Predicting Chronic Postoperative Pain After Total Knee Replacement Surgery in Patients with Knee Osteoarthritis

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Declaration

This is to certify that the work submitted in this thesis is the result of original research conducted by myself in Academic Orthopaedics, Trauma and Sports Medicine, Division of Rheumatology, Orthopaedics and Dermatology, at the University of Nottingham during the years 2014-2017.

The study design was based on discussion with myself and my supervisors Professor Brigitte Scammell, Professor Dorothee Auer, Dr Richard Pearson and Professor David Walsh in collaboration with Dr Kristian Petersen, Professors Lars Arendt-Nielsen and Thomas Graven Nielsen at the Centre for Sensory-Motor Interaction and Centre for Neuroplasticity and Pain at the University of Aalborg, Denmark. The data collection, analysis and writing was conducted by myself all except the functional brain MRI analysis which was conducted by Dr Sarina Iwabuchi and Professor Dorothee Auer at the Sir Peter Mansfield Imaging Centre at the University of Nottingham

Supervision of this thesis was undertaken by Professor Brigitte Scammell and Dr Richard Pearson. This thesis has not already been accepted for any degree.

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Abbreviations

BMLs- Bone Marrow Lesions

BOLD- Blood Oxygen-Dependant Level

CPM- Condition Pain Modulations

DMN- Default Mode Network

DRG- Dorsal Root Ganglion

fMRI- functional magnetic resonance imaging

HP- Hippocampus

IASP- International Association for the Study of Pain

IL- Interleukin

K-L- Kellgren Lawrence Radiographic Grade

MOAKS MRI Osteoarthritis Knee Score

MRI- Magnetic Resonance Imaging

NAc- Nucleus Accumbens

NSAID- Non-Steroidal Anti-Inflammatory Drug

OA –Osteoarthritis

OKS –Oxford Knee Score

PAG: Peri-Aqueductal Gray

PCS- Pain Catastrophizing Scale

PDT- Pain Detection Threshold

PPT- Pressure Pain Threshold

PTT- Pain Tolerance Threshold

QST- Quantitative Sensory Testing

RVM- Rostral ventromedial medulla

SNRI - Serotonin-Noradrenaline Reuptake Inhibitor

TNF – Tumour Necrosis Factor

TSP- Temporal Summation of Pain

VAS- Visual Analogue Scale

Abstract

We hypothesise that preoperative pain characteristics in knee osteoarthritis (OA) patients may explain persistent pain after total knee replacement (TKR) surgery. Fifty patients awaiting TKR surgery and twenty-two asymptomatic healthy controls were recruited to evaluate the degree of neuropathic pain symptoms and central sensitisation of pain. OA patients were pain phenotyped into two groups based on the PainDETECT questionnaire: Group-A (scores ≥19) indicating neuropathic pain-like symptoms, Group-B (scores <19) indicating nociceptive or mixed pain. Controls were assigned to Group-C.

Cuff algometry assessing pain detection thresholds (PDT) and pain tolerance (PTT) was conducted on the lower legs. Temporal summation of pain (TSP) was assessed using ten sequential cuff stimulations set at the subject's individual PTT and a von Frey stimulator. Conditioning pain modulation (CPM) was assessed by cuff pain conditioning on one leg and parallel assessment of PDT on the contralateral leg. Pressure pain thresholds (PPTs) were recorded by pressure handheld algometry local and distant to the knee. Knee pain intensity assessed using the visual analogue scale (VAS score (0-10cm) as well as questionnaires to assess knee function, depression, anxiety, pain catastrophizing and quality of life were collected before and 6 months post-TKR.

30% of knee OA patients demonstrated neuropathic pain-like symptoms (Group-A). Facilitated TSP and reduced PPTs distant to the knee were found in Group-A compared to Group-B and Group-C ($p<0.001$). Group-A had higher postoperative VAS scores than Group-B patients ($p<0.0001$) and facilitated TSP ($p=0.022$) compared with Group-C.

Twenty-eight knee OA patients also agreed to undergo a BOLD functional brain MRI scan preoperatively and again six months post TKR to determine the neural signature of TSP using a novel cuff algometer applied to the gastrocnemius muscle ipsilateral to the arthritic knee. Seventeen age and sex matched healthy volunteers also agreed to be in this study for comparison. All subjects underwent a 3-Tesla knee MRI scan which was graded by 2 independent observers for bone marrow lesions (BMLs), Hoffa Synovitis and effusion synovitis using the MRI Osteoarthritis Knee Score (MOAKS). The OA patients also underwent a metal artefact reduction MRI knee scan six months post TKR to identify if there was a continued or new presence of BMLs, Hoffa-synovitis and effusion synovitis which may contribute to the development of chronic postoperative pain.

Our study has demonstrated that 30% of patients with knee OA listed for TKR surgery have neuropathic pain like symptoms. Patients with these symptoms report higher preoperative pain with longer pain duration, increased anxiety levels, poor knee function and lower quality of life measures prior to TKR surgery. The same patients respond less favourably to TKR surgery with significantly higher postoperative VAS pain scores, continued pain sensitization (lower PPTs, facilitated TSP and impaired CPM), scores, lower Oxford Knee Scores and quality of life. Increased neural brain activity in the somatosensory region S2 of the brain was found to be an imaging biomarker in central sensitization in knee OA patients. This neural activity is stimulated by chronic Hoffa-synovitis in the knee driving facilitation of the central integrative mechanisms of pain. Responders to TKR normalize

their brain related activity with similar neural pattern to the healthy volunteers and show no evidence of central sensitization assessed using quantitative sensory testing (QST). Non-responders to TKR continue to report significant postoperative pain, lower Oxford Knee Scores, continued facilitated TSP, increased S2 neural brain activity along with postoperative BMLs and synovitis that may drive their postoperative pain. This thesis has identified the neural signature of TSP in knee OA patients and shown that brain related changes to TSP are maintained in patients with chronic postoperative pain after TKR. Preoperative identification of OA patients with central sensitization pain and subsequent pharmacological and behavioural therapy along with the eradication of painful BMLs and synovitis may significantly reduce the number of patients developing postoperative pain after TKR surgery.

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1 Introduction

Pain is a complex multifactorial, subjective unpleasant experience which encompasses the interpretation of nociceptive input influenced by memories, emotions, pathological, genetic or cognitive factors.(1) However, in chronically painful diseases like osteoarthritis (OA) the resultant pain experienced is not always linearly related to the nociceptive input and neither does it provide a solely protective function to the body.(2) For these reasons pain is very difficult to assess, investigate, quantify and treat successfully.

OA is a highly prevalent painful disease throughout the world with over 30 million adult suffers in the US (3) and 8.75 million in the United Kingdom. (4) Currently, over 4 million adults suffer with knee OA in the UK with the incidence of knee OA expected to double by 2035 as a result of our ever increasing ageing population and the rising numbers of obesity in the country, therefore putting further strain on our already overstretched National Health Service.(4) Total knee replacement (TKR) surgery is considered a safe, effective surgical intervention to improve pain and function in patients with painful end stage osteoarthritis (OA) of the knee. However, it is still worrying that up to 20% of patients continue to suffer debilitating chronic postoperative pain after TKR in spite of objective measures of surgical success.(5-13) Chronic postoperative pain is defined by the International Association for the study of Pain (IASP) as persistent pain six months following surgery. Increasing evidence suggests that preoperative sensitization of the nervous system is prognostic for the development of postoperative pain after TKR surgery.(5, 13-21) Improved understanding of the preoperative complex pain

mechanisms in OA may aid orthopaedic surgeons identify which patients are at higher risk of developing chronic postoperative pain. This work has the potential for the development of a stratified individualised medical approach to all knee OA patients undergoing TKR surgery that could reduce the incidence of postoperative pain after TKR surgery. This thesis will focus on pain mechanisms that may predispose to the development of chronic postoperative pain after TKR surgery in knee OA patients and look specifically at subgroups of knee OA patients with preoperative sensitization of the nervous system and neuropathic pain like symptoms. The thesis aims to understand the connection between the preoperative parameters in knee OA patients that possibly predict the development of postoperative chronic pain six months after TKR surgery,

1.1 Osteoarthritis

Osteoarthritis (OA) is the most common musculoskeletal condition in the world(22) and is a progressive multifactorial disease of synovial joints that affects the cartilage, joint lining, synovium, ligaments and underlying bone. (23) It is the most common type of arthritis and is a chronic irreversible degenerative joint disease. OA is a result of the breakdown of these joint tissues resulting in severe pain, stiffness and functional impairment, which can have a substantial effect on the quality of life.(24, 25) It is often more painful in weight bearing joints such as the knee, hip, and spine than in the wrist, elbow, and shoulder joints.(22) It most commonly affects the middle aged and elderly as well as those individuals that are overweight, although younger people can be affected as a result of injury or overuse of a joint.(26) The goal of treatment is to reduce pain and improve function but currently there is no cure for the disease.

