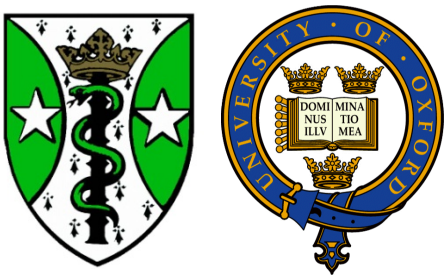
Pain Characterisation in Knee Osteoarthritis



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University of Oxford

A thesis submitted in partial fulfilment for the degree of

Doctor of Philosophy

Trinity Term 2015

Supervisors: Associate Professor M Kassim Javaid, Professor Andrew

Price and Professor Irene Tracey

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Abstract

Osteoarthritis (OA) is the most common form of arthritis in the world, and it has been estimated that about one tenth of the world's population, aged over 60, have symptoms that can be attributed to OA. Despite the size of the global impact of OA, there is a significant unmet need for effective treatments. Knee replacement surgery is commonly used in patients with moderate to severe knee OA, in order to reduce pain. However, 10-34% of patients report an unfavourable long-term outcome with persistent pain after surgery.

The neural mechanisms for the generation of pain in knee OA are not fully understood. Previous work has shown that around 20% of patients have features of neuropathic pain, and that the underlying mechanism for this may be through central sensitisation. This mechanism-based understanding of pain is important in order to aid targeted intervention, and it may be that this patient group is more likely to have an adverse outcome following surgery.

This thesis uses a combination of methods to investigate the neural mechanisms underlying pain experienced by patients with knee OA, across the full spectrum of disease severity. Quantitative sensory testing (QST) was initially used in a community-based cohort to show that pain sensitisation can be detected in early disease, and also contributes to the observed discordance between radiographic structural and symptomatic disease.

The clinical relevance of neuropathic pain was then investigated in patients with knee OA, who were awaiting knee replacement surgery. Prior to surgery patients with neuropathic pain had increased sensitivity to experimental pain, as well as higher symptom severity and psychological distress. Functional magnetic resonance imaging (fMRI) was then used to confirm that these features were also associated with central sensitisation in the form of increased descending facilitation as well as reduced descending inhibition prior to surgery. The presence of neuropathic pain prior to surgery was associated with statistically and clinically significantly worse outcome following surgery, compared to those with purely nociceptive pain in the absence of any significant structural differences between the two groups.

Taken together, this mechanism-based understanding of the pain provides an opportunity for targeted therapy prior to surgery, which may enhance outcome following surgery.

Acknowledgements

In many ways this is the most important section of all. I have learnt a lot about science and research, but the biggest learning point has been the power of teamwork, in all walks of life.

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Tables

Figures

Abbreviations

ANOVA Analysis of Variance
BOLD Blood-Oxygen Level Dependent
CBT Cognitive Behavioural Therapy
CDT Cold detection threshold
CPT Cold Pain Threshold
CS Central Sensitisation
CNS Central Nervous System
COASt Clinical Outcomes in Arthroplasty Study
CPM Conditioned Pain Modulation
DPMS Descending Pain Modulatory System
EPIONE Evaluation of **P**eri-operative pain **I**n **O**steoarthritis of the k**NE**e
fMRI functional Magnetic Resonance Imaging
HAD Hospital Anxiety and Depression Scale
HPT Heat Pain Threshold
ICOAP Measure of Intermittent and Constant Osteoarthritis Pain
KL Kellgren and Lawrence
LOT-R Revised Life Orientation Test
mPD-Q Modified PainDETECT Questionnaire
MPT Mechanical Pain Threshold
NCF Nucleus Cuneiformis
NSAIDs Non-Steroidal Anti-inflammatory Drugs
OA Osteoarthritis
OKS Oxford Knee Score
PAG Peri-aqueductal grey
PCS Pain Catastrophising Scale
PDI Pain Disability Index
PD-Q PainDETECT Questionnaire
PPSP Persistent Post Surgical Pain
PPT Pressure Pain Threshold
PSQI Pittsburgh Sleep Quality Index
QST Quantitative Sensory Testing
rACC Rostral Anterior Cingulate Cortex
ROA Radiographic Osteoarthritis
ROI Region of Interest
RVM Rostral Ventromedial Medulla
SF-MPQ Short-form McGill Pain Questionnaire
STAI State-Trait Anxiety Inventory
STT Spinothalamic tract
TKR Total Knee Replacement
TS Temporal Summation
TSK Tampa Scale of Kinesophobia
UKR Unicompartment Knee Replacement
VAS Visual Analogue Score
WDT Warm Detection Threshold
WOMAC Western Ontario McMaster Universities Osteoarthritis Index

Publications arising from this work

Journal article

Soni, A., Batra, R. N., Gwilym, S. E., Spector, T. D., Hart, D. J., Arden, N. K., . . . Javaid, M. K. (2013). Neuropathic features of joint pain: a community-based study.

Arthritis Rheum, *65*(7), 1942-1949. doi:10.1002/art.37962

Conference abstracts

Soni, A., Mezue, M, Wanigasekera, V, Javaid, MK, Price, A, Tracey, I. Neuroimaging Evidence of Central Sensitization in Patients with Knee Osteoarthritis. *British Journal of Pain, April 2015; vol. 9, 2 suppl: pp. 5-75.*

Soni, A., Leyland K.M., Batra R.N., Gwilym S.E., Spector T.D., Hart D.J., Price A.J., Cooper C., Arden N.K., Tracey I., Javaid M.K.

Pragmatic Approach To Quantitative Sensory Testing In Knee Osteoarthritis: Measures Of Mechanical Pain Sensitivity Predict Concordant Pain And Structural Status.

Osteoarthritis and Cartilage, April 2014, Vol. 22, pp.S418

Soni, A., Gwilym S.E., Arden N.K., Cooper C., Tracey I., Price A.J., Javaid M.K.

Pre-Operative Experimental Thermal Sensitivity Predicts Oxford Knee Score 1-Year Post-Operatively: A Preliminary Study.

Osteoarthritis and Cartilage, April 2014, Vol. 22, pp.S414–S415

Soni, A., Batra, R. N., Arden, E. J., Hart, D., Spector, T. D., Arden, N. K., . . . Javaid, M. K. (2012). Prevalence And Predictors Of Knee Pain With Neuropathic Features In A Community Based Cohort.

Osteoarthritis and Cartilage, April 2012, Vol. 20 pp.S255-S256.

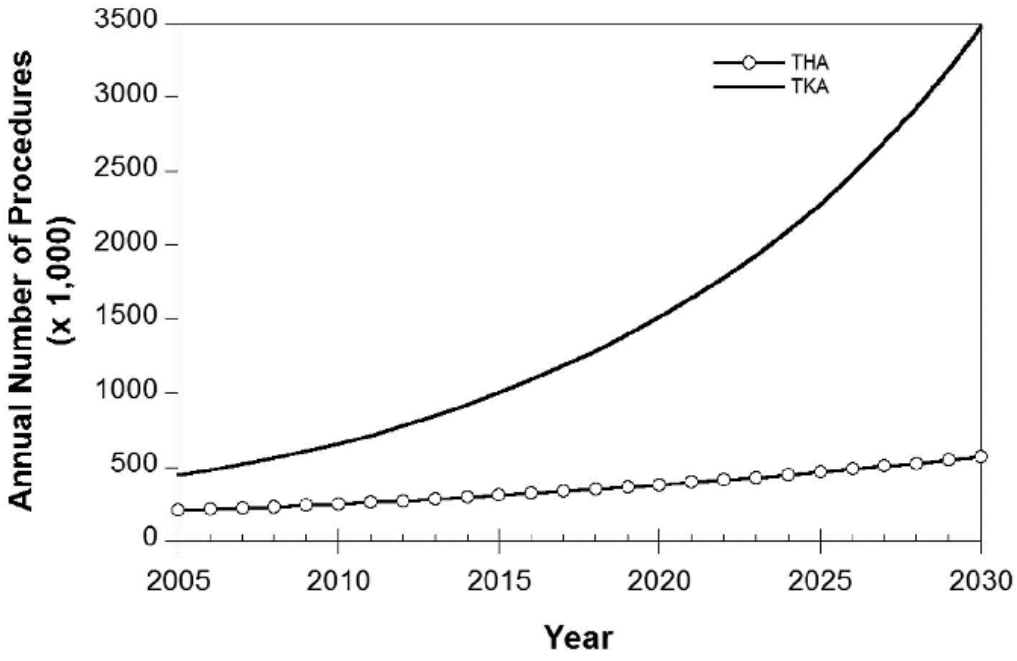
Contents

1 Introduction

1.1 The prevalence of osteoarthritis

Osteoarthritis (OA) is the most common cause of arthritis in the world, and typically presents with joint pain, stiffness and loss of function. It has been estimated that about one tenth of the world's population, aged over 60, have symptoms that can be attributed to OA (Cooper *et al*, 2013). OA of the knee, in particular, had a global estimated prevalence of symptomatic and radiographically confirmed disease of 3.8% (95% uncertainty interval (UI) 3.6% to 4.1%) in 2010, with a peak prevalence occurring around the age of 50 years (Cross *et al*, 2014). Symptomatic knee OA is increasing in prevalence over time, with obesity being a contributory factor (Nguyen *et al*, 2011). In combination with an ageing population, the number of people suffering from knee OA is predicted to rise. This is in turn associated with a projected exponential rise in demand for costly surgery. It is anticipated that the demand for primary total knee arthroplasty will grow by 673% over 25 years, equating to a total of 3.48 million procedures (95% prediction interval, 2.95 to 4.14 million) by 2030, in the United States alone, Figure 1.1 (Kurtz *et al*, 2007). More recent data from the UK shows that the projected demand for TKR increases by a further 7%, equating to an extra 8000 TKRs between 2015 and 2035, when the future estimated change in BMI distribution is taken account of, rather than using fixed estimated BMI distribution based on data from 2010 (Culliford *et al*, 2015).

Figure 1.1 Predicted rise in demand for arthroplasty



The projected number of primary total hip arthroplasty (THA) and total knee arthroplasty (TKA) procedures in the United States from 2005 to 2030 (Kurtz *et al*, 2007)

In reality, the actual size of the problem is likely to be significantly underestimated because many people do not consult medical care, as they perceive OA to be part of the normal ageing process with very little in the way of effective treatment options available to them (Sanders *et al*, 2004). As awareness amongst physicians and the general public increases, it is likely that consultation and in turn intervention rates will also increase.

1.2 The burden of osteoarthritis

OA is a global problem. In 2010, OA accounted for 2.2% (95% UI 1.7% to 2.9%) of total Years Lived with Disability, worldwide (Cross *et al*, 2014). Hip and knee OA specifically were ranked 11th highest contributor to global disability out of the 291 conditions being studied (Cross *et al*, 2014).

At an individual level, pain in large joints restricts people's mobility, particularly climbing stairs and walking (Felson *et al*, 2000), causes reduced participation (Wilkie *et al*, 2007) and also impacts on mood, functioning and well being (Bookwala *et al*, 2003; Jinks *et al*, 2007).

The impact on health services is considerable given that the incidence of a new General Practitioner consultation for knee pain in adults aged 50 and over is approximately 10% per year (Jordan *et al*, 2006). In 2014 69, 383 hip replacements and 70,281 knee replacements were registered on the national joint registry for England and Wales (National Joint Registry for England and Wales, 2014).

The impact of OA on society at large is also substantial. In the UK alone, 36 million working days were lost due to osteoarthritis, at an estimated cost of £3.2 billion in lost production over one year. At the same time, £43 million was spent on community services and £215 million was spent on social services for osteoarthritis. The total cost of OA in the UK has been estimated as being equivalent to 1% of gross

national product per year (National Collaborating Centre for Chronic Conditions, 2008).

Patients with OA are also at higher risk of death compared to the general population, and this is particularly pronounced for cardiovascular associated mortality (standardized mortality ratio 1.71, 95% CI 1.49 to 1.98) (Nuesch *et al*, 2011). Total joint replacement, in patients with moderate to severe hip or knee OA, has been shown to be cardio protective (Ravi *et al*, 2013). This makes the rationalization and timing of surgical intervention an even more crucial area to crystalize.

1.3 Current management strategies

There are a huge number of treatment options available for the management of OA, with several practice guidelines in place (Fernandes *et al*, 2013; McAlindon *et al*, 2014; National Institute for Health and Care Excellence, 2014; Nelson *et al*, 2013). The current options can be considered in terms of non-pharmacological, pharmacological and surgical treatments and are often utilized in a corresponding generic, step-wise fashion.

1.3.1 Non-pharmacological treatments

A holistic approach to the assessment and subsequent management is a core part of the current treatment strategy for OA (Fernandes *et al*, 2013; 2008; National Institute for Health and Care Excellence, 2014). Comprehensive assessment of patients and the impact of their condition on day to day life should be conducted,

including physical status, activities of daily living, participation, mood, health education needs, health beliefs and the motivation for self-management (Fernandes *et al*, 2013; 2008; National Institute for Health and Care Excellence, 2014). This information should then be used to derive an individualized treatment package, comprising a combination of treatment strategies rather than a single intervention (Fernandes *et al*, 2013).

The three main themes of non-pharmacological therapy in OA are: patient education and self-management; weight loss and exercise; and assistive devices, braces and taping. Most guidelines include moderate to strong recommendations for patient education and self-management, with regular contact to promote self-care being a common theme. In general the recommendations advise low impact land or water based aerobic exercise, particularly for hip and knee OA, although the benefit in hand OA is less clear. Many guidelines strongly recommend weight loss in those with hip or knee OA who are overweight. Some groups have also suggested a combination of manual therapy, which includes massage and joint mobilization/manipulation, and exercise but manual therapy alone has not been recommended. Whilst walking aids and other assistive devices to improve activities of daily living are generally recommended, there is a lack of consensus on the use of braces and taping (Nelson *et al*, 2013).

1.3.2 Pharmacological treatments

First-line pharmacological therapy comprises acetaminophen/paracetamol. Conservative dosing and treatment duration are recommended in view of recent evidence suggesting associated adverse effects including gastrointestinal adverse events and multi-organ failure, especially associated with prolonged use (McAlindon *et al*, 2014; Nelson *et al*, 2013).

Second-line therapy includes topical or oral Non-Steroidal Anti-inflammatory Drugs (NSAIDs), and topical capsaicin. The use of NSAIDs must be carefully balanced against the risk of cardiovascular, gastrointestinal and renal disease. Appropriate NSAID selection and use of proton pump inhibitors, combined with restricted does and treatment duration are compulsory for patient safety (McAlindon *et al*, 2014; Nelson *et al*, 2013).

Further pharmacological options include opioids such as tramadol, but the evidence suggests a small to moderate effect size only, with many patients withdrawing from treatment due to adverse events (McAlindon *et al*, 2014; Nelson *et al*, 2013). Glucosamine and chondroitin therapy have received much attention in the past but current guidelines have deemed these agents as inappropriate for structural disease modification and of uncertain benefit in symptom relief (McAlindon *et al*, 2014).

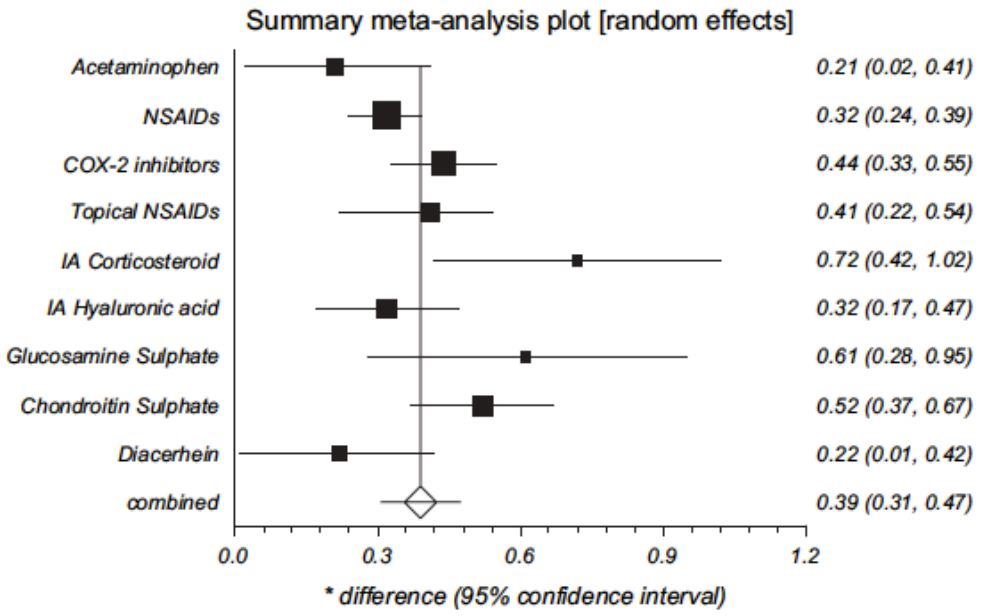
Intra-articular therapy is also an important component of the treatment armamentarium with corticosteroids being recommended for hip and knee OA

(McAlindon *et al*, 2014; Nelson *et al*, 2013). The guidance on the use of intra-articular corticosteroids in hand OA is conflicting (Manara *et al*, 2013; Zhang *et al*, 2007). The use of hyaluronic acid is controversial with conflicting evidence making it difficult for definitive recommendations to be made (McAlindon *et al*, 2014; Nelson *et al*, 2013).

1.3.3 Potential future pharmacological treatments

Despite the number of pharmacological agents available, the effect sizes for pain are moderate at best, Figure 1.2 (Zhang *et al*, 2007), and the high frequency of medication change amongst patients suggests a lack of long-term efficacy and tolerability of current therapies (Kingsbury *et al*, 2013). Targeted treatment strategies are currently being developed with preliminary evidence of success.

Figure 1.2 Efficacy of pharmacological treatments in osteoarthritis



Effect size for pain relief with pharmacological therapies (Zhang *et al*, 2007).

Treatments targeting inflammation are currently under investigation with preliminary evidence suggesting a positive effect of methotrexate in knee OA (Abou-Raya *et al*, 2014) and anti-TNF therapy in hand OA (Verbruggen *et al*, 2012).

Bone may also be a useful target in OA. There is some evidence that bisphosphonates can reduce pain severity in OA (Laslett *et al*, 2014), although this is not a consistent finding and the evidence for structural modification of disease is limited (Davis *et al*, 2013; Laslett *et al*, 2014). Although there is evidence that Strontium ranelate can reduce structural progression with a clinically meaningful effect on symptoms in knee OA, the use of this drug has recently been restricted due

to its cardiovascular risk profile (Bruyere *et al*, 2014; Reginster *et al*, 2013; Rossini *et al*, 2015).

Nerve growth factor, which is increased in the synovial fluid of patients with osteoarthritis, is a further potential target for the treatment of OA (Lane *et al*, 2010). Tanezumab, a humanized IgG2 monoclonal antibody directed against nerve growth factor, has been shown to reduce joint pain and improve function in patients with hip and knee OA (Lane *et al*; Spierings *et al*, 2013). The investigation of this treatment in OA was temporarily placed on hold, due to concerns regarding accelerated joint destruction and need for arthroplasty, and then peripheral nervous system effects, but further study of this target has now been sanctioned (Brown *et al*, 2013).

1.3.4 Surgical treatments

Patients with moderate to severe hip or knee OA, who are not gaining sufficient benefit from non-surgical measures, should be considered for joint replacement surgery (Nelson *et al*, 2013; Zhang *et al*, 2008). Traditionally, the success of joint arthroplasty has been judged based on measures of technical success, such as revision rates and the frequency of loosening around the prosthesis (Dieppe *et al*, 2011). The development of the Oxford Hip and Knee Scores, designed to measure the patients' perceptions of response to treatment, has led the way towards more emphasis being placed on patient reported outcome measures (Dawson *et al*, 1998;

Murray *et al*, 2007). This change in focus has revealed that around 20% of patients experience ongoing long-term pain after knee arthroplasty (Beswick *et al*, 2012).

The optimal timing of surgical intervention and identifying who should be considered for surgery is not easy to ascertain (Dieppe *et al*, 2011; Kennedy *et al*, 2003; Woolhead *et al*, 2002; Wylde *et al*, 2007). Significant variation in patterns of referral for and provision of surgery are currently seen. For example women are less likely to be recommended surgery than men (Dieppe *et al*, 2011; Fraenkel *et al*, 2014; Wright *et al*, 2011). The need for shared decision making, between patients and practitioners, in order to narrow this discord has been highlighted and strategies to facilitate this process are being developed (Marrin *et al*, 2014).

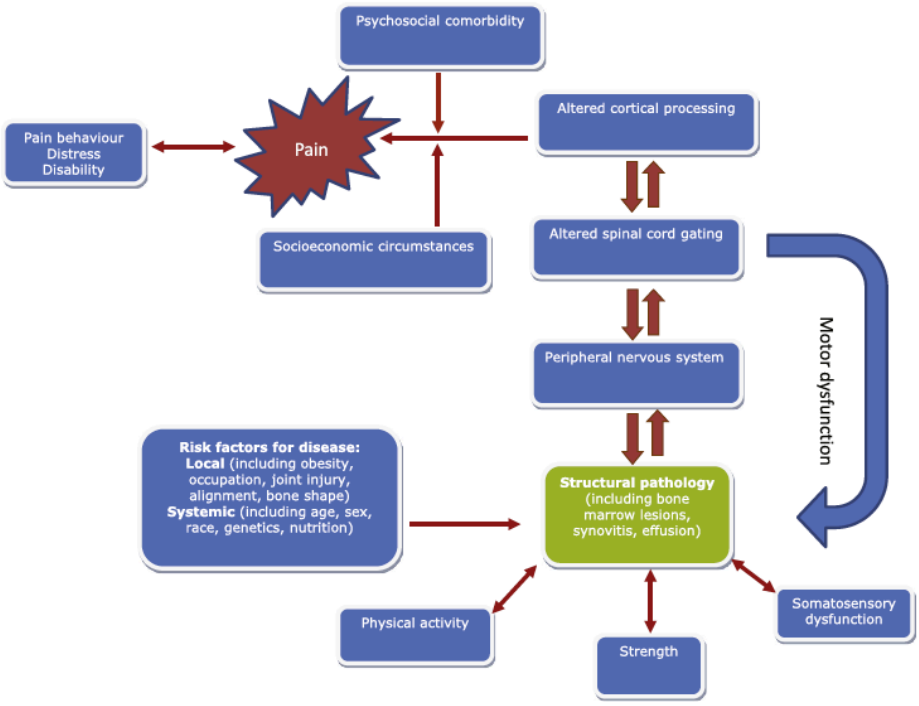
The risk factors for poor outcome remain unclear with numerous possible determinants (Dieppe *et al*, 2011). The most consistent factors in the literature to date are female gender, younger age and worse pre-operative pain severity (Singh *et al*, 2008; Singh *et al*, 2012; Singh *et al*, 2014). A recent systematic review and meta-analysis, which aimed to quantify the effect of any variables that are associated with persistent post-surgical pain after total knee arthroplasty (TKA), showed that pain catastrophising, mental health, preoperative knee pain, and pain at other sites were the strongest independent predictors of outcome, whereas age and gender were found to have small effects with only minimal clinical importance (Lewis *et al*, 2015). This highlights the importance of considering the multi-dimensional nature of pain experience and not just the technical details of surgical intervention.

1.4 The mechanisms for nociception to pain in osteoarthritis

Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage", according to the International Association for the Study of Pain (IASP) (Merskey *et al*, 1994). Nociception is defined as "the neural process of encoding noxious stimuli" (Merskey *et al*, 1994). This introduces the possibility for a theoretical disconnect between peripheral nociceptive inputs and the conscious experience of pain, one which is observed in the case of knee OA as discussed below.

The precise mechanisms of pain in OA are not fully understood and the sources of pain in OA have been the subject of frequent review in the literature (Bradley, 2004; Dieppe *et al*, 2005; Felson, 2005; Gwilym *et al*, 2008; Hunter *et al*, 2013; Kidd, 2012; Mease *et al*, 2011; Phillips *et al*, 2013). The concept that pain is likely to be multifactorial in nature and that it should be considered in the framework of a bio-psychosocial model is now widely accepted, including contribution from peripheral structural abnormalities within the joint at one end of the spectrum through to centrally mediated sensitivity and mood at the other, Figure 1.3.

Figure 1.3 Biopsychosocial model of pain in osteoarthritis



Biopsychosocial model depicting the relation of structural pathology to the experience of pain (Hunter *et al*, 2013).

The next section will consider the potential structural sources of noxious stimulation in knee OA, including the accepted discordance between symptoms and structural disease, and the subsequent process of signal transmission, perception and modulation of nociceptive stimuli within the nervous system.

1.4.1 Structural sources of pain in the joint

The articular cartilage, subchondral bone and the presence of synovitis or an effusion are currently considered to be the key structural sources of pain in knee OA (Hunter *et al*, 2013). Although articular cartilage is aneural and therefore unable to

directly generate pain, it is proposed that the destruction of cartilage releases factors which may result in synovitis or increased intraosseous pressure thereby generating pain via a range of secondary mechanisms (Hunter *et al*, 2013). Within the subchondral bone, bone marrow lesions are currently thought to be best associated with the incidence and severity of pain. Bone marrow lesions arise as a result of bone remodelling with histological features of fibrosis and microfractures. Although the literature is conflicting, it is felt that on balance that they are related to pain (Hunter *et al*, 2013). Synovitis and effusion are frequently present in OA and correlate with pain (Hunter *et al*, 2013). This is corroborated by the recommendation of the use of intra-articular corticosteroid injection for short-term pain reduction in the recent OARSI guidelines for the non-surgical management of knee OA (McAlindon *et al*, 2014).

1.4.2 Discordance between radiographic osteoarthritis and pain

Traditionally, a lot of emphasis has been placed on the radiographic features of OA. For example longer-term studies of the progression of OA have tended to focus on radiographic disease rather than the presence or severity clinical symptoms (Arden *et al*, 2006). Consistent with this is the fact that the presence of features of radiographic OA remains an important component of the decision making process in the context of patient care, even in the context of primary care (Bedson *et al*, 2003).

The discrepancy between the presence of radiographic OA and symptoms, particularly in the earlier stages of the disease, is now well recognized. A systematic review revealed that the proportion of people with knee pain found to also have

radiographic knee OA ranged from 15–76%, and in those with radiographic knee OA the proportion with concurrent pain ranged from 15–81% (Bedson *et al*, 2008). The authors proposed three possible explanations for the variation seen (Bedson *et al*, 2008). Firstly the detection of structural changes may be limited by the number and type of radiographic views used to assess the joint. This aspect has been further investigated by using more sensitive techniques such as MRI, which can detect abnormalities within other tissue structures including subchondral bone marrow lesions, meniscal damage, and the presence of synovitis and effusion (Hunter *et al*, 2013). The evidence so far does not convincingly support the use of MRI in routine clinical practice, and at present it is no better than radiographs in terms of discriminating between those with and without pain (Guermazi *et al*, 2012). The second factor described was the numerous different methods, which are used to define pain which in turn has a huge potential impact on the link seen with radiographic disease. Finally it was suggested that characteristics of the population being studied, including age, gender and ethnicity may impact the relationship between structural and symptomatic OA.

A further possibility is that factors affecting pain processing, beyond the diseased joint, may contribute to this discordance and its variation. For example, neural processing and the plasticity of pain sensitivity have also been investigated as potential explanations for the observed discordance between structural and symptomatic OA (Finan *et al*, 2012; McDougall *et al*, 2009). To date this work has suggested that central sensitisation (CS) may account for the high pain reports seen

in people without moderate to severe structural disease, and this will be discussed in more detail below (Finan *et al*, 2012).

1.4.3 Peripheral nociception

Nociceptors are peripheral sensory receptors, which detect noxious stimuli and transform this signal to electrical action potentials that are conducted to the central nervous system. Nociceptors have a relatively high threshold for activation and are often polymodal, i.e. respond to more than one stimulus type. There are two main types of nociceptors. C-fibre nociceptors are the smallest in diameter and un-myelinated with slow conduction velocities of less than $2ms^{-1}$. In contrast Aδ –fibre nociceptors are myelinated and so have faster conduction velocities of greater than $2ms^{-1}$.

1.4.4 Ascending pathways

Peripheral nociceptors synapse at the dorsal horn of the spinal cord with second order central neurons. Most second order neurons involved in pain processing are either wide dynamic range (WDR) neurons or nociceptive-specific (NS) neurons (Price *et al*, 2003). WDR neurons respond over a broad range of stimulus intensities, ranging from mild to severely painful stimuli. In contrast to NS neurons, they also receive inputs from non-nociceptive Aβ-fibres as well as nociceptive neurons (Price *et al*, 2003).

The nociceptive signal is then relayed to the thalamus, via the spinothalamic tract (STT), and the medulla and brainstem via the spinoreticular and spinomesencephalic

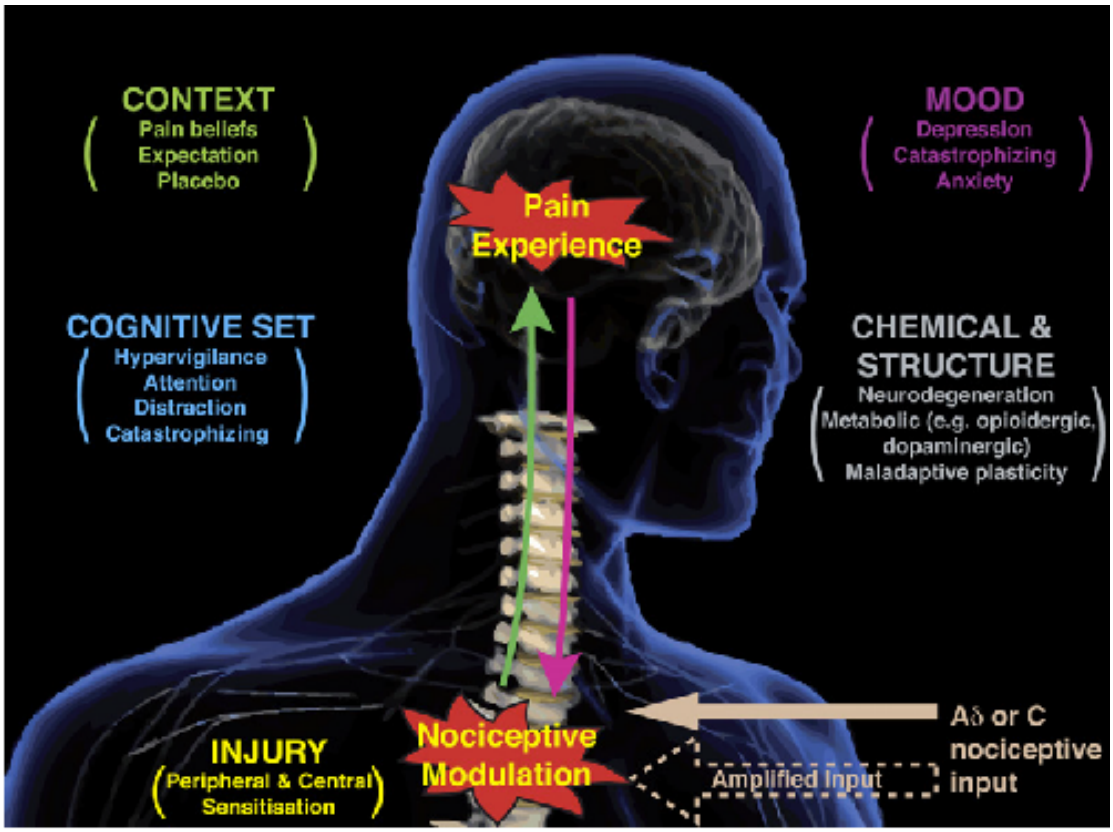
tracts respectively. These tracts enable the integration of nociceptive input with other processes involved in homeostasis, arousal and autonomic activity. They can also directly influence forebrain and spinal processing, therefore directly affecting the pain experience (Tracey *et al*, 2007).

1.4.5 Cortical representation of pain

Many areas of the cortex are activated during nociceptive processing, reflecting the multi-dimensional and complicated nature of pain perception. Melzack first described the theory of a pain "neuromatrix", which proposed the parallel processing of multiple inputs in order to generate the final output of pain (Melzack, 1999). The inputs were thought to be derived from not only nociceptive sensory inputs from the periphery, but also other sensory inputs contributing to the cognitive interpretation of the situation context, cognitive and emotional inputs from other parts of the brain, intrinsic inhibitory modulation present in all brain function, and the body's stress regulation systems, such as the endocrine, autoimmune, autonomic and opioid systems (Melzack, 1999). Three main dimensions of the pain experience were proposed: sensory-discriminative, affective-motivational, and evaluative-cognitive. The first neuroimaging study in humans confirmed that multiple discrete brain areas are indeed activated during painful stimulation, including the cingulate cortex, primary somatosensory cortex and secondary somatosensory cortex (Talbot *et al*, 1991). Subsequent neuroimaging work has shown that the areas of the brain which are most commonly activated during an acute painful experience are: primary and secondary somatosensory, insular, anterior cingulate, and prefrontal cortices and thalamus (Apkarian *et al*, 2005). The

need to consider the “neuromatrix” as a fluid and changing entity, depending on factors such as context, attention, and emotion, rather than a fixed anatomical structure has been highlighted, Figure 1.4 (Tracey *et al*, 2007). In particular there is increasing evidence for the contribution of the descending modulatory network, which either inhibits or facilitates nociceptive processing, mainly in the dorsal horn, in both healthy and diseased states (Denk *et al*, 2014; Tracey *et al*, 2007).

Figure 1.4 Schematic illustrating the main factors that influence nociceptive inputs to affect pain perception.

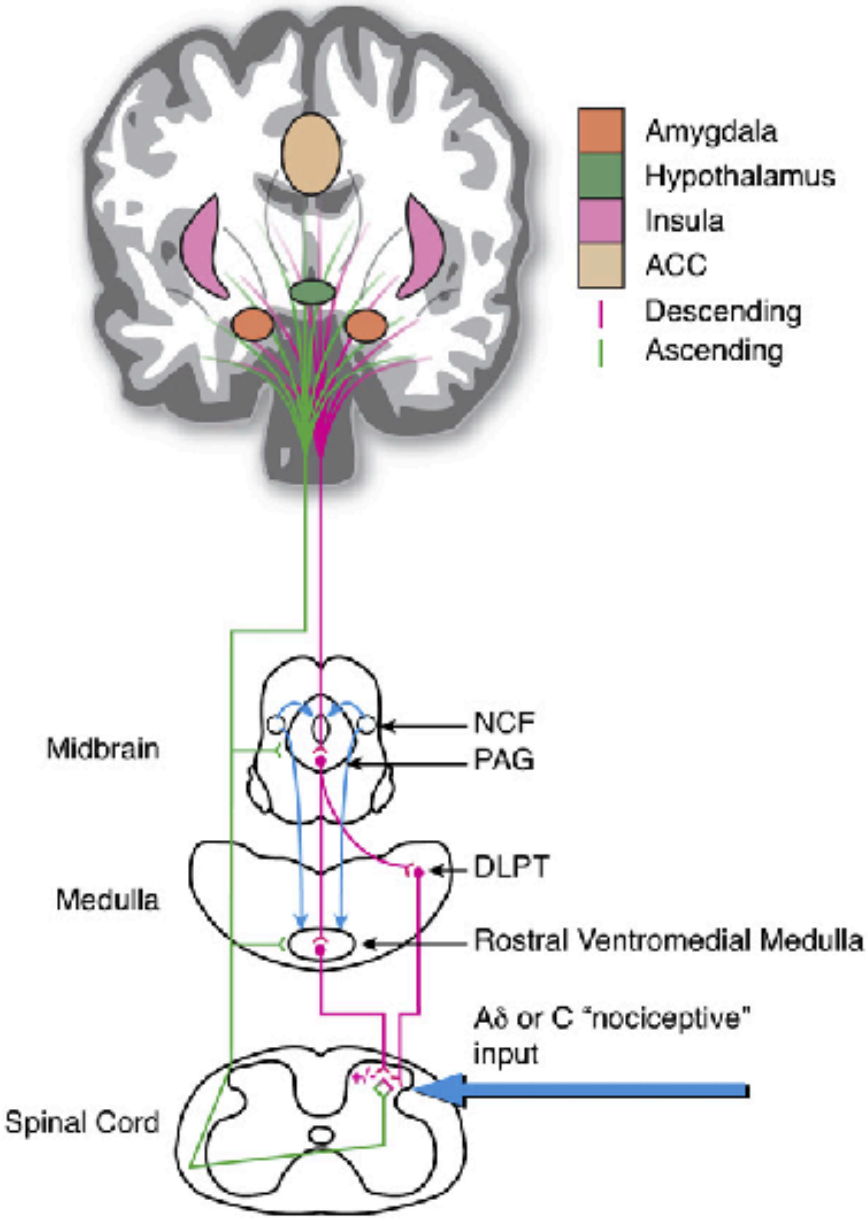


(Tracey *et al*, 2007)

1.4.6 Descending modulation of pain

The descending pain modulatory system (DPMS) is a network, which regulates nociceptive processing in the dorsal horn, Figure 1.5 (Tracey *et al*, 2007).

Figure 1.5 The descending pain modulatory system



NCF (nucleus cuneiformis); PAG (periaqueductal gray); DLPT (dorsolateral pontine tegmentum); ACC (anterior cingulated cortex); +/_ indicates both pro- and anti- nociceptive influences, respectively. (Reproduced with permisson, Tracey et al, 2007)

It is therefore responsible for controlling which signals enter the brain and the subsequent pain experience (Heinricher *et al*, 2009; Tracey *et al*, 2012).

The first evidence of descending modulation of pain comes from a study in rats, which showed that electrical stimulation of midbrain PAG resulted in an electrical analgesia which abolished responses to aversive stimulation (Reynolds, 1969). Within the brainstem, the other main structure involved in the DPMS is the rostral ventromedial medulla (RVM) (Basbaum *et al*, 1984; Gebhart, 2004; Heinricher *et al*, 2009; Ossipov *et al*, 2014). The RVM is considered to be the final common output for descending modulation, and this effect may either be inhibitory or facilitatory in nature (Gebhart, 2004). This bi-directional effect is explained by the fact that there is a population of cells, known as ON-cells, in the RVM which facilitate dorsal horn processing and a separate population of cells known as OFF-cells, which are inhibitory (Ossipov *et al*, 2010). It has been shown that descending facilitation in the RVM is important in the development of long-term neuropathic pain following peripheral nerve injury (Wang *et al*, 2013) whereas descending inhibition protects against neuropathic pain (De Felice *et al*, 2011).

The DPMS regulates spinal neurons via the monoamine neurotransmitters noradrenaline (NA) and 5-hydroxytryptamine (5HT). NA has an inhibitory effect, whereas 5HT can have a facilitatory effect by activating 5HT-2 or 5HT-3 receptors, or an inhibitory effect via 5HT-1 receptors (Tracey *et al*, 2012). Correspondingly, monoamine reuptake inhibitors are an important class of drug treatments used for

the management of neuropathic pain. Ideally, treatment choices should be tailored to the underlying predominant mechanism responsible for generating pain in an individual (Kwon *et al*, 2013). There is currently no gold-standard method for identifying the presence of abnormal DPMS function in patients, but preliminary data in patients with diabetic neuropathy suggest that it may be of predictive value (Yarnitsky *et al*, 2012). In this study, conditioned pain modulation (CPM), which measures DPMS function via diffuse noxious inhibitory control, was assessed prior to commencing treatment with duloxetine. Poor CPM at baseline predicted a better response to treatment with duloxetine, a selective serotonin reuptake inhibitor, which has an anti-nociceptive effect by improving descending inhibition.

Cortical and subcortical areas of the brain are also involved in the DPMS including the anterior cingulate cortex, amygdala, insula and hypothalamus (Denk *et al*, 2014; Tracey *et al*, 2007). The link between these higher order areas and the DPMS is likely to explain how other centrally mediated factors such as sleep, mood, and attention, are able to influence the experience of pain (Phillips *et al*, 2013; Tracey *et al*, 2012).

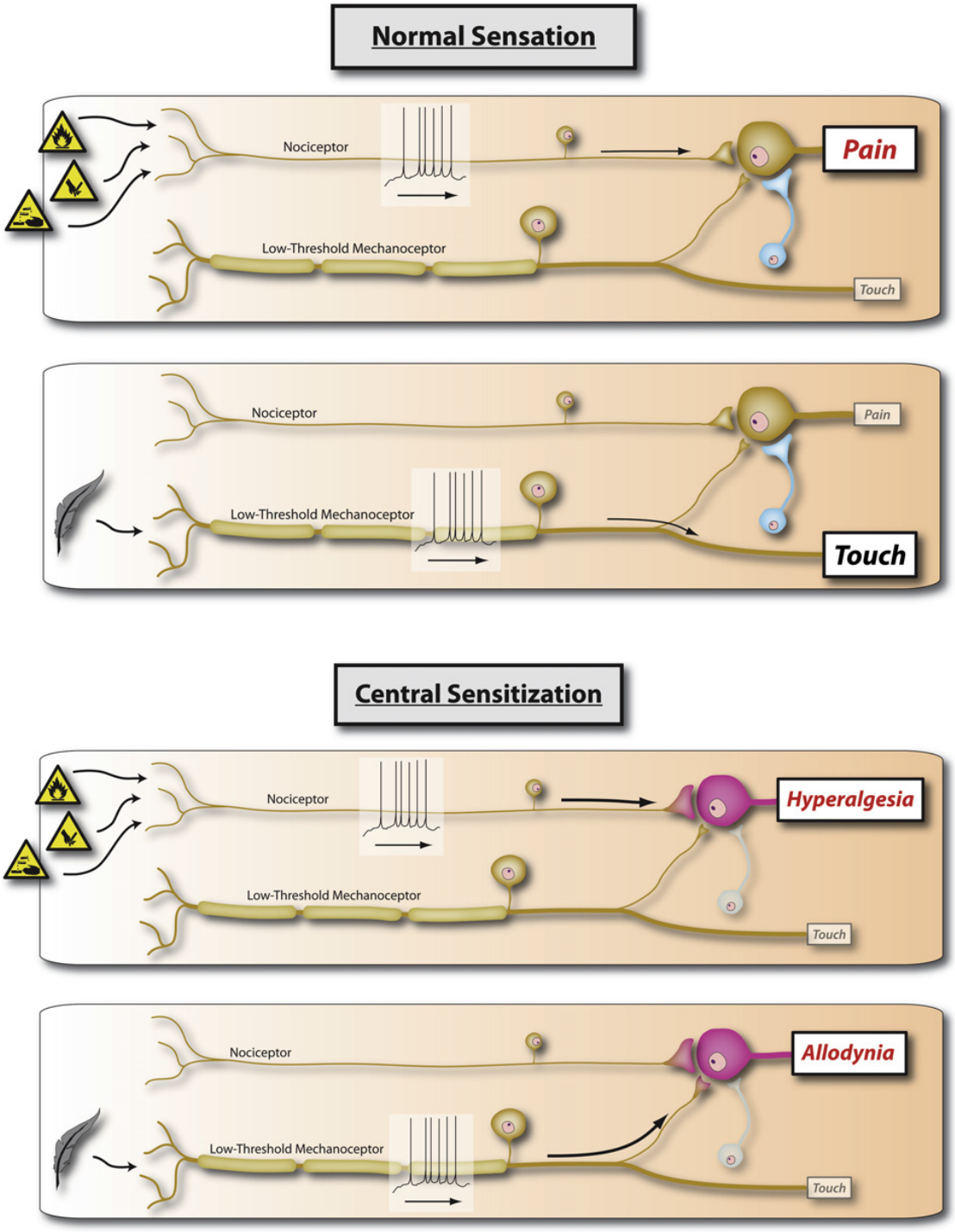
1.5 Central sensitisation and neuropathic pain in knee osteoarthritis

Central sensitisation (CS) was first described by Woolf in 1983 (Woolf, 1983) and is defined as “an amplification of neural signaling within the central nervous system (CNS) that elicits pain hypersensitivity” (Woolf, 2011). The unique characteristic of this type of CNS adaptability is that the amplification, or facilitation, persists even after the original triggering stimulus has stopped (Woolf, 2011). Furthermore

stimulation of one set of nociceptor sensory fibres is able to amplify the subsequent response by an entirely independent, nociceptive or non-nociceptive sensory fibre, also known as heterosynaptic facilitation (Woolf, 2011). Physiologically CS results in an increased receptive field, increased responsiveness to a previously painful stimulus as well as altered responsiveness such that low threshold stimuli begin to evoke a painful response,

Figure 1.6 (Cook *et al*, 1987; Woolf, 2011).

Figure 1.6 Central sensitisation



With the induction of central sensitisation in somatosensory pathways with increases in synaptic efficacy and reductions in inhibition, a central amplification occurs enhancing the pain response to noxious stimuli in amplitude, duration and spatial extent, while the strengthening of normally ineffective synapses recruits subliminal inputs such that inputs in low threshold sensory inputs can now activate the pain circuit. The two parallel sensory pathways converge. (Reproduced with permission, Woolf, 2011)

The presence of central sensitisation is associated with the following clinical features:

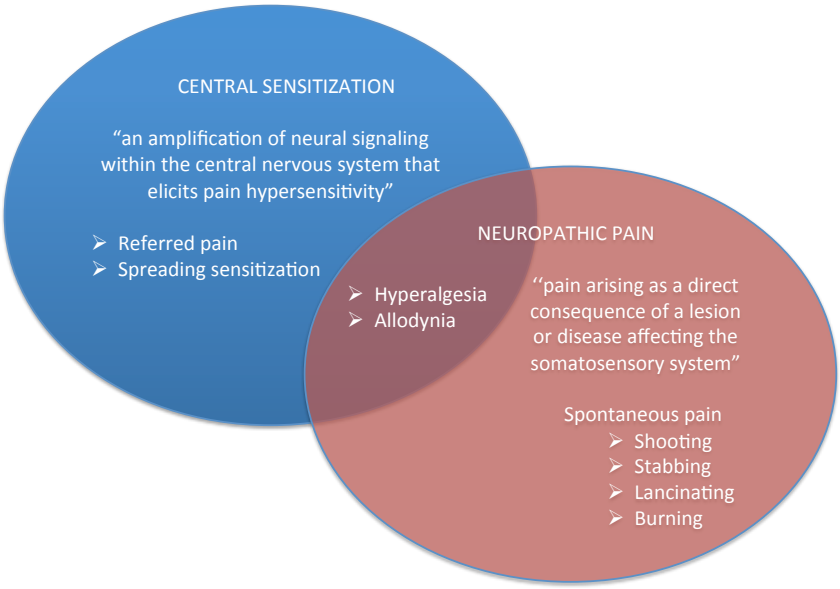
1. Secondary hyperalgesia: increased pain from a nociceptive stimulus, distant to the primary site of injury (Torebjork *et al*, 1992)
2. Allodynia: pain due to a stimulus which does not normally evoke pain (Torebjork *et al*, 1992),
3. Referred pain: pain which is felt remote to the tissue being stimulated, usually in a segmental distribution (Treede *et al*, 1992)
4. Spreading sensitisation: a spread of pain sensitivity across peripheral nerve territories (Sang *et al*, 1996)

Pain sensitisation can also be mediated by peripheral nociceptors. In contrast to CS, peripheral sensitisation is defined as an "increased responsiveness and reduced threshold of nociceptive neurons in the periphery to the stimulation of their receptive fields" (Merskey *et al*, 1994). Although the anatomical site of neural abnormality is distinct in these two types of sensitisation, it can be difficult to distinguish them clinically. For example, features such as allodynia and spreading sensitisation can be either peripherally or centrally mediated. Furthermore, CS can be driven by sensitised peripheral nociceptors. However in these circumstances activation of sensitised peripheral nociceptors is usually dependent on movement and therefore causes fluctuating levels of central sensitisation (Thakur *et al*, 2014). The sensory abnormalities demonstrated in patients with knee OA have been

demonstrated to be stable and independent of movement, suggesting that this is less likely to be the case in this group of patients (Wylde *et al*, 2011). Furthermore psychophysical evidence of the development of secondary hyperalgesia despite peripheral nerve blockade shows that CS can develop in the absence of peripheral sensitisation (Treede *et al*, 1992).

There is also considerable overlap between the features of neuropathic pain and CS. Neuropathic pain is defined as ‘‘pain arising as a direct consequence of a lesion or disease affecting the somatosensory system”(Treede *et al*, 2008). In contrast, nociceptive pain is used to describe pain occurring in the context of a normally functioning somatosensory nervous system and is defined as “pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors” (Merskey *et al*, 1994). Neuropathic pain may therefore be generated by a number of mechanisms affecting the peripheral or central nervous system, with CS being one possibility (von Hehn *et al*, 2012). The relationship between CS and neuropathic pain is summarised in **Figure 1.7**

Figure 1.7 The overlap between the clinical features of central sensitisation and neuropathic pain.



The typical characteristics of neuropathic pain can be considered in terms of stimulus-independent or spontaneous pain, and stimulus-evoked pain. Spontaneous pain can be shooting, lancinating or burning and may be persistent or paroxysmal in nature (Woolf *et al*, 1999). The two key features of stimulus-evoked pain are hyperalgesia and allodynia (Woolf *et al*, 1999).

The literature supports the role of CS and neuropathic pain in knee OA. For example, qualitative work by Hochman *et al* was the first to identify a subgroup of patients with knee OA who used neuropathic like pain quality descriptors (Hochman *et al*,

2010). This was present in 0.34 (95% CI 0.24,0.45) of the patients studied. Compared to patients who did not have features of neuropathic pain, they were younger, had a longer mean duration of OA and greater OA severity, and were more likely to be female (Hochman *et al*, 2010).

The optimal methods for the clinical assessment of CS and the impact of identifying and specifically treating CS are unclear (Lluch *et al*, 2014). This is further complicated by a change in the definition of neuropathic pain during the time when much of work in the musculoskeletal field was conducted. The original definition of neuropathic pain was "pain initiated or caused by a primary lesion, dysfunction, or transitory perturbation of the peripheral or central nervous system" (Merskey *et al*, 1994). The more recent definition removed the term "dysfunction" and specified that the abnormality should be in the somatosensory system (Treede *et al*, 2008). The main reason for making these changes was to introduce more homogeneity amongst the neuropathic pain syndromes, with the long term aim of improving understanding of the underlying mechanisms and subsequently the treatment of these patients (Jensen *et al*, 2011). The techniques commonly applied in this area of musculoskeletal research are not able to identify or localise a specific somatosensory disease or lesion and so technically the term neuropathic pain, using the current definition, should not be applied. However in recognition of the change in the definition over time, the term neuropathic pain will be used in this thesis according to its use by the authors in their original work. In the context of the new data collected for this thesis, unless otherwise stated, the term neuropathic pain will be

used to describe patients who fall into the “positive” group using the PainDETECT Questionnaire (PD-Q), a screening tool discussed below. Those who fall into the “unclear” group will be referred to as the unclear group, and those who are deemed “negative” according to the PD-Q will be considered as having nociceptive pain (Freynhagen *et al*, 2006).

The section below will discuss the evidence currently available in knee OA, using three of the most commonly used tools to assess CS and neuropathic pain: screening tools, quantitative sensory testing (QST), and neuroimaging.

1.5.1 Screening tools and questionnaires

Screening questionnaires, such as the PainDETECT Questionnaire (PD-Q) (Freynhagen *et al*, 2006), have been recommended for the identification of patients with possible neuropathic pain (Haanpaa *et al*, 2011). The PD-Q, in its original and modified form (mPD-Q), has shown that around 20% of patients with knee OA describe characteristics suggestive of neuropathic pain (Ohtori *et al*, 2012) (Hochman *et al*, 2011).

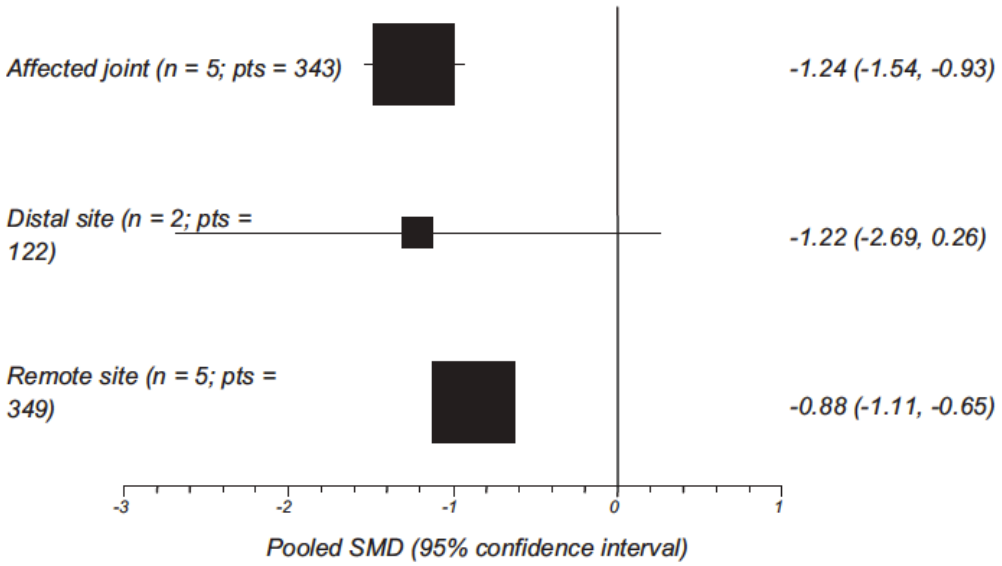
Neuropathic pain detected using the mPD-Q has been shown to be significantly associated with CS in patients with knee OA identified using QST (Hochman *et al*, 2013). This is thought to be the primary mechanism for neuropathic pain in knee OA (Hochman *et al*, 2010). There is also neuroimaging data to support this hypothesis, which will be discussed below (Gwilym *et al*, 2009).

1.5.2 Quantitative sensory testing

QST is a noninvasive, psychophysical technique used to measure somatosensory function by quantifying responses to a range of calibrated stimuli, which may be non-noxious or noxious in nature. It commonly consists of a battery of tests involving thermal, mechanical and pressure stimuli and indicates overall loss and gain of function rather than spatially locating a specific somatosensory lesion.

Much of the original QST research in knee OA patients focused on demonstrating the presence of sensory abnormalities local to and distant from the affected knee compared to healthy, pain-free control subjects (Arendt-Nielsen *et al*, 2010; Brucini *et al*, 1981; Courtney *et al*, 2009; Courtney *et al*, 2010; Creamer *et al*, 1998; Finan *et al*, 2012; Graven-Nielsen *et al*, 2012; Hendiani *et al*, 2003; Imamura *et al*, 2008; Kosek *et al*, 2000; Lee *et al*, 2011; Wylde *et al*, 2011). Previous work has utilized numerous different QST methodologies with different anatomical sites, stimulus modalities and analysis methodologies. Overall many of them do demonstrate that patients with knee OA have lower pain thresholds than healthy controls. Pressure stimulus has been the most commonly used modality when investigating OA in general and a systematic review and meta-analysis of the literature has shown that pain pressure thresholds (PPT) both over and remote from the affected joint are lower in patients with OA when compared to healthy controls, Figure 1.8, (Suokas *et al*, 2012).

Figure 1.8 Pain pressure thresholds in patients with knee osteoarthritis.



Forest plot showing the pooled SMD (95%CIs, n=number of studies, pts=number of study participants) for PPT between people with OA and healthy controls. The smallest SMD for the affected joint, distal site, and the remote site were selected from each study and pooled within these three categories. Negative SMD means lower pain threshold in OA compared with control (Reproduced with permisson, Suokas et al, 2012).

A more recent meta-analysis extended this further by estimating the difference in PPT between patients with knee OA and healthy controls, as well as comparing patients with high symptom severity to those with low symptom severity (Fingleton *et al*, 2015). This study reported large differences between patients and healthy controls for both local and remote PPTs (overall point estimate -0.86, 95% confidence interval (95% CI) -1.09 to -0.62) as well as a moderate difference between patients with high and low symptom severity (overall point estimate -0.51, 95% CI -0.73 to -0.30) (Fingleton *et al*, 2015).

The potential clinical utility of using QST to predict pain following arthroplasty is not known. In general surgery it was estimated to explain 4–54% of the variance in

postoperative pain, depending on the test paradigm used (Werner *et al*, 2010). Few studies have addressed this in knee arthroplasty specifically: the preliminary data are inconclusive but suggest that there may be some association between pre-operative experimental pain sensitivity and post-operative outcome (Lundblad *et al*, 2008; Lunn *et al*, 2013; Martinez *et al*, 2007; Petersen *et al*, 2015; Rakel *et al*, 2012; Wylde *et al*, 2013).

1.5.3 Neuroimaging evidence

Neuroimaging provides a non-invasive, objective method for measuring the central processing of pain in humans. Functional magnetic resonance imaging (fMRI) enables us to directly compare brain activation patterns in response to a specific nociceptive stimulus between different participant groups (stimulus-evoked fMRI), as well as investigate functional connectivity between different regions at rest and how these may differ in those with and without chronic pain (task-free or resting state fMRI) (Davis *et al*, 2013). More recently, other MRI based techniques such as diffusion tensor imaging, spectroscopy, and volumetric imaging are being used to investigate changes in connectivity, neurochemistry and structure in the context of chronic pain both in cross-sectional and longitudinal studies (Lee *et al*, 2013). Furthermore, once different patterns of activation have been observed, the underlying mechanisms can also be investigated by combining neuroimaging with other techniques such as QST (Schweinhardt *et al*, 2006).

The principles of MRI are well established, and so will not be discussed in detail (Huettel *et al*, 2008). To briefly summarize, blood oxygen level dependent (BOLD) imaging is the most common technique used in fMRI. BOLD imaging relies on the serendipitous finding that oxyhaemoglobin and deoxyhaemoglobin possess different magnetic properties. During activation, neurons consume oxygen and this in turn triggers a rapid increase in local blood flow, resulting in a relative oversupply of oxygenated blood. As the concentration of oxyhaemoglobin, which is diamagnetic, increases compared to deoxyhaemoglobin, which is paramagnetic, the magnetic susceptibility of the blood in the region of neural activation changes. This difference in magnetic properties causes a small change in the magnetic resonance signal, which can be detected and used to measure local changes in blood supply.

The use of neuroimaging techniques to further our understanding of the mechanisms of pain, and suitable treatment developments, is being increasingly recognized (Sofat *et al*, 2011). The work done on patients with hip or knee OA is summarised below, Table 1-1.

Table 1-1 Summary of studies using neuroimaging in lower limb osteoarthritis

First Author	Year	Joint	N	Method	Result
Kulkarni	2007	Knee	12	18F-fluorodeoxyglucose positron emission tomography (FDG PET) with arthritic knee pain, experimental knee pain, and when pain-free.	Arthritic pain was associated with increased activity in the cingulate cortex, thalamus, and amygdala compared to experimental pain.
Baliki	2008	Knee	5	fMRI. Pressure applied to most sensitive part of knee. Baseline and 2 weeks after topical lidocaine therapy.	Bilateral thalamic activity was correlated with pain ratings and showed significantly decreased activity following treatment.
Gwilym	2009	Hip	20 20*	fMRI. Cold and punctate stimuli in area of referred pain.	Significantly greater brainstem activation with punctate stimulation compared to controls. Magnitude of activation positively correlated with the painDETECT questionnaire score.
Gwilym	2010	Hip	16	Voxel-based morphometry (VBM) before and after hip replacement surgery.	Areas of the thalamus in patients exhibited decreased grey matter volume, which 'reversed' after surgery.
Baliki (Baliki *et al*, 2011)	2011	Knee	20 46*	VBM.	Decreased grey matter density in the insula, mid anterior cingulate cortex (ACC), hippocampus, paracentral lobule and the inferior temporal cortex.
Parks	2011	Knee	14 9*	fMRI. Spontaneous pain and pressure applied to most sensitive part of knee. 6 patients were rescanned after valdecoxib use.	Small differences in brain activity for pressure-evoked knee pain between OA patients and healthy controls. Prefrontal-limbic structures activated during spontaneous pain. Rostral ACC and medial prefrontal cortex (PFC) activation changed with change in blood and CSF valdecoxib levels.
Baliki (Baliki *et al*, 2014)	2014	Knee	14 36*	Resting-state fMRI.	Default mode network (DMN) was significantly different in patients compared to controls. The medial PFC showed increased connectivity with the insula, and decreased connectivity with posterior parts of the DMN.
Hiramatsu (Hiramatsu *et al*, 2014)	2014	Knee	12 11*	fMRI. Intra-epidermal electrical stimulation of the knee.	Increased activity in the dorsolateral PFC, which was not associated with normal connections to the pain neuromatrix.
Gimenez	2014	Knee	25	fMRI. Pressure applied to the most tender point on the medial articular joint line following naproxen 500mg, placebo, or no treatment.	Activation in the thalamus, primary and secondary somatosensory cortices, ACC, supplementary area, and frontal cortex was seen during the no-treatment session. After naproxen, activation in superior parietal cortex, ACC and lateral frontal cortex was reduced.

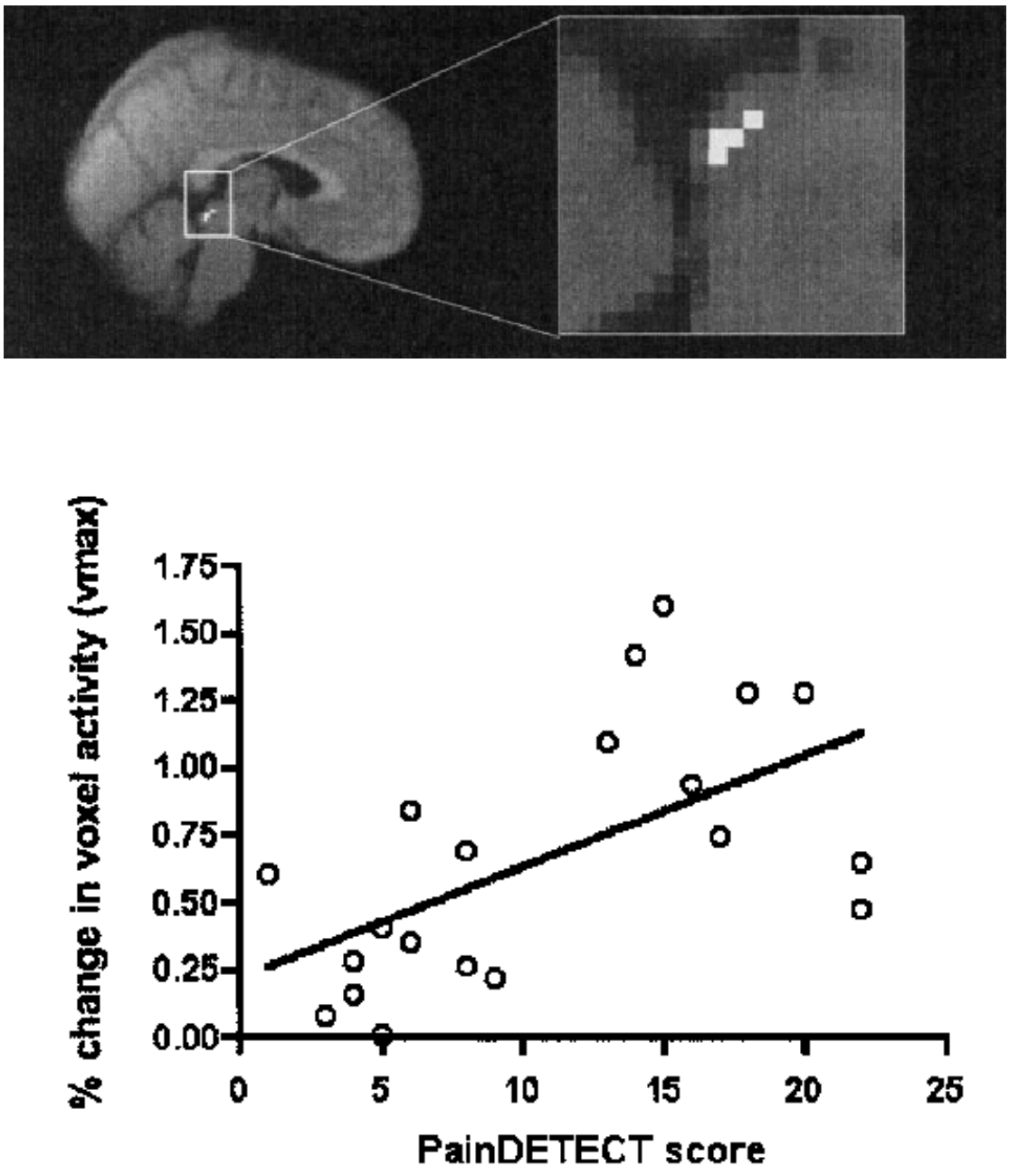
N=number of patients included in the study, *=control participants, fMRI=functional magnetic resonance imaging.

Together these data suggest that both the anatomy and function of the brain are likely to be affected in patients with knee OA, compared to healthy pain free controls. The data also suggest that there may be significant differences between the pathways for processing experimental pain compared to clinical pain (Kulkarni *et al*, 2007; Parks *et al*, 2011). The difficulty of studying clinical pain in OA is that is fluctuates in severity over days and weeks (Allen *et al*, 2009; Wise *et al*, 2011), but it may provide more clinically relevant information on the impact of CS on the response to treatment.

The increased activation in the PAG seen in patients with hip OA, compared to controls, suggests that the DPMS may be an important contributor to pain perception in OA (Gwilym *et al*, 2009). Furthermore, the relationship between PAG activation and PD-Q score suggests that descending facilitation is related to the presence of neuropathic pain in some patients and provides support for the role of CS in the generation of neuropathic pain in this context, Figure 1.9 (Gwilym *et al*, 2009).

The data also suggest that cortical components of the DPMS such as the anterior cingulate cortex, amygdalae, insula amygdala, prefrontal cortex, may also disrupted in patients with knee OA. Neuroimaging has not yet been used to investigate the neural correlates of neuropathic pain in knee OA, and the impact on outcome following surgery is unknown.

Figure 1.9 Neuroimaging evidence of central sensitisation in osteoarthritis.



Above: Mixed-effects group analysis for periaqueductal grey (PAG) activation for the contrast of high PainDETECT > low PainDETECT, and below: correlation between clinical manifestations of central sensitisation, as shown by total score on the PainDETECT, and PAG activation in response to punctate stimulation in patients. (Gwilym *et al*, 2009).

1.6 Identifying phenotypes in osteoarthritis

OA is a heterogeneous disease with variation in clinical features, aetiopathology and response to treatments. It is recognized that tailored patient therapy, which is called for in many of the current practice guidelines (Fernandes *et al*, 2013; McAlindon *et al*, 2014; 2008), is needed in order to optimize therapeutic effects but the methodology for identifying robust, clinically meaningful phenotypes is not well established (Driban *et al*, 2010) .

A phenotype is defined as "…the sum total of the observable characteristics of an individual, regarded as the consequence of the interaction of the individual's genotype with the environment…" (Simpson *et al*, 1989) Two main approaches to defining a phenotype in OA have been suggested. The first method uses a hypothesis free, data driven method, such as cluster analysis or principal component analysis to statistically derive significantly different subgroups within a population (Felson, 2010; Knoop *et al*, 2011; Murphy *et al*, 2011). This method depends entirely on the nature of the data included in the analysis and the threshold set for accepting a separate phenotype. For example in knee OA this method has been used to derive five phenotypes based on differing levels of joint disease, muscle strength, obesity and depression (Knoop *et al*, 2011). Equally, a different study used the same approach to define three phenotypes based on varying degrees of pain, fatigue, sleep disturbance and low mood (Murphy *et al*, 2011).

The second method starts with the a priori clinical observation that different clinical patterns of disease or underlying biological mechanisms exist and strives to prove this by demonstrating differences in baseline clinical characteristics or natural history of the disease, for example (Felson, 2010). This approach was used in hand OA to confirm the presence of the following subsets of patients: thumb base OA (22.4%), nodal interphalangeal joint OA (15.5%), generalised hand OA (10.4%), non-nodal interphalangeal joint OA (4.9%), erosive OA (1.0%). Differences in gender, associated disability and co-morbidities were used to distinguish between the subtypes identified (Marshall *et al*, 2013).

The ultimate challenge once a novel phenotype has been proposed is to validate it and evaluate its use in the clinical setting. Although clear consensus has not been reached, it has been proposed that validation should involve showing a relation to response to treatment or prevention strategy (Felson, 2010). As one of the reasons for searching for new phenotypes is to aid the development of novel therapies, this strategy is at risk of being circular and restrictive and supplementary methods are required.

1.7 Motivation and rationale for thesis

OA is the most common cause of arthritis in the world and is associated with a huge burden on society, both in terms of the loss of working days as well as the cost of treatment itself (2008; 2008; NICE). The prevalence of OA of the knee is predicted to rise rapidly due to a combination of an ageing population and the obesity epidemic (Arden *et al*, 2006; Nguyen *et al*, 2011). Despite the size of the global impact of OA, there is a significant unmet need for effective treatments, with a recent study showing that 54% of patients with symptomatic knee OA requiring analgesics had inadequate pain relief (Conaghan *et al*, 2015).

The successful management of patients with knee OA is currently limited by the small to moderate effect sizes of commonly used treatments, such as paracetamol and non-steroidal anti-inflammatory drugs (Zhang *et al*, 2010). Total Knee Replacement (TKR) surgery is an effective treatment for those with severe disease (Dieppe *et al*, 1999; 2008; Zhang *et al*, 2008). However, as the measurement of success has moved towards a greater emphasis on patient reported outcome measures, such as the Oxford Knee Score (Dawson *et al*, 1998; Murray *et al*, 2007), it is being recognised that around 20% of patients experience on-going long term pain even after knee arthroplasty (Beswick *et al*, 2012).

The precise mechanisms of pain in OA are not fully understood and has been the subject of frequent review in the literature (Bradley, 2004; Dieppe *et al*, 2005; Felson, 2005; Gwilym *et al*, 2008; Hunter *et al*, 2013; Kidd, 2012; Mease *et al*, 2011;

Phillips *et al*, 2013). A combination of animal studies (Orita *et al*, 2011; Thakur *et al*, 2012), symptom-based assessment (Hochman *et al*, 2010; Hochman *et al*, 2011; Ohtori *et al*, 2012), quantitative sensory testing (QST) (Arendt-Nielsen *et al*, 2010; Bajaj *et al*, 2001; Hendiani *et al*, 2003; Kosek *et al*, 2000; Kosek *et al*, 2000; Nikolajsen *et al*, 2008; Ordeberg, 2004; Suokas *et al*, 2012; Wylde *et al*, 2011) and neuroimaging research (Baliki *et al*, 2008; Gwilym *et al*, 2009; Parks *et al*, 2011) support the role of central sensitisation (CS) in knee OA.

CS may help to explain the observed discordance between radiographic and symptomatic knee OA (Bedson *et al*, 2008; Hannan *et al*, 2000). This may, in turn, help to identify a subset of patients who would benefit from treatments designed to target the centrally mediated component of their symptoms.

It is not clear whether the identification of patients in whom CS is observed will help to improve treatment responses by allowing more targeted therapies. For example TKR, which targets peripheral structural disease, would be expected to be less successful in those with marked CS.

My project used a novel combination of screening tools, QST, and neuroimaging to identify the characteristics of pain relating to CS. The study encompassed the full spectrum of disease severity, ranging from asymptomatic individuals to those with moderate to severe disease requiring surgery. The effect of CS on structural and

symptomatic discordance was assessed. Finally in those requiring surgery, the impact of CS on short and long-term post-operative outcome was investigated.

1.8 Thesis outline

The aim of this thesis is to investigate the relationship between the characteristics of pain in knee OA and the underlying neural mechanism. In particular it will focus on the presence of features of neuropathic pain and its associated psychophysical and central neural mechanisms, and the association with symptom severity and the impact on response to surgical treatment.

Chapter two describes the three study cohorts, which have been used in order to characterize the pain experienced by those in a community setting as well as patients with moderate to severe disease who are awaiting knee replacement surgery.

Chapter three investigates the features of neuropathic pain in people who have musculoskeletal pain in a community setting. The performance of painDETECT questionnaire (PD-Q), a screening tool used to identify neuropathic pain, and quantitative sensory testing (QST), are then compared in this setting.

In Chapter four, QST is then used to measure pain sensitisation and its contribution to the observed discordance between structural and symptomatic OA in the community.

Chapter five uses the PainDETECT questionnaire to determine the prevalence of neuropathic pain amongst patients with moderate to severe clinician diagnosed knee OA, who are waiting knee replacement surgery. Differences in the psychophysical characteristics between those with and without features of neuropathic pain are also investigated.

In chapter six, the mechanisms underlying neuropathic pain in the surgical patient cohort are further investigated using fMRI. The changes in pain processing, in response to experimentally induced pain, before and after surgery are then reported.

Chapter seven describes the impact of having neuropathic pain prior to surgery on short and long-term outcome following knee replacement surgery. The main findings from the initial study are validated using a second, independent, larger patient dataset.

In chapter eight, the clinical significance of these findings are discussed as well as the possible directions for future research.

Cluster analysis, a data driven method for identifying potential subgroups within a population, was also applied to the surgical patient cohort. The relationship between these statistically derived groups and short and long-term outcome is explored (see Appendix).

1.9 Objectives

The overall aim of this project is to examine the degree to which central sensitisation, at different stages of knee OA, contributes to pain severity and the prediction of response to arthroplasty. Specifically the hypotheses are:

1. That central sensitisation contributes to the observed discordance between radiographic knee OA and the presence or severity of pain.
2. That the presence of neuropathic pain features will be associated with central sensitisation in knee OA.
3. That the presence of central sensitisation prior to surgery will predict a worse outcome following knee replacement surgery for knee OA related pain.

2 Study Cohorts

2.1 Introduction

This thesis has utilized a range of research methods in order to study the underlying pain mechanisms of knee osteoarthritis (OA) across the spectrum of disease. Two separate studies have been specifically designed and conducted to achieve this aim. The first dataset is a community-based study and the second study recruited patients from an orthopaedic clinic, after they had been listed for knee replacement surgery. Data from a third study have been used to validate some of the longitudinal findings of the surgical cohort study. This chapter will outline the details of the participants and data acquisition for each cohort, followed by an overview of the study design and statistical methods used to address each individual research objective.

Chapters three and four address the contribution of neuropathic pain and central sensitisation to pain in early OA. They use data collected by Dr Anushka Soni as part of the 20-year follow up visit of the Chingford Study. The Chingford Study is a pre-existing population-based UK cohort study, which provides the unique opportunity to study symptoms and radiographic features of early knee OA in participants drawn from the community. This addresses the significant proportion of people who are managed within primary care. Dr Anushka Soni designed and conducted a bespoke musculoskeletal pain assessment, including symptoms of neuropathic pain as well as sensory thresholds using quantitative sensory testing.

Chapters five to eight are based on data from The **E**valuation of **P**eri-operative pain **I**n **O**steoarthritis of the k**NE**e (EPIONE) Study. This study, funded by a personal NIHR doctoral research fellowship awarded to Dr Anushka Soni, is a prospective cohort study of patients awaiting knee replacement surgery. Dr Anushka Soni designed and conducted the data collection required for this study. Patients were recruited from the Nuffield Orthopaedic Centre, as part of Oxford University Hospitals NHS Trust. This longitudinal study was designed and established to enable the study of pain characteristics and their relationship with outcome following surgery specifically for this thesis. In addition to the tools used in standard clinical practice, measures of psychological distress, qualitative pain descriptors and sensory thresholds were also measured prior to surgery. Dr Anushka Soni, also conducted Neuroimaging studies in a sub-group of participants before and after their surgery.

The Clinical Outcomes in Arthroplasty Study (COASt) is a prospective, dual-centre longitudinal cohort study, recruiting patients listed for knee or hip replacement surgery across two hospitals: Southampton University Hospital NHS Foundation Trust (UHS) and Nuffield Orthopaedic Centre (NOC) as part of Oxford University Hospitals NHS Trust. It had been originally agreed that recruitment for the EPIONE study would take place in conjunction with COASt. This promise was subsequently reneged and an independent strategy for recruitment to the EPIONE Study was devised so as not to overlap with patients recruited to COASt. Fortunately, the modified PainDETECT questionnaire was retained in the COASt questionnaire, which

allowed a validation study of some of the observations made using data from the EPIONE study. A subset of the data collected was made available by the COASt team to allow a preliminary validation analysis to be performed.

2.2 The Chingford Study

2.2.1 Setting and subjects

The Chingford Study is a well-described prospective population-based longitudinal study of osteoarthritis and osteoporosis, comprising 1,003 women, derived from the register of a large general practice in Chingford, North London (Hart *et al*, 1993; Hart *et al*, 1993; Soni *et al*, 2012). The women, aged 44 – 67 years at baseline are representative of women in the UK general population with respect to weight, height and smoking characteristics (Hart *et al*, 1993). The study was established in 1989 and 516 women attended the year 20 follow-up visit. 158 women had died, and 329 were lost to follow up.

A musculoskeletal pain assessment was conducted in 462 women who were included in the present analysis. Pilot data from 100 participants in Chingford was used to perform a sample size estimate. The data showed that the mean heat pain threshold was 12.9 (SD 3.4). From the radiographic data available at the year 15 follow-up visit, 226 of the participants had knee pain in the absence of radiographic structural disease (Kellgren and Lawrence grade 0 or 1) and 513 did not have pain. In order to detect a 0.4SD difference in mean heat pain threshold between these two groups, with 80% power, a sample size of 314 knees is needed. As the number of

people without radiographic disease formed 60% of the overall sample, it was estimated that a total of 518 knees, or 259 participants would need to be assessed in order to fulfil the estimated requirements.

The local ethics committee approved the study and written consent was obtained from each woman (Outer North East London Research Ethics Committee (formerly Barking & Havering and Waltham Forest RECs), LREC (R&WF) 96).

2.2.2 Data collection

2.2.2.1 Population demographics

For each participant age, height and weight were recorded. Height was measured in centimeters (to the nearest 0.1 cm) in a standing position, with shoes removed, using a wall-mounted stadiometer (Leicester Height Measure, Seca) and weight was measured in kilograms (to the nearest 0.1 kg) by electronic scales with shoes removed.

2.2.2.2 Radiographs

Anterio-posterior, fully-extended, weight bearing, bilateral knee radiographs were taken in line with standardized protocols established at baseline. The back of the knee kept in contact with the cassette and the patella centered over the lower portion of the femur. A tube-to-film distance of 100 cm was used, with the beam centered 2.5 cm below the apex of the patella (Hart *et al*, 1999). The year 20 x-rays were taken on a digital x-ray machine using the same protocols as previous x-ray visits.

Radiographs were scored using the Kellgren and Lawrence global score (Kellgren *et al*, 1957; Kellgren JH, 1963), and were read by a single observer (KML) who was blinded to patient identity and symptoms.

2.2.2.3 Quantitative sensory testing

Quantitative Sensory testing (QST) was used to determine warm detection, heat pain and mechanical pain thresholds and sharpness rating score, based on the protocol devised by Rolke et al (Rolke *et al*, 2006). A limited version of the research protocol was conducted due a time restriction on the time available for sensory testing. The initial modalities selected for testing were based on data available at the time from Stephen Gwilym's work using QST in patients with hip OA. These were reviewed once preliminary data had been collected in this cohort, and at this point a sharpness rating score was added to the protocol. Dr Anushka Soni, who was trained by Dr Stephen Gwyilm with further training in Professor Lars Arendt-Neilson's laboratory, conducted the majority of the testing. Dr Nicholas Bottomley and Mrs Elizabeth Arden were subsequently trained by Dr Anushka Soni and provided cover. All assessors followed a standard operating procedure. At the time of testing, all assessors were blind to the results of the radiographic and pain assessments.

The tests were conducted over the medial joint line of both knees in order to capture changes associated with any local pathology, as well as a site 3cm distal to the sternal notch to measure potentially centrally mediated effects (Soni *et al*, 2013;

Suokas *et al*, 2012; Wylde *et al*, 2011). Participants were asked to close their eyes during testing.

Warm detection (WDT) and heat pain thresholds (HPT)

Thermal thresholds for warm and heat pain detection were assessed using the Thermotest Modular Sensory Analyzer (MSA), Somedic, Sweden, thermode 25x50mm. The method of limits algorithm was used, with a thermode adaptation temperature of 32^{o} C. Each stimulus was generated after a randomized 4 to 6 second interval. Both thresholds were obtained with ramped stimuli (10/Second) that were terminated when the participant pressed a button. Each threshold was tested 5 times. The MSA thermotest has an in-built safety cut-off temperature of 50^{o}C to ensure no harm to the patients. If the limit was reached and the participant did not report any sensation, the threshold was recorded at that limit.

Mechanical pain threshold (MPT)

Mechanical pain thresholds were measured using a set of seven custom-made weighted pinprick simulators that exert a force of between 8 and 512 mN with a flat contact area of 0.25mm in diameter, following a binary logarithmic scale (MRC Systems, Germany). Using the method of limits a series of five ascending and descending stimulus intensities were measured.

Sharpness rating score (SRS)

The 512mN pinprick was applied three times and the participant was asked to give a rating for each stimulus on a 0-10 numeric rating scale, "0" indicating no sharpness and "10" the most sharp imaginable. The final result was calculated by taking the arithmetic mean of the three readings.

2.2.2.4 Pain assessment

Pain was assessed using the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC), a validated instrument for the assessment of pain and function in osteoarthritis of the knee or hip (Bellamy *et al*, 1988) and the PainDETECT questionnaire (Freynhagen *et al*, 2006). Data on pain modifying medication used in the preceding 72 hours, thought to potentially affect QST results, were recorded. These included both analgesics, defined as any compounds containing acetaminophen, non-steroidal anti-inflammatory drugs or opioids, and neuropathic medications, including anti-depressants, selective serotonin and norepinephrine reuptake inhibitors and anti-convulsants including gabapentin and pregabalin, prescribed for any indication. Participants were subsequently categorized according to whether they had used any of the above pain modifying medications or not.

2.2.2.5 Psychological factors

Participants were asked to complete the Hospital Anxiety and Depression Scale questionnaire (HADS) (Bjelland *et al*, 2002; Zigmond *et al*, 1983).

2.3 The EPIONE Study

The data presented in chapters five to eight were collected during the EPIONE study.

2.3.1 Setting and subjects

The EPIONE Study is a prospective cohort study of patients with primary OA, awaiting primary knee replacement surgery. The Knee Team at the Nuffield Orthopaedic Centre, Oxford, identified patients suitable for the study. Patients were recruited between October 2011 and May 2014 (the recruitment phase was extended due to 2 periods of 12 months maternity leave). The following exclusion criteria were applied: unwilling or unable to give informed consent; unable to complete questionnaires; poor understanding of English; known Charcot's arthropathy or other severe neurological disorder; revision arthroplasty.

The study was designed so that data collection was coordinated with scheduled hospital attendance for clinical purposes. Data collection took place prior to surgery alongside their routine pre-operative assessment clinic appointment, and at 2 and 12 months post-operatively. The follow-up assessments were conducted by post.

In order to detect the minimal clinically important difference in OKS of 5 points (Beard *et al*, 2015) between the neuropathic and nociceptive pain groups, with a power of 80%, it was calculated that a minimum sample size of 37 patients in each group would be needed. As it has been previously estimated that around 25% of patients with knee OA have neuropathic pain (Hochman *et al*, 2010; Hochman *et al*,

2011), the total target sample size was increased to 148 patients. The local ethics committee approved the study and written consent was obtained from each participant (NRES Committee-South Central-Oxford B, 09/H0605/76).

2.3.2 Data collection

2.3.2.1 Demographic Data

At baseline age, sex, marital and employment status were recorded.

2.3.2.2 Clinical Data

Data collected as part of routine clinical assessment included side predominantly affected, the type of surgery planned, and Oxford Knee Score (OKS). The OKS is a 12-item composite score which was developed in order to measure patient reported outcome after total knee replacement (TKR) (Dawson *et al*, 1998). Studies have also shown that the pre-operative measures for OKS are important predictors of outcome (Murray *et al*, 2007). Pain and function subscales, which can be calculated using original data from the OKS, have now also been defined and validated (Harris *et al*, 2013).

Further clinical data were collected from the electronic patient clinical record system. This included height, weight and medications prior to surgery. The side of operation, and procedure performed were extracted and recorded after their surgery had taken place.

2.3.2.3 Radiographs

Radiographs conducted as part of routine clinical care were available for analysis in this study. Routinely, weight-bearing anterio-posterior films are taken. All available radiographs were scored using the Kellgren and Lawrence global score (Kellgren *et al*, 1957; Kellgren JH, 1963), and were read by a single observer (KML) who was blinded to patient identity and symptoms.

2.3.2.4 Pain assessment

The quality of pain was assessed using the modified form of the PainDETECT questionnaire and the short form of the McGill Pain Questionnaire (SF-MPQ). The PainDETECT Questionnaire (PD-Q) has been validated against expert diagnosis in patients with chronic lower back pain as being able to distinguish those with predominantly neuropathic pain from those with non-neuropathic pain (Freynhagen *et al*, 2006). It contains a body drawing for patients to indicate the sites of pain and any radiation present, their assessment of pain quality (severity rated from "hardly noticed" to "very strong"), their pattern of pain, and measures of current, worst, and average pain severity. The seven pain qualities included in the PD-Q are: burning, tingling or prickling, light touch causing pain, sudden pain attacks like electrical shocks, cold or heat causing pain, numbness, and slight pressure causing pain. An overall PD-Q score is then generated that summarizes everything but the pain severity and body drawing data, which results in a score of –1 to 38. A score $\geq$18 indicates likely neuropathic pain, 13–18 possible neuropathic pain, and <13 makes neuropathic pain unlikely (18). A modified form has been developed and validated

for the use in patients with knee OA (Hochman *et al*, 2011). The presence of widespread pain may represent spreading sensitisation in the context of centrally mediated pain and has also been linked to acute post-operative opioid consumption after lower limb arthroplasty (Brummett *et al*, 2013) as well as longer term outcome (Lewis *et al*, 2015). As the modified form of the PD-Q does not include a body diagram, this was included separately and patients were asked to mark any areas, which had been painful for at least three months.

The SF-MPQ was developed in order to capture information about the quality of pain as well as its intensity, and takes only two to five minutes to complete (Melzack, 1987). Three scores can be derived from this questionnaire by summing the rank of intensity reported for sensory, affective and total descriptors. There are also two intensity ratings: a visual analogue score (VAS) for pain severity in the preceding seven days and the present pain intensity index, which asks participants to rate the severity of their current pain as one of: “No pain”, “Mild”, “Discomforting”, “Distressing”, “Horrible”, “Excruciating”.

Focus group work in patients with painful hip or knee OA has shown that patients experienced two main types of pain: a dull aching pain which gradually became more constant over time; and a more distressing intermittent and unpredictable pain which had more impact on mood, mobility and sleep (Hawker *et al*, 2008). The Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP) was developed in response to this finding (Hawker *et al*, 2008). It was used in this study, as it may be

more likely to capture the effect of spontaneous pain, typically associated with neuropathic pain.

The Pain Disability Index is a self-report instrument, which is designed to assess how much chronic pain interferes with daily activities (Pollard, 1984; Tait *et al*, 1987). This measure was included in order to complement the OKS by measuring impact of pain from any source.

2.3.2.5 Psychological and sleep assessment

Measures of psychological distress including anxiety, depression, pain catastrophising and fear of movement have been shown to impact on pain severity in knee OA, as well as outcome following arthroplasty surgery (Edwards *et al*, 2006; Lewis *et al*, 2015; Lingard *et al*, 2007; Marks, 2007; Riddle *et al*, 2010; Sullivan *et al*, 2009; Witvrouw *et al*, 2009). Personality optimism-pessimism have also been shown to influence physical functioning in this patient group (Brenes *et al*, 2002). Furthermore, psychological factors such as anxiety and depression have also been linked to the presence of neuropathic pain in patients with knee OA (Hochman *et al*, 2013; Oteo-Alvaro *et al*, 2014). These traits were therefore measured in this study using the following validated questionnaires: the Hospital Anxiety and Depression Scale (HADS) (Bjelland *et al*, 2002), the state/trait anxiety inventory (Spielberger, 1983), the pain catastrophising scale (PCS) (Sullivan, 1985), the Tampa scale for kinesiophobia (TSK) (Kori KS, 1990), and the revised Life Orientation Test (LOT-R) (Scheier *et al*, 1985).

Sleep disturbance has been linked to pain after TKR and has been recognized as a possible marker of centrally mediated symptoms in patients with knee OA (Cremeans-Smith *et al*, 2006; Murphy *et al*, 2011). Sleep problems were assessed using the Pittsburgh Sleep Quality Index (PSQI) (Buysse *et al*, 1989).

2.3.2.6 Quantitative sensory testing

QST was conducted over the medial joint line of the index knees in order to capture changes associated with any local pathology. A site 5cm distal to the tibial tuberosity on the index side, over tibialis anterior, was tested to act as a segmental reference point. Finally, the medial joint line of the contralateral knee and a site 3cm distal to the sternal notch were used as distant sites in order to measure potentially centrally mediated effects (Soni *et al*, 2013; Suokas *et al*, 2012; Wylde *et al*, 2011). Participants were asked to close their eyes during testing. Data on pain modifying medication used in the preceding 72 hours was recorded as for the Chingford Cohort.

Warm detection, heat pain, mechanical pain and sharpness rating scores were taken as for the Chingford Cohort. As there was some additional time available for testing compared to the Chingford Cohort, cold detection and cold pain thresholds were added based on data made available by Dr Stephen Gwilym at that time. Pressure pain thresholds were also added to the protocol in view of emerging data from Professor Lars Arendt-Nielson's laboratory The methods used for each modality were based on the protocol devised by Rolke et al (Rolke *et al*, 2006). Dr

Anushka Soni conducted the majority of the testing. Mrs Rhea Zambellas, who was trained by Dr Anushka Soni, provided cover. Both assessors, who were blinded to radiographic and pain assessment results at the time of testing, followed a standard operating procedure.

Cold detection (CDT) and cold pain thresholds (CPT)

Thermal thresholds for cold detection and cold pain were assessed using the Thermotest Modular Sensory Analyzer (MSA), Somedic, Sweden, thermode 25x50mm. The method of limits algorithm was used, with a thermode adaptation temperature of 32^{o} C. Each stimulus was generated after a randomized 4 to 6 second interval. Both thresholds were obtained with ramped stimuli (10/Second) that were terminated when the participant pressed a button. Each threshold was tested 5 times and the mean of all five readings was calculated. The lower limit was 10^{o}C. If the limit was reached and the participant didn't report any sensation, the threshold was recorded at that limit.

Pressure pain threshold.

This was measured using a hand-held pressure gauge device (Algometer, Somedic, Sweden) with a probe area of $1cm^2$, which exerts a force of up to 200kPa. The pressure pain threshold was determined by taking the mean of three series of ascending stimulus intensities.

2.3.2.7 Neuroimaging

All patients recruited to the study were invited to take part in the neuroimaging sub-study. Patients were included if they were willing to take part, didn't have any contra-indications to undergoing MRI, and in whom it was possible to conduct a baseline scan prior to their surgery. See chapter 6 for further details of this sub-study.

2.3.2.8 Follow up data collection

The primary outcome measure was the OKS, which was collected as part of a postal questionnaire at two and 12 months post-operatively. The participants who did not initially respond were sent two postal reminders.

The following questionnaires were repeated at each follow-up time point: ICOAP, SF-MPQ, M-PDQ, HADS, STAI, PCS, PDI, PSQI. In addition to these validated questionnaires, participants were asked to record on a body diagram the areas where they had experienced pain for at least 3 months.

Finally, participants were asked to record any medications they were taking at each time point.

2.4 COASt

Data from COASt were used in chapter 7 in order to further validate some of the findings initially observed in the EPIONE Study.

2.4.1 Setting and subjects

Patients who were placed on the waiting list for knee or hip replacement surgery were recruited to the study. Patients were recruited across two hospitals: Southampton University Hospital NHS Foundation Trust (UHS) and Nuffield Orthopaedic Centre (NOC) as part of Oxford University Hospitals NHS Trust. Data were collected prior to surgery as well as at 6 weeks and then annually for five years thereafter. For this thesis, data analysis was restricted to the patients who were

listed for knee replacement surgery and in whom 12-month follow up data were available.

2.4.2 Data collection

This section will only describe the selected data, which were made available by the COASt research team for analysis in this thesis.

2.4.2.1 Demographic Data

At baseline data for age, sex, BMI and employment status were available.

2.4.2.2 Clinical Data

Prior to surgery the data available included side predominantly affected, duration of symptoms, OKS and the type of surgery planned.

2.4.2.3 Pain assessment

Pain was assessed before surgery using the following questionnaires: mPD-Q and the ICOAP.

2.4.2.4 Follow up data collection

Only the OKS data at 12-months post-operatively were available for the current analysis.

3 Neuropathic Features of Joint Pain in the Community

3.1 Abstract

Objective

Quantitative sensory testing (QST) and screening tools have previously been used to demonstrate features of neuropathic pain in subjects with musculoskeletal pain. The purpose of this study was to examine the features of neuropathic pain in a community setting and compare the use of QST and the PainDETECT Questionnaire (PD-Q), a validated screening tool for identifying neuropathic pain.

Methods

462 of the participants attending the 20-year follow-up visit as part of the Chingford Study were included in the present study. Warm detection, heat pain, and mechanical pain thresholds as well as sharpness rating score over the sternum were determined. The PD-Q was used to identify individuals with features suggestive of neuropathic pain in those with self-reported joint pain. QST measures were compared between subjects with and those without joint pain. Logistic regression modeling was used to describe the association between neuropathic pain features, as determined by the PD-Q score, and each of the QST measures individually, adjusting for age, body mass index, and use of pain-modifying medications.

Results

A total of 66.2% of the subjects reported recent joint pain and the median average pain severity was 5 out of 10. The knee accounted for 46.4% of the painful areas reported. There was increased sensitivity to painful stimuli in the group with pain as

compared to the pain-free group, and this persisted after stratification by pain-modifying medication use. While only 6.7% of subjects had possible neuropathic pain features and 1.9% likely neuropathic pain features according to the standard PD-Q thresholds, features of neuropathic pain were common and were present in >50% of those reporting pain of at least moderate severity. Heat pain thresholds (HPT) and sharpness rating score (SRS) were significantly associated with features of neuropathic pain identified using the PD-Q, with an odds ratio (OR) of 0.88 (95% confidence interval [95% CI] 0.79–0.97; p = 0.011) and an OR of 1.24 (95% CI 1.04–1.48; p = 0.018), respectively.

Conclusion

QST measures and the PD-Q identified features of neuropathic pain in subjects in this community-based study, with significant overlap between the findings of the two techniques.

3.2 Introduction

Musculoskeletal pain is common, disabling and often poorly managed, especially in the elderly (Brown *et al*, 2011; Cimmino *et al*, 2011). Current treatment, which most commonly takes place in the primary care setting, and the development of new effective therapies for musculoskeletal pain is hindered by poor understanding of the underlying mechanisms (Arendt-Nielsen *et al*, 2011). Whilst previous research focused on articular and peri-articular mechanisms of pain, accumulating evidence now suggests that features of neuropathic pain may be present in some patients with musculoskeletal pain syndromes, including chronic widespread pain (Arendt-Nielsen *et al*, 2003; Carli *et al*, 2002) and osteoarthritis (Brown *et al*, 2011; Gwilym *et al*, 2009; Hochman *et al*, 2010; Hochman *et al*, 2011; Kosek *et al*, 2000; Kosek *et al*, 2000; Lane *et al*; Wylde *et al*, 2011). The appreciation that pain can be due to not only joint pathology but also central and peripheral sensitisation may then be translated to mechanism-based clinical diagnosis and management options (Arendt-Nielsen *et al*, 2015; Curatolo *et al*, 2015; Hawker, 2009).

Neuropathic pain is defined as ‘‘pain arising as a direct consequence of a lesion or disease affecting the somatosensory system”(Treede *et al*, 2008). While thought to be common, affecting up to 25% of those with chronic pain (Bowsher, 1991), it is clinically under-recognized and associated with an array of comorbidity resulting in reduced quality of life (Nicholson *et al*, 2004).

A key factor in the under-recognition of patients with neuropathic pain is the lack of a gold-standard diagnostic tool. Evidence-based guidelines recommend screening questionnaires, such as the Leeds assessment of neuropathic symptoms and signs (Bennett, 2001) and PainDETECT (Freynhagen *et al*, 2006) to identify patients with possible features of neuropathic pain, particularly by non-specialists (Haanpaa *et al*, 2011; Haanpaa *et al*, 2009). Although in one-third of patients with musculoskeletal pain conditions, the use of such guidelines has resulted in reclassification to a diagnosis of neuropathic pain (Jespersen *et al*, 2010), such tools still fail to recognize 10-20% of patients and can only provide a guide to diagnosis (Bennett *et al*, 2007).

Quantitative sensory testing (QST), which measures psychophysical responses to controlled stimuli with the aim of identifying neural dysfunction, is also used to identify sensory changes in patients with neuropathic pain features (Rolke *et al*, 2006; Rolke *et al*, 2006) and is being increasingly used in musculoskeletal research (Curatolo *et al*, 2015; Finan *et al*, 2012; Graven-Nielsen *et al*, 2010; Suokas *et al*, 2012; Wylde *et al*, 2011; Wylde *et al*, 2011). Allodynia or hyperalgesia, identified using QST may indirectly suggest sensitisation of nociceptive neurons. If these phenomena are identified distant from the site of index pain, they may represent central, rather than peripheral sensitisation. Although sensitisation is a feature of neuropathic pain it can also occur in the context of non-neuropathic pain, which means that QST can only be used to identify possible features of neuropathic pain, rather than provide a definitive diagnosis.

Evidence for neuropathic features in musculoskeletal conditions arises from studies of QST measures (Amris *et al*, 2010; Arendt-Nielsen *et al*, 2003; Carli *et al*, 2002; Kosek *et al*, 2000; Kosek *et al*, 2000; Wylde *et al*, 2011) as well as symptom-based screening tools (Amris *et al*, 2010; Hochman *et al*, 2010; Hochman *et al*, 2011). There is limited information on the performance of QST compared to the PD-Q. Since the design of the current study, it has been reported that a higher score on the modified PainDETECT questionnaire (mPD-Q) is more likely to be associated with signs of central sensitisation (CS) using QST, in patients with knee OA (Hochman *et al*, 2013). The current study examined the direct relationship between these two potential tools for joint pain in a community-based cohort. It was hypothesised that the presence of neuropathic pain, defined using the PD-Q, would be associated with increased experimental pain sensitivity distant to the affected site, detected using QST, suggestive of central sensitisation. Much of this work has been previously published and the full manuscript is available in Appendix A (Soni *et al*, 2013).

3.3 Aim

The aims of this study were to:

1. Describe the characteristics of joint pain in a community-based sample.
2. Examine the relationship between neuropathic features identified using the PainDETECT questionnaire and QST measures, distant to the affected site.

3.4 Methods

3.4.1 Setting and Subjects

The study participants were the 462 women who attended the 20-year visit of the Chingford Study and also completed a musculoskeletal pain assessment, as described in section 2.2.1

3.4.2 Data collection

Details on data collection of population demographics, QST measures, pain assessment and psychological factors are given in section 2.2.2

In order to focus on potentially centrally mediated effects and minimize the influence of any local pathology associated with musculoskeletal conditions, QST data from a site 3cm distal to the sternal notch was used in the present analysis.

3.4.3 Statistical analysis

Demographic details, medication use and QST measures of the women were compared in those with and without any self-reported joint pain in the preceding month using Student's t-test, Wilcoxon-Mann-Whitney, and Chi-square test for normally distributed, non-normally distributed, and categorical data respectively. The comparison was then repeated after further dividing the groups according to the use of pain-modifying medication using one-way ANOVA for normally distributed data, Kruskal-Wallis for non-normal data and Chi-square test for categorical data.

For those with pain, the proportion of women with a PD-Q score reflecting possible or likely neuropathic pain in at least one area was calculated. Fisher's exact test was to identify any significant effect of pain-modifying medication use, in view of the small numbers in some categories.

The frequency of the different sites of pain and the distribution of overall PD-Q scores for these sites were recorded. Data gathered from the measures of pain severity, the presence of radiation, and the presence of at least moderate severity for each of the seven pain qualities measured by the PD-Q were used to describe the characteristics of joint pain.

The main outcome variable was the overall PD-Q score, which was dichotomised using published thresholds into unlikely neuropathic pain (<13) versus possible/likely neuropathic pain ($\geq$ 13). This approach has been previously reported in the literature and was selected in this instance because few of the PD-Q scores were above 18 (Hochman *et al*, 2013; Hochman *et al*, 2011). Univariable logistic regression modeling, adjusting for clustering of sites within a person, was used to describe separately the association between the binary features of neuropathic pain variable (determined by the PD-Q score) and each QST measure. In view of the binary logarithmic scale for Mechanical Pain Thresholds (MPT), logarithmic transformation was used prior to regression analyses. This was done so that a one-step increase in the transformed MPT variable was of the same order as the step between successive probes used to measure this threshold. Multivariable logistic regression was used to

adjust for the potential confounders of age, BMI and analgesic or neuropathic pain medication use, determined a priori. Fractional polynomial regression modeling was used to model any non-linear relationships for continuous variables.

For the QST measures found to be significant predictors of neuropathic pain, a receiver operating characteristic (ROC) curve was used to define the cut-off values that predict the binary neuropathic pain variable with optimal sensitivity and specificity. Using these cut-off values, the proportion of participants with QST measures indicative of possible or likely neuropathic pain was determined.

3.5 Results

Of the 462 women included in the present study, 306 (66.2%) reported joint pain in the preceding month with 125 women (27.1%) experiencing pain in more than one area. BMI was normally distributed. Ages, PD-Q scores, and all QST measures were non-normally distributed. Subjects with pain had a significantly higher BMI (mean $\pm$ SD 28.2 $\pm$ 4.5 versus 26.8 $\pm$ 5.2; p = 0.004) and were more likely to have taken analgesia in the past 72 hours (39.2% versus 16.7%; p<0.001). All of the sternal QST measures, apart from the warm detection threshold (WDT), showed increased sensitivity to the experimental stimuli in those with joint pain compared to those without joint pain: median of 45.3 (interquartile range [IQR] 42.4–47.6) versus 46.4 (IQR 43.7–48.3), p = 0.006 for the heat pain threshold (HPT), median of 22.4 (IQR 9.6–102.4) versus 64.0 (IQR 16.0–140.8), p = 0.002 for the MPT, and median of 6.0 (IQR 4.7–8.3) versus 5.3 (IQR 3.3–7.7), p = 0.024 for SRS. This trend was maintained when medication use was considered, Table 3-1.

Table 3-1 Characteristics of the 462 women in the Chingford Study who were assessed for pain at the 20-year visit, stratified by reported pain and use of pain-modifying medication.

	No pain reported (n=156)		**Pain reported (n=306)**		
	No pain-modifying medication (n=123)	Pain-modifying medication (n=33)	No pain-modifying medication (n=162)	Pain-modifying medication (n=144)	P
Age, median (IQR) years	70 (67-75)	73 (67-78)	72 (67-77)	71 (68-75)	0.229
BMI, mean ± SD kg/m^2	26.9 (4.4)	26.7 (5.0)	27.5 (4.7)	29.0 (5.5)	0.001
Warm detect threshold, median (IQR) ^{o}C	4.8 (3.7- 6.7)	5.6 (4.4-6.7)	4.8 (3.7-6.2)	4.9 (3.8-6.1)	0.324
Heat pain threshold median (IQR) ^{o}C	46.4 (43.7-48.4)	46.1 (43.7-48.0)	45.5 (42.6-48.0)	45.0 (42.2-47.4)	0.020
Mechanical pain threshold median (IQR) mN	64.0 (16.0-164.0)	40.0 (16.0-128.0)	32.0 (11.2-153.6)	19.2 (8.2-70.4)	0.001
Sharpness rating score median (IQR) range 0-10†	5.3 (3.3-7.7)	6.0 (4.0-7.7)	6.0 (4.0-8.0)	6.5 (5.3-8.3)	0.019
PainDETECT≥13, no. positive/total no. tested (%)‡	-	-	4/157 (2.5%)	29/143 (20.1%)	<0.001

p values are for comparisons across groups. IQR = interquartile range; BMI = body mass index.† Measures of Sharpness rating to 512mn probe were available for 90 participants without pain (71 had not taken pain-modifying medication and 19 had) and for 219 participants with pain (113 had not taken pain-modifying medication and 106 had). ‡ Using the highest score on the PainDETECT Questionnaire (PD-Q) in those with >1 painful area.

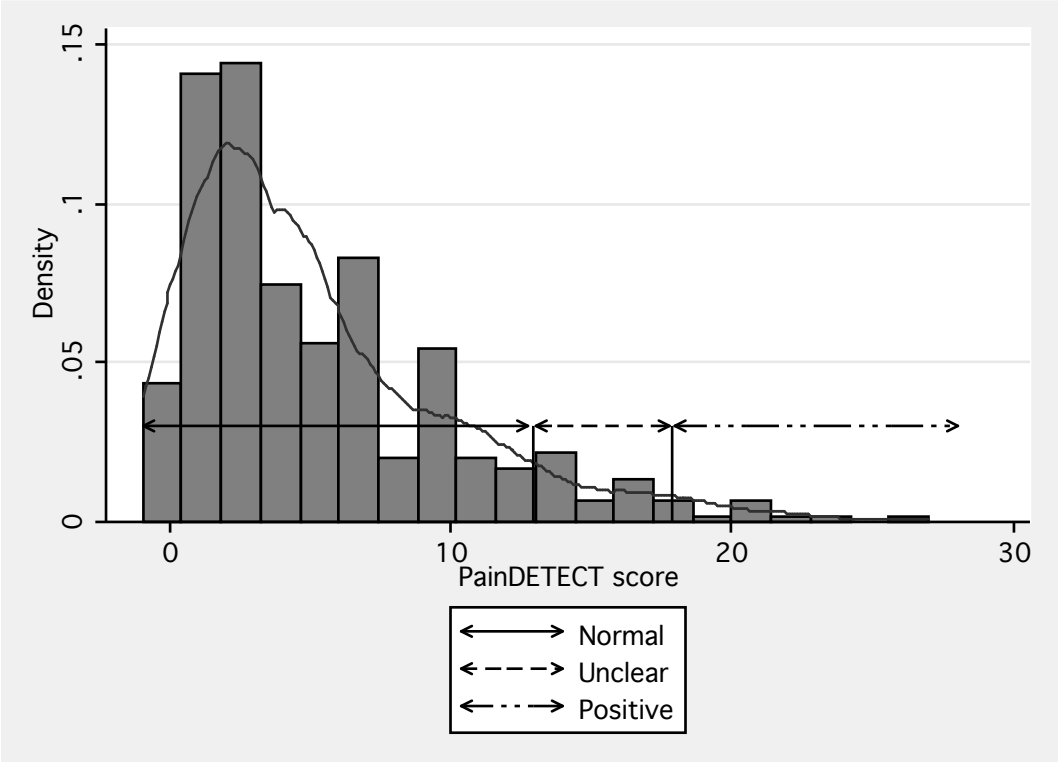
The proportion of participants with likely neuropathic pain is significantly higher in those who had taken pain-modifying medication, compared to those who had not (2.5% versus 20.1%, p<0.001).

The 431 painful sites assessed were located in the knee (46.4%), hip (13.9%), back (14.2%), shoulder (10.0%), hand/wrist (8.8%), and other (6.7%). None of the

participants reported pain at the sternum, where QST was conducted. The median pain severity for current pain was 0 (IQR 0-3), worst pain was 6 (IQR 4-8) and average pain was 5 (IQR 3-6).

The distribution of the total PD-Q scores for each area assessed is shown in Figure 3.1. Of the 431 painful areas, 29 (6.7%) had scores of 13-18, representing possible neuropathic pain, and 8 (1.9%) had scores above 18, representing likely neuropathic pain. In contrast, only 26 (6.0%) had no features of neuropathic pain.

Figure 3.1 Distribution of the total scores on the PainDETECT Questionnaire in subjects with self-reported musculoskeletal pain.

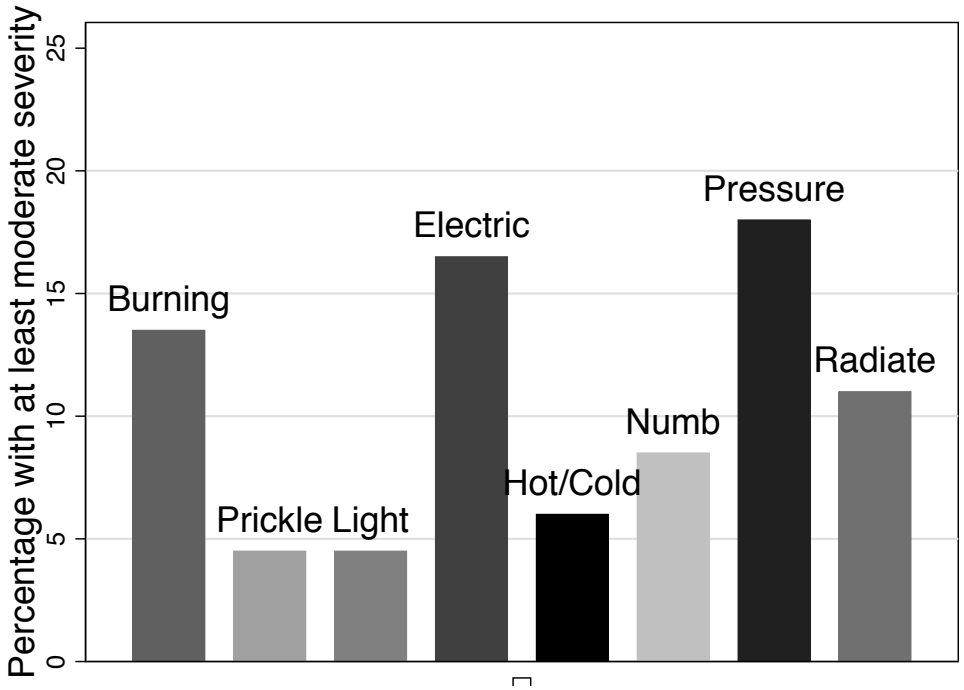


The breakdown of the PainDETECT scores in terms of the presence or absence of radiating pain and at least moderate severity of the other seven qualities is shown in

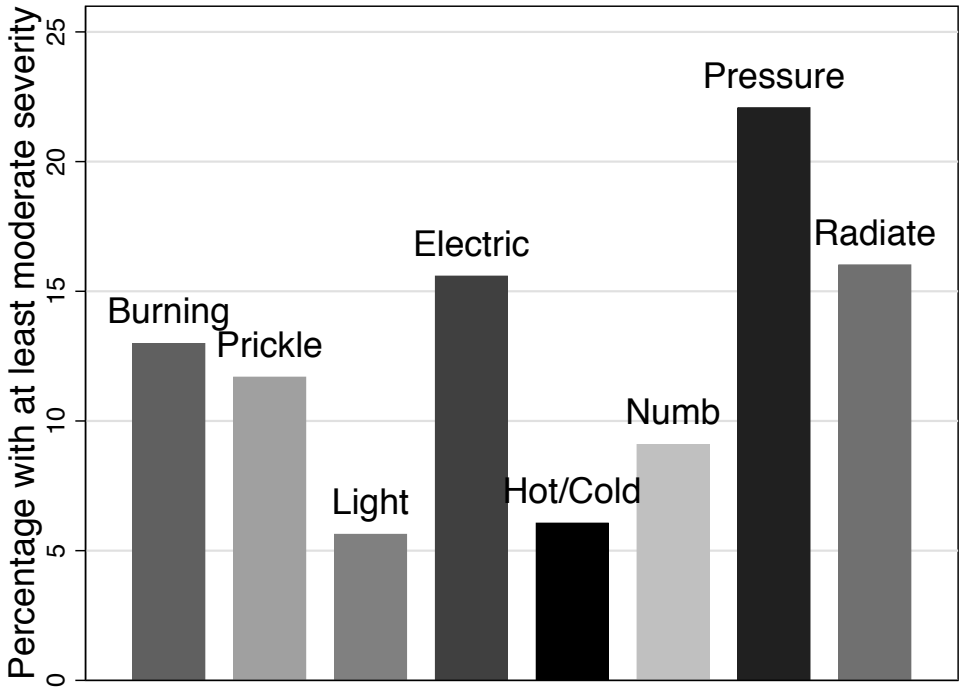
Figure 3.2. The most common qualities were pain upon light pressure (20.2%); sudden attacks of pain that felt like electrical shocks (16.1%), radiating pain (13.7%) and burning pain (13.2%). Overall, 47.3% of the areas had no associated radiating pain and no pain qualities of at least moderate severity, 32.5% showed a single pain quality, 9.5% showed 2, 6.5% showed 3 and 4.2% showed 4 or more qualities.

Figure 3.2 Qualities of pain, as determined using the PainDETECT Questionnaire, evaluating A, the knee and B, other musculoskeletal sites.

A



B



The relationship between the values from QST and the findings from the PD-Q was then investigated. Univariable analysis showed heat pain thresholds and sharpness rating score were significantly associated with possible or likely neuropathic pain, as determined by PainDETECT score. This effect remained after adjustment for potential confounders (Table 3-2).

Table 3-2 Logistic regression model of predictors of possible/likely neuropathic pain features on the PainDETECT Questionnaire, clustered by person

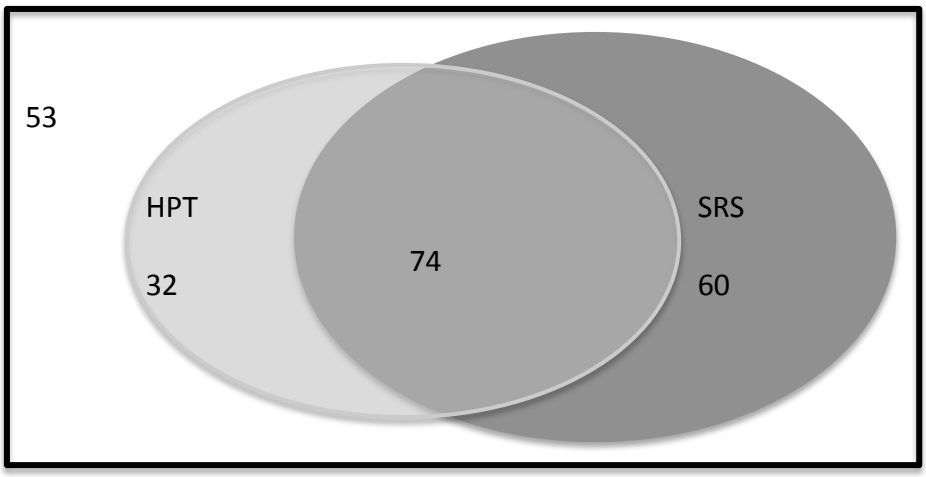
	Univariable model		**Multivariable model***	
Predictor	OR (95% CI)	P	OR (95% CI)	P
Warm detect threshold, per ^{o}C increase	1.00 (0.86-1.16)	0.949	0.98 (0.85-1.14)	0.905
Heat pain threshold, per ^{o}C increase	0.88 (0.80-0.97)	0.012	0.88 (0.79-0.97)	0.011
Mechanical pain threshold, per step increase	0.97 (0.83-1.13)	0.657	1.01 (0.86-1.17)	0.945
Sharpness rating score, per unit increase	1.26 (1.07-1.48)	0.005	1.24 (1.04-1.48)	0.018

*Adjusted for age, body mass index, and use of analgesic or neuropathic pain medication.
OR = odds ratio; 95% CI = 95% confidence interval.

Using a ROC curve analysis, which did not take account of clustering of sites within an individual, cut-off values for HPT and SRS representative of neuropathic pain, with optimal sensitivity and specificity were determined. Heat pain thresholds under 45.2^{o}C (area under the curve 0.61 [95% confidence interval (95% CI), 0.51–0.71]), and sharpness rating scores above 6, (area under the curve 0.62 [95% CI 0.52–0.72]) predicted possible or likely neuropathic pain, as determined by the PD-Q scores.

Using these cut-off values, the proportion of participants with one or both QST measures indicating possible or likely neuropathic pain was determined, Figure 3.3.

Figure 3.3 Venn diagram demonstrating the number of participants in whom one or both quantitative sensory testing measures indicated possible or likely neuropathic pain.



Values are the percentage of the total (n = 219). HPT=heat pain threshold; SRS= sharpness rating to 512mn probe.

3.6 Discussion

An important finding of this study was that QST at the sternum, a central point distant from the region of pain, demonstrated increased sensitivity to painful stimuli in subjects with pain as compared to those without pain, and this relationship persisted after stratification by use of pain-modifying medications. In subjects with joint pain, possible or likely neuropathic pain was present in 20.1% of those taking pain-modifying medications, as compared to only 2.5% of those not taking pain-modifying medications. While overall only 6.7% had possible neuropathic pain and 1.9% had likely neuropathic pain based on the PD-Q thresholds, features of neuropathic pain were common and present in >50% of those reporting pain of at least moderate severity. In those with pain, heat pain thresholds and mechanical pain sensitivity were significantly associated with likely neuropathic pain identified with the PD-Q (odds ratio [OR] 0.88 [95% CI 0.80–0.97], p = 0.012 and OR 1.24 [95% CI 1.04–1.48], p = 0.018, respectively). Thirty-four percent of the participants with musculoskeletal pain demonstrated increased sensitivity to both heat and supra-threshold mechanical stimuli.

The prevalence of musculoskeletal pain has previously been estimated at around 30% (Cimmino *et al*, 2011) in the general population. The higher rate seen in this study may be accounted for by 3 factors. First, the Chingford Study is restricted to women, and women are known to be at greater risk of developing musculoskeletal pain. Second, the women were between the ages of 64 and 87 years at the time of the current study, and the prevalence of musculoskeletal pain is known to increase

strongly with age. Third, the duration and chronicity of musculoskeletal pain have varied among studies. For example, in one study, 58% of 20–72-year-olds reported musculoskeletal pain in the previous week, as compared to 15% who had musculoskeletal pain every day during the previous year. In the current study, we measured pain within the previous 4 weeks, which is most similar to the former definition, with a correspondingly similar estimate. The estimated prevalence of neuropathic pain varies from 1% to 8.8% in the general population (Bowsher, 1991; Yawn *et al*, 2009) and from 6.9% to 8.2% amongst those with chronic pain (Bouhassira *et al*, 2008; Torrance *et al*, 2006). Although the present study was not designed to estimate the prevalence of neuropathic pain, the proportion of areas we assessed that fulfilled the criteria for likely neuropathic pain according to the PD-Q is reassuringly similar.

To date, no other studies of QST have been conducted with regard to joint pain in the community, but the results can be compared to those from a study of somatosensory abnormalities in osteoarthritis of the knee (Wylde *et al*, 2011). Consistent with the current study, Wylde and colleagues (Wylde *et al*, 2011) demonstrated increased sensitivity to a pressure stimulus applied distant to the site of pain (the right forearm) in patients as compared to healthy controls and no significant difference in distant warm detection. In contrast, distant heat pain thresholds were not found to be significantly different, whereas in our study, subjects with pain demonstrated significantly lower heat pain thresholds than those without pain. While this may represent a true difference between the populations

being studied, it may also reflect differences in the analysis methods and sites assessed. Overall, these studies emphasize the potential for altered pain sensitivity in areas away from the site of pain, implicating possible central nervous system involvement.

Since there is no gold standard test for neuropathic pain, we sought to compare 2 of the tools that are currently used: the PD-Q versus QST. Although there are no previous studies that specifically assess the association between PD-Q scores and QST values in the community, a study of patients with chronic pain showed that self-reported neuropathic pain features identified using the Neuropathic Pain Symptom Inventory correlate with related modalities identified by QST (Attal *et al*, 2008). Furthermore, a study of patients with fibromyalgia demonstrated that pressure–pain thresholds were correlated with PD-Q scores (Amris *et al*, 2010). More recently, a study of patients with knee OA demonstrated that patients with a higher score on the modified PD-Q were more likely to have signs of CS, measured using QST (Hochman *et al*, 2013).

Hochman and colleagues demonstrated the same group of most common pain qualities as identified in the present study in their patients with knee osteoarthritis, using the modified PD-Q: radiating pain (59.2%), electrical shocks (50.4%), sensitivity to pressure (34.9%), and burning pain (33.3%) (Hochman *et al*, 2011). The actual frequency of symptoms was much higher than in the current study, which is expected, since only patients with moderate-to-severe symptoms of arthritis were

recruited. This suggests that a similar set of qualities may be important in musculoskeletal conditions in general, although further exploration of this is required.

The strengths of this study include its large sample size, the use of an unselected community-based cohort, with the participating women being representative of those in the general population of the UK, and incorporation of potential confounding factors, such as BMI, age, and use of pain-modifying medications. The main limitation is the use of the PD-Q to assess separate areas affected by pain within an individual. Although not formally validated for use in this manner, the modified PD-Q, which has been found to have adequate face and content validity, follows a similar principle (Hochman *et al*, 2011). A further limitation is the lack of definitive diagnostic information regarding the presence of any actual lesions of the somatosensory system. For this reason, it is possible to comment only on the presence of features suggestive of neuropathic pain. As details of widespread pain were not formally collected, the effect of this on the QST results also cannot be assessed. Finally, the study findings are applicable only to women between the ages of 64 and 87 years.

We demonstrated in the current study that pain-modifying medications did not eradicate sensory changes detected by QST, but rather, they acted as a marker of severity. Standard practice is to cease pain medication for at least 24 hours prior to QST (22,23), a practice that contributes to the ethical and logistical constraints of its transferability as a clinically viable tool. These data reassure us that meaningful

changes can still be detected despite the use of pain medications, increasing the potential clinical utility of QST. Furthermore, the presence of possible or likely neuropathic pain in 20.1% of subjects requiring pain-modifying medications for joint pain highlights the potential burden of neuropathic pain features in this group of individuals living in the community.

The association between heat pain thresholds, mechanical pain sensitivity, and PD-Q scores provides reassuring concurrent validation of significant overlap between the paradigms being measured using both techniques in this setting. While these findings complement the results of a neuroimaging study of patients with hip osteoarthritis conducted by investigators in our group, which demonstrated a significant correlation between the PD-Q score and periaqueductal grey matter activation in response to punctate stimuli (Gwilym *et al*, 2009), further work on establishing the underlying mechanisms and benefits of treatments specifically targeting these features is needed. Furthermore, the presence of increased sensitivity to heat in isolation of changes in mechanical pain sensitivity (15%) and vice versa (27%) suggests that testing multiple modalities may differentiate clinically important subgroups of patients.

In summary, the findings of this study confirm that musculoskeletal pain is common in the community, and despite the likely tendency toward mild disease and the continuation of pain-modifying medication, QST and the PD-Q identify features suggestive of neuropathic pain with significant overlap between the two techniques.

Further validation of the findings is required before transferring these techniques to the clinical setting.

4 Pain Sensitisation Contributes to the Discordance Between Structural and Symptomatic Knee Osteoarthritis

4.1 Abstract

Objective

Central sensitisation (CS) may help explain the discordance between radiographic and symptomatic knee osteoarthritis (OA). The aim of this study was to examine whether participants of a population-based cohort, sub-grouped according to the congruence or discordance radiographic and symptomatic knee OA, showed any differences in pain sensitisation measured using quantitative sensory testing (QST), independent of psychological and demographic measures.

Methods

Warm detection, heat pain, mechanical pain thresholds and sharpness rating score were determined in 426 participants from the Chingford Study, a community-based cohort study. Subgroups were generated based on the presence or absence of pain and radiograph knee OA for each knee separately. Multinomial regression modeling was used to investigate and quantify any association between QST measures and subgroup membership for each knee, adjusting for age, BMI, mood and pain-modifying medication use.

Results

After excluding 24 participants who had previously undergone knee replacement surgery, 804 knees, from the remaining 402 women, were sub-grouped as follows: 163 (20%) had no pain and no radiographic osteoarthritis (ROA), 344 (42%) had no pain with ROA, 47 (6%) had pain but no ROA, and 267 (33%) had pain and ROA.

Compared to the group with no pain and ROA, each unit increase in SRS measured at the sternum was associated with a 42% increase in the chance of being in the pain and no ROA group and a 26% increase in the chance of being in the pain and ROA group. At the knee each unit increase in SRS was associated with a 19% increase in the chance of being in the pain and no ROA group compared to the no pain and ROA group.

Conclusion

Pain sensitisation, measured using QST does contribute to the discordance seen between symptomatic and structural knee OA, in a community-based setting. In particular SRS, is a relatively simple tool, and may be easily translated to the bedside in the future in order to identify CS in patients and potentially optimize treatment strategies.

4.2 Introduction

Discordance between symptomatic and structural evidence of knee osteoarthritis (OA) is well described (Bedson *et al*, 2008). One possible explanation is that factors affecting pain processing, beyond the diseased joint, may contribute to this discordance and its variation. For example, the presence of central sensitisation may help to explain the apparent discordance seen between radiographic and symptomatic knee OA.

Central sensitisation (CS) is defined as "an amplification of neural signaling within the central nervous system that elicits pain hypersensitivity" (Merskey *et al*, 1994). There is currently no gold standard method for measuring central sensitisation in humans (Woolf, 2011). However, quantitative sensory testing (QST) has been frequently used to assess pain sensitisation in musculoskeletal conditions (Neogi *et al*, 2013; Suokas *et al*, 2012). QST is a technique that measures psychophysical responses to controlled stimuli, with the aim of identifying neural dysfunction. Allodynia, pain due to a stimulus that does not normally evoke pain, or hyperalgesia, increased pain from a nociceptive stimulus, identified by QST may indirectly suggest the sensitisation of nociceptive neurons. If these phenomena are identified distant from the site of the index pain, they may represent central, rather than peripheral, sensitisation.

Evidence for the role of abnormal centrally mediated pain processing, in addition to the traditionally accepted peripheral nociceptive driver, arises from a combination of

animal studies (Orita *et al*, 2011; Thakur *et al*, 2012), symptom based assessment (Hochman *et al*, 2010; Hochman *et al*, 2011; Ohtori *et al*, 2012), quantitative sensory testing (QST) (Arendt-Nielsen *et al*, 2010; Bajaj *et al*, 2001; Hendiani *et al*, 2003; Kosek *et al*, 2000; Kosek *et al*, 2000; Nikolajsen *et al*, 2008; Ordeberg, 2004; Suokas *et al*, 2012; Wylde *et al*, 2011) and neuroimaging research (Baliki *et al*, 2008; Gwilym *et al*, 2009; Parks *et al*, 2011). Collectively these studies suggest that central sensitisation may have an important role to play in the generation of pain in OA.

There are also data to suggest that CS may contribute to the discordance seen between structural and symptomatic knee OA. For example, a previous study of 113 patients with established knee OA investigated the differences in QST and psychosocial distress profiles, between those with discordant versus congruent clinical reports of intensity of knee pain relative to severity of radiographic disease (Finan *et al*, 2013). The authors reported that patients with higher levels of pain, in the absence of moderate to severe radiographic evidence of knee OA were more sensitive to experimental pain stimuli distant to the affected knee, suggestive of CS. This effect remained significant after adjusting for psychosocial measures.

The current study was designed to investigate whether the previous findings could be replicated in a community-based population, where much of the assessment and management of knee OA take place.

4.3 Aim

The aim of this study was to examine whether participants of a population-based cohort, sub-grouped according to the congruence or discordance of radiographic and symptomatic knee OA, showed any differences pain sensitisation measured using QST. It was hypothesised that participants with evidence of radiographic OA but no corresponding pain symptoms would demonstrate less local and distant pain sensitivity compared to those with symptomatic radiographic OA, as well as those with pain in the absence of radiographic OA.

4.4 Methods

4.4.1 Setting and Subjects

The study participants were selected from the 516 women who attended the year 20 visit for the Chingford Study, as described in 2.2.1 The included cohort comprised the 426 women who also had complete data for quantitative sensory testing measures, and radiographic assessment at the knee.

4.4.2 Data Collection

Full details on data collection of population demographics, QST measures, pain assessment, psychological factors and radiographic assessment are given in section 2.2.2. In brief, the variables utilised in this analysis included height, weight, and HADS as well as Kellgren and Lawrence global score and WOMAC pain subscale for each knee. QST was conducted at the medial joint of each knee and 3cm distal to the sternal notch; in order to capture both peripherally and centrally mediated changes in pain sensitivity. The QST modalities measured at each site were: warm detection threshold, mechanical pain detection threshold, heat pain threshold and sharpness rating score.

4.4.3 Statistical analysis

The characteristics of the women in the excluded and included study cohorts were compared using Student's t-test, Wilcoxon-Mann-Whitney, and Chi-square test for normally distributed, non-normally distributed, and categorical data respectively. The sample was then divided into four subgroups using dichotomous splits of knee pain and radiographic osteoarthritis (ROA) status for each knee separately. Pain was

defined as any knee pain captured using the WOMAC pain subscale, and ROA was defined as a Kellgren and Lawrence global score of grade two or more (Leyland *et al*, 2012). Cases of total knee replacement were excluded from the current analysis. The congruency of subgrouping for right and left knees was then assessed for each participant.

Multinomial regression modeling was used to investigate and quantify any association between QST measures and subgroup membership for each knee. The subgroups were used as the outcome measure: the no pain and ROA group was used as the reference group, as it was the largest. The QST measures were used as predictors, with a separate model for each modality and site assessed. The clustering of knees from the same participant was accounted for in the models. Potential confounding factors were selected *a priori* and were all included in each model. The confounding factors selected were: age, BMI, use of pain-modifying medication and the Hospital Anxiety and Depression Scale questionnaire (HADS) score. A sensitivity analysis was conducted in order to further investigate the effect of any pain modifying medication on QST measures. For this sub-analysis, only participants who were not on any pain medication were included. Finally, given the literature on sensory changes at the opposite knee (Kosek *et al*, 2000), the effect of QST measures at the contralateral knee on group membership was assessed by repeating the models, with the contralateral measures included as additional predictor variables. The variable inflation factor was used to estimate collinearity between the two knee measures for each QST modality tested.

4.5 Results

There were no significant differences in age, BMI, HAD score or use of pain-modifying medication between the 426 women who were included in the present study and the 90 who were excluded (Table 4-1).

Table 4-1. Characteristics of the women in the Chingford Study at the 20-year visit who were included in the present study, compared to those who were excluded.

	Excluded cohort (n=90)	**Included cohort (n=426)**	**P[§]**
Age, median (IQR) years	72 (68-77)	71 (67-76)	0.081
BMI, mean ± SD kg/m^2	27.7 ± 4.5	27.8 ± 5.0	0.888
HAD, mean ± SD range 0-42	18.0 ± 2.8	17.6 ± 3.0	0.142
Use of pain modifying medications n (%)	36 (40.0)	161 (37.8)	0.733

The excluded cohort comprised all the women in the Chingford cohort who attended the 20-year visit but did not have complete data for quantitative sensory testing measures and radiographic assessment at the knee. The included cohort comprised all the women in the Chingford cohort who attended the 20-year visit who did have complete data for quantitative sensory testing measures and radiographic assessment at the knee. [§]*P*-values are for comparisons between the two groups using Student's t-test for normally distributed data, Kruskal-Wallis for non-normally distributed data and Chi-square test for categorical data. BMI=body mass index; SD= standard deviation; IQR=interquartile range; HAD=Hospital Anxiety and Depression Scale.

Summary statistics for QST measures and KL grades for the study cohort are shown in Table 4-2.

Table 4-2 Quantitative sensory testing measures and radiographic features at the sites assessed, for the 426 women included in the study.

Quantitative Sensory Testing			
	Sternum	Right Knee	Left Knee
Warm Detection Threshold, median (IQR) ^{0}C	4.9 (3.8-6.6)	6.2(4.7-9.0)	6.0 (4.5-8.4)
Heat Pain Threshold, median (IQR) ^{0}C	45.1 (42.3-47.4)	47.0 (43.8-48.8)	46.7 (43.5-48.5)
Mechanical Pain Threshold, median (IQR) mN	38.4 (11.2-128.0)	99.2 (38.4-281.6)	102.4 (32.0-281.6)
Sharpness rating score, mean ± SD range 0-10†	5.6 (2.4)	5.0 (2.3)	5.1 (2.4)
Radiographic Features			
		Right Knee	Left Knee
KL grade, n (%)			
0		47 (11)	40 (9)
1		46 (11)	77 (18)
2		183 (43)	164 (39)
3		123 (29)	121 (28)
4		13 (3)	7 (2)
TKR		14 (3)	17 (4)
Self-reported Pain			
		Right Knee	Left Knee
WOMAC pain, median (IQR) range 0-20		0 (0-3)	0 (0-4)

† Measures of Sharpness rating to 512mn probe were available for 284 of the women included in the study. IQR=interquartile range; SD= standard deviation; KL= Kellgren and Lawrence; TKR=total knee replacement; WOMAC pain= Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) pain subscale.

After excluding 24 participants who had previously undergone knee replacement surgery, 804 knees, from the remaining 402 women, were sub-grouped as follows: 163 (20%) had no pain and no ROA, 344 (42%) had no pain with ROA, 47 (6%) had pain but no ROA, and 267 (33%) had pain and ROA. For 262 (65%) of the women both knees were placed in the same subgroup. The congruency between left and right knee subgroups for each of the women is shown in Table 4-3.

Table 4-3 Congruency between left and right knee subgroups, defined by the presence or absence of pain and structural features of knee osteoarthritis, for each participant*.

		Right Knee			
		No Pain & No ROA (n=76)	No Pain & ROA (n=167)	Pain & No ROA (n=16)	Pain & ROA (n=143)
Left Knee	No Pain & No ROA (n=86)	49/86 (57%)	31/86 (36%)	2/86 (2%)	4/86 (5%)
	No Pain & ROA (n=173)	21/173 (12%)	114/173 (66%)	2/173 (1%)	36/173 (21%)
	Pain & No ROA (n=30)	5/30 (17%)	5/30 (17%)	8/30 (27%)	12/30 (40%)
	Pain & ROA (n=113)	1/113 (1%)	17/113 (15%)	4/113 (4%)	91/113 (80%)

* Pain was defined as any knee pain captured using the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) pain subscale and ROA was defined as Kellgren and Lawrence global score of grade 2 or more. Cases of total knee replacement were excluded. ROA=radiographic osteoarthritis.

At the knee, heat pain threshold (HPT) and sharpness rating score (SRS) showed a significant association with subgroup membership (Table 4-4). Compared to the group with no pain with ROA, each degree increase in HPT at the knee was

associated with a 7% reduction in the chance of being in the no pain and no ROA group, and a 6% reduction in the chance of being in the pain and ROA group. For SRS, each unit increase was associated with a 19% increase in the chance of being in the pain and no ROA group compared to the no pain and ROA group.

At the sternum, only the sharpness rating score (SRS) showed a significant association with subgroup membership, which persisted after adjusting for potential confounding factors (Table 4-5). Compared to the group with no pain and ROA, each unit increase in SRS measured at the sternum was associated with a 42% increase in the chance of being in the pain and no ROA group and a 26% increase in the chance of being in the pain and ROA group.

Table 4-4 Logistic regression model of quantitative sensory testing measures at the knee as predictors of subgroup, defined by the presence or absence of pain and structural features of knee osteoarthritis for each knee*.

QST measure as predictor	Subgroup as outcome measure	Knee			
		Univariable Model RRR (95% CI) [§]	P	Multivariable Model RRR (95% CI) [§§]	P
Warm Detection Threshold, per ^{0}C increase	No Pain & No ROA	0.94 (0.88-1.02)	0.127	0.94 (0.88-1.02)	0.127
	No Pain & ROA	Reference group	-	Reference group	-
	Pain & No ROA	0.96 (0.88-1.04)	0.310	0.93 (0.85-1.02)	0.102
	Pain & ROA	1.01 (0.96-1.08)	0.519	0.99 (0.93-1.05)	0.778
Heat Pain Threshold, per ^{0}C increase	No Pain & No ROA	0.92 (0.86-0.98)	0.013	0.93 (0.87-0.99)	0.026
	No Pain & ROA	Reference group	-	Reference group	-
	Pain & No ROA	0.95 (0.86-1.04)	0.282	0.96 (0.87-1.06)	0.448
	Pain & ROA	0.94 (0.88-0.99)	0.027	0.94 (0.89-1.00)	0.050
Mechanical Pain Threshold, per step increase	No Pain & No ROA	0.95 (0.81-1.12)	0.576	0.97 (0.83-1.15)	0.778
	No Pain & ROA	Reference group	-	Reference group	-
	Pain & No ROA	0.95 (0.75-1.21)	0.684	1.01 (0.79-1.28)	0.949
	Pain & ROA	0.95 (0.81-1.09)	0.434	0.99 (0.85-1.15)	0.890
Sharpness rating score, per unit increase	No Pain & No ROA	1.04 (0.92-1.18)	0.490	1.02 (0.90-1.15)	0.813
	No Pain & ROA	Reference group	-	Reference group	-
	Pain & No ROA	1.18 (1.00-1.42)	0.021	1.19 (1.00-1.42)	0.049
	Pain & ROA	1.10 (0.99-1.22)	0.064	1.11 (0.99-1.26)	0.070

* Pain was defined as any knee pain captured using the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) pain subscale and ROA was defined as Kellgren and Lawrence global score of grade 2 or more. [§]Multinomial logistic regression modelling was used, predictors were clustered by person, to take account of the knee level modeling [§§]Multivariate modelling adjusted for age, body mass index, anxiety and depression, and use of analgesic or neuropathic pain medication. OR = odds ratio; 95% CI = 95% confidence interval; RRR=relative risk ratio; QST=quantitative sensory testing, ROA=radiographic osteoarthritis.

Table 4-5 Logistic regression model of quantitative sensory testing measures at the sternum as predictors of subgroup, defined by the presence or absence of pain and structural features of knee osteoarthritis for each knee*.

QST measure as predictor	Subgroup as outcome measure	Sternum			
		Univariate Model RRR (95% CI)[§]	P	Multivariate Model RRR (95% CI)[§§]	P
Warm Detection Threshold, per ^{0}C increase	No Pain & No ROA	1.00 (0.91-1.11)	0.906	0.99 (0.90-1.10)	0.862
	No Pain & ROA	Reference group	-	Reference group	-
	Pain & No ROA	1.00 (0.88-1.15)	0.939	1.00 (0.897-1.16)	0.986
	Pain & ROA	1.01 (0.94-1.10)	0.649	1.03 (0.95-1.12)	0496
Heat Pain Threshold, per ^{0}C increase	No Pain & No ROA	0.98 (0.92-1.05)	0.560	0.97 (0.91-1.04)	0.381
	No Pain & ROA	Reference group	-	Reference group	-
	Pain & No ROA	0.97 (0.87-1.07)	0.529	0.97 (0.89-1.10)	0.861
	Pain & ROA	0.97 (0.92-1.02)	0.234	1.00 (0.94-1.06)	0.941
Mechanical Pain Threshold, per step increase	No Pain & No ROA	0.87 (0.74-1.02)	0.088	0.87 (0.75-1.02)	0.089
	No Pain & ROA	Reference group	-	Reference group	-
	Pain & No ROA	0.92 (0.70-1.21)	0.559	0.97 (0.73-1.27)	0.804
	Pain & ROA	0.86 (0.75-0.98)	0.025	0.89 (0.77-1.03)	0.121
Sharpness rating score, per unit increase	No Pain & No ROA	1.12 (0.99-1.24)	0.082	1.09 (0.97-1.22)	0.155
	No Pain & ROA	Reference group	-	Reference group	-
	Pain & No ROA	1.38 (1.12-1.35)	0.004	1.42 (1.14-1.77)	0.005
	Pain & ROA	1.21 (1.10-1.35)	<0.001	1.26 (1.12-1.42)	<0.001

* Pain was defined as any knee pain captured using the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) pain subscale and ROA was defined as Kellgren and Lawrence global score of grade 2 or more. [§]Multinomial logistic regression modelling was used, predictors were clustered by person, to take account of the knee level modeling [§§]Multivariate modelling adjusted for age, body mass index, anxiety and depression, and use of analgesic or neuropathic pain medication. OR = odds ratio; 95% CI = 95% confidence interval; RRR=relative risk ratio; QST=quantitative sensory testing, ROA=radiographic osteoarthritis.

When the model was repeated including only those participants who were not taking any pain-modifying medication, the QST measures at the sternum that were significantly associated with group membership remained the same but the associations with QST measures at the knee were no longer significant, (Appendix B).

The effect of contralateral QST measures on group membership was then investigated. The variable inflation factors were less than 2.5 in all cases suggesting that collinearity between the predictor variables was of an acceptable level in all the models. There was no significant association between any of the contralateral QST measures and subgroup membership (Table 4-6).

Table 4-6 Logistic regression model of quantitative sensory testing measures, at the contralateral knee, as predictors of subgroup defined by the presence or absence of pain and structural features of knee osteoarthritis for each knee*.

QST measure as predictor	Subgroup as outcome measure	Knee			
		Univariable Model[§] RRR (95% CI)	P	Multivariable Model RRR (95% CI)[§§]	P
Warm Detection Threshold, per ^{0}C increase	No Pain & No ROA	0.96 (0.90-1.02)	0.247	0.96 (0.90-1.03)	0.271
	No Pain & ROA	Reference group	-	Reference group	-
	Pain & No ROA	1.02 (0.92-1.12)	0.742	1.01 (0.91-1.11)	0.906
	Pain & ROA	1.00 (0.94-1.06)	0.992	0.99 (0.93-1.05)	0.768
Heat Pain Threshold, per ^{0}C increase	No Pain & No ROA	1.00 (0.94-1.07)	0.993	1.01 (0.94-1.08)	0.826
	No Pain & ROA	Reference group	-	Reference group	-
	Pain & No ROA	1.06 (0.97-1.12)	0.216	1.07 (0.97-1.18)	0.186
	Pain & ROA	0.99 (0.93-1.05)	0.774	0.99 (0.93-1.06)	0.855s
Mechanical Pain Threshold, per step increase	No Pain & No ROA	1.01 (0.86-1.19)	0.894	1.02 (0.87-1.21)	0.774
	No Pain & ROA	Reference group	-	Reference group	-
	Pain & No ROA	1.14 (0.83-1.56)	0.421	1.16 (0.84-1.60)	0.358
	Pain & ROA	1.07 (0.94-1.24)	0.309	1.09 (0.94-1.27)	0.230
Sharpness rating score, per unit increase	No Pain & No ROA	1.06 (0.92-1.21)	0.429	1.04 (0.92-1.19)	0.513
	No Pain & ROA	Reference group	-	Reference group	-
	Pain & No ROA	0.96 (0.68-1.35)	0.807	0.96 (0.67-1.38)	0.830
	Pain & ROA	0.98 (0.87-1.10)	0.745	0.99 (0.87-1.12)	0.837

* Pain was defined as any knee pain captured using the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) pain subscale and ROA was defined as Kellgren and Lawrence global score of grade 2 or more. Corresponding measures from the contralateral knee were used as predictors [§]Multinomial logistic regression modelling was used, predictors were clustered by person, to take account of the knee level modeling [§§]Multivariate modelling adjusted for age, body mass index, anxiety and depression, and use of analgesic or neuropathic pain medication. OR = odds ratio; 95% CI = 95% confidence interval; RRR=relative risk ratio; QST=quantitative sensory testing, ROA=radiographic osteoarthritis.

4.6 Discussion

The present study was designed in order to investigate whether the congruence or discordance of radiographic and symptomatic knee OA, was associated with any differences in pain sensitisation measured using QST. The main finding is that a higher sensitivity to a fixed punctate stimulus of 512mN, applied at the sternum, was significantly associated with the presence of congruent self-reported pain and radiographic OA, compared to the discordant absence of pain with ROA. Furthermore, increased pain sensitivity at the sternum was also associated with the presence of pain in the absence of ROA. The fact that these associations were present at the sternum, a site distant from the area of pain, suggests that this pain sensitisation is likely to be centrally rather than peripherally mediated. This effect was present despite adjustment for demographic factors, the use of pain-modifying medication, and measures of psychological distress.

The current findings complement those of Finan and colleagues, who demonstrated that pain sensitivity across measures distal to the index knee was highest in those with discordant high levels of clinical pain in the absence of moderate-to-severe radiographic change, suggesting evidence for the role of central sensitisation (Finan *et al*, 2013). The present study extends these findings to a community-based setting and suggests that CS may also play a role at the milder end of the disease spectrum. There may therefore also be a need to recognize the contribution of CS in primary care. This may prompt earlier, and better-targeted therapeutic strategies, which could in turn improve symptom control and associated morbidity.

The cross sectional nature of the data means that it is impossible to disentangle cause from effect. It may be that CS is part of the mechanism for the generation of pain in knee OA. In this case CS would develop in response to underlying pathology or persistent symptoms, and could be described as a 'state' (Neogi *et al*, 2013). This would make the timing of treatment crucial in order to prevent chronic pain and may also provide additional therapeutic targets. Alternatively if CS behaves as a 'trait' whereby its presence is independent of OA, different strategies would be needed to identify and minimize the effect of CS on the pain (Neogi *et al*, 2013). Previous work on patients with knee OA has suggested that CS behaves as a trait based on its lack of association with duration of symptoms and radiographic severity (Neogi *et al*, 2013). In support of these findings, the concept of pain vulnerability and resilience in the general pain context has been highlighted (Denk *et al*, 2014). There is evidence to suggest that genetics and early life stressors may confer increased risk of central sensitisation (Denk *et al*, 2014). Furthermore, it is hoped that in the future it will be possible to identify those who are more vulnerable to develop chronic pain conditions in order to allow preventative measures, to encourage better 'brain resilience', as well as more tailored treatment once a painful condition has developed (Denk *et al*, 2014).

Although univariable analysis showed significantly increased pain sensitivity at the knee, measured using SRS, amongst those with pain and ROA compared to the group with discordant absence of pain with ROA, the results of multivariate analysis were not significant. This is surprising, as the effect of CS should be seen at the affected

site as well as at unaffected sites. The QST measures at the contralateral knee also didn't reveal any association with subgrouping. It is interesting that the study by Finan and colleagues was also unable to show any significant differences between QST measures at the affected knee (Finan *et al*, 2013). It may be that a peripheral component that was not measured in the present study, such as the presence of synovitis, may have masked the effect of CS in the periphery. In addition the presence of clinical knee pain may make it harder to disentangle the response to artificially induced experimental pain. This is supported by the observation that the effect size seen on univariate analysis was smaller than that seen at the sternum, and a larger sample size may be needed to detect this local difference in pain sensitivity.

The potential clinical implications of these findings are broad. The identification of a relatively simple QST measure, which could theoretically be translated to the bedside setting, makes the possibility of assessing for CS in large numbers of patients more realistic. For example, SRS could be used in order to assess the contribution of CS in an individual patient, which in turn may identify those who would benefit most from centrally acting agents, such as duloxetine, which already appears in clinical practice (Brown *et al*, 2013; McAlindon *et al*, 2014). A previous study of duloxetine in diabetic patients showed that QST measures of conditioned pain modulation prior to treatment predicted response to duloxetine, whereas pre-intervention pain intensity didn't (Yarnitsky *et al*, 2012).

The main strength of the study is the use of relatively simple and short QST measures without cessation of any medication beforehand, making the techniques more easily translatable to the bedside. By studying a community-based population, the results are generalizable to a larger knee pain patient cohort rather than being restricted to those seen in secondary care. Finally the relatively large numbers involved in most aspects of the study has enabled meaningful adjustment for potential confounding factors. The main limitation of the study is its cross-sectional design preventing cause and effect from being differentiated from one another. The method used to dichotomise pain and ROA is also limited by the potential for residual confounding. For example the distribution of KL grades may not be the same in the asymptomatic and radiographic OA group and the symptomatic radiographic OA group. The current study also did not include the measurement of pain pressure thresholds. Since the design and data collection stages of this study, considerable data has been published on the use of pain pressure threshold testing, temporal summation and conditioned pain modulation in OA (Egsgaard *et al*, 2015; Fingleton *et al*, 2015; Petersen *et al*, 2015; Suokas *et al*, 2012). These QST modalities may also be of potential use in identifying different underlying mechanisms associated with subgroup membership. Finally, the study findings are also restricted to women between the ages of 64 and 87 years.

In conclusion, this study confirms that pain sensitisation measured using QST does contribute to the discordance seen between symptomatic and structural knee OA, in a community-based setting. In particular SRS, measured at the sternum, is a

relatively simple tool, which can be used to detect features suggestive of CS and may be easily translated to the bedside in order to identify CS in patients to potentially optimize treatment strategies.

5 Pre-operative psychophysical features of knee osteoarthritis pain in a surgical patient cohort

5.1 Abstract

Objective

Knee replacement surgery is commonly used in patients with moderate to severe knee osteoarthritis (OA) in order to reduce pain. It is now recognised that 10-34% of patients report an unfavourable long-term outcome with persistent pain after surgery. Previous studies have shown that around 20% of patients with knee OA reported features of neuropathic pain, and it may be that this patient group is more likely to have an adverse outcome following surgery. The aims of this study were to describe the prevalence of neuropathic pain in a cohort of patients with knee OA, awaiting knee replacement surgery; and investigate any differences in psychophysical characteristics between those with and without features of neuropathic pain.

Methods

Patients with clinician-diagnosed knee OA, placed on the waiting list for joint replacement surgery, were recruited to the study and were assessed prior to surgery. A questionnaire pack was used to collect pre-operative demographic, clinical, pain, psychological and sleep characteristics. Specifically, the modified PainDETECT (mPD-Q) score was used to divide the cohort into those with nociceptive (<13), unclear (13–18) and neuropathic pain (>18) prior to surgery. Quantitative sensory testing (QST) was used to measure experimental pain sensitivity at local, regional and distant sites. Comparisons were made between those with and without

features of neuropathic pain. Multinomial logistic regression modelling was used to measure associations between pain and psychological characteristics as well as QST measures and pain grouping according to the mPD-Q score, adjusting for age, sex, BMI, pain severity and use of pain-modifying medications.

Results

120 patients were recruited to the study: 63 (52.5%) had nociceptive pain; 32 (26.7%) had unclear pain; and 25 (20.8%) had likely neuropathic pain. Patients with neuropathic pain had significantly more debilitating disease with a worse overall OKS (mean $\pm$ SD 20.5 (7.3) versus 13.1 (5.5), $p<0.001$). The neuropathic group also demonstrated significantly higher levels of psychological distress including: pain catastrophising (median (IQR) 21 (10-36) versus 11 (6-17), $p<0.001$) and trait anxiety (mean $\pm$ SD 43.2 (15.9) versus 33.4 (10.7)). The association between neuropathic pain and heat pain and pressure pain thresholds when measured over tibialis anterior ipsilateral to the index knee remained significant, even after adjusting for all potential confounding factors (median (IQR) 46.7(44.3-47.7) versus 49.1 (45.3-50.0), $p<0.05$ and mean $\pm$ SD 271(67.8) versus 361.1 (119.8), $p<0.05$ respectively). Heat pain thresholds measured at the index knee were also significantly lower in the neuropathic group compared to the nociceptive group, having adjusted for potential confounding factors (median (IQR) 44.3(42.1-46.5) versus 46.3 (42.9-49.3), $p<0.05$).

Conclusion

Neuropathic pain is common amongst patients with moderate to severe knee OA, and is associated with significantly higher symptom severity, psychological distress and pain sensitivity. The identification of individuals with neuropathic pain in this

patient group may allow targeted adjunctive therapy prior to surgery, which may in turn improve outcome post-operatively. A longitudinal study is needed to assess the long-term impact of pre-operative neuropathic pain on surgical outcome.

5.2 Introduction

Joint replacement surgery for osteoarthritis (OA) of the knee is usually reserved for patients with end-stage disease when, non-surgical management has not been effective (National Collaborating Centre for Chronic Conditions, 2008; Nelson *et al*, 2013; Zhang *et al*, 2008; Zhang *et al*, 2010). The main aims for surgery are to reduce pain in the affected joint and therefore improve a patient's quality of life. However, it is now recognised that a significant number of patients report on-going pain after surgery. Previous studies have shown that an unfavourable long-term pain outcome was reported in 10-34% of patients, with 15% of patients reporting severe to extreme persistent pain at three to four years after surgery (Beswick *et al*, 2012; Wylde *et al*, 2011).

The number of people suffering from knee OA is predicted to rise due to the combination of an ageing population and the obesity epidemic. Symptomatic knee OA has previously shown an increasing trend, over a 20-year period, with obesity contributing to part of this effect (Nguyen *et al*, 2011). This is in turn associated with a projected exponential rise in demand for costly surgery. The demand for primary total knee arthroplasty is predicted to grow by 673% over a 25 year period, equating to 3.48 million procedures (95% prediction interval, 2.95 to 4.14 million) by 2030, in the United States alone (Kurtz *et al*, 2007). Data from the UK suggests that, taking account of projected changes in age and BMI, 118,666 TKR procedures will be performed in 2035. The problem of persistent pain after joint replacement surgery is therefore likely to increase too.

The risk factors for persistent pain following total knee replacement surgery (TKR) have been recently reviewed with the inclusion of a meta-analyses to enable the quantification of the effect size of each predictor variable (Lewis *et al*, 2015). This study showed that catastrophising, mental health, preoperative knee pain, and pain at other sites were the strongest independent predictors of persistent pain after TKA. This highlights the need to focus on pre-operative pain and its associated multi-dimensional features, rather than the biomechanical aspects of the surgery.

The features suggestive of neuropathic pain are not currently routinely assessed in clinical practice, when patients are being considered for knee replacement surgery. The two main tools available for potential use in clinical practice are quantitative sensory testing (QST) and screening tools such as the PainDETECT questionnaire (PD-Q), which has also been modified for use in knee OA specifically (Bennett *et al*, 2007; Cruz-Almeida *et al*, 2013; Hochman *et al*, 2011; Thakur *et al*, 2014). It has been proposed that if a subgroup of patients with features of neuropathic pain is identified, there may be potential for tailoring analgesic therapy accordingly (Dimitroulas *et al*, 2014; Thakur *et al*, 2014).

Neuropathic pain medications have previously been used in the peri-operative period, in an attempt to reduce the severity of post-operative pain (Diaz-Heredia *et al*, 2015). Although there is some indication that drugs such as pregabalin may reduce the incidence of neuropathic pain 6 months after surgery, longer-term data are not yet available (Buvanendran *et al*, 2010). Furthermore targeted therapy

according to the presence or absence of neuropathic pain has not been trialled in patients with knee OA.

Previous work using the PainDETECT Questionnaire (PD-Q) showed that 28% of patients with knee OA, drawn from community and non-surgical knee OA cohorts, demonstrated features of possible or likely neuropathic pain (Hawker *et al*, 2008; Hochman *et al*, 2013; Hochman *et al*, 2011). In this context, patients with features of neuropathic pain reported more severe OA symptom severity and psychological distress, such as depression and pain catastrophising, compared to their counterparts without neuropathic pain symptoms (Hochman *et al*, 2011). It has also been reported that 14.8% of patients with knee OA, recruited via secondary care, had features suggestive of likely neuropathic pain (Valdes *et al*, 2014). In this context, the presence of features of neuropathic pain was associated with younger age, higher body mass index (BMI), and worse sleep, quality of life, pain intensity, stiffness, function scores as well as a higher prevalence of tiredness. The prevalence and associations of neuropathic pain features in patients with end-stage disease, who are listed for knee replacement surgery, has not been studied.

5.3 Aim

The aims of this study were to:

1. Describe the prevalence of neuropathic pain, and the specific pain qualities present, in a cohort of patients with knee osteoarthritis, awaiting knee replacement surgery.
2. Investigate any differences in psychophysical characteristics between those with and without features of neuropathic pain, identified using the modified PainDETECT (mPD-Q) questionnaire prior to surgery.

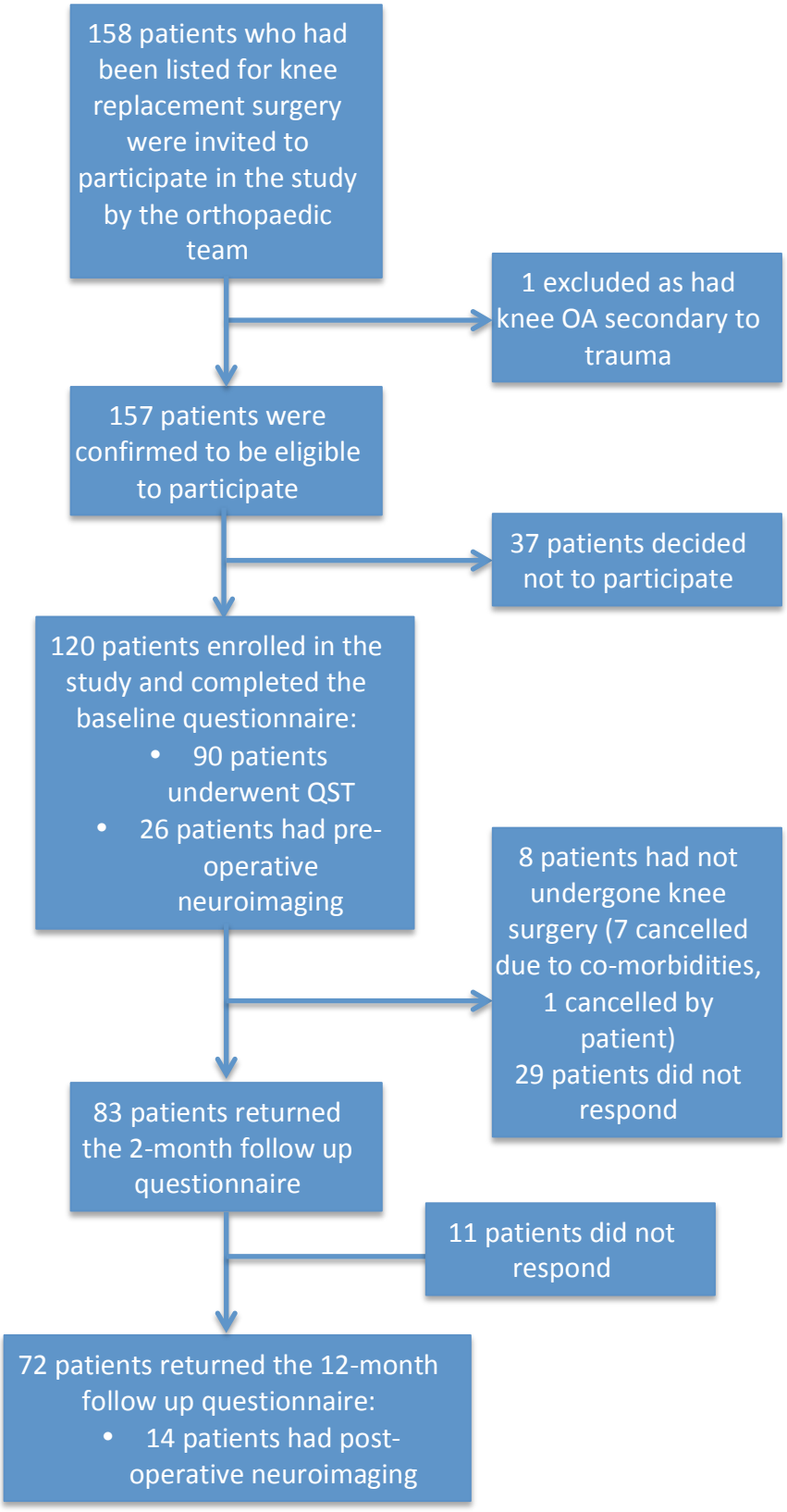
It was hypothesised that patients with neuropathic pain, identified using the mPD-Q, would demonstrate increased psychological distress, and more debilitating knee pain, as well as increased local and distant experimental pain sensitivity.

5.4 Methods

5.4.1 Setting and Subjects

The study participants were the 120 patients recruited to the The **E**valuation of **P**eri-operative pain **I**n **O**steoarthritis of the k**NE**e (EPIONE) Study. As described in full in section 2.3.1, all the patients were diagnosed with primary knee OA by a senior orthopaedic surgeon and had been placed on the waiting list for primary knee replacement surgery. The recruitment process and study visits are outlined in Figure 5.1.

Figure 5.1 Diagram of study recruitment and follow up visits for the EPIONE study.



OA=Osteoarthritis; QST=Quantitative Sensory Testing.

5.4.2 Data Collection

Details on data collection of population demographics, clinical data, radiographs, QST measures, pain assessment and psychological factors and sleep disturbance prior to surgery are given in 2.3.2 As this chapter will focus on the patient characteristics prior to surgery, only the baseline data will be considered here.

5.4.3 Statistical analysis

First the distribution of mPD-Q scores for all the patients was recorded. Data gathered from the presence of radiation, and the presence of at least moderate severity for each of the seven pain qualities measured by the mPD-Q was then used to describe the characteristics of knee pain in the whole patient cohort.

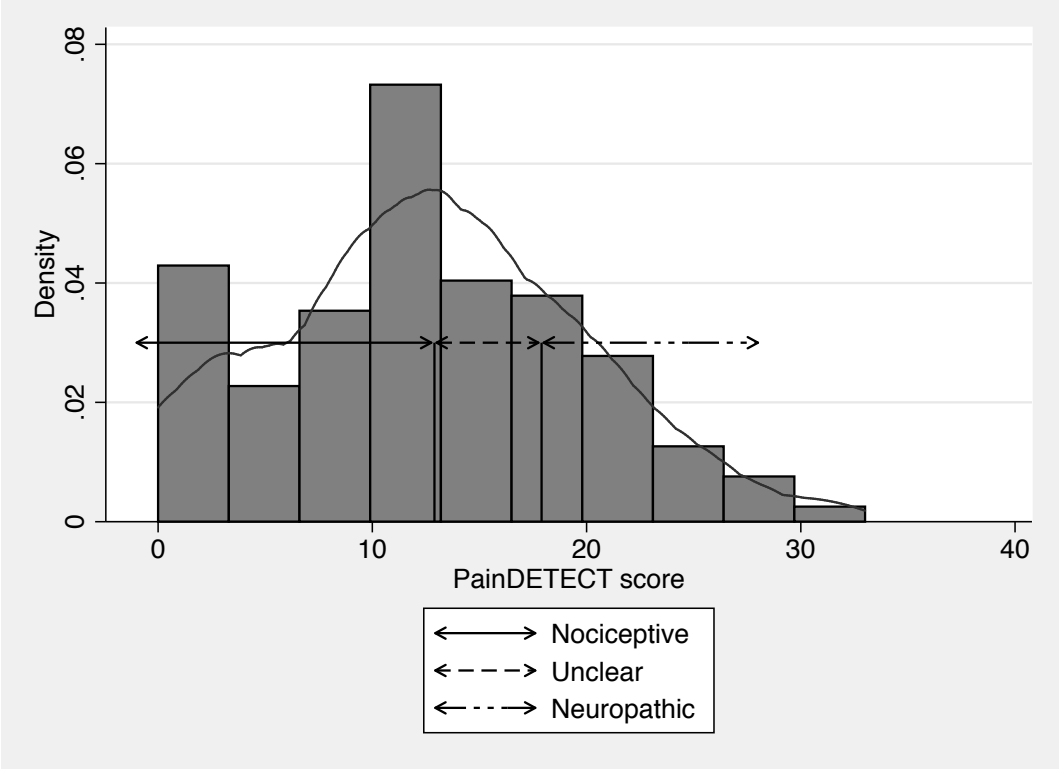
The mPD-Q score was then used to divide patients, according to established cut-off values, into those with nociceptive (<13), unclear (13–18) and neuropathic pain (>18) (Freynhagen *et al*, 2006). Pre-operative demographic and clinical patient characteristics for the unclear and neuropathic pain groups were compared to the nociceptive group, using Student's t-test, Wilcoxon-Mann-Whitney, and Chi-square test for normally distributed, non-normally distributed, and categorical data respectively. As the patients in this study were deemed to have clinician-determined moderate to severe disease, it was felt that the most relevant way to consider the radiographic measures of structural change was according to the absence or presence of definite joint space narrowing. Using the Kellgren and Lawrence scoring system, this translates to a cut-off of grade three or higher (Kellgren JH, 1963).

Multinomial logistic regression modelling was used to measure associations between neuropathic pain grouping, according to the mPD-Q score, pain and psychological characteristics, and QST measures. The nociceptive, unclear and neuropathic pain groups were used as the outcome measure, with the nociceptive group being used as the reference group. The first model was a univariable model and measured any association between the predictor of interest and pain grouping. A second model included age, BMI and sex, as potential confounding factors selected a priori. A third model further adjusting for pain severity, measured using the visual analogue score (VAS) from the Short-form McGill Pain Questionnaire (SF-MPQ), and use of pain-modifying medication, was used for the psychological and QST measures only. A final model tested the effect of pain-modifying medication on QST measures by further adjusting for the use of analgesics or neuropathic medications. Analgesics were defined as any compounds containing acetaminophen, non-steroidal anti-inflammatory drugs or opioids, and neuropathic medications included anti-depressants, selective serotonin and norepinephrine reuptake inhibitors and anti-convulsants including gabapentin and pregabalin, prescribed for any indication. Participants were subsequently categorized according to whether they had used any of the above pain modifying medications or not and this binary variable was included in the final regression model.

5.5 Results

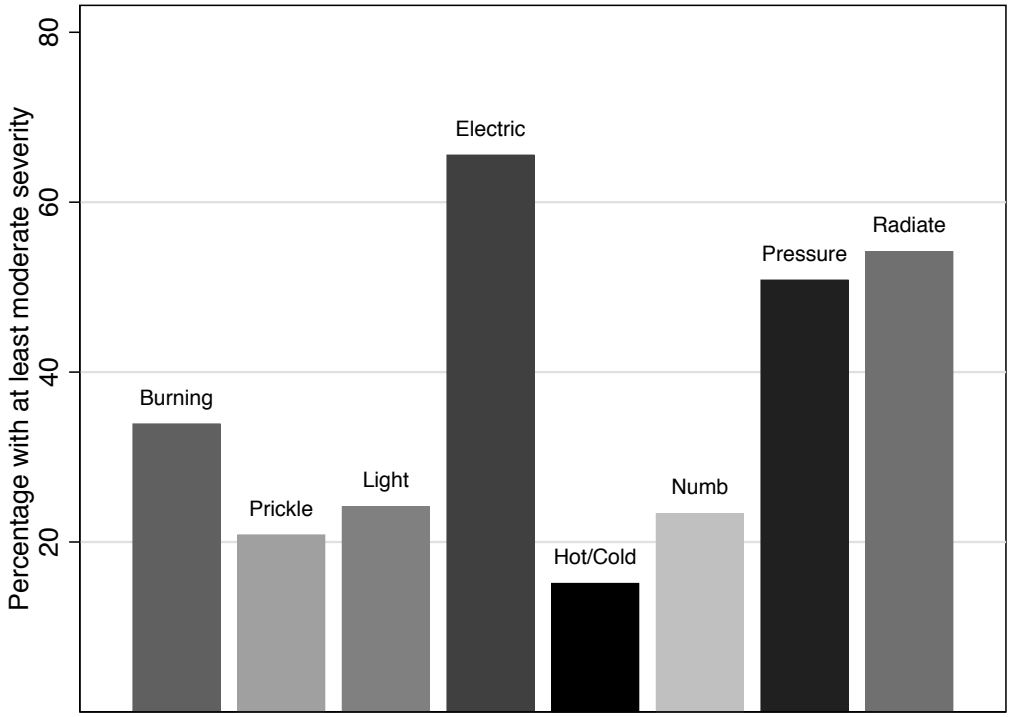
The distribution of the mPD-Q scores for the whole study cohort is shown in Figure 5.2. Among the 120 patients recruited, 63 (52.5%) had a mPD-Q score corresponding to nociceptive pain, 32 (26.7%) had a mPD-Q score corresponding to unclear pain, and 25 (20.8%) had a mPD-Q score corresponding to likely neuropathic pain. In contrast only 3 patients (2.5%) did not report any features associated with neuropathic pain.

Figure 5.2 Kernel density distribution plot of the total scores on the PainDETECT Questionnaire for all the 120 patients recruited to EPIONE.



The breakdown of the mPD-Q scores in terms of the presence or absence of radiating pain and at least moderate severity of the other seven qualities is shown in Figure 5.3. The most common qualities were sudden attacks of pain that felt like electrical shocks (65.6%), radiating pain (54.2%); pain upon light pressure (50.8%); and burning pain (13.9%). Overall, 47.3% of the patients did not report any associated radiating pain or neuropathic pain qualities of at least moderate severity, 32.5% showed a single pain quality, 9.5% showed 2, 6.5% showed 3 and 4.2% showed 4 or more qualities. Overall 17.5% of the patients had no features of radiating pain or pain qualities of at least moderate severity, 19.2% had a single pain feature, 20.8% had two features, 19.2% had three features and 13.3% had four or more features.

Figure 5.3 Qualities of pain at baseline, as determined using the PainDETECT Questionnaire, for all the 120 patients recruited to EPIONE.



The demographic and clinical features of the patients recruited to EPIONE, according to their neuropathic pain subgrouping, are shown in Table 5-1. The patients with unclear and neuropathic pain tended to be younger than those with nociceptive pain, but this only reached statistical significance for the unclear pain group. There was a trend for patients with unclear or neuropathic pain to report a longer duration of knee pain symptoms, compared to the nociceptive group, but this did not reach statistical significance. The group with neuropathic pain had significantly worse Oxford Knee Score (OKS) compared to those with nociceptive pain. This was also significant when the OKS pain and function subscales were considered separately. There was no significant difference in KL grades amongst the three pain groups (Table 5-1.).

Table 5-1 Pre-operative patient characteristics of the 120 patients recruited to EPIONE divided into nociceptive, unclear and neuropathic pain groups*.

	Nociceptive pain (n=63)	Unclear pain (n=32)	Neuropathic pain (n=25)
Demographic features			
Age, mean ± SD years	72 (8)	68 (8) †	70 (10)
Female, n (%)	27 (43)	20 (63)	14 (56)
BMI, mean ± SD kg/m^2	29.5 (5.1)	30.2 (5.2)	31.8 (4.9)
Employed, n (%)	14 (22)	12 (38)	3 (13)
Married or living with partner, n (%)	47 (75)	18 (58)	15 (60)
Clinical features			
Right knee affected, n (%)	35 (55)	18 (56)	10 (43)
Duration of pain, median (IQR) months	36 (15-90)	60 (24-120)	48 (36-120)
Use of pain-modifying medication, n(%)	36 (57)	22 (69)	17 (68)
Oxford knee score, mean ± SD range 0-48	20.5 (7.3)	19.2 (7.5)	13.1 (5.5) ††
Oxford knee score pain subscale, mean ± SD range 0-100	61.4 (15.1)	62.3 (13.1)	74.7 (9.7) ††
Oxford knee score function subscale, mean ± SD range 0-100	74.4 (22.9)	77.8 (16.4)	93.4 (12.1) ††
Kellgren and Lawrence grade, n (%):			
0-2	4 (7.1)	6 (20.7)	4 (17.4)
3-4	52 (92.9)	23 (79.3)	19 (82.6)
Procedure conducted, n (%):			
UKR	28 (53)	17 (68)	11 (65)
TKR	25 (47)	8 (32)	6 (35)

* The Pain-DETECT questionnaire was used to divide patients, according to established cutoff values, into those with nociceptive (<13), unclear (13–18) and neuropathic pain (>18).
P-values were calculated in comparison to the nociceptive group, †p<0.05 ††p<0.001.
BMI=body mass index; SD= standard deviation; IQR=interquartile range;
UKR=unicompartment knee replacement; TKR=total knee replacement.

The pain and psychological characteristics of the patients, according to their neuropathic pain subgrouping is shown in Table 5-2. There was a trend for patients in the unclear and neuropathic pain groups to be more likely to report pain in four or more body areas, when compared to the nociceptive group. This only reached statistical significance for the unclear group.

Table 5-2. Pre-operative pain and psychological patient characteristics of the 120 patients recruited to EPIONE divided into nociceptive, unclear and neuropathic pain groups*.

	Nociceptive pain (n=63)	Unclear pain (n=32)	Neuropathic pain (n=25)
Pain characteristics			
Number of additional body areas which have caused pain for at least 3 months:			
0, n (%)	19 (30)	15(47)	7 (28)
1, n (%)	16 (25)	3 (9)	5 (20)
2, n (%)	11 (17)	2 (6)	2 (8)
3, n (%)	7 (11)	1 (3)	2 (8)
≥4, n (%)	10 (16)	11 (34) †	9 (36)
SF-MPQ pain severity in past 7 days, mean ± SD range 0-10	6.3 (2.1)	6.9 (1.7)	7.2 (1.1) †
SF-MPQ total score, mean ± SD range 0-45	16.3 (9.5)	23.0 (9.4) † [a,b]	24.5 (7.7) †† [a,b]
SF-MPQ sensory subclass, mean ± SD range 0-33	12.2 (7.0)	17.1 (6.6) † [a,b]	18.7 (5.4) †† [a,b]
SF-MPQ affective subclass, mean ± SD range 0-12	4.3 (3.3)	5.9(3.8) † [a]	6.0 (2.7) †
ICOAP, mean ± SD range 0-44	29.6 (11.0)	32.9 (9.2)	37.3 (6.8) † [a]
Pain disability index, mean ± SD range 0-60	30.8 (12.8)	31.8 (13.1)	39.0 (9.4) † [a,b]
Psychological characteristics			
HAD Anxiety, mean ± SD range 0-21	6.44 (4.2)	7.2 (5.0)	9.3 (4.0) †
HAD Depression, mean ± SD range 0-21	6.3 (3.3)	7.3 (4.8)	8.6 (4.2) †
STAI State anxiety, mean ± SD range 20-80	34.0 (12.5)	39.7 (14.2) † [a]	41.0 (14.7) †
STAI Trait anxiety, mean ± SD range 20-80	33.4 (10.7)	37.3 (12.9)	43.2 (15.9) † [a,b]
Pain Catastrophising Score, median (IQR) range 0-52	11 (6-17)	19 (10-28) † [a,b]	21 (10-36) †† [a,b]
Life orientation Test-R, mean ± SD range 0-24	16.8 (4.3)	15.4 (5.5)	12.5 (5.9) †† [a,b]
Pittsburgh Sleep Quality Index, mean ± SD range 0-21**	8.6 (3.3)	10.0 (3.9)	10.8 (4.0) †
Tampa scale of kinesophobia, mean ± SD range	38.3 (9.8)	39.7 (7.6)	42.4 (4.9)

* The Pain-DETECT questionnaire was used to divide patients, according to established cutoff values, into those with nociceptive (<13), unclear (13–18) and neuropathic pain (>18). P-values were calculated using the nociceptive group as the reference group. †p-value <0.05,††p<0.001; [a]P-value <0.05, after adjusting for age, sex and BMI; [b]p<0.05 after also adjusting for pain severity.

**Measures of Pittsburgh Sleep Quality Index were only available for 49, 23 and 20 participants in the nociceptive, unclear and neuropathic pain groups respectively.

SF-MPQ=Short-form McGill Pain Questionnaire; ICOAP= The Measure of Intermittent and Constant Osteoarthritis Pain; HAD= Hospital Anxiety and Depression Scale; STAI=State-Trait Anxiety Inventory.

Pain severity in the preceding seven days, recorded using the SF-MPQ VAS, was higher in the unclear and neuropathic pain groups when compared to the

nociceptive pain group. This only reached statistical significant for the neuropathic pain group. Patients with unclear and neuropathic pain were significantly more likely to use sensory and affective pain descriptors to describe their knee pain, than patients in the nociceptive pain group. Pain severity captured using the Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP) showed that patients in the neuropathic group reported significantly worse pain, compared to the nociceptive group. Disability associated with knee pain was also reported to be significantly higher in patients with neuropathic pain, compared to those with nociceptive pain.

Levels of psychological distress were significantly higher in the neuropathic pain group compared to the nociceptive pain group (Table 5-2.). The associations with the pain groups were then examined after adjusting for confounders with and without pain severity. This effect remained significant when adjusting for confounders, including pain severity, for trait anxiety, measured using the State-Trait Anxiety Inventory (STAI) and pain catastrophising. The neuropathic group also showed significantly higher levels of pessimism, measured using the Life Orentation Test-R (LOT-R), compared to the nociceptive group, which persisted after adjusting for confounders, including pain severity. Sleep quality was significantly lower in the neuropathic pain group compared to the nociceptive group, but this effect did not remain significant after adjusting for confounding factors. The QST measures for the 90 patients who attended the pre-assessment study visit are shown in Table 5-3.

Table 5-3 Quantitative sensory testing results for the 90 patients who attended the pre-assessment study visit divided into nociceptive, unclear and neuropathic pain groups, prior to surgery*.

		Nociceptive (n=51)	Unclear (n=21)	Neuropathic (n=18)
Warm detection threshold, median (IQR) ^{0}C	Index knee	38.0 (36.6-42.1)	38.8 (35.4-41.1)	37.9 (36.5-43.0)
	Tibialis anterior	42.7 (39.2-46.6)	43.2 (38.1-45.8)	40.9 (38.2-45.8)
	Contralateral knee	38.9 (36.1-43.0)	37.5 (35.4-39.5) †	38.7 (36.1-41.0)
	Sternum	38.8 (36.9-41.8)	38.2 (36.3-41.5)	38.5 (36.5-44.2)
Cold detection threshold, median (IQR) ^{0}C	Index knee	27.2 (25.9-28.3)	27.4 (24.7-28.9)	28.0 (26.6-29.3) †[a]
	Tibialis anterior	25.8 (23.5-27.6)	27.5 (26.4-28.4) †[a,b,c]	26.0 (23.9-27.8)
	Contralateral knee	26.7 (25.3-28.3)	27.1 (26.1-28.1)	28.0 (27.3-29.4) †[a,b,c]
	Sternum	27.4 (25.7-28.5)	28.3 (25.3-28.6)	27.5 (26.5-28.5)
Heat pain threshold, median (IQR) ^{0}C	Index knee	46.3 (42.9-49.3)	43.6 (42.5-46.6) †	44.3 (42.1-46.5) †[a,b,c]
	Tibialis anterior	49.1 (45.3-50.0)	47.2 (43.5-49.3)	46.7 (44.3-47.7) †[a,b,c]
	Contralateral knee	47.1 (43.4-49.1)	45.5 (41.5-46.8)	44.0 (41.5-46.6)
	Sternum	38.3 (36.1-41.1)	38.6 (36.4-44.0)	38.9 (35.5-43.5)
Cold pain threshold, median (IQR) ^{0}C	Index knee	18.1 (10.0-23.2)	20.2 (10.0-24.8)	21.9 (11.3-24.8)
	Tibialis anterior	10.0 (10.0-20.5)	10.0 (10.0-23.8)	12.9 (10.0-17.2)
	Contralateral knee	16.6 (10.0-23.2)	20.8 (10.0-25,0)	21.4 (16.8-25.3)
	Sternum	10.0 (10.0-18.6)	10.0 (10.0-17.7)	17.2 (10.0-24.1) †[a, b,c]
Mechanical pain threshold, median (IQR) mN	Index knee	101.6 (50.8-203.2)	28.7 (16.0-64.0) †	48.0 (12.7-161.3)
	Tibialis anterior	101.6 (40.3-256.0)	64.0 (32.0-128.00	36.2 (16.0-161.3)
	Contralateral knee	80.6 (40.3-161.3)	57.4 (32.0-203.2)	32.0 (16.0-101.6)
	Sternum	40.3 (10.1-101.6)	36.2 (20.2-80.6)	20.2 (10.1-40.3)
Sharpness rating to 512mN probe, mean ± SD range 0-10	Index knee	4.6 (2.5)	5.3 (2.9)	6.0 (2.6) †
	Tibialis anterior	3.0 (2.3)	4.8 (3.0) †	3.4 (2.7)
	Contralateral knee	3.9 (2.2)	5.1 (2.8)	5.3 (2.9) †
	Sternum	5.0 (2.7)	5.6 (3.4)	6.1 (2.5)
Pressure pain threshold, mean ± SD kPa	Index knee	320.1 (97.1)	285.4 (87.5)	268.9 (111.2) †
	Tibialis anterior	361.1 (119.8)	287.6 (96.8) †	271.7 (67.8) †[a,b,c]
	Contralateral knee	361.3 (122.1)	328.6 (119.5)	299.8 (100.0) †
	Sternum	268.0 (72.8)	251.1 (86.7)	238.2 (87.3)

* The Pain-DETECT questionnaire was used to divide patients, according to established cut-off values, into those with nociceptive (<13), unclear (13–18) and neuropathic pain (>18). P-values were calculated using the nociceptive group as the reference group. †p-value <0.05; [a]P-value <0.05, after adjusting for age, sex and bmi; [b]p<0.05 after adjusting for [a] as well as pain severity, [c]p<0.05 after adjusting for [b] as well as use of pain-modifying medication. IQR = interquartile range.

Cold detection thresholds (CDT), measured at the index and contralateral knee, were significantly higher in the neuropathic group compared to the nociceptive group. This effect persisted at the contralateral knee when adjusting for potential confounding factors including pain severity and the use of pain-modifying medication. CDTs were also found to be significantly higher, even after adjusting for all potential confounding factors when measured over tibialis anterior in the unclear group.

Heat pain thresholds (HPT) were significantly lower at the index knee and tibialis anterior in the neuropathic pain group when compared to the nociceptive group, even after adjusting for confounding factors.

Mechanical pain thresholds (MPT) for the unclear and neuropathic groups were lower at all the sites measured, compared to the nociceptive group, but this trend only reached statistical significance at the index knee for the unclear pain group and this did not persist after adjusting for confounding factors. Sharpness rating score (SRS) was also higher in the unclear and neuropathic groups, compared to the nociceptive group. This trend reached statistical significance, for tests done over tibialis anterior in the unclear group, and those done at the index and contralateral knees for the neuropathic group, but the association was not significant after adjusting for confounding factors.

Compared to the nociceptive pain group, the neuropathic and unclear pain groups demonstrated lower pressure pain thresholds (PPT) at all the sites tested. This was statistically significant for all the measurements, apart from at the sternum, in the neuropathic group and only when tested over tibialis anterior in the unclear pain group. The measures at tibialis anterior remained statistically significant for the neuropathic group after adjustment for pain severity.

5.6 Discussion

This study has confirmed that neuropathic pain is common amongst patients with severe clinician-diagnosed knee OA, awaiting knee replacement surgery. 27% of patients had a mPD-Q score corresponding to unclear or possible neuropathic pain, and a further 21% had a mPD-Q score corresponding to likely neuropathic pain.

These findings are in keeping with previous qualitative and quantitative studies of patients with knee OA drawn from the community and secondary care, which have shown that around 15 to 30% fulfill the criteria for likely neuropathic pain, using the mPD-Q (Hochman *et al*, 2013; Hochman *et al*, 2010; Hochman *et al*, 2011; Valdes *et al*, 2014). It is interesting to note that the data available to date suggest that neuropathic pain is more common amongst patients with more severe disease. Although not formally designed to calculate prevalence, chapter 3 demonstrated only 1.9% of the participants from the community-based study had a PD-Q score high enough to meet the criteria for neuropathic pain. The prevalence of neuropathic pain in a study of patients recruited from secondary care, with evidence of lower KL scores compared to the participants of EPIONE, was 14.8% (Valdes *et al*, 2014). *Hochman et al* reported a prevalence of neuropathic pain of 19%, excluding those with neurological comorbidities, in a cohort of patients with likely severe knee OA (Hochman *et al*, 2011) (Hawker *et al*, 2000). This is comparable to the 20.8% in the current study of patients listed for knee arthroplasty who had neuropathic pain. Taken together, this would suggest that the development of neuropathic pain is more of a 'state' as a result of ongoing peripheral pathology and nociceptive signals.

It would therefore be expected that patients with neuropathic pain would have a longer duration of symptoms. However, the current study did not show any significant relationship between disease duration and the presence of neuropathic pain. This may have been limited by the small sample size of the study. Interestingly, a previous cross-sectional study in participants from the Multicenter Osteoarthritis Study (MOST), a cohort of persons with or at risk of knee OA, showed that there was no relationship between sensitisation and sensitivity, assessed by PPT and mechanical temporal summation (TS), and disease duration (Neogi *et al*, 2013). These observations are more in keeping with neuropathic pain being more of a "trait" characteristic, predisposing certain individuals to developing neuropathic pain, independent of OA duration or severity. The clinical implication of distinguishing state or trait characteristics is that if pain sensitisation behaves as a trait, it may be important to screen for neuropathic pain at all points in the healthcare system, including primary and secondary care settings, and select treatment appropriately.

The most common neuropathic pain qualities reported were sudden attacks of pain that felt like electrical shocks (65.6%), radiating pain (54.2%); pain upon light pressure (50.8%); and burning pain (13.9%). Hochman et al (Hochman *et al*, 2011) demonstrated the same group of most common pain qualities in their patients with knee osteoarthritis: radiating pain (59.2%), electrical shocks (50.4%), sensitivity to pressure (34.9%), and burning pain (33.3%) (Hochman *et al*, 2011). The frequency of symptoms was similar, if not higher, in the current study, apart from burning pain,

which was around twice as common in the previous non-surgical patient cohort. It would be interesting to establish whether burning pain is a quality which orthopaedic surgeons are concerned about attributing to knee OA pain which would respond to surgery, which is one possible explanation for the apparent difference observed.

Patients with neuropathic pain had significantly more debilitating disease, in the absence of any significant difference in structural disease severity, with a worse overall OKS (mean $\pm$ SD 20.5 (7.3) versus 13.1 (5.5), $p<0.001$) as well as a higher pain disability index (PDI) (mean $\pm$ SD 39.0 (9.4) versus 30.8 (12.8), $p<0.05$). The neuropathic group also demonstrated significantly higher levels of psychological distress including: pain catastrophising (median (IQR) 21 (10-36) versus 11 (6-17), $p<0.001$) and trait anxiety (mean $\pm$ SD 43.2 (15.9) versus 33.4 (10.7)). In addition, patients with neuropathic pain were also significantly more pessimistic than those with nociceptive pain (mean $\pm$ SD 12.5 (5.9) versus 16.8 (4.3), $p<0.001$).

The results of this study are consistent with the previous reports that neuropathic pain is associated with more severe symptom severity, psychological distress and reduced quality of life (Hochman *et al*, 2013; Hochman *et al*, 2011; Valdes *et al*, 2014). The observation that pain catastrophising and trait anxiety remained significant associations with neuropathic pain, even after adjusting for pain severity, suggests that these may be factors contributing to the trait characteristics associated with a higher risk of developing neuropathic pain, rather than simply occurring in

response to severe pain. Neuroimaging data has shown that functional connectivity prior to a sensory stimulus affects subsequent susceptibility to noxious events, and moreover these effects were shown to co-vary with anxiety and pain vigilance (Ploner *et al*, 2010). This provides further evidence to suggest that these factors may be contributing to an increased vulnerability to pain in general, and by virtue of the fact that these are centrally mediated mechanisms, it may be more likely to manifest with features of neuropathic pain.

Experimental pain sensitivity, measured using QST, revealed local and regional sensitivity to multiple stimulus modalities, but consistent changes at a distant site were not recorded. In particular, the association between neuropathic pain and both HPT and PPT remained significant, after adjusting for confounding factors as well as pain severity and use of pain-modifying medication, when measured over tibialis anterior ipsilateral to the index knee (median (IQR) 46.7(44.3-47.7) versus 49.1 (45.3-50.0), $p<0.05$ and mean $\pm$ SD 271(67.8) versus 361.1 (119.8), $p<0.05$ respectively).

A previous study comparing QST measures and mPD-Q scores in patients with knee OA showed that neuropathic features were significantly associated with central sensitisation (CS). Furthermore a neuroimaging study in patients with hip OA showed that the magnitude of activation in the brainstem positively correlated with features of neuropathic pain measured using the PD-Q (Gwilym *et al*, 2009). Based on these observations, we would have expected to detect differences in QST measures between the neuropathic and nociceptive pain groups in areas distant to the index

knee, i.e. the sternum and contralateral knee, as well as areas in the same region, i.e. tibialis anterior, and the index knee itself. This is certainly true for many studies that have compared QST measures in patients to healthy controls (Arendt-Nielsen *et al*, 2010; Lee *et al*, 2011; Suokas *et al*, 2012; Wylde *et al*, 2011). A more recent systematic review and meta-analysis shows that patients with knee OA who report high levels of pain have significantly lower PPT at local as well as remote sites, compared to those with low levels of pain (Fingleton *et al*, 2015). These data can be compared to the current study as the neuropathic pain group also demonstrated significantly higher symptom severity than the nociceptive group. The unadjusted results for PPT, apart from those measured at the sternum, in the present study are consistent with the findings of the meta-analysis. Furthermore for the present analysis, when PPT was measured over tibialis anterior the difference between the neuropathic and nociceptive groups remained significant, even after adjusting for pain severity. The meta-analysis also showed that patients with knee OA had lower HPT than healthy controls, but this effect was only significant for remote and not local measures (Fingleton *et al*, 2015). In the present study it was the local and regional HPT measures that showed a significant association with neuropathic pain, rather than the remotes ones. Although the neuropathic pain group reported significantly higher symptom severity, compared to the nociceptive group, it is possible that this group is still different to one selected on the basis of symptom severity alone. The mechanism behind the higher symptom severity may vary and it may, for example, include those with differing levels of peripheral drivers for pain, which can in turn impact on measures of sensitisation (Finan *et al*, 2012).

This study has identified a sub-group of patients awaiting knee replacement surgery for knee OA who demonstrate features of neuropathic pain identified using the mPD-Q. This group of patients reported significantly more severe symptoms from their knee OA, greater psychological co-morbidity as well as increased pain sensitisation measured using QST, despite the absence of any differences in structural disease severity. This sub-group may represent a valid phenotype in OA, and the associated characteristics of the group may help to guide targeted treatment (Felson, 2010). For example, it has previously been shown that pain catastrophising has a negative impact on outcome in those who receive non-surgical as well as surgical treatment for their knee OA (Alschuler *et al*, 2013; Riddle *et al*, 2010; Sinikallio *et al*, 2014). Furthermore there is preliminary data to suggest that pain coping skills may help to improve outcome following surgery (Riddle *et al*, 2011), and more definitive data is awaited (Dowsey *et al*, 2014; Helminen *et al*, 2013; Riddle *et al*, 2012). Another alternative would be the targeted use of neuropathic pain medications, such as duloxetine. Duloxetine is a serotonin and norepinephrine reuptake inhibitor that is active in the central nervous system. It is thought that the analgesic effect of duloxetine is via potentiation of 5-hydroxytryptamine and noradrenaline in the brainstem, resulting in increased descending inhibition (Brown *et al*, 2013; Woolf, 2004). Randomized controlled trial data suggests that duloxetine is associated with clinically meaningful improvement in pain intensity in patients with knee OA after around four weeks of treatment (Brown *et al*, 2013; Hochberg *et al*, 2012) and it has been recommended for the non-surgical management of knee OA (McAlindon *et al*, 2014). Duloxetine has also been tested as an analgesic adjuvant

for acute post-operative pain and was shown to reduce morphine consumption in the first 48 hours after knee replacement surgery, when two peri-operative doses were given (Ho *et al*, 2010). It may be that duloxetine therapy could be commenced prior to surgery, as an adjunct, to improve post-operative outcome in the neuropathic pain sub-group. The use of personalized drug therapy is highlighted in a study of patients with painful diabetic neuropathy, which showed that duloxetine was more efficacious in patients with less efficient conditioned pain modulation (CPM) prior to therapy (Yarnitsky *et al*, 2012).

The main strength of this study is that it was conducted in a patient cohort recruited on the basis of their clinical treatment, i.e. they were all awaiting knee replacement surgery, which allows meaningful translation directly to the clinical setting. Previous studies on this group of patients, with more severe end-stage knee OA, are relatively lacking. In addition, the study captured concurrent pain, psychological and QST measures allowing for the relationships between these measures to be investigated, and adjusted for where appropriate. The main limitation of this study is that it did not reach its target for recruitment. The sample size required for the study to be adequately powered was 148, see section 2.3.1, whereas only 120 patients were recruited and of that only 80 patients completed the QST assessment. This means that some important associations may not have been detected, and the findings of this study should be validated in a larger patient cohort. Finally, as the study was nested within the normal hospital appointment visits, limited time was available for study assessments. For this reason, an abbreviated QST protocol based on the

standard research protocol was developed (Rolke *et al*, 2006; Rolke *et al*, 2006). This may have also resulted in important differences in pain sensitisation not being detected. For example, it is now thought that dynamic QST, including CPM and temporal summation, may be of importance when assessing patients with knee OA (Graven-Nielsen *et al*, 2010; Neogi *et al*, 2013; Petersen *et al*, 2015; Skou *et al*, 2013). In summary, this study has shown that patients with severe knee OA, who are awaiting knee replacement surgery, frequently report features of neuropathic pain. This sub-group of patients experience significantly worse symptom severity prior to surgery, which is also associated with significantly higher levels of psychological distress, as well as increased experimental pain sensitivity, even after adjusting for pain severity. This sub-group may represent an important phenotype in OA, and may benefit from targeted therapy in conjunction with conventional surgical management. These are preliminary findings and validation of these findings in a larger study cohort is required, particularly given that it is an underpowered study. Longitudinal data investigating the effect of neuropathic pain on post-operative outcome is needed to establish any clinical significance of this finding.

6 Neuroimaging Evidence of Central Sensitisation in Patients with Knee Osteoarthritis

6.1 Abstract

Objective

The neural mechanisms for the generation of pain in knee OA are not fully understood. A proportion of patients have been found to have features of neuropathic pain, and previous work suggests that the underlying mechanism for this is through central sensitisation. This mechanism-based understanding of pain is important in order to aid targeted intervention. The aim of this study was to identify the neural correlates, with a particular focus on changes in the brainstem's descending pain modulatory circuit, known to be involved in the establishment and maintenance of central sensitisation, of neuropathic pain in patients with moderate to severe knee OA, using functional magnetic resonance imaging (fMRI). The differences in supraspinal pain processing before and after knee replacement surgery were also investigated.The hypothesis was that patients with features of neuropathic pain prior to surgery would also demonstrate increased activation in areas of the brainstem involved in central sensitisation, namely the nucleus cuneiformis, periaqueductal grey, and rostral ventromedial medulla.

Methods

Patients with knee OA, placed on the waiting list for joint replacement surgery, were recruited to the study. All the patients underwent quantitative sensory testing (QST) and completed psychological assessment prior to surgery. fMRI was conducted

whilst the skin in the region of the affected knee was stimulated using punctate stimuli (512mN) and cold stimuli (15^{o}C). Twenty patients completed both the punctate and cold paradigms, whilst the remaining four patients underwent punctate stimulation only. Fourteen patients completed fMRI prior to and 12-months after surgery.

Results

Patients with neuropathic pain were found to have increased sensitivity to punctate and cold stimuli, as well as significantly higher levels of pain catastrophising prior to surgery. fMRI demonstrated significantly lower levels of activation in the rostral anterior cingulate cortex (rACC) and higher levels of activation in the rostral ventromedial medulla (RVM) and ipsilateral nucleus cuneiformis (NCF) in response to punctate stimulation prior to surgery, in patients with features of neuropathic pain compared to those without. The magnitude of rACC activation was significantly negatively correlated to the severity of neuropathic pain, represented by the modified painDETECT questionnaire (mPD-Q) score. Similarly, RVM activation was significantly positively correlated to the mPD-Q score. Comparison of brain activation after surgery to that seen prior to surgery showed increased deactivation in the rostral anterior cingulate cortex, anterior paracingulate cortex, precuneous and the lingual cortex in response to punctate stimulation. These changes may reflect changes in resting state networks in association with the relief of pain following surgery.

Conclusion

The psychophysical and neuroimaging data suggest that neuropathic pain is associated with centrally mediated pain sensitisation in patients with knee OA. Specifically this is likely to be due to both a reduction in descending inhibitory pain modulation (evidenced by decreased rACC activation) as well as increased supraspinal facilitation of nociceptive signaling in the dorsal horn. The neurobiological confirmation of CS in patients with neuropathic pain, identified using the mPD-Q, provides further support for the use of drug and behavioral treatments to target this mechanism, which may in turn have a positive impact on outcome following knee replacement surgery.

6.2 Introduction

The precise mechanisms for pain in osteoarthritis (OA) are not fully understood. There is evidence to suggest that a sub-group of patients with knee OA have features suggestive of neuropathic pain (Hochman *et al*, 2010; Hochman *et al*, 2011; Valdes *et al*, 2014), and the previous chapter has confirmed that neuropathic pain is common amongst patients with severe, end-stage knee OA. Neuropathic pain is defined as ‘‘pain arising as a direct consequence of a lesion or disease affecting the somatosensory system” (Treede *et al*, 2008) and so may be due to a number of distinct mechanisms, of which central sensitisation is one possibility (von Hehn *et al*, 2012). Data from animal studies, symptom-based assessment, quantitative sensory testing and neuroimaging studies show that central sensitisation (CS) may be an important mechanism involved in the development of pain in knee OA (Dimitroulas *et al*, 2014; Fingleton *et al*, 2015; Lluch *et al*, 2014). Furthermore neuropathic pain has been linked to signs of CS using QST (Hochman *et al*, 2013).

Central sensitisation is defined as “an amplification of neural signaling within the central nervous system that elicits pain hypersensitivity” (Woolf, 2011). Central sensitisation arises from a wide variety of underlying mechanisms ranging from sensitisation within the spinal cord to signal amplification secondary to active descending pain facilitation pathways. The exact mechanisms, by which central sensitisation develops in OA, and its impact on response to current treatment options, remain unclear.

Neuroimaging provides a non-invasive, objective method for measuring the central processing of pain in humans. The use of neuroimaging techniques to further our understanding of the mechanisms of pain in patient populations, and suitable treatment developments, is being increasingly recognized (Lee *et al*, 2013; Schweinhardt *et al*, 2006; Wartolowska *et al*, 2009).

Previous studies of patients with knee OA have investigated the neural correlates of spontaneous and experimentally induced pain in patients with knee OA, as well as the effects on gray matter volume (Baliki *et al*, 2008; Baliki *et al*, 2014; Baliki *et al*, 2011; Gimenez *et al*, 2014; Hiramatsu *et al*, 2014; Kulkarni *et al*, 2007; Parks *et al*, 2011). Together these studies demonstrate that both experimentally induced pain and spontaneous arthritic pain are associated with increased neural activation in areas of the brain involved in sensory discrimination as well as the affective and cognitive-evaluative components of nociception (Baliki *et al*, 2008; Gimenez *et al*, 2014; Hiramatsu *et al*, 2014; Kulkarni *et al*, 2007; Parks *et al*, 2011). A study of resting state fMRI suggests disruption of the default mode network in knee OA patients compared to healthy controls (Baliki *et al*, 2014), whilst a brain morphology study showed that patients with knee OA demonstrated decreased gray matter volume in areas such as the insula and mid anterior cingulate cortex when compared to healthy controls (Baliki *et al*, 2011). Together these data suggest that both the anatomy and function of the brain are likely to be affected in patients with knee OA, with associated abnormal central pain processing, compared to healthy pain free controls.

Neuroimaging techniques have also been used to investigate the difference in pain processing between different patients with the same clinical condition. For example, a previous study of patients with hip OA investigated the role of the periaqueductal gray (PAG), a brainstem structure which forms part of the descending pain modulatory system (DPMS), in pain perception (Gwilym *et al*, 2009). This study showed that punctate stimulation, in an area of referred pain, was associated with increased activation in the PAG when compared to healthy participants. Furthermore the patients with features of neuropathic pain, identified using the PainDETECT questionnaire (PD-Q), showed significantly greater activation within the PAG compared to those with a low PD-Q score. This formed the first direct evidence of CS in patients with OA, as well as the link between activity in the DPMS and neuropathic pain.

The descending pain modulatory system (DPMS) is a network, which regulates nociceptive processing in the dorsal horn. The first evidence of descending modulation of pain comes from a study in rats, which showed that electrical stimulation of midbrain PAG resulted in an electrical analgesia which abolished responses to aversive stimulation (Reynolds, 1969). Subsequent investigation has demonstrated that the DPMS may exert inhibitory as well as facilitatory effects on spinal nociceptive processing (Gebhart, 2004). Neuroimaging techniques have been used to translate these findings to healthy humans using experimentally induced models of CS (Lee *et al*, 2008; Zambreanu *et al*, 2005). The PAG and the adjacent nucleus cuneiformis (NCF) have both been shown to be involved in CS in humans

(Zambreanu *et al*, 2005). Both structures are major sources of input to the rostral ventromedial medulla (RVM), which in turn is likely to represent the final relay in descending modulation from supra-spinal sites (Ossipov *et al*, 2010).

The overall purpose of this study was to investigate the neural correlates of neuropathic pain in patients with moderate to severe knee OA, compared to those with purely nociceptive pain. . The current study was designed to replicate and expand upon the findings by Gwilym et al using a larger cohort of patients with knee OA, in whom the presence or absence of features of neuropathic pain was identified a priori. Based on the previous literature, we chose to specifically examine areas in the brainstem involved in descending modulation of incoming nociceptive signals including the PAG, NCF and RVM. It was hypothesised that these brainstem regions would show higher levels of activation amongst patients with neuropathic pain, compared to those with nociceptive pain. Furthermore, it was hypothesised that higher the activation in these areas, would be associated with a worse outcome following knee replacement surgery. Finally we wished to investigate any differences in brain activation, in response to provocation of their hyperalgesia, before and after knee replacement surgery.

6.3 Aim

The aims of this study were to:

1. Use fMRI to compare brain activation during experimentally induced pain in patients with severe end-stage knee OA with features of neuropathic pain, to those with purely nociceptive pain, identified using the modified PD-Q.
2. Investigate the relationship between CS, determined using fMRI, and outcome following surgery.
3. Investigate the change in brain activation in response to experimental pain, pre-operatively to 12-months post-operatively.

6.4 Methods

6.4.1 Subjects

Participants recruited to EPIONE (see section 2.3) were invited to take part in this neuroimaging sub-study. Those willing to take part, without any contra-indications to undergoing MRI and for whom it was possible to conduct a baseline scan prior to their surgery were included in the present study.

6.4.2 Data collection

6.4.2.1 Psychophysical Assessment

These data were collected at the pre-operative assessment clinic appointment, which took place prior to the scanning session. Details on data collection of population demographics, clinical data, radiographs, quantitative sensory testing (QST) measures, pain assessment and psychological factors and sleep disturbance

prior to surgery as well as the 2 and 12-month follow-up data collection are given in section 2.3.2.

Cold and punctate stimuli were included in the stimulation paradigm for the scanning experiment and so the corresponding quantitative sensory testing (QST) measures were of particular interest in this sub-group of patients. These included: cold detection and cold pain thresholds, as well as mechanical pain threshold and mechanical pain sensitivity in alignment with the standard research protocol for QST (Rolke *et al*, 2006; Rolke *et al*, 2006).

In addition, patients were asked to rate the severity of their current knee pain using a visual analogue scale (VAS) just prior to commencing the scanning experiment.

6.4.2.2 fMRI scanning protocol

Patients were invited to attend an additional study visit in order to complete the neuroimaging part of the study. Scans were conducted prior to scheduled surgery and 12-months after knee replacement surgery had been completed.

Brain images were acquired using a 3.0T Siemens MAGNETOM® Verio Magnetic Resonance Imaging System and a 32-channel head coil. A whole-brain gradient echo-planar imaging sequence was used to acquire blood oxygenation level–dependent (BOLD) functional images. For functional scans the parameters were: echo time (TE) of 30 msec, 46 contiguous 3-mm–thick slices, field of view 192x192mm, voxel size 3.0 x 3.0 x 3.0 mm^3 and repetition time (TR) of 3000msec. After the BOLD imaging T-

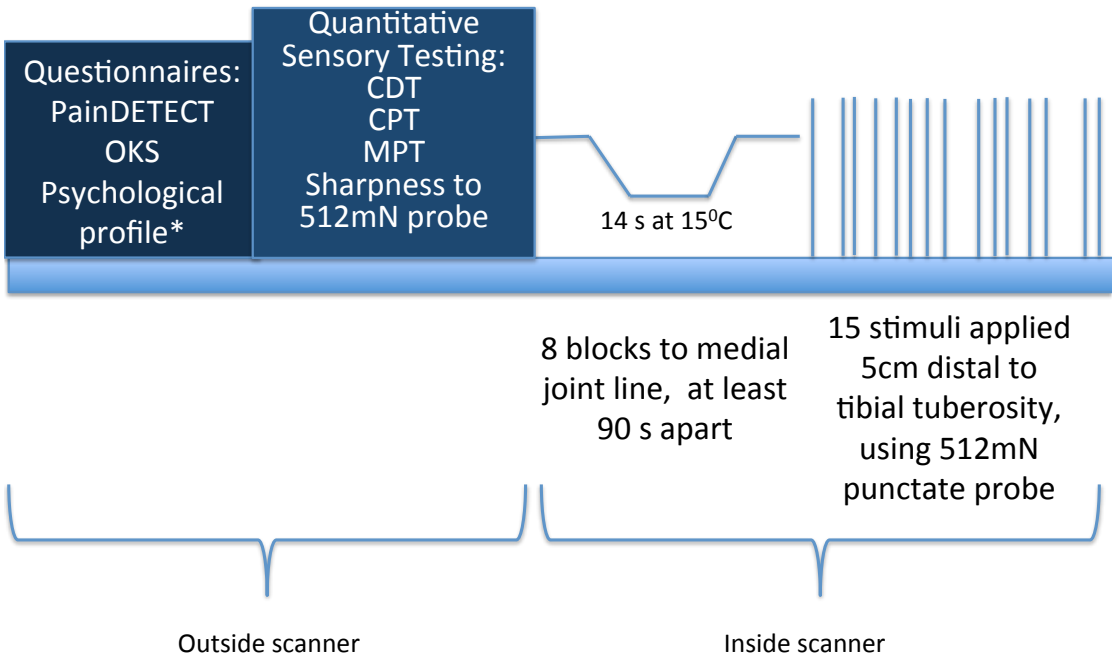
1weighted structural scans, 1 x 1 x 1mm^3, were acquired for registration and overlay of brain activation.

Physiological noise data was collected using respiratory bellows and a pulse oximeter, together with volume triggers from the scanner. All data was recorded using an MP150 system (BIOPAC Systems, Inc., Goleta, CA) at a sample rate of 50Hz. B_0 field maps were also acquired to correct for regions of field inhomogeneity.

6.4.2.3 Stimulation paradigm

The fMRI scan paradigm is summarised in Figure 6.1.

Figure 6.1 Illustration of the scanning experimental paradigm performed by the study participants



*Questionnaires used to assess the psychological characteristics of the participants included: Hospital Anxiety and Depression Scale; STAI=State-Trait Anxiety Inventory; Pain Catastrophising Score; Life orientation Test-R; Pittsburgh Sleep Quality Index; and Tampa scale of kinesophobia. CDT=cold detection threshold, CPT=cold pain threshold, MPT=mechanical pain threshold; OKS=Oxford Knee Score.

Cold stimuli were generated using 30 x 30 mm ATS thermode (Medoc, Ramat Yishai, Israel). Eight stimuli at 15°C, each of 14-second duration were applied to the medial joint line of the affected knee in a block design. The inter-stimulus interval (ISI) was jittered with a minimum of 90 seconds. Mechanical punctate stimuli were generated using a custom-made weighted pinprick simulator, which exerted a force of 512mN (MRC Systems). In an event-related design, 15 stimuli were applied to the anterior aspect of the lower limb on the affected knee, at least 5cm distal to the tibial

tuberosity. The ISI was jittered with a minimum of 15 seconds. Participants were instructed to keep their eyes open and fixate on a cross during stimulation.

Participants completed perception ratings at the end of the cold and punctate stimulation paradigms. This was done using a computerized VAS displayed on a projector screen, which was visible whilst in the scanner. For both paradigms participants were asked to rate how unpleasant stimuli had felt on average. The anchor statements were 'not unpleasant' and 'extremely unpleasant'. After the cold paradigm, participants were asked to rate how painful the stimuli had felt on average. The anchor statements for this rating were 'not painful' and 'extremely painful'. The corresponding rating after the punctate paradigm captured the average sharpness of the stimuli, with the anchor statements 'not sharp' and 'extremely sharp'. The final rating for each paradigm recorded the intensity of any ongoing knee pain attributed to the patients' usual arthritis pain, using the anchor statements 'not painful' and 'extremely painful'. The ratings were collected using Presentation software (version 16.0; Neurobehavioral Systems, Albany, CA) and a button box controlled by the participant in the scanner.

6.4.3 Data analysis

The modified Pain-DETECT questionnaire (mPD-Q) was used to divide patients, according to established cutoff values, into those with nociceptive, unclear and neuropathic pain (Freynhagen *et al*, 2006). For the purposes of comparing those with purely nociceptive clinical pain to those with features of neuropathic pain, the unclear group was combined with the neuropathic group. This approach is consistent

with previous studies and ensures that those with possible neuropathic pain are included (Hochman *et al*, 2013; Hochman *et al*, 2011). The differences in psychophysical characteristics between those in the nociceptive and the neuropathic pain groups at each time-point were investigated using Student's t-test, Wilcoxon-Mann-Whitney, and Chi-square test for normally distributed, non-normally distributed, and categorical data respectively. For comparisons between baseline and follow-up characteristics, paired t-test and Wilcoxon signed rank test were used for parametric and non-parametric variables respectively.

6.4.4 BOLD imaging analysis

Prior to analysis, the BOLD data for those with left sided knee pain was flipped so that the left-right orientation was comparable for the group as a whole. FMRI data processing was carried out using FEAT (FMRI Expert Analysis Tool) Version 6.00, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Registration to high-resolution structural and standard space images was carried out using FLIRT (Jenkinson *et al*, 2002; Jenkinson *et al*, 2001). Registration from high resolution structural to standard space was then further refined using FNIRT nonlinear registration (J.L.R. Andersson, 2007; Jesper L. R. Andersson, 2007).

The following pre-statistics processing was applied; motion correction using MCFLIRT (Jenkinson *et al*, 2002); non-brain removal using BET (Smith, 2002); spatial smoothing using a Gaussian kernel of FWHM 5mm; grand-mean intensity normalisation of the entire 4D dataset by a single multiplicative factor; highpass

temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma=50.0s) and physiological noise correction (cardiac and respiratory) using modified RETROICOR (Brooks *et al*, 2008). The tool *fsl_motion_outlier* was used to remove any time-points that had been corrupted by large motion. The functional images were field-map corrected to reduce B_0 distortion in the orbital-frontal and temporal regions (Jenkinson, 2003). Time-series statistical analysis, for both the cold pain and pin prick paradigms, was carried out using FILM (FMRIB's Improved Linear Model) with local autocorrelation correction (Woolrich *et al*, 2001).

Higher-level analysis was carried out using FLAME (FMRIB's Local Analysis of Mixed Effects) stage 1 with automatic outlier detection (Beckmann *et al*, 2003; Woolrich, 2008; Woolrich *et al*, 2004). Z (Gaussianised T/F) statistic images were thresholded using clusters determined by Z>2.3 and a (corrected) cluster significance threshold of P=0.05 (Worsley *et al*, 1996). A mixed effects analysis (FLAME 1) was conducted in order to generate average activations for each of the contrasts, for the punctate and cold paradigms. Z-score images were generated at a threshold of Z=2.3 with corrected cluster significance of $p \leq 0.05$. A repeated measures analysis of variance (ANOVA) model was used to investigate differences between brain activation prior to and 12-months after knee replacement surgery.

Region of interest (ROI) analyses in the brainstem were conducted using a non-parametric permutation tool, Randomise, which is integrated within FSL (Nichols *et al*, 2002). Test statistics were generated from the GLM design and thresholded using

threshold-free cluster enhancement (TFCE) and corrected to a p-value of <0.05 (Smith *et al*, 2009). Based on the established literature, the brainstem areas selected for ROI analyses were the PAG, nucleus cuneiformis (NCF) and the rostral ventromedial medulla (RVM) (Bee *et al*, 2008; Gebhart, 2004; Hemington *et al*, 2015; Ossipov *et al*, 2010; Vincent *et al*, 2013; Zambreanu *et al*, 2005). These areas were masked by former pain group members using hand-drawn anatomical masks referenced from Duvernoy's Brainstem Atlas (Naidich *et al*, 2009).

Post hoc analyses were conducted in order to further investigate the relationship between clinical measures of neuropathic pain severity and change in BOLD signal in brain areas found to show significantly different levels of activation between the nociceptive and neuropathic groups. Functional masks were generated using a 5mm sphere from the peak voxel of activation in the cluster corresponding to the rostral anterior cingulate cortex (rACC) and from significant clusters of activation detected by the RVM and NCF ROI analyses. Parameter estimates were extracted from the relevant BOLD acquisitions using *Featquery* and the relationship with the mPD-Q score for each patient was interrogated using Spearman's rank correlation. The relationship between pre-operative CS, represented by the extracted parameter estimates described above and 12-month post-operative outcome, represented by pain severity using a visual analogue scale, was investigated using Spearman's rank correlation.

Finally, it was observed that the neuropathic group reported higher levels of pain catastrophising. Although the underlying mechanisms for pain catastrophising are

not fully understood, it has been suggested that the way that catastrophising may affect the pain experience is by promoting central sensitisation (CS). This is supported by a number of studies which have demonstrated increased temporal summation in association with the presence of high levels of pain catastrophising (Campbell *et al*, 2015; Edwards *et al*, 2006; Goodin *et al*, 2013; Rhudy *et al*, 2011), suggesting that it may play a central facilitatory role in pain processing. A final post hoc analysis was therefore conducted in order to investigate whether this personality trait was also linked to RVM activation, using Spearman's rank correlation.

6.5 Results

26 participants were enrolled in the study. One participant was excluded from all analyses due to excess motion artifact and a second participant was excluded due to incidental structural abnormality precluding adequate registration. Of the remaining 24 participants, the cold paradigm was not completed in four participants due to technical problems with the thermode. 14 of the 24 patients were also scanned 12-months after surgery: two patients had their surgery cancelled on medical grounds, one patient had delayed surgery for personal reasons, two patients could not be re-scanned due to a new contra-indication to MRI, three patients withdrew from the imaging part of the study due to health or personal reasons, and two patients had not yet reached the appropriate window for rescanning. Data for the cold paradigm were available for 11 patients prior to and after surgery.

6.5.1 Psychophysical characteristics prior to surgery

Ten of the patients met the criteria for nociceptive pain using standard cutoff criteria for the PD-Q. The remaining 14 patients were included in the neuropathic pain group. Although there was a trend towards the neuropathic group being younger, more likely to be female, have had knee pain symptoms for a shorter duration, and report more severe symptom severity prior to surgery, none of these differences reached statistical significance (Table 6-1). The psychological measures demonstrated significantly increased fear of movement as well as pain catastrophising in the neuropathic group compared to the nociceptive group.

Table 6-1 Pre-operative characteristics of the participants who participated in the neuroimaging sub-study, divided according to the presence or absence of features of neuropathic pain*

	Nociceptive (n=10)	Neuropathic (n=14)
Clinical features		
Age, mean ± SD years	70 (7)	67 (10)
Female, n (%)	3 (30)	8 (57)
Right knee affected, n (%)	3 (30)	7 (50)
Duration of pain, median (IQR) months	60 (24-108)	24 (18-60)
Oxford knee score, mean ± SD range 0-48	20.5 (6.7)	17.0 (6.5)
Oxford knee score pain subscale, mean ± SD range 0-100	69.2 (12.0)	74.8 (11.2)
Oxford knee score function subscale, mean ± SD range 0-100	61.2 (13.1)	67.1 (11.2)
Psychological features		
HAD Anxiety, mean ± SD range 0-21	6.4 (4.5)	8.0 (3.4)
HAD Depression, mean ± SD range 0-21	6.9 (2.3)	7.3 (3.0)
STAI State anxiety, mean ± SD range 20-80	31.8 (16.2)	39.9 (13.5)
STAI Trait anxiety, mean ± SD range 20-80	31.6 (12.9)	38.1 (13.7)
Pain Catastrophising Score, median (IQR) range 0-52	11 (3-14)	18 (7-30) †
Life orientation Test-R, mean ± SD range 0-24	16.7 (4.0)	14.1 (6.3)
Pittsburgh Sleep Quality Index, mean ± SD range 0-21**	8.6 (1.7)	10.7 (4.4)
Tampa scale of kinesophobia, mean ± SD range	33.4 (5.3)	39.2 (4.4) †
Quantitative sensory testing measures at the knee		
Mechanical pain threshold, median (IQR) mN	96.0 (32.0-128.0)	32.0 (25.4-101.6)
Sharpness rating to 512mN probe, mean ± SD, range 0-10	4.5 (2.4)	5.1 (2.8)
Cold detection threshold, median (IQR) ^{0}C	27.7 (27.1-28.3)	28.7 (27.8-29.6)
Cold pain threshold, median (IQR) ^{0}C	10 (10-12.0)	20.4 (10-23.1) †
Stimulus ratings in the scanner		
Unpleasantness of cold stimulus, median (IQR) range 0-100	0.0 (0.0-0.0)	4.5 (0.0-9.5)
Pain with cold stimulus, median (IQR) range 0-100	0.0 (0.0-24.0)	3.5 (0.0-24.0)
Sharpness of poke paradigm, median (IQR) range 0-100	0.0 (0.0-27.0)	17.5 (10.0-36.0)
Unpleasantness of poke paradigm, median (IQR) range 0-100	0.0 (0.0-10.0)	11.0 (5.0-20.0) †
Knee pain ratings in the scanner		
Pain severity immediately prior to experiment, median (IQR) range 0-100	0.0 (0.0-20.0)	20.0 (0.0-50.0)
Pain severity after cold paradigm, median (IQR) range 0-100	3.5 (0.0-10.5)	3.0 (0.0-18.5)
Pain severity after poke paradigm, median (IQR) range 0-100	0.0 (0.0-0.0)	5.5 (0.0-27.0) †

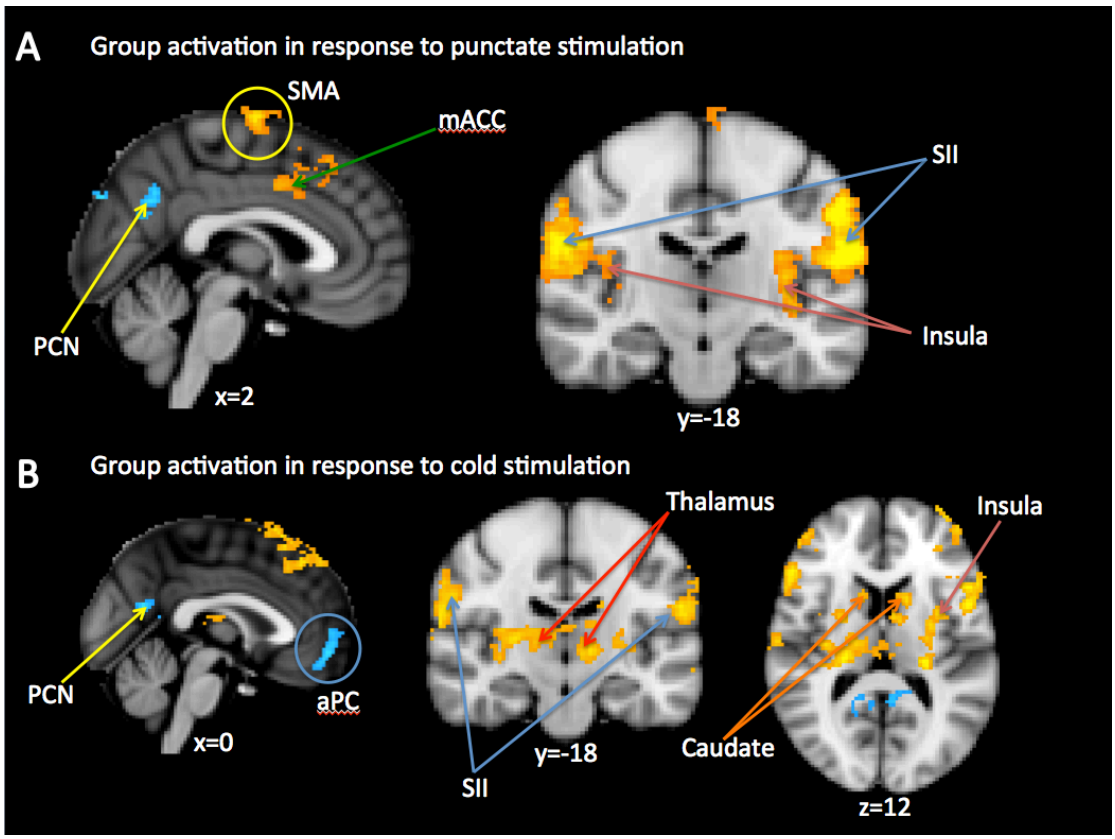
*The pre-operative Pain-DETECT questionnaire score was used to divide patients into those with nociceptive (<13), and neuropathic pain (≥13).**Measures of Pittsburgh Sleep Quality Index were only available for 8 and 12 participants in the nociceptive and neuropathic pain groups respectively.P-values were calculated for differences between the two groups: †p<0.05.HAD= Hospital Anxiety and Depression Scale; STAI=State-Trait Anxiety Inventory.

Outside the scanner, the neuropathic pain group showed significantly increased sensitivity to cold pain ($p<0.05$). The remaining QST parameters showed a non-significant trend towards increased sensitivity in the neuropathic group compared to the nociceptive group. In the scanner, the neuropathic group reported significantly greater levels of unpleasantness in response to the poke paradigm, $p<0.05$. The neuropathic group tended to report higher scores for the other ratings, but these did not reach statistical significance. Finally the neuropathic group reported significantly greater pain immediately after the punctate paradigm compared to the nociceptive group, $p<0.05$.

6.5.2 fMRI prior to surgery

The punctate stimuli evoked increased brain activity in the secondary somatosensory cortex, insula, and supplementary motor area bilaterally, as well the mid anterior cingulate cortex, n=24 (Figure 6.2). Deactivation was seen in the precuneous, and contralateral primary motor cortex. The cold paradigm was associated with activation in the following areas bilaterally: secondary somatosensory cortex, caudate, thalamus and cerebellum, as well as the contralateral insula and putamen, n=20 (Figure 6.2). Deactivation during the cold paradigm was seen in the precuneous and anterior paracingulate gyrus.

Figure 6.2 Results of mixed-effects analysis of the average group response to punctate, n=24 (A) and cold, n=20 (B) stimuli prior to surgery.

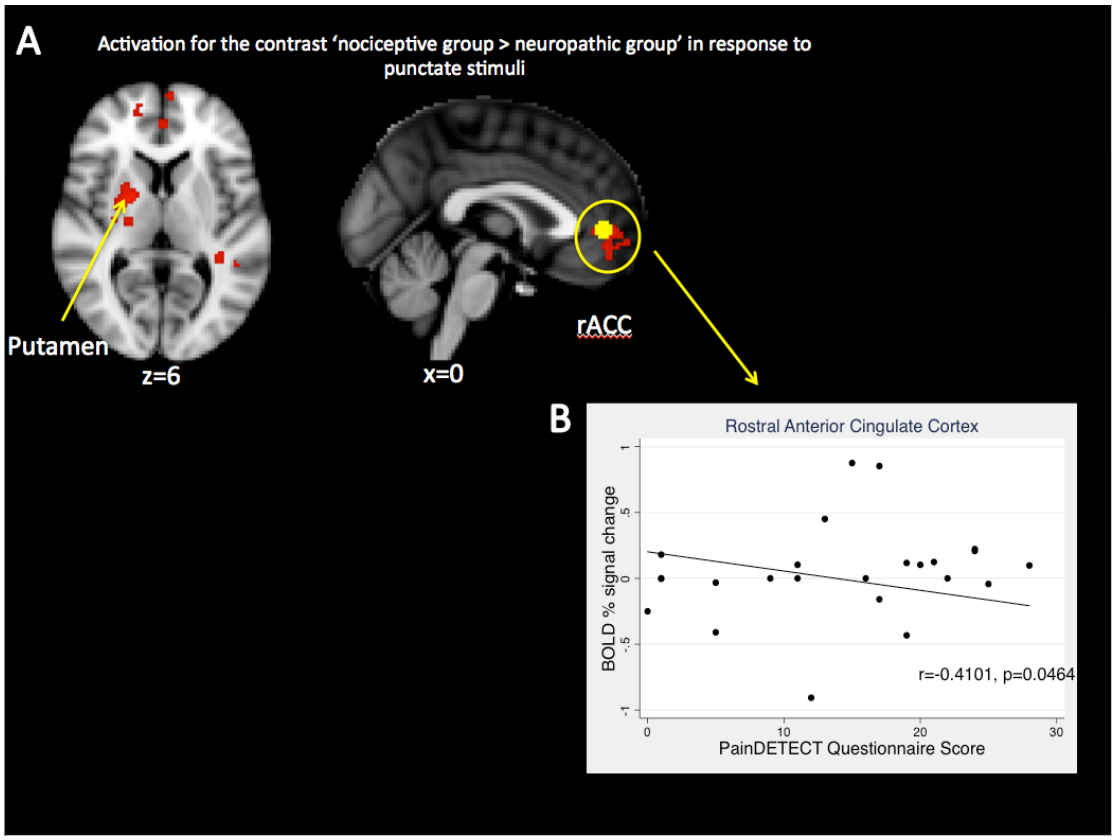


All results are corrected for multiple comparisons (Z score >2.3, P<0.05).Yellow=significantly increased activity, blue=significantly decreased activity. SMA=supplementary motor area; mACC=mid anterior cingulate cortex; SII=secondary somatosensory area; PCN=precuneous; aPC=anterior paracingulate cortex. Images are displayed in radiological convention with MNI co-ordinates given.

For the punctate paradigm, the nociceptive group (n=10) demonstrated significantly higher activation in the rACC and the ipsilateral putamen using whole brain comparisons, compared to the neuropathic group (n=14) (Figure 6.3). The change in BOLD activation in the rACC showed a significant moderate inverse relationship with the severity of neuropathic pain features, measured using the mPD-Q, r=-0.4101, p<0.05 (Figure 6.3). No significant areas of activation were seen for the contrast

neuropathic > nociceptive. The small sample size precluded meaningful sub-group analysis for the cold paradigm.

Figure 6.3 Mixed-effects, whole brain analysis, for the contrast of nociceptive > neuropathic, in response to punctate stimulation (A), and correlation between the change in BOLD activity in the rostral anterior cingulate cortex and the severity of neuropathic pain symptoms (B), n=24.

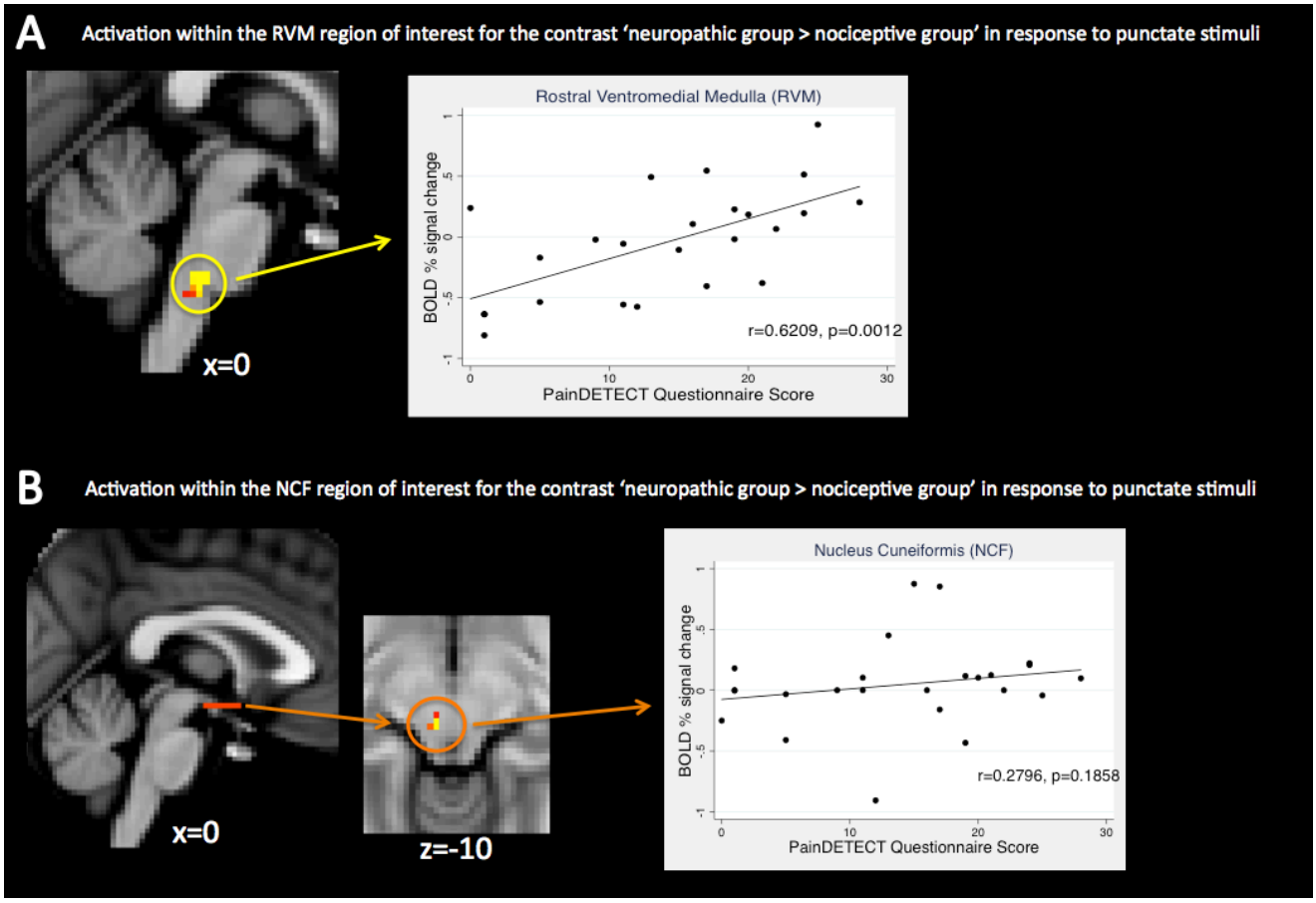


All results are corrected for multiple comparisons (Z score >2.3, P<0.05). No significant areas of activation were found for the contrast neuropathic > nociceptive. Red=significantly increased activity in nociceptive group compared to neuropathic group, yellow=functional mask generated using a 5mm sphere from the peak voxel of activation in rACC cluster. rACC=rostral anterior cingulate cortex. Images are displayed in radiological convention with MNI co-ordinates given.

ROI analyses revealed increased activation in the ipsilateral NCF ($p<0.05$) and RVM ($p<0.05$) in the neuropathic compared to the nociceptive group, during punctate stimulation (Figure 6.4). There was no significant difference in activation in the PAG. There was no significant association between BOLD signal change and the mPD-Q

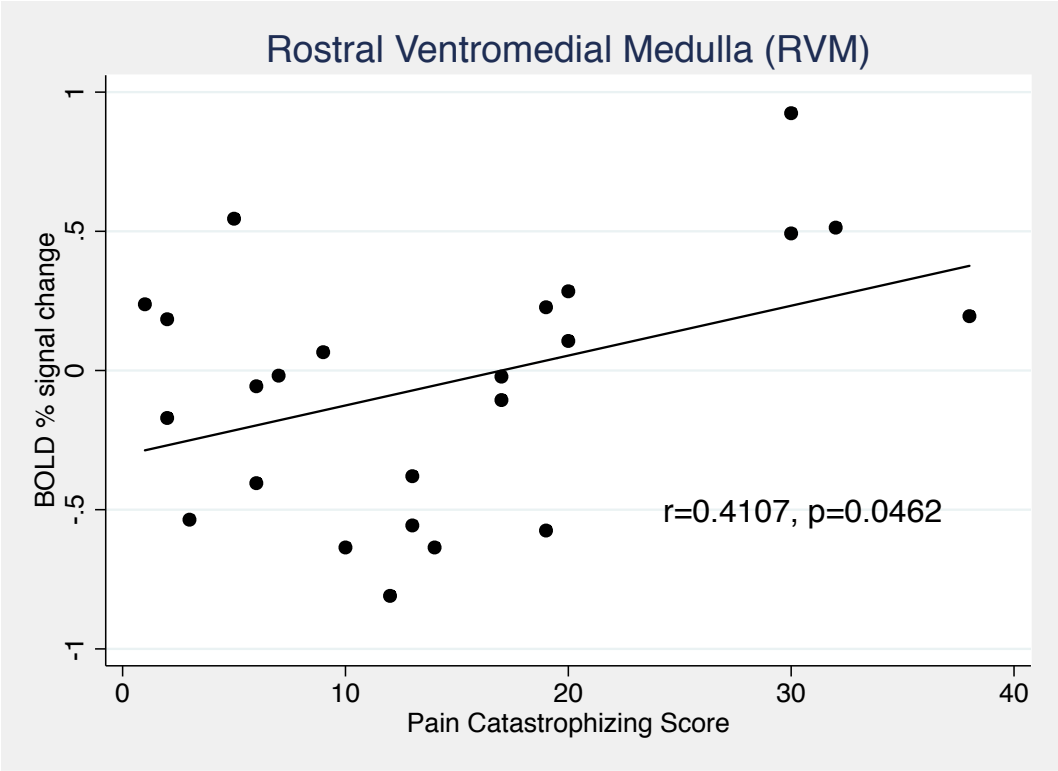
score in the NCF (Figure 6.4). The change in BOLD activation in the RVM was significantly strongly positively correlated to the mPD-Q score, r=0.6209, p=0.0012. In addition, the pain catastrophising score was found to be significantly moderately positively correlated with RVM activation, r= 0.4107, p= 0.0462 (Figure 6.5).

Figure 6.4 Region of interest analysis for the contrast of neuropathic > nociceptive, in response to punctate stimulation, and correlation between change in % BOLD signal response and severity of neuropathic pain symptoms for the RVM (A) and NCF (B), n=24.



Test statistics were generated from the GLM design and thresholded using threshold-free cluster enhancement (TFCE) and corrected to a p-value of <0.05. Images are displayed in radiological convention with MNI co-ordinates given.

Figure 6.5 Pain catastrophising is associated with RVM activation in response to punctate stimulation prior to surgery.



r=Spearman's Rank Correlation Coefficient between pain catastrophising and RVM activation, in response to punctate stimulation, prior to surgery.

6.5.3 Clinical and psychological features 12-months post-operatively

Long-term follow-up data was available for 19 of the patients who had participated in the neuro-imaging study prior to planned surgery. All the clinical and psychological features showed significant improvement compared to baseline ($p<0.05$) apart from state and trait anxiety, pain catastrophising and sleep disturbance, measured using the Pittsburgh Sleep Quality Index (PSQI). The post-operative characteristics of the patients, according to the presence or absence of neuropathic pain at baseline are shown in Table 6-2. The psychological measures of anxiety, measured using the Hospital Anxiety and Depression (HAD) scale, and pain catastrophising were found to

be significantly worse in the neuropathic group compared to the nociceptive group. There was a non-significant trend towards the neuropathic group having worse clinical symptom severity, but there was no significant association between pain severity reported at the 12-month post-operative assessment and activation in the RVM (r=0.2094, p=0.4363), NCF (r=-0.0184, p=0.9461) or rACC (r=-0.1073, p=0.6925).

Table 6-2 12-month post-operative characteristics of the participants who participated in the neuroimaging sub-study, divided according to the presence or absence of features of neuropathic pain*

	Nociceptive (n=10)	**Neuropathic (n=9)**
Clinical features		
Oxford knee score, mean ± SD range 0-48	46.0 (40.0-47.0)	40.0 (33.0-48.0)
Oxford knee score pain subscale, mean ± SD range 0-100	26.0 (24.0-32.0)	36.0 (20.0-52.0)
Oxford knee score function subscale, mean ± SD range 0-100	20.0 (20.0-28.6)	31.7 (21.5-37.2)
Psychological features		
HAD Anxiety, mean ± SD range 0-21	0.5 (0.0-2.0)	3.0 (1.0-7.0) †
HAD Depression, mean ± SD range 0-21	1.0 (0.0-3.0)	1.0 (0.0-7.0)
STAI State anxiety, mean ± SD range 20-80	24.0 (10.2)	33.0 (15.8)
STAI Trait anxiety, mean ± SD range 20-80	28.0 (5.5)	33.9 (12.7)
Pain Catastrophising Score, median (IQR) range 0-52	5 (0-6)	14 (2-17) †
Pittsburgh Sleep Quality Index, mean ± SD range 0-21	7.8 (2.9)	8.7 (4.3)

*The pre-operative Pain-DETECT questionnaire score was used to divide patients into those with nociceptive (<13), and neuropathic pain (≥13).
P-values were calculated for differences between the two groups: †p<0.05.
HAD= Hospital Anxiety and Depression Scale; STAI=State-Trait Anxiety Inventory.

6.5.4 Change in psychophysical characteristics following surgery

Of the 14 patients who underwent repeat scanning 12 months after surgery, there were seven patients in each of the neuropathic and nociceptive groups according to their baseline mPD-Q scores. All the clinical features had improved significantly in the group as a whole (p<0.05). HAD anxiety and depression also both significantly

improved ($p<0.05$), whereas state and trait anxiety measured using the State-Trait Anxiety Inventory (STAI) did not significantly change. In addition there was no significant change in pain catastrophising and sleep disturbance. For the stimulus and knee pain ratings measured in the scanner, only the unpleasantness and sharpness of the poke paradigm had significantly improved after surgery ($p<0.05$). The post-operative characteristics of these patients are summarised in Table 6-3.

Table 6-3 12-month post-operative characteristics of the participants who completed the longitudinal neuroimaging sub-study, divided according to the presence or absence of features of neuropathic pain*

	Nociceptive (n=7)	Neuropathic (n=7)
Clinical features		
Oxford knee score, mean ± SD range 0-48	41.0 (30.0-47.0)	38.5 (33.3-45.0)
Oxford knee score pain subscale, mean ± SD range 0-100	28.6 (20.0-31.4)	32.9 (22.9-40.0)
Oxford knee score function subscale, mean ± SD range 0-100	28.0 (24.0-40.0)	40.0 (20.0-52.0)
Psychological features		
HAD Anxiety, mean ± SD range 0-21	1.0 (0.0-3.0)	4.0 (2.0-7.0) †
HAD Depression, mean ± SD range 0-21	1.0 (0.0-4.0)	2.0 (1.0-7.0)
STAI State anxiety, mean ± SD range 20-80	27.4 (6.7)	35.2 (16.1)
STAI Trait anxiety, mean ± SD range 20-80	28.5 (5.7)	36.2 (12.2)
Pain Catastrophising Score, median (IQR) range 0-52	5.0 (3.0-12.0)	14.5 (8.0-17.0) †
Pittsburgh Sleep Quality Index, mean ± SD range 0-21	8.3 (3.0)	8.7 (4.3)
Stimulus ratings in the scanner		
Unpleasantness of cold stimulus, median (IQR) range 0-100	0 (0-0)	0 (0-0)
Pain with cold stimulus, median (IQR) range 0-100	0 (0-0)	0 (0-0)
Sharpness of poke paradigm, median (IQR) range 0-100	0 (0-13)	0 (0-8)
Unpleasantness of poke paradigm, median (IQR) range 0-100	0 (0-11)	0 (0-0)
Knee pain ratings in the scanner		
Pain severity immediately prior to experiment, median (IQR) range 0-100	0 (0-0)	0 (0-30)
Pain severity after cold paradigm, median (IQR) range 0-100	0 (0-15)	5 (0-30)
Pain severity after poke paradigm, median (IQR) range 0-100	0 (0-4)	0 (0-11)

*The pre-operative Pain-DETECT questionnaire score was used to divide patients into those with nociceptive (<13), and neuropathic pain (≥13).
P-values were calculated for differences between the two groups: †p<0.05.
HAD= Hospital Anxiety and Depression Scale; STAI=State-Trait Anxiety Inventory.

The neuropathic group significantly higher levels of anxiety, measured using the Hospital Anxiety and Depression (HAD) scale, and pain catastrophising. The neuropathic group tended to report worse clinical symptom severity after surgery, but this did not reach statistical significance. Both the nociceptive and neuropathic groups reported virtually no knee pain prior to and during the scanning session. In

addition the stimulus ratings in the scanner for both groups showed that neither group experienced any significant unpleasantness or pain in response to the stimuli applied (Table 6-3).

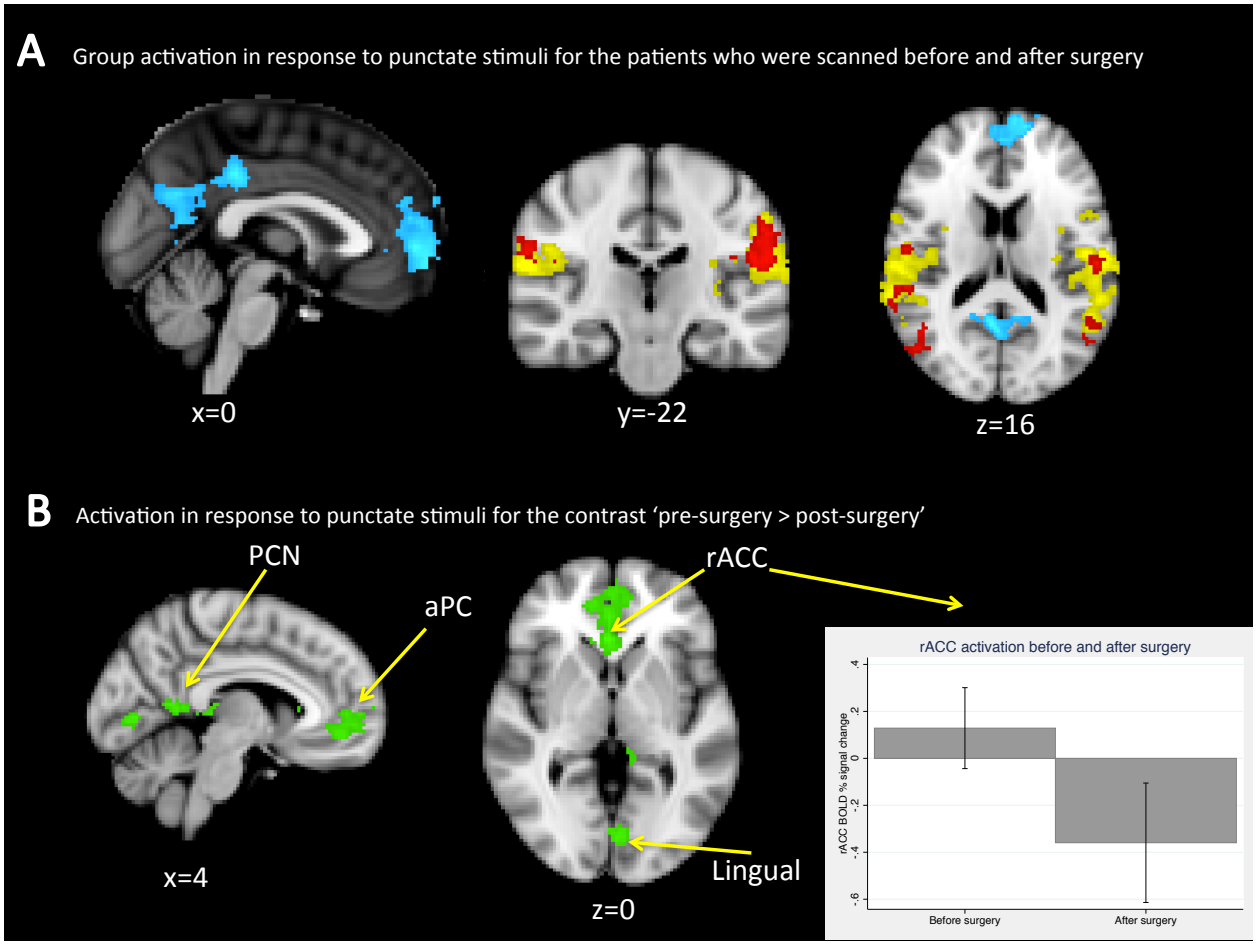
6.5.5 Change in fMRI in the follow-up cohort

When the analysis prior to surgery was restricted to the patients who subsequently completed the follow-up imaging session, the poke paradigm prior to surgery evoked significant activation bilaterally in the secondary somatosensory cortex, and insula as well as the contralateral superior parietal lobule. Significant deactivation was seen in the ipsilateral lateral occipital cortex.

Post-operatively, the poke paradigm evoked significant brain activation in the secondary somatosensory cortex and lateral occipital cortex. Significant deactivation was seen in the anterior cingulate and paracingulate cortex, and precuneous (Figure 6.6).

Figure 6.6 shows the areas that were found to be significantly different between the two scan sessions, for the contrast pre-operative scan> post-operative scan during the poke paradigm. These include the rostral anterior cingulate cortex, anterior paracingulate cortex, precuneous and the lingual cortex. Comparison to the areas of activity seen post-operatively and further investigation of the individual level data showed that these differences were driven by increased levels of deactivation post-operatively rather than increased activation prior to surgery.

Figure 6.6 Results of mixed-effects analysis of the average group response to punctate stimuli before and after surgery (A) and areas demonstrating significant change in activation between the two scanning sessions (B), n=14.



All results are corrected for multiple comparisons (Z score >2.3, P<0.05). Yellow=significantly increased activity prior to surgery, red=significantly increased activity after surgery, blue=significantly decreased activity after surgery, and green=areas showing significant change in activation for the contrast pre-surgery>post-surgery. No significant areas of activation were found for the contrast post-surgery > pre-surgery. rACC=rostral anterior cingulate cortex; PCN=precuneous; aPC=anterior paracingulate cortex. Images are displayed in radiological convention with MNI co-ordinates given.

6.6 Discussion

The main finding of this study is that patients with knee OA and features of neuropathic pain demonstrated psychophysical and functional imaging evidence of centrally mediated pain sensitisation, when compared to the group with nociceptive pain. The neuropathic group evoked significantly lower levels of activation in the rACC (Z score >2.3, $p<0.05$) and higher levels of activation in the RVM ($p=0.00182$) and ipsilateral NCF ($p=0.02962$) in response to punctate stimulation prior to surgery, compared to those without features of neuropathic pain. Psychophysical data also confirmed that the neuropathic group demonstrated significantly higher sensitivity to cold and punctate stimuli as well as significantly higher levels of pain catastrophising and kinesophobia. RVM activation was significantly correlated to mPD-Q, as well as pain catastrophising. Finally, there was increased deactivation in the rostral anterior cingulate cortex, anterior paracingulate cortex, precuneous and the lingual cortex in response to punctate stimulation after surgery, compared to pre-operatively.

The rACC is an important cortical area involved in the descending inhibitory control of pain, which works by recruiting an anti-nociceptive subcortical network including the amygdalae and PAG (Bingel *et al*, 2006). Its role in regulating pain has been most extensively investigated in the context of the placebo analgesia, where the effect is mediated by the endogenous opioid system, via μ-opioid receptor activation in specific brain regions including the rACC (Zubieta *et al*, 2005). The connectivity between the rACC and the PAG has also been shown to be reliant on opioidergic

signaling (Eippert *et al*, 2009). More recently real-time fMRI has highlighted the importance of the rACC in pain regulation, whereby increased unpleasantness associated with a painful stimulus was only seen when activation in the insula was achieved in conjunction with corresponding decrease in rACC activation (Rance *et al*, 2014). The current study shows that patients with knee OA, who demonstrated increased rACC activation in response to punctate stimulation, were also less likely to report features of neuropathic pain with respect to their clinical knee pain. The mechanism underlying the differences in the manifestation of the same clinical condition, may therefore be associated with the differential ability to successfully engage the endogenous inhibitory system in nociceptive patient sub-group compared to the neuropathic sub-group. Although the role of the rACC in patients with knee OA has not been previously reported, the current results are consistent with the previous observation that brainstem activation, in particular in the PAG which is known to be connected to the rACC, is associated with features of neuropathic pain in patients with hip OA (Gwilym *et al*, 2009).

The current study did not find any significant differences in PAG activation between the two patient groups. This is surprising, given the previous findings in patients with hip OA (Gwilym *et al*, 2009) as well as the knowledge of the functional connectivity of the rACC and the descending modulation of pain. It is possible that the involvement of the PAG in more than one function and its multiple connections in conjunction with its relatively small size have contributed to the lack of a significant difference between the patient groups in this study (Hemington *et al*, 2015).

The NCF is known to be part of the descending pain modulatory system and a previous study of experimentally induced central sensitzation in healthy participants showed increased activation in the contralateral NCF during hyperalgesia (Zambreanu *et al*, 2005). The current results support a similar involvement of the NCF in the context of clinical pain sensitisation secondary to knee OA.

The RVM is known to receive input from the PAG and adjacent NCF and is thought of as the final relay point for the descending supraspinal signals before modifying incoming nociceptive signals in the spinal cord (Basbaum *et al*, 1984; Lee *et al*, 2013) The descending modulation of spinal cord function was originally thought to involve only inhibitory mechanisms, but over time the role of facilitatory effects on nociceptive processing has been recognized (Gebhart, 2004). In the current study, increased activation in the RVM in patients with neuropathic pain, compared to those with nociceptive pain, may reflect increased activity in RVM ON-cells resulting in descending facilitation (Fields *et al*, 1983). This mechanism has been shown to be involved in hypersensitivity seen after nerve injury (Bee *et al*, 2008) and may contribute to chronic pain states more generally. fMRI data alone does not allow us to distinguish between facilitatory and inhibitory activity in the RVM, but this hypothesis is supported by the fact that the mPD-Q score was significantly associated with the level RVM activity (Figure 6.4.A.).

Comparison of brain activation after surgery to that seen prior to surgery showed that there was increased deactivation in the rostral anterior cingulate cortex, anterior paracingulate cortex, precuneous and the lingual cortex in response to punctate stimulation ($z>2.3$, $p<0.05$). These changes may reflect changes in resting state networks in association with the relief of pain following surgery. During fMRI studies, the presence of task-independent decreases in activation have been previously recognized (Gusnard *et al*, 2001). This observation, and the consistency of the brain areas involved across a variety of experiments, led to the focus on studying baseline brain activity, or so-called resting state networks and their associated functions (Gusnard *et al*, 2001). One of the most studied is the default mode network, which includes a number of brain areas, which consistently deactivate during a range of goal-directed tasks (Raichle *et al*, 2001). It comprises the ventral medial prefrontal cortex, the posterior cingulate cortex and adjacent precuneous, as well as the lateral parietal cortex (Raichle, 2015). Together these areas are thought to allow the integration of emotional information, self-referential processing and recall of previous experiences when there are no other competing tasks (Raichle, 2015). There is evidence to suggest that numerous conditions including sleep disturbance, pain, dementia and psychiatric conditions are associated with disruption of resting state networks and this may help to improve our understanding of overall brain function in health as well as diseased states (Barkhof *et al*, 2014). A study of resting state function in the context of chronic pain, including knee OA, has shown that there is increased coupling of the default mode network with pain-related regions such as the insula, as well as decreased connectivity with the

precuneous compared to healthy controls (Baliki *et al*, 2014). The latter observation supports the explanation for increased deactivation seen in the precuneous following the alleviation of pain by knee replacement surgery, being due to a return to normal resting state function.

One further interesting observation is that compared to the nociceptive group, the neuropathic pain group had significantly higher levels of pain catastrophising, both before and after surgery. Furthermore there was no significant change in pain catastrophising for the whole group, in response to surgery, which is consistent with it being thought of as a relatively stable personality trait. It is known that pain catastrophising is associated with more severe pain in patients with knee OA, as well as having a negative impact on their outcome following knee replacement surgery (Edwards *et al*, 2006; Riddle *et al*, 2010; Witvrouw *et al*, 2009). There is also preliminary, short-term evidence to suggest that behavioral intervention in those with high levels of pain catastrophising prior to knee replacement surgery may reduce pain and disability experienced post-operatively (Riddle *et al*, 2011). However, the neurobiological basis for pain catastrophising is less well understood. It has been suggested that the way that catastrophising may affect the pain experience is by promoting central sensitisation (CS), and this is supported by a number of studies which have demonstrated increased temporal summation in association with the presence of high levels of pain catastrophising (Campbell *et al*, 2015; Edwards *et al*, 2006; Goodin *et al*, 2013; Rhudy *et al*, 2011), suggesting that it may play a central facilitatory role in pain processing. A neuroimaging study of pain rumination, a

component of pain catastrophising, suggests that communication between the DMN and the DPMS may be a mechanism for this characteristic (Kucyi *et al*, 2014). Furthermore, a study of grey matter changes after an 11-week cognitive-behavioral therapy intervention in patients with chronic pain showed increased grey matter in bilateral dorsolateral prefrontal cortex (DLPFC), posterior parietal cortex as well as other regions involved in sensory, motor and affective processing after completing the treatment (Seminowicz *et al*, 2013). The change in DLPFC grey matter was negatively correlated with change in catastrophising, and the authors proposed that this might represent mechanisms to increase descending modulation of pain (Seminowicz *et al*, 2013). In support of the current literature, a post-hoc analysis of the current data shows that there is a moderate positive relationship between baseline pain catastrophising and RVM activation suggesting that it may enhance descending facilitatory pain modulation (Figure 6.5).

The main strength of this study is that it recruited patients with clinically homogenous disease severity, in that they were all deemed to warrant knee replacement surgery. The longitudinal nature of the study also allowed the examination of the reversibility of any aberrant pain processes to be evaluated. Furthermore, the neuroimaging data were compared to behavioral and QST measures. The main limitation of the study is that only the responses to experimental pain have been measured, and the processing of spontaneous pain may differ. Pain in knee OA is very variable, but is often triggered by weight-bearing exercise. This could therefore be further explored using resting-state fMRI after a

period of weight-bearing exercise. Finally, the relatively small sample size has precluded meaningful sub-group analysis for some of the test paradigms.

In summary, this study furthers our understanding of the underlying neurobiological mechanisms for neuropathic pain in patients with knee OA. The data suggest that centrally mediated pain sensitisation is present in patients with neuropathic pain. Specifically the neuroimaging data suggest that this is likely to be due to both reduced descending inhibitory mechanisms as well as increased supraspinal facilitation of nociceptive signals in the dorsal horn. The neurobiological confirmation of CS in patients with neuropathic pain, identified using the mPD-Q, provides further support for the use of drug and behavioral treatments to target this mechanism, which may in turn have a positive impact on outcome following knee replacement surgery.

7 Neuropathic pain as a predictor of short and long-term outcome following knee replacement surgery.

7.1 Abstract

Objective

Neuropathic pain is present in a subgroup of patients with knee OA, and is associated with pain sensitisation. Knee replacement surgery corrects the structural pathology associated with OA within the knee joint, so patients who have a significant neuropathic pain component driving their symptoms may not gain the same level of improvement in symptoms, compared to those with nociceptive pain. The aim of this study was to compare the response to knee replacement surgery in patients from a study cohort identified pre-operatively as having nociceptive, unclear, or neuropathic pain using the modified PainDETECT questionnaire. A validation study was also conducted in a separate patient cohort.

Methods

Patients with knee OA, who had been placed on the waiting list for joint replacement surgery, were recruited to the study and were assessed before surgery. A questionnaire pack was used to collect clinical, pain, psychological and sleep characteristics prior to surgery as well as at 2 and 12-months after surgery. Specifically, the modified PainDETECT (mPD-Q) score was used to divide the cohort into those with nociceptive (<13), unclear (13–18) and neuropathic pain (>18) and was the predictor variable. Oxford Knee Score (OKS) was the primary outcome variable. Clinical, pain and psychological patient characteristics for the unclear and neuropathic pain groups were then compared to the nociceptive group, at each

time-point independently, using multinomial logistic regression modelling, adjusting for age, sex, BMI and pain severity. A repeated measures generalized estimating equations (GEE) linear regression model was then used to test the differences in OKS for each pain group over time, adjusting for age, sex and BMI. The analyses were then replicated in a larger, independent, validation cohort.

Results

Of the 120 patients recruited to the study cohort, 83 (69%) completed the 2-month assessment and 72 (60%) completed the 12-month assessment. Data for 384 patients who had completed a pre-operative and 12-month post-operative assessment was available for analysis in the validation cohort. Patients with neuropathic pain, defined using the mPD-Q, had significantly worse OKS than those with nociceptive pain at 2 months in the study cohort (median (IQR) OKS of 32.0 (18.0-41.0) versus 39.0 (29.0-43.0), $p<0.05$). The larger validation cohort showed that the 12-months post-operative OKS was also significantly worse in the neuropathic group, compared to the nociceptive group: median (IQR) 37.0 (25.0-43.0) versus 42.0 (35.0-46.0), $p<0.001$, respectively. The validation cohort also showed that patients in the neuropathic pain group were significantly more likely to report PPSP 12-months post-operatively than the nociceptive group, (OR (95% CI) 3.0 (1.6-5.8), $p=0.001$).

Conclusion

A sub-group of patients with knee OA, who have features of neuropathic pain, have significantly worse outcome at 2 and 12-months post-operatively compared to those with nociceptive pain. These patients may benefit from increased awareness of their projected outcome to aid informed decision making with respect to surgical

intervention. Post-operative outcome may also be improved by the utilisation of targeted therapy in the pre, peri and post-operative periods.

7.2 Introduction

The current guidelines for the management of knee osteoarthritis (OA) follow a generic stepwise approach starting with non-pharmacological and pharmacological treatments, and ending with surgical treatments (Fernandes *et al*, 2013; McAlindon *et al*, 2014; Nelson *et al*, 2013; Zhang *et al*, 2010). This approach results in a focus on severity and duration of symptoms as a means of rationing treatment strategies. It is now being recognized that these are not necessarily the most useful factors when aiming to optimize therapy, and it has been hypothesised that adopting a mechanism-based approach to the assessment and treatment of pain might be much more effective (Malfait *et al*, 2013; Woolf, 2004).

Although knee replacement surgery is effective for most patients with severe end-stage knee OA, 15% of patients report severe-extreme persistent pain at 3 to 4 years after surgery (Beswick *et al*, 2012; Wylde *et al*, 2011). The need to study baseline characteristics that relate to patient-based outcomes has been highlighted in the past (Dieppe *et al*, 2011), and a vast range of patient, clinical, psychological, peri-operative, and biomechanical potential predictor variables have been investigated (Lewis *et al*, 2015). To date pre-operative catastrophising and knee pain severity are reported to be the strongest independent predictors of persistent pain after TKA (Lewis *et al*, 2015). These findings emphasize the importance of considering the multidimensional nature of pain and it may be that factors operating beyond the constraint of the primary affected joint itself, such as sensitisation of the nervous system, should be taken in to account.

Neuropathic pain, and its associated peripheral and central sensitisation mechanisms, is being increasingly recognised in OA and may represent an opportunity for targeted therapy (Lluch *et al*, 2014; Thakur *et al*, 2014). Knee replacement surgery, assuming technical success has been achieved, corrects the structural pathology associated with OA within the knee joint. It is therefore possible that patients who have a significant neuropathic pain component driving their symptoms would not show the same improvement in symptoms, compared to those with predominantly nociceptive pain. Preliminary data suggests that measures of sensitisation, using quantitative sensory testing, may be mechanistic pre-operative predictors of persistent post-operative pain, (Lundblad *et al*, 2008; Lunn *et al*, 2013; Petersen *et al*, 2015; Rakel *et al*, 2012; Wylde *et al*, 2013). To our knowledge the presence of features of neuropathic pain, measured using a screening questionnaire such as the modified PainDETECT questionnaire (mPD-Q), has not been studied in relation to outcome following knee replacement surgery. Chapter five confirmed that there is a high prevalence of features of neuropathic pain, amongst patients with knee OA who are awaiting knee replacement surgery. This chapter will focus on the relationship between neuropathic pain elicited pre-operatively and the short and long-term response to surgery. It was hypothesised that the patients with neuropathic pain, identified using the mPD-Q prior to surgery, would have a worse outcome following surgery.

7.3 Aim

The aims of this study were to:

1. Compare the response to knee replacement surgery in patients identified pre-operatively as having nociceptive, unclear, or neuropathic pain using the modified PainDETECT questionnaire.
2. Validate the findings by replicating them in a second, larger patient cohort.

7.4 Methods

7.4.1 EPIONE STUDY

7.4.1.1 Setting and Subjects

Participants of the **E**valuation of **P**eri-operative pain **I**n **O**steoarthritis of the k**NE**e (EPIONE) Study were used as the primary study cohort for the present analysis. Details of recruitment are given in 2.3.1. The recruitment process and study visits are outlined in Figure 5.1.

7.4.1.2 Data collection

Details on data collection of population demographics, clinical data, radiographs, QST measures, pain assessment and psychological factors and sleep disturbance prior to surgery as well as the 2 and 12-month follow-up data collection are given in 2.3.2

7.4.1.3 Statistical analysis

The mPD-Q score was used to divide patients, according to established cut-off values, into those with nociceptive (<13), unclear (13–18) and neuropathic pain (>18) (Freynhagen *et al*, 2006). The prevalence of these pain groups as well as pre-operative demographic, clinical, psychological and patient features were compared between responders and non-responders at each time point, using Student's t-test, Wilcoxon-Mann-Whitney, and Chi-square test for normally distributed, non-normally distributed, and categorical data respectively.

Clinical, pain and psychological patient characteristics for the unclear and neuropathic pain groups at 2 and 12-months were then compared to the nociceptive group, using multinomial logistic regression modelling. The nociceptive, unclear and neuropathic pain groups were used as the outcome measure, with the nociceptive group being used as the reference group. The first model was univariable and measured any association between the predictor and pain grouping. A second model included age, BMI and sex, as potential confounding factors selected a priori. A final model further adjusting for pain severity, measured using the visual analogue score (VAS) from the Short-form McGill Pain Questionnaire (SF-MPQ), was used for the psychological measures only.

The difference in Oxford Knee Score (OKS) between those with nociceptive, unclear and neuropathic pain was compared, pre-operatively and at 2 and 12-months post-operatively, using repeated measures generalized estimating equations (GEE) regression models. The models were initially adjusted for pre-operative age, sex and BMI. This method was then repeated with pain severity, measured using the visual analogue score (VAS) from the Short-form McGill Pain Questionnaire (SF-MPQ), as well as the use of pain-modifying medication included as additional confounding factors. Regression diagnostics checking for normality of residuals, collinearity, homoscedasticity, and linearity were conducted to ensure that the assumptions of the GEE regression models were met.

The difference in change in OKS over time between the three pain groups was then investigated. The distribution of change in OKS, pre-operative to 12-months post-operatively, was then plotted for the whole patient cohort, as well for the nociceptive, unclear and neuropathic pain groups separately. ANOVA was used to test for the differences in means between the three groups and Bartlett's test for equal variances was used to test for any significant differences in variance between the three groups. The proportion of patients who met the criteria for the minimally important change in OKS for use in individual patients, of 6.5 points, was calculated and compared between the three sub-groups using Chi-square test.

Finally logistic regression modelling was used to test if there was any significant relationship between the presence of persistent post-surgical pain (PPSP) and pain grouping. PPSP was defined as an average pain severity score of three or more for the preceding week, measured using the visual analogue score (VAS) from the Short-form McGill Pain Questionnaire (SF-MPQ), at the 12-month follow up assessment (Petersen *et al*, 2015). In a univariable model, PPSP was used as the outcome variable and pain grouping was used as the predictor variable. A multivariable model was then conducted, adjusting for the potential confounding factors age, sex, BMI, and pain severity at baseline, measured using the VAS from the SF-MPQ prior to surgery. The analyses were repeated with the definition of PPSP as a VAS of 4 and then 4.5 in order to assess the effect of a more stringent definition of PPSP.

7.4.2 COASt

7.4.2.1 Setting and Subjects

Participants of the Clinical Outcomes in Arthroplasty Study (COASt) were used as the validation cohort for the present analysis. Details of recruitment and study visits are given in 2.4.1.

7.4.2.2 Data collection

Details on data collection of population demographics, clinical data, pain assessment and psychological factors prior to surgery as well as the 12-month follow-up data collection are given in 2.4.2.

7.4.2.3 Statistical analysis

The mPD-Q score was used to divide patients, according to established cut-off values, into those with nociceptive (<13), unclear (13–18) and neuropathic pain (>18) (Freynhagen *et al*, 2006). Pre-operative demographic and clinical patient characteristics for the unclear and neuropathic pain groups were compared to the nociceptive group, using Student's t-test, Wilcoxon-Mann-Whitney, and Chi-square test for normally distributed, non-normally distributed, and categorical data respectively.

Multinomial logistic regression modelling was used to measure associations between pain and psychological characteristics and pain grouping according to the mPD-Q score. The nociceptive, unclear and neuropathic pain groups were used as the outcome measure, with the nociceptive group being used as the reference group.

The first model was univariable and measured any association between the predictor and pain grouping. A second model included age, BMI and sex, as potential confounding factors selected a priori. A final model further adjusting for pain severity was used for the psychological measures only. Pain severity was measured using the average pain severity score for the preceding month, captured using the mPD-Q: this score does not contribute to the final summary score generated from the mPD-Q.

The difference in Oxford Knee Score (OKS) between those with nociceptive, unclear and neuropathic pain was compared, pre-operatively and at 12-months post-operatively, using repeated measures generalized estimating equations (GEE) regression models. The models were initially adjusted for pre-operative age, sex and BMI. This method was then repeated with pain severity also included in the model, as described above. Data on medication use prior to surgery was not available in this dataset at the time of analysis, and so use of pain-modifying medication could not be included as a potential confounding factor. Regression diagnostics checking for normality of residuals, collinearity, homoscedasticity, and linearity were conducted to ensure that the assumptions of the GEE regression models were met.

The difference in change in OKS over time between the three pain groups was then analysed. The distribution of change in OKS, pre-operative to 12-months post-operatively, was then plotted for the whole patient cohort, as well for the nociceptive, unclear and neuropathic pain groups separately. ANOVA was used to

test for the differences in means between the three groups and Bartlett's test for equal variances was used to test for any significant differences in variance between the three groups. The proportion of patients who met the criteria for the minimally important change in OKS for use in individual patients, of 6.5 points, was calculated and compared between the three sub-groups using Chi-square test.

Finally logistic regression modelling was used to test if there was any significant relationship between the presence of persistent post-surgical pain (PPSP) and pain grouping. PPSP was defined as an average pain severity score of three or more for the preceding month, measured using the average pain severity score, captured using the mPD-Q at the 12-month follow up assessment (Petersen *et al*, 2015). In a univariable model, PPSP was used as the outcome variable and pain grouping was used as the predictor variable. A multivariate model was then conducted, adjusting for the potential confounding factors age, sex, BMI, and pain severity at baseline, measured using average pain severity score for the preceding month, captured using the mPD-Q prior to surgery. The analyses were repeated using the definition of PPSP as a pain score of 4 and then 4.5 in order to assess the effect of a more stringent definition of PPSP.

7.5 Results

7.5.1 Descriptive data for EPIONE and COASt

The table below summarises the unadjusted descriptive data for OKS in both study cohorts before and after surgery, Table 7-1.

Table 7-1 Unadjusted OKS data for EPIONE and COASt before and after surgery.

	Nociceptive pain (n=63)*	**Unclear pain (n=32)***	**Neuropathic pain (n=25)***
EPIONE			
OKS, mean (SD) [or median (IQR)]			
Pre-operative score	20.5 (7.3)	19.2 (7.5)	13.1 (5.5)
2 months post-operative score	39.0 (29.0-4.0)	35.0 (29.0-40.0)	32.0 (18.0-41.0)
12 months post-operative score	43.0 (38.0-46.0)	43.5 (35.0-44.5)	39.0 (32.0-43.0)
Minimally clinically important change in OKS pre-operatively to 12-months post-operatively, n(%)	37/43 (88)	15/16 (94)	12/14 (85)
Persistent post-surgical pain, n(%)	6/43 (14)	6/16 (38)	5/14 (36)
	Nociceptive pain (n=233) †	**Unclear pain (n=112) †**	**Neuropathic pain (n=59) †**
COASt			
OKS, mean (SD) [or median (IQR)]			
Pre-operative score	22.3 (7.7)	18.9 (6.8)	15.5 (5.4)
12 months post-operative score	42.0 (35.0-46.0)	39.0 (29.5-44.0)	37.0 (25.0-43.0)
Minimally clinically important change in OKS pre-operatively to 12-months post-operatively, n(%)	119/219 (91)	89/107 (83)	46/58 (79)
Persistent post-surgical pain, n(%)	53/219 (24)	44/107 (41)	29/58 (50)

*number at baseline; at 2-month visit there were 63, 32, and 25 patients in the nociceptive, unclear and neuropathic groups respectively. At 12-months there were 42, 16 and 14 patients in the nociceptive, unclear and neuropathic groups respectively. †number at baseline; at 12-month visit there were 219, 107, and 58 patients in the nociceptive, unclear and neuropathic groups respectively. OKS=Oxford Knee Score.

7.5.2 EPIONE STUDY

Of the 120 patients recruited to EPIONE, 83 (69%) completed the 2-month assessment and 72 (60%) completed the 12-month assessment. The pre-operative characteristics of the patients who completed the 2 and 12-month assessments compared to those who didn't respond are summarised in Table 7-2 and Table 7-3, respectively.

Table 7-2 Pre-operative patient characteristics of the patients who completed the 2-month assessment compared to those who didn't respond.

	Responders (n=83)	Non-responders (n=29)
Demographic features		
Age, mean ± SD years	71 (8)	72 (9)
Female, n (%)	44 (53)	12 (41)
BMI, mean ± SD kg/m^2	29.8 (4.5)	31.3 (5.7)
Employed, n (%)	23 (28)	5(18)
Married or living with partner, n (%)	57 (70)	18 (62)
Clinical features		
Right knee affected, n (%)	40 (49)	19 (66)
Duration of pain, median (IQR) months	48 (23-120)	36 (17-96)
Oxford knee score, mean ± SD range 0-48	20.0 (7.2)	16.3 (7.9) †
Oxford knee score pain subscale, mean ± SD range 0-100	70.1 (13.0)	76.0 (12.8) †
Oxford knee score function subscale, mean ± SD range 0-100	62.0 (13.8)	68.7 (15.6) †
Kellgren and Lawrence grade, n (%):		
0-2	10 (12.8)	4 (13.8)
3-4	68 (87.2)	25 (86.2)
Procedure conducted, n (%)*:		
UKR	48 (62)	8 (50)
TKR	30 (38)	8 (50)
Psychological features		
HAD Anxiety, mean ± SD range 0-21	6.5 (4.3)	8.7 (4.2) †
HAD Depression, mean ± SD range 0-21	6.1 (3.9)	8.4 (3.1) ††
STAI State anxiety, mean ± SD range 20-80	35.0 (13.6)	40.4 (11.5) †
STAI Trait anxiety, mean ± SD range 20-80	35.3 (13.3)	38.8 (10.1)
Pain Catastrophising Score, median (IQR) range 0-52	12(6-21)	14 (11-28)
Life orientation Test-R, mean ± SD range 0-24	15.8 (5.3)	14.7 (4.1)
Pittsburgh Sleep Quality Index, mean ± SD range 0-21**	8.9 (3.5)	10.6 (3.7) †
Tampa scale of kinesophobia, mean ± SD range	38.0 (6.9)	44.0 (11.5) †
Neuropathic features on mPD-Q		
Nociceptive group, n (%)	46 (55)	13 (45)
Unclear group, n (%)	23 (28)	8 (28)
Neuropathic group, n (%)	14 (17)	8 (28)

p-values were calculated for differences between the two groups. †p<0.05, ††p<0.001. *Procedure conducted was only available in 78 of the responders and 16 of the non-responders. **Measures of Pittsburgh Sleep Quality Index were only available for 67 and 19 participants in the responder and non-responder groups respectively. BMI=body mass index; SD= standard deviation; IQR=interquartile range; UKR=unicompartment knee replacement; TKR=total knee replacement. SF-MPQ=Short-form McGill Pain Questionnaire; ICOAP= The Measure of Intermittent and Constant Osteoarthritis Pain; HAD= Hospital Anxiety and Depression Scale; STAI=State-Trait Anxiety Inventory.

Table 7-3 Pre-operative patient characteristics of the patients who responded to the 12-month assessment compared to those who didn't respond.

	Responders (n=72)	Non-responders (n=38)
Demographic features		
Age, mean ± SD years	71 (10)	71 (10)
Female, n (%)	33 (46)	22 (58)
BMI, mean ± SD kg/m^2	29.9 (4.2)	30.8 (5.9)
Employed, n (%)	18 (25)	9 (24)
Married or living with partner, n (%)	50 (70)	23 (61)
Clinical features		
Right knee affected, n (%)	35 (49)	22 (58)
Duration of pain, median (IQR) months	48.0 (18.0-120.0)	36.0 (19.0-72.0)
Oxford knee score, mean ± SD range 0-48	20.0 (7.5)	17.4 (7.4) †
Oxford knee score pain subscale, mean ± SD range 0-100	70.0 (13.3)	74.8 (12.3) †
Oxford knee score function subscale, mean ± SD range 0-100	62.6 (14.6)	65.7 (14.6)
Kellgren and Lawrence grade, n (%):		
0-2	5 (7.5)	7 (21.9)
3-4	62 (92.5)	25 (78.1) †
Procedure conducted, n (%)*:		
UKR	41 (62)	12 (50)
TKR	25 (38)	12 (50)
Psychological features		
HAD Anxiety, mean ± SD range 0-21	6.6 (4.3)	7.7 (4.6)
HAD Depression, mean ± SD range 0-21	6.4 (4.1)	7.4 (3.2)
STAI State anxiety, mean ± SD range 20-80	33.9 (12.6)	40.9 (13.6) †
STAI Trait anxiety, mean ± SD range 20-80	35.1 (12.9)	38.4 (12.9)
Pain Catastrophising Score, median (IQR) range 0-52	11.0 (6.0-20.0)	18.0 (12.0-27.0) †
Life orientation Test-R, mean ± SD range 0-24	16.1 (5.3)	14.3 (4.5)
Pittsburgh Sleep Quality Index, mean ± SD range 0-21**	8.8 (3.4)	10.2 (4.0)
Tampa scale of kinesophobia, mean ± SD range	38.2 (9.0)	42.2 (7.5) †
Neuropathic features on mPD-Q		
Nociceptive group, n (%)	42 (58)	16 (42)
Unclear group, n (%)	16 (22)	14 (37)
Neuropathic group, n (%)	14 (19)	8 (21)

p-values were calculated for differences between the two groups. †p<0.05 *Procedure conducted was only available in 66 of the responders and 24 of the non responders.**Measures of Pittsburgh Sleep Quality Index were only available for 59 and 25 participants in the responder and non-responder groups respectively. BMI=body mass index; SD= standard deviation; IQR=interquartile range; UKR=unicompartment knee replacement; TKR=total knee replacement. SF-MPQ=Short-form McGill Pain Questionnaire; ICOAP= The Measure of Intermittent and Constant Osteoarthritis Pain; HAD= Hospital Anxiety and Depression Scale; STAI=State-Trait Anxiety Inventory.

The non-responders tended to have a worse pre-operative OKS, as well as OKS pain and function sub-scores, at both time-points. This association was statistically significant, apart from the OKS function subscale at the 12-month assessment. Non-responders were also more likely to have higher levels of psychological distress at baseline, compared to responders. In particular: depression, measured using the Hospital Anxiety and Depression Scale (HAD); state anxiety, measured using the State-Trait Anxiety Inventory (STAI); and kinesophobia, measured using the Tampa scale of kinesophobia (TSK), were significantly worse at both time-points.

At 2-months post-operatively, the neuropathic pain group had significantly worse OKS, as well as OKS pain and function sub-scores, compared to the nociceptive group, Table 7-3.

At 12-months the same trends were seen but this was no longer statistically significant, Table 7-5. Disability associated with pain was significantly higher amongst those with neuropathic pain compared to the nociceptive group, even after adjusting for age, sex and BMI, at the 2-month post-operative assessment. This trend persisted at 12-months but was no longer statistically significant. Psychological distress was significantly higher in the neuropathic group at both time-points for: anxiety, measured using the Hospital Anxiety and Depression Scale (HAD); state and trait anxiety, measured using the State-Trait Anxiety Inventory (STAI); and pain catastrophising, Table 7-4.

Table 7-4 2-month post-operative clinical, pain and psychological characteristics of the 83 patients divided into nociceptive, unclear and neuropathic pain groups*.

	Nociceptive pain (n=63)	Unclear pain (n=32)	Neuropathic pain (n=25)
Clinical characteristics			
Oxford knee score, median (IQR) range 0-48	39.0 (29.0-43.0)	35.0 (29.0-40.0)	32.0(18.0-41.0) †[a]
Oxford knee score pain subscale, mean ± SD range 0-100	38.1 (13.8)	42.5 (13.2)	49.4 (17.9) †[a]
Oxford knee score function subscale, mean ± SD range 0-100	40.3 (15.4)	43.1 (13.3)	51.1 (20.3) †
Pain characteristics			
SF-MPQ pain severity in past 7 days, median (IQR) range 0-10	1.5 (0.5-2.6)	1.8(0.8-4.2)	2.3 (1.9-4.8)
SF-MPQ total score, median (IQR) range 0-45	4.0 (2.0-7.0)	4.0 (2.0-13.0)	7.5 (5.0-11.0)
SF-MPQ sensory subclass, median (IQR) range 0-33	3.0 (2.0-6.0)	4.0 (2.0-11.0)	6.5 (4.0-10.0)†
SF-MPQ affective subclass, median (IQR) range 0-12	0.5 (0.0-1.0)	0.0 (0.0-1.0)	1.0 (0.0-2.0)
ICOAP, median (IQR) range 0-44	9.0 (4.0-15.0)	13.0 (7.0-24.0)	12.0 (5.0-23.0)
Pain disability index, median (IQR) range 0-60	11 (6-26)	20 (12-30)	25 (10-41) †[a]
Psychological characteristics			
HAD Anxiety, median (IQR) range 0-21	2.5 (0.0-4.5)	3.0 (1.0-7.0)	6.0 (4.5-7.0)†[a,b]
HAD Depression, median (IQR) range 0-21	2.0 (1.0-5.0)	2.0 (1.0-6.0)	3.0 (1.0-7.0)
STAI State anxiety, mean ± SD range 20-80	28.0 (9.7)	30.2 (10.2)	36.1 (13.0) †[a,b]
STAI Trait anxiety, mean ± SD range 20-80	28.9 (9.1)	29.4 (8.3)	38.8 (12.6) †[a,b]
Pain Catastrophising Score, median (IQR) range 0-52	5(2-10)	10 (2-15)	14 (6-20) †[a]
Pittsburgh Sleep Quality Index, mean ± SD range 0-21**	8.4 (3.0)	8.5 (3.0)	9.4 (2.2)

*The pre-operative Pain-DETECT questionnaire score was used to divide patients, according to established cutoff values, into those with nociceptive (<13), unclear (13–18) and neuropathic pain (>18). P-values were calculated using the nociceptive group as the reference group. †p-value <0.05,††p<0.001; [a]P-value <0.05, after adjusting for age, sex and bmi; [b]p<0.05 after also adjusting for pain severity. **Measures of Pittsburgh Sleep Quality Index were only available for 38,18 and 11 participants in the nociceptive, unclear and neuropathic pain groups respectively. SF-MPQ=Short-form McGill Pain Questionnaire; ICOAP= The Measure of Intermittent and Constant Osteoarthritis Pain; HAD= Hospital Anxiety and Depression Scale; STAI=State-Trait Anxiety Inventory.

Table 7-5 12-month post-operative clinical, pain and psychological characteristics of the 72 patients divided into nociceptive, unclear and neuropathic pain groups*.

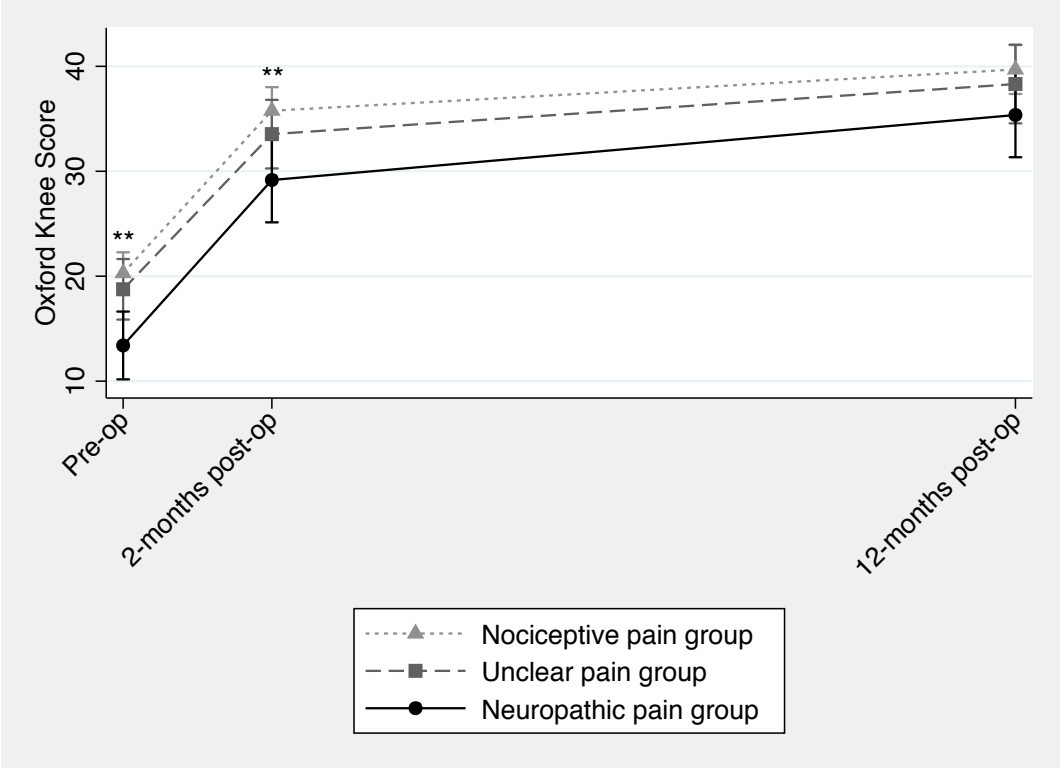
	Nociceptive pain (n=42)	Unclear pain (n=16)	Neuropathic pain (n=14)
Clinical characteristics			
Oxford knee score, median (IQR) range 0-48	43.0 (38.0-46.0)	43.5 (35.0-44.5)	39.0 (32.0-43.0)
Oxford knee score pain subscale, median (IQR) range 0-100	25.7 (20.0-34.3)	28.6 (21.5-40.0)	34.3 (20.0-51.5)
Oxford knee score function subscale, median (IQR) range 0-100	32.0 (24.0-40.0)	36.0 (26.0-48.0)	38.0 (36.0-48.0)
Pain characteristics			
SF-MPQ pain severity in past 7 days, median (IQR) range 0-10	0.5 (0.0-1.7)	1.5 (0.4-4.2)	1.3 (0.7-3.0)
SF-MPQ total score, median (IQR) range 0-45	1.0 (0.0-3.0)	2.0 (0.5-5.5)	3.5 (1.0-10.0)
SF-MPQ sensory subclass, median (IQR) range 0-33	1.0 (0.0-3.0)	1.5 (0.5-5.0)	3.5 (1.0-7.0)
SF-MPQ affective subclass, median (IQR) range 0-12	0.0 (0.0-0.0)	0.0 (0.0-1.0)	0.0 (0.0-3.0)
ICOAP, median (IQR) range 0-44	0.5 (0.0-9.0)	6.0 (2.0-17.0)	4.5 (0.0-16.0)
Pain disability index, median (IQR) range 0-60	6.0 (1.0-17.0)	8.5 (1.5-24.5)	13.0 (7.0-30.0)
Psychological characteristics			
HAD Anxiety, median (IQR) range 0-21	2.0 (0.0-5.0)	2.0 (1.0-5.5)	6.0 (2.0-8.0) †[a,b]
HAD Depression, median (IQR) range 0-21	1.0 (1.0-4.0)	2.5 (0.5-5.0)	4.0 (1.0-8.0) †
STAI State anxiety, mean ± SD range 20-80	32.3 (13.4)	31.6 (12.3)	37.9 (13.1)
STAI Trait anxiety, mean ± SD range 20-80	29.5 (11.2)	33.4 (12.8)	40.2 (16.5) †[a,b]
Pain Catastrophising Score, median (IQR) range 0-52	2.5 (0.0-8.0)	10.0 (1.5-15.0)	15.0 (7.0-18.0) †[a]
Pittsburgh Sleep Quality Index, mean ± SD range 0-21**	8.1 (3.3)	8.9 (2.9)	9.5 (2.7)

*The pre-operative Pain-DETECT questionnaire score was used to divide patients, according to established cutoff values, into those with nociceptive (<13), unclear (13–18) and neuropathic pain (>18). P-values were calculated using the nociceptive group as the reference group. †p-value <0.05,††p<0.001; [a]P-value <0.05, after adjusting for age, sex and bmi; [b]p<0.05 after also adjusting for pain severity. **Measures of Pittsburgh Sleep Quality Index were only available for 35, 13 and 11 participants in the nociceptive, unclear and neuropathic pain groups respectively. SF-MPQ=Short-form McGill Pain Questionnaire; ICOAP= The Measure of Intermittent and Constant Osteoarthritis Pain; HAD= Hospital Anxiety and Depression Scale; STAI=State-Trait Anxiety Inventory.

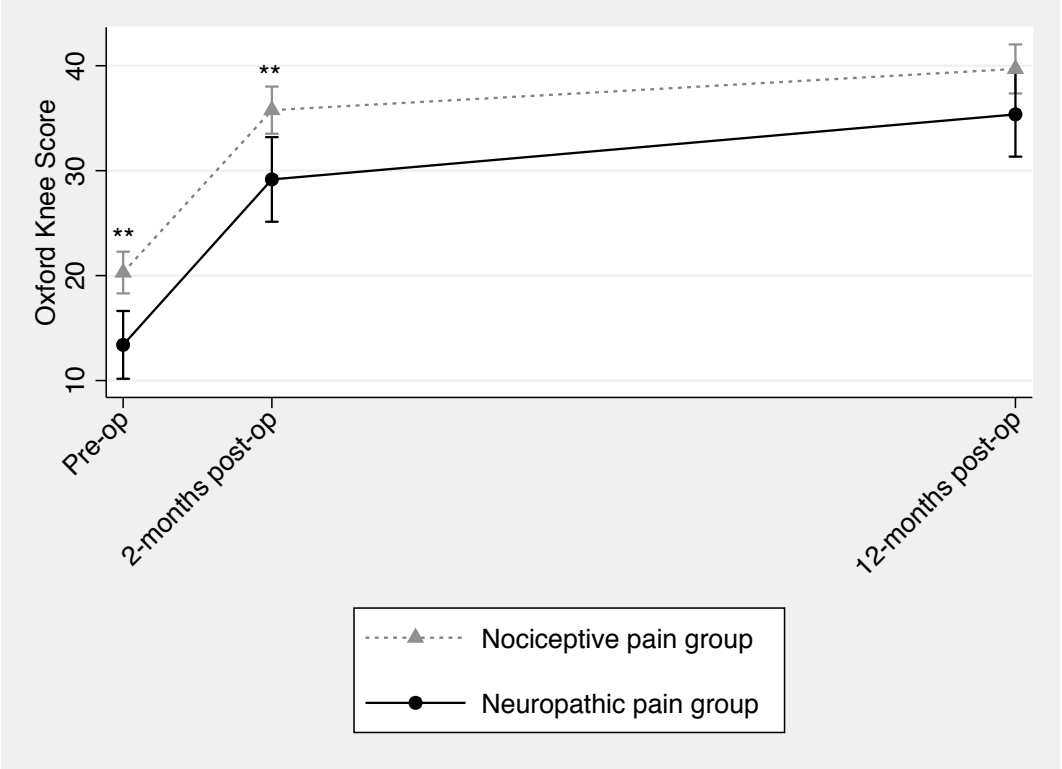
The repeated measures model, adjusting for age, sex and BMI, for the three pain subgroups showed that the neuropathic pain group had significantly worse OKS compared to the nociceptive group, prior to surgery (mean (95% CI) 20.3 (18.3-22.3) versus 13.4 (10.2-16.6) respectively) and at 2-months after surgery (mean (95%CI) 35.8 (33.5-38.0) versus 29.2 (25.1-33.2) respectively). The same trend was present at 12-months post-operatively, but this did not reach statistical significance (mean (95%CI) 35.4 (31.3-39.4) versus 39.7 (37.4-42.0)), Figure 7.1. When pre-operative pain severity and pain-modifying medication use were included in the models, the OKS remained significantly lower in the neuropathic group compared to the nociceptive group prior to surgery (mean (95%CI) 20.7 (17.9-23.4) versus 25.8 (24.0-27.5)) and at 2-months post-operatively, (mean (95%CI) 24.3 (21.1-27.4) versus 30.4 (28.5-32.3)). Regression diagnostics confirmed that the assumptions of the GEE regression models were met.

Figure 7.1 Oxford Knee Score for the participants of EPIONE, taking into account time, for all pain subgroups (A) and nociceptive and neuropathic pain groups only (B).

(A)



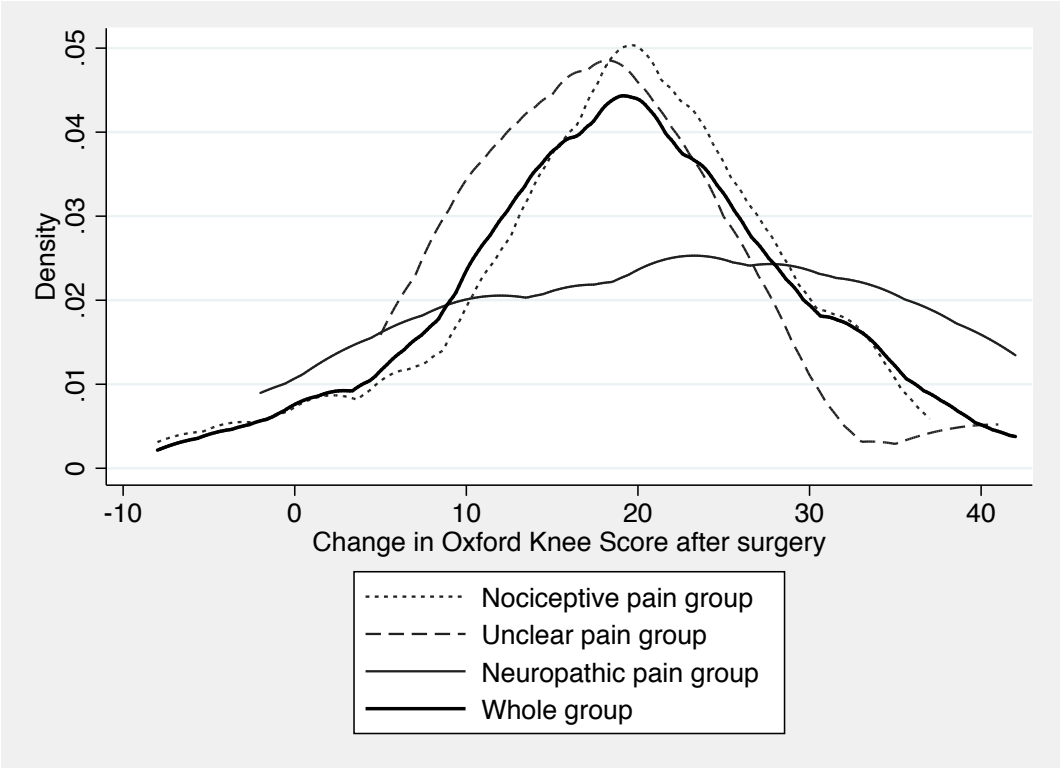
(B)



**p<0.05, after adjusting for age, sex and BMI.

There was no significant difference in the change in OKS, pre-operatively to 12-months post-operatively between the three groups with a mean (SD) of 18.7 (9.5), 18.2 (8.5), 21.4 (13.1), ANOVA p=0.637 for the nociceptive, unclear and neuropathic groups respectively. The distribution plots of the change in OKS are shown in Figure 7.2. The variance of change in OKS for the neuropathic group appears to be larger than for the other pain groups, but this difference was not significant on Bartlett's testing (p=0.213). The proportion of patients in each subgroup who met the criteria for minimally important change in OKS (6.5 units) was 37/43 (88%), 15/16 (94%) and 12/14) 85% for the nociceptive, unclear and neuropathic groups respectively. The proportions were statistically similar (Chi-square test, p=0.759).

Figure 7.2 Change in Oxford Knee Score, pre-operatively to 12 months after surgery for 72 patients recruited to EPIONE.



Overall, 17/72 (23%) of the patients met the criteria for PPSP at the 12-month follow up assessment. Of those with nociceptive pain prior to surgery, 6/43 (14%) reported PPSP compared to 6/16 (38%) in the unclear group, and 5/14 (36%) in the neuropathic pain group. Univariable logistic modelling showed that patients in the unclear pain group prior to surgery were significantly more likely to report PPSP at 12-months post-operatively, compared to the nociceptive group, Table 7-6. There was a similar, but non-significant trend, in the neuropathic pain group. When confounding factors, including age, sex, BMI and pain severity at baseline, were included in the model, there was no significant difference in the prevalence of PPSP between the pain groups. When a higher cut-off value was used to define PPSP, there was no significant association between pain grouping prior to surgery, and the presence of PPSP (Appendix C).

Table 7-6 Logistic regression model of the association between pain group at baseline and persistent post surgical pain at 12-month follow up assessment.

	Univariable model		**Multivariable model***	
Predictor	OR (95% CI)	p	OR (95% CI)	p
Nociceptive group	Reference group	-	Reference group	-
Unclear group	3.7 (1.00-13.99)	0.051	3.4 (0.87-13.77)	0.080
Neuropathic group	3.4 (0.85-13.79)	0.083	2.6 (0.55-12.43)	0.228

*Adjusted for age, sex, BMI and pain severity prior to surgery. OR=odds ratio; 95% CI=95% confidence interval.

7.5.3 COASt

404 patients, with pre-operative data available for analysis, were included in the present study. Of these 233 (58%) had nociceptive pain, 112 (28%) had unclear pain, and 59 (15%) had neuropathic pain. The pre-operative characteristics for the participants are summarised in Table 7-7.

Table 7-7. Pre-operative clinical, pain and psychological characteristics of 404 patients recruited to COASt, divided into nociceptive, unclear and neuropathic pain groups*.

	Nociceptive pain (n=233)	Unclear pain (n=112)	Neuropathic pain (n=59)
Demographic features			
Age, mean ± SD years	70 (9)	67 (9)	66 (9) ††
Female, n (%)	116 (50)	62 (55)	37 (63)
BMI, mean ± SD kg/m^2	29.6 (4.9)	31.2 (5.6) ††	31.5 (5.5) ††
Employed, n (%)	68 (29)	41 (37)	18 (31)
Clinical features			
Right knee affected, n (%)	129 (55)	56 (50)	29 (49)
Oxford knee score, mean ± SD range 0-48	22.3 (7.7)	18.9 (6.8) ††[a,b]	15.5 (5.4) ††[a,b]
Oxford knee score pain subscale, mean ± SD range 0-100	67.2 (13.1)	73.4 (11.3) ††[a,b]	78.5 (9.0) ††[a,b]
Oxford knee score function subscale, mean ± SD range 0-100	56.3 (14.9)	61.6 (13.7) ††[a]	68.1 (11.6) ††[a,b]
Procedure conducted, n (%):	114 (49)	58 (52)	25 (42)
UKR	118 (51)	54 (48)	34 (58)
TKR			
Pain characteristics			
ICOAP, median (IQR) range 0-44	15.6 (7.6)	17.4 (8.5) †	20.0 (8.5) †[a]
Psychological characteristics			
HAD Anxiety, mean ± SD range 0-21**	4.4 (3.9)	6.4 (3.9)	6.0 (2.9)
HAD Depression, mean ± SD range 0-21**	4.2 (3.0)	5.3 (3.6) †[a]	5.0 (3.1)

*The pre-operative Pain-DETECT questionnaire score was used to divide patients, according to established cutoff values, into those with nociceptive (<13), unclear (13–18) and neuropathic pain (>18). **HAD data were only available for 171 of the study participants. P-values were calculated using the nociceptive group as the reference group. †p-value <0.05,††p<0.001; [a]P-value <0.05, after adjusting for age, sex and bmi; [b]p<0.05 after also adjusting for pain severity. ICOAP= The Measure of Intermittent and Constant Osteoarthritis Pain; HAD= Hospital Anxiety and Depression Scale.

Compared to the nociceptive group, the neuropathic group and unclear pain groups tended to be younger, with a higher BMI prior to being listed for surgery. BMI was significantly higher for both groups, and age was also significantly lower in the neuropathic group. The neuropathic and unclear pain groups also had significantly worse pre-operative OKS, including OKS pain and function sub-scores, as well as a significantly higher score on the Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). The neuropathic and unclear pain groups tended to have higher scores for anxiety and depression on the HAD scale but this only reached statistical significance for depression in the unclear pain group.

12-month follow-up data were available for 384 of the study participants. The neuropathic group and unclear pain groups both demonstrated significantly worse OKS, including OKS pain and function sub-scores, 12-months postoperatively compared to the nociceptive group (Table 7-8).

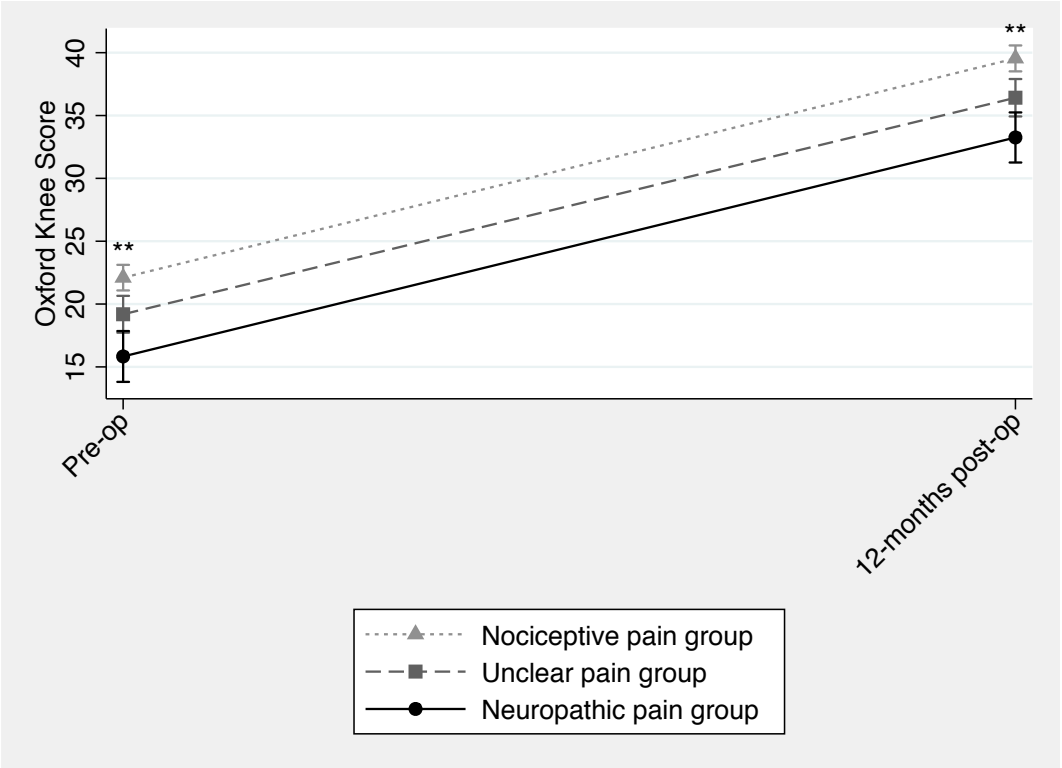
Table 7-8 12-month post-operative clinical characteristics of 384 patients recruited to COASt, divided into nociceptive, unclear and neuropathic pain groups*.

	Nociceptive pain (n=219)	Unclear pain (n=107)	Neuropathic pain (n=58)
Oxford knee score, median (IQR) range 0-48	42.0 (35.0-46.0)	39.0 (29.5-44.0) †† [a,b]	37.0 (25.0-43.0) †† [a,b]
Oxford knee score pain subscale, median (IQR) range 0-100	25.7 (20.0-40.0)	31.5 (22.9-51.5) †† [a,b]	37.2 (25.7-57.2) †† [a,b]
Oxford knee score function subscale, median (IQR) range 0-100	32.0 (24.0-44.0)	36.0 (28.0-52.0) † [a]	44.0 (32.0-60.0) †† [a,b]

*The pre-operative Pain-DETECT questionnaire score was used to divide patients, according to established cutoff values, into those with nociceptive (<13), unclear (13–18) and neuropathic pain (>18). P-values were calculated using the nociceptive group as the reference group. †p-value <0.05,††p<0.001; [a]P-value <0.05, after adjusting for age, sex and bmi; [b]p<0.05 after also adjusting for pain severity.

The repeated measures model, adjusting for age, sex and BMI, for the three pain subgroups showed that the neuropathic pain group had significantly worse OKS compared to the nociceptive group, prior to surgery (mean (95% CI) 15.8 (13.8-17.9) versus 22.1 (21.1-23.1) respectively) and at 12-months after surgery (mean (95%CI) 33.3 (31.3-35.2) versus 39.5 (38.5-40.6) respectively), Figure 7.3. After adjusting for pain severity, the OKS remained significantly worse in patients with neuropathic pain both pre-operatively (mean (95% CI) 17.4 (15.4-19.4) versus 21.5 (20.5-22.5) and at 12-months post-operatively (mean (95% CI) 34.8 (32.8-36.8) versus 39.0 (20.5-22.5). Regression diagnostics confirmed that the assumptions of linear regression modelling were met.

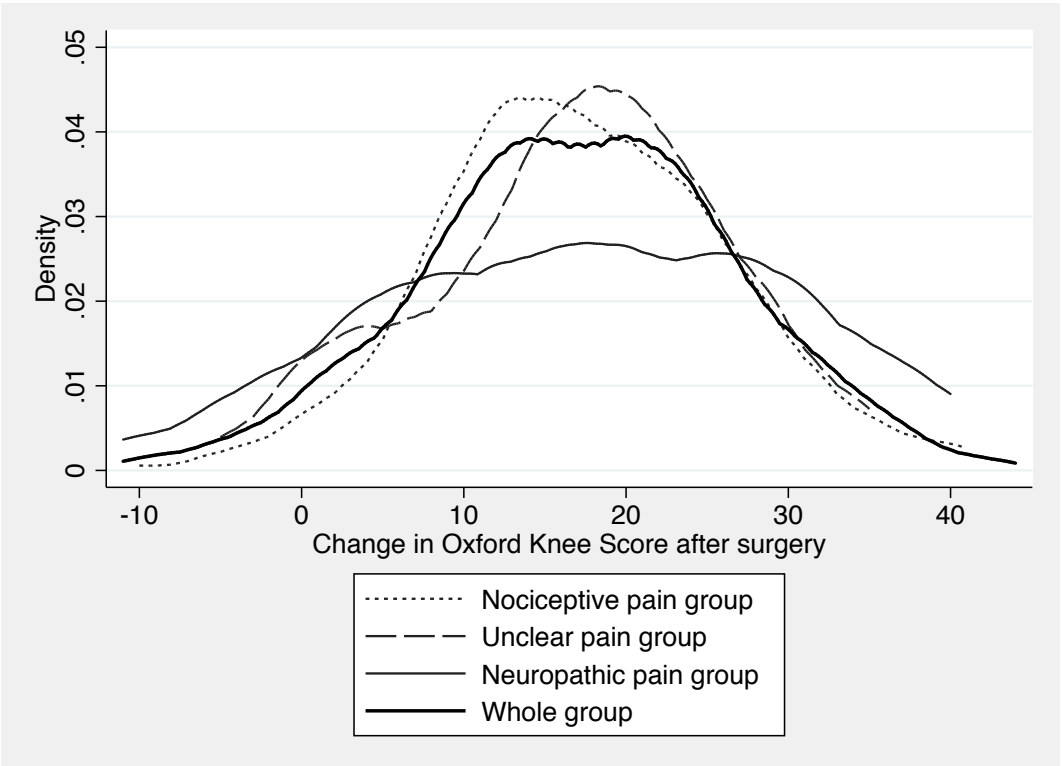
Figure 7.3 Oxford Knee Score for the participants of COASt, taking into account time, for all pain subgroups.



**p<0.05, after adjusting for age, sex and BMI.

There was no significant difference in change in the OKS, pre-operatively to 12-months post-operatively, between the three groups with a mean (SD) of 17.3 (8.8), 17.1 (9.0), and 17.3 (12.5), ANOVA p=0.637 for the nociceptive, unclear and neuropathic groups respectively. The distribution plots of the change in OKS are shown in Figure 7.4. The variance of change in OKS for the neuropathic group appears to be larger than for the other pain groups, and this difference was statistically significant on Bartlett's testing (p=0.001). The proportion of patients in each subgroup who met the criteria for minimally important change in OKS was 199/219 (91%), 89/107 (83%) and 46/58 (79%) for the nociceptive, unclear and neuropathic groups, respectively. This was found to be of statistical significance (Chi-square test, p=0.026).

Figure 7.4 Change in Oxford Knee Score, pre-operatively to 12 months after surgery for 384 patients recruited to COASt.



Overall 126/384 (33%) of the study participants met the criteria for PPSP 12-months post-operatively. Of those with nociceptive pain prior to surgery, 53/219 (24%) reported PPSP, compared to 44/107 (41%) in the unclear group and 29/58 (50%) in the neuropathic group. Patients in the unclear and neuropathic groups, as determined prior to surgery, were significantly more likely to report PPSP, when compared to the nociceptive group, Table 7-9. This relationship remained significant after adjusting for the effects of age, sex, BMI and pain severity prior to surgery. The relationship between PPSP and neuropathic pain remained significant when a higher threshold for PPSP was used (Appendix C).

Table 7-9 Logistic regression model of the association between pain group at baseline and persistent post surgical pain at 12-month follow up assessment.

	Univariable model		**Multivariable model***	
Predictor	OR (95% CI)	p	OR (95% CI)	p
Nociceptive group	Reference group	-	Reference group	-
Unclear group	2.3 (1.4-3.8)	0.001	2.0 (1.2-3.4)	0.006
Neuropathic group	3.6 (2.0-6.6)	<0.001	3.0 (1.6-5.8)	0.001

*Adjusted for age, sex, BMI and pain severity prior to surgery. OR=odds ratio; 95% CI=95% confidence interval.

7.6 Discussion

The main finding of this study is that patients with neuropathic pain, defined using the mPD-Q, have significantly worse OKS at 2 and 12-months after surgery compared to those with nociceptive pain. In the EPIONE cohort the neuropathic group had a median (IQR) OKS of 32.0 (18.0-41.0) compared to 39.0 (29.0-43.0), $p<0.05$ for the nociceptive group. This trend was maintained at the 12-month follow-up assessment, but did not achieve statistical significance. Data from the larger COASt cohort, showed that the 12-months post-operative OKS was significantly worse in the neuropathic group, compared to the nociceptive group: median (IQR) 37.0 (25.0-43.0) versus 42.0 (35.0-46.0), $p<0.001$, respectively.

Data from COASt showed that, compared to the nociceptive group, patients in the unclear and neuropathic pain groups were significantly more likely to report PPSP 12-months post-operatively, (OR (95% CI) 2.0(1.2-3.4), p=0.006 and OR (95% CI) 3.0 (1.6-5.8), p=0.001 respectively).

Although there was no significant difference in the change in OKS at 12-months post-operatively in either cohort, the variance of this change was greater in the neuropathic group and achieved statistical significance in the COASt validation cohort (Chi^2=13.30, P=0.001). At the individual patient level, the proportion of patients in the COASt cohort who improved by the minimally important change in OKS was significantly lower in the neuropathic group (79%) compared to the nociceptive group (91%).

The follow-up data from the EPIONE cohort enabled any differences in the psychological features between patients with neuropathic and nociceptive pain to be identified at each time-point. These data suggest that patients with neuropathic pain continue to have more psychological distress in the short and long-term post-operative period with anxiety and pain catastrophising being the most consistent domains to be significantly different at both 2 and 12-months post-operatively.

The clinical relevance of the magnitude of the difference between the neuropathic and nociceptive pain groups must be assessed before we can consider it as having potential to improve patient care. The difference in OKS between the two pain groups in the present study was in the order of 7 and 5 points at the 2 and 12-month post-operative time-points, respectively. Recent work has determined that the minimally important difference estimate for group comparisons is of the order of 5 points for the OKS (Beard *et al*, 2015). This suggests that the observations of the current study are clinically relevant and so may warrant further investigation.

The fact that there was no significant difference in the change in OKS, at a group level, between the patients with nociceptive and neuropathic pain suggests that surgical therapy is still warranted in those with neuropathic pain. The most conservative change in OKS for the neuropathic pain group was seen at 12-months in the COASt participants: mean (SD) 17.3 (12.5). This is clearly in excess of the minimally important change estimate of around 9 points, for a single group over time, which also supports the value of knee replacement therapy in this group

(Beard *et al*, 2015). When the data is evaluated from a more individual patient perspective the increased variability amongst the response in patients with neuropathic pain, in combination with the significantly lower proportion of patients who meet the criteria for minimally important change suggests that surgery for some patients with neuropathic pain may not be appropriate. Therefore patients in the neuropathic pain group would be in a better position to make a fully informed decision regarding undertaking surgery if they were aware of these more specific projected outcomes.

To our knowledge, there are no previous studies examining the influence of pre-operative neuropathic pain in knee OA on the outcome following knee replacement surgery. The data can however be compared to those from a study of 17 patients with shoulder impingement who underwent QST and assessment using the PD-Q prior to decompression surgery (Gwilym *et al*, 2011). Although this study did not show any significant relationship between pre-operative PD-Q score, when used as a continuous measure, and post-operative Oxford Shoulder Score (OSS), the presence of radiating pain or mechanical hyperalgesia pre-operatively was significantly associated with a worse OSS post-operatively (Gwilym *et al*, 2011). It is interesting to note that the pre-operative OSS also appears to be worse in the patients with radiating pain or mechanical hyperalgesia, although this was not formally tested or reported on. It is possible that the lack of an association between pre-operative PD-Q and outcome following surgery is partly due to the small sample size for the previous study.

Previous work on patients with knee OA has shown that neuropathic features, identified using the mPD-Q, are related to the presence of central sensitisation, measured using QST (Hochman *et al*, 2013). Although there are currently no studies that have used symptom-based assessment of neuropathic pain for direct comparison, the results from a small number of studies that have used QST in this context are relevant. A systematic review of 14 studies that investigated the relationship between pre-operative experimental pain sensitivity and post-operative pain in a range of operations, including 2 studies on patients undergoing total knee arthroplasty (TKA), reported that pre-operative pain sensitivity might explain between 4% and 54% of the variance in post-operative pain (Werner *et al*, 2010). The large variability seen in the results is likely to reflect the diversity of QST measures used as well as the inclusion of a number of different types of surgery. Since this review, further studies have reported on the use of QST in the prediction of post-operative pain following knee replacement surgery specifically (Lunn *et al*, 2013; Petersen *et al*, 2015; Rakel *et al*, 2012; Wylde *et al*, 2013; Wylde *et al*, 2015). It is difficult to draw meaningful conclusions from these studies as they have selected a variety of QST predictors, outcome measures, and statistical techniques to address the same question. The details of the studies to date, which have focussed on patients undergoing knee replacement surgery are summarised in **Table 7-10.**

Table 7-10. Summary of published studies reporting on the use of Quantitative Sensory Testing (QST) to predict outcome following knee replacement surgery.

First Author	Year	QST Modalities Tested	N	Follow-up duration	Summary of results of study
Martinez (Martinez *et al*, 2007)	2007	MPT, HPT, CPT, Brush Allodynia.	20	4 months	Preoperative heat hyperalgesia (VAS scores) did not correlate with pain severity but did correlate with PCA morphine use over the first 24 hours (Rho=0.63, P=0.01).
Lundblad (Lundblad *et al*, 2008)	2008	Electrical detection and pain thresholds, using the Pain matcher.	69	18 months	A lower pain threshold predicted a high pain score at rest: OR 9.19 (95% CI 1.69 to 50.07).
Rakel (Rakel *et al*, 2012)	2012	MPS, HPT, PPT.	215	2 days	MPS and HPT both predicted pain on movement but not resting pain intensity post-operatively, OR 1.3 (95%CI 1.04–1.63|) and 0.88 (95% CI 0.77–1.01) respectively.
Wylde (Wylde *et al*, 2013)	2013	HPT, PPT	51	12 months	PPT was correlated with WOMAC pain score (Rho=0.37, P=0.008).
Lunn (Lunn *et al*, 2013)	2013	Sensitivity to a short and long heat stimulus.	97	30 days	Neither heat pain stimulation paradigm predicted post-operative pain severity.
Petersen (Petersen *et al*, 2015)	2015	PPT, TS, CPM	78	12 months	Preoperative TS level correlated with the postoperative pain intensity ($p<0.05$).
Wylde (Wylde *et al*, 2015)	2015	PPT	239	12 months	PPT was not associated with post-operative pain

N=number of participants included in study; MPT=Mechanical Pain threshold; HPT=Heat Pain Threshold; CPT=Cold Pain Threshold; MPS=Mechanical Pain Sensitivity; PPT=Pressure Pain Threshold; HPS=Heat Pain Sensitivity; WOMAC= Western Ontario McMaster Universities Osteoarthritis Index; TS=Temporal Summation; CPM=Conditioned Pain Modulation.

Although the overall trend seems to be that pre-operative experimental pain sensitivity may be related to post-operative pain outcome, further validation is required prior to translation to the clinical setting. It may be that symptom-based assessment of neuropathic pain, if validated, is more practical for the grouping of patients.

The main strengths of this study are the use of prospective, longitudinal data to investigate the relationship between pre-operative neuropathic pain and short and long-term outcome. A variety of clinical, pain and psychological features were measured in the study cohort, enabling the simultaneous assessment of these factors in conjunction with one another. The main limitation is the fact that the primary study cohort did not reach its target recruitment and so is underpowered, meaning that it is more likely to inappropriately accept the null hypothesis. In addition, there is evidence of significant responder bias at both the 2 and 12-month post-operative assessments, with patients reporting more severe disease severity at baseline being less likely to respond. As it is known that pre-operative pain severity is a predictor of poor outcome (Lewis *et al*, 2015), the direction of the bias is also towards falsely accepting the null hypothesis. Therefore, further associations might not have been detected by this study. The inclusion of data from the larger, validation cohort partly compensates for the relatively small sample size in the study cohort. However, it must be noted that the breadth of data collected in the study cohort is not replicated in the validation cohort.

A recent study of patients undergoing knee replacement surgery demonstrated that it may be possible to identify the patients who will go on to develop persistent post-operative pain with a neuropathic component, early in the post-operative period (Lavand'homme *et al*, 2014). The authors suggested that this could in turn lead to the development of effective preventive strategies in the acute post-operative period. The results of the present study extend this observation further, and suggest

that it might be beneficial to identify patients with features of neuropathic pain even prior to surgery. It is possible that this patient sub-group would benefit from more targeted analgesic or psychological therapy prior to as well as after surgery. The importance of confirming a potential subgroup of patients in OA in a large more definitive study, as well as validating it by its differential response to therapy has been previously highlighted (Felson, 2010) These data together demonstrate that both these criteria have been met and provide a good basis for further investigation of the value of identifying features of neuropathic pain in a clinical setting.

In summary, this study has shown that the sub-group of patients with knee OA, who have features of neuropathic pain, have significantly worse outcome at 2 and 12-months post-operatively compared to those with nociceptive pain. These patients demonstrate on-going psychological distress, in particular anxiety and pain catastrophising, which may be amenable to intervention. Although the change in OKS suggests knee replacement surgery is beneficial in the group as a whole, the response to surgery is highly variable and the proportion of patients who achieve the minimally important change is significantly lower than in the nociceptive group. These patients may benefit from increased awareness of their projected outcome to aid informed decision making with respect to surgical intervention. Post-operative outcome may also be improved by the utilisation of targeted therapy in the pre, peri and post-operative periods. Further investigation of the effect of neuropathic pain on long-term patient satisfaction following surgery is warranted.

8 Discussion

8.1 Main Findings

This thesis has used a combination of methods to investigate the neural mechanisms underlying pain experienced by patients with knee OA, across the full spectrum of disease severity. I have shown that a subgroup of patients with knee OA, who are awaiting knee replacement surgery, demonstrate features of neuropathic pain. In turn, this is associated with increased levels experimental pain, as well as higher symptom severity and psychological distress prior to surgery. Neuroimaging was used to confirm that these features were also associated with central sensitisation in the form of increased descending facilitation as well as reduced descending inhibition prior to surgery. The presence of neuropathic pain prior to surgery was associated with statistically and clinically significantly worse outcome following surgery, compared to those with purely nociceptive pain in the absence of any significant radiographic structural differences between the two groups. Taken together, this mechanism-based understanding of the pain provides an opportunity for targeted therapy prior to surgery, which may enhance outcome following surgery. Furthermore, evidence of pain sensitisation has been detected in early disease, as well as contributing to the observed discordance between structural and symptomatic disease, suggesting that the identification and appropriate treatment of neuropathic pain within primary care may also help to improve symptom control in early disease in the community setting.

8.2 Clinical assessment of pain in knee osteoarthritis

It is now being recognised that pain is not a homogenous entity but that there are a number of different types of pain including nociceptive, inflammatory and neuropathic pain as well as functional and mixed (Woolf, 2004). Furthermore, it is anticipated that it should be possible to work towards a targeted therapeutic strategy, based on the underlying neurobiological mechanisms responsible, rather than the empirical approach currently being adopted in clinical practice (Woolf, 2004).

Previous work had already identified the presence of neuropathic pain in a proportion of patients with knee OA (Hawker *et al*, 2008; Hochman *et al*, 2013; Hochman *et al*, 2011; Valdes *et al*, 2014), and the presence of neuropathic pain has been linked to central sensitisation assessed using quantitative sensory testing (QST) (Hochman *et al*, 2013). This thesis has confirmed that, amongst patients with moderate to severe knee OA; around 20% demonstrate features of likely neuropathic pain. QST was also able to show a link with increased experimental pain sensitivity, but by combining this technique with the use of neuroimaging, it was possible to elucidate some of the centrally mediated mechanisms involved in generating these features of pain.

This work was also able to investigate the role of central sensitisation and features of neuropathic pain at the earlier end of the disease spectrum by studying the characteristics of pain in a community-based cohort. In this context, QST was used to

demonstrate that central sensitisation is an important mechanism contributing to the discordance seen between the presence of structural and symptomatic OA. Participants with painful radiographic knee OA had increased sensitivity to supra-threshold punctate stimulation distant to the affected knee, compared to those with asymptomatic radiographic knee OA. Furthermore, those with pain in the absence of structural disease also demonstrated heightened experimental pain sensitivity to punctate stimulation compared to those with pain-free radiographic knee OA. Measurement of the presence of secondary mechanical hyperalgesia in primary care is feasible, and this mechanism-based assessment may help to identify patients with early disease who could benefit from centrally acting pharmacological agents as discussed above. Heightened sensitivity to supra-threshold punctate stimulation distant to the painful site was also significantly associated with the detection of possible or likely neuropathic pain using the PainDETECT questionnaire in the community setting. Finally in the surgical patient cohort, the same QST modality was also able to demonstrate significant differences between the nociceptive and neuropathic pain sub-groups.

Cluster analysis (see Appendix D), a data driven approach to identifying distinct patient profiles, also identified a sub-group of patients with higher levels of pain severity, psychological distress, as well as pain sensitivity. Although this group was not significantly associated with the score generated using the mPD-Q, this group did have the highest proportion of patients who also met the criteria for neuropathic pain, compared to the other two clusters. These findings, which have been derived

using completely distinct methodology, somewhat substantiate the need to perform a more multi-dimensional assessment of the pain experienced by patients prior to knee replacement surgery, including pain qualities, pain sensitivity, and psychological factors, so that the strategies described above can be suitably employed.

8.3 Central mechanisms of pain

Functional magnetic resonance imaging conducted in patients prior to surgery demonstrated that patients with features of neuropathic pain had evidence of decreased rostral anterior cingulate activation in response to experimentally induced pain. This area is important in the descending inhibitory control of pain via connections with subcortical areas such as the amygdalae and the peri-aqueductal grey (Bingel *et al*, 2006). In addition, there was evidence of increased descending facilitation of nociceptive signals within the brainstem, with increase activation in the rostral ventromedial medulla and nuclueus cuneiformis.

The impact of the presence of neuropathic pain on outcome following surgery has not been previously studied. The longitudinal data collected specifically for this thesis, in combination with the validation data available have shown that features of neuropathic pain prior to surgery predicted significantly worse outcome at both 2 and 12-months post-operatively. In addition, the neuropathic pain group response to surgery was more variable, with only 79% of patients achieving the minimally

important change in Oxford Knee Score after surgery, compared to 91% of the nociceptive group.

8.4 Limitations

The limitations specific to an individual study have already been discussed in the corresponding chapters. This section will consider the more generic limitations of this work, focussing mainly on factors affecting the outcome measures and populations studied.

8.4.1 Oxford Knee Score as an outcome measure

The Oxford Knee Score was used as the main outcome measure for the surgical patient cohort study. Whilst this is an appropriate, patient reported outcome measure developed for this context (Dawson *et al*, 1998), there are a number of ways to interpret OKS following surgery, and it may not fully capture all the attributes of a good or bad outcome as determined by the patient (Kiran *et al*, 2015). For example, it may be of value to study whether patient expectations have been met and participation levels after surgery in more detail.

8.4.2 Population factors

The main limitation of using data from the Chingford Study is that it is comprised solely of predominantly Caucasian origin, and so its generalizability is limited. The EPIONE Study was more representative of the population being studied, but the responder bias is likely to have affected the results generated. This may have been overcome by the use of COASt data to validate the findings, but due to the fact that

only data for participants who completed the follow-up assessment is available, it is currently not possible to assess whether or not any significant responder bias is present in this population.

8.4.3 Pain assessment

Due to the time constraints during research study visits in both the Chingford and EPIONE Study, the QST research protocol was abbreviated. This may have resulted in important omissions and it is possible that differences in pain sensitivity, for example those seen with conditioned pain modulation or temporal summation, have been missed.

Furthermore, participants were allowed to continue using any on-going analgesic medication prior to assessment, as it was not deemed practical or ethical to ask patients to stop their analgesic medications in either the Chingford or EPIONE Study. In theory, this may have masked some of the changes seen using QST and neuroimaging. In the Chingford Study, the differences in QST were stratified to take into account the use of analgesic or neuropathic pain medication. This demonstrated that, if anything, the use of pain modifying medication acted as a severity marker of sensitisation rather than eradicating any differences in QST as might be expected. Similarly the baseline data from the EPIONE study showed that the differences in QST, that were detected between patients with neuropathic pain and those with nociceptive pain, persisted after adjusting for the use of pain-modifying medication. This is reassuring, and may make it easier for translation of the tool as a bedside test, but the true effect on the underlying pain mechanisms is not known.

8.5 Potential translation to clinical care.

Taken together this work has identified a subgroup of patients with neuropathic pain, who demonstrate evidence of central sensitisation, which may be helpful to identify prior to surgery. The first potential benefit to patients is that the awareness of their more variable projected outcome would allow them to make a more informed decision regarding whether or not to opt for surgery. Whilst the outcome for this patient group is more variable, the neuropathic group as a whole achieved the same mean change in OKS as the nociceptive group. This suggests that treating the peripheral component of disease is still of considerable benefit in this sub-group. This is also substantiated by the longitudinal neuroimaging data, which demonstrated a change in central pain processing, with a likely return to normal resting state function after surgery.

The second potential opportunity for benefit to patients is to introduce pharmacological therapies, which are used in the management of neuropathic pain, prior to surgery. Current guidelines support the use of amitriptyline, duloxetine, gabapentin, or pregabalin as initial treatment for neuropathic pain (apart from trigeminal neuralgia) (National Institute for Health and Clinical Excellence, 2013). The descending pain modulatory system asserts its effect through the neurotransmitters serotonin and noradrenalin. Anti-depressant drugs are able to modulate these neurotransmitters, and so it is logical that tri-cyclic antidepressants such as amitriptyline, and serotonin noradrenaline reuptake inhibitors, such as duloxetine, may be of benefit in this context. In addition, selective serotonin reuptake inhibitors

such as paroxetine may be of benefit, with supporting data available from animal models of post-operative pain (Deumens *et al*, 2013). Pregabalin and gabapentin are classed as calcium channel a2δ ligands and work as gamma-aminobutyric acid (GABA) agonists (Nijs *et al*, 2014). Inhibitory neurons within the spinal cord release glycine and GABA, whereas descending inhibitory signalling from the brainstem is mainly mediated by serotonin and noradrenaline (Woolf, 2004) , and so based on the current findings, these agents may be less effective in this patient group. Although in theory opioids, such as morphine, are able to excite OFF cells in the RVM as well as supress ON cells, their use is limited by the side effect profile, which includes pain hypersensitivity, the potential for addiction as well as gastro-intestinal upset (Gilron *et al*, 2015; 2013; Nijs *et al*, 2014).

The final strategy, which might benefit patients with neuropathic pain, is to consider the use of non-pharmacological strategies to address the presence of central sensitisation prior to surgery (National Institute for Health and Clinical Excellence, 2013; Nijs *et al*, 2014). The three main options for the conservative management of central sensitisation comprise education, exercise therapy and cognitive behavioural therapy. Education in this context would aim to help the patient to understand that their symptoms may be due to hypersensitivity within the central nervous system as well as the pathology within the joint. There is evidence in patients with fibromyalgia that therapeutic pain neuroscience education improved endogenous analgesia, compared to activity pacing combined with self-management education (Nijs *et al*, 2014; Van Oosterwijck *et al*, 2013).

Exercise is theoretically able to activate powerful descending endogenous analgesia and this so-called "exercise-induced endogenous analgesia" has been demonstrated in some forms of musculoskeletal pain (Nijs *et al*, 2014). Exercise is recommended as part of the generic non-surgical management of knee OA (McAlindon *et al*, 2014), but it would be interesting to see whether an exercise programme for patients with neuropathic pain prior to surgery could modulate these pain characteristics before surgery, and more importantly to have an impact on the outcome after surgery. Encouraging patients to undertake exercises, which may exacerbate their pain can be challenging. The proposed time-contingent approach, whereby a patient is instructed to perform the exercise for a specific amount of time, rather than until it hurts, may improve adherence as well as help to de-activate top-down cognitive-emotional sensitisation (Nijs *et al*, 2014).

Cognitive behavioural therapy (CBT) can be used to address maladaptive pain cognitions such as pain catastrophising, anxiety and depression that have been linked to central sensitisation (Nijs *et al*, 2014). This thesis has shown a consistent link between neuropathic pain and the presence of pain catastrophising both before and after surgery. Furthermore, the neuroimaging data suggest that it may cause central sensitisation by virtue of increased descending facilitatory pain modulation via brainstem mechanisms.

The staff at The Nuffield Orthopaedic Hospital, Oxford currently run a multidisciplinary session for patients listed for hip replacement surgery, called 'Hip

School'. Members of the physiotherapy, occupational therapy, nursing and surgical staff present brief presentations on what will happen to the patient once they are admitted for surgery. This format could be adapted to provide a combined education, exercise, and CBT session for patients with neuropathic pain identified using the mPD-Q. The effectiveness of such an intervention could then be tested using a randomised control trial design. The two comparison groups of interest would be a non-intervention nociceptive group, as well as a non-intervention neuropathic pain group.

8.6 Future research

The results of this thesis lead to a number of future directions of research. The first line of investigation to consider is whether targeted treatment strategies, according to the presence of neuropathic pain prior to surgery, do indeed result in improved outcome following surgery. It would be interesting to see if conservative or pharmacological or a combination of these treatments can improve symptom severity prior to surgery and in turn if this affects the outcome after surgery. This approach could also be tested in the primary care setting, where features of neuropathic pain and central sensitisation have been identified. It might also be beneficial to consider surgical treatment options earlier in patients with features of neuropathic pain in order to optimize their outcome.

Although the mPD-Q has successfully identified an at risk sub-population, it might be possible to develop a more custom-made tool which is more amenable to being

incorporated into daily clinical practice. For example, the mPD-Q could be used to recruit a homogenous group of patients with knee OA to a focus group study. This method would allow the comprehensive examination of the pain experience in this group of patients with a view to developing a corresponding tool to capture these pain characteristics in a similar format to the Oxford Knee Score, which already forms a key component of routine pre-operative assessment. Alternatively the existing data could be further analysed in order to identify if there are any redundant components of the mPD-Q when being applied in this patient group. It is possible that a distilled version could then be more easily completed and interpreted within timeframe of a standard orthopaedic consultation.

The data from the Chingford Study showed that pain sensitisation contributes to the discordance seen between symptomatic and structural knee OA. It would be interesting to extend this further and assess whether using a more refined measure of structural change, such as quantitative joint space width, had an effect on this relationship. Furthermore, it would be useful to know whether participants with neuropathic pain in the cross-sectional analysis experienced a different trajectory of symptom progression over time, compared to those without features of neuropathic pain.

Finally, the neuroimaging work in this thesis has focussed on the brain activation seen in response to experimentally evoked mechanical hyperalgesia. It is known that processing of experimental and clinical pain is similar but not identical. It would

therefore be informative to study the responses to pure clinical pain, which can be done using alternative neuroimaging techniques such as resting state network analysis or arterial spin labelling.

Overall this work suggests that the (modified) PainDETECT questionnaire, which has been shown to be a surrogate for central sensitisation, may be a useful bedside tool for clinicians in the assessment and management of knee OA, at all stages of the disease.

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9 Appendix

9.1 APPENDIX A

ARTHRITIS & RHEUMATISM
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Neuropathic Features of Joint Pain

A Community-Based Study

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Objective. **Quantitative sensory testing (QST) and questionnaire-based assessments have been used to demonstrate features of neuropathic pain in subjects with musculoskeletal pain. However, their direct relationship has not been investigated in the community. The purpose of this study was to conduct an observational study to describe the characteristics of joint pain and to examine the relationship between QST measures and the PainDETECT Questionnaire (PD-Q).**

Methods. **Warm detection, heat pain, and mechanical pain thresholds as well as mechanical pain sensitivity over the sternum were determined and the PD-Q scores were calculated in a cross-sectional study of 462 participants in the Chingford Study. Comparisons were made between subjects with and those without joint pain. Logistic regression modeling was used to describe the association between neuropathic pain features, as determined by the PD-Q score, and each of the QST measures individually, adjusting for age, body mass index, and use of pain-modifying medications.**

Results. **A total of 66.2% of the subjects reported recent joint pain, with a median average pain severity of 5 of 10. There was increased sensitivity to painful stimuli in the group with pain as compared to the pain-free group, and this persisted after stratification by pain-modifying medication use. While only 6.7% of subjects had possible neuropathic pain features and 1.9% likely neuropathic pain features according to the standard PD-Q thresholds, features of neuropathic pain were common and were present in >50% of those reporting pain of at least moderate severity. Heat pain thresholds and mechanical pain sensitivity were significantly associated with features of neuropathic pain identified using the PD-Q, with an odds ratio (OR) of 0.88 (95% confidence interval [95% CI] 0.79–0.97; $P = 0.011$) and an OR of 1.24 (95% CI 1.04–1.48; $P = 0.018$), respectively.**

Conclusion. **QST measures and the PD-Q identified features of neuropathic pain in subjects in this community-based study, with significant overlap between the findings of the two techniques.**

Musculoskeletal pain is common, disabling, and often poorly managed, especially in the elderly (1,2). Current treatment and development of new effective therapies for musculoskeletal pain are hindered by poor understanding of the underlying mechanisms (3). While previous research focused on articular and periarticular mechanisms of pain, accumulating evidence now suggests that features of neuropathic pain may be present in some patients with musculoskeletal pain syndromes, including chronic widespread pain (4,5) and osteoarthritis (1,6–12). The appreciation that pain can be due to not only joint pathology, but also central and peripheral

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sensitization may then be translated to mechanism-based clinical diagnosis and management options (13).

Neuropathic pain is defined as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" (14). While thought to be common, affecting up to 25% of those with chronic pain (15), neuropathic pain is clinically underrecognized and is associated with an array of comorbid conditions, resulting in reduced quality of life (16).

A key factor in the underrecognition of patients with neuropathic pain is the lack of a gold-standard diagnostic tool. Evidence-based guidelines recommend the use of screening questionnaires, such as the Leeds Assessment of Neuropathic Symptoms and Signs (17) and the PainDETECT (PD-Q) (18), particularly by nonspecialists, to identify patients with possible features of neuropathic pain (19). Although in one-third of patients with musculoskeletal pain conditions, the use of such guidelines has resulted in the reclassification to a diagnosis of neuropathic pain (20), such tools still fail to identify 10–20% of patients and can only provide a guide to diagnosis (21).

Quantitative sensory testing (QST), which measures psychophysical responses to controlled stimuli with the aim of identifying neural dysfunction, is also used to identify sensory changes in patients with features of neuropathic pain (22,23) and is being increasingly used in musculoskeletal research (6,24,25). Allodynia or hyperalgesia identified by QST may indirectly suggest the sensitization of nociceptive neurons. If these phenomena are identified distant from the site of the index pain, they may represent central, rather than peripheral, sensitization. Although sensitization is a feature of neuropathic pain, it can also occur in the context of non-neuropathic pain, which means that QST can only be used to identify possible features of neuropathic pain, rather than provide a definitive diagnosis.

Evidence of neuropathic features in musculoskeletal conditions arises from studies of QST measures (4–6,11,12,26) as well as symptom-based assessments (7,9,26), but to date, no studies have examined the direct relationship between these two potential screening tools for joint pain in a community-based population. The aims of this study were to describe the characteristics of joint pain in a community-based sample and to examine the relationship between neuropathic pain features identified using the PD-Q and QST measures.

SUBJECTS AND METHODS

Setting and subjects. The study subjects were selected from the participants in the Chingford Study, a well-described, prospective, population-based longitudinal study of osteoarthritis and osteoporosis, comprising 1,003 women, derived from the register of a large general practice in Chingford, North London, UK (27–29). The women, ages 44–67 years at baseline, are representative of those in the general population of the UK with respect to weight, height, and smoking characteristics (28). The study was established in 1989, and 516 women attended the 20-year followup visit. A musculoskeletal pain assessment was conducted in 462 women who were included in the present analysis. The local ethics committee approved the study and written consent was obtained from each woman (Outer North East London Research Ethics Committee [REC; formerly, Barking & Havering and Waltham Forest RECs]; LREC [R&WF] 96).

For each participant, we recorded the age, height while in a standing position with shoes removed, using a wall-mounted stadiometer (in cm, to the nearest 0.1 cm; Leicester Height Measure), and weight with shoes removed, using electronic scales (in kg, to the nearest 0.1 kg).

Quantitative sensory testing. QST was used to determine warm detection, heat pain, and mechanical pain thresholds as well as mechanical pain sensitivity, based on the protocol devised by Rolke et al (23). In order to focus on potentially centrally mediated effects and minimize the influence of any local pathology associated with musculoskeletal conditions, a site 3 cm distal to the sternal notch was tested. Participants were asked to close their eyes during testing.

Warm detection and heat pain thresholds. Thermal thresholds for warm and heat pain detection were assessed using a Thermotest Modular Sensory Analyzer (MSA; Somedic) thermode (25 × 50 mm). The method-of-limits algorithm was used, with a thermode adaptation temperature of 32°C. Each stimulus was generated after a randomized 4–6-second interval. Both thresholds were obtained with ramped stimuli (1°/second) that were terminated when the participant pressed a button. Each threshold was tested 5 times, and the mean value from all 5 readings was calculated. The MSA Thermotest has a built-in safety cutoff temperature of 50°C to ensure that the patient is not harmed. If the limit was reached and the participant had not pressed the button (had not reported any sensation), the value at that limit was recorded.

Mechanical pain threshold. Mechanical pain thresholds were measured using a set of 7 custom-made weighted pinprick simulators that exert a force of between 8 and 512 mN, following a binary logarithmic scale, with a flat contact area of 0.25 mm in diameter (MRC Systems). Using the method-of-limits algorithm, the final threshold was the geometric mean of 5 series of ascending and descending stimulus intensities.

Mechanical pain sensitivity. This was tested using the same weighted pinprick stimuli as above. The 512-mN pinprick was applied 3 times, and the participant was asked to give a rating for each stimulus on a 0–10 numeric rating scale, where 0 = no sharpness and 10 = the most sharp imaginable. The mean of the 3 measures was taken. Assessment of mechanical pain sensitivity was added to the protocol after the study had begun, since it was thought that suprathreshold testing might provide important additional information. The order of attendance of participants was random, so the missing data were not a source of systematic bias. Sensitivity analysis subsequently confirmed that there was no significant difference in age or

Table 1. Characteristics of the 462 women in the Chingford Study who were assessed for pain at the 20-year visit, stratified by reported pain and use of pain-modifying medication*

	No pain reported (n = 156)		Pain reported (n = 306)		
	No pain-modifying medication (n = 123)	Pain-modifying medication (n = 33)	No pain-modifying medication (n = 162)	Pain-modifying medication (n = 144)	*P*
Age, median (IQR) years	70 (67–75)	73 (67–78)	72 (67–77)	71 (68–75)	0.229
BMI, mean ± SD kg/m^2	26.9 ± 4.4	26.7 ± 5.0	27.5 ± 4.7	29.0 ± 5.5	0.001
Warm detection threshold, median (IQR) °C	4.8 (3.7–6.7)	5.6 (4.4–6.7)	4.8 (3.7–6.2)	4.9 (3.8–6.1)	0.324
Heat pain threshold, median (IQR) °C	46.4 (43.7–48.4)	46.1 (43.7–48.0)	45.5 (42.6–48.0)	45.0 (42.2–47.4)	0.020
Mechanical pain threshold, median (IQR) mN	64.0 (16.0–164.0)	40.0 (16.0–128.0)	32.0 (11.2–153.6)	19.2 (8.2–70.4)	0.001
Mechanical pain sensitivity, median (IQR) (range 0–10)†	5.3 (3.3–7.7)	6.0 (4.0–7.7)	6.0 (4.0–8.0)	6.5 (5.3–8.3)	0.019
PD-Q score ≥13, no. positive/total no. tested (%)‡	–	–	4/157 (2.5)	29/143 (20.1)	<0.001

* *P* values are for comparisons across groups. IQR = interquartile range; BMI = body mass index.
† Measures of mechanical pain sensitivity were available for 90 participants without pain (71 had not taken pain-modifying medication and 19 had) and for 219 participants with pain (113 had not taken pain-modifying medication and 106 had).
‡ Using the highest score on the PainDETECT Questionnaire (PD-Q) in those with >1 painful area.

body mass index (BMI) between the tested and nontested participants.

Pain assessment. The PD-Q was used to assess the features of pain experienced by participants during the preceding 4 weeks (18). The PD-Q is a self-administered questionnaire that has been validated against expert diagnosis in patients with chronic lower back pain as being able to distinguish those with predominantly neuropathic pain from those with nonneuropathic pain (18). It contains a body drawing for patients to indicate the sites of pain and any radiation present, their assessment of pain quality (severity rated from "hardly noticed" to "very strong"), their pattern of pain, and measures of current, worst, and average pain severity. An overall PD-Q score is then generated that summarizes everything but the pain severity data, which results in a score of –1 to 38. A score >18 indicates likely neuropathic pain, 13–18 possible neuropathic pain, and <13 makes neuropathic pain unlikely (18).

In this study, each woman initially completed the body diagram, and those reporting >1 painful area were asked to complete the questionnaire with a single location of pain in mind, similar to the modified PD-Q for knee pain (7). Up to 2 areas were assessed per subject, with a priority of capturing data on knee, hip, and hand pain, consistent with our research interests.

Data on analgesic and neuropathic pain medications used in the preceding 72 hours, which are thought to potentially affect the QST results, were recorded. Analgesics were defined as any compounds containing acetaminophen, nonsteroidal antiinflammatory drugs, or opioids. Neuropathic pain medications consisted of antidepressants, selective serotonin and norepinephrine reuptake inhibitors, and anticonvulsants, including gabapentin and pregabalin, prescribed for any indication. Participants were subsequently categorized according to whether they had used any of the above pain-modifying medications or not.

Statistical analysis. Demographic features, medication use data, and QST data in the study participants were compared in the group with versus the group without self-reported joint pain during the preceding month. Wilcoxon's rank sum test (non-normal distribution), unpaired *t*-test (normal distribution), and chi-square test (categorical data) were used to compare the data. The groups were then further divided according to the use of pain-modifying medication, and analysis of variance (ANOVA) and Kruskal-Wallis one-way ANOVA were used to assess differences in normal and non-normal data, respectively. For those with pain, the proportion of women with a PD-Q score reflecting possible or likely neuropathic pain in at least 1 area was calculated, and Fisher's exact test was used to identify any significant effect of pain-modifying medication use.

The painful sites and the distribution of overall PD-Q scores for these sites were recorded. Data gathered from the measures of pain severity, the presence of pain radiation, and the presence of at least moderate severity for each of the 7 pain qualities measured by the PD-Q were used to describe the characteristics of the joint pain.

The main outcome variable was the overall PD-Q score, which was dichotomized using published thresholds into unlikely neuropathic pain (score <13) versus possible/likely neuropathic pain (score ≥13) (18). This cutoff was selected because there were few PD-Q scores above 18 in this study. Univariate logistic regression modeling, adjusting for clustering of sites within a person, was used to describe separately the association between the binary features of the neuropathic pain variable (determined by the PD-Q score) and each QST measure. In view of the binary logarithmic scale for mechanical pain thresholds, logarithmic transformation was used prior to regression analyses. This was done so that a 1-step increase in the transformed mechanical pain threshold variable was of the same order as the step between successive probes used to measure this threshold. Multivariate logistic regression was used to adjust for the potential confounders of age, BMI, and analgesic or neuropathic pain medication use, as determined a priori. Fractional polynomial regression modeling was used to model nonlinear relationships for continuous variables.

For the QST measures that were found to be significant predictors of neuropathic pain, a receiver operating characteristic (ROC) curve was used to define the cutoff values

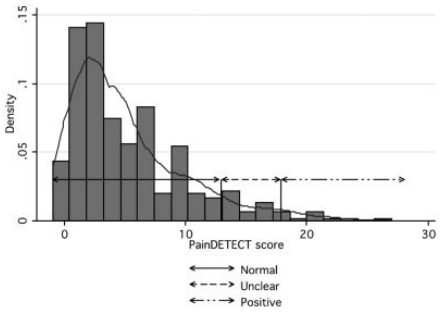

Figure 1. Kernel density distribution plot of the total scores on the PainDETECT Questionnaire in subjects with self-reported musculoskeletal pain.

that predict the binary neuropathic pain variable with optimal sensitivity and specificity. Using these cutoff values, the proportion of participants with QST measures indicative of possible or likely neuropathic pain was determined.

All statistical analyses were performed using Stata SE version 12 software (StataCorp).

RESULTS

Of the 462 women included in the present study, 306 (66.2%) reported joint pain during the preceding month, with 125 women (27.1%) experiencing pain in >1 area. BMI was found to be normally distributed. Ages, PD-Q scores, and all QST values were nonnormally distributed. Subjects with pain had a significantly higher BMI (mean ± SD 28.2 ± 4.5 versus 26.8 ± 5.2; $P = 0.004$) and were more likely to have taken analgesics in the previous 72 hours (39.2% versus 16.7%; $P < 0.001$). All of the sternal QST measures, apart from the warm detection threshold, showed increased sensitivity to the experimental stimuli in subjects with joint pain as compared to those without joint pain: median of 45.3 (interquartile range [IQR] 42.4–47.6) versus 46.4 (IQR 43.7–48.3), $P = 0.006$ for the heat pain threshold, median of 22.4 (IQR 9.6–102.4) versus 64.0 (IQR 16.0–140.8), $P = 0.002$ for the mechanical pain threshold, and median of 6.0 (IQR 4.7–8.3) versus 5.3 (IQR 3.3–7.7), $P = 0.024$ for mechanical pain sensitivity. This trend was maintained when medication use was considered (Table 1). The proportion of participants with likely neuropathic pain was significantly higher in those who had taken pain-modifying medications than in those who had not (2.5% versus 20.1%; $P < 0.001$).

The 431 painful sites assessed were located in the knee (46.4%), hip (13.9%), back (14.2%), shoulder (10.0%), hand/wrist (8.8%), and other sites (6.7%). None of the participants reported pain at the sternum, where QST was conducted. The median pain severity for current pain was 0 (IQR 0–3), worst pain was 6 (4–8), and average pain was 5 (IQR 3–6).

The distribution of the total PD-Q scores for each area assessed is shown in Figure 1. Of the 431 painful areas, 29 (6.7%) had scores of 13–18, representing possible neuropathic pain, and 8 (1.9%) had scores >18, representing likely neuropathic pain. In contrast, only 26 of the 431 painful areas (6.0%) had no features of neuropathic pain.

The breakdown of the PD-Q scores in terms of the presence or absence of radiating pain and at least moderate severity of the other 7 qualities is shown in Figure 2. The most common qualities were pain upon

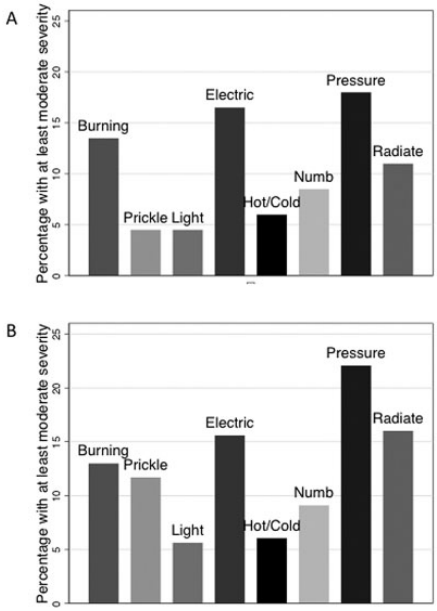

Figure 2. Qualities of pain, as determined using the PainDETECT Questionnaire, evaluating **A,** the knee and **B,** other musculoskeletal sites.

Table 2. Logistic regression model of predictors of possible/likely neuropathic pain features on the PainDETECT Questionnaire, clustered by person

Predictor	Univariate model		Multivariate model*	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Warm detection threshold, per °C increase	1.00 (0.86–1.16)	0.949	0.98 (0.85–1.14)	0.905
Heat pain threshold, per °C increase	0.88 (0.80–0.97)	0.012	0.88 (0.79–0.97)	0.011
Mechanical pain threshold, per step increase	0.97 (0.83–1.13)	0.657	1.01 (0.86–1.17)	0.945
Mechanical pain sensitivity, per unit increase	1.26 (1.07–1.48)	0.005	1.24 (1.04–1.48)	0.018

* Adjusted for age, body mass index, and use of analgesic or neuropathic pain medication. OR = odds ratio; 95% CI = 95% confidence interval.

light pressure (20.2%), sudden attacks of pain that felt like electrical shocks (16.1%), radiating pain (13.7%), and burning pain (13.2%). Overall, 47.3% of the areas had no associated radiating pain and no pain qualities of at least moderate severity, 32.5% showed a single pain quality, 9.5% showed 2, 6.5% showed 3, and 4.2% showed ≥4 pain qualities.

We then explored the relationship between the values from QST and the findings from the PD-Q. Univariate analysis showed that heat pain thresholds and mechanical pain sensitivity were significantly associated with possible or likely neuropathic pain, as determined by the PD-Q score, and the effect remained after adjustment for potential confounders (Table 2).

Using a ROC curve analysis, cutoff values with optimal sensitivity and specificity were determined. Heat pain thresholds <45.2°C (area under the curve 0.61 [95% confidence interval (95% CI), 0.51–0.71]) and mechanical pain sensitivity >6 (area under the curve 0.62 [95% CI 0.52–0.72]) predicted possible or likely neuropathic pain, as determined by the PD-Q scores. Using these cutoff values, the proportion of participants with one or both QST measures indicating possible or likely neuropathic pain was determined (Figure 3).

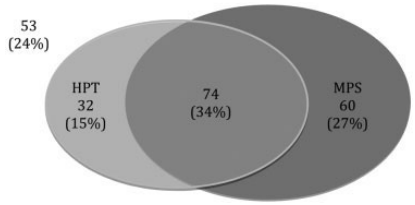

Figure 3. Venn diagram demonstrating the number of participants in whom one or both quantitative sensory testing measures (heat pain threshold [HPT] or the mechanical pain sensitivity [MPS]) indicated possible or likely neuropathic pain. Values are the percentage of the total (n = 219).

DISCUSSION

An important finding of this study was that QST at the sternum, a central point distant from the region of pain, demonstrated increased sensitivity to painful stimuli in subjects with pain as compared to those without pain, and this relationship persisted after stratification by use of pain-modifying medications. In subjects with joint pain, possible or likely neuropathic pain was present in 20.1% of those taking pain-modifying medications, as compared to only 2.5% of those not taking pain-modifying medications. While overall, only 6.7% had possible neuropathic pain and 1.9% had likely neuropathic pain based on the PD-Q thresholds, features of neuropathic pain were common and present in >50% of those reporting pain of at least moderate severity. In those with pain, heat pain thresholds and mechanical pain sensitivity were significantly associated with likely neuropathic pain identified with the PD-Q (odds ratio [OR] 0.88 [95% CI 0.80–0.97], $P = 0.012$ and OR 1.24 [95% CI 1.04–1.48], $P = 0.018$, respectively). Thirty-four percent of the participants with musculoskeletal pain demonstrated increased sensitivity to both heat and suprathreshold mechanical stimuli.

The prevalence of musculoskeletal pain has previously been estimated to be ~30% in the general population worldwide (2). The higher rate seen in this study may be accounted for by 3 factors. First, the Chingford Study is restricted to women, and women are known to be at greater risk of developing musculoskeletal pain. Second, the women were between the ages of 64 and 87 years at the time of the current study, and the prevalence of musculoskeletal pain is known to increase strongly with age. Third, the duration and chronicity of musculoskeletal pain have varied among studies. For

example, in one study, 58% of 20–72-year-olds reported musculoskeletal pain in the previous week, as compared to 15% who had musculoskeletal pain every day during the previous year. In the current study, we measured pain within the previous 4 weeks, which is most similar to the former definition, with a correspondingly similar estimate. The estimated prevalence of neuropathic pain varies from 1% to 8.8% in the general population worldwide (15,30) and from 6.9% to 8.2% among those with chronic pain (31,32). Although the present study was not designed to estimate the prevalence of neuropathic pain, the proportion of areas we assessed that fulfilled the criteria for likely neuropathic pain according to the PD-Q is reassuringly similar.

To our knowledge, no other studies of QST have been conducted with regard to joint pain in the community, but the results can be compared to those from a study of somatosensory abnormalities in osteoarthritis of the knee (6). Consistent with the current study, Wylde et al (6) demonstrated increased sensitivity to a pressure stimulus applied distant to the site of pain (the right forearm) in patients as compared to healthy controls and no significant difference in distant warm detection. In contrast, distant heat pain thresholds were not found to be significantly different, whereas in our study, subjects with pain demonstrated significantly lower heat pain thresholds than those without pain. While this may represent a true difference between the populations being studied, it may also reflect differences in the analysis methods and sites assessed. Overall, these studies emphasize the potential for altered pain sensitivity in areas away from the site of pain, implicating possible central nervous system involvement.

Since there is no gold standard test for neuropathic pain, we sought to compare 2 of the tools that are currently used: the PD-Q versus QST. Although there are no previous studies that specifically assess the association between PD-Q scores and QST values in the community, a study of patients with chronic pain showed that self-reported neuropathic pain features identified using the Neuropathic Pain Symptom Inventory correlate with related modalities identified by QST (33). Furthermore, a study of patients with fibromyalgia demonstrated that pressure–pain thresholds were correlated with PD-Q scores (26).

Hochman et al (7) demonstrated the same group of most common pain qualities as identified in the present study in their patients with knee osteoarthritis, using the modified PD-Q: radiating pain (59.2%), electrical shocks (50.4%), sensitivity to pressure (34.9%), and burning pain (33.3%) (7). The frequency of symptoms was much higher than in the current study, which is expected, since only patients with moderate-to-severe symptoms of arthritis were recruited. This suggests that a similar set of qualities may be important in musculoskeletal conditions in general, although further exploration of this idea is required.

The strengths of this study include its large sample size, the use of an unselected community-based cohort, with the participating women being representative of those in the general population of the UK, and incorporation of potential confounding factors, such as BMI, age, and use of pain-modifying medications. The main limitation is the use of the PD-Q to assess separate areas affected by pain within an individual. Although not formally validated for use in this manner, the modified PD-Q, which has been found to have adequate face and content validity, follows a similar principle (7). A further limitation is the lack of definitive diagnostic information regarding the presence of any actual lesions of the somatosensory system. For this reason, it is possible to comment only on the presence of features suggestive of neuropathic pain. As details of widespread pain were not formally collected, the effect of this on the QST results also cannot be assessed. The study findings are applicable only to women between the ages of 64 and 87 years.

We demonstrated in the current study that pain-modifying medications did not eradicate sensory changes detected by QST, but rather, they acted as a marker of severity. Standard practice is to cease pain medication for at least 24 hours prior to QST (22,23), a practice that contributes to the ethical and logistical constraints of its transferability as a clinically viable tool. These data reassure us that meaningful changes can still be detected despite the use of pain medications, increasing the potential clinical utility of QST. Furthermore, the presence of possible or likely neuropathic pain in 20.1% of subjects requiring pain-modifying medications for joint pain highlights the potential burden of neuropathic pain features in this group of individuals living in the community.

The association between heat pain thresholds, mechanical pain sensitivity, and PD-Q scores provides reassuring concurrent validation of significant overlap between the paradigms being measured using both techniques in this setting. While these findings complement the results of a neuroimaging study of patients with hip osteoarthritis conducted by investigators in our group, which demonstrated a significant correlation between the PD-Q score and periaqueductal grey matter activation in response to punctate stimuli (10), further work on establishing the underlying mechanisms and benefits of

treatments specifically targeting these features is needed. Furthermore, the presence of increased sensitivity to heat in isolation of changes in mechanical pain sensitivity (15%) and vice versa (27%) suggests that testing multiple modalities may differentiate clinically important subgroups of patients.

In summary, the findings of this study confirm that musculoskeletal pain is common in the community, and despite the likely tendency toward mild disease and the continuation of pain-modifying medication, QST and the PD-Q identify features suggestive of neuropathic pain with significant overlap between the two techniques. Further validation of the findings is required before transferring these techniques to the clinical setting.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Javaid had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Soni, Gwilym, Spector, Hart, Javaid.

Acquisition of data. Soni, Spector, Hart, Javaid.

Analysis and interpretation of data. Soni, Batra, Arden, Cooper, Tracey, Javaid.

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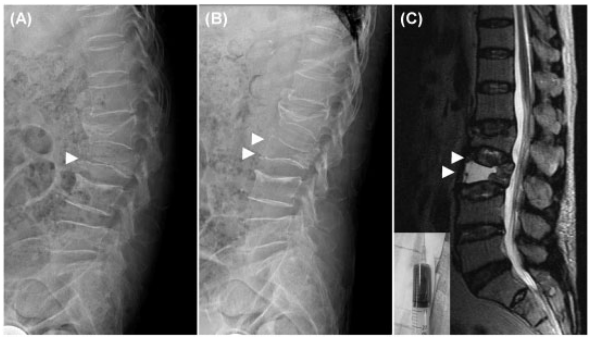
Clinical Images: Mobile vertebral fluid collection associated with compression fracture



The patient, a 63-year-old woman with chronic back pain, was admitted for aggravated, intractable back pain, which was not relieved by conservative treatment. The patient had no history of diabetes mellitus or hypertension and was in good health before this episode. Interestingly, a maximal degree of height loss in the L3 vertebra was seen on dynamic flexion view radiographs (**arrowhead** in **A**), but restored height was seen on extension view radiographs (**arrowheads** in **B**). A preoperative T2-weighted magnetic resonance image (MRI) revealed signs of extensive fluid in the L3 vertebral body (**arrowheads** in **C**). Balloon kyphoplasty was performed after aspiration (13 ml of fluid were aspirated) (**inset**). Osteoporotic vertebral compression fractures and related conditions are common causes of disability and morbidity in the elderly. Mobile vertebral fluid collection is an unusual feature, even in Kümmell's disease, which occurs when a fracture does not heal and avascular necrosis develops, often presenting as intravertebral clefts. Intravertebral clefts are almost always confirmed on MRI as signal void. The void content may vary (air or fluid) (McKiernan F, Faciszewski T. Intravertebral clefts in osteoporotic vertebral compression fractures. Arthritis Rheum 2003;48:1414–9). Although signs of fluid within vertebra are associated with benign vertebral compression fractures, the clefted mobile condition seen in this patient was considered significantly severe (Thawait SK, Marcus MA, Morrison WB, Klufas RA, Eng J, Carrino JA. Research synthesis: what is the diagnostic performance of magnetic resonance imaging to discriminate benign from malignant vertebral compression fractures? Systematic review and meta-analysis. Spine [Phila Pa 1976] 2012;37:E736–44).

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9.2 APPENDIX B

Supplementary results to chapter 4

Supplementary Table 1: Logistic regression model of quantitative sensory testing measures at the knee as predictors of subgroup, defined by the presence or absence of pain and structural features of knee osteoarthritis for each knee, in participants who were not using any pain modifying medication, n=265*.

QST measure as predictor	Subgroup as outcome measure	Knee			
		Univariate Model RRR (95% CI)	P	Multivariate Model RRR (95% CI)[§]	P
Warm Detection Threshold, per ^{0}C increase	No Pain & No ROA	0.97 (0.89-1.05)	0.491	0.97 (0.90-1.07)	0.594
	No Pain & ROA	Reference group	-	Reference group	-
	Pain & No ROA	0.96 (0.84-1.09)	0.520	0.95 (0.84-1.08)	0.468
	Pain & ROA	1.05 (0.98-1.13)	0.147	1.04 (0.97-1.12)	0.241
Heat Pain Threshold, per ^{0}C increase	No Pain & No ROA	0.95 (0.88-1.02)	0.228	0.96 (0.89-1.03)	0.264
	No Pain & ROA	Reference group	-	Reference group	-
	Pain & No ROA	0.97 (0.85-1.10)	0.595	0.99 (0.87-1.12)	0.835
	Pain & ROA	0.93 (0.87-1.00)	0.065	0.95 (0.88-1.02)	0.157
Mechanical Pain Threshold, per step increase	No Pain & No ROA	0.96 (0.80-1.17)	0.718	1.00 (0.83-1.21)	0.989
	No Pain & ROA	Reference group	-	Reference group	-
	Pain & No ROA	0.96 (0.70-0.33)	0.827	1.04 (0.74-1.46)	0.823
	Pain & ROA	0.97 (0.80-1.17)	0.742	1.02 (0.84-1.24)	0.837
Sharpness rating score, per unit increase	No Pain & No ROA	1.03 (0.90-1.18)	0.672	1.01 (0.87-1.16)	0.936
	No Pain & ROA	Reference group	-	Reference group	-
	Pain & No ROA	1.11 (0.90-1.37)	0.328	1.16 (0.96-1.40)	0.115
	Pain & ROA	1.08 (0.94-1.24)	0.263	1.11 (0.94-1.31)	0.209

*Pain was defined as any knee pain captured using the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) pain subscale and ROA was defined as Kellgren and Lawrence global score of grade 2 or more. [§]Multinomial logistic regression modelling was used, adjusting for age, body mass index, anxiety and depression. Predictors were clustered by person, to take account of the knee level modeling. OR = odds ratio; 95% CI = 95% confidence interval; RRR=relative risk ratio; QST=quantitative sensory testing, ROA=radiographic osteoarthritis.

Supplementary Table 2 Logistic regression model of quantitative sensory testing measures at the sternum as predictors of subgroup, defined by the presence or absence of pain and structural features of knee osteoarthritis for each knee, in participants who were not using any pain modifying medication, n=265*.

QST measure as predictor	Subgroup as outcome measure	Sternum			
		Univariate Model RRR (95% CI)[§]	P	Multivariate Model RRR (95% CI)[§]	P
Warm Detection Threshold, per ^{0}C increase	No Pain & No ROA	1.02 (0.90-1.15)	0.767	1.01 (0.90-1.15)	0.821
	No Pain & ROA	Reference group	-	Reference group	-
	Pain & No ROA	1.09 (0.93-1.28)	0.300	1.13 (0.96-1.33)	0.143
	Pain & ROA	1.05 (0.95-1.17)	0.304	1.07 (0.96-1.20)	0.199
Heat Pain Threshold, per ^{0}C increase	No Pain & No ROA	0.99 (0.92-1.08)	0.848	0.98 (0.91-1.06)	0.700
	No Pain & ROA	Reference group	-	Reference group	-
	Pain & No ROA	0.98 (0.86-1.11)	0.728	1.01 (0.88-1.15)	0.904
	Pain & ROA	0.99 (0.93-1.06)	0.837	1.02 (0.95-1.10)	0.558
Mechanical Pain Threshold, per step increase	No Pain & No ROA	0.86 (0.72-1.02)	0.084	0.85 (0.72-1.01)	0.070
	No Pain & ROA	Reference group	-	Reference group	-
	Pain & No ROA	0.90 (0.64-1.28)	0.579	0.93 (0.65-1.32)	0.671
	Pain & ROA	0.83 (0.70-0.99)	0.036	0.86 (0.72-1.04)	0.121
Sharpness rating score, per unit increase	No Pain & No ROA	1.12 (0.99-1.27)	0.059	1.12 (0.98-1.27)	0.094
	No Pain & ROA	Reference group	-	Reference group	-
	Pain & No ROA	1.37 (1.01-1.86)	0.045	1.46 (1.06-2.01)	0.019
	Pain & ROA	1.21 (1.05-1.39)	0.007	1.26 (1.09-1.47)	0.003

*Pain was defined as any knee pain captured using the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) pain subscale and ROA was defined as Kellgren and Lawrence global score of grade 2 or more. [§]Multinomial logistic regression modelling was used, adjusting for age, body mass index, anxiety and depression. Predictors were clustered by person, to take account of the knee level modeling. OR = odds ratio; 95% CI = 95% confidence interval; RRR=relative risk ratio; QST=quantitative sensory testing, ROA=radiographic osteoarthritis.

9.3 APPENDIX C

Supplementary results to chapter 7

Supplementary Table 3 Logistic regression model of the association between pain group at baseline and persistent post surgical pain (PPSP), at the 12-month follow up assessment, using data from the EPIONE study.

PPSP was defined as an average pain severity score of 4 or more for the preceding week, measured using the visual analogue score (VAS) from the Short-form McGill Pain Questionnaire (SF-MPQ)

	Univariate model		**Multivariate model***	
Predictor	OR (95% CI)	P	OR (95% CI)	P
Nociceptive group	Reference group	-	Reference group	-
Unclear group	1.75 (0.37-8.38)	0.481	1.51 (0.29-7.78)	0.620
Neuropathic group	3.04 (0.69-13.46)	0.143	1.89 (0.35-10.24)	0.459

PPSP was defined as an average pain severity score of 4.5 or more for the preceding week, measured using the visual analogue score (VAS) from the Short-form McGill Pain Questionnaire (SF-MPQ)

	Univariate model		**Multivariate model***	
Predictor	OR (95% CI)	P	OR (95% CI)	P
Nociceptive group	Reference group	-	Reference group	-
Unclear group	1.75 (0.37-8.38)	0.481	1.51 (0.29-7.78)	0.620
Neuropathic group	3.04 (0.69-13.46)	0.143	1.89 (0.35-10.24)	0.459

*Adjusted for age, sex, BMI and pain severity prior to surgery. OR=odds ratio; 95% CI=95% confidence interval.

Supplementary Table 4. Logistic regression model of the association between pain group at baseline and persistent post surgical pain (PPSP), at the 12-month follow up assessment, using data from COASt.

PPSP defined as an average pain severity score of 4 or more for the preceding month captured using the mPD-Q

	Univariate model		**Multivariate model***	
Predictor	OR (95% CI)	P	OR (95% CI)	P
Nociceptive group	Reference group	-	Reference group	-
Unclear group	2.01 (1.18-3.44)	0.010	1.66 (0.95-1.89)	0.075
Neuropathic group	2.77 (1.48-5.18)	0.001	2.41 (1.22-4.74)	0.011

PPSP defined as an average pain severity score of 4.5 or more for the preceding month captured using the mPD-Q

	Univariate model		**Multivariate model***	
Predictor	OR (95% CI)	P	OR (95% CI)	P
Nociceptive group	Reference group	-	Reference group	-
Unclear group	2.00 (1.11-3.60)	0.020	1.55 (0.83-2.9)	0.166
Neuropathic group	3.33 (1.72-6.42)	<0.001	2.74 (1.34-5.62)	0.006

*Adjusted for age, sex, BMI and pain severity prior to surgery. OR=odds ratio; 95% CI=95% confidence interval; mPD-Q= modified PainDETECT-Questionnaire.

9.4 APPENDIX D

9.4.1 Identification of individual patient profiles using cluster analysis in patients with knee OA

9.4.2 Abstract

Objective

Osteoarthritis (OA) is a heterogeneous condition and this raises the possibility that the characterisation of distinct patient profiles could help to understand symptoms at a mechanism-based level. This in turn might improve our ability to predict outcome, as well as guide therapy. The aim of this study was to use a hypothesis-free, data driven approach to classify patients into separate groups based on differences in measurements of pain quality, psychological factors and experimental pain. The relationship between group membership and measures of pre-operative disease severity as well as response to knee replacement surgery was then investigated.

Methods

Patients with knee OA, placed on the waiting list for joint replacement surgery, were recruited to the study. A questionnaire pack was used to collect clinical, pain, and psychological characteristics prior to surgery as well as at 2 and 12-months after surgery. Specifically, data from the Short-form McGill Pain Questionnaire (SF-MPQ), Hospital Anxiety and Depression Scale (HAD), Pain Catastrophizing Score (PCS), revised Life Orientation Test (LOT-R), Tampa scale for kinesiophobia (TSK), and measures of pain pressure threshold (PPT) were entered into a hierarchical agglomerative cluster analysis, using Ward's method with squared Euclidean

distance. Multinomial logistic regression modelling was used to measure associations between pre- and post-operative clinical and QST variables, not entered into the cluster analysis, and cluster assignment. Discriminant function analysis was then performed in order to further investigate the contribution of each variable to group membership. The accuracy of predicting cluster membership at the individual level was then assessed.

Results

90 patients were included in the present study and a three-cluster solution was selected. Cluster one comprised 34 (38%) of the patients, and had the best scores for all the psychological and pain symptom severity with moderate experimental pain compared to the other two groups. Cluster two was the smallest cluster and comprised only 22 (24%) of the patients, and was characterized by having the worst scores for all the psychological and pain variables with the highest level of experimental pain, compared to the other two clusters. Cluster three comprised 34 (38%) of the patients, and demonstrated moderate levels of psychological and pain symptom severity but the least experimental pain, compared to the other two clusters. The pre-operative OKS, including both pain and function subscales, were significantly worse for cluster two compared to cluster one. There was no significant difference between OKS at 2 and 12-months post-operatively. There was a trend towards cluster two having a worse OKS at the 12-month follow-up assessment (median (IQR) 37.5 (33.5-43.5)), compared to clusters one (median (IQR) 44.0 (40.0-45.0)) and three (median (IQR) 41.5 (38.0-46.5)).

Conclusion

In this preliminary analysis of patients with knee OA, three distinct patient profiles were identified. In particular, there appears to be a group of patients with high levels of psychological distress and increased experimental pain who demonstrate increased clinical severity prior to surgery and a trend towards to worse outcome at 12-months post-operatively. Further replication of these early findings is required, but it might be possible to use this method in order to identify sub-groups of patients who could benefit from specific targeted therapeutic strategies.

9.4.3 Introduction

OA is a heterogeneous disease with considerable variation in clinical features, aetiopathology and response to treatment. It has been suggested that the difficulty in defining distinct subgroups or phenotypes of patients with OA, which prevents clinical trials from targeting therapies accordingly, may partly explain the modest effect sizes seen for many OA therapies (Lane *et al*, 2011). Although tailored patient therapy, which is called for in many of the current practice guidelines (Fernandes *et al*, 2013; McAlindon *et al*, 2014; 2008), is needed in order to optimize therapeutic effects, the methodology for identifying robust clinically meaningful phenotypes is not well defined (Driban *et al*, 2010) .

Two main approaches to defining a phenotype in OA have been suggested. The first method relies on the identification of distinct patient populations based on clinical observation. These are then validates by demonstrating significant differences in other clinical characteristics, disease progression, or response to therapy for example.

The second method uses a hypothesis-free and data driven method, such as cluster analysis to statistically derive significantly subgroups within a population (Felson, 2010; Knoop *et al*, 2011). This method depends entirely on the nature of the data included in the analysis and the threshold set for accepting a separate phenotype. There are four examples in the literature where this method has been used to identify distinct patients profiles amongst patients with knee OA (Cruz-Almeida *et al*,

2013; Egsgaard *et al*, 2015; Knoop *et al*, 2011; Murphy *et al*, 2011). Despite the use of different methods and variables for clustering, all four of the studies consistently report a cluster associated with higher levels of psychological distress. It has been suggested that this cluster or knee pain profile may represent a group with a greater contribution of their pain from centrally mediated mechanisms. In turn, it has been hypothesized that this group may benefit from appropriately tailored treatment strategies and also may be at risk of developing post-operative pain after knee replacement surgery, but to date this has not yet been formally tested (Egsgaard *et al*, 2015).

The ultimate challenge once a novel phenotype has been proposed is to validate it and prove its use in the clinical setting. It has been suggested that a novel phenotype should first be confirmed by replicating it in an independent study (Felson, 2010). Although clear consensus has not been reached, it has been proposed that validation should involve showing a relation to response to treatment or prevention strategy or alternatively be important for understanding the biological differences between different disease types (Felson, 2010).

9.4.4 Aim

The aims of this study were to:

1. Identify distinct knee OA patient profiles, in patients with moderate to severe disease, using a combination of pain descriptor, psychological and experimental pain measures.
2. To investigate any association between the profiles and outcome following knee replacement surgery.

9.4.5 Methods

9.4.5.1 Setting and Subjects

Data from participants recruited to the **E**valuation of **P**eri-operative pain **I**n **O**steoarthritis of the k**NE**e (EPIONE) Study, were used for the present analysis. Details of recruitment are given in 2.3.1. The recruitment process and study visits are outlined in Figure 5.1. As cluster analysis does not accommodate missing data, the present analysis was restricted to those patients who had completed quantitative sensory testing (QST) prior to surgery.

9.4.5.2 Data collection

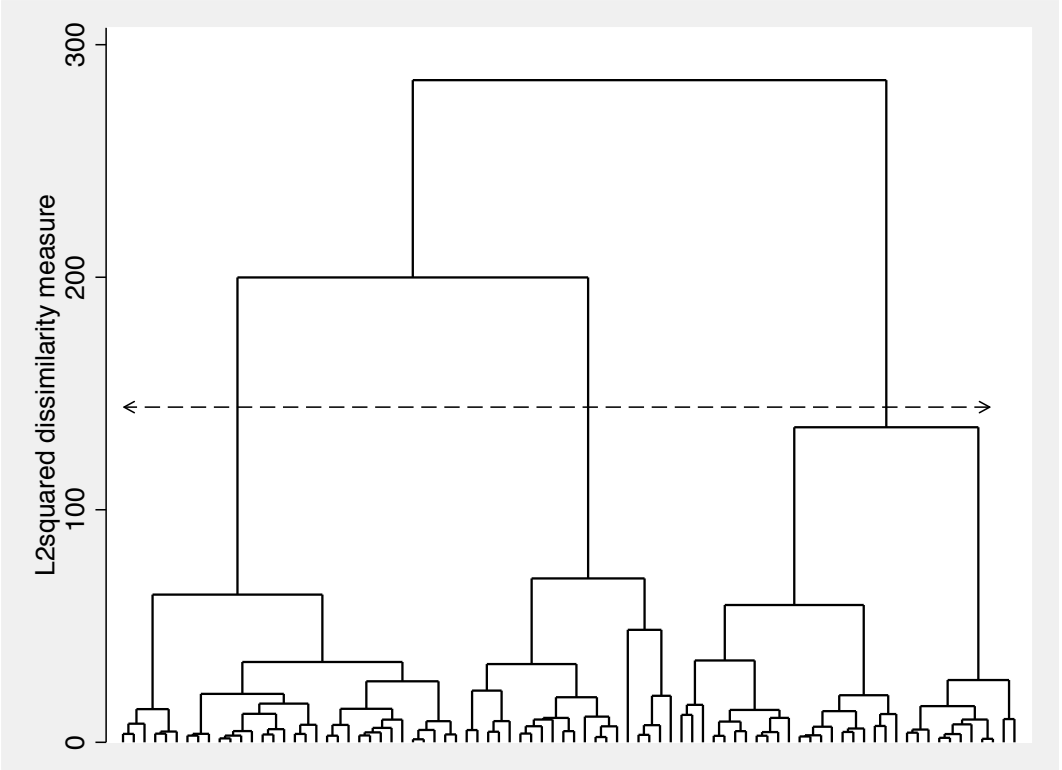
Details on data collection of population demographics, clinical data, radiographs, QST measures, pain assessment, psychological factors and sleep disturbance prior to surgery, as well as the 2 and 12-month follow-up data collection are given in 2.3.2.

9.4.5.3 Statistical analysis

This study used cluster analysis, which is a data driven statistical method used to group participants according to how similar they are according to a number of descriptor variables considered together. This method does not require any preconception about which participants should be grouped together and allows novel groups to be uncovered for further analysis. It can be considered as an exploratory method, and the groups are not defined based on any outcome measure.

Hierarchical agglomerative cluster analysis was selected for the current analysis. This method starts by defining each participant as an individual cluster and then repeatedly merges the two closest clusters until a single cluster containing all the participants is generated. This process can be illustrated using a cluster dendrogram, where the vertical lines represent the magnitude of the proximity between the clusters which have been merged, Figure 9.1.

Figure 9.1 Dendrogram of the hierarchical cluster analysis, using Ward method with squared Euclidean distance.



The three-cluster solution is marked with a dashed line.

There are statistical different methods for establishing the proximity between clusters in order to determine which clusters should be merged at each step. The most commonly used approach is based on the proximity between cluster centroids. Proximity can be calculated using the Euclidean distance, or the squared Euclidean distance. This study used Ward's method, which determines the distance between cluster centroids and aims to minimize the sum of the squared Euclidean distances (Cruz-Almeida *et al*, 2013; Egsgaard *et al*, 2015; Giesecke *et al*, 2003; Murphy *et al*, 2011).

Visual inspection of the cluster dendrogram was used to identify the optimal number of clusters to best fit the data. The dissimilarity measure represents the proximity between adjacent clusters, in this case was calculated using the sum of the squared Euclidean distances between the cluster centroids, as described above. The larger this value, the greater the separation between the clusters. The cut-off was therefore selected so that the maximum separation between the chosen clusters was maintained.

The variables included in the cluster analysis were representative of the multi-dimensional aspects of pain and were selected based on their likely link with centrally mediated mechanisms, rather than being reflective of the severity of local pathology alone. The variables selected included: quality of pain, measured using the Short-form McGill Pain Questionnaire (SF-MPQ) (Melzack, 1987); anxiety and depression, measured using the Hospital Anxiety and Depression Scale (HAD) (Bjelland *et al*, 2002); pain catastrophising, measured using the Pain Catastrophising Score (PCS) (Sullivan, 1985), personality optimism-pessimism, measured using the revised Life Orientation Test (LOT-R)(Scheier *et al*, 1985); and fear of movement, measured using the Tampa scale for kinesiophobia (TSK) (Kori KS, 1990). From the QST variables available, pressure pain threshold (PPT) at each site was selected in view of the available literature supporting the potential use of this particular modality in detecting pain sensitisation in patients with knee OA and as a potential tool for phenotyping (Egsgaard *et al*, 2015; Fingleton *et al*, 2015; Suokas *et al*, 2012).

All the variables entered into the cluster analysis were standardized to obtain similar metrics so that all variables contributed equally to the distance measured between individual participants. A dendrogram, which illustrates the process of cluster formation, in conjunction with evaluation of the dissimilarity measure was used to determine the most appropriate number of clusters present within the dataset. Following the formation of clusters, multivariate analysis of variance (MANOVA) was used to confirm that each variable used to define the clusters was differentiated by the cluster solution. Univariate analysis of variance (ANOVA) was then used to test if each of the variables significantly differentiated the clusters. Chi-square testing was used to compare the clusters on categorical data. Multinomial logistic regression modelling was used to measure associations between cluster assignment and pre-operative clinical and QST variables, which were not entered into the cluster analysis. The cluster groups were used as the outcome measure, with cluster one being used as the reference group. The first model was univariate and measured any association between the predictor and pain grouping. A second model included age, BMI and sex, as potential confounding factors selected a priori.

Discriminant function analysis was then used in order to identify the contribution of each variable to the assignment of individuals to a cluster group. The number of discriminant dimensions needed to describe the differences between the cluster groups was tested using canonical linear discriminant analysis. Standardized discriminant coefficient functions were used to generate equations for the significant discriminant functions identified, so that the contribution of each

individual variable could be assessed. Finally the predictive ability of the discriminant analysis was tested, by calculating the proportion of participants who were correctly classified using the discriminant functions identified.

Multinomial logistic regression modelling was used to measure any association between cluster group membership and outcome following knee replacement surgery. The cluster groups were used as the outcome measure, with cluster one being used as the reference group. The OKS at 2 months post-operatively was initially entered into the model as the predictor variable. In a separate model, this was repeated, using the OKS at the 12-month post-operative assessment as the predictor variable. The models were adjusted for the potential pre-operative confounding factors age and sex, which were selected a priori. ANOVA was then used to test for the difference in mean change in OKS from baseline to 2 and 12-months post-operatively between the clusters.

Finally logistic regression modeling was used to test if there was any significant relationship between the presence of persistent post-surgical pain (PPSP) and cluster assignment. PPSP was defined as an average pain severity score of three or more for the preceding week, measured using the visual analogue score (VAS) from the Short-form McGill Pain Questionnaire (SF-MPQ), at the 12-month follow up assessment (Petersen *et al*, 2015). In a univariate model, PPSP was used as the outcome variable and cluster grouping was used as the predictor variable. A multivariate model was then conducted, adjusting for the potential confounding factors age and sex.

9.4.6 Results

The characteristics of the 90 patients included in the present study are summarised in Table 9-1.

Table 9-1 Characteristics of the 90 patients included in the cluster analysis

Demographic features	
Age, mean ± SD years	71 (9)
Female, n (%)	43 (48)
BMI, mean ± SD kg/m^2	30.1 (4.9)
Employed, n (%)	29 (32)
Married or living with partner, n (%)	63 (70)
Clinical features	
Right knee affected, n (%)	45 (50)
Duration of pain, median (IQR) months	48 (18-96)
Oxford knee score, mean ± SD range 0-48	19.3 (7.2)
Oxford knee score pain subscale, mean ± SD range 0-100	71.3 (12.5)
Oxford knee score function subscale, mean ± SD range 0-100	63.3 (14.0)
Kellgren and Lawrence grade, n (%)*:	
0-2	12 (15)
3-4	67 (85)
Procedure conducted, n (%):**	
UKR	43 (60)
TKR	29 (40)

*Kellgren and Lawrence grades were only available for 79 of the patients included in the cluster analysis. **Procedure conducted was only available in 72 of the patients included in the study. BMI=body mass index; SD= standard deviation; IQR=interquartile range; UKR=unicompartment knee replacement; TKR=total knee replacement.

A three-group cluster solution was selected based on consideration of the dissimilarity measures represented in the dendrogram, which summarizes the results of the clustering process (Figure 8.1). The distribution of the variables used for cluster assignment, across the three clusters, is summarised in Table 9-2.

Table 9-2 Cluster characteristics for each variable used for cluster assignment in the 90 patients awaiting surgery.

		Cluster 1 (n=34)	Cluster 2 (n=22)	Cluster 3 (n=34)
Pain characteristics				
SF-MPQ total score, mean ± SD range 0-45		15.2 (7.2)	27.2 (8.0)	18.8 (9.8)
Psychological characteristics				
HAD Anxiety, mean ± SD range 0-21		4.5 (2.3)	11.3 (2.8)	7.1 (3.9)
HAD Depression, mean ± SD range 0-21		4.8 (2.5)	7.8 (3.7)	7.3 (3.7)
Pain Catastrophising Score, median (IQR) range 0-52		10.2 (7.3)	23.2 (13.4)	15.9 (9.6)
Life orientation Test-R, mean ± SD range 0-24		17.6 (3.6)	12.8 (6.4)	15.0 (4.6)
Tampa scale of kinesophobia, mean ± SD range		35.8 (5.8)	45.3 (11.7)	38.6 (7.5)
Pressure pain threshold, mean ± SD kPa	Index knee	273.1 (76.0)	215.8 (62.7)	375.7 (80.5)
	Tibialis anterior	274.0 (81.9)	252.3 (66.5)	427.3 (90.4)
	Contralateral knee	297.4 (93.0)	252.6 (61.3)	439.8 (101.7)
	Sternum	223.1 (69.4)	219.6 (54.0)	320.9 (64.2)

Multivariate ANOVA confirmed that each variable was differentiated by the cluster solution (Wilk's lambda = 0.145, F(11.70), p<0.001). Univariate ANOVAs confirmed that each variable significantly differentiated all the clusters, all p<0.001.
SF-MPQ=Short-form McGill Pain Questionnaire; HAD= Hospital Anxiety and Depression Scale; IQR=interquartile range.

Multivariate ANOVA confirmed that each variable was differentiated by the cluster solution (Wilk's lambda = 0.145, F (11.70), p<0.001) and univariate ANOVA confirmed that each variable in the cluster analysis significantly differentiated the clusters, all p<0.001. The clinical and QST variables for each cluster group, which were not entered into the cluster analysis, are summarised in Table 9-3 and Table 9-4.

Table 9-3 Clinical characteristics of patients by cluster membership at baseline

	Cluster 1 (n=34)	Cluster 2 (n=22)	Cluster 3 (n=34)
Demographic features			
Age, mean ± SD years	70.1 (8.7)	70.2 (10.3)	71.0 (8.4)
Female, n (%)	24 (71)	13 (59)	8 (24)**
BMI, mean ± SD kg/m^2	31.3 (5.1)	30.7 (4.8)	28.4 (4.6)
Employed, n (%)	11 (32)	14 (64)	23 (68)
Married or living with partner, n (%)	27 (79)	15 (68)	25 (74)
Clinical features			
Right knee affected, n (%)	11 (32)	13 (59)	23 (68)
Duration of pain, median (IQR) months	30 (16-120)	48 (24-120)	42 (24-78)
Oxford knee score, mean ± SD range 0-48	22.6 (5.9)	14.7 (7.1) ††[a]	19.1 (6.5) †[a]
Oxford knee score pain subscale, mean ± SD range 0-100	64.5 (10.4)	79.5 (10.7) ††[a]	72.2 (11.8) †[a]
Oxford knee score function subscale, mean ± SD range 0-100	59.4 (12.1)	70.2 (16.0) ††[a]	62.5 (12.4)
Kellgren and Lawrence grade, n (%)*:			
0-2	3 (11)	3 (16)	6 (20)
3-4	24 (89)	16 (84)	24 (80)
Procedure conducted, n (%):			
UKR	16 (59)	13 (72)	13 (54)
TKR	11 (41)	5 (28)	11 (46)
Neuropathic features on mPD-Q			
Nociceptive group, n (%)	20 (59)	9 (41)	22 (65)
Unclear group, n (%)	9 (26)	4 (18)	6 (18)
Neuropathic group, n (%)	5 (15)	9 (41)	6 (18)

Kellgren and Lawrence grades were only available for 27, 19 and 30 patients in clusters 1, 2 and 3 respectively.** p-value<0.001 for comparison across the three groups using Chi-square test. P-values calculated for between group differences using cluster 1 as the reference group. †p-value <0.05,††p<0.001; [a]P-value <0.05, after adjusting for age, sex and BMI. BMI=body mass index; SD= standard deviation; IQR=interquartile range; UKR=unicompartment knee replacement; TKR=total knee replacement.

Table 9-4 QST measures, other than those used for clustering, by cluster assignment

		Cluster 1 (n=34)	Cluster 2 (n=22)	Cluster 3 (n=34)
Warm detection threshold, median (IQR) ^{0}C	Index knee	37.5 (35.4-40.2)	37.1 (36.1-42.1)	40.4 (37.7-43.4)†
	Tibialis anterior	41.9 (36.5-45.1)	42.4 (37.1-45.7)	45.5 (41.1-48.7)†[a,b]
	Contralateral knee	36.4 (35.5-40.9)	39.0 (36.1-41.4)	38.7 (35.7-43.4)
	Sternum	37.3 (36.3-42.6)	38.4 (36.8-42.8)	40.0 (37.5-41.6)
Cold detection threshold, median (IQR) ^{0}C	Index knee	27.4 (26.6-28.9)	27.3 (26.3-28.6)	27.4 (25.9-28.2)
	Tibialis anterior	27.6 (25.5-29.0)	27.7 (25.6-29.1)	27.0 (25.7-28.1)
	Contralateral knee	27.1 (24.4-27.7)	26.4 (24.8-28.1)	26.0 (23.2-26.7)
	Sternum	27.8 (26.0-28.5)	26.5 (23.4-28.2)	27.9 (26.0-28.5)
Heat pain threshold, median (IQR) ^{0}C	Index knee	45.7 (42.3-48.9)	42.3 (38.5-46.5) †[a,b]	46.9 (44.0-49.3)
	Tibialis anterior	47.3 (44.0-49.7)	45.6 (40.3-48.2)†[a,b]	49.5 (47.9-50.0)†[a,b]
	Contralateral knee	45.7 (41.4-47.8)	44.0 (41.6-46.8)	46.6 (42.7-49.1)
	Sternum	39.0 (34.1-46.4)	37.5 (35.5-40.5)	39.3 (37.5-45.6)
Cold pain threshold, median (IQR) ^{0}C	Index knee	17.2 (10.0-23.4)	21.9 (10.7-25.8)	21.2 (10.0-23.9)
	Tibialis anterior	10.0 (10.0-19.8)	15.1 (10.0-23.8)	10.0 (10.0-14.7)
	Contralateral knee	20.1 (10.0-24.1)	22.5 (10.0-25.6)	16.5 (10.0-23.2)
	Sternum	10.0 (10.0-20.6)	14.7 (10.0-24.7)	10.0 (10.0-20.3)
Mechanical pain threshold, median (IQR) mN	Index knee	50.8 (10.2-161.3)	80.6 (32.0-161.3)	64.0 (32.0-256.0)
	Tibialis anterior	80.6 (32.0-161.3)	40.3 (16.0-161.3)	128.0 (25.4-256.0)
	Contralateral knee	50.8 (25.4-101.6)	64.0 (20.2-161.3)	101.6 (50.8-203.2)
	Sternum	25.4 (16.0-128.0)	25.4 (10.1-101.6)	50.8 (12.7-101.6)
Sharpness rating to 512mN probe, mean ± SD range 0-10	Index knee	5.4 (2.6)	6.0 (2.2)	4.5 (2.7)
	Tibialis anterior	3.5 (2.7)	3,9 (2.3)	3.2 (2.9)
	Contralateral knee	4.9 (2.4)	5.0 (2.7)	3.5 (2.4)†
	Sternum	5.9 (3.0)	5.5 (2.6)	4.7 (2.8)

P-values were calculated for between group differences using cluster 1 as the reference group. †p-value <0.05; [a]p-value <0.05, after adjusting for age, sex and BMI, [b]p<0.05 after also adjusting for pain severity and use of any pain-modifying medication. IQR=interquartile range; SD= standard deviation.

Cluster one comprised 34 (38%) of the patients, 24 (71%) of whom were female. This group had the lowest scores for all the psychological and pain symptom severity compared to the other two groups. The measures of pressure pain threshold (PPT) suggested that this group had moderate pain at all the sites tested, compared to the other two clusters.

Cluster two was the smallest cluster and comprised only 22 (24%) of the patients, of whom 13 (59%) were female. This cluster was characterized by having the worst scores for all the psychological and pain variables compared to the other two groups. In addition, the QST showed that PPT was consistent with the highest level of pain, compared to the other two clusters. The pre-operative OKS, including both pain and function subscales, were significantly worse for cluster two compared to cluster one.

Cluster three comprised 34 (38%) of the patients, of whom only 8 (24%) were female. This cluster demonstrated moderate levels of psychological and pain symptom severity compared to the other groups, apart from depression, which was very similar to cluster two. QST measures for PTT showed that this cluster had the least pain, compared to the other two clusters. Compared to cluster one, cluster three had significantly worse total OKS and pain, using the OKS pain subscale, prior to surgery (Table 9-3)

Cluster two had the highest proportion of patients who met the criteria for neuropathic pain (41%), compared to clusters one (15%) and three (18%), but this

observation did not reach statistical significance (Table 9-3). QST measures showed that cluster two was significantly more sensitive to heat, compared to cluster one, at both the index knee and tibialis anterior, and this remained significant after adjusting for age, sex, BMI and pain severity (Table 9-4).

The function discriminant analysis identified two discriminant functions, which significantly differentiated the three clusters, $p<0.001$, Equation 1 & Equation 2.

Equation 1

Score 1= (0.706xHADa)-(0.654xHADd)-(0.070xPCS)+(0.060xTSK)+(0.038xLOTR)-(0.021xMcGILL)-(0.367xPPTt)-(0.299xPPTc)-(0.214xPPTs)-(0.536xPPTi)

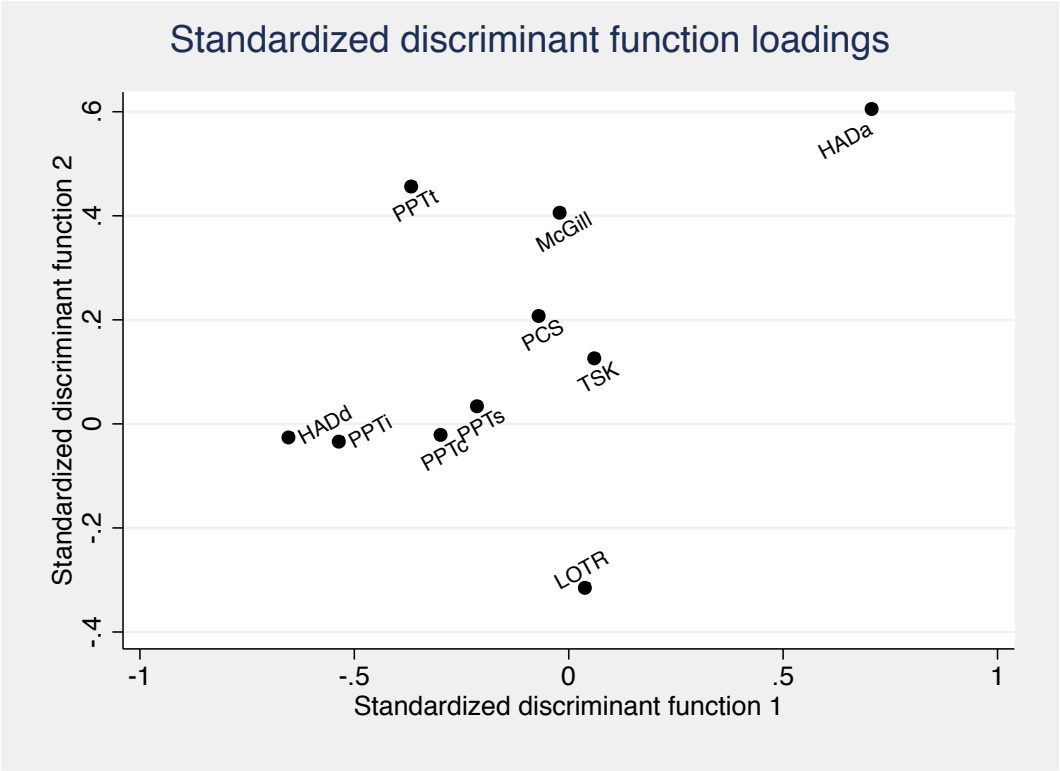
Equation 2

Score 2= (0.605xHADa)-(0.026xHADd)+(0.207xPCS)+(0.126xTSK)-(0.406xLOTR)-(0.021xMcGILL)+(0.456xPPTt)-(0.021xPPTc)+(0.034xPPTs)-(0.034xPPTi)

HADa= Hospital Anxiety and Depression Scale, anxiety subscale; HADd= Hospital Anxiety and Depression Scale, depression subscale; PCS= Pain Catastrophising Score; TSK= Tampa scale of kinesophobia; LOTR= Life orientation Test-R; McGILL=Short-form McGill Pain Questionnaire; PPT=pressure pain threshold, measured at the following sites: t (tibialis anterior), c (contralateral knee), s (sternum), and i (index knee).

The contribution of each cluster variable to both of the discriminant functions is further illustrated in Figure 9.2.

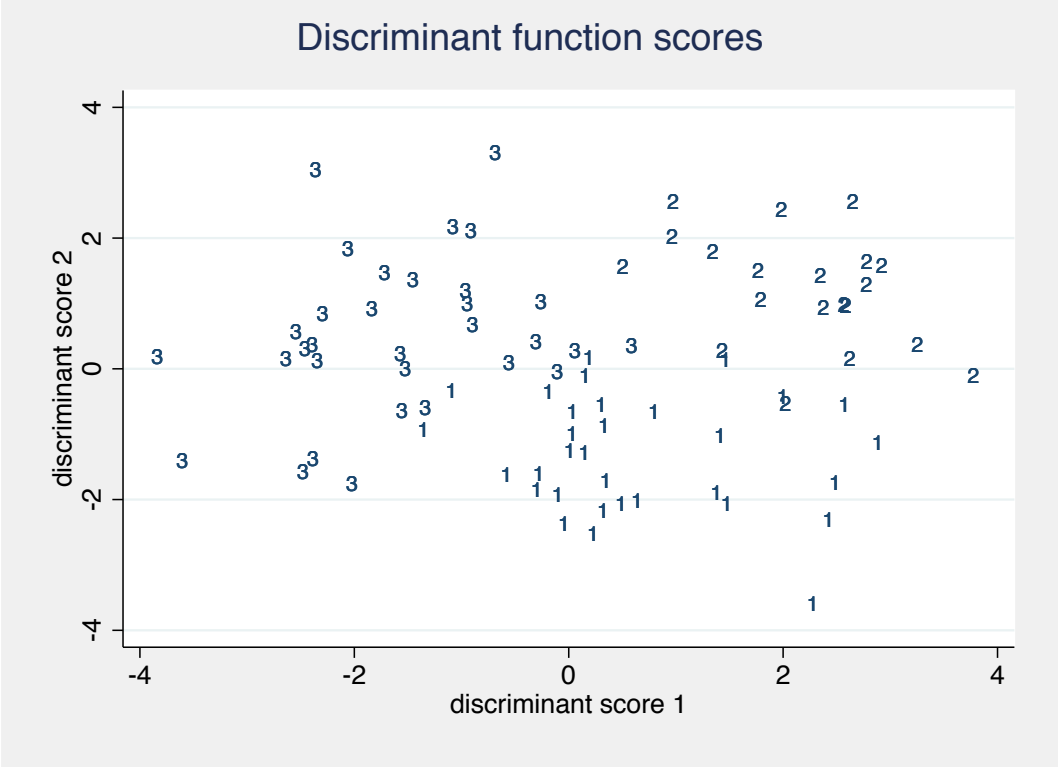
Figure 9.2 Illustration of the discriminant loadings for each of the cluster variables



The data plots represent the standardized discriminant function coefficients for each of the variables entered in the preceding cluster analysis. HADa= Hospital Anxiety and Depression Scale, anxiety subscale; HADd= Hospital Anxiety and Depression Scale, depression subscale; PCS= Pain Catastrophising Score; TSK= Tampa scale of kinesophobia; LOTR= Life orientation Test-R; McGILL=Short-form McGill Pain Questionnaire; PPT=pressure pain threshold, measured at the following sites: t (tibialis anterior), c (contralateral knee), s (sternum), and i (index knee).

The first function was weighted towards anxiety, depression and PPT at the index knee. The second equation was weighted towards anxiety, PPT at tibialis anterior and sensory qualities of pain, measured using the SF-MPQ. The performance of the two discriminant functions to differentiate each of the three clusters is further illustrated in Figure 9.3.

Figure 9.3 Illustration of the discriminant functions required to differentiate clusters 1, 2 and 3.



Each data point represents an individual participant and is allocated a number according to the cluster assigned to them during the preceding cluster analysis. The x-axis represents the calculated score for each individual for function 1 and the y-axis represents that for function 2.

As shown in Figure 9.3, the first discriminant function serves to differentiate between cluster three and the remainder of the study group. The second dimension is then needed in order to distinguish between clusters one and two.

Using the scores generated by the discriminant dimensions, the proportion of participants who were allocated to the correct cluster group was: 30 (88%), 21 (95%), and 32 (94%) for clusters 1, 2 and 3 respectively.

The OKS was very similar for all three clusters at 2-months post-operatively (Table 9-5). At 12-months cluster two had the worst OKS, median (IQR) 37.5 (33.5-43.5), compared to clusters one, 44.0 (40.0-45.0), and three, 41,5 (38,0-46.5), but this did not reach statistical significance (Table 8.5.). The change in OKS at 2-months post-operatively was mean (sd) 12.2 (8.5), 18.1 (8.7) and 13.7 (8.2) for clusters one, two and three respectively. At 12-months post-operatively the change in OKS was 17.9 (7.4), 23.7 (9.7), and 17.5 (10.1) for clusters one, two and three respectively. There was no statistically different change in OKS at either time-point.

Table 9-5 Follow-up outcome measures for the three different clusters at 2-months (A) and 12-months (B) post-operatively
(A)

	Cluster 1 (n=25)	**Cluster 2 (n=13)**	**Cluster 3 (n=24)**
Oxford knee score, median (IQR) range 0-48	37.0 (30.0-43.0)	37.0 (29.0-41.0)	35 (28.0-41.5)
Oxford knee score pain subscale, mean ± SD range 0-100	38.7 (14.3)	43.8 (13.7)	43.7 (14.7)
Oxford knee score function subscale, mean ± SD range 0-100	42.6 (15.9)	42.8 (16.9)	42.0 (16.5)

(B)

	Cluster 1 (n=23)	**Cluster 2 (n=12)**	**Cluster 3 (n=20)**
Oxford knee score, median (IQR) range 0-48	44.0 (40.0-45.0)	37.5 (33.5-43.5)	41.5 (38.0-46.5)
Oxford knee score pain subscale, mean ± SD range 0-100	22.9 (20.0-31.5)	31.5 (20.0-37.2)	20.0 (30.0-38.60
Oxford knee score function subscale, mean ± SD range 0-100	32.0 (28.0-40.0)	42.0 (34.0-50.0)	32.0 (24.0-38.0)

No significant differences between the groups were seen on either univariable or multivariable modeling.

Multinomial modelling showed that there was no significant association between cluster assignment prior to surgery, and the presence of PPSP at 12-months post-operatively, Table 9-6.

Table 9-6 Logistic regression model of the association between cluster assignment and persistent post surgical pain at 12-month follow up assessment

	Univariable model		**Multivariable model***	
Predictor	OR (95% CI)	P	OR (95% CI)	P
Cluster 1	Reference group	-	Reference group	-
Cluster 2	1.2 (0.2-8.4)	0.855	1.2 (0.2-9.0)	0.882
Cluster 3	1.2 (0.2-6.8)	0.837	1.2 (0.2-8.8)	0.844

*Adjusted for age and sex. OR=odds ratio; 95% CI=95% confidence interval.

9.4.7 Discussion

This study has identified three, independent patient profiles amongst patients with moderate to severe knee OA, using cluster analysis. The first cluster comprised patients with low levels of psychological distress, who experienced few different qualities of pain and had moderate levels of experimental pain. This group may be considered to represent the 'typical' knee OA patient. The second cluster was the smallest and included patients with the worst pain quality and psychological profile, alongside QST measures suggesting high levels of experimental pain at all the sites tested. This group may be considered as the 'highly sensitive' patient group. The third group was characterized by moderate levels of pain quality severity and psychological distress but had very low pain levels of experimental pain. This group might be considered as the 'hypoalgesic' patient group.

Cluster assignment was associated with independent measures of clinical severity, and both cluster two and three both demonstrated significantly worse OKS prior to surgery, compared to cluster one. Furthermore cluster two also demonstrated increased levels of local and regional experimental pain when compared to cluster one. There was no significant difference in OKS between the clusters 2-months post-operatively, but at 12-months post-operatively cluster two had a lower OKS compared to cluster one. Although this did not reach statistical significance, it was of the order of 4.5 points, which is just below the proposed minimally important difference for group comparisons of around 5 points for the OKS (Beard *et al*, 2015).

This finding of a 'highly sensitive' group associated with high levels of psychological distress is similar to that of other studies, which have utilized cluster analysis in patients with knee OA (Cruz-Almeida *et al*, 2013; Egsgaard *et al*, 2015; Knoop *et al*, 2011; Murphy *et al*, 2011). As in the present study, this cluster was also found to be have significantly worse clinical knee symptom severity when compared to the other cluster groups. However, the association between response to surgery, or other treatment strategies, and group membership has not been previously tested.

QST measures have been incorporated into two of the previous studies. In one study PPTs, at multiple sites, were used as clustering variables (Egsgaard *et al*, 2015). The second study utilized QST to provide external validation for the clusters generated (Cruz-Almeida *et al*, 2013). These studies both demonstrated a lower PPT in the cluster equivalent to the 'highly sensitive' cluster also identified in the present study. Furthermore, these studies also showed increased temporal summation (TS) in this group, suggesting that central sensitization may be an important mechanism underpinning this group. It is interesting to note that a very similar cluster profile was also seen in a study of patients with fibromyalgia, suggesting that this type of subgroup may be more widely recognized across different musculoskeletal conditions, rather than being disease specific (Giesecke *et al*, 2003).

Previous studies also support the presence of a 'typical' knee OA patient with relatively lower levels of pain and psychological distress (Cruz-Almeida *et al*, 2013; Egsgaard *et al*, 2015; Knoop *et al*, 2011; Murphy *et al*, 2011). In the previous studies,

this cluster was also shown to have the least experimental pain (Cruz-Almeida *et al*, 2013; Egsgaard *et al*, 2015). The present study shows that the 'typical' knee OA cluster had less experimental pain than the 'highly sensitive' cluster, but that the highest PPTs were demonstrated in the third 'hypoalgesic' cluster. The latter cluster has not been previously reported, and further replication to determine whether this is a generalizable finding. It is interesting that the consideration of experimental pain and psychological distress together seems to provide additional information with respect to profiling this group of patients. The use of different cluster variables, a different patient cohort, or both of these factors together may explain the apparent discrepancy observed between the current work and the results of previous studies.

The main clinical implication for the findings of this study is that the distinct subgroups identified could help to achieve a mechanism-based approach to the development of a more personalised and targeted treatment approach. It may be for example that the 'highly sensitive' cluster would benefit from treatments addressing the central component of their symptoms, such as cognitive behavioural therapy or relevant drug therapy. These are preliminary data and further evaluation of this technique is required prior to translation to the clinical setting.

The main strength of this study is that patients were clinically homogenous, with moderate to severe disease, and that the effect on treatment response to knee replacement surgery could be assessed. Although there is no formal minimum sample size for cluster analysis, the minimum sample size of a group required to

detect a meaningful difference in OKS between groups is 34 patients in each group, and so this study was underpowered to detect differences in outcome following surgery. A further limitation is the omission of sleep disturbance as a clustering variable, which has previously been identified as a valuable factor in discriminating patient subgroups (Murphy *et al*, 2011). The inclusion of this dimension may have improved the identification of clinically relevant clusters.

In summary, this study shows that cluster analysis can be used to identify distinct patient profiles amongst those with moderate to severe knee OA. The subgroups were significantly different in terms of pain quality, psychological distress and experimental pain prior to knee replacement surgery. There was no significant difference in OKS at the 2 or 12-month follow up assessment. In addition there was no significant difference in the prevalence of PPSP between the three clusters. However cluster two, or the "highly sensitive" group, demonstrated a non-significant trend towards to worse outcome at 12-months post-operatively, compared to the 'typical' knee OA patient cluster. These are preliminary data and further replication with a larger sample size is needed before translation to the clinical arena can be considered.