 20%. The test was discontinued if the participant reported pain of > 3/10 which persisted despite these decreases in knee angle and weight. Prior to testing, PPTs were assessed at the index MJL, forearm and index quadriceps. During exercise, PPTs were assessed at the contracting quadriceps femoris muscle and at the forearm 45 seconds after beginning the contraction and then every 60 seconds during the contraction. Reassessment of PPTs at the knee, forearm and quadriceps femoris was performed immediately following exercise.

7.3.3 Subgrouping
Knee OA participants were subdivided based on whether they demonstrated abnormal or normal function of CPM. For CPM measurement, PPTs were assessed before and after a cold pressor test as described above. A decrease in PPTs or absence of change in PPTs was classified as ‘abnormal CPM’ and an increase in PPTs post-cold pressor test was classified as ‘normal CPM’.3,58

7.3.4 Statistical Analysis
Data were analysed using SPSS v 20. Sample size was calculated for a repeated measures ANOVA interaction effect, with 3 groups, and 2 time-points (pre and post). Based on an intraclass correlation coefficient of 0.08, it was determined that 17 participants in each of the 3 groups would be required in order to detect a small effect size (eta-squared of 0.02). Descriptive data are presented as means ± standard deviations (SDs). Baseline differences between sub-groups of knee OA participants and controls were analysed using the non-parametric Kruskal–Wallis test for continuous data and the Chi-square test for categorical data. Post hoc analysis of subgroups was carried out using Mann Whitney U tests and Chi-square tests for continuous and categorical data respectively. Repeated measures ANOVAs were used to examine the effect of cold pressor test and exercise tests on pain sensitivity as measured by PPTs. Possible changes in pain sensitivity (as measured by PPT) in response to the cold pressor test and aerobic exercise were compared between the 3 groups using repeated measures ANOVAs examining time*group interaction effects, with between-subject factor ‘group’ (knee OA group 1, knee OA group 2 and
controls) and within-subject factor ‘time’ (pre and post). The same method of repeated measures ANOVA was used for comparing changes in pain sensitivity during isometric exercise between groups, but the ‘time’ factor had 4 levels (pre, middle, end, post) and a Greenhouse-Geisser Correction was used for data that violated the assumption of sphericity. Post hoc analysis of subgroups was also carried out using the same method of repeated measures ANOVA, but with 2 levels in the ‘group’ factor (i.e. knee OA group 1, knee OA group 2). Within-group changes in pain sensitivity between pre- and post-exercise measurements were analysed using non-parametric Wilcoxon signed rank tests for paired comparisons. Significance was set at P < 0.05. No adjustment of the P value was made for multiple comparisons as all tests were planned and reasonable.

7.4 Results

7.4.1 Participant Characteristics

Knee OA participants were subdivided based on whether they demonstrated a decrease/lack of change in PPTs post-cold pressor test (abnormal CPM, n = 19) or an increase in PPTs post-cold pressor test (normal CPM, n = 21). 47.5% (19 of 40) of knee OA participants and 35% (7 of 20) of controls demonstrated an abnormal CPM response. Due to the high frequency of abnormal CPM responses in controls, a secondary exploratory analysis was undertaken to investigate for potential differences in EIH response between control participants with normal CPM (n = 13) and abnormal CPM (n = 7) and knee OA participants with normal CPM and abnormal CPM, and is detailed in supplemental information (Appendix E, Page 238).

There were no significant differences between abnormal and normal CPM groups and controls for age (P = 0.754), radiographic disease severity (P = 0.603), number of participants with bilateral knee pain (P = 0.059) or number of females and males in each group (P = 0.123) (Table 7.1). At baseline, there were no significant differences between knee OA groups for WOMAC total score (P = 0.708) or for PCS total score (P = 0.649) and no significant differences between the abnormal CPM, normal CPM and control groups for total PPT score (abnormal CPM group, 166.36 ± 41.64; normal CPM group, 184.34 ± 58.11; control group, 217.95 ± 93.20; P = 0.239) (Table 7.2).
There was a significant difference between the abnormal CPM, normal CPM and control groups for changes in total PPT score (average of MJL & forearm) pre- and post-aerobic exercise (F (2, 55) = 4.860, P = 0.011) (Figure 7.2) (Table 7.2). The abnormal CPM group showed a decrease in PPTs (dysfunctional EIH), while the normal CPM and control groups showed an increase in PPTs (normal EIH). Post hoc tests showed significant differences between the abnormal CPM and normal CPM groups (P = 0.003) and between the abnormal CPM and control groups for changes in PPTs (P = 0.020), while there was no significant difference between the normal CPM group and controls (P = 0.885).

There was a significant difference between the abnormal CPM, normal CPM and control groups for changes in total PPT score (average of MJL & forearm) pre- and post-isometric exercise (F (2, 57) = 4.727; P = 0.013) (Figure 7.3) (Table 7.2). The abnormal CPM group showed a decrease in PPTs (dysfunctional EIH), while the normal CPM and control groups showed an increase in PPTs (normal EIH). According to post hoc tests, there were significant differences between the abnormal CPM and normal CPM groups (P = 0.002) and between the abnormal CPM and control groups.

### Table 7.1 Participant Characteristics

<table>
<thead>
<tr>
<th>Condition</th>
<th>Abnormal CPM</th>
<th>Normal CPM</th>
<th>Controls</th>
<th>Kruskal-Wallis / Mann-Whitney U/Chi square P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (%)/Male (%)</td>
<td>N=19</td>
<td>N=21</td>
<td></td>
<td>0.123</td>
</tr>
<tr>
<td>Age (years), Mean ± SD</td>
<td>64.05 ± 11.04</td>
<td>63.29 ± 9.02</td>
<td></td>
<td>0.754</td>
</tr>
<tr>
<td>Radiographic disease severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild-moderate (%)/severe (%)*</td>
<td></td>
<td></td>
<td></td>
<td>0.603</td>
</tr>
<tr>
<td>WOMAC pain 0-50</td>
<td>21.98 ± 9.28</td>
<td>23.27 ± 12.04</td>
<td></td>
<td>0.872</td>
</tr>
<tr>
<td>WOMAC stiffness 0-20</td>
<td>11.11 ± 5.77</td>
<td>11.07 ± 4.95</td>
<td></td>
<td>0.830</td>
</tr>
<tr>
<td>WOMAC activities daily living 0-170</td>
<td>80.76 ± 33.26</td>
<td>77.52 ± 39.86</td>
<td></td>
<td>0.630</td>
</tr>
<tr>
<td>WOMAC total 0-240</td>
<td>113.86 ± 42.46</td>
<td>111.83 ± 53.38</td>
<td></td>
<td>0.708</td>
</tr>
<tr>
<td>PCS rumination</td>
<td>4.89 ± 4.93</td>
<td>5.00 ± 5.11</td>
<td></td>
<td>0.915</td>
</tr>
<tr>
<td>PCS magnification</td>
<td>3.26 ± 3.89</td>
<td>3.38 ± 3.50</td>
<td></td>
<td>0.830</td>
</tr>
<tr>
<td>PCS helplessness</td>
<td>4.68 ± 4.87</td>
<td>5.90 ± 5.76</td>
<td></td>
<td>0.630</td>
</tr>
<tr>
<td>PCS total</td>
<td>12.84 ± 13.03</td>
<td>14.29 ± 13.67</td>
<td></td>
<td>0.649</td>
</tr>
</tbody>
</table>

WOMAC, Western Ontario & McMaster Universities Osteoarthritis Index; PCS, Pain Catastrophising Scale; *Participants were classified as having either 1) mild-moderate or 2) severe radiographic knee OA based on their radiology report.

There were no significant differences between groups for any measures.

### 7.4.2 Between-Group Differences for Changes in Pain Sensitivity

There was a significant difference between the abnormal CPM, normal CPM and control groups for changes in total PPT score (average of MJL & forearm) pre- and post-aerobic exercise (F (2, 55) = 4.860, P = 0.011) (Figure 7.2) (Table 7.2). The abnormal CPM group showed a decrease in PPTs (dysfunctional EIH), while the normal CPM and control groups showed an increase in PPTs (normal EIH). Post hoc tests showed significant differences between the abnormal CPM and normal CPM groups (P = 0.003) and between the abnormal CPM and control groups for changes in PPTs (P = 0.020), while there was no significant difference between the normal CPM group and controls (P = 0.885).

There was a significant difference between the abnormal CPM, normal CPM and control groups for changes in total PPT score (average of MJL & forearm) pre- and post-isometric exercise (F (2, 57) = 4.727; P = 0.013) (Figure 7.3) (Table 7.2). The abnormal CPM group showed a decrease in PPTs (dysfunctional EIH), while the normal CPM and control groups showed an increase in PPTs (normal EIH). According to post hoc tests, there were significant differences between the abnormal CPM and normal CPM groups (P = 0.002) and between the abnormal CPM and control groups.
for changes in PPTs (P = 0.015), while there was no significant difference between the normal CPM group and controls (P = 0.796). There were no significant differences between the abnormal CPM, normal CPM and control groups for changes in PPTs at the forearm (F (4.1, 118) = 2.027, P = 0.093) or the quadriceps (F (4.9, 140.6) = 0.253, P = 0.936) during isometric exercise. All groups showed some degree of an increase in PPTs during isometric exercise.

![Graph showing changes in Total Pressure Pain Threshold Score (PPTs) pre- and post-isometric exercise.](image1)

**Figure 7.3** Between-Group Differences for Changes in Total Pressure Pain Threshold Score (average of medial joint line & forearm) Pre- and Post-Isometric Exercise

![Graph showing changes in Total Pressure Pain Threshold Score (PPTs) pre- and post-aerobic exercise.](image2)

**Figure 7.2** Between-Group Differences for Changes in Total Pressure Pain Threshold Score (average of medial joint line & forearm) Pre- and Post-Aerobic Exercise
7.4.3 Within-group changes in Pain Sensitivity

In the abnormal CPM group, PPTs decreased or stayed the same post-aerobic exercise (MJL, \(P = 0.554\); forearm, \(P = 0.015\); total, \(P = 0.102\)) and isometric exercise (MJL, \(P = 0.355\); forearm, \(P = 0.028\); total, \(P = 0.024\)), and these changes were significant at the remote forearm site only for aerobic exercise and at the forearm and overall for isometric exercise (Table 7.2). PPTs increased in the normal CPM group post-aerobic (MJL, \(P = 0.027\); forearm, \(P = 0.092\); total, \(P = 0.007\)) and isometric exercise (MJL, \(P = 0.003\); forearm, \(P = 0.768\); total, \(P = 0.019\)) and these changes were significant locally at the MJL and for the average of the two sites (normal EIH) (Table 7.2). In the control group, PPTs increased or stayed the same post-aerobic (MJL, \(P = 0.011\); forearm, \(P = 0.737\); total, \(P = 0.108\)) and isometric exercise (MJL, \(P = 0.011\); forearm, \(P = 0.204\); total, \(P = 0.0.57\)) and were significantly increased at the local MJL site only (Table 7.2).

During isometric exercise, the abnormal CPM group showed no significant change in PPTs at the middle (quadriceps, \(P = 0.904\); forearm, \(P = 0.286\)) or end (quadriceps, \(P = 0.936\); forearm, \(P = 0.398\)) time-points, while the normal CPM and control groups showed a significant increase in forearm PPTs at the middle (normal CPM, \(P = 0.017\); controls, \(P = 0.09\)) and end (normal CPM, \(P = 0.003\); controls, \(P = 0.002\)) time-points, but no significant changes in PPTs at the quadriceps at the middle (normal CPM, \(P = 0.244\), controls, \(P = 0.588\)) or end (normal CPM, \(P = 0.404\); controls, \(P = 0.279\)) of exercise (Table 7.2).
### Table 7.2 Knee OA abnormal conditioned pain modulation (CPM) & knee OA normal CPM & control groups: Changes in pain sensitivity

<table>
<thead>
<tr>
<th></th>
<th>Abnormal CPM</th>
<th>Normal CPM</th>
<th>Controls</th>
<th>Interaction Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=19</td>
<td>N=21</td>
<td>N=20</td>
<td></td>
</tr>
<tr>
<td><strong>Aerobic exercise</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pressure pain thresholds (KPa)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee</td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td></td>
<td>162.32 ± 62.75</td>
<td>157.48 ± 66.14</td>
<td>173.13 ± 64.23</td>
<td>197.03 ± 76.44</td>
</tr>
<tr>
<td>Forearm</td>
<td>175.41 ± 44.68</td>
<td>148.02 ± 51.80</td>
<td>195.54 ± 62.67</td>
<td>214.42 ± 91.49</td>
</tr>
<tr>
<td>Average of 2 sites</td>
<td>168.87 ± 43.06</td>
<td>152.75 ± 52.31</td>
<td>184.34 ± 58.11</td>
<td>205.73 ± 76.07</td>
</tr>
<tr>
<td><strong>Resistance exercise</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pressure pain thresholds (KPa)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee</td>
<td>Pre</td>
<td>Middle</td>
<td>End</td>
<td>Post</td>
</tr>
<tr>
<td></td>
<td>158.32 ± 60.47</td>
<td>182.74 ± 50.75</td>
<td>195.54 ± 22.45</td>
<td>234.00 ± 66.17</td>
</tr>
<tr>
<td>Forearm</td>
<td>174.39 ± 44.63</td>
<td>248.97 ± 80.92</td>
<td>305.64 ± 323.21</td>
<td>321.90 ± 115.59</td>
</tr>
<tr>
<td>Average of 2 sites (knee &amp; forearm)</td>
<td>166.36 ± 41.64</td>
<td>184.34 ± 58.11</td>
<td>209.96 ± 92.17</td>
<td>217.95 ± 93.20</td>
</tr>
<tr>
<td></td>
<td>Pre</td>
<td>Middle</td>
<td>End</td>
<td>Post</td>
</tr>
<tr>
<td></td>
<td>150.46 ± 52.50</td>
<td>184.34 ± 58.11</td>
<td>209.96 ± 92.17</td>
<td>217.95 ± 93.20</td>
</tr>
</tbody>
</table>

*Significant between-group differences for changes in PPTs pre and post exercise, P < 0.05

*Significant within-group increase in PPTs from pre to middle, pre to end or pre to post-exercise, Wilcoxon signed rank test, P < 0.05

*Significant within-group decrease in PPTs from pre to middle, pre to end or pre to post-exercise, Wilcoxon signed rank test, P < 0.05

†Two participants were unable to complete the aerobic exercise protocol due to pain > 3/10

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7.5 Discussion

7.5.1 Findings

The current report was the first to demonstrate significant differences in EIH response between people with knee OA with normal and abnormal CPM and pain-free controls. Knee OA patients with abnormal CPM demonstrated significantly increased pain sensitivity (decreased PPTs) in response to exercise, suggestive of EIH dysfunction, while knee OA patients with normal CPM and controls demonstrated a significant decrease in their pain sensitivity (increased PPTs) in response to exercise suggestive of normal function of EIH.

This is the first study to identify a subgroup of knee OA patients who exhibit worsened pain sensitivity in response to exercise, though findings from a recent report suggested lesser efficiency of EIH in knee OA patients with high PPS compared to those with low PPS\(^\text{27}\). Yarnitsky et al\(^\text{38}\) reported that abnormal CPM was associated with a positive response to SNRIs in chronic neuropathy patients\(^\text{41}\), while patients with normal efficiency of CPM did not gain benefits from the drug. Nir and Yarnitsky\(^\text{59}\) have thus proposed that identifying a patient with dysfunctional pain modulation (i.e. abnormal CPM) may usefully inform analgesic drug prescription. Clinical guidelines recommend the inclusion of therapeutic exercise for the treatment of knee OA\(^\text{60, 61}\); findings from the current study suggest that identifying the presence/absence of normal CPM may also be important when deciding the appropriateness of exercise interventions for people with knee OA and may allow for a more individualised and graded approach to exercises in individuals with inefficient endogenous pain modulation. However, the effects of type and intensity of exercise on EIH in people with knee OA pain require further investigation.

Abnormal CPM is considered to be an indicator of pain sensitization\(^\text{32, 33}\) and numerous studies have demonstrated dysfunctional CPM in chronic pain cohorts\(^\text{9}\). However, inefficient CPM has also been shown in subgroups of healthy pain-free individuals who went on to develop chronic pain post-surgically\(^\text{34-36}\), and lesser efficiency of CPM has been reported in healthy older adults compared to younger
adults\textsuperscript{62}; of note, 35\% of controls in the current study demonstrated dysfunctional CPM. This raises the question of whether dysfunctional pain inhibition may be a pre-pathological trait\textsuperscript{38, 63, 64}. Neogi et al\textsuperscript{63} has proposed that there may be individuals who are predisposed to pain sensitization, and that this trait is uncovered in the presence of nociceptive input from knee OA pathology. It is possible that the abnormal CPM patients in the current study who exhibited dysfunctional EIH may reflect individuals with a phenotypic trait for pain sensitization and a consequentially dysfunctional response to exercise. The concept of abnormal CPM as a trait that may precede knee OA pathology warrants further investigation.

An overlap between EIH and CPM mechanisms\textsuperscript{42, 65} may partially explain the co-occurrence of abnormal CPM and dysfunctional EIH in participants in the current study. While CPM is thought to be primarily mediated by DNIC via a spinal-bulbo-spinal loop and EIH is thought to be driven by opioid and non-opioid supra-spinal systems, similarities between these mechanisms have been identified\textsuperscript{42, 65}. Ellingson et al\textsuperscript{65} questioned whether EIH could be mediated by the CPM response; they found that EIH was initiated by both painful and non-painful exercise, but a larger hypoalgesic effect was produced by painful exercise, suggesting that CPM may contribute to EIH but may not be the primary mechanism. As the exercise protocols in the current study were required not to provoke pain of < 3/10, we postulate that changes in pain sensitivity may not have been driven primarily by CPM.

Opioidergic analgesia and baroreceptor inhibition are two mechanisms also thought to be shared by EIH and CPM\textsuperscript{42}. Both EIH and CPM have been shown to be partially inhibited by the opioid antagonist naloxone\textsuperscript{66, 67}, implying that activation of opioids may be a common mechanism involved in both the EIH and CPM response. Additionally, activation of arterial baroreceptors has been shown to result in CNS inhibition\textsuperscript{68}, and an inverse relationship between blood pressure and pain perception has been demonstrated during both exercise\textsuperscript{69, 70} and the cold
pressor test, suggesting that baroreceptor inhibition could also potentially be a mechanism shared by EIH and CPM.

Results from the current study reflecting a subgroup of knee OA participants who exhibit dysfunctional EIH are of clinical importance due to the central role of exercise in the management pain and disability of knee OA. Clinically, identification of people with knee OA with inefficient endogenous pain modulation (i.e. abnormal CPM) may afford the opportunity to offer a more individualised and graded approach to exercise in these individuals, in addition to targeted pharmacological interventions. While this study demonstrated an association between abnormal CPM and increased pain sensitivity in response to acute exercise, further research is needed to establish if abnormal CPM is associated with worsening of pain sensitivity and clinical pain intensity in response to exercise interventions. In addition, further study regarding abnormal CPM as a phenotypic trait that precedes knee OA pathology warrants further investigation using longitudinal studies with long term follow-ups.

7.5.2 Limitations
A limitation of this study is that multiple measures of endogenous inhibition were carried out in the same session, creating a potential risk of carry-over effects. However, participants were given 15-minute breaks between each test, which has been deemed sufficient for effects to wear off due to the short duration of each protocol. A further limitation is that testing was carried out by an unblinded assessor and replication is required using independent, blinded assessment to corroborate our findings. Furthermore, the lack of a control resting condition meant that pre-exercise pain tests could potentially have influenced post-exercise pain sensitivity, though reliability tests have shown the effects of repeated pain testing on measures of pain sensitivity to be small and trivial.

7.5.3 Conclusions
The current report was the first to demonstrate significant differences in EIH response between knee OA patients with normal and abnormal endogenous pain
inhibition and pain-free controls. Results demonstrated significantly increased pain sensitivity (decreased PPTs) in response to exercise in knee OA patients with abnormal CPM suggestive of EIH dysfunction, while significant decreases in pain sensitivity (increased PPTs) suggestive of normal EIH were demonstrated in response to exercise in knee OA patients with normal CPM and controls. Identification of people with knee OA with inefficient endogenous pain modulation may allow for more individualised and graded approaches to exercise in these patients and merits further investigation.

7.6 References


Chapter 8

General Discussion

This chapter contains a discussion of the main findings of the thesis, in addition to the implications of these findings and directions for future research. Limitations of the research and thesis conclusions are also discussed.
8.1 Thesis Aims
The overall aim of the thesis was to investigate pain sensitization in people with knee OA using clinically reproducible measures. The aims of the studies were to investigate the existing evidence for the presence of pain sensitization in people with knee OA, to investigate the presence of neural mechanosensitivity in people with knee OA, in addition to further investigating features of pain sensitization in people with knee OA, to investigate potential differences in pain sensitization signs between subgroups of people with knee OA with high and low pressure pain sensitivity (PPS) and to investigate the presence of exercise-induced hypoalgesia (EIH) in response to aerobic and isometric lower limb exercise in people with knee OA with varying degrees of pain sensitization.

8.2 Main Findings
The results of the literature review (study 1) demonstrated firstly that evidence from previous studies was suggestive of the presence of pain sensitization in people with knee OA, which may be linked to the level of symptom severity in this cohort, and suggested that further research was warranted in relation to: understanding mechanisms of pain sensitization in knee OA; identifying knee OA patients with higher degrees of sensitization; and assessing the impact of commonly-used treatment strategies such as exercise on pain-sensitized knee OA groups. The reliability of lower limb nerve palpation was demonstrated (study 2) and case-control studies on knee OA patients with moderate to high symptom severity demonstrated signs of neural tissue sensitization (neural mechanosensitivity) and pain sensitization in people with knee OA (study 3), in addition to higher levels of sensitization in a knee OA subgroup with high pressure pain sensitivity (PPS) (study 4). Findings in relation to PPS were in keeping with the results of our meta-analysis, with a large point estimate for differences in PPS between knee OA patients and controls demonstrated locally and a moderate to large point estimate demonstrated remotely. Results also demonstrated no significant difference between knee OA patients and controls, or between knee OA subgroups with high and low PPS, for EIH in response to aerobic and isometric exercise; however within-group results suggested a lesser efficiency of EIH in the
knee OA patients, particularly in those with high PPS (study 5), and a further study demonstrated a dysfunctional EIH response in knee OA patients who had abnormal conditioned pain modulation (CPM) (study 6).

8.3 Implications of Findings and Directions for Future Research

Findings from this thesis provide a novel contribution to the body of work on pain processing in knee OA. Our findings of hypoaesthesia and neural mechanosensitivity (NM) on the contralateral (asymptomatic/less symptomatic) side in people with knee OA, which had not previously been demonstrated, in addition to findings of contralateral hyperalgesia, are suggestive of the contralateral spread of sensitization in this knee OA cohort and may implicate a number of centrally-mediated mechanisms contributing to this phenomenon which merit further investigation in people with knee OA. These central mechanisms include the activation of bilateral brain areas associated with descending control and the projection of neurons across the spinal cord. In addition, the study findings demonstrating a significantly greater frequency of cold sensitivity (thermoroller test) in people with knee OA compared to controls have not previously been reported and were suggestive of cold hyperalgesia in people with knee OA, a finding which is contrary to existing evidence in relation to cold pain thresholds and cold pressor test pain ratings in people with knee OA. This method of recording a positive or negative response for hyperalgesia in response to a cold stimulus has not previously been reported in people with knee OA and could be employed by future studies investigating cold hyperalgesia in knee OA. This method is also appropriate for assessing cold hyperalgesia clinically and investigation into the utility of this measure in a clinical setting is warranted.

The study findings of sensitization of neural tissue (neural mechanosensitivity) implicate neural tissue as a potential mechanism of pain in knee OA. This finding is in line with reports of NM in other chronic musculoskeletal pain cohorts e.g. nonspecific arm pain and whiplash-associated disorders. Nerve palpation is a technique that can be easily performed by clinicians without the need for equipment, making it a useful tool for the assessment of neural tissue involvement.
and potentially for the assessment of sensitization in people with knee OA and other chronic musculoskeletal conditions. Clinically, identification of NM could create significant additional treatment targets in people with knee OA in the form of nerve mobilisation and desensitization techniques\(^{11,12}\). Further investigation is warranted to establish whether NM may contribute to the maintenance of pain and sensitization in people with knee OA\(^{13}\) and to investigate whether nerve palpation may be clinically useful in the identification of knee OA patients with a high degree of pain sensitization. In addition, future studies could investigate the effects of neural tissue-targeted treatments in this cohort.

Findings from this thesis of a higher degree of pain sensitization in knee OA patients with high PPS compared to those with low PPS support the concept that pain sensitization exists as a dominant mechanism in a subgroup of people with knee OA\(^{14-16}\). Identification of a knee OA subgroup with a high degree of pain sensitization is clinically relevant with regard to choice of treatment pathways\(^{17}\). For people with knee OA with a high degree of sensitization, a modified treatment approach including targeted pharmacological, psychological and exercise-based interventions may be appropriate\(^{17}\). Future studies could further investigate pain sensitization in high and low PPS groups using more conservative cut-offs for high and low PPS (e.g. high PPS cut off = 25\(^{th}\) percentile PPT; low PPS cutoff = 75\(^{th}\) percentile PPT) rather than the median split used in the current study. Findings demonstrated that a number of pain sensitization signs were unique to the high PPS group, including the presence of mechanical allodynia, increased temporal summation, increased vibration detection thresholds (VDTs) and NM of the femoral and peroneal nerves. These measures may therefore be clinically useful for identifying people with knee OA with high levels of sensitization and could be quickly and easily performed by clinicians at the bedside. Further research is warranted regarding the clinical utility of these tests.

This is the first report to investigate EIH in response to aerobic exercise in people with knee OA. In relation to aerobic exercise, our findings of significant within-group increases in PPTs post-aerobic and isometric exercise in the control group
but not in the knee OA group were indicative of the presence of inefficient EIH in the knee OA group, which had not previously been reported. In addition, findings of significant within-group PPT increases post-isometric exercise in the knee OA low PPS group but not the high PPS group (indicative of inefficient EIH in the high PPS group) were contrary to previous reports of normal EIH in knee OA; these findings suggested a lesser efficiency of EIH in knee OA patients, particularly in those with high PPS and pointed to the need for further investigation into EIH in knee OA patients with varying degrees of pain sensitization. Currently, exercise is strongly recommended in the clinical guidelines for people with knee OA and our findings suggest that a uniform approach to exercise may not be appropriate for this population.

A further study demonstrated dysfunction of the EIH response in knee OA patients with abnormal CPM, and an efficient EIH response in knee OA patients with normal CPM and controls. Findings from the current study suggest that identifying the presence/absence of normal CPM may be important when deciding the appropriateness of exercise interventions for people with knee OA and may allow for a more individualised and graded approach to exercise in individuals with inefficient endogenous pain modulation. Further research is needed to investigate the predictive value of CPM for the effectiveness of exercise interventions on pain outcomes as well as the effect of type and intensity of exercise on EIH in people with knee OA.

8.4 Limitations
This research should be interpreted in light of a number of limitations. Data collection for studies 3 to 6 was carried out by an unblinded assessor, which introduced the potential for measurement bias. Standardised instructions were read out to participants prior to each test to minimise the risk of measurement bias, however replication is required using independent, blinded assessment to corroborate our findings. In relation to studies 4 and 5, a median split of PPT data was used to subdivide knee OA participants in the absence of normative values for high and low degrees of pain sensitization; a limitation of this method is that the
size of between-group differences in these studies may have been underestimated due to similarity of participants whose scores were close to the median. In studies 5 and 6, multiple measures of endogenous inhibition were carried out in the same session, which could potentially have introduced the risk of carry-over effects. However, participants were given 15-minute breaks between each test, which has been deemed a sufficient amount of time for effects to wear off due to the short duration of each of the protocols\textsuperscript{32,33}.

### 8.5 Conclusions

This thesis provides novel contributions to the body of research regarding pain sensitization in people with knee OA. This is the first report of NM in people with knee OA, a finding suggestive of the sensitization of neural tissue and which may be clinically relevant in terms of identifying new treatment targets. Pain sensitization was also shown to exist to a higher degree in a subgroup of knee OA patients who exhibit high PPS, and certain features of pain sensitization were found to be unique to the high PPS subgroup, including high frequency of dynamic mechanical allodynia, diminished vibration sense, increased TS and high frequency of femoral and tibial nerve sensitivity, suggesting that these measures may be useful for identifying knee OA patients who are more pain-sensitized. Results were suggestive of a lesser efficiency of EIH in response to aerobic and isometric exercise in people with knee OA, particularly in those with high PPS, and suggested the presence of dysfunctional EIH in knee OA patients with abnormal CPM; clinically, identification of people with knee OA with inefficient endogenous pain modulation may allow for a more individualised and graded approach to exercise in these individuals. Further investigation is warranted in relation to identifying knee OA patients with a high degree of pain sensitization, as well as the clinical utility of pain sensitization signs, including NM measures. In addition, further research is needed regarding EIH in knee OA, particularly regarding the effect of exercise interventions on pain outcomes in knee OA patients with differing degrees of pain sensitization.
8.6 References


APPENDIX A

Ethical Approval Letters
Appendix A.1 University College Dublin Ethical Approval Letter for Study 2

21st November 2012

Ms Caitriona Fingleton
c/o Dr Catherine Doody
UCD School of Public Health, Physiotherapy and Population Science
Health Sciences Centre
Belfield
Dublin 4

RE: LS-12-178-Fingleton-Doody: Pressure Pain Thresholds of the femoral & sciatic nerve: A reliability study

Dear Ms Fingleton

Thank you for your response to the Human Research Ethics Committee – Sciences (21/11/12). The Decision of the Committee is to grant approval for this application which is subject to the conditions set out below.

Please note that approval is for the work and the time period specified in the above protocol and is subject to the following:

• If applicable, all permissions to access participants, whether internal (heads of Schools/Registrar) or external are obtained before the recruitment of the participants is commenced;
• Any amendments or requests to extend the original approved study will need to be approved by the Committee. Therefore you will need to submit by email the Request to Amend/Extend Form (HREC Doc 10);
• Any unexpected adverse events that occur during the conduct of your research should be notified to the Committee. Therefore you will need to Submit, by email, an Unexpected Adverse Events Report (HREC Doc 11);
• You or your supervisor (if applicable) are required to submit a signed End of Study Report Form (HREC Doc 12) to the Committee upon the completion of your study;
• This approval is granted on condition that you ensure that, in compliance with the Data Protection Acts 1988 and 2003. If applicable, all data will be destroyed in accordance with your application and that you will confirm this in your End of Study Report (HREC Doc 12), or indicate when this will occur and how this will be communicated to the Human Research Ethics Committee;...
• You may require copies of submitted documentation relating to this approved application and therefore we advise that you retain copies for your own records;
• Please note that the granting of this ethical approval is premised on the assumption that the research will be carried out within the limits of the law;
• Please also note that approved applications and any subsequent amendments are subject to a Research Ethics Compliance Review.

The Committee wishes you well with your research and look forward to receiving your End of Study Report. All forms are available on the website www.ucd.ie/researchethics please ensure that you submit the latest version of the relevant form. If you have any queries regarding the above please contact the Office of Research Ethics and please quote your reference in all correspondence.

Yours sincerely,

________________

Professor William Watson
Chair, Human Research Ethics Committee - Sciences
Appendix A.2 University College Dublin Ethical Approval Letter for Study 3/4

17th October 2012

Ms Caitriona Fingleton
c/o Dr Catherine Doody
UCD School of Public Health, Physiotherapy & Population Science
Health Sciences Centre
Belfield
Dublin 4

Re: LS-12-119-Fingleton-Doody: Somatosensory Characteristics of Chronic Somatic Pain Associated with Osteoarthritis of the Knee compared to a normal group

Dear Ms Fingleton

Thank you for your response to the Human Research Ethics Committee – Sciences (16/10/12). The Decision of the Committee is to grant approval for this application which is subject to the conditions set out below.

Please note that approval is for the work and the time period specified in the above protocol and is subject to the following:

• If applicable, all permissions to access participants, whether internal (heads of Schools/Registrar) or external are obtained before the recruitment of the participants is commenced;
• Any amendments or requests to extend the original approved study will need to be approved by the Committee. Therefore you will need to submit by email the Request to Amend/Extend Form (HREC Doc 10);
• Any unexpected adverse events that occur during the conduct of your research should be notified to the Committee. Therefore you will need to Submit, by email, an Unexpected Adverse Events Report (HREC Doc 11);
• You or your supervisor (if applicable) are required to submit a signed End of Study Report Form (HREC Doc 12) to the Committee upon the completion of your study;
• This approval is granted on condition that you ensure that, in compliance with the Data Protection Acts 1988 and 2003. If applicable, all data will be destroyed in accordance with your application and that you will confirm this in your End of Study Report (HREC Doc 12), or indicate when this will occur and how this will be communicated to the Human Research Ethics Committee;
• You may require copies of submitted documentation relating to this approved application and therefore we advise that you retain copies for your own records;

• Please note that the granting of this ethical approval is premised on the assumption that the research will be carried out within the limits of the law;
• Please also note that approved applications and any subsequent amendments are subject to a Research Ethics Compliance Review.

The Committee wishes you well with your research and look forward to receiving your End of Study Report. All forms are available on the website www.ucd.ie/researchethics please ensure that you submit the latest version of the relevant form. If you have any queries regarding the above please contact the Office of Research Ethics and please quote your reference in all correspondence.

Yours sincerely,

________________________
Professor William Watson
Chair, Human Research Ethics Committee - Sciences
A.3 University College Dublin Ethical Approval Letter for Amendment to Study 3/4

6th November 2012

Ms Caitriona Fingleton
c/o Dr Catherine Doody
UCD School of Public Health, Physiotherapy & Population Science
Health Sciences Centre
Belfield
Dublin 4

Re: LS-12-119-Fingleton-Doody: Somatosensory Characteristics of Chronic Somatic Pain Associated with Osteoarthritis of the Knee compared to a normal group

Dear Ms Fingleton

Thank you for your recent Amendment Request Form to the Human Research Ethics Committee – Sciences (02/11/12). The Decision of the Committee is to grant approval for your request to amend this application which is subject to the following.

Please note that approval is for the work and the time period specified in the above protocol and is subject to the following:

• If applicable, all permissions to access participants, whether internal (heads of Schools/Registrar) or external are obtained before the recruitment of the participants is commenced;
• Any amendments or requests to extend the original approved study or subsequent approved amended revisions of that study will need to be approved by the Committee. Please submit by email the Request to Amend/Extend Form (HREC Doc 10);
• Any unexpected adverse events that occur during the conduct of your research should be notified to the Committee. Therefore you will need to Submit, by email, an Unexpected Adverse Events Report (HREC Doc 11);
• You or your supervisor (if applicable) are required to submit a signed End of Study Report Form (HREC Doc 12) to the Committee upon the completion of your study;
• This approval is granted on condition that you ensure that, in compliance with the Data Protection Acts 1988 and 2003. If applicable, all data will be destroyed in accordance with your application and that you will confirm this in your End of Study Report (HREC Doc 12), or indicate when this will occur and how this will be communicated to the Human Research Ethics Committee;

.../

• You may require copies of submitted documentation relating to this approved application and therefore we advise that you retain copies for your own records;
• Please note that the granting of this ethical approval is premised on the assumption that the research will be carried out within the limits of the law;
• Please also note that approved applications and any subsequent amendments are subject to a Research Ethics Compliance Review.

All forms are available on the website www.ucd.ie/researchethics please ensure that you submit the latest version of the relevant form. If you have any queries regarding the above please contact the Office of Research Ethics and please quote your reference in all correspondence.

Yours sincerely,

___________________
Professor William Watson
Chairman, Human Research Ethics Committee – Sciences
Appendix A.4 St Vincent’s University Hospital Ethical Approval Letter for Study 3/4

3rd October, 2012

Dr. C. Mc Loughlin,
Physiotherapy Manager,
Physiotherapy Department
St. Vincent’s University Hospital,
Elm Park,
Dublin 4.


Dear Dr. Mc Loughlin,

Thank you for the correspondence in response to the queries which were raised at the Ethics and Medical Research Committee meeting held on Wednesday 5th September, 2012 at which the above study was reviewed.

Following review of the responses, this study is now granted full ethical approval.

Yours sincerely,

[Signature]

Dr. B. Kirby,
Chairman,
Ethics & Medical Research Committee

cc Dr. C. Doody, College Lecturer, UCD Health Sciences Centre, UCD.
Appendix A.5 University College Dublin Ethical Approval Letter for Study 5/6

29th November, 2013

Ms Caitriona Fingleton
c/o Dr Catherine Doody
School of Public Health, Physiotherapy and Population Science
Health Sciences Centre
Belfield
Dublin 4


Dear Ms Fingleton

Thank you for your response to the Human Research Ethics Committee – Sciences (28/11/13). The Decision of the Committee is to grant approval for this application which is subject to the conditions set out below.

Please note that approval is for the work and the time period specified in the above protocol and is subject to the following:

- If applicable, all permissions to access participants, whether internal (heads of Schools/Registrar) or external are obtained before the recruitment of the participants is commenced;
- Any amendments or requests to extend the original approved study will need to be approved by the Committee. Therefore you will need to submit by email the Request to Amend/Extend Form (HREC Doc 10);
- Any unexpected adverse events that occur during the conduct of your research should be notified to the Committee. Therefore you will need to submit, by email, an Unexpected Adverse Events Report (HREC Doc 11);
- You or your supervisor (if applicable) are required to submit a signed End of Study Report Form (HREC Doc 12) to the Committee upon the completion of your study;

.../.
• This approval is granted on condition that you ensure that, in compliance with the Data Protection Acts 1988 and 2003. If applicable, all data will be destroyed in accordance with your application and that you will confirm this in your End of Study Report (HREC Doc 32), or indicate when this will occur and how this will be communicated to the Human Research Ethics Committee;
• You may require copies of submitted documentation relating to this approved application and therefore we advise that you retain copies for your own records;
• Please note that the granting of this ethical approval is premised on the assumption that the research will be carried out within the limits of the law;
• Please also note that approved applications and any subsequent amendments are subject to a Research Ethics Compliance Review.

The Committee wishes you well with your research and look forward to receiving your End of Study Report. All forms are available on the website www.ucd.ie/researchethics please ensure that you submit the latest version of the relevant form. If you have any queries regarding the above please contact the Office of Research Ethics and please quote your reference in all correspondence.

Yours sincerely,

[Signature]

Mr John O’Dowd
Chair, Human Research Ethics Committee - Sciences
Appendix A.6 University College Dublin Ethical Approval Letter for Amendment to Study 5/6

31st January 2014

Ms Caitriona Fingleton
c/o Dr Catherine Doody
School of Public Health, Physiotherapy and Population Science
Health Sciences Centre
Belfield
Dublin 4


Dear Ms Fingleton

Thank you for your recent Amendment Form to the Human Research Ethics Committee – Sciences (29/01/14). The Decision of the Committee is to grant approval for your request to add Ms Helen O’Leary to this application which is subject to the following.

Please note that approval is for the work and the time period specified in the above protocol and is subject to the following:

- If applicable, all permissions to access participants, whether internal (heads of Schools/Committee) or external are obtained before the recruitment of the participants is commenced;
- Any amendments or requests to extend the original approved study or subsequent approved amended revisions of that study will need to be approved by the Committee. Please submit by email the Request to Amend/Extend Form (HREC Doc 10);
- Any unexpected adverse events that occur during the conduct of your research should be notified to the Committee. Therefore you will need to Submit, by email, an Unexpected Adverse Events Report (HREC Doc 11);
- You or your supervisor (if applicable) are required to submit a signed End of Study Report Form (HREC Doc 12) to the Committee upon the completion of your study;

.../.
This approval is granted on condition that you ensure that, in compliance with the Data Protection Acts 1988 and 2003. If applicable, all data will be destroyed in accordance with your application and that you will confirm this in your End of Study Report (HREC Doc 12), or indicate when this will occur and how this will be communicated to the Human Research Ethics Committee;

- You may require copies of submitted documentation relating to this approved application and therefore we advise that you retain copies for your own records;
- Please note that the granting of this ethical approval is premised on the assumption that the research will be carried out within the limits of the law;
- Please also note that approved applications and any subsequent amendments are subject to a Research Ethics Compliance Review.

All forms are available on the website www.ucd.ie/researchethics please ensure that you submit the latest version of the relevant form. If you have any queries regarding the above please contact the Office of Research Ethics and please quote your reference in all correspondence.

Yours sincerely,

____________________________

Mr T. John O'Dowd
Chairman, Human Research Ethics Committee - Sciences
11th February, 2014.

Dr. C. McLoughlin,
Physiotherapy Manager,
Physiotherapy Department,
St. Vincent’s University Hospital,
Elm Park,
Dublin 4.


Dear Dr. McLoughlin,

The above amendment was reviewed at the Ethics and Medical Research Committee meeting held on Wednesday 4th December 2013.

This amendment was approved.

Yours sincerely,

Dr. E. McKone,
Chairman,
- Ethics and Medical Research Committee.

Cc Dr. C. Doody, College Lecturer, UCD Health Sciences Centre, UCD.
Appendix A.8 Cappagh National Orthopaedic Hospital Ethical Approval Letter for Studies 3-6

From: Gordon Dunne <gordon.dunne@cappagh.ie>
Date: 11 June 2014 10:18
Subject: RE: FW: RE: Pain sensitization in OA Knee research study
To: Ursula Gormally <ursula.gormally@cappagh.ie>
Cc: Catherine Doody <c.doody@ucd.ie>, Jill Long <jill.long@cappagh.ie>, Sandra O’Donovan <sandra.odonovan@cappagh.ie>

All,

This study has been approved to proceed.

Official letter will follow in the post but you may commence based on this e mail.

Rgds,

Gordon Dunne
Chief Executive Officer
Cappagh National Orthopaedic Hospital
Finglas
Dublin 11
Appendix A.9 Beaumont Hospital Ethical Approval Letter for Studies 3-6

Ethics (Medical Research) Committee - Beaumont Hospital
Notification of ERC/IRB Approval

Principal Investigator: Ms. Catherine Doody (UCD)
Consultant co-investigator: Paul O’Connell / Dennis Collins
REC reference: 14/68
Protocol Title: Pain Sensitivity and exercise in osteoarthritis of the knee

Ethics Committee Meeting Date: 19th September 2014
Final Approval Date: 17th October 2014

From: Ethics (Medical Research) Committee - Beaumont Hospital, Beaumont, Dublin 9

Document and Date | Documents Reviewed | Approved
--- | --- | ---
Application Form, V2 | 17/10/14 | Yes
Study Protocol, no version no. | 17/10/14 | Yes
Participant Information Leaflet & Consent Form, Version 2 | 17/10/14 | Yes
Questionnaires, no version no. | 17/10/14 | Yes
CV: C. Doody | 17/10/14 | Yes
Cert of Insurance, UCD | 17/10/14 | Noted

Dr. Peter Branagan
ERC/IRB Convenor’s Signature
Approval # 1, dated 17th October 2014
APPENDIX B

Participant Information and Consent Forms
PARTICIPANT INFORMATION
PALPATION OF LOWER LIMB NERVES OF HEALTHY INDIVIDUALS: A RELIABILITY STUDY

You are invited to participate in a research study investigating the reliability of a clinical test involving palpation of 2 lower limb nerves. This test will be performed on healthy volunteers with no lower limb problems. The study is being conducted by Caitriona Fingleton and Lucy Dempsey from the School of Public Health, Physiotherapy and Population Science in University College Dublin (UCD) as part of their respective Master’s Degrees. This project is being supervised by Dr. Catherine Doody. Funding is provided by the Irish Research Council. Before deciding whether or not to take part in this research study, it is important that you read and understand this information sheet. Your participation is entirely voluntary.

What is this research about & why is it being conducted?
This study seeks to find out whether a simple non-harmful test for detecting nerve involvement in lower limb problems can be carried out consistently and reliably. This type of test is helpful for diagnosing people with lower limb nerve problems correctly so that they can get the most appropriate treatment.

What will happen if I decide to take part in this research study?
If you agree to participate in the research, you will attend for one 20 minute testing session in the School of Public Health, Physiotherapy and Population Science Laboratory. You will be asked to wear shorts for the testing which will take place in a screened area of the Laboratory. Testing will involve the following:

1. Collecting basic information about your person i.e. your age, weight, height and general health.
2. Nerve palpation tests
   ▪ The pressure to the nerves will be applied by the examiners in 2 ways. You will be asked to lie down on a couch and firstly the examiners will use digital pressure (using the thumb) to exert pressure on a nerve in front of the pelvis in line with your hip and on a second nerve at the back of the pelvis over the buttock on both your left and right sides. You will be asked to tell the examiner when you feel a mild discomfort.
   ▪ Secondly the examiners will use an electronic digital pressure gauge device to exert pressure on the same points in front and behind your hip. You will be asked to press a switch when you feel the sensation under the probe changes from pressure to pain. When you press the button this will automatically stop the pressure device. You are free to stop the examination at any time.
   ▪ This test will be carried out by the first examiner and then the second examiners on your right and left hip. Finally the first examiner will repeat the tests.
How will the data be used & how will you protect my privacy?
The data from this study will be analysed in University College Dublin (UCD) to determine whether this test is reliable. All information obtained from you will be kept strictly confidential and will be stored in a locked filing cabinet in UCD. Data will also be stored in two files on a computer. One file will act as a master-sheet, linking each participant’s name, age etc. to a code. The other file will link the codes to the participants’ testing data. These files will be stored in separate folders in encrypted format on a password protected computer. Identifying information about you will not be used in any research reports. When the study is completed in 6 months, the file with your personal details will be destroyed. The results of this study may be published in a scientific journal or presented at a scientific conference; however none of the people who take part in the study will be identified in any way.

What are the benefits & risks of taking part?
There are no direct benefits to you to taking part in the study; however the results may help medical professionals to better assess and treat lower limb disorders. There are no risks to your health or wellbeing involved in taking part in the study because none of the tests are harmful. The tests are commonly used by Physiotherapists in usual clinical practice.

Can I change my mind at any stage and withdraw from the study?
If you consent to take part in this study and later decide not to participate, you are free to withdraw from the study without giving a reason.

How will I find out what happens with this project?
The results of this study will be submitted for publication in a peer reviewed journal and may be presented at an international conference. You are welcome to ask any questions about the research and you can request a copy of the final results of the study.

Contact Details:
If you have any further questions about the research and/or wish to participate, please contact one of the researchers:

Researchers: Caitriona Fingleton (caitriona.fingleton@ucdconnect.ie) 087 7740841
Lucy Dempsey lucy.dempsey@ucdconnect.ie
Supervisor: Dr. Catherine Doody (c.doody@ucd.ie) 7166514
INFORMED CONSENT

PALPATION OF LOWER LIMB NERVES OF HEALTHY INDIVIDUALS: A RELIABILITY STUDY

Declaration
I have read the Participant Information Leaflet and have had time to consider whether to take part in this study.

I understand that my participation is voluntary (it is my choice) and that I am free to withdraw from the research at any time without disadvantage.

I agree to take part in this research study. I understand that, as part of this research project, I consent to undergo the testing procedures as explained.

I understand that my name will not be identified in any way.

I agree that the data can be used in the publication of a higher degree and scientific publications

I am voluntarily signing this form. I will be given a copy of this consent form.

Name of Participant (in block capitals): ______________________________

Signature:__________________________________________________________

Date: / /

Name of researcher (in block capitals) ________________________________

Signature _______________________________________________________

Date: / /

Researcher: Castriona Fingleton (castriona.fingleton@ucdconnect.ie)
Supervisor: Dr. Catherine Doody (c.doody@ucd.ie) 7166514
PARTICIPANT INFORMATION AND CONSENT FORM

STUDY TITLE: An Investigation of Pain Associated with Osteoarthritis of the Knee

NAME OF PRINCIPAL INVESTIGATORS: Caitriona Fingleton and Dr Catherine Doody

You are being invited to participate in a research study. Thank you for taking time to read this.

WHAT IS THE PURPOSE OF THIS STUDY?
We are investigating whether people with pain resulting from Osteoarthritis of the knee have alterations in the way they process pain compared to people with no pain.

WHY HAVE I BEEN CHOSEN?
You have been chosen to participate because you have been diagnosed with Osteoarthritis of your Knee

WHAT WILL HAPPEN IF I VOLUNTEER?
Your participation is entirely voluntary. If you initially decide to take part you can subsequently change your mind without difficulty. This will not affect your future treatment in any way.

If you agree to participate, we will make an appointment for you to come in to the Physiotherapy Department of ________ Hospital or the School of Public Health, Physiotherapy and Population Science Laboratory at University College Dublin where we will carry out the following tests:

Sensory testing
These tests will be performed on your knees and on a point on your arm.

• Your response to warm and cold sensations will be measured by warm and cold thermal rollers which will be rolled over your skin on your leg. You will be asked to indicate when you start to feel the warm and cold sensations. The warm and cold sensations are within normal limits and are not uncomfortable

• A soft nylon hair will be pressed against your skin to measure your ability to detect light pressure. You will be asked to close your eyes and indicate when you can feel the light pressure.
• Pressure will be applied to your skin using a pressure gauge device until you feel the first sensation of pain. Pressure will be applied slowly and stopped as soon as you indicate any discomfort.

• Your response to light touch will be measured using a soft brush stroke against your skin. You will be asked to close your eyes and indicate when you feel the brush stroke.

• Your ability to detect vibration will be tested by placing a tuning fork against your skin. You will be asked to close your eyes and state when you can feel any vibrations.

**Neurological examination**

• The sensation in your legs will be measured by lightly touching the sharp end of a medical pin off your skin. You will be asked to close your eyes and indicate when you feel the sharp sensation.

• The sensitivity of the nerves in your legs will be tested by asking/assisting you to lie or sit in different postures and also by feeling the nerves in your leg.

You may experience some slight discomfort when some of these tests are being carried out but there is no risk involved and you should be aware that these tests are part of normal clinical practice used routinely by physiotherapists and doctors.

**Questionnaires**

We will ask you to complete 4 questionnaires. The questionnaires are to assess your levels of pain and disability you may have as a result of your knee osteoarthritis.

These tests and the completion of questionnaires will take up to one and a half hours. The testing will take place in the School of Physiotherapy Laboratory which is located in the Health Science Centre at University College Dublin. We will ask you to bring a pair of shorts to wear during the tests.

**ARE THERE ANY BENEFITS FROM MY PARTICIPATION?**

There are no direct benefits to you to taking part in the study; however the results may help medical professionals to better understand, treat and manage pain associated with arthritis.

**ARE THERE ANY RISKS INVOLVED IN PARTICIPATING?**

There are no risks to your health or well-being associated with this study.

**WHAT HAPPENS IF I DO NOT AGREE TO PARTICIPATE?**

If you decide not to participate in this study, your treatment will not be affected in any way.

**CONFIDENTIALITY**

All information obtained from you will be kept strictly confidential. Data will be brought to University College Dublin for analysis and stored in a locked filing cabinet. Data will also be stored in two files on a computer. One file will act as a master-sheet, linking each participant’s name, age etc. to a code. The other file will link the codes to the participants’ testing data. This means that your data will not be identifiable.
These files will be stored in separate folders in encrypted format on a password protected computer. Your name will not be published or disclosed to anyone. Identifiable information about you will not be used in any research reports. When the study is completed in 1 year’s time, all of this information will be destroyed. The results of this study may be published in a scientific journal or presented at a scientific conference, however, none of the people who take part in the study will be identified in any way.

**COMPENSATION**

The researchers are adequately insured by virtue of their participation in the clinical indemnity scheme.

You will not receive payment for taking part in the study, however we can pay for your travelling expenses to attend for testing at UCD.

**WHO IS ORGANISING AND FUNDING THIS RESEARCH?**

This study is being conducted by Caitriona Fingleton from the School of Public Health, Physiotherapy and Population Science in University College Dublin (UCD) as part of a research PhD which is being supervised by Dr Catherine Doody and Dr Keith Smart. This study is funded by the Irish Research Council for Science, Engineering and Technology.

**HAS THIS STUDY BEEN REVIEWED BY AN ETHICS COMMITTEE?**

The University College Dublin Research Ethics Committee and St. Vincent’s Healthcare Group, Ethics and Medical Research Committee have reviewed and approved this study.

**CONTACT DETAILS**

For further information please contact Caitriona Fingleton 085 836 5897
or Dr Catherine Doody 7166514
PLEASE TICK YOUR RESPONSE IN THE APPROPRIATE BOX

• I have read and understood the Participant Information
  YES   NO

• I have had the opportunity to ask questions and discuss the study
  YES   NO

• I have received satisfactory answers to all my questions
  YES   NO

• I have received enough information about this study
  YES   NO

• I understand that I am free to withdraw from the study at any time without giving a reason and without this affecting my future medical care
  YES   NO

• I agree to take part in the study
  YES   NO

Participant’s Signature: ___________________________  Date: ______
Participant’s Name in print: ________________________

Investigator’s Signature: _________________________  Date: ______
Investigator’s Name in print: _______________________
PARTICIPANT INFORMATION
PAIN MECHANISMS IN PEOPLE WITH KNEE OSTEOARTHRITIS AND PEOPLE WITH NO PAIN

You are invited to participate in a research study investigating pain mechanisms in people with Osteoarthritis of the knee compared to people with no pain. This study is being conducted by Caitriona Fingleton from the School of Public Health, Physiotherapy and Population Science in University College Dublin (UCD) as part of a research PhD which is being supervised by Dr Catherine Doody. Before deciding whether to take part in this research study, it is important that you read and understand this information sheet.

What is this research about & why is it being conducted?
In order for us to understand this type of pain associated with Osteoarthritis it is important to look at people who do not have the condition as well as those who have it. We are investigating whether people with pain resulting from Osteoarthritis of the knee have alterations in the way they process pain compared to people with no pain.

What will happen if I decide to take part in this research study?
If you agree to participate in the research, you will be asked to come on one occasion at a time that suits you to the School of Public Health, Physiotherapy and Population Science Motion Analysis Laboratory. You will be asked to wear shorts, which we can provide, and to remove your shoes and socks for the testing. For one of the tests, it may be necessary for us to trim a 1cm² area of hair on the inside of your knee with a scissors. Testing will take place in a screened area of the laboratory and will take approximately 60 minutes to complete. Testing will involve the following:

Screening Questionnaire
Collecting basic information about your person, your age, any relevant general medical history and any current medication you may be taking.

Sensory testing
The following tests will be performed on your knees and on a point on your arm

- Your response to light touch will be measured using a soft brush stroke against your skin.
- A soft nylon hair will be pressed against your skin to measure your ability to detect light pressure. You will be asked to close your eyes and indicate when you can feel the light pressure.
- The sensation in your legs will be measured by lightly touching the sharp and blunt end of a medical pin off your skin. You will be asked to close your eyes and say whether the stimulus is sharp or blunt.
- Your response to warm and cold sensations will be measured by warm and cold thermal rollers which will be rolled over your skin on your leg. You will be asked to indicate when you start to feel the warm and cold sensations. The warm and cold sensations are within normal limits and are not uncomfortable.
Pressure will be applied to your skin using a pressure gauge device until you feel the first sensation of pain. Pressure will be applied slowly and stopped as soon as you indicate any discomfort.

Your ability to detect vibration will be tested by placing a tuning fork against your skin.

**Clinical examination**
The sensitivity of the nerves in your legs will be tested in two ways:

- by carefully feeling the nerves in your leg.
- by asking/assisting you to lie or sit in different postures

*You may experience some slight discomfort when some of these tests are being carried out but there is no risk involved and you should be aware that these tests are part of normal clinical practice used routinely by physiotherapists and doctors.*

**How will the data be used & how will you protect my privacy?**
The data from this study will be analysed and compared to data from people with Osteoarthritis of the knee. All information obtained from you will be kept strictly confidential and will be stored in a locked filing cabinet in UCD. Each person that participates in the study will be given a code so it will not be possible to identify your information once the data is collected. A master sheet will contain details of participants’ names, ages etc., and will link this information to the code. This master sheet and data file will be encrypted and stored on a password protected computer. Identifying information about you will not be used in any research reports. When the study is completed in 1 years’ time all this information will be destroyed. The results of this study may be published in a scientific journal or presented at a scientific conference; however none of the people who take part in the study will be identified in any way. Your participation in this research is entirely voluntary. You are free to refuse to take part or withdraw from the study at any time without giving a reason. This study is being funded by the Irish Research Council. We are not in a position to pay you for your participation in this study. The University College Dublin Life Sciences Research Ethics Committee has reviewed and approved this research study.

**What are the benefits & risks of taking part?**
There are no direct benefits to you to taking part in the study; however the results may help medical professionals to better understand, treat and manage pain associated with arthritis. There are no risks to your health or wellbeing by taking part in the study because none of the tests are harmful.

**Can I change my mind at any stage and withdraw from the study?**
If you consent to take part in this study and later decide not to participate, you are free to withdraw from the study without giving a reason.

**How will I find out what happens with this project?**
The results of this study will be submitted for publication in a peer reviewed journal and may be presented at an international conference. You are welcome to ask any questions about the research and you can request a copy of the final results of the study.

**Contact Details:**
If you have any further questions about the research and/or wish to participate please contact: Caitriona Fingleton (caitriona.fingleton@ucdconnect.ie) 085 836 5897
PARTICIPANT CONSENT FORM

PLEASE TICK YOUR RESPONSE IN THE APPROPRIATE BOX

• I have read and understood the Participant Information

  YES  NO

• I have had the opportunity to ask questions and discuss the study

  YES  NO

• I have received satisfactory answers to all my questions

  YES  NO

• I have received enough information about this study

  YES  NO

• I understand that I am free to withdraw from the study at any time without giving a reason and without this affecting my future medical care

  YES  NO

• I agree to take part in the study

  YES  NO

Participant’s Signature: ______________________  Date: ______

Participant’s Name in print: ______________________

Investigator’s Signature: ______________________  Date: ______

Investigator’s Name in print: ______________________
PARTICIPANT INFORMATION AND CONSENT FORM

STUDY TITLE: Pain Sensitivity & Exercise in Osteoarthritis of the Knee

You are being invited to participate in a research study. Thank you for taking the time to read this.

WHAT IS THE PURPOSE OF THIS STUDY?
We are investigating whether people with pain resulting from Osteoarthritis of the knee have alterations in the way they process pain and the way they respond to exercise compared to people with no pain.

WHY HAVE I BEEN CHOSEN?
You have been chosen to participate because you have been diagnosed with Osteoarthritis of your Knee.

WHAT WILL HAPPEN IF I VOLUNTEER?
Your participation is entirely voluntary. If you initially decide to take part, you can subsequently change your mind without difficulty. This will not affect your future treatment in any way.

If you agree to participate, we will make an appointment for you to come in to the Physiotherapy department in _______ Hospital or the Physiotherapy Lab in University College Dublin, depending on your preference. The testing will take approximately 1.5 hours. We will ask you to bring a pair of shorts to wear during the tests. Shorts can also be provided. The following tests will be carried out:

1. Sensory testing

   • Your response to warm and cold sensations will be measured by warm and cold thermal rollers which will be rolled over your skin on your leg. You will be asked to indicate when you start to feel the warm and cold sensations. The warm and cold sensations are within normal limits and are not uncomfortable

   • A soft nylon hair will be pressed against your skin to measure your ability to detect light pressure. You will be asked to close your eyes and indicate when you can feel the light pressure
• Pressure will be applied to your skin using a pressure gauge device until you feel the first sensation of pain. Pressure will be applied slowly and stopped as soon as you indicate any discomfort. You will be given a button that allows you to stop the pressure at any time.

• Your response to light touch will be measured using a soft brush stroke against your skin. You will be asked to close your eyes and indicate when you feel the brush stroke.

• Your ability to detect vibration will be tested by placing a tuning fork against your skin. You will be asked to close your eyes and state when you can feel any vibrations.

• You will be asked to put your non-dominant hand in a bath of very cold water (4 degrees) for up to 60 seconds, however you will be free to withdraw your hand before this time should you wish to. After this we will measure your response to the pressure gauge again (See figure 1).

• The sensation in your legs will be measured by lightly touching the sharp end of a medical pin off your skin. You will be asked to close your eyes and indicate when you feel the sharp sensation.

• The sensitivity of the nerves in your legs will be tested by asking/assisting you to lie or sit in different postures and also by feeling the nerves in your leg.

You may experience some minor discomfort when some of these tests are being carried out but you should be aware that there is no risk involved.

Figure 1. Cold Water Test

2. Exercise Testing

Stationary Bike
You will be asked to exercise on a stationary exercise bicycle for 2 - 7 minutes at a rate of 75% of your maximum capacity. Your maximum capacity is
predicted using a standard formula based on your age and heart rate. This method is commonly used by physiotherapists when prescribing exercise in the clinic. Prior to the test, we will adjust the seat and handle bars of the bicycle to what is most comfortable for you.

**Strength Exercise**
We will ask you to hold your leg out against resistance (20% of your maximum ability) for 5 minutes. We will test your response to the pressure gauge during this test (Figure 2)

Should you feel pain or shortness of breath during either test you can stop the test at any stage. The researcher carrying out all testing is a Chartered Physiotherapist and she will be with you for the duration of the test.

![Figure 2. Strength Exercise](image)

3. **Sensory Retest**
Following exercise testing, we will measure your response to the pressure gauge & pin prick again.

**Questionnaires**
We will ask you to complete 5 questionnaires. The questionnaires are to assess your levels of pain and disability you may have as a result of your knee osteoarthritis.

**ARE THERE ANY BENEFITS FROM MY PARTICIPATION?**
There are no direct benefits to you to taking part in the study; however the results may help medical professionals to better understand, treat and manage pain associated with arthritis.

**ARE THERE ANY RISKS INVOLVED IN PARTICIPATING?**
As this protocol involves exercise testing, there is a small risk of injury. However, all participants are screened for eligibility to exercise prior to the test, and all testing is supervised by a physiotherapist, trained in first aid.
WHAT HAPPENS IF I DO NOT AGREE TO PARTICIPATE?
If you decide not to participate in this study, your treatment will not be affected in any way.

CONFIDENTIALITY
All information obtained from you will be kept strictly confidential. Data will be brought to University College Dublin for analysis and stored in a locked filing cabinet. Data will also be stored in two files on a computer. One file will act as a master-sheet, linking each participant’s name, age etc. to a code. The other file will link the codes to the participants’ testing data. This means that your data will not be identifiable. These files will be stored in separate folders in encrypted format on a password protected computer. Your name will not be published or disclosed to anyone. Identifiable information about you will not be used in any research reports. When the study is completed in 2 years’ time, all of this information will be destroyed. The results of this study may be published in a scientific journal or presented at a scientific conference, however, none of the people who take part in the study will be identified in any way.

COMPENSATION
The researchers are adequately insured by virtue of their participation in the clinical indemnity scheme. You will not receive payment for taking part in the study, though we can compensate you for parking expenses.

WHO IS ORGANISING AND FUNDING THIS RESEARCH?
This study is being conducted by Caitriona Fingleton from the School of Public Health, Physiotherapy and Population Science in University College Dublin (UCD) as part of a PhD Degree which is being supervised by Dr Catherine Doody and Dr Keith Smart. This study is funded by the Irish Research Council.

HAS THIS STUDY BEEN REVIEWED BY AN ETHICS COMMITTEE?
The Beaumont Hospital Ethics and Medical Research Committee have reviewed and approved this study.

CONTACT DETAILS
For further information or queries, please contact Caitriona Fingleton on 085 836 5897
### PLEASE TICK YOUR RESPONSE IN THE APPROPRIATE BOX

- I have read and understood the Participant Information
  - YES
  - NO

- I have had the opportunity to ask questions and discuss the study
  - YES
  - NO

- I have received satisfactory answers to all my questions
  - YES
  - NO

- I have received enough information about this study
  - YES
  - NO

- I understand that I am free to withdraw from the study at any time without giving a reason and without this affecting my future medical care
  - YES
  - NO

- I agree to take part in the study
  - YES
  - NO

Participant’s Signature: __________________________ Date: _________

Participant’s Name in print: __________________________

Investigator’s Signature: __________________________ Date: _________

Investigator’s Name in print: __________________________
PARTICIPANT INFORMATION
Pain Sensitivity & Exercise in People with Osteoarthritis of the Knee & People with No Pain

You are invited to participate in a research study investigating the effect of exercise in people with Osteoarthritis of the knee compared to people with no pain. This study is being conducted by Caitriona Fingleton from the School of Public Health, Physiotherapy and Population Science in University College Dublin (UCD) as part of a PhD Degree which is being supervised by Dr Catherine Doody. Before deciding whether to take part in this research study, it is important that you read and understand this information sheet.

What is this research about & why is it being conducted?
We are comparing the effects of exercise on healthy people with no pain to people with osteoarthritis who have varying levels of pain. This helps us to learn about the effect of exercise on pain in people with osteoarthritis and also helps us to understand which osteoarthritis patients are best suited to exercise. This study is funded by the Irish Research Council.

What will happen if I decide to take part in this research study?
If you agree to participate in the research, you will be asked to come on one occasion, at a time that suits you, to the Physiotherapy Laboratory in UCD. Testing takes approx. 1.5 hours. You will be asked to wear shorts for the testing which we can provide or you are free to bring your own shorts. The researchers can provide you with a day parking permit which will be sent to you by post prior to testing. Testing will involve the following:

1. Sensory & Clinical testing
   • Your response to warm and cold sensations will be measured by warm and cold thermal rollers which will be rolled over your skin on your knee. You will be asked to indicate when you start to feel the warm and cold sensations. The warm and cold sensations are within normal limits (25 degree to 40 degrees) and are not uncomfortable
   
   • A soft nylon hair will be pressed against the skin on your knee to measure your ability to detect light pressure. You will be asked to close your eyes and indicate when you can feel the light pressure.
   
   • Pressure will be applied to the skin on your knee and forearm using a pressure gauge device until you feel the first sensation of pain. Pressure will be applied slowly and stopped as soon as you indicate any discomfort.
• You will be asked to put your non-dominant hand in a bath of cold water (4 degrees) for up to 45 seconds, however you will be free to withdraw your hand before this time should you wish to. After this we will measure your response to the pressure gauge again (See Figure 1).

• Your response to light touch will be measured using a soft brush stroke against the skin on your knee. You will be asked to close your eyes and indicate when you feel the brush stroke.

• We will lightly touch the skin on your knee with a pin to measure sensitivity of nerves in your legs

• The sensitivity of the nerves in your legs will also be tested by asking/assisting you to lie or sit in different postures and also by feeling the nerves in your leg.

You may experience some slight discomfort when some of these tests are being carried out but there is no risk involved and you should be aware that there is no risk involved

Figure 1: Cold Water Test

2. Exercise Testing

Stationary bicycle exercise: For this part of the test, you will be asked to exercise on a stationary bicycle for 2-8 minutes at a rate of 75% of your maximum capacity (this is not intensive exercise). Prior to the test we will adjust the seat and handle bars of the bicycle to what is most comfortable for you

Strength exercise: We will ask you to hold your leg out against resistance (20% of your maximum ability) for 5 minutes, as seen in picture below. We will test your response to the pressure gauge during this test.
3. Sensory Retest
Following exercise testing, we will measure your response to the pressure gauge & pinprick again.

How will the data be used & how will you protect my privacy?
The data from this study will be analysed and compared to data from people with Osteoarthritis of the knee. All information obtained from you will be kept strictly confidential and will be stored in a locked filing cabinet in UCD. Data will also be stored in two password protected and encrypted files on a computer. One file will act as a master-sheet, linking each participant’s name, age etc. to a code. The other file will link the codes to the participants’ testing data. This means that your data will not be identifiable by anyone except the study researcher (Caitriona Fingleton). Identifying information about you will not be used in any research reports. When the study is fully completed in 3 years’ time all this information will be destroyed. The results of this study may be published in a scientific journal or presented at a scientific conference, however none of the people who take part in the study will be identified in any way. The University College Dublin Life Sciences Research Ethics Committee has reviewed and approved this research study.

What are the benefits & risks of taking part?
There are no direct benefit to you by taking part in the study; however the results may help medical professionals to better understand, treat and manage pain associated with arthritis. There are no risks to your health or wellbeing by taking part in the study because none of the tests are harmful.

Can I change my mind at any stage and withdraw from the study?
If you consent to take part in this study and later decide not to participate, you are free to withdraw from the study without giving a reason.

How will I find out what happens with this project?
The results of this study will be submitted for publication in a peer reviewed journal and may be presented at an international conference. You are welcome to ask any questions about the research and you can request a copy of the final results of the study.

Contact Details:
If you have any further questions about the research and/or wish to participate, please contact Caitriona Fingleton.
Tel: 085 836 5897; Email: caitriona.fingleton@ucdconnect.ie
PARTICIPANT CONSENT FORM

PLEASE TICK YOUR RESPONSE IN THE APPROPRIATE BOX

• I have read and understood the Participant Information
  YES  NO

• I have had the opportunity to ask questions and discuss the study
  YES  NO

• I have received satisfactory answers to all my questions
  YES  NO

• I have received enough information about this study
  YES  NO

• I understand that I am free to withdraw from the study at any time without giving a reason and without this affecting my future medical care
  YES  NO

• I agree to take part in the study
  YES  NO

Participant’s Signature: __________________________  Date: ______
Participant’s Name in print: __________________________

Investigator’s Signature: __________________________  Date: ______
Investigator’s Name in print: __________________________
APPENDIX C

Questionnaires and Standardised Instructions
Appendix C.1 Western Ontario & McMaster Universities Osteoarthritis Index (WOMAC) v3.0 VAS

WOMAC VA3.1 QUESTIONNAIRE

Section A

PAIN

Think about the pain you felt in your __________ (study joint) due to your arthritis during the last 48 hours.

(Please mark your answers with an “X”.)

QUESTION: How much pain do you have?

1. Walking on a flat surface.
   No Pain ➔ Extreme Pain

2. Going up or down stairs.
   No Pain ➔ Extreme Pain

3. At night while in bed, i.e. pain that disturbs your sleep.
   No Pain ➔ Extreme Pain

4. Sitting or lying.
   No Pain ➔ Extreme Pain

5. Standing upright.
   No Pain ➔ Extreme Pain

Study Coordinator
Use Only

PAIN1
PAIN2
PAIN3
PAIN4
PAIN5

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English for Ireland - V1
WOMAC VA3.1 QUESTIONNAIRE

Section B

STIFFNESS

Think about the stiffness (not pain) you felt in your__________ (study joint) due to your arthritis during the last 48 hours.

Stiffness is a sensation of decreased ease in moving your joint.

(Please mark your answers with an "x").

6. How severe is your stiffness after you first awakening in the morning?
   - No Stiffness
   - Extreme Stiffness

7. How severe is your stiffness after sitting, lying or resting later in the day?
   - No Stiffness
   - Extreme Stiffness

Study Coordinator Use Only

STIFF6

STIFF7

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English for Ireland - V1
WOMAC VA3.1 QUESTIONNAIRE

Section C

DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities due to arthritis in your _________ (study joint) during the last 48 hours. By this we mean your ability to move around and look after yourself. (Please mark your answers with an " X ".)

<table>
<thead>
<tr>
<th>QUESTION: What degree of difficulty do you have?</th>
<th>Study Coordinator Use Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>8. Descending stairs.</td>
<td>PFTN8</td>
</tr>
<tr>
<td>No Difficulty</td>
<td></td>
</tr>
<tr>
<td>Extreme Difficulty</td>
<td></td>
</tr>
<tr>
<td>9. Ascending stairs.</td>
<td>PFTN9</td>
</tr>
<tr>
<td>No Difficulty</td>
<td></td>
</tr>
<tr>
<td>Extreme Difficulty</td>
<td></td>
</tr>
<tr>
<td>10. Rising from sitting.</td>
<td>PFTN10</td>
</tr>
<tr>
<td>No Difficulty</td>
<td></td>
</tr>
<tr>
<td>Extreme Difficulty</td>
<td></td>
</tr>
<tr>
<td>11. Standing.</td>
<td>PFTN11</td>
</tr>
<tr>
<td>No Difficulty</td>
<td></td>
</tr>
<tr>
<td>Extreme Difficulty</td>
<td></td>
</tr>
<tr>
<td>12. Bending to the floor.</td>
<td>PFTN12</td>
</tr>
<tr>
<td>No Difficulty</td>
<td></td>
</tr>
<tr>
<td>Extreme Difficulty</td>
<td></td>
</tr>
<tr>
<td>13. Walking on a flat surface.</td>
<td>PFTN13</td>
</tr>
<tr>
<td>No Difficulty</td>
<td></td>
</tr>
<tr>
<td>Extreme Difficulty</td>
<td></td>
</tr>
</tbody>
</table>

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English for Ireland - V1
DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities due to arthritis in your [study joint] during the last 48 hours. By this we mean your ability to move around and look after yourself. (Please mark your answers with an 'x'.)

QUESTION: What degree of difficulty do you have?

14. Getting in or out of a car, or getting on or off a bus.
   No Difficulty
   Extreme Difficulty

15. Going shopping.
   No Difficulty
   Extreme Difficulty

16. Putting on your socks or tights/pantyhose.
   No Difficulty
   Extreme Difficulty

17. Rising from bed.
   No Difficulty
   Extreme Difficulty

18. Taking off your socks or tights/pantyhose.
   No Difficulty
   Extreme Difficulty

19. Lying in bed.
   No Difficulty
   Extreme Difficulty

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English for Ireland - V1
DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities due to arthritis in your ________ (study joint) during the last 48 hours. By this we mean your ability to move around and look after yourself. (Please mark your answers with an "x").

<table>
<thead>
<tr>
<th>QUESTION: What degree of difficulty do you have?</th>
<th>Study Coordinator Use Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>20. Getting in or out of the bath.</td>
<td>PFTN20</td>
</tr>
<tr>
<td>No Difficulty</td>
<td>Extreme Difficulty</td>
</tr>
<tr>
<td>21. Sitting.</td>
<td>PFTN21</td>
</tr>
<tr>
<td>No Difficulty</td>
<td>Extreme Difficulty</td>
</tr>
<tr>
<td>22. Getting on or off the toilet.</td>
<td>PFTN22</td>
</tr>
<tr>
<td>No Difficulty</td>
<td>Extreme Difficulty</td>
</tr>
<tr>
<td>23. Performing heavy domestic duties.</td>
<td>PFTN23</td>
</tr>
<tr>
<td>No Difficulty</td>
<td>Extreme Difficulty</td>
</tr>
<tr>
<td>24. Performing light domestic duties.</td>
<td>PFTN24</td>
</tr>
<tr>
<td>No Difficulty</td>
<td>Extreme Difficulty</td>
</tr>
</tbody>
</table>
Appendix C.2 PainDETECT

<table>
<thead>
<tr>
<th>PainDETECT PAIN QUESTIONNAIRE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Date:</strong></td>
</tr>
</tbody>
</table>

**How would you assess your pain now, at this moment?**

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>max.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**How strong was the strongest pain during the past 4 weeks?**

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>max.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**How strong was the pain during the past 4 weeks on average?**

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>max.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Mark the picture that best describes the course of your pain:**

- Persistent pain with slight fluctuations
- Persistent pain with pain attacks
- Pain attacks without pain between them
- Pain attacks with pain between them

**Does your pain radiate to other regions of your body?**

- yes
- no

If yes, please draw the direction in which the pain radiates.

**Do you suffer from a burning sensation (e.g., stinging nettles) in the marked areas?**

- never
- hardly noticed
- slightly
- moderately
- strongly
- very strongly

**Do you have a tingling or prickling sensation in the area of your pain (like crawling ants or electrical tingling)?**

- never
- hardly noticed
- slightly
- moderately
- strongly
- very strongly

**Is light touching (clothing, a blanket) in this area painful?**

- never
- hardly noticed
- slightly
- moderately
- strongly
- very strongly

**Do you have sudden pain attacks in the area of your pain, like electric shocks?**

- never
- hardly noticed
- slightly
- moderately
- strongly
- very strongly

**Is cold or heat (bath water) in this area occasionally painful?**

- never
- hardly noticed
- slightly
- moderately
- strongly
- very strongly

**Do you suffer from a sensation of numbness in the areas that you marked?**

- never
- hardly noticed
- slightly
- moderately
- strongly
- very strongly

**Does slight pressure in this area, e.g., with a finger, trigger pain?**

- never
- hardly noticed
- slightly
- moderately
- strongly
- very strongly

(To be filled out by the physician)

**Total score** out of 35

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SCORING OF PAIN QUESTIONNAIRE

Date: ___________  Patient:  Last name: ___________  First name: ___________

Please transfer the total score from the pain questionnaire:

Total score  

Please add up the following numbers, depending on the marked pain behavior pattern and the pain radiation. Then total up the final score:

Persistent pain with slight fluctuations: 0
Persistent pain with pain attacks: -1 if marked, or
Pain attacks without pain between them: +1 if marked, or
Pain attacks with pain between them: +1 if marked
Radiating pains?: +2 if yes

Final score

Screening Result

Final score

nociceptive  unclear  neuropathic

A neuropathic pain component is unlikely (< 15%)
Result is ambiguous, however a neuropathic pain component can be present
A neuropathic pain component is likely (> 90%)

This sheet does not replace medical diagnostics. It is used for screening the presence of a neuropathic pain component.

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Appendix C.3 Short-form McGill Pain Questionnaire (SF-MPQ)

**Short-Form McGill Pain Questionnaire**

Ronald Melzack

<table>
<thead>
<tr>
<th>Patient Name: __________________________ Date: __________________________</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Throbbing</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Shooting</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Stabbing</td>
<td>0</td>
<td>1</td>
<td>2</td>
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NO PAIN —————————————————— I WORST POSSIBLE PAIN

**Present Pain Intensity**

0  No pain
1  Mild
2  Discomforting
3  Distressing
4  Horrible
5  Excruciating

The short-form McGill Pain Questionnaire (SF-MPQ): Descriptors 1-11 represent the sensory dimension of pain experience and 12-15 represent the affective dimension. Each descriptor is ranked on an intensity scale of 0 = None, 1 = Mild, 2 = Moderate, 3 = Severe. The Present Pain Intensity (PPI) of the standard long-form McGill Pain Questionnaire (LF-MPQ) and the visual analogue (VAS) are also included to provide overall intensity scores. © R. Melzack, 1984
Appendix C.4 EuroQOL

Health Questionnaire

English version for the UK
Under each heading, please tick the ONE box that best describes your health TODAY

**MOBILITY**
- I have no problems in walking about
- I have slight problems in walking about
- I have moderate problems in walking about
- I have severe problems in walking about
- I am unable to walk about

**SELF-CARE**
- I have no problems washing or dressing myself
- I have slight problems washing or dressing myself
- I have moderate problems washing or dressing myself
- I have severe problems washing or dressing myself
- I am unable to wash or dress myself

**USUAL ACTIVITIES** (e.g. work, study, housework, family or leisure activities)
- I have no problems doing my usual activities
- I have slight problems doing my usual activities
- I have moderate problems doing my usual activities
- I have severe problems doing my usual activities
- I am unable to do my usual activities

**PAIN / DISCOMFORT**
- I have no pain or discomfort
- I have slight pain or discomfort
- I have moderate pain or discomfort
- I have severe pain or discomfort
- I have extreme pain or discomfort

**ANXIETY / DEPRESSION**
- I am not anxious or depressed
- I am slightly anxious or depressed
- I am moderately anxious or depressed
- I am severely anxious or depressed
- I am extremely anxious or depressed
We would like to know how good or bad your health is TODAY.
This scale is numbered from 0 to 100.
100 means the best health you can imagine.
0 means the worst health you can imagine.
Mark an X on the scale to indicate how your health is TODAY.
Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =
Appendix C.5 Pain Catastrophising Scale

Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, joint or muscle pain. People are often exposed to situations that may cause pain such as illness, injury, dental procedures or surgery.

We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

0 – not at all  1 – to a slight degree  2 – to a moderate degree  3 – to a great degree  4 – all the time

When I’m in pain …

☐ I worry all the time about whether the pain will end.
☐ I feel I can’t go on.
☐ It’s terrible and I think it’s never going to get any better.
☐ It’s awful and I feel that it overwhelms me.
☐ I feel I can’t stand it anymore.
☐ I become afraid that the pain will get worse.
☐ I keep thinking of other painful events.
☐ I anxiously want the pain to go away.
☐ I can’t seem to keep it out of my mind.
☐ I keep thinking about how much it hurts.
☐ I keep thinking about how badly I want the pain to stop.
☐ There’s nothing I can do to reduce the intensity of the pain.
☐ I wonder whether something serious may happen.

...Total

Updated 11/11
Appendix C.6 Standardised Instructions

Standardised instructions
In these tests, I’m going to explore how you perceive touch, vibration, hot & cold and pressure stimuli (and your response to exercise). None of these tests are harmful. The results of your test will be compared to people who (do not) have osteoarthritis of the knee. This helps us to learn more about pain mechanisms in people with osteoarthritis and thereby understand how to better direct their treatment. If at any point you haven’t understood the instructions, feel free to ask for clarification.

Brush stroke hypersensitivity/allodynia
The first test assesses your sensitivity to light brush strokes on your skin. I’m going to lightly brush the skin around your knee with this brush. It will feel like this (Demonstrate). I will ask you throughout the test ‘how does that feel?’.
If it feels normal just say ‘normal’. Please state if you feel any pain such as stinging or burning, any numbness, or if the brushstrokes feel different in any area.

Light Touch Detection
The next test assesses your ability to detect light touch. I’m now going to carefully touch the skin on your knee and arm with these thin hairs (Demonstrate). Please don’t look at the skin area I’m testing during the test procedure. Please say ‘YES’ as soon as you feel a touch sensation.

Thermal Test
The next test assesses your ability to feel cold and warm sensations. I’m now going to roll this cold/warm roller over your skin. (Demonstrate). I will ask you throughout the test “how does that feel”.
If it just feels cold, then you can say ‘normal’. Please tell me if the roller feels particularly cold/hot in any area of if you any other abnormal sensations such as stinging, burning or numbness.

Vibration Sense
This is a test of your ability to feel vibrations. I’m going place this vibrating tuning fork on your skin. Please don’t look at the skin area I’m testing during the test procedure. Please tell me if you are able to feel the vibrations. Please immediately say ‘now’ as soon as you are no longer able to feel any further vibrations.

Straight leg raise neurodynamic test
This is a test of the sensitivity of nerves at the back of your leg. Please lie with both legs out straight and your arms down by your side. I am going to lift this leg up slowly. Please say ‘now’ as soon as you begin to feel pain and I will immediately stop lifting the leg.

Nerve Palpation
This is a test of the sensitivity of the nerves in your leg.
I will apply mild to moderate pressure with my thumb to nerves in your legs and I want you to tell me whether you feel pain or no pain.

**Pressure Pain Thresholds**
This is a test of your sensitivity to pressure.
I’m going to press this pressure measuring device against your skin.
You will feel pressure on your skin which will gradually increase.
As soon as the feeling of pressure begins to change to that of pressure and pain, please press the button. Please press the button at the very first instance of pain and remember this is not a test of endurance.
As soon as you press the button, I will immediately stop applying pressure.

**Temporal Summation**
The next test assesses your response to sharp touch.
I’m now going to carefully touch the skin on your arm with this pin (It will feel like this).
I will ask to rate your level of pain due to the pinprick between 0 and 10, 0 being no pain and 10 being the worst pain imaginable.
I’m now going to touch the skin on your knee 10 times in a row with this pin.
I will then ask you to give a pain rating between 0 and 10 for the 10 pinpricks overall.

**Conditioned Pain Modulation**
The next test assesses your sensitivity to cold pain.
The goal is to put your hand into this cooler of water and keep it there for 60 seconds.
The cold water may feel painful but will not cause any harm.
If you feel the need to take your arm out before the end of the test, you are free to do so.
Immediately afterwards, I am going to re-measure your response to the pressure algometer at the knee and the arm.

**Aerobic Exercise Test**
The next test measures your response to aerobic exercise on an exercise bike.
I will adjust the seat and handle bar until you’re comfortable.
I will ask you to pedal on this bike for 5 – 12 minutes.
Each minute, the resistance on the bike will go up.
I will ask you to rate your pain at regular intervals throughout the test.
If you have pain > 3/10, I will modify the test until you are comfortable.
If you continue to have pain, the test will be stopped.
I will be measuring your heart-rate on this monitor and will stop you when your heart rate reaches a certain level.
Please let me know if you want to stop at any stage.

**Isometric Exercise Test**
The next test measures your response to a weighted leg exercise.
I’m going to use this measuring device to assess the maximum force you can push with your leg.
After a count of three, I’ll ask you to push as hard as you can for 3 seconds.
Then I will calculate 10% of your score and strap this weight to your ankle.
I’ll then ask you to hold your leg out with the ankle weight for as long as you can up to a maximum of 5 minutes.
During this 5 minutes, I will be remeasuring your response to pressure.
Afterwards I will retest your response to pressure and pinprick.
APPENDIX D
Supplemental Information for Studies 3 and 4
# Appendix D.1 Frequency of Allodynia and Hypoaesthesia to Touch (%)

<table>
<thead>
<tr>
<th>Dynamic mechanical touch</th>
<th>Knee OA group N = 52</th>
<th>Knee OA-High PPS group N = 26</th>
<th>Knee OA-Low PPS group N = 26</th>
<th>Control group N =38</th>
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</thead>
<tbody>
<tr>
<td><strong>Index Knee</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>5.8</td>
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<td>7.7</td>
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1 Hypo, hypoesthesia; PPS, pressure pain sensitivity

# Appendix D.2 Frequency of Hyperalgesia and Hypoaesthesia to Cold (%)

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<th>Cold</th>
<th>Knee OA group N = 52</th>
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<th>Knee OA-Low PPS group N = 26</th>
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1 Hyper, hyperalgesia; Hypo, hypoesthesia; PPS, pressure pain sensitivity
## Appendix D.3 Frequency of Hyperalgesia and Hypoaesthesia to Heat (%)

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Hyper, hyperalgesia; Hypo, hypoaesthesia; PPS, pressure pain sensitivity
APPENDIX E
Supplemental Information for Study 6
Appendix E. Exploratory analysis of exercise-induced hypoalgesia in knee OA patients & healthy controls with normal & abnormal conditioned pain modulation (CPM)

Supplemental information for Study 6. Exercise-induced hypoalgesia in people with knee osteoarthritis with normal and abnormal conditioned pain modulation

Study 6 was conducted to compare exercise-induced hypoalgesia (EIH) in knee OA patients with abnormal and normal conditioned pain modulation (CPM) and healthy age and sex-matched controls; however due to the high frequency of CPM responses in controls (35%) demonstrated in this study, an exploratory subgroup analysis was undertaken to investigate for potential differences in EIH response between control participants with normal CPM (n = 13) and abnormal CPM (n = 7) and knee OA participants with normal CPM (n = 21) and abnormal CPM (n = 19).

Between-group changes in PPTs
There were significant differences between the four groups for changes in total pressure pain threshold (PPT) score (average of MJL & forearm) pre and post-aerobic (F (3, 54) = 10.129, P < 0.001) and isometric exercise (F (3, 56) = 6.392, P = 0.001)(Figure 1). Knee OA patients and controls with abnormal CPM showed a decrease in PPTs (dysfunctional EIH), while knee OA patients and controls with normal CPM showed an increase in PPTs (normal EIH). Controls with abnormal CPM demonstrated significant differences for changes in total PPT score compared to controls with normal CPM (aerobic, P < 0.001; isometric, P = 0.022) (Table 1) and knee OA participants with normal CPM (aerobic, P = 0.003; isometric, P = 0.041), and there were no significant differences between controls with abnormal CPM and knee OA participants with abnormal CPM (aerobic, P = 0.559; isometric, P = 0.910).

Within-group changes in PPTs
Controls with normal CPM showed an increase in PPTs post-aerobic (MJL, P = 0.002; forearm, P = 0.152; total, P = 0.004) and isometric (MJL, P = 0.003; forearm, P = 0.011; total, P = 0.002) exercise. In controls with abnormal CPM, there were no significant changes in PPTs post-aerobic (MJL, P = 0.398; forearm, P = 0.091; total, P = 0.091) or isometric (MJL, P = 0.993; forearm, P = 0.237; total, P = 0.310) exercise (Table 1).
Implications

Variability has been previously been demonstrated in the CPM response of pain-free individuals\(^1,2\), with lesser efficiency of CPM reported in healthy older adults\(^3\). Our findings of dysfunctional EIH in pain-free controls with abnormal CPM may be interpreted in the context of the model of pro-nociceptive and anti-nociceptive pain modulation profiles (PMPs) put forward by Yarnitsky et al\(^1\) and Granovsky\(^4\). The PMP model proposes that pain-free individuals exhibiting dysfunctional pain inhibition (i.e. abnormal CPM) may be at

---

**Table 1.** Controls with Normal & Abnormal CPM: Changes in PPTs in Response to Exercise

<table>
<thead>
<tr>
<th></th>
<th>Controls with normal CPM</th>
<th>Controls with abnormal CPM</th>
<th>Between-group comparisons (DF; F-value; P-value)</th>
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<tr>
<td><strong>Aerobic exercise</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>Pressure pain thresholds</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee</td>
<td>255.64 ± 139.23</td>
<td>318.33 ± 178.12</td>
<td>217.02 ± 86.50</td>
</tr>
<tr>
<td>Forearm</td>
<td>179.76 ± 76.43</td>
<td>205.34 ± 100.29</td>
<td>219.79 ± 74.99</td>
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<tr>
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<td>217.70 ± 106.09</td>
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<td>218.41 ± 70.67</td>
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<td><strong>Resistance exercise</strong></td>
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<td>Pressure pain thresholds</td>
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<tr>
<td>Knee</td>
<td>255.64 ± 139.23</td>
<td>291.56 ± 145.76</td>
<td>217.02 ± 86.50</td>
</tr>
<tr>
<td>Forearm</td>
<td>179.76 ± 76.43</td>
<td>228.18 ± 146.11</td>
<td>219.79 ± 74.99</td>
</tr>
<tr>
<td>Average of 2 sites</td>
<td>217.70 ± 106.09</td>
<td>259.87 ± 141.58</td>
<td>218.41 ± 70.67</td>
</tr>
</tbody>
</table>

CPM, conditioned pain modulation; PPTs, pressure pain thresholds; DF, degrees of freedom
*Significant between-group differences for changes in PPTs, P < 0.05
†Significant within-group increase in PPTs from pre to post-exercise, P < 0.05
‡Significant within-group decrease in PPTs from to post-exercise, P < 0.05
higher risk of chronic pain acquisition. Indeed the presence of pre-operative CPM inefficiency has been shown to predict the development of post-operative pain and hyperalgesia\textsuperscript{5,7}, and it is possible that the controls in our study with abnormal CPM could reflect a pro-nociceptive PMP group who potentially have a higher risk of pain acquisition compared to controls with normal CPM. This PMP model is also in keeping with the concept of pain sensitization as a pre-pathological trait in people with knee OA, as described by Neogi et al\textsuperscript{8} in response to findings that duration and radiographic severity of knee OA were not associated with pain sensitization. The results of this supplementary analysis should be interpreted in the light of the small numbers of subjects. Further investigation is warranted in a larger fully powered study.

References
APPENDIX F
Publications and Presentations
Appendix F.1 Journal Article: Intraexaminer and interexaminer reliability of manual palpation and pressure algometry of the lower limb nerves in asymptomatic subjects

Journal of Manipulative & Physiological Therapeutics 2014

INTRAEXAMINER AND INTEREXAMINER RELIABILITY OF MANUAL PALPATION AND PRESSURE ALGOMETRY OF THE LOWER LIMB NERVES IN ASYMPTOMATIC SUBJECTS

Caitriona P. Fingleton, BSc (Physio), a Lucy Dempsey, BSc (Physio), b Keith Smart, PhD, c and Catherine M. Doody, Dip TP, PhD d

ABSTRACT

Objective: Nerve palpation is a method of clinically identifying mechanosensitivity of neural tissue by means of pressure algometry and manual palpation. There are few investigations of the reliability of lower limb nerve palpation, and femoral nerve palpation has never been previously reported. The aim of this study was to investigate the reliability of nerve palpation of the femoral, sciatic, tibial, and common peroneal nerves and to report normative values for the femoral nerve.

Methods: The 4 lower limb nerves were palpated in 39 healthy volunteers using pressure algometry and manual digital palpation. Measurements were taken twice by 1 rater (intrarater reliability) and once by a second rater (interrater reliability).

Results: Intraclass correlation coefficients for pressure pain thresholds (PPTs) via pressure algometry of the femoral, common peroneal, tibial, and sciatic nerves were 0.69, 0.84, 0.64, and 0.9 for intrarater reliability, respectively, and 0.82, 0.7, 0.56, and 0.75 for interrater reliability. κ Values for manual palpation were 0.59, 0.55, 0.42, and 0.60 for intrarater reliability and 0.30, 0.49, 0.37, and 0.60 for interrater reliability. Males demonstrated significantly higher PPTs than females for the femoral, sciatic, and tibial nerves, and differences in PPTs were present between right and left sides.

Conclusion: Nerve palpation of the femoral, common peroneal, and sciatic nerves using pressure algometry demonstrated good to excellent reliability, whereas the tibial nerve PPTs showed moderate to good reliability. Manual palpation measurements demonstrated fair to moderate reliability. (J Manipulative Physiol Ther 2014;37:97-104)

Key Indexing Terms: Peripheral Nerves; Musculoskeletal Pain; Reliability and Validity

Neural tissue mechanosensitivity may be assessed by neural tissue provocation tests such as nerve palpation. Mechanical palpation using pressure algometry and manual palpation with the thumb have a high degree of clinical utility as they may be performed as part of a standard bedside examination. 1,2

Findings of localized and widespread hyperalgesia are suggestive of pain sensitization. 1 Increased sensitivity to nerve palpation has been observed in a number of chronic pain conditions, for example, nonspecific arm pain, 4 low back pain, 5 and work-related upper limb pain. 6 It has been suggested that nerve sensitivity may be explained by peripheral sensitization mechanisms, 7 in which neurogenic inflammation leads to the sensitization of neural mechano-receptors (nervi-nervorum). 8 In addition, central sensitization mechanisms may play a role in nerve sensitization, whereby nonnoxious stimuli from the nervi-nervorum are processed abnormally in the central nervous system. 9

There are reports of the reliability of nerve palpation in relation to nerves of the upper limb, 10,11 and very limited data exist in relation to the reliability of lower limb nerve

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despite its use in a number of studies on clinical decision making in relation to low back and leg pain disorders.\textsuperscript{2,12,13} Walsh et al\textsuperscript{11} investigated the reliability of mechanically palpating the sciatic, tibial, and common peroneal nerves of the lower limb using a pressure algometer and provided normative pressure pain threshold (PPT) values for these nerves. Walsh and Hall\textsuperscript{5} carried out digital (manual) palpation of lower limb nerves bilaterally and simultaneously in patients with low back and leg pain and rated pain or discomfort on the symptomatic side in relation to the symptomatic side. However, there are conflicting reports in relation to differences in PPT measurements between symptomatic and asymptomatic sides in subjects with chronic pain, with reports of no significant differences\textsuperscript{3}, as well as reports of significant differences between sides.\textsuperscript{14} A possible explanation is the presence or absence of peripheral and central sensitization of the nervous system in chronic pain states, and it may, therefore, be important to carry out nerve palpation of right and left sides separately. In relation to the femoral nerve, no studies have investigated the reliability of femoral nerve palpation or reported normative PPT values. The femoral nerve crosses the hip joint, supplying muscles of the anterior thigh and innervating the knee joint,\textsuperscript{15} which may make it vulnerable to sensitization in patients with longstanding pain disorders of the lower limb. In addition, there have been no studies investigating the reliability of manual palpation of lower limb nerves, which have reported separate right- and left-sided palpation.

The purpose of this study was to investigate the reliability of femoral nerve palpation, using manual pressure and pressure algometry, in addition to further testing the reliability of manual palpation and pressure algometry of the sciatic, common peroneal, and tibial nerves by means of alternate unilateral palpation. The study also sought to provide normative PPT data for the femoral nerve.

**Methods**

**Subjects**

The Quality Appraisal Tool for Studies of Diagnostic Reliability guidelines was used in the design of this study.\textsuperscript{16} Based on previous reliability studies, a sample of 39 participants was selected for the study.\textsuperscript{1,5,6,11} All subjects were students of University College Dublin (UCD) who were over 18 years, with no chronic pain or neurologic disorders and no previous history of lumbar spine or lower limb pathologies. Subjects were invited via email to take part in the study and provided written informed consent before participation. Ethical approval was obtained from the UCD Human Research Ethics Committee.
Design

Procedure. Two raters palpated the participants’ femoral, sciatic, tibial, and common peroneal nerves using manual pressure with the thumb in addition to pressure algometry (Figs 1 and 2). All testing was carried out in a laboratory in UCD. Both raters were Chartered Physiotherapists. Rater 1 (CF) had 6-month experience of nerve palpation techniques, and rater 2 (LD) underwent training in nerve palpation before the commencement of the study. Rater 1 (CF) tested subjects’ right and left lower limbs to gather normative data. Rater 2 (LD) performed the assessment on subjects’ left lower limb only, to determine interrater reliability. Rater 1 repeated the assessment on the right lower limb to establish intrarater reliability. Randomization software was used to determine a random order for testing, that is, to determine which rater went first and whether rater 1 tested the left or right side first, to minimize a potential order effect.

Participants wore shorts provided by the researchers and were positioned on a plinth in supine for palpation of the femoral and common peroneal nerves and in prone for palpation of the tibial and sciatic nerves. The femoral nerve was palpated lateral to the femoral artery inferior to the inguinal ligament; the common peroneal nerve where it passes behind the head of the fibula as it winds forwards around the neck; the tibial nerve where it bisects the popliteal fossa, lateral to the popliteal artery; and the sciatic nerve midway between the ischial tuberosity and the greater trochanter, deep to the gluteus maximus muscle. At each nerve site, palpation was performed first with manual pressure and thereafter with the pressure algometer. An initial trial was carried out at the subject’s wrist to familiarize them with the testing protocol.

Manual Palpation. Digital pressure with the thumb was used to manually palpate each of the nerve sites using the standardized procedure established by the researchers, in which a similar mild-to-moderate steady pressure was applied by each examiner; the rate of pressure was established before the commencement of the study by means of practice sessions on a blinded third party, who provided feedback on the consistency of the pressure applications; this was repeated until consistency in pressure application was reported at all nerve sites. The method described by Jepsen et al. in a study on asymptomatic and symptomatic subjects was used, whereby mechanical allodynia was quantified according to none, mild, moderate, or severe. As very few subjects were categorized as severe, these scores were subsequently collapsed into normal or abnormal (ie, normal, none; abnormal, mild, moderate, or severe), as described by Jepson et al.
**Table 1. Pressure algometry: intrarater reliability**

<table>
<thead>
<tr>
<th>Site</th>
<th>Rater 1A, mean (SD)</th>
<th>Rater 1B, mean (SD)</th>
<th>ICC (95% CI)</th>
<th>SEM</th>
<th>Mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral</td>
<td>168 (51)</td>
<td>163 (41)</td>
<td>0.69 (0.41, 0.84)</td>
<td>26</td>
<td>5 (−16, 26)</td>
</tr>
<tr>
<td>Peroneal</td>
<td>125 (41)</td>
<td>114 (37)</td>
<td>0.84 (0.69, 0.91)</td>
<td>16</td>
<td>11 (−7, 29)</td>
</tr>
<tr>
<td>Tibial</td>
<td>141 (45)</td>
<td>140 (38)</td>
<td>0.64 (0.32, 0.81)</td>
<td>25</td>
<td>1 (−18, 20)</td>
</tr>
<tr>
<td>Sciatic</td>
<td>244 (89)</td>
<td>233 (82)</td>
<td>0.90 (0.81, 0.95)</td>
<td>27</td>
<td>11 (−28, 50)</td>
</tr>
</tbody>
</table>

CI, confidence interval; ICC, intraclass correlation coefficient; SD, standard deviation; SEM, standard error of measurement.

**Table 2. Pressure algometry: interrater reliability**

<table>
<thead>
<tr>
<th>Site</th>
<th>Rater 1, mean (SD)</th>
<th>Rater 2, mean (SD)</th>
<th>ICC (95% CI)</th>
<th>SEM</th>
<th>Mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral</td>
<td>158 (55)</td>
<td>176 (53)</td>
<td>0.82 (0.65, 0.9)</td>
<td>23</td>
<td>−17 (−41, 7)</td>
</tr>
<tr>
<td>Peroneal</td>
<td>127 (38)</td>
<td>136 (35)</td>
<td>0.70 (0.43, 0.84)</td>
<td>20</td>
<td>−10 (−26, 7)</td>
</tr>
<tr>
<td>Tibial</td>
<td>136 (35)</td>
<td>124 (34)</td>
<td>0.56 (0.16, 0.77)</td>
<td>23</td>
<td>12 (−3, 28)</td>
</tr>
<tr>
<td>Sciatic</td>
<td>244 (86)</td>
<td>256 (69)</td>
<td>0.75 (0.53, 0.87)</td>
<td>39</td>
<td>−13 (−48, 23)</td>
</tr>
</tbody>
</table>

CI, confidence interval; ICC, intraclass correlation coefficient; SD, standard deviation; SEM, standard error of measurement.

**Pressure Algometry.** An electronic digital algometer (Somedic AB, Hörby, Sweden) was used for all test sites. The algometer consisted of a circular probe with a 2-cm² round rubber tip at the end connected to a pressure transducer within the handle of the unit. The applied pressure was indicated on a digital display in kilopascals (kPa). Pressure was applied at a rate of 30 kPa/s, and subjects were instructed to press the button (terminating the pressure) as soon as the feeling of pressure began to change to that of pressure and pain. The classification system established by Shrout and Fleiss was used to determine the level of reliability (0, poor; 0.01-0.20, slight; 0.21-0.40, fair; 0.41-0.60, moderate; 0.61-0.80, substantial; and 0.81-1, almost perfect). Intraclass correlation coefficients (ICCs) were calculated to assess reliability of the mechanical PPT data. A 2-way analysis of variance (random effects model) was used to calculate interrater reliability, and a 1-way analysis of variance (random effects model) was used to find intrarater reliability. The classification system established by Shrout and Fleiss was used to determine the level of reliability (0.75, excellent; 0.6-0.75, good; 0.4-0.59, fair; and <0.4, poor).

The SEM was calculated to assess the amount of variability between PPT measures attributable to measurement error. The formula used was SEM = S/√N, where S is the pooled SD.

Mean differences with 95% CIs were calculated to determine the level of agreement between PPT measurements. Bland-Altman plots were created for intrarater and interrater reliability of the femoral nerve to examine for the presence of systematic bias and random error.

**Normative PPT Data.** The means and standard deviation (SD) at each site were calculated. Paired t-tests were used to identify whether there were significant differences between right and left sides at each site and independent t-tests were used to determine whether there were any differences between the PPTs of males and females.

**Results**

Twenty males and nineteen females between 18 and 33 years, with a mean age of 22 years (SD = 4 years) participated in the study.
The SEM values and 95% CIs are reported in Tables 1 and 2. These scores demonstrate good to excellent reliability for PPTs of the femoral, common peroneal, and sciatic nerves and moderate to good reliability for tibial nerve PPTs. Mean differences between PPT measures ranged from −17 to 12, indicating a good level of agreement as both measures were close to zero.

The limits of agreement for femoral nerve intrarater and interrater reliability are shown in Bland-Altman plots (Figs 3 and 4). For intrarater and interrater reliability, values were evenly scattered above and below zero, and approximately 95% of values were within the limits of agreement suggesting there was no significant systematic bias or random error. The SEM values of 16 to 39 kPa for pairs of PPT readings give an indication as to the differences in 2 PPT readings that may be considered a result of measurement error.

Manual Palpation. Manual palpation measurements showed \( \kappa \) scores of 0.59, 0.55, 0.42, and 0.60 for intrarater reliability of the femoral, common peroneal, tibial, and sciatic nerves and \( \kappa \) scores of 0.30, 0.49, 0.37, and 0.60, respectively, for interrater reliability (Table 3 and 4). Interrater reliability was classified as fair for the femoral nerve and tibial nerve and moderate for the common peroneal and sciatic nerve. Intrarater reliability was classified as moderate for all nerves.

Table 3. Manual palpation: intrarater reliability

<table>
<thead>
<tr>
<th>Site</th>
<th>( \kappa )</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral</td>
<td>0.59</td>
<td>0.17</td>
</tr>
<tr>
<td>Peroneal</td>
<td>0.55</td>
<td>0.15</td>
</tr>
<tr>
<td>Tibial</td>
<td>0.42</td>
<td>0.18</td>
</tr>
<tr>
<td>Sciatic</td>
<td>0.60</td>
<td>0.14</td>
</tr>
</tbody>
</table>

\( \kappa \), kappa; SE, standard error.

Table 4. Manual palpation: interrater reliability

<table>
<thead>
<tr>
<th>Site</th>
<th>( \kappa )</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral</td>
<td>0.30</td>
<td>0.13</td>
</tr>
<tr>
<td>Peroneal</td>
<td>0.49</td>
<td>0.15</td>
</tr>
<tr>
<td>Tibial</td>
<td>0.37</td>
<td>0.18</td>
</tr>
<tr>
<td>Sciatic</td>
<td>0.60</td>
<td>0.13</td>
</tr>
</tbody>
</table>

\( \kappa \), kappa; SE, standard error.

Preliminary Normative Values

Means (SD) for all test sites, males and females, and for left and right sides are shown in Tables 5 and 6. There were significant differences between left and right sides for PPT measures of the common peroneal and tibial nerves \((P = .007; P = .003)\), with no significant differences between sides for the femoral or sciatic nerve. Males demonstrated significantly higher PPTs than females for the femoral, sciatic, and tibial nerves \((P < .0001)\) and showed no difference for the common peroneal nerve on either the left or right side \((P = .09; P = .93)\).

Discussion

This is the first study to report on reliability of femoral nerve palpation, and results demonstrated good to excellent reliability for palpation via pressure algometry of the femoral nerve, in addition to the sciatic and common peroneal nerves, and moderate reliability for the tibial nerve. Manual palpation of nerve trunks demonstrated fair to moderate reliability for all measures.

For PPT measurements via pressure algometry, ICCs of the femoral, common peroneal, and sciatic nerves demonstrated good to excellent reliability \((ICC, 0.69-0.9)\) and moderate to good reliability for the tibial nerve \((ICC, 0.56-0.64)\); these ICCs were lower than those reported in previous investigations. Walsh and Hall and Walsh et al reported ICCs for lower limb nerve PPTs via pressure algometry, which ranged from 0.83 to 0.96, and Sterling et al reported ICCs of 0.92 to 0.97 in a study on upper limb nerve palpation. This discrepancy may be in part due to the experience of the 2 raters in the current study in palpating these anatomical landmarks and in the practice of pressure algometry. Stubhaug et al suggest that hand-held pressure algometry only works well in examiners with extensive training; however, this concept is disputed by other authors.

Fig 3. Bland-Altman plot: femoral nerve intrarater reliability. (Color version of figure is available online.)

Fig 4. Bland-Altman plot: femoral nerve interrater reliability. (Color version of figure is available online.)
Table 5. Pressure pain thresholds males vs females

<table>
<thead>
<tr>
<th>Site</th>
<th>Left, mean (SD)</th>
<th>Right, mean (SD)</th>
<th>Mean difference</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral</td>
<td>167 (54)</td>
<td>165 (46)</td>
<td>2</td>
<td>(−8, 11)</td>
<td>.73</td>
</tr>
<tr>
<td>Peroneal</td>
<td>132 (37)</td>
<td>120 (39)</td>
<td>12</td>
<td>(4, 21)</td>
<td>.003</td>
</tr>
<tr>
<td>Tibial</td>
<td>130 (35)</td>
<td>141 (42)</td>
<td>−11</td>
<td>(−19, −3)</td>
<td>.007</td>
</tr>
<tr>
<td>Sciatic</td>
<td>250 (78)</td>
<td>238 (85)</td>
<td>12</td>
<td>(−3, 26)</td>
<td>.12</td>
</tr>
</tbody>
</table>

CI: confidence interval; L: left; R: right; SD: standard deviation.

Table 6. Pressure pain thresholds left vs right

<table>
<thead>
<tr>
<th>Site</th>
<th>Left, mean (SD)</th>
<th>Right, mean (SD)</th>
<th>Mean difference</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral</td>
<td>187 (58)</td>
<td>148 (42)</td>
<td>39</td>
<td>(16, 61)</td>
<td>.001</td>
</tr>
<tr>
<td>Peroneal</td>
<td>139 (36)</td>
<td>125 (36)</td>
<td>14</td>
<td>(−2, 31)</td>
<td>.07</td>
</tr>
<tr>
<td>Tibial</td>
<td>148 (29)</td>
<td>113 (32)</td>
<td>35</td>
<td>(22, 49)</td>
<td>0</td>
</tr>
<tr>
<td>Sciatic</td>
<td>290 (74)</td>
<td>212 (61)</td>
<td>77</td>
<td>(47, 108)</td>
<td>0</td>
</tr>
</tbody>
</table>

CI: confidence interval; L: left; R: right; SD: standard deviation.

The ICC should be considered along with the SEM to provide an estimate of measurement precision. The SEM scores for PPT measurements in this study ranged from 16 to 39 kPa, indicating that changes in PPTs must be more than 16 to 39 kPa before an examiner can be confident that a clinical change has occurred.

In the current study, sciatic nerve PPTs showed excellent reliability according to the ICC (0.75, 0.9) but was also found to have the lowest level of measurement precision (SEM, 27-39). Changes in sciatic nerve PPT scores of up to 27 to 39 kPa may be entirely due to measurement error, which needs to be considered by examiners when interpreting the clinical importance of a change in PPT scores. Lower precision of sciatic nerve palpation may be due to the deeper anatomical location of the nerve.

It is unclear as to why the tibial nerve ICCs showed lower reliability compared with interrater reliability (ICC, 0.82; SEM, 23). Despite this, both intrarater and interrater reliability Bland-Altman plots for the femoral nerve showed that there was no significant level of random error or systematic bias.

It was found that PPTs differed between individual nerve trunks of the lower limb. Of note, the sciatic nerve had the highest PPT mean values (233-256 kPa), followed by the femoral nerve (158-176 kPa). The lowest PPT mean values were shared by the common peroneal and tibial nerves (114-140 kPa). These findings were in keeping with previous reports. It is suggested that such variations in nerve PPTs are related to differences in the anatomical position and accessibility of nerve trunks.

Significant differences between left- and right-sided PPTs were found in the current study and are in contrast with previous reports. It is unclear whether differences observed in this study are inherent or secondary to measurement error. However, researchers attempted to reduce the potential for measurement error due to an order effect by randomizing the order of testing between sides. The finding that males had significantly higher PPTs than females was in keeping with the literature reporting differences in pain perception between men and women. Racine et al in a systematic review of the literature over 10 years on sex differences in pain perception reported that females demonstrate lower pressure pain measurements than males. In a meta-analysis of sex differences in the perception of noxious experimental stimuli, Riley et al reported that the largest effect sizes were for pressure pain and tolerance measures. Differences in pain perception between males and females may be influenced by many factors including gonadal hormones, genetics, and psychosocial factors.
Manual digital palpation of nerve trunks was found to have fair to moderate reliability ($\kappa = 0.30-0.60$), whereas palpation via pressure algometry was found to have moderate to excellent reliability (ICC, 0.56-0.90). These $\kappa$ scores differed from those in a previous investigation by Walsh et al., which demonstrated excellent reliability for manual palpation of lower limb nerves ($\kappa = 0.7-0.8$). However, these discrepancies may be partially explained by methodological differences between the 2 studies. Participants in the study by Walsh and Hall had low back–related leg pain, and in addition, examiners palpated both sides simultaneously and asked patients to compare sides; this method appears to assume normal responses in the unaffected side and does not take into account the possible presence of mechanosensitivity on the unaffected side due to secondary hyperalgesia and peripheral and central sensitization processes. Higher levels of intrarater ($\kappa = 0.83$) and lower levels of interrater reliability ($\kappa = 0.14$) of lower limb palpation-based neural tissue pain provocation tests in patient populations with low back and leg pain have also been found; findings that may also be due to differences in methodology and testing procedures. Of note, $\kappa$ scores from this study were consistent with those from a previous investigation of upper limb manual nerve palpation in another asymptomatic group ($\kappa = 0.29-0.69$), suggesting that this technique may have greater reliability in a clinical population; however, this requires further investigation.

**LIMITATIONS**

One limitation of this study was that the order of manual palpation techniques and pressure algometry was not randomized, which may have created an order effect; authors attempted to minimize this by randomizing the order of testing between sides and between raters. A 4-point rating scale (none, mild, moderate, severe) was used in this study for manual palpation based on previous study and a lack of published research in relation to palpation of the femoral nerve. However, very few subjects reported severe responses, and the scale was subsequently dichotomized in the reliability analysis. The use of a dichotomous scale recording responses as normal or abnormal from the outset would have simplified the study design. In addition, the limited experience of raters in this study in the practice of pressure algometry could have affected the level of measurement error in this study, although this concept has been disputed by other authors. Accurate palpation of nerve sites, particularly in relation to the sciatic nerve, which lies deep to other sensitive structures, is another limitation of the study. Raters attempted to ensure accuracy of palpation by carefully locating nerve sites in relation to standardized anatomical landmarks.

**CONCLUSION**

In this study, nerve palpation using pressure algometry showed a good to excellent level of reliability for the femoral, sciatic, and common peroneal nerves. Further investigation of the reliability of nerve palpation of the femoral nerve, in addition to the tibial nerve, is warranted given the limited empirical study to date, which has shown some discrepancies between findings. In particular, future studies could investigate the reliability of manual nerve palpation in both normal and clinical populations by means of separate right- and left-sided palpation. Further study of manual palpation is pertinent, as the technique requires no equipment, making it accessible to clinicians.

**Practical Applications**

- In this study, nerve palpation of the femoral, common peroneal, and sciatic nerves using pressure algometry demonstrated good to excellent reliability, and the tibial nerve PPTs showed moderate to good reliability.
- Manual palpation measurements demonstrated fair to moderate reliability.
- Males demonstrated significantly higher PPTs than females for the femoral, sciatic, and tibial nerves, and differences in PPTs were present between right and left sides.

**ACKNOWLEDGMENT**

The authors thank Dr Ricardo Segurado for help with statistical analysis and students from UCD who participated in this study.

**FUNDING SOURCES AND POTENTIAL CONFLICTS OF INTEREST**

This project was funded by an Irish Research Council Embark Postgraduate Scholarship. No conflicts of interest were reported for this study.

**CONTRIBUTORSHIP INFORMATION**

Concept development (provided idea for the research): CD, CF.
Design (planned the methods to generate the results): CF, CD, LD.
Supervision (provided oversight, responsible for organization and implementation, writing of the manuscript): CD, KS.
Data collection/processing (responsible for experiments, patient management, organization, or reporting data): CF, LD.
Analysis/interpretation (responsible for statistical analysis, evaluation, and presentation of the results): CF, CD, LD.

Literature search (performed the literature search): CF, LD, CD.

Writing (responsible for writing a substantive part of the manuscript): CF, CD.

Critical review (revised manuscript for intellectual content, this does not relate to spelling and grammar checking): CD, KS.

REFERENCES

26. Drouin J. How should we determine a measurement is appropriate for clinical practice. Athl Ther Today 2003;8:2-4.
Appendix F.2 Journal Article: Pain sensitization in people with knee osteoarthritis: A systematic review and meta-analysis

Osteoarthritis and Cartilage 2015

Osteoarthritis and Cartilage

Review
Pain sensitization in people with knee osteoarthritis: a systematic review and meta-analysis

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A R T I C L E   I N F O

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Keywords:
Sensitization
Central hyperexcitability
Pain processing
Knee osteoarthritis

S U M M A R Y

Objective: Emerging evidence suggests that pain sensitization plays an important role in pain associated with knee osteoarthritis (OA). This systematic review and meta-analysis examined the evidence for pain sensitization in people with knee OA and the relationship between pain sensitization and symptom severity.

Methods: A search of electronic databases and reference lists was carried out. All full text observational studies published between 2000 and 2014 with the aim of investigating pain sensitization in humans with knee OA using quantitative sensory testing (QST) measures of hyperalgesia and central hyperexcitability were eligible for inclusion. Meta-analysis of data was carried out using a random effects model, which included results comparing knee OA participants to controls, and results comparing high symptom severity to low symptom severity.

Results: Fifteen studies were identified following screening and quality appraisal. For the meta-analysis, pressure pain threshold (PPT) and heat pain threshold (HPT) means and standard deviations were pooled using random effects models. The point estimate was large for differences in PPTs between knee OA participants and controls (−0.51; confidence interval (CI): −1.1 to 0.1), and moderate for PPT differences between knee OA participants with high symptom severity vs those with low symptom severity (0.51; CI: −0.33 to 0.22). A small point estimate was found for differences in HPTs between knee OA participants and controls (−0.42; CI: −0.87 to 0.02).

Conclusion: Evidence from this systematic review and meta-analysis suggests that pain sensitization is present in people with knee OA and may be associated with knee OA symptom severity.

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Introduction

Osteoarthritis (OA) of the knee is traditionally considered a progressive disorder of articular cartilage in the knee joint. Pain presentations associated with knee OA vary considerably and often do not correlate with the severity of joint changes observed radiographically. However, emerging evidence suggests that alterations in nociceptive processing within the peripheral and/or central nervous system may be an important factor in accounting for such variations in clinical presentations of pain associated with knee OA. A number of recent studies have investigated the presence of altered pain processing in knee OA but the precise mechanisms underlying pain sensitization in OA remain elusive. Both peripheral and central neurophysiological mechanisms contribute to the pain of OA. Pain may result from nociceptors of the deep somatic tissue local to the knee becoming sensitized during inflammation (peripheral sensitization) and/or pathological neural signals from the joint causing central nervous system changes (central sensitization). A greater understanding of, and ability to clinically identify, pain mechanisms in knee OA could be integral to the designation and development of appropriate treatment interventions aimed at optimizing pain relief.

There is currently no gold standard measure with which to assess for and identify the presence of pain sensitization in humans. A number of different measures have been used to assess pain sensitization in people with knee OA. A commonly used method of assessment is quantitative sensory testing (QST), which...
involves the assessment of sensitivity to noxious or innocuous stimuli using standardized mechanical, thermal and/or electrical test modalities. Studies have also employed tests of central pain augmentation processes believed to be involved in pain sensitization such as temporal summation (TS), conditioned pain modulation (CPM) and the flexor withdrawal response (FWR). Methods of assessing these mechanisms are described below. A recent systematic literature review considered evidence for the presence of sensitization in people with OA of the hip, knee, first carpometacarpal joint and lower limb, and reported that the majority of the literature suggests that the central nervous system becomes hypersensitized in people with OA pain, while another systematic review presented a meta-analysis of pressure pain threshold (PPT) data in people with OA compared to healthy controls and reported that people with OA had lower PPTs at affected and remote anatomical test sites, suggesting pain sensitization. No study to date has provided a meta-analysis of the evidence for pain sensitization specifically in people with OA of the knee. Therefore, to advance and expand upon the work of previous reviews, the aim of the current study was to conduct a meta-analytic review of the evidence for pain sensitization as measured by QST in people with knee OA specifically — with the secondary aim of meta-analytically investigating the presence of pain sensitization in people with knee OA who have high symptom severity vs those with low symptom severity.

**Methods**

**Search strategy**

The study is reported in accordance with the PRISMA guidelines for the reporting of systematic reviews. Systematic searches of the following databases were conducted in June 2014: PubMed 1950–2014, Web of Science 1970–2014, Medline 1948–2014, EMBASE 1980–2014, CINAHL Plus 1937–2014 and The Cochrane Library. Each database was searched using key word combinations. Three groups of keywords were compiled and combined (Fig. 1). Search terms relating to pain sensitization, features of pain sensitization and knee OA were included for identification of relevant articles. Titles were screened by CF and abstracts of potentially relevant articles were reviewed independently by two researchers (CF and CD). Full text articles of relevant abstracts were retrieved for further review by CF and CD. The two researchers then met to discuss which articles were suitable for inclusion and exclusion. Citations were imported into Endnote.

**Inclusion/exclusion criteria**

The main aim of potentially relevant studies had to be the investigation of pain sensitization using QST measures of hyperalgesia and central hyperexcitability in adult human participants, diagnosed with knee OA via the American College of Rheumatology classification, radiographic evidence or people on a waiting list for total knee replacement (TKR). Papers had to be full text observational studies published in the English language in peer-reviewed academic journals, between 2000 and June 2014. A time limit was implemented in order to identify recent evidence. The exclusion criteria ruled out studies in which QST was not the primary testing method, experimental studies i.e., where an intervention was being evaluated, studies that did not assess measures of pain processing, review papers, and studies that included non-knee OA participants in the analysis. A flow diagram of study selection is detailed in Fig. 2.

**Data extraction**

Data extraction and analysis was carried out according to QST measures of pain sensitization utilized — only measures relating to pain processing were extracted and analysed. These included QST measures of hyperalgesia i.e., pressure hyperalgesia, thermal hyperalgesia, and hyperalgesia to punctate and electrical stimuli, as well as QST measures of central hyperexcitability i.e., TS, CPM and FWR. For meta-analysis of data, means and standard deviations were sourced from the original papers when available, or by contacting the authors. Data that could not be retrieved was interpreted from graphs using digital ruler software (Pascal Free Ruler Version 1.7b5). Studies were classified by study design (case—control, cross sectional or cohort) for the purpose of quality appraisal.

**Quality appraisal**

The methodological quality of case—control and cohort studies was assessed by two independent reviewers using the Newcastle Ottawa Quality Assessment Scale (NOS). The NOS is an appraisal tool for assessing the quality of non-randomized studies. The NOS is validated and has been recommended by the Cochrane Non-Randomized Studies Methods Working Group. The scale uses a star rating system to judge quality based on three aspects of the study: selection of groups, comparability, and ascertainment of the outcomes of interest. A maximum of nine stars can be awarded. Studies scoring ≥7/9 are considered good quality; those scoring ≥5/9 are fair quality and studies scoring 0–2/9 are poor quality. For cross-sectional studies, quality appraisal was carried out using the relevant criteria of the NOS checklist for cohort studies, as has previously been reported by Meeus et al. For the purpose of this review, 3/3 was considered a good quality cross sectional study, 2/3 was fair and 1/3 was considered poor quality. Studies scoring less than 40% on methodological appraisal were excluded from the review i.e., studies with ≤4/9 stars and studies with <2/3 stars.

**Data analysis**

The analysis was undertaken using Review Manager Software Package RevMan 5.1 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). Meta-analysis of data comparing knee OA participants to healthy controls was performed. In addition, meta-analysis was carried out on data comparing knee OA participants vs non-knee OA participants.
Fig. 2. PRISMA flow chart.
with high symptom severity to those with low symptom severity. Point estimates on the left side of the forest plots indicated increased features of pain sensitization in knee OA participants and were labelled ‘Sensitized’, while point estimates on the right side represented the opposite situation and were labelled ‘Non-sensitized’. Data which could not be pooled were summarized in narrative format. For continuous data where different scales were utilized for the assessment of the same outcome e.g., PPTs, the standardized mean differences (SMD) with 95% confidence intervals (CIs) were calculated. For continuous data where assessments were made on the same scale e.g., heat pain thresholds (HPTs), the mean differences (MDs) with 95% CI were calculated.

Meta-analyses were performed using a random effects model for analyses and pooled point estimate and 95% CIs were calculated with tests of heterogeneity. A funnel plot was conducted for visual inspection of publication bias in the primary meta-analysis (Fig. 6). Point estimates of 0.20 were considered ‘small’, 0.50 was ‘medium’ and 0.80 was considered ‘large’.

### Table 1: People with Knee OA vs Controls

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>People with Knee OA</th>
<th>Controls</th>
<th>Std. Mean Difference</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wykle 2013</td>
<td>187</td>
<td>130</td>
<td>51</td>
<td>417.3</td>
<td>192</td>
</tr>
<tr>
<td>Wykle 2011</td>
<td>209.5</td>
<td>132.89</td>
<td>107</td>
<td>417.22</td>
<td>191.61</td>
</tr>
<tr>
<td>Lee 2011</td>
<td>511.5</td>
<td>221.1</td>
<td>26</td>
<td>732.3</td>
<td>397.3</td>
</tr>
<tr>
<td>King 2013 Low</td>
<td>334.9</td>
<td>153.22</td>
<td>113</td>
<td>368.6</td>
<td>163.61</td>
</tr>
<tr>
<td>King 2013 High</td>
<td>273.1</td>
<td>168.71</td>
<td>96</td>
<td>368.6</td>
<td>163.61</td>
</tr>
<tr>
<td>Kavchak 2012</td>
<td>172.1</td>
<td>161.2</td>
<td>16</td>
<td>315.3</td>
<td>161.2</td>
</tr>
<tr>
<td>Imamura 2008</td>
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<td>215.73</td>
<td>44</td>
<td>1,098.34</td>
<td>311.21</td>
</tr>
<tr>
<td>Graven-Nielsen 2012</td>
<td>221</td>
<td>90</td>
<td>48</td>
<td>350</td>
<td>55</td>
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<tr>
<td>Arendt-Nielsen 2010 Low</td>
<td>351</td>
<td>299</td>
<td>24</td>
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<td>250</td>
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<tr>
<td>Arendt-Nielsen 2010 High</td>
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<td>230</td>
<td>24</td>
<td>542</td>
<td>250</td>
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<td>Subtotal (95% CI)</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>454</td>
<td>49.6%</td>
<td>0.97 [-1.38, -0.56]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Test for overall effect:** $Z = 4.86 (P < 0.00001)

**Heterogeneity:** $Tau^2 = 0.37; Chi^2 = 75.79, df = 9 (P < 0.00001); I^2 = 88$

### Table 2: Study or Subgroup vs Controls

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wykle 2011</td>
<td>219</td>
<td>164</td>
<td>51</td>
<td></td>
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<tr>
<td>Wykle 2011</td>
<td>227.83</td>
<td>149.5</td>
<td>107</td>
<td>372.6</td>
<td>193.5</td>
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<td>Lee 2011</td>
<td>260.7</td>
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<td>26</td>
<td>405.1</td>
<td>159.44</td>
</tr>
<tr>
<td>King 2013 Low</td>
<td>255.3</td>
<td>162.44</td>
<td>133</td>
<td>310.7</td>
<td>172.31</td>
</tr>
<tr>
<td>King 2013 High</td>
<td>218.6</td>
<td>178.46</td>
<td>96</td>
<td>310.7</td>
<td>172.31</td>
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<tr>
<td>Kavchak 2012</td>
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<td>124.2</td>
<td>165</td>
<td>272.3</td>
<td>118.4</td>
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<tr>
<td>Imamura 2008</td>
<td>240.1</td>
<td>149.15</td>
<td>44</td>
<td>490.33</td>
<td>152.54</td>
</tr>
<tr>
<td>Graven-Nielsen 2012</td>
<td>240</td>
<td>111</td>
<td>48</td>
<td>373</td>
<td>83</td>
</tr>
<tr>
<td>Arendt-Nielsen 2010 Low</td>
<td>369</td>
<td>162</td>
<td>24</td>
<td>361</td>
<td>142</td>
</tr>
<tr>
<td>Arendt-Nielsen 2010 High</td>
<td>294</td>
<td>167</td>
<td>24</td>
<td>361</td>
<td>142</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Weight</td>
<td>IV, Random, 95% CI</td>
</tr>
<tr>
<td></td>
<td>454</td>
<td>50.4%</td>
<td>0.74 [-0.95, -0.49]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Test for overall effect:** $Z = 3.74 (P < 0.00001)

**Heterogeneity:** $Tau^2 = 0.11; Chi^2 = 29.36, df = 9 (P = 0.0006); I^2 = 69$

**Test for subgroup differences:** $Chi^2 = 0.92, df = 1 (P = 0.34); I^2 = 0$

### Fig. 3: Results from meta-analysis of PPTs in knee OA participants vs controls

Note: data from Arendt-Nielsen & Graven-Nielsen are interpreted from graphed results.

### Fig. 4: Results from meta-analysis of PPTs in knee OA participants with high vs low symptom severity

Note: data from Arendt-Nielsen are interpreted from graphed results.
affected by radiographic change. Remote was defined as a site that was anatomically distant from the primary area of pain. When QST was measured at several remote sites, the furthest site from the knee was chosen (see Figs. 3–5).

Results

Search strategy

The study selection process is presented in Fig. 2. The screening process was carried out by two reviewers. Disagreement between authors was resolved by review of the full paper and further discussion. Fifteen studies were included in the final review (Table 1).

Study characteristics

Seven case–control studies, three cohort studies and five cross sectional studies were included in the review.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>People with Knee OA</th>
<th>Controls</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2.1 Local</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>King 2013 High</td>
<td>41.6</td>
<td>4.5</td>
<td>96</td>
<td>42.2</td>
</tr>
<tr>
<td>King 2013 Low</td>
<td>42.1</td>
<td>2.98</td>
<td>113</td>
<td>42.2</td>
</tr>
<tr>
<td>Wylde 2011</td>
<td>44.07</td>
<td>3.75</td>
<td>107</td>
<td>43.2</td>
</tr>
<tr>
<td>Wylde 2013</td>
<td>43.77</td>
<td>3.91</td>
<td>51</td>
<td>43.2</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>367</td>
<td>314</td>
<td>48.2%</td>
<td>0.04 [-0.58, 0.66]</td>
</tr>
</tbody>
</table>
| Heterogeneity: $\tau^2 = 0.11$, $\chi^2 = 4.13$, df = 3 ($p = 0.25$); $I^2 = 27%$ Test for overall effect: $Z = 0.12$ ($p = 0.90$)

1.2.2 Remote

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>People with Knee OA</th>
<th>Controls</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>King 2013 High</td>
<td>41.4</td>
<td>3.25</td>
<td>96</td>
<td>42.7</td>
</tr>
<tr>
<td>King 2013 Low</td>
<td>42.1</td>
<td>2.98</td>
<td>113</td>
<td>42.7</td>
</tr>
<tr>
<td>Wylde 2011</td>
<td>43.7</td>
<td>3.5</td>
<td>26</td>
<td>44.7</td>
</tr>
<tr>
<td>Wylde 2013</td>
<td>45.5</td>
<td>4.08</td>
<td>51</td>
<td>43.5</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>393</td>
<td>347</td>
<td>51.8%</td>
<td>-0.86 [-1.36, -0.36]</td>
</tr>
</tbody>
</table>
| Heterogeneity: $\tau^2 = 0.00$, $\chi^2 = 1.70$, df = 4 ($p = 0.79$); $I^2 = 0%$ Test for overall effect: $Z = 3.39$ ($p = 0.0007$)

Total (95% CI)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>People with Knee OA</th>
<th>Controls</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2.2 Remote</td>
<td></td>
<td>661</td>
<td>100.00</td>
<td>-0.42 [-0.87, 0.02]</td>
</tr>
</tbody>
</table>
| Heterogeneity: $\tau^2 = 0.13$, $\chi^2 = 11.35$, df = 8 ($p = 0.18$); $I^2 = 30%$ Test for overall effect: $Z = 1.88$ ($p = 0.06$)

Test for subgroup differences: $\chi^2 = 4.95$, df = 1 ($p = 0.03$), $I^2 = 79.8%$

Methodological quality

Quality assessment was carried out by two researchers independently. There was an initial 86% agreement between researchers. Any disagreements were resolved by further review of papers until a consensus was reached. Six of the case–control cohort studies were awarded 5/9 stars (fair quality), while four case–control/cohort studies were awarded 4/9 stars (poor–fair quality). Two cross-sectional studies were awarded 3/3 stars (good quality) and three were awarded 2/3 stars (fair quality). All studies exceeded the 40% threshold for inclusion in the review. Methodological quality was compromised most commonly due to insufficiencies in the representativeness of the knee OA group and appropriate selection of controls (Tables II and III).

Evidence for pain sensitization

Results are presented under headings according to the measures of pain sensitization employed. Meta-analyses of pressure hyperalgesia and heat hyperalgesia are reported below. Results that could not be pooled are summarized in narrative format. Table 1 outlines the characteristics of included studies.

1 Pressure hyperalgesia

Eleven studies evaluated the presence of hyperalgesia in people with knee OA using measures of PPT. Eight studies compared PPTs in knee OA participants to healthy controls using handheld pressure algometry and were included in the meta-analysis. From a total of 1003 participants: from whom one local and one remote PPT were included (total assessments $n = 2006$), the point estimate for differences in PPTs between knee OA participants and controls was $-0.86$ ($-1.09$ to $-0.62$), indicating greater pressure pain sensitivity in people with knee OA ($p < 0.001$). A high level of heterogeneity was present ($I^2 = 82%$, $p < 0.001$). The
<table>
<thead>
<tr>
<th>Article</th>
<th>Participants</th>
<th>Hyperalgesia measures (hyperalgesia to pressure, thermal, punctate and electrical stimulation)</th>
<th>Measures of central hyperexcitability (CPM, TS, FWR)</th>
<th>Results summary</th>
</tr>
</thead>
</table>
| Arendt-nielson, 2010 | A. 24 moderate/severe (VAS=6) knee OA participants (50% female) Mean age: 63.6  
B. 24 mild/moderate (VAS < 6) knee OA participants (50% female) Mean age: 61.5 | 1. PPTs using pressure algometry on eight sites in periarticular region, TA & extensor carpi radialis longus bilaterally | 1. TS of pressure pain using repeated stimuli from computer controlled pressure algometer  
2. CPM provocation with cuff compression on arm. PPTs at the knee measured during and 5 min after test. | Group A PPTs were greater than control PPTs. Group A & B TS was higher than control TS. Group A & B CPM was greater than control CPM. |
| Courtney, 2009  | A. 20 knee OA participants Mean age: 61 Mean pain duration: 12.5 yrs B. 20 controls Mean age: 60 (60% female) Diagnosis: >2 Kellgren–Lawrence scale | No hyperalgesia measure used | 1. Flexor withdrawal response using electrotactile stimulation at medial arch of foot | Significantly reduced FWR threshold in OA affected limb vs control group. |
| Finan, 2012     | 113 participants with knee OA (66.7% female) Four subgroups:  
A. low pain/low knee OA grade = 24  
B. high pain/high knee OA grade = 32  
C. low pain/high knee OA grade = 27  
D. high pain/low knee OA grade = 30 Mean pain duration: 6.53 yrs Diagnosis: ACR classification, >1 Kellgren–Lawrence scale, pain >2/10 on NRS >4 days/week | 1. PPTs (handheld algometry) at upper trapezius bilaterally & quadriceps insertion on index knee | 1. TS assessed by repeated punctate stimulation at dorsal aspect middle finger & patella of index knee  
2. TS assessed by VAS response to repeated heat pulses (51°C) to dorsal forearm  
3. CPM provocation by cold pressor test. PPTs measured at trapezius before & after test. | Significantly heightened pain sensitivity in the high pain/low knee OA grade group, while the low pain/high knee OA grade group was less pain-sensitive. |
| Graven-nielson, 2012 | A. 48 knee OA patients (75% female) Mean age: 65 Mean pain duration: 80 months (20 of these underwent TKR) B. 21 age and sex matched controls Mean age: 60 Diagnosis: radiographic | 1. PPTs (handheld pressure algometry) at seven sites in periarticular region, lower leg & forearms bilaterally  
2. PPT (Cuff pressure algometry) at lower leg | 1. CPM was provoked by cuff compression of arm with ischemic arm exercise. PPTs at two knee sites & lower leg cuff algometry was carried out during the test | Significantly reduced PPTs in knee, lower leg and forearm muscle in OA patients compared to controls. Dysfunctional CPM present in OA participants. Normalization of PPTs and CPM post TKR. |
| Imamura, 2008   | A. 62 female knee OA patients Mean age: 71.5 Mean pain duration: 99.8 months B. 22 healthy controls Mean age: 68.95 Diagnosis: ACR classification, 2–4 on Kellgren–Lawrence scale, VAS ≤ 4 | 1. PPTs with handheld algometry for:  
Subcutaneous hyperalgesia on dermatome L1–52, Myotomal hyperalgesia on nine lower limb muscles; Sclerotomal hyperalgesia on supraspinous ligaments L1–52, patellar tendon, pes anserinus bursae bilaterally | No measure of central hyperexcitability used | Significantly reduced PPTs at subcutaneous dermatomes (P < 0.001), myotomal structures (P < 0.001) & sclerotomal structures compared to controls. |
| Kavchak, 2012   | A. 16 knee OA patients (81.25% female) Mean age: 52 Mean pain duration: 4:09 yrs B. 16 healthy controls Mean age: 51 Diagnosis: by orthopaedic physician, Kellgren-Lawrence scale ≥ 2 | 1. PPTs using handheld algometry at MFL & lower leg unilaterally | No measure of central hyperexcitability used | Significantly reduced PPTs at MFL. in knee OA participants |
King, 2013
A. 113 with low symptom severity (73% female)
  Mean pain duration: 24.7 months
B. 96 with high symptom severity (67% female)
  Mean pain duration: 57.8 months
C. 107 healthy controls (66.7% female)
  Diagnosis: ACR classification, including self reported knee pain

Lee, 2011
A. 26 knee OA participants (76.9% female)
  Mean age: 64
  Diagnosis: radiographic
  Mean pain duration: not reported

B. 24 controls
  Mean age: 68
  Diagnosis: documented in medical record
  Mean pain duration: 8.5yrs

C. 107 healthy controls (66.7% female)
  Mean age: 57.7
  Diagnosis: ACR classification
  Mean pain duration: 57.8 months

Skou, 2013a
A. 20 with pain (70% female)
  Mean age: 68
  Mean pain duration: 167 months
  Diagnosis: end stage knee OA patients who underwent TKR & revision TKR

B. 20 without pain (40% female)
  Mean age: 65.7
  Mean pain duration: 64.3 months

Lundblad, 2008
A. 69 knee OA participants for TKR (51% female)
  Mean age: 68
  Mean pain duration: 8.5yrs
  Diagnosis: on TKR waiting list

Neogi, 2013
2126 participants with/at risk of knee OA (61% female)
  Mean age: 68
  Diagnosis: on TKR waiting list

Skou, 2013b
17 knee OA participants (24% female)
  Mean age: 65.1
  Mean pain duration: 115.1 months
  Diagnosis: radiological & symptomatic knee OA

Skou, 2013c
73 knee OA/revision TKR participants
  A. 26 knee OA participants with high local PPTs (38% female)
  Mean age: 64
  Mean pain duration: 86.6 months

PPTs at lower leg and forearm using pressure algometry unilaterally
  1. TS at most sensitive site & lower leg
  2. CPM was provoked by cuff compression of arm. PPT sites assessed before, & 5 min after.
  1. TS using computer-controlled pressure algometry at most knee & lower leg

Significantly reduced PPTs in knee OA participants compared to controls.
Significantly reduced PPTs in high symptom severity group compared to low symptom severity group.
Greater facilitation of TS in high symptom severity group compared to low symptom severity group.
No significant difference for HPT between groups.

Significantly reduced PPTs locally & remotely in knee OA group compared to controls.
Significantly higher heat pain ratings in knee OA group compared to controls.
Non-significant trend for lower HPTs in knee OA group vs controls.
No significant difference in cold pain ratings between knee OA group & controls.

No measure of central hyperexcitability used

Significantly reduced pain threshold remotely at the hand compared to controls.

PPT and TS were significantly associated with pain severity.
Knee OA duration and radiographic severity were not associated with PPT or TS.

Significantly decreased cuff PPTs at the lower leg in the group with pain post revision TKR compared to the group without pain post revision TKR.
Dysfunctional CPM and significantly greater facilitation of TS were present in the group with pain post revision TKR compared to the group without pain post revision TKR.

PPTs at the lower leg and TS accounted for 55% of the variance in perceived maximal pain intensity in people with knee OA.

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Table I (continued)

<table>
<thead>
<tr>
<th>Article</th>
<th>Participants</th>
<th>Hyperalgesia measures (hyperalgesia to pressure, thermal, punctate and electrical stimulation)</th>
<th>Measures of central hyperexcitability (CPM, TS, FWR)</th>
<th>Results summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wylde et al., 2011</td>
<td>A. 107 knee OA participants (48% female)</td>
<td>1. PPTs with handheld algometry at forearm &amp; medial knee unilaterally</td>
<td></td>
<td>Significantly lower median PPTs in knee OA participants compared to controls.</td>
</tr>
<tr>
<td></td>
<td>Mean age: 69</td>
<td>2. Warm/cold detection &amp; hot/cold PPTs using a QST analyser at forearm &amp; medial knee</td>
<td></td>
<td>32% had local pressure hyperalgesia &amp; 20% had distant pressure hyperalgesia.</td>
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<tr>
<td></td>
<td>Mean pain duration: 6 years</td>
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<td>No significant difference in HPTs between groups.</td>
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<td></td>
<td>B. 50 healthy controls</td>
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<tr>
<td></td>
<td>Diagnosis: on waiting list for TKR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wylde et al., 2013</td>
<td>A. 51 knee OA patients (57% female)</td>
<td>1. PPTs with handheld algometry at forearm &amp; medial knee unilaterally</td>
<td></td>
<td>Significantly lower PPTs in knee OA group at knee &amp; forearm compared to controls.</td>
</tr>
<tr>
<td></td>
<td>Mean age: 68</td>
<td>2. HPTs using a QST analyser at forearm &amp; medial knee</td>
<td></td>
<td>Statistically significant correlation between pre-op forearm PPTs and WOMAC pain 1 year post TKR.</td>
</tr>
<tr>
<td></td>
<td>Mean pain duration: not reported</td>
<td></td>
<td></td>
<td>No significant difference in HPTs between groups &amp; no significant correlation between HPTs and post op WOMAC pain.</td>
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<td>All underwent TKR</td>
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<td></td>
<td>B. 50 healthy controls (42% female)</td>
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<tr>
<td></td>
<td>Mean age: 69</td>
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<td></td>
<td>Diagnosis: on waiting list for TKR</td>
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</table>

TS = temporal summation; CPM = conditioned pain modulation; FWR = flexor withdrawal response; ACR = American College of Rheumatology; OA = osteoarthritis; CPM = conditioned pain modulation; PPT = pressure pain threshold; QST = quantitative sensory testing; HPT = heat pain threshold; MJL = medial joint line; TKR = total knee replacement; *Other Non-QST or non-pain processing outcome measures were not included in the analysis.
<table>
<thead>
<tr>
<th>Table II</th>
<th>Quality appraisal case—control studies</th>
</tr>
</thead>
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<tr>
<td>Case—control studies</td>
<td>S1: Adequate case definition</td>
</tr>
<tr>
<td>Arendt-Nielsen, 2010</td>
<td>*</td>
</tr>
<tr>
<td>Courtney, 2009</td>
<td>*</td>
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<tr>
<td>Imamura, 2008</td>
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<tr>
<td>Kavchak, 2012</td>
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<tr>
<td>Wylde, 2012</td>
<td>*</td>
</tr>
<tr>
<td>King, 2013</td>
<td>*</td>
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<tr>
<td>Lee, 2011</td>
<td>*</td>
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</table>

S = selection, C = comparability, E = exposure.

<table>
<thead>
<tr>
<th>Table III</th>
<th>Quality appraisal cohort/cross-sectional studies</th>
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<tr>
<td>Cohort/Cross sectional studies</td>
<td>S1: Representativeness of exposed cohort</td>
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<tr>
<td>Finan, 2012</td>
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<tr>
<td>Graven-Nielsen, 2012</td>
<td>*</td>
</tr>
<tr>
<td>Lundblad, 2008</td>
<td>*</td>
</tr>
<tr>
<td>Neogi, 2013</td>
<td>*</td>
</tr>
<tr>
<td>Skou, 2013a</td>
<td>*</td>
</tr>
<tr>
<td>Skou, 2013b</td>
<td>*</td>
</tr>
<tr>
<td>Skou, 2013c</td>
<td>*</td>
</tr>
<tr>
<td>Wylde, 2013</td>
<td>*</td>
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</tbody>
</table>

S = selection, C = comparability, O = outcome.

Cohort studies marked out of nine stars, cross-sectional studies marked out of three stars.
funnel plot indicated no significant publication bias (Fig. 6). A meta-analysis comparing Local PPTs between participants with knee OA and controls found that, from 1003 participants, the point difference was -0.97 (-1.38 to -0.56) indicating greater local pressure pain sensitivity in people with knee OA (P < 0.001). Again, a high level of heterogeneity was present (I² = 88%, P < 0.001). Similarly, a meta-analysis of Remote PPTs from 1003 participants demonstrated a point prevalence of -0.74 (-0.99 to -0.49) in favour of greater remote pressure pain sensitivity in the knee OA group (P < 0.001). Heterogeneity was high (I² = 89%, P < 0.01).

Results from three studies comparing knee OA participants with high symptom severity to knee OA participants with low symptom severity[29,30,31] were pooled in a meta-analysis. From a total of 316 participants: from whom one local and one remote PPT were included (total assessments n = 632), the point estimate was -0.51 (-0.73 to -0.30), indicating greater pressure pain sensitivity in the high symptom severity group (P < 0.001). Heterogeneity was low (I² = 36%, P = 0.16). A meta-analysis of Local PPTs in knee OA participants with high vs low symptom severity found that, from 316 participants, the point difference was -0.57 (-0.80 to -0.34), in favour of greater local pressure pain sensitivity in those with high symptom severity (P < 0.001). There was no evidence of heterogeneity found (I² = 0%, P < 0.58). Similarly, a meta-analysis of Remote PPTs from 316 participants demonstrated a point prevalence of -0.48 (-0.91 to -0.06) in favour of greater remote pressure pain sensitivity in the high symptom severity group (P < 0.05). Heterogeneity was moderate (I² = 62%, P = 0.07).

Three additional studies[18,19,20,21] including one large cross-sectional study of 2,126 people with knee OA,26 found a significant correlation between pressure pain sensitivity and symptom severity. Neogi et al.27 also reported that knee OA duration and radiographic severity were not significantly associated with pressure pain sensitivity (P > 0.05). Similarly, Skou et al.28 found no correlation between knee OA pain duration and pressure pain sensitivity (P = 0.17).

In relation to studies which measured PPTs pre and post TKR, Graven-Nielsen et al.23 showed that at 5–8 weeks post TKR, pressure pain sensitivity significantly reduced at all sites (P < 0.04). However, Skou et al.29 identified increased pressure pain sensitivity in people who had pain post revision-TKR compared to those who were pain-free post revision-TKR. A further study by Skou et al.30 demonstrated that people with high pressure pain sensitivity at the knee post revision-TKR had greater levels of widespread pressure pain sensitivity than people with knee OA (who had not undergone TKR). Wylde et al.31 investigated predictors of persistent pain post TKR and found that people with pressure pain sensitivity at the forearm (remote site) prior to TKR had significantly worse 1 year WOMAC pain scores than people with less pressure pain sensitivity at the forearm preoperatively (P = 0.031).

2 Thermal hyperalgesia

The presence of hyperalgesia to hot and cold stimuli has been found in people with chronic musculoskeletal pain[21,22,23,24]. The response of participants with knee OA to thermal stimuli was investigated in five studies[18,20,25,26,27]. Both Arendt-Nielsen et al.27 and King et al.28 demonstrated greater facilitation of TS in participants with knee OA with higher levels of symptom severity than in participants with less symptom severity and controls. Similarly, in the study by Finan et al., participants with high pain intensity/low OA severity had a greater TS response at a remote site (finger), than other knee OA participants; however, no significant differences were found between groups in TS measures taken locally at the knee. In a large
cross-sectional study of 2126 knee OA participants, Neogi et al.\textsuperscript{29} found a significant correlation between TS and pain severity ($P < 0.05$). Neogi et al.\textsuperscript{29} also found TS was not associated with radiographic changes or knee OA duration; conversely, Arendt-Nielsen et al.\textsuperscript{30} and Skou et al.\textsuperscript{31} both demonstrated a statistically significant correlation between TS and knee OA pain duration ($P < 0.05$).

In relation to TS pre and post TKR, Skou et al.\textsuperscript{32} showed that increased TS was present in participants with pain post revision-TKR compared to participants without pain post revision-TKR when measured remotely at the tibialis anterior (TA) muscle. A further report by Skou et al.\textsuperscript{33} indicated that TS was facilitated in people with and without high pressure pain sensitivity post revision-TKR compared to people with knee OA (who had not undergone TKR).

5 Flexor withdrawal response

The FWR is a measure of spinal excitability\textsuperscript{1} and has been used to demonstrate sensitization in other chronic pain conditions, including chronic whiplash and fibromyalgia\textsuperscript{34}. Courtney et al.\textsuperscript{35} found people with knee OA to have significantly lower FWR threshold than healthy controls ($P < .001$), with specific differences between the more affected limb in the knee OA participants ($P = .0005$).

6 Conditioned pain modulation

CPM is an endogenous pain inhibitory mechanism, which has been found to be impaired in many chronic pain populations\textsuperscript{36,37}. Assessment of CPM involves the evaluation of a painful test stimulus in the absence and presence of a second painful (conditioning) stimulus applied to a remote site\textsuperscript{38}.

Two studies demonstrated a dysfunctional CPM response in people with knee OA\textsuperscript{39,40}. Both Arendt-Nielsen et al.\textsuperscript{41} and Graven-Nielsen et al.\textsuperscript{42} showed dysfunctional CPM at local (knee) sites in a knee OA group compared to a non-knee OA group; however results differed in relation to remote sites. Graven-Nielsen et al.\textsuperscript{43} reported CPM dysfunction at the TA, while Arendt-Nielsen et al.\textsuperscript{41} found a normal CPM response at the TA, but an abnormal response at the forearm — both studies evoked CPM using cuff pressure and used handheld pressure algometry as the test stimulus. Using the cold pressor test as the conditioning stimulus with the test stimulus being handheld pressure algometry, Finan et al.\textsuperscript{44} found a normal CPM response at the trapezius muscle in four groups of knee OA participants with varying levels of symptom and disease severity. In relation to CPM pre and post TKR, Graven-Nielsen et al.\textsuperscript{43} found that a CPM stimulus caused a reduction in pressure sensitivity at the knee and a non-significant trend for reduced pressure sensitivity at the lower leg in knee OA participants after TKR. In contrast, Skou et al.\textsuperscript{45} found that participants who still had pain post revision-TKR demonstrated a dysfunctional CPM response, but a normal CPM response was found in those without pain post revision-TKR. In King et al.\textsuperscript{46}, CPM, provoked by the cold pressor test and tested using HPTs, showed no significant pain inhibiting effect on knee OA or control participants.

Discussion

Findings

Large SMDs in pressure pain sensitivity between people with knee OA and healthy controls is suggestive of nervous system sensitization in this population. This evidence is supported by additional findings of widespread hyperalgesia in response to pressure, punctate and electrical stimuli and by findings from a previous meta-analysis of PPTs\textsuperscript{47}. While local findings may indicate peripheral nervous system changes due to prolonged inflammatory processes, findings of hyperalgesia remote to the knee suggest the involvement of the central nervous system. These central changes are thought to be initiated by ongoing pathological neuronal signals from the joint\textsuperscript{1,48}. Spinal hyperexcitability was demonstrated in knee OA participants in five studies in this review, exhibited via increased TS\textsuperscript{49,50,51,52} and an exaggerated flexor withdrawal reflex\textsuperscript{53}. Results from this review also suggest that endogenous pain inhibitory mechanisms such as CPM are dysfunctional in people with knee OA\textsuperscript{54,55}. These findings of sensitization in people with knee OA indicate the potential for additional treatment targets in this cohort where treatment options are generally limited.

Results reported in this review are largely in keeping with sensitization characteristics that have been reported in other chronic pain conditions\textsuperscript{56,57}. As such, these conditions appear to share similar pain mechanisms; though, the degree to which this altered processing drives pain appears to vary between conditions and from person to person. While central mechanisms seem to be the driving force behind chronic pain conditions such as chronic whiplash\textsuperscript{58} and fibromyalgia\textsuperscript{59}, it appears to be a subgroup of people with knee OA whose pain is dominated by sensitization. For example, in Finan et al.\textsuperscript{60}, features of pain sensitization were especially apparent in participants with high pain intensity and low disease severity. Additionally, in contrast to findings from other chronic pain populations,\textsuperscript{61} results from the current review suggest that cold hyperalgesia may not be a dominant feature in knee OA pain, with three studies showing no difference in cold pain sensitivity between knee OA participants and controls\textsuperscript{62,63,64}. In relation to heat hyperalgesia, the meta-analysis indicated no significant difference in HPTs between people with knee OA and controls. Though, interestingly, when HPTs were sub-grouped into local and remote sites, people with knee OA were found to have significantly greater heat pain sensitivity at remote sites compared to controls, but not at local sites. It is possible that the lack of a significant difference locally between knee OA participants and controls may be linked to the presence of local hypoaesthesia, another sensory abnormality which has been found in people with knee OA\textsuperscript{65} and other pain conditions\textsuperscript{66,67}, and which could potentially influence sensitivity to heat pain. However, such analysis is beyond the scope of this review and warrants further investigation.

The comparison between knee OA participants and healthy controls, while invaluable for determining the presence of altered pain processing in people with knee OA, is limited in terms of deciphering the role that peripheral disease state and pain severity play in pain sensitization. Comparing knee OA participants to each other (e.g., high symptom severity vs low symptom severity; pre-surgery vs post-surgery etc.) provides additional information regarding factors that influence pain sensitization in people with knee OA. A relationship between symptom severity and pain sensitization, as measured by widespread hyperalgesia and TS, is suggested by results from this review. Meta-analysis of data demonstrated significantly greater widespread hyperalgesia in knee OA participants with high symptom severity compared to those with low symptom severity (SMD = $-0.51$). A cross-sectional study of 2126 people with knee OA supports this relationship, showing symptom severity to be significantly correlated with pressure pain sensitivity and TS. Three additional studies reported greater spinal hyperexcitability, via TS, in subjects with high symptom severity vs lower symptom severity\textsuperscript{68,69,70}. Furthermore, the large cross-sectional study by Neogi et al.\textsuperscript{29} reported that pain sensitization was not associated with radiographic severity\textsuperscript{71} and Finan et al.\textsuperscript{72} demonstrated significantly heightened pain sensitivity in a group with high pain severity and low disease severity.
These results indicate a possible link between symptom severity and sensitization, which is independent of radiographic disease severity, and lend support to the concept that peripheral pathology is not the sole driver of painful symptoms in knee OA. However, conflicting results in relation to sensitization and symptom severity have also been reported by studies that used alternative outcome measures. Courtney et al. found no significant relationship between FWR threshold, another measure of spinal hyperexcitability, and resting pain. Drivers of spinal hyperexcitability are not fully understood; it is possible that FWR and TS are mediated by slightly different mechanisms. Additionally, Finnan et al. found no significant difference in CPM levels between four groups of knee OA participants with varying symptom severity; though CPM was within normal limits in all participants in this study. Further investigation is recommended to establish this possible association.

While there is some evidence suggesting that sensitization is linked to pain severity in knee OA, it is yet to be established whether pain sensitivity in this cohort is principally maintained by peripheral pathology. Indeed, the degree of sensitization in knee OA may differ from chronic pain conditions such as fibromyalgia and chronic whip lash due to the presence of an identifiable peripheral pathology in knee OA. Graven-Nielsen et al. demonstrated normalization of PPTs and CPM post joint replacement, and normalization of pain sensitivity tests has also been reported post total hip replacement; these findings imply that central changes may be reversible after interventions directed towards peripheral pain generators. However, Skou et al. demonstrated pain sensitivity in people with ongoing pain post revision-TKR. The existence of a cohort whose pain is unresolved post repeated surgical intervention suggests that sensitization post surgery may be associated with maintained changes in central pain processing and may be independent of peripheral drivers of pain.

For individuals whose disorder is characterized by sensitization, there is the possibility that central hyperexcitability may be present before knee OA develops, as suggested by Neogi et al. in response to findings that duration and radiographic severity of knee OA were not associated with sensitization. The absence of a relationship between disease course and sensitization suggests that there are individuals who may be predisposed to sensitization, and that this trait is uncovered in the presence of nociceptive input from knee OA pathology. Phenotypic and genetic markers associated with chronic pain have been identified. Phenotypic markers such as pain catastrophizing and depression have been found to be significantly associated with QST measures of pain sensitization, while genetic markers most commonly linked to musculoskeletal pain are those relating to adrenergic and serotonergic pathways. A recent review of genetic studies points to certain genes that contribute to increased pain sensitivity and that are also associated with an increased risk of developing chronic pain conditions. Identification of how these markers contribute to pain perception would enable more specific and personalized therapies for individuals with knee OA in whom sensitization is a primary feature.

**Weakness in study quality** was most often related to representation of the knee OA population. Most knee OA participants were sampled from an outpatient hospital population, therefore the extent to which these findings may be generalized to primary care is not known.

**Implications for research and clinical practice**

Investigation is needed regarding criteria to identify people with knee OA in whom sensitization plays a dominant role. Studies, thus far, have used a wide variety of assessment methods, which is likely to be responsible for some of the variation in results reported in this review. Greater standardization of measures is recommended to allow for replication and verification of findings on this topic. Based on this review, suggested methods for measuring sensitization are PPT measurement at a local and remote site to test for widespread hyperalgesia; CPM using PPT as the test stimulus to assess a descending inhibitory pathway; and TS to assess spinal hyperexcitability. The FWR could also be used where feasible as an objective measure of spinal hyperexcitability alongside TS. It is also recommended that average pain over the past month and radiographic severity be recorded. Assessment of a phenotypic marker such as pain catastrophizing would also be beneficial in terms of recognizing people who may be sensitized. Further investigation into the co-occurrence of thermal hyperalgesia and hyperaesthesia is warranted. In addition, longitudinal research to investigate predictors of ongoing sensitization post TKR is needed. Identifying individuals at risk of persistent sensitization post TKR could allow for targeted pharmacological interventions aimed at reducing sensitization preoperatively. Research is also needed to assess the impact of therapies such as physiotherapy, exercise and psychological interventions on people with knee OA with features of sensitization.

**Conclusions**

Evidence from this systematic review and meta-analysis of widespread hyperalgesia, spinal hyperexcitability and CPM suggests the presence of a degree of sensitization in people with knee OA. However, the mechanisms by which sensitization may occur in people with knee OA are still unclear. Of note, heat hyperalgesia was shown to be present at remote but not local sites, while there was no evidence for the presence of cold hyperalgesia. In addition, sensitization, as measured via pressure pain sensitivity and TS, was shown to be significantly associated with symptom severity, while results suggested no association between sensitization and radiographic severity. Reversibility of sensitization post TKR suggests an association between peripheral pathology and central changes. However, sensitization has also been demonstrated in people post revision TKR, suggesting the presence of a subgroup of people with knee OA whose condition is characterized by central hyperexcitability. The lack of association between disease course and sensitization suggests that the hyperexcitability may, in some cases, exist the knee OA pathology. Future research is needed to identify people with knee OA in whom sensitization is a dominant feature; to establish predictors of ongoing sensitization post TKR and to assess the response of sensitized knee OA groups to commonly used conservative treatments.

**Author contributions**

Conception and design: CD, CF.

Systematic search: CF.

Study screening: CF, CD.

Quality appraisal: CF, CD.

Interpretation of data: CF, KS, NM, BF, CD.

**Limitations**

This review had a number of limitations. Heterogeneity was high for the meta-analysis of PPT data. The source of heterogeneity could not be explained by variations in testing site, as the I2 value was high in the subgroup analysis also. A random effects model was used to help account for this. Results could not be pooled for all pain sensitization measures, as assessment methods for many of the outcomes were not homogeneous. However, results that could not be pooled are summarized and discussed in narrative format and are considered in relation to pooled results. Studies in this review did not rank as high quality on the Newcastle Ottawa Scale.
Meta-analysis of data: CF, BF, CD.
Drafting of the article: CF.
Critical revision of the article for important intellectual content: CD, KS, NM, BF.

Funding
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Conflicts of interest
There are no conflicts of interest.

Appendix 1. Search string example

“pain sensitization” OR “pain sensitisation” OR “central sensitization” OR “central sensitation” OR “peripheral sensitization” OR “peripheral sensitation” OR “hyperalgesia” OR “central hypersensitivity” OR “central hyperexcitability” OR allodynia OR “pain processing” OR “pain modulation” OR “pain threshold” OR algometry OR “neuropathic pain” OR “neuropathic-like pain” OR “pain pathophysiology” OR somatosensory OR hyperalgesia [MeSH] OR central nervous system sensitization [MeSH].
AND
“knee osteoarthritis” OR “knee OA” OR “knee arthritis” OR “knee arthralgia” OR “ostearthritis of the knee” OR “OA of the knee” OR “arthrosis of the knee” OR “arthralgia of the knee” OR “degeneration of the knee” OR knee osteoarthritis [MeSH].

References


Appendix F.3 Oral Presentation: Exercise induced analgesia in people with osteoarthritis of the knee

**Exercise induced analgesia in people with osteoarthritis of the knee**

Caitríona Fingleton BSc (PhD Candidate), Keith Smart PhD, Catherine Doody PhD

---

**Background – What is EIA?**

- Decreased pain sensitivity due to exercise
- Suggested mechanisms: endogenous opioids & anti-inflammatory macrophages
- Normal response in healthy, pain-free people
- Sometimes dysfunctional in people with chronic pain

---

**Background – Evidence to Date**

**Dysfunctional EIA** has been found in:
- Fibromyalgia (Vierck et al 2001, Lannerston & Kosek 2010)
- Chronic fatigue syndrome (Meeus et al 2010, Meeus et al 2015)
- Whiplash-associated disorders (Van oostervijck et al 2012)

**Normal EIA** has been found in:
- Chronic low back pain (Hoffman et al 2005)
- Knee osteoarthritis (Kosek et al 2013, Burrows et al 2014)

---

**Study Aim**

To investigate EIA in:

- Knee OA participants who are **Sensitised** V **Non-sensitised**
- & pain-free age/sex matched controls

---

**Study Sample**

**Inclusion criteria**
- Diagnosis of knee OA via ACR criteria
- Pain >3/10 on the majority of days

**Power calculation**

A sample size of 51 in total (17 in each of the 3 groups) was found to be required to find a "small" eta-squared of 0.02

---

**Study Protocol**

![Study Protocol Diagram]
Pressure pain thresholds
- Measured at local, distal & remote sites
- Handheld pressure algometer

Conditioned Pain Modulation
- Conditioning stimulus = Cold pressor test: participants submerged a hand in water (temp 4 degrees) for 45 – 60 seconds
- Test stimulus = PPTs measured at local & remote site pre & post cold pressor test

Exercise Protocols
- Aerobic power index test
  - Workload increased by 25 watts every minute until submaximal heart rate was reached
  - Submaximal heart rate = 75% of age-predicted HR max
- Isometric knee extension test
  - Seated knee extension with ankle weight held for 5 minutes
  - Ankle weight was 10% of participants’ max voluntary contraction

Analysis
- ‘Sensitised’ & ‘Non sensitised’ were operationalised & analysed in 2 ways:
  1. Low PPTs (sensitised) VS High PPTs (non sensitised)
  2. Abnormal CPM (sensitised) VS Normal CPM (non sensitised)

Statistical test
- Repeated measures ANOVAs with 3 groups (sensitised, non sensitised & controls) & 2 time-points (pre & post exercise)
- ANOVAs using 2 groups (knee OA V controls, High V low sensitivity)
- Results reported for amalgamated PPTs, local PPT site & remote PPT site

Results
1a. Low PPT group VS High PPT group VS Controls - Aerobic Exercise

1b. Low PPT group VS High PPT group VS Controls - Isometric Exercise
2a. Abnormal CPM group VS Normal CPM group VS controls

**Aerobic Exercise**

<table>
<thead>
<tr>
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2b. Abnormal CPM group VS Normal CPM group VS controls

**Isometric Exercise**

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**Summary**

- Increased PPTs post cycling and isometric knee extension in knee OA participants with high & low PPTs & pain-free controls are suggestive of EIA in these groups.
- Increased PPTs post cycling and isometric knee extension in knee OA participants with normal CPM & pain-free controls are suggestive of EIA.
- A greater increase in PPTs post exercise was found in knee OA participants with normal CPM & in pain-free controls compared to knee OA participants with abnormal CPM.
- This may be suggestive of dysfunctional EIA in people with knee who have abnormal CPM.

**Limitations**

- All measures depended on the participants’ subjective reporting of pain.
- Repeated PPT testing may have caused sensitivity which could impact on results.
- Preliminary results.
- Control group is currently underpowered as testing is not yet complete.

**Discussion/Implications**

- Stationary cycling and isometric knee extension seem to be appropriate exercise for people with knee OA.
- The role of dysfunctional CPM as an indicator for poor response to exercise in people with knee OA merits further investigation.
- Research methods may impact significantly on results of a study.

**Thanks!**
Peripheral and Central Sensitization in People with Osteoarthritis of the Knee: A SYSTEMATIC REVIEW

Caitríona Fingleton¹, Keith Smart², Catherine Doody³
¹Dept. of Public Health, Physiotherapy and Population Science, Health Sciences Centre, University College Dublin, Belfield, Dublin 4, Ireland
²St. Vincent’s University Hospital, Elm Park, Dublin 4, Ireland
³School of Medicine, St. Vincent’s University Hospital, Dublin 4, Ireland

INTRODUCTION
Emerging evidence suggests that changes in central pain processing play an important role in pain associated with osteoarthritis (OA) of the knee. Sensitization of the nervous system appears to be important in the development of chronic pain in this condition. A greater understanding of the pain mechanisms which underlie knee OA is integral to the design & development of appropriate treatment interventions. There are many recent studies investigating the presence of altered pain processing in OA of the knee which have used a variety of different testing methods and have reported a wide variety of results.

STUDY AIMS
To systematically review the scientific literature addressing peripheral and central sensitisation in patients with OA of the knee.

METHODS
A search was carried out of the databases PubMed, Web of Science, Embase, Cinahl and Cochrane combining knee OA with pre-defined keywords relevant to pain sensitisation.

Inclusion Criteria
• Observational studies available in English carried out between 2000 & 2013
• The primary aim of the study was to investigate the presence of altered pain processing in osteoarthritis of the knee.
• Study participants were humans aged ≥18 years

Methodological Appraisal
Quality assessment of case-control & cohort studies was performed using the Newcastle-Ottawa Scale (NOS). For cross sectional studies, relevant checklist items from the NOS for cohort studies were utilised (Table 2 and 3).

RESULTS
Following screening of 537 titles, 66 abstracts were identified by 2 reviewers. Thirteen full text articles were included in the review. There were 5 case control studies, 6 cross-sectional studies and 2 cohort studies.

A variety of assessment methods were reported in the included studies (Table 1). Results are presented according to assessment methods.

CONCLUSIONS
• Current evidence of reported widespread hyperalgesia, patient self-reported neuropathic symptoms, in addition to hypoalgesia and indicators of hyperexcitability of the central nervous system is suggestive of peripheral & central sensitisation in people with OA of the knee.
• Future research is necessary to further understand the underlying pain mechanisms in OA of the knee, in addition to the clinical implications of assessment and treatment of pain sensitisation.

References
Appendix F.5. Poster Presentation: Pressure pain thresholds of the lower limb using pressure algometry and manual palpation 8th congress of EFIC, Italy 2013

Pressure Pain Threshold Measurements of the Lower Limb using Pressure Algometry & Manual Palpation: A Reliability Study

Caitriona Fingleton¹, Lucy Dempsey¹, Keith Smart², Catherine Doody³
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²St. Vincent’s University Hospital, Elm Park, Dublin 4, Ireland

INTRODUCTION

Neural tissue mechanosensitivity may be assessed by neural tissue provocation tests such as nerve palpation. Mechanical palpation using pressure algometry and manual palpation with the thumb have a high degree of clinical utility as they may be performed as part of a standard bedside examination.

Increased sensitivity to nerve palpation has been observed in a number of chronic pain conditions for example non-specific arm pain¹, low-back pain² and work-related upper limb pain³.

There are reports of the reliability of nerve palpation in relation to nerves of the upper limb⁴ but very limited data exists in relation to the reliability of lower limb nerve palpation. No studies have investigated the reliability of femoral nerve palpation, or reported normative PPT values.

STUDY AIMS

This aims of this study were:

➢ to investigate the reliability of femoral nerve palpation, using manual pressure and pressure algometry.
➢ to further test the reliability of mechanical and manual palpation of the sciatic, common peroneal and tibial nerves by means of alternate unilateral palpation.
➢ to provide normative PPT data for the femoral nerve.

METHODS

The Quality Appraisal Tool for Studies of Diagnostic Reliability (QAREL) guidelines was used in the design of this study.

Subjects

Subjects were 39 students from University College Dublin (UCD) with no chronic pain or neurological disorders and no previous history of lumbar spine or lower limb pathologies.

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c.doody@ucd.ie

Design

The femoral, common peroneal, tibial & sciatic nerves were palpated bilaterally in each subject using pressure algometry and manual digital palpation to establish pressure pain thresholds (PPTs). Measurements were taken twice by 1 rater (intra-rater reliability) and once by a 2nd rater (inter-rater reliability).

Data Analysis

Intraclass correlation coefficients (ICCs) were calculated to assess reliability of the mechanical PPT data and Kappa correlation coefficients were used to determine reliability of the manual nerve palpation data.

Normative Data

Paired t-tests and independent t-tests were used to identify whether there were significant differences between right and left sides and between males and females.

RESULTS

Reliability: Pressure Algometry

Intraclass correlation coefficients for the femoral, common peroneal, tibial and sciatic nerves were 0.69, 0.84, 0.64 and 0.9 for intra-rater reliability respectively and 0.82, 0.7, 0.56, and 0.75 for inter-rater reliability.

Reliability: Manual Palpation

Manual palpation measurements showed Kappa scores of 0.59, 0.55, 0.42 and 0.50 for intra-rater reliability of the femoral, common peroneal, tibial and sciatic nerves and Kappa scores of 0.30, 0.49, 0.37 and 0.54 respectively for inter-rater reliability.

These scores demonstrate good to excellent reliability for palpation of the femoral, common peroneal and sciatic nerves, and moderate to good reliability for tibial nerve palpation.

CONCLUSIONS

➢ Nerve palpation using pressure algometry showed good to excellent reliability for the femoral, sciatic and common peroneal nerves, and fair to moderate reliability for the tibial nerve.
➢ Reliability of manual palpation measurements was lower than that of pressure algometry, demonstrating fair to moderate reliability for all nerves.
➢ Further investigation of the reliability of nerve palpation of the femoral nerve, in addition to the tibial nerve, is warranted given the limited empirical data to date which has shown some discrepancies between findings.
➢ In particular, future studies could investigate the reliability of manual nerve palpation in both normal and clinical populations by means of separate right and left sided palpation.
➢ Further study of manual palpation is pertinent as the technique requires no equipment making it accessible to clinicians.

REFERENCES

Peripheral & Central Sensitization in Osteoarthritis of the Knee: A Systematic Review

Caitriona Fingleton1, Keith Smart2, Catherine Doody3

1Dept. of Public Health, Physiotherapy and Population Science, Health Sciences Centre, University College Dublin, Belfield, Dublin 4, Ireland
2St. Vincent’s University Hospital, Elm Park, Dublin 4, Ireland

INTRODUCTION
Emerging evidence suggests that changes in central pain processing plays an important role in pain associated with osteoarthritis (OA) of the knee.
There are many recent studies investigating the presence of altered pain processing in OA of the knee which have used a variety of different testing methods and have reported a wide range of results.

STUDY AIMS
To systematically review the scientific literature addressing peripheral and central sensitization in patients with OA of the knee.

METHODS
A search was carried out of the databases Pubmed, Web of Science, Embase, Cinahl and Cochrane.

Inclusion Criteria
➢ Observational studies available in English carried out between 2000 & 2013
➢ The primary aim of the study was to investigate the presence of altered pain processing in OA of the knee.

Methodological Appraisal
Quality assessment was performed using the Newcastle-Ottawa Scale (NOS).

RESULTS
Following screening of 537 titles, 66 abstracts were identified by 2 reviewers. 13 full text articles were included in the review.

Table 1: Mode of Assessment Reported in Studies

<table>
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<tr>
<th>Method Description</th>
<th>Self &amp; Reported</th>
<th>Observer &amp; Measured</th>
<th>Pain</th>
<th>Hyperexcitability</th>
<th>Flexor Withdrawal Reflex</th>
<th>Temporal Summation</th>
<th>CPM Efficacy</th>
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HYPERALGESIA/ALLODYnia
Pressure Pain Thresholds (PPTs)
➢ Knee OA patients reported lower PPTs at affected and unaffected sites than controls.2, 3, 4
➢ There was a significant correlation between pain intensity & PPTs at affected and unaffected sites.5
➢ Post TKR, PPTs significantly increased at all sites. However, PPTs remained decreased in patients who had pain post TKR.

Table 2: Methodological Appraisal: Case-control

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<th>Study</th>
<th>Self &amp; Reported</th>
<th>Observer &amp; Measured</th>
<th>Pain</th>
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CENTRAL HYPEREXCITABILITY
Temporal Summation
➢ Greater facilitation of temporal summation (TS) in knee OA patients than controls.1, 5
➢ Greater facilitation of TS in patients with high pain intensity/low OA severity than in patients with low pain intensity/high OA severity and/or high pain intensity/high OA severity.5
➢ Significant correlation between TS and greater duration of pain.1, 5

Conditioned Pain Modulation
➢ Decreased efficacy of CPM on PPTs of the knee.1, 2
➢ Efficacy of CPM was comparable to a normal population on PPTs of the upper body.1, 2 & results differed in relation to CPM effects on lower leg PPTs.1, 2

Flexor Withdrawal Reflex
➢ Knee OA patients showed significantly lower FWR threshold than healthy controls.12
➢ No significant relationships were reported between FWR threshold of the more impaired limb and resting pain.12

HYPOAESTHESIA
➢ Knee OA patients had an increased mechanical detection threshold at the knee6, 9 and forearm8 compared to controls.
➢ Knee OA patients had decreased vibration perception in the lower limb compared to controls.7- 15

NEUROPATHIC-LIKE PAIN
(Self Reported)
➢ Neuropathic pain scores were found in 19% of knee OA patients16 & in 15% of patients.17
➢ 55% of patients experienced moderate/serve shooting pain & 42% experienced moderate/severe hot-burning pain.

CONCLUSIONS
➢ Current evidence of widespread hyperalgesia, patient self-reported neuropathic symptoms, in addition to hypoesthesia & hyperexcitability of the central nervous system is suggestive of peripheral & central sensitization in people with OA of the knee.
➢ Future research is necessary to further understand the underlying pain mechanisms in OA of the knee, in addition to the clinical implications of assessment and treatment of pain sensitization.

Table 3: Methodological Appraisal: Cohort/ Cross-sectional

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<th>Study</th>
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References
3. Belfield, Dublin 4, Ireland
8. Belfield, Dublin 4, Ireland
13. Belfield, Dublin 4, Ireland
18. Belfield, Dublin 4, Ireland

Poster Presentation: Peripheral and central sensitization in osteoarthritis of the knee: A systematic review
ISCP conference, Ireland 2013

Appendix F.6

Table 3: Methodological Appraisal: Cohort/ Cross-sectional

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Reliability of manual palpation and pressure algometry of the lower limb nerves in asymptomatic subjects

Caitriona Fingleton¹, Lucy Dempsey², Keith Smart³, Catherine Doody⁴
¹Dept. of Public Health, Physiotherapy and Population Science, Health Sciences Centre, University College Dublin, Belfield, Dublin 4, Ireland
²St. Vincent’s University Hospital, Elm Park, Dublin 4, Ireland

INTRODUCTION

Neural tissue hypersensitivity may be assessed by nerve palpation – Manual palpation & pressure algometry have a high degree of clinical utility as they can be performed as part of a standard bedside examination.

Increased sensitivity to nerve palpation has been observed in a number of chronic pain conditions e.g. work-related upper limb pain1 & low-back pain2.

There are reports of nerve palpation reliability in nerves of the upper limb1, 3 but very limited data exists regarding the reliability of lower limb nerve palpation2, 4. No studies have investigated the reliability of femoral nerve palpation.

STUDY AIMS

This aims of this study were:

- to investigate the reliability of femoral nerve palpation, using manual pressure and pressure algometry
- to further test the reliability of palpat ing the sciatic, common peroneal and tibial nerves.

METHODS

The Quality Appraisal Tool for Studies of Diagnostic Reliability (QUAREL) guidelines was used in the design of this study5.

Subjects

Subjects were 39 students from University College Dublin (UCD) with no chronic pain or neurological disorders

Design

The femoral, common peroneal, tibial & sciatic nerves were palpated bilaterally in each subject using:

- pressure algometry to determine pressure-pain thresholds
- Manual palpation with the thumb (response rated on a 4-point scale)

Measurements were taken twice by 1 rater (intra-rater reliability) and once by a 2nd rater (inter-rater reliability).

Data Analysis

Reliability

Intraclass correlation coefficients (ICCs) were calculated to assess reliability of the pressure algometry PPT data, and Kappa correlation coefficients were used to determine reliability of the manual nerve palpation data.

RESULTS

Reliability: Manual Palpation

Femoral 0.55 (0.37)
Peroneal 0.55 (0.35)
Tibial 0.42 (0.18)
Sciatic 0.50 (0.12)

These scores demonstrate: 
- intra-rater reliability was moderate for all nerves
- inter-rater reliability was fair for the femoral nerve & tibial nerve and moderate for the common peroneal & sciatic nerve7.

Normative Data

Males demonstrated significantly higher PPTs than females for the femoral, sciatic and tibial nerves, and differences in PPTs were present between right and left sides.

CONCLUSIONS

- Nerve palpation using pressure algometry showed good to excellent reliability for femoral, peroneal & sciatic nerves, and moderate to good reliability for the tibial nerve
- Manual nerve palpation demonstrated fair to moderate reliability
- Further investigation regarding manual palpation of the lower limb nerves in a clinical population is warranted

REFERENCES


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NEURAL TISSUE MECHANOSENSITIVITY AND NERVOUS SYSTEM SENSITIZATION IN OSTEOARTHRITIS OF THE KNEE
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St. Vincent’s University Hospital, Elm Park, Dublin 4, Ireland

INTRODUCTION
Recent literature has demonstrated neuropathic-like symptoms in people with osteoarthritis of the knee (OA knee), suggestive of nervous system sensitization1,2.

Neural tissue mechanosensitivity has been associated with measures of neuropathic pain and nervous system sensitization in other musculoskeletal conditions for example non-specific arm pain1.

STUDY AIMS
The aims of this study were:
- To investigate the presence of neural tissue mechanosensitivity (NTM) in people with OA knee.
- To explore the possible associations between NTM and other symptoms of nervous system sensitization in people with OA knee.

METHODS

Subjects
Fifteen participants with OA knee (females = 53%, mean age = 67 ± 8) and 15 age and sex matched controls (females = 67%, mean age = 65 ± 8) were tested bilaterally for neural tissue mechanosensitivity (by means of nerve palpation and neurodynamic testing), and tested for nervous system sensitization (by means of quantitative sensory testing and self-reported neuropathic pain). 66% had bilateral OA symptoms. For participants with bilateral OA, the most symptomatic side was noted.

Design
Participants underwent bilateral nerve palpation of the sciatic, tibial, common peroneal and femoral nerves using pressure algometry and manual palpation, as well as neurodynamic testing (NDT) with the passive straight leg raise test (SLR) and the femoral slump test (FST).

Participants also completed PainDETECT and underwent bilateral quantitative sensory testing including evaluation of pressure pain thresholds (PPTs), and vibration perception threshold (VPT) at the knee and remote sites (remote sites included the lower leg and arm for PPT measures and the wrist and ankle for VPT).

Data Analysis
Mann–Whitney U tests were used to analyse differences between the OA knee group and control group. Spearman Rho tests were used to examine correlations between measures.

RESULTS

OA Knee Group Vs. Control Group
OA knee participants demonstrated significantly increased sensitivity to pressure algometry compared to controls, at the sciatic, tibial and peroneal nerves, but not at the femoral nerve (Fig 5), and demonstrated increased sensitivity to manual nerve palpation at all sites (Fig 6).

CONCLUSIONS

The results of this preliminary study suggest that:
- People with OA knee demonstrate increased neural tissue mechanosensitivity (NTM) compared to a normal healthy group, as measured by neural tissue palpation and NDT.
- Increased NTM is associated with heightened measures of nervous system sensitization as measured by decreased pressure pain thresholds and self-reported neuropathic-like pain, in addition to decreased vibration perception.
- Additional larger studies are required to further investigate the presence of NTM in people with OA knee, in addition to establishing the possible clinical implications of these abnormalities.

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References