1.1.1 Epidemiology

OA affects 8.75 million people aged 45 years and over (33%) in the UK (4) and is a leading cause of ill health worldwide with pain being the most reported primary symptom by sufferers. (22) By the year 2030 the prevalence of OA will steadily increase and will be the greatest cause of disability in our country.(27) The condition represents a massive and growing problem for our ageing and overweight population placing enormous demands on our already overstretched National Health Service as well as carers and society at large. As well as the huge social costs, the financial costs are extremely high with vast sums of money being spent on drug treatments and joint replacement surgery worldwide.(28) In the US alone, OA is the highest cause of loss of work costing the US economy more than $100 billion annually. (29) Recent research has also identified the association of OA and increased mortality from cardiovascular diseases.(30, 31)

1.1.2 Osteoarthritis Definition

OA is a heterogeneous degenerative joint disease and is defined by a combination of x-ray appearances and patient reported symptoms including joint pain and stiffness. The underlying joint pathology is characterised by degeneration in articular cartilage, synovial inflammation, changes to the periarticular and subchondral bone and meniscal degeneration and extrusion.(26, 32, 33) The condition is widely considered a failure of joint repair and abnormal remodelling in response to trauma or mechanical stress with the resultant pathological changes visualised within the subchondral bone and synovium being a response of the attempted repair.(34) Currently the imaging standard for evaluating the structural changes in knee OA is using plain radiographs, which allows the objective assessment of the degree of joint space narrowing which is considered a marker for cartilage loss within the tibiofemoral joint as well as

osteophyte formation.(35) The classic radiographic findings in OA are joint space narrowing, osteophyte formation, subchondral bone sclerosis, subchondral bone cyst formation which can all be graded using the Kellgren Lawrence (KL) classification system to determine the severity of the knee OA.(36) Table 1.1

Table 1.1 Kellgren-Lawrence Grading for Knee OA

Grade	Radiological Finding
I	Doubtful joint space narrowing, possible osteophyte lipping
II	Definite osteophytes and possible joint space narrowing
III	Moderate multiple osteophytes, definite narrowing of joint space, some sclerosis and possible deformity of bony contour
IV	Large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bony contour

One of the main limitations of radiographs in knee is the poor correlation with significant discordance between the subjective pain scores of patients and the radiological severity seen on plain x-ray.(37) It has been reported that up to 50% of patients with KL grade 2 changes on their knee radiographs do not experience any clinical symptoms and a similar proportion of patients without radiological evidence of the disease report severe knee pain suggestive of knee OA. (38)

1.1.3 Current Treatments of Knee Osteoarthritis

Several pharmacological and non–pharmacological treatments are available in the early stages of knee osteoarthritis. The National Institute of Clinical Excellence (NICE) recommends

weight loss and moderate exercise to relieve the severe pain associated with the condition as part of the published 2014 Osteoarthritis Guidelines.(39) Total knee replacement surgery (TKR) is an effective treatment for severe end stage knee osteoarthritis with nearly 98,147 primary arthroplasty procedures performed in the UK in 2016.(40)

1.2 Normal Articular Cartilage

The articular surface of the normal knee joint is lined with hyaline cartilage. The only cells within this cartilage are individual chondrocytes bound together by an extracellular matrix. This extracellular matrix consists of 80% water, collagen, proteoglycans, glycosaminoglycans and some non-collagenous proteins. Type II collagen is the most prominent type of collagen seen in articular cartilage (80-90%). The primary function of the hyaline cartilage is to distribute load and resist compression. Normal articular cartilage is aneural, avascular and alymphatic therefore the chondrocytes receive the nutrition from diffusion of molecules from the synovial fluid within the joint via the extraceullar matrix.(26, 41)

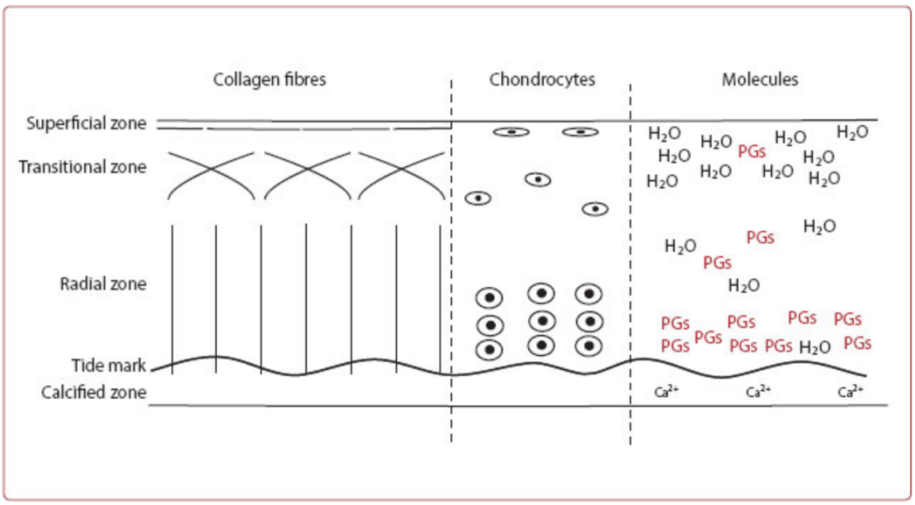


Figure 1.1 Histological Structure of Normal Articular Cartilage

From Basic Sciences in Orthopaedics 2017 M. Ramachandran et al. (41) Legend: H_20 is water and PGs are proteoglycans

Histologically cartilage is seen as the upper non-calcified layer divided into a series of zones as described below and shown in Figure 1.1.(41)

Superficial zone – separates the cartilage from the surrounding tissue and synovial fluid. Its contains flattened chondrocytes between 1 and 3 cells thick. The superficial zone is the thinnest layer but has the highest water and collagen content and the lowest proteoglycan synthesis. The collagen fibres are arranged in parallel to the articular surface and this tangential arrangement of fibres allows the articular surface to resist shear stress forces.

Transitional Zone In this zone the collagen fibres are orientated obliquely and the region has a higher proteoglycan content This zone forms the transition between the shearing forces in the superficial zone and the compressive forces in the deeper zones.

Radial Zone. This is the largest zone within the articular cartilage and the collagen fibres are arranged in a vertical orientation to distribute load and resist compression. Within the radial zone increased densities of chondrocytes are seen producing all the components of the extraceullar matrix.

Tidemark – This is the boundary between the calcified and uncalcified cartilage which can be easily identified using histological staining.

Deep calcified Zone – In this region hydroxyapapatite crystals and collagen fibres anchor the cartilage to the underlying subchondral bone, thereby forming a barrier to diffusion of blood vessels supplying the subchondral bone. Type X collagen is present within the calcified cartilage zone.

Proteoglycans are responsible for the water content within articular cartilage These hydrophilic molecules contain glycosaminoglycans (GAGs) which include chondroitin sulphate and keratin sulphate bound by covalent bonds to a core protein. GAGs have a high negative charge from the carboxy and sulphate groups that attracts cations and water thereby increasing the osmotic pressure within cartilage. Aggrecan is the most predominant proteoglycan in articular cartilage; it interacts with hyaluronic acid and is stabilised via a link protein to form a large proteoglycan aggregate. Aggrecan gives cartilage its viscoelastic properties and provides the compressive strength of the tissue to mechanical loading.(26, 41)

1.2.1 Normal Articular Cartilage Homeostasis

Homeostasis of the cartilage within the knee joint is maintained by a delicate balance between the synthesis and degradation of the components of the extracellular matrix by chondrocytes and the local release of growth factors from the cartilage itself or the surrounding synovial tissue. Matrix metalloproteinases (MMPs), especially MMP13 and ADAMTS (ADAMTS-4 and ADAMTS-5) (a disintegrin and metalloproteinase with thrombospondin-like motifs), are key in the degradation of Type II collagen and aggregan. The activity of these ADAMTS and MMPs is increased by the presence of interleukin-1 (IL-1) and tumour necrosis factor (TNF-α). Naturally occurring tissue-induced metalloproteinase inhibitors (TIMPs) work by inhibiting the degradation by the MMPs and growth factors produced by the cartilage or the synovium including fibroblast growth factor (FGP), epidermal growth factor (EGF), transforming growth factor-β (TGF-β) and bone morphogenic proteins (BMPs) stimulate the production of proteoglycans and collagens therefore maintaining cartilage homeostasis.(41)

1.2.2 Articular Cartilage Degeneration in OA

As OA progresses subsequent degeneration and loss of the structural integrity of articular cartilage is caused by associated changes within the extracellular matrix. Articular chondrocytes contribute to their own destruction by the production of proteolytic enzymes (MMPs and ADAMTS) and pro-inflammatory cytokines including IL-1 which degrade the extracellular matrix.(34) This leads to a catabolic cascade resulting in loss of cartilage structure and integrity, calcification of the cartilage and fissure formation. As a result of these biochemical and structural changes the cartilage surface becomes rough and fibrillates resulting in a reduction in overall articular cartilage thickness.(26)

1.3 Bony Changes in Osteoarthritis

Although OA has for many years been considered a disease of articular cartilage, there is recent evidence that the subchondral bone contributes significantly to the pathophysiology of the disease. During the initial phase of OA and during the disease progression the subchondral bone is a site for multiple dynamic processes that occur as a result of altered osteoblast metabolism, which is part of the pathological process.(26) Subchondral bone remodelling in OA leads to increased bone resorption resulting in the development of sclerosis within this tissue. Subchondral sclerosis, osteophyte formation and progressive cartilage degradation are considered the key pathological features seen in OA.(42, 43) Osteophytes are bony outgrowths capped by fibro-cartilage and develop due to a number of processes. In animal studies osteophytes can be induced by mechanical instability and it is proposed that there are a feature of remodelling in an attempt to stabilise the joint.(44) Other theories include the abnormal repair of stress fractures in the subchondral bone near joint margins or as a

mechanical response to abnormal loading and stress transmission at the joint margins.(44)

1.3.1 Bone Marrow Lesions (BMLs)

The use of MRI has become increasingly common for the evaluation of joint pathology in OA.(33, 45-48) In research, this imaging modality plays a critical part enabling researchers to visualise many pathological and structural changes associated with OA including cartilage, meniscus, synovitis and more recently subchondral bone marrow lesions (BMLs) that are not seen on conventional radiographs. The first description of bone marrow signal alteration detected using MRI was described by Wilson *et al* in 1988. The authors used the term 'bone marrow edema (BME)' to describe the hyperintensive signal changes seen on T2- weighted MRI sequences within the subchondral bone, in patients with painful joints with no detectable radiographic abnormalities.(49) More recently these lesions have been defined as non-cystic subchondral areas of ill-defined high signal intensity directly adjacent to cartilage on T2-weighted, fat saturated or short tau inversion recovery (STIR) images on MRI.(50) (Figure 1.2) *(Red arrow point at large femoral BML)*

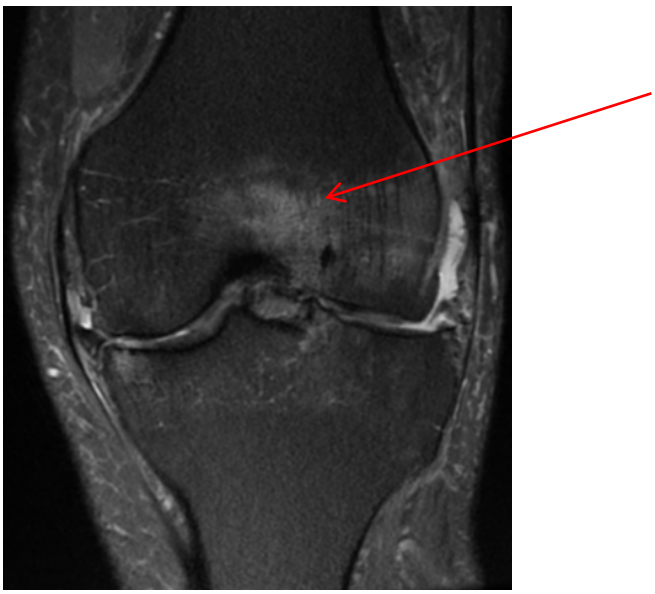


Figure 1.2. Large Femoral BML on 3-Tesla Knee MRI

As many studies have shown that these areas of interest contain more than just water, therefore the use of the term 'Bone Marrow Lesion (BML) has become more common in the clinical and OA research community and has largely replaced the term 'bone marrow edema' (BME).(51, 52) Most research into BMLs has been conducted in knee OA but BMLs are not confined to just the knee. Other joints including the hip(53, 54), ankle(55, 56), shoulder(57), the hand(58-60) and spine(61) have been shown to be associated with the development of BMLs.

Bone marrow lesions are emerging as a potential imaging biomarker in knee osteoarthritis and have been associated with pain(32, 62-64), cartilage loss (48, 52, 65), meniscal pathology(50) and bone attrition(66, 67) in many studies.

1.3.2 Pathogenesis of BMLs

Bone marrow lesions are strongly associated with pain in patients with OA and are frequently identified in patients with progressive OA using MRI. These lesions are not exclusively found in patients with OA pain but are also observed in the healthy, asymptomatic population and predict an increased risk of developing OA in the future.(68)

The pathological cause of the development of BMLs is still uncertain, however several theories have been postulated. Subchondral bone ischaemia has been suggested as a possible cause of the development of BMLs resulting in loss of cartilage integrity and progression of OA.(69) Impaired venous drainage as a result of the ischaemia may contribute to the pain experienced in patients with OA.(70) Hunter *et al* proposed that mechanical changes in limb alignment were associated with the formation of BMLs since medial BMLs were seen mostly in varus-aligned knees compared with lateral BMLs seen more commonly in those with valgus deformity of the knee joint.(52) Another theory is that BMLs are a result of intruded synovial fluid penetrating though defects within the articular cartilage

therefore entering the subchondral bone resulting in subchondral micro-fracture and oedema.(71)

1.3.3 Histological Changes of BMLs in OA Subchondral Bone

In recent years the histological processes within BMLs have been investigated. BMLs have been shown to represent areas of micro fracture and fibrosis beneath the cortical bone surface and they have been linked to bone trauma. Table 1.2 outlines the current literature regarding the histological changes seen within these structures.

1.3.4 BMLs and Pain

Several studies have reported the correlation of subchondral BMLs and pain in patients with knee OA. Although the pain experienced by these patients is multifactorial, changes within the subchondral bone marrow have been shown to be a peripheral nociceptive driver of pain. Pioneering work conducted by Felson *et al* in 2001 reported that BMLs are associated with the presence of pain in knee OA. Bone marrow lesions were found in 272 of 351 (77.5%) of people with painful knee OA compared with just 15 out of 50 people (30%) with no knee pain but radiological evidence of OA ($p<0.001$). This study also highlighted the striking difference in prevalence of large BMLs between OA patients with knee pain and those without knee pain (35.9% vs 2%; $p<0.001$).(72) In a population based study in patients with knee OA, Ip *et al* showed that BMLs were present in 11% of subjects with no OA, 38% of subjects with

Table 1.2 Histology of BMLs

Species	Joint	Histology		Reference
Human	Knee	1.Normal Tissue • Fatty Marrow (53%) • Intact Trabeculae (16%) • Blood Vessels (2%)	2. Abnormal Tissue • Bone Marrow Necrosis (11%) • Necrotic or remodelled trabeculae (8%) • Bone Marrow Fibrosis (4%) • Bone Marrow oedema (4%) • Bone Marrow Bleeding (2%)	Zanetti *et a(73)l*
	Knee	1.Normal Tissue Sclerotic Trabeculae	2. Abnormal Tissue Abnormal Marrow Infiltration: • Granulation • Oedema • Diffuse Necrosis • Fibrosis • Hyperplasia of blood vessel walls	Hunter *et al(74)*
	Knee	1.Normal Tissue Sclerotic Trabeculae	2. Abnormal Tissue Abnormal Marrow Infiltration: • Fibrosis collagen • Woven bone	Kazakia *et al(75)*
	Knee	1.Normal Tissue Trabecular thickening	2. Abnormal Tissue Bone Marrow Fibrosis	Bergman *et al(76)*
	Knee	Fibrovascuar replacement of adipose tissue within BML		Walsh *et al(77)*
Canine	Knee	1.Normal Tissue • Osteosclerosis • Intra-osseous cysts	2. Abnormal Tissue Abnormal Marrow Infiltration: • Fibrosis • New bone formation	Nolte-Ernsting *et al(78)*
	Knee	1.Normal Tissue Remodelled Trabeculae	2. Abnormal Tissue • Fibro-reactive marrow • Vascular congestion	Baird *et al(79)*
	Knee	Haematopoiesis and myxomatous transformation of the bone marrow, fibrosis		Martig *et al(80)*

pre-radiographic OA (Kellgren Lawrence grade <2 on plain radiographs but with significant cartilage damage on knee MRI) and 71% of subjects with radiographic OA (Kellgren Lawrence ≥2). Bone marrow lesions were significantly associated with pain on climbing stairs but not with pain on walking. In a study assessing patients with severe hip OA pain undergoing total hip replacement surgery, Taljanovic *et al* found that the number of

BMLs identified using MRI correlated with the severity of pain and number of microfractures seen in histology.(54)

The Multicentre Osteoarthritis Centre (MOST) study assessed 570 subjects and showed that changes in the severity of BMLs and synovitis were associated with the fluctuation of frequent knee pain severity. This study also showed that out of the two structural changes in OA, BMLs were a better predictor of knee pain.(81) Some longitudinal studies have elucidated the relationship between the progression of BMLs and pain. Extracting data from the MOST study, Felson *et al* demonstrated the incidence or progression of BMLs was higher at the follow up visits in in those patients with knee pain as opposed to control subjects without knee pain.(64)

Kornaat *et al* reviewed 182 patients with knee OA at baseline and at 2-year follow up. The study showed that the total size of BMLs changes in 66% of patients, with a change in size of individual lesions being 45%. New BMLs were seen in 21% cases and lesions that had completely disappeared at the 2-year follow up accounted for 10% of cases. This study confirmed that BMLs were a dynamic pathology seen in OA.(82)

Long-term follow up studies have shown that BMLs predict adjacent cartilage loss(52) and that the pain experienced by patients with BMLs changes depending on the size of the BML. Studies have shown the development of knee pain correlates with the enlargement of these lesions(83) and that a decrease in pain is related to their shrinkage.(84) Fluctuations in size of the BMLs have been reported over a period as short as 6 weeks.(85) A randomised controlled trial has shown that in patients with painful knee OA the use of zoledronic acid, a bisphosphonate drug, can significantly reduce the size of BMLs with a corresponding reduction in knee pain over 1 year.(86) It is hoped that with further research into these BMLs, new

treatments can be offered to patients to reduce their pain and the progression of OA.

1.4 The Normal Synovium

The normal synovium is a specialized connective tissue that lines synovial joints. It seals the synovial cavity and fluid from the surround tissue structures and is responsible for the production and maintenance of synovial fluid. This synovial fluid is essential for chondrocyte nutrition as articular cartilage is aneural, avascular an alymphatic. The synovium consists of an outer fibrous layer which makes up the joint capsule and an inner more cellular layer called the synovial membrane which produces the lubricating synovial fluid which allow smooth joint motion. The outer fibrous layer is up to 5mm thick, is rich in Type I collagen and highly vascular and attaches to the end of each bone by Sharpey's fibres. This outer layer densely innervated by nerve fibres which are responsible for proprioception and joint stability.(87)

The intimal layer is in direct contact with the joint cavity and consist of a layer that is 1-4 cells and is only 20-40μm thick and is responsible for the production of the synovial fluid. This synovial fluid contains 2 important lubricating agents that ae responsible for reducing friction which are lubricin (proteoglycan-4 PRG4) and hyaluronic acid.(26)

1.4.1 Synovitis in Knee OA

OA was traditionally considered a non-inflammatory arthritis; however histological evidence has identified synovium rich in inflammatory cells in patients with OA. The origin of synovitis is strongly linked to cartilage and meniscal degeneration and synovitis has now been identified as an integral process in the self-destruction of the joint seen in the pathogenesis of OA.(87, 88) Synovial inflammation is classically identified on histology

where it is characterised by synovial hypertrophy, proliferation and recruitment of inflammatory cells, nerve growth and angiogenesis.(26)

1.4.2 Synovitis and Pain in Knee OA

Inflammation within the joint plays a crucial role in the initial activation of nociceptors and maintenance of pain in OA. Many of the substances that are release in the inflamed synovium also stimulate chemo-sensitive nociceptors and these can be divided into 3 main groups (Table 1.3). Synovitis in OA differs from that seen in rheumatoid arthritis, a known inflammatory arthropathy, with the OA response being a more predominantly innate rather than an acquired immune response, characterised by macrophage instead of a lymphocyte infiltration. The synovial fluid in OA patients contains increased concentrations of pro-inflammatory cytokines including tumour necrosis factor (TNF)-α and interleukin (IL)-1, growth factors including nerve growth factor (NGF) as well as neuropeptides and inflammatory mediators such as E series prostaglandins.(87, 88) These mediators are responsible for hyperalgesia (increased pain response that is disproportionate to the pain stimuli) by activating nociceptive receptors or by sensitizing fine unmyelinated nerve fibres in the OA joint. IL-6 and (TNF)-α can caused prolonged mechanical hyperalgesia.IL-17 directly sensitizes joint nociceptors but can also indirectly lead to sensitization via the activation of other cytokines and prostaglandins.(89)

Table 1.3 Mediators of Pain in Knee Synovitis

Origin	Mediator	Details	References
Damaged Cells	Hydrogen ions H^+	H^+ ions released from damaged tissues activate nociceptors	(90, 91)
Inflammatory Cells	1.Bradykinin 2.Prostaglandins 3.Leukotrienes	Bradykinin increases capillary permeability and is a highly painful potent substance. Prostaglandins and leukotrienes are inflammatory cytokines that sensitize nociceptors resulting in primary hyperalgesia (an increased painful response disproportionate to the intensity of the painful stimulus)	(89-92)
	Pro-inflammatory Cytokines • TNF Alpha • IL-1 • IL-6 • IL-17		
	Anti-inflammatory Cytokines • IL-4 • IL-10	Anti-inflammatory cytokines suppress pro-inflammatory cytokine expression and macrophage activation providing strong pain inhibition	
Nociceptors	Substance–P	Released by the nociceptors, can directly or indirectly activate nociceptors resulting in a continuous pain stimulation	(93, 94)

1.5 Neurobiology of Pain in Knee OA

The International Association for the Study of Pain (IASP) defines pain as 'an unpleasant sensory and emotional experience with actual or potential tissue damage'. (95) Pain is the principal reason patients with OA seek medical attention and is the primary focus of treatment.(4) OA pain involves a complex interplay between the peripheral and central pain mechanisms within the nervous system influenced by genetic, emotional, sociocultural and cognitive factors.(1) Through an improved understanding of the contribution of both the peripheral and central pain mechanisms in each individual OA patient, we have the potential to more effectively target current treatments like TKR surgery, as well as develop new therapies in the future.

1.5.1 Peripheral Mechanisms in OA Pain

Osteoarthritis is recognised as a disease involving all joint tissues (96) and is a disorder of articular cartilage with adjacent bone degeneration and remodelling.(34) As cartilage degenerates, inflammatory changes within the synovium(87) cause further articular cartilage degeneration with subsequent changes within the subchondral bone as well as the ligaments and tendons.(97) Cartilage is aneural but the adjacent structures are not. The knee joint is innervated directly from nerve cell bodies or branches of nerves supplying the skin, muscle and periosteum. Thick A-beta nerve fibres are myelinated and terminate on the joint in the meniscus, the capsule, ligaments and periosteum. They are responsible for the withdrawal reflex response and have a lower threshold response and primarily conduct innocuous mechanical and thermal stimuli.(98) A-delta fibres (thin myelinated fibres) and C fibres (unmyelinated fibres) terminate in the same tissues as the A-beta fibres but also in the fat pad and the synovium. The C

fibres are responsible for the slow burning pain experienced by many OA patients. Both these fibres have a high threshold for activation therefore serving to alert the body to more noxious, thermal, mechanical or chemical stimuli that may lead to tissue damage or injury.(99)

Nociceptors are cells with an axonal stalk that extend from the cell body in the dorsal root ganglion and split into two terminals, (Fig 1.3)(100) Thus nociceptors can both receive and send pain signals at both terminals. At the peripheral terminal within the joint specific receptors can detect specific stimuli for heat, pressure, or chemicals and activation of these receptors triggers a series of voltage gated sodium and potassium channels which are essential for action potential generation.

These action potentials carry the painful signals from the joint along nociceptor axons, which are either medium sized myelinated A-delta fibres or slow unmyelinated C fibres to the dorsal horn of the spinal cord.

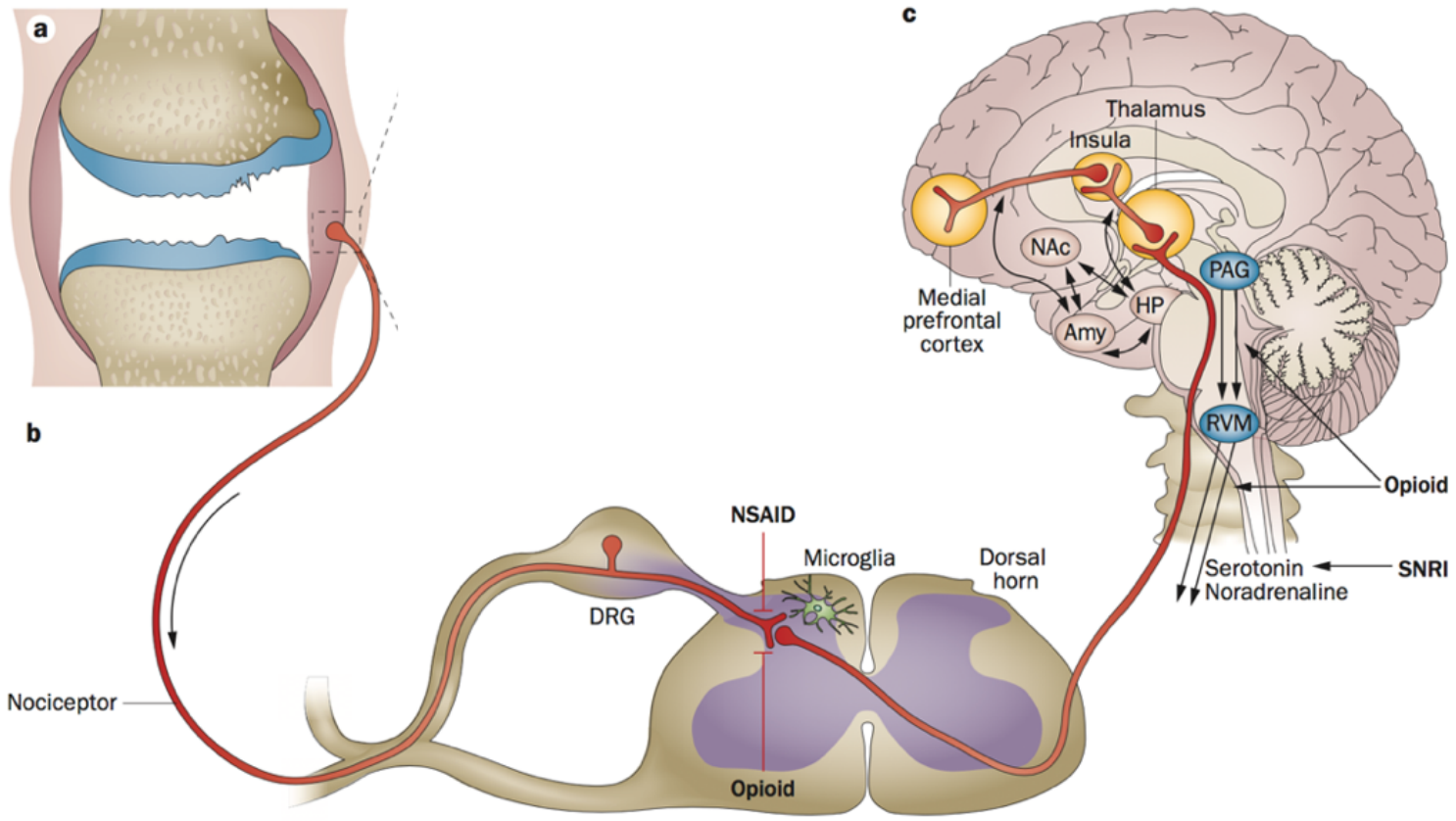


Figure 1.3. Pain Pathways in Knee OA

From Malfait AM, Schnitzer TJ. Towards a mechanism-based approach to pain management in osteoarthritis. Nature Rev Rheum 2013; 9:654-64.

Legend Key Abbreviations: DRG: dorsal root ganglion, NSAID: non-steroidal anti-inflammatory drug, SNRI serotonin-noradrenaline reuptake inhibitor, RVM: rostral ventromedial medulla, PAG: peri-aqueductal gray, HP: hippocampus, Amy: amygdala, NAc: nucleus accumbens

In the dorsal horn, the primary afferent neuron will synapse with the secondary neuron that will constitute the spinothalamic tract which immediately decussates in the spinal cord and sends contralateral projection of pain and temperature to the higher centres in the brain. The spinothalamic tract reaches the brainstem, specifically the rostral ventromedial medulla, and moves dorsally and synapses with third order neurons in the thalamus, which project to the insula, medial prefrontal cortex and primary and secondary somatosensory cortices (S1 and S2). Both the S1 and S2 regions are involved in sensory quality of pain which include location, duration and intensity. Tertiary neurons also project to limbic structures which are involved in the affective and emotional component of pain which include the anterior cingulate cortex.(101) Afferent spinal cord neurons that originate from the knee joint can be inhibited by descending inhibitory modulatory pathways. Neurons from brain regions such as the amygdala, the hypothalamus, the insula and frontal cortex project to the periaqueductal gray (PAG) and indirectly to the rostral ventromedial medulla (RVM). Descending inhibitory neurotransmitters including GABA, noradrenaline and serotonin can reduce the ascending painful signals from the joint. Conditional pain modulation (CPM) paradigms are often used in pain research to reliably assess the descending inhibitory modulating pathways in chronic pain condition using multiple test stimuli.(102) Dysfunctional descending inhibitory pathways measured as impaired CPM has been identified in knee OA patients(14, 15, 103), which is restored after TKR surgery in those patients who are pain free after the operation.(15, 16, 103)

1.5.2 Central Sensitization in Knee OA

It is now recognised that OA pain and other chronic pain conditions can generate central sensitization.(104) This pain

phenomenon is a result of persistent nociceptive input which results in these neurons becoming sensitized and hyper-responsive to noxious stimuli.(14, 104) Intense, repeated or prolonged signalling from peripheral nociceptors from damage within the OA knee joint (synovitis, BMLs, ligaments, tendons and periosteum) drives central changes within the brain and spinal cord in a subgroup of patients with knee OA resulting in increased spontaneous neural activity, reduced activation thresholds or receptors and expansion of the pain receptive field.(2, 99) Changes that have been associated with central sensitisation include allodynia (pain in response to a non-painful stimuli), distant and remote site hyperalgesia (increased sensitivity to noxious stimuli), loss of descending pain inhibitory mechanisms and increased temporal summation, characterised by an increased pain response to a repetitive mechanical painful stimulation.(105, 106) Central sensitisation may trigger the transition from acute pain to a chronic pain state and may influence responses to treatment in patients.(106) The complexity of OA pain means that treating one mechanism of pain for all patients may have low efficacy if the pain in some patients is mediated by other mechanisms. This may explain why up to 20% of patients who undergo TKR surgery for their knee OA continue to suffer debilitating pain post-surgery.(5-13) Therefore, treatment guidelines where individualised medical treatment is offered based on pain phenotyping may improve the outcome for patients with knee OA.

1.6 Quantitative Sensory Testing

In the early 2000's methods of sensory testing became available, however there was no agreed standard on test procedures. Rolke and colleagues in Germany proposed the use of quantitative sensory testing (QST) in 2006 to diagnose sensitization seen in neuropathic pain using 13 different sensory

modalities.(107) QST is an objective assessment tool used to quantify the somatosensory function, diagnose peripheral and central sensitisation in OA pain and detect alterations in pain processing in participants. QST involves assessing somatosensory evoked responses to noxious and innocuous stimuli using either mechanical pressure, electrical, thermal or chemical test modalities. Assessment of the participants responses to controlled external stimuli at the joint as well as remote body sites can give invaluable information regarding the mechanisms of pain processing in that individual under standardised conditions. Pressure pain threshold (PPT) is a measure of sensitivity to evoked pain by mechanical stimulation of nociceptors, which can reliably be assessed using hand held pressure algometry. Lower PPTs on the affected knee joint in varies sites including the medial joint line, the superior-medial patella and superior-lateral patella are thought to be a reflection of peripheral sensitisation where pathological changes within the OA joint affect the pain sensitivity in the adjacent normal skin. Lower PPTs assessed at a distant site, for example the extensor carpi radialis longus muscle, reflects widespread hyperalgesia indicating altered pain processing suggestive of central sensitisation.(14)

QST provides individualised information regarding the subject's pain sensitivity. The use of multiple stimulus modalities for example, pressure, thermal, electrical with different intensities or one prolonged stimulus with increasing intensity, makes it possible to construct stimulus-response relationships, which characterize the individual's pain sensitivity. An increase in pain sensitivity (hyperalgesia) can be quantified objectively by a leftward shift in the stimulus response curve when compared to a healthy control subject as shown in Figure 1.4.

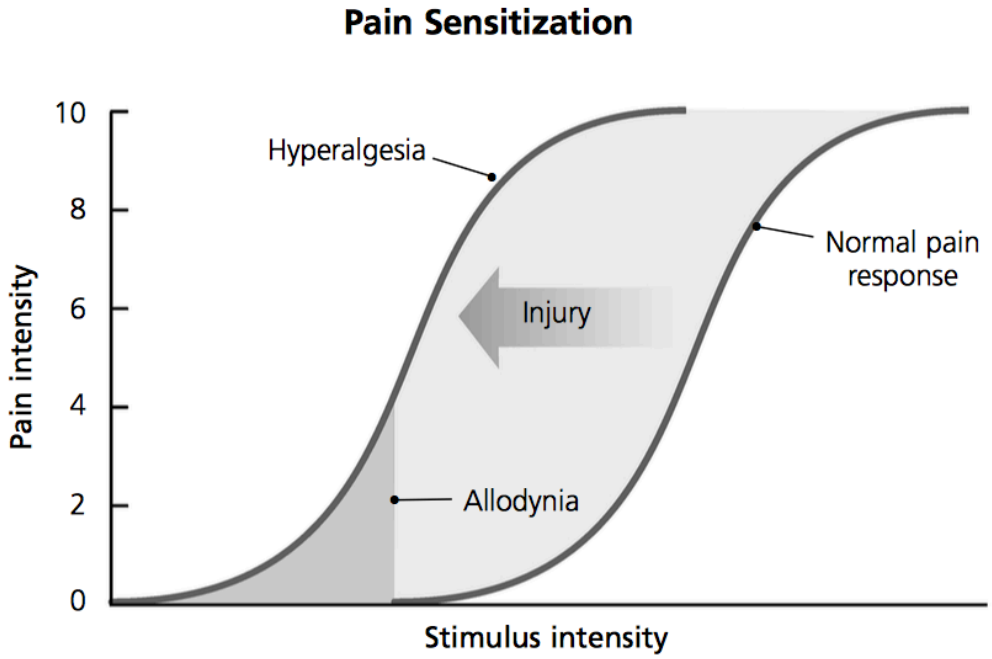


Figure 1.4 Stimulus Response Curves and Pain Sensitization in Knee OA

Figure 1.4 taken from Gottschalk A et al Am. Fam Physician 2001, 63(10) 1979-84(108). Stimulus response curves for an OA centrally sensitized patient and a healthy control subject. The sensitized OA patient has a stimulus response curve that is shifted to the left by the nociceptive stimulus resulting in hyperalgesia and allodynia.

QST is currently a research assessment tool that allows insight into the complex pain mechanisms seen in OA pain that cannot be determined using simple tools like the subjective visual analogue scale (VAS) score for pain. One of the disadvantages of QST is that it is time consuming and requires training to perform the techniques reliably. The use of multiple painful stimulation techniques allows for a detailed quantification of the nervous system to be obtained for that individual subject.

Three main protocols for QST have been developed and been generally applied when assessing pain sensitivity in OA. These include pressure-pain thresholds (PPTs), temporal summation of pain (TSP) and condition pain modulation (CPM).(14)

OA patients demonstrate widespread hyperalgesia having lower PPTs in remote body sites away from the affected arthritic knee

joint alongside facilitated TSP and impaired CPM(105), which are pain characteristics of central sensitization.

Test-retest reliability of QST has been summarised in a meta-analysis conducted by Soukas *et al*. Measurement across test occasions was assessed using interclass correlation coefficients (ICC) where excellent correlation was seen with ICC > 0.75, adequate correlation 0.40-0.74 and poor correlation if < 0.40. QST assessment was shown to be very reliable with studies reporting adequate to excellent test-retest reliability when repeat measurements were taken at 48 hours (ICC of 0.98,95%CI 0.96,0.99)(109) and 5-10 days apart (ICC varied from 0.58-0.91).(110)

1.6.1 Temporal Summation of Pain

Temporal summation (TSP) is a sensitive and valid measurement of central sensitization and is induced by a sequence of stimuli of the same intensity, which result in a progression of pain intensity. TSP requires a sufficiently short interval between repeated stimuli of constant strength such as 10 stimuli with a 1 second inter-stimulus interval(14) and represents excitatory pain modulation processes.(111) Using a 25.6g pin-prick monofilament or cuff algometry, 10 sequential pin prick or cuff pressure stimulations to the knee in patients with knee OA has identified subgroups of patients that have facilitated TSP. Figure 1.5 demonstrates the pain response (0-10 VAS score) for each of the 10 painful stimuli. OA patients that are centrally sensitized (yellow line) showed facilitated TSP with an exacerbated pain response comparing the VAS pain score of the 1st stimuli to the 10th. Knee OA patients that do not have central sensitization (blue line) demonstrate a similar TSP response for each of the 10 painful stimuli as healthy volunteers (green line) with no pain.(2, 14, 105)

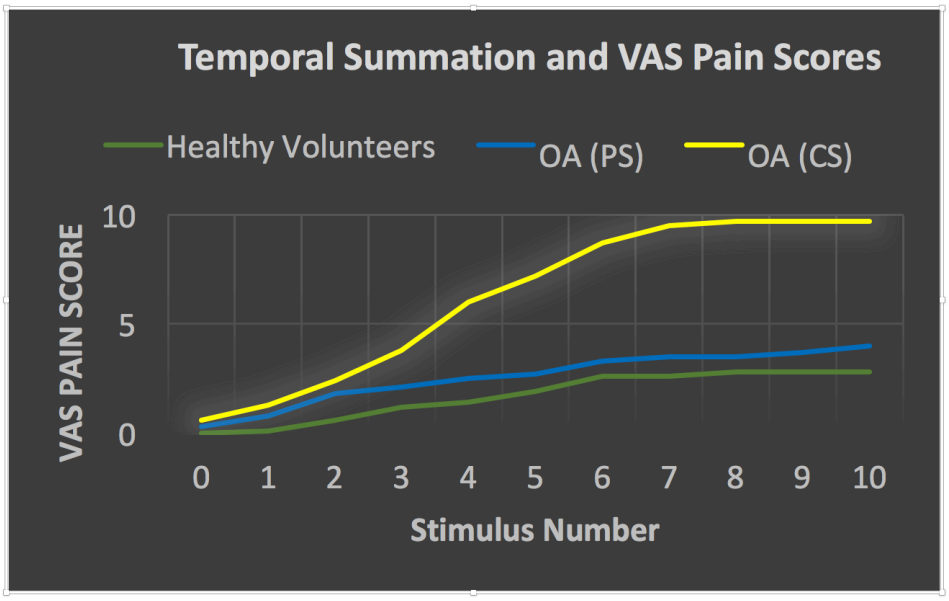


Figure 1.5 Temporal Summation of Pain in OA Patients and Healthy Volunteers

Figure 1.5 Legend: X-axis shows the visual analogue pain score (0-10cm), the Y-axis shows the individual cuff pressure stimuli. The green line highlights the temporal summation response for the healthy volunteers, the blue line highlights the temporal summation response of those knee OA patients that are just peripherally sensitized (PS) and the yellow line highlights the temporal summation response of those knee OA patients that are centrally sensitized (CS).

In conditions of central sensitization, the central integrative mechanisms are upregulated resulting in facilitated TSP. In many groups of patients suffering with chronic musculoskeletal pain, the involvement of central sensitization has been proposed based on the findings of facilitated TSP. (112-114)

Facilitated TSP involves the neurotransmitter N-methyl-D aspartate (NMDA)(115, 116) and the administration of ketamine, (an NMDA antagonist) can significantly reduce clinical pain and temporal summation in patients with fibromyalgia.(117) TSP has also been shown to predict acute postoperative pain in patients undergoing thoracotomy.(118) Petersen *et al* have shown that the preoperative facilitated TSP predicts the development of chronic postoperative pain 12

months after TKR surgery indicating that TSP may be a preoperative mechanistic predictor for the development of chronic postoperative pain.(17) Pre and postoperative treatment with Pregablin (an NMDA antagonist) has been shown to reduce the risk of postoperative pain after TKR surgery in patients with knee OA.(119)

1.6.2 Condition Pain Modulation

In the healthy subjects, excitability within the nervous system can be regulated by inhibition. Powerful descending inhibitory mechanisms can modulate excitatory nociceptive transmission within the spinal dorsal horn, which receive peripheral nociceptive inputs. Descending inhibition originates in the medulla and midbrain and the loss of the ability to generate an inhibitory response as well as the development of facilitated temporal summation is considered an important factor in the cause of spreading sensitization. Conditioned pain modulation (CPM) is an example in humans of this phenomenon, which is also termed diffuse noxious inhibitory control. CPM refers to a change in response to a painful stimulus following the administration of a second conditioning stimulus. CPM is a measure of the net effect of the ascending pain pathways and the inhibitory system and can be induced by e.g. cold pressor test or cuff pressure pain. Studies have shown the restoration of the CPM response in hip OA following total hip replacement surgery, indicating that the changes in the descending inhibitory mechanisms are maintained by peripheral nociceptive inputs but are reversible after the painful stimulus is removed.(103)

Graven-Nielsen *et al* published work showing widespread hyperalgesia and enhanced spatial summation as well as a loss of condition pain modulation (CPM) in knee OA patients implying central sensitisation of pain. However, after total knee replacement surgery the study showed normalisation of pressure

pain thresholds, spatial summation thresholds and restoration of CPM.(15) This work implies that the peripheral joint pathology is the key driver of the initiation and maintenance of the central sensitisation process in OA. These results correlate with functional imaging studies of the brain. Gwilym *et al* assessed patients with hip OA and a cohort of healthy controls and found increased activity within the brainstem periaqueductal gray (PAG) in the hip OA group.(120) The PAG is known to be involved in the modulation of mechanical stimuli via the descending inhibitory pathways.

1.6.3 Treatment of Knee Osteoarthritis

Several pharmacological and non–pharmacological treatments are available in the early stages of knee osteoarthritis. The National Institute of Clinical Excellence (NICE) recommends a holistic approach to OA assessment and management with patient education, self-management, weight loss and moderate exercise to relieve the severe pain associated with the condition as part of the published 2014 guidelines.(39) Non pharmacological treatments include localised muscle strengthening of the quadriceps as well as improved generalised aerobic fitness.(121) First line pharmacological treatment is traditionally paracetamol but many studies have recently shown the low effect size for OA pain, however it is still commonly recommended and if effective is the only long-term analgesic for OA pain.(122) This is largely due to the perceived safety, widespread availability and low cost of paracetamol compared to other analgesics like non-steroidal anti-inflammatory (NSAIDs) and opioids. Recently however the safety of paracetamol has come into question as it shares some of the common side effects as NSAIDs including gastrointestinal bleeding, renal impairment and hypertension.(123-125) With growing concerns regarding prolonged paracetamol use for OA pain in many guidelines the

alternative first line analgesic for OA is topical NSAIDs especially for those patients with significant comorbidities.(121) Topical NSAIDs can be as effective as systemic NSAIDS but provide little systemic toxicity making them a good alternative to paracetamol. The only side effect associated with topical NSAID treatment is localised skin reactions. NICE also recommends the use of intraarticular corticosteroid injection which should be considered as an adjunct to core treatments including exercise and weight loss for the relief of moderate to severe pain in patients with OA.(39) The benefit of intra-articular injection therapy is that it can provide targeted pain relief to the joint. The anti-inflammatory properties of corticosteroid are thought to be the mechanism of pain relief associated with intra-articular steroid treatment and this is consistent with their rapid onset of effect. As previously described synovitis is well recognized feature in OA and histological studies in knee OA patients have identified inflammatory changes within the synovium which are similar to changes seen in patients with rheumatoid arthritis.(126) Recent studies have demonstrated synovial shrinkage following intra-articular steroid treatment and an increase in synovial thickening associated with the recurrence of pain suggesting the synovium is a potential therapeutic target.(127) Neogi *et al* demonstrated the association of synovitis with widespread hyperalgesia and central sensitization (128) therefore treatments to reduce the inflammation within the synovium may reduce central sensitization in knee OA patients.

1.7 Total Knee Replacement Surgery

Total knee replacement surgery (TKR) is one of the most common orthopaedic procedures performed worldwide. It is usually performed in patients with end-stage severe osteoarthritis of the knee when non-surgical management is no

longer an effective treatment. TKR surgery is an effective treatment for severe end stage knee osteoarthritis with 98,147 primary TKR procedures performed in the UK in 2016.(40) The numbers of procedures performed are increasing each year with 120,000 primary TKRs expected to be performed by orthopaedic surgeons by 2030.(129) Based on estimates on United States data, the projections of incidence of primary TKR show a potential growth of 673% from the years 2005-2035, with total knee revision surgery burden projected as 7.2% by 2030.(130)Primary TKR is a standardised procedure performed worldwide for the treatment of painful osteoarthritis of the knee. As part of the surgery approximately 1cm of the arthritic distal femur and proximal tibia is resected prior to the insertion of the metal prosthesis (Figure 1.6).

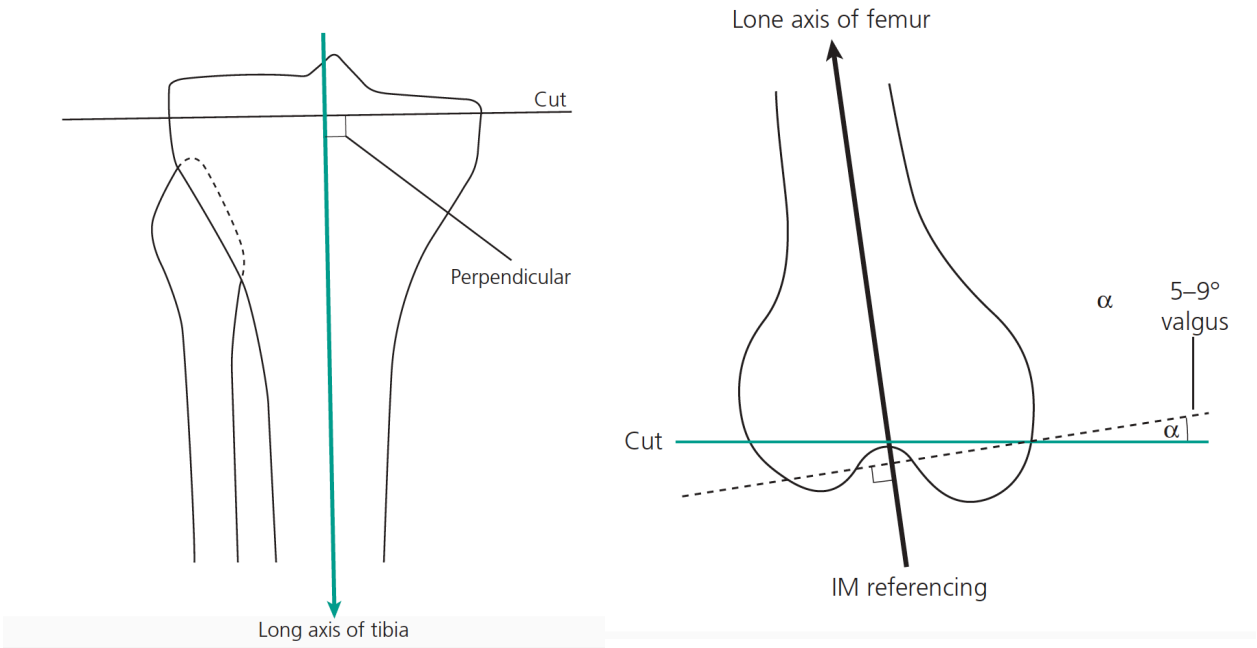


Figure 1.6 Resection Cuts for Total Knee Replacement

Figure 1.6. outlining the approximate 1cm distal femoral and proximal tibia bone cuts when performing a primary total knee replacement- from 'Operative Orthopaedics: The Stanmore Guide'. (131)

Even though TKR has a low rate of technical errors, it is worrying that up to 20% of patients continue to experience chronic post-operative pain in-spite of objective measures of surgical success.(5-13) With the rising numbers of patients suffering with knee OA, and the increase in number operations due to be performed the potential numbers of patients who may suffer chronic postoperative pain after TKR surgery is worrying and needs addressing.

Around 90% of revision TKR procedures are performed due to pain, aseptic loosening, joint infection, instability and stiffness.(40) However after revision TKR surgery up to 50% of patients continue to suffer chronic postoperative pain and those patients that undergo revision TKR surgery are less satisfied with the operation than those patients undergoing primary TKR surgery.(11)

1.8 Chronic Pain after Total Knee Replacement

Chronic postoperative pain is defined by the International Association for the Study of Pain (IASP) as pain that is present in a subject six months after surgery. For many patients TKR is an effective surgical intervention however, unfortunately approximately 20% of all patients who undergo this surgery report severe chronic postoperative pain in spite of objective measures of surgical success.(5-13) Preoperative prediction of which patients will continue to develop postoperative pain after TKR surgery remains an elusive goal for orthopaedic surgeons worldwide. There is a clinically unmet need to develop a pre-operative screening tool that could be used by clinicians to identify those patients that may go onto a poor outcome after TKR surgery. Those patients who are likely to gain less benefit from TKR could be offered targeted individualised treatment with interventions to reduce their risk of developing chronic post surgical pain prior to undergoing surgery or could be offered an

alternative treatment. The identification of non-responders to surgery is of particular interest because of the moves nationally to improve patient selection and improve patient reported outcome measures (PROMS) after surgery, therefore reducing the financial burden on our National Health Service.

Increasing evidence suggests non-pharmacological treatments like exercise and weight loss can reduced OA patients pain in knee OA however a recent study showed TKR surgery is still superior to exercise in patients with severe end-stage knee OA(132), although exercise may postpone surgery.

To identify those patients at most risk of developing chronic postoperative pain after TKR surgery, researchers have made attempts to preoperatively pain phenotype patients based on pain sensitization and pain quality characteristics. This has identified subgroups of OA patients with different preoperative sensory profiles based on central sensitization and neuropathic pain like symptoms assessed using QST and questionnaires(16, 17, 37, 133-138) with different outcomes following TKR surgery.(16, 17, 20) This approach, of pain phenotyping OA patients preoperatively, may help predict those patients that are most at risk of developing chronic postoperative pain after TKR surgery. Risk factors associated with the development of chronic postoperative pain after TKR include female gender, lower age, greater pre-operative pain, pain at remotes sites, pain catastrophizing, depression, anxiety and sleep disturbance(10). A study treating OA knee patients with Pregabalin (licensed for treating neuropathic pain) pre and post TKR surgery has shown it to inhibit postoperative pain indicating that pre-operative sensitization of the nervous system may be connected with the development of postoperative pain.(119) Pain intensity and duration of knee OA have also been associated with the degree of sensitisation.(2, 14, 16, 18, 137, 138) Continued presence of central sensitisation after TKR surgery may play an important

contribution behind why up to 20% of patients who undergo TKR still suffer chronic post-operative pain.

1.9 Knee MRI imaging

Magnetic resonance imaging (MRI) is a non-invasive technique that allows direct visualisation of the subchondral bone, the overlying cartilage as well as the meniscus and other joint tissues. MRI is reproducible and has been shown to be sensitive to change.(84) One of the great advantages of this mode of imaging OA is that it is able to detect the presence of OA with high specificity and moderate sensitivity when comparing standard radiographs or arthroscopy.(139) In respect to BMLs, MRI is the only imaging modality currently that allows the visualisation of these pathological findings seen commonly in OA. The MRI selective sequences to allow accurate assessment and evaluation of BMLs have been extensively investigated. To assess BMLs, the general consensus is that three methods are useful. Firstly, fluid sensitive fat suppressed (FS) sequences, for example, T2- weighted (T2w), (long repetition time (TR) and long echo time (TE), e.g. TR/TE = 3500/120), secondly proton density weighted (PDw), (long TR, short TE, e.g. TR/TE 3500/20) fast spin echo (FSE) sequences or thirdly short tau inversion recovery (STIR) sequences. There is no current evidence to guide the number of planes in which pulse sequences should be acquired to visualise BMLs, however acquisition of fluid sensitive fat suppressed (FS) sequences in 2 or 3 planes is commonly used to avoid misinterpretation of these structures when seen only on one plane. One disadvantage of MRI is that currently there is no consensus on a standardised scoring system to assess the whole joint pathology in OA or more specifically for BMLs. Recently there has been the introduction of semi quantitative scoring systems to help analyse the structural changes in OA.(33, 51, 140-142)

1.9.1 Grading Knee Osteoarthritis using MRI

The Whole-Organ Magnetic Resonance Imaging Score (WORMS) was the first semi-quantitative scoring system for knee OA and involved grading 8 pathological structures of the knee visualised on MRI including cartilage, bone cysts, bone attrition, BMLs, osteophytes, ligaments, synovitis and menisci.(143) Each feature is individually scored to give an overall WORMS score of the OA knee joint. The five structural features that are linked to the articular surface (cartilage, BMLs, bone cysts, bone attrition and osteophytes) are graded by subdividing the knee into 15 sub-regions based on anatomical landmarks of the knee.(143) One of the major limitations of the WORMS score is the assessment of cartilage where multiple measurement assessments including cartilage width, cartilage depth and signal intensity are required to be combined to give an overall MRI cartilage score of the knee.(51) Despite this limitation the WORMS MRI score has proven to be a reliable semi quantitative scoring tool for knee OA with high inter-rater reproducibility reported in the literature.(140, 143)

Hunter *et al* in 2007 improved on the WORMS score by developing the Boston-Leeds Osteoarthritis Knee Score (BLOKS) which overcame the multiple measurement assessment problem of cartilage identified with the WORMS score. Individual scores were recorded for extent and size of cartilage loss and a more comprehensive assessment of BMLs was also included were each individual BML is grade for its size, the percentage of the surface area of the lesion that is adjacent to the subchondral plate and the percentage of the lesion that is a BML and not a bone cyst. Studies have shown that the BLOKS score for BMLs has a better association with subjective knee pain intensity assessed with the VAS score than the WORMS MRI score. (51) With some components of each scoring system being better than the others Lynch *et al* in 2010 recommend an amalgamation of both the

WORMS and BLOKS semi-quantitative scoring system for the MRI assessment of knee OA. (140)

The MRI Osteoarthritis Score of the Knee (MOAKS) was later developed to address the previous concerns regarding the WORMS and BLOKS semi-quantitative scores.(33) MOAKS assesses seven articular features including BMLs and subchondral cysts, articular cartilage, osteophytes, synovitis/effusion, meniscus, ligaments/tendons and periarticular features in the same 15 sub-regions of the knee previously described in the WORMS score. In contrast to the BLOKS score, BML scoring using the MOAKS score assesses the size of BML in each of the 15 sub-regions with no score to measure the proximity of the BML to the subchondral plate. The MOAKS score has additional scores for the meniscus including hypertrophy, maceration and subluxation. The inter (0.650-1.0, weighted Kappa) and intra-rater (0.5-1.0 weighted Kappa)(33) reliability results for the MOAKS score show good reliability and it is now the most commonly used grading system for semi-quantitative MRI scoring of knee OA.

One of the disadvantages of semi-quantitative scoring systems is that there are reader dependant and require extensive training.(46) Quantitative assessment is an alternative method to score pathological features in OA visualised on MRI.(144) The advantage of this approach is that they less observer dependent than subjective scoring. However errors have been reported when scoring for BMLs which often have ill-defined margins resulting in potential inaccuracies when reporting their true volumes.(145) Most quantitative analyses are labour intensive due these manual segmentation methods.(46, 144, 145)

1.9.2 Post-TKR Metal Artefact Reduction MRI scanning

Total knee replacement (TKR) surgery is one of the most commonly performed procedures worldwide for the aging population. In recent years there have been marked improvements in the component design as well as the surgical technique to perform this operation successfully. However, despite the success, up to 20% of patients continue to experience debilitating pain post operatively, often requiring complex revision surgery.(5-13) As the number of TKR procedures increases each year, there has been an associated increase in the number of revision TKR's performed with patients citing pain as their principal reason for undergoing a second surgical procedure.(40) Traditional radiography of the prosthesis is routinely used by the orthopaedic surgeon as part of the clinical assessment in all post-operative pain cases.(6) Assessment of the restoration of normal alignment and position of the components is undertaken as well as a detailed inspection looking for loosening, osteolysis and wear of the polyethylene insert with loss of joint space is performed. Tibial component overhang on the medial side is a common cause of postoperative pain and should also be assessed using plain radiographs.(6) However routine radiographs are unable to detect subchondral bone marrow lesions as well as synovitis, which are common causes of pain in the preoperative state. Conventional MRI of the knee in symptomatic patients with TKR is often limited due to the significant metal artefacts produced, resulting in signal loss, in plane distortions (signal loss and signal pileup) and failure of fat suppression particularly at higher field strengths.(146) Recently GE Ltd have introduced the multi-acquisition variable resonance image combination (MAVRIC®) sequence available on high field 3-Tesla MRI which, can significantly reduce susceptibility artefact around metal implants (147, 148) (Figure 1.7).

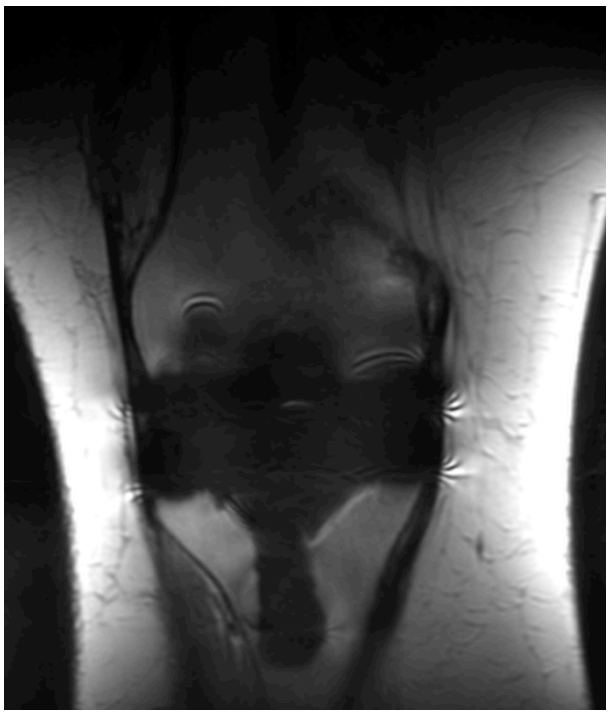


Figure 1.7 MAVRIC(R) Post TKR Knee MRI Scan

Figure 1.7. *3-Telsa MAVRIC® MRI scan of the Knee showing significantly reduced metal artefact allowing visualisation of the bone-prosthesis interface*

The MAVRIC® sequence allows excitation of a series of frequency bandwidths and uses a three dimensional spin echo readout thereby avoiding in-plane distortion resulting in superior imaging in the presence of metallic hardware.(149) Recent published work using MAVRIC® at 3-Tesla in hip and knee arthroplasty showed that this imaging sequence had significantly improved image quality and decreased image artefact compared to conventional fast-spin echo(150, 151) MRI and that it can directly impact on the management of patients.(149) With this new imaging technique, it may be possible to explain why some patients continue to have pain post operatively by the identification of synovitis and BMLs that may continue to be present postoperatively, maintaining pain and sensitization. BMLs have never been visualised postoperatively mainly a result on inadequate imaging techniques. However, with the

introduction of the MAVRIC® sequence at 3-Tesla, assessment of possible continued drivers of postoperative pain such as retained BMLs due to incomplete resection or the presence of new BMLs around the prosthesis and synovitis, may be achieved using this novel MRI sequence.

1.10 Functional MRI of the Brain (fMRI)

Functional brain MRI (fMRI) is a non-invasive powerful imaging technique that can investigate the mechanisms underlying pain perception by identifying dynamic changes in brain activity due to alterations in brain metabolism.(152) The poor relationship between structural damage seen on knee radiographs and OA pain has led researchers to investigate central sensitization using QST and this has coincided with the new imaging techniques (fMRI) that can visualise brain activity. Regardless of the peripheral origin of pain and irrespective of the presence or absence of a continued peripheral nociceptive input post TKR surgery, the brain is the only constant that mediates pain perception, and therefore improved understanding of central pain processing may help explain why some patients fail to respond to TKR surgery.

Currently, brain imaging studies have identified that there is not one region of the brain that is responsible for pain processing and Melzack reported a complex network of brain regions named the 'pain matrix' which are responsible for pain processing.(153) The pain matrix consists of regions that are associated with pain, but also encompasses regions that are involved in other sensory, motor and cognitive functions when the pain information is processed and interpreted (Fig 1.8). The conscious interpretation of nociceptive signals as pain appears in the later stages of pain processing when the painful neural information is conveyed across multiple regions of the cortex. Functional brain imaging studies in patients with knee OA have

identified 6 main regions of the brain that are involved in the sensory-discriminative (i.e location and intensity of pain), and affective and cognitive (unpleasantness) aspects of pain processing. These include the primary and secondary somatosensory cortices (SI and SII), the thalamus, the insula, the anterior cingulate cortex (ACC) and the prefrontal cortex (PFC) (Fig 1.8).(101) The brain activity identified with (fMRI) within these six regions is dependent on the type of pain experienced, the duration and stimulus used as well as psychological state of the subjects as well as the statistical methods of analysis.

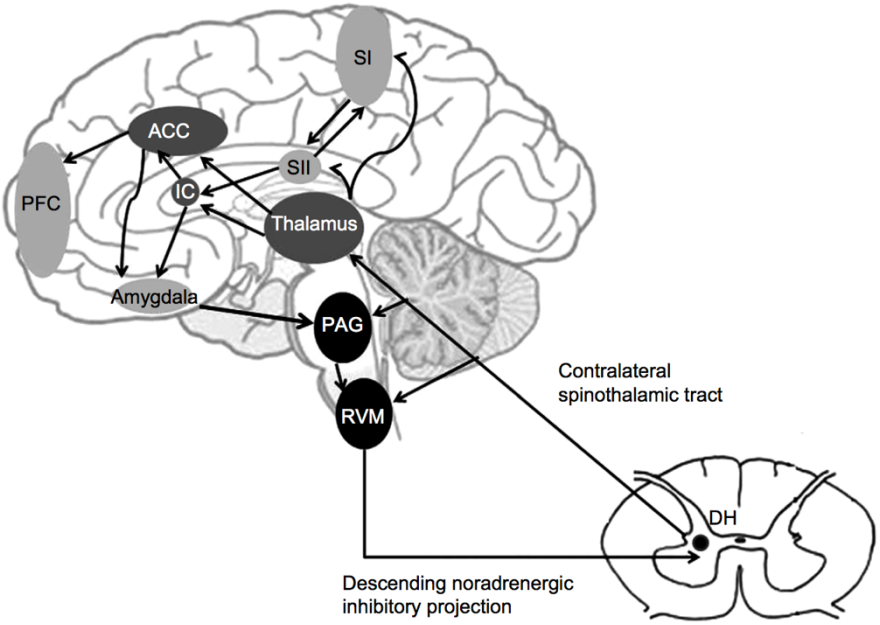


Figure 1.8 Pain Matrix and Pain Circulatory Pathways

Figure 1.8 outlines the pain matrix and pain circulatory pathways. From Morton DL, Sandhu JS, and Jones AKP. Brain Imaging of Pain: State of the Ar.t Journal of Pain Research 2016: 9, 613-624.(101). Legend: See text for full explanation.

Nociceptive signals are transmitted via primary afferent nerves fibres to the spinal dorsal horn (DH). The synapse at the DH and decussate and ascend via the contralateral spinothalamic tract to the thalamus but also have projections that target the

periaqueductal-gray (PAG) and the rostra-ventromedial medulla (RVM). Within the pain matrix there are 2 pain processing pathways. The medial pathway (dark gray) projects from the medial thalamus to anterior cingulate cortex (ACC) and insula cortex (IC) and processes the 'unpleasantness' of pain known as the affective-cognitive component. The lateral pathway (light gray) projects from the lateral thalamus to the primary and secondary somatosensory cortices (S1 and S2) processes the sensory-discriminative aspect of pain including pain location and pain intensity. Increased activation in the prefrontal cortex (PFC) is related to a decreased pain effect by the inhibition of the functional connectivity between the medial thalamus and the midbrain regions.

The descending inhibition pathways which are responsible for reducing the ascending pain processing signals from the spinothalamic tract, and these descending pathways originate from the hypothalamus, amygdala and rostral ACC. Signals descend to the midbrain to the PAG and rostral ventromedial medulla (RVM), which in turn send signals to the dorsal horn of the spinal cord to inhibit the pain experience.(101)

fMRI is a commonly used imaging method in pain research and it has the potential to untangle the underlying pain mechanisms involved in chronic OA pain as well as chronic pain after TKR surgery.

1.11 Blood Oxygen Level Dependant (BOLD) fMRI

When a region of the brain becomes activated as a result of experimental pain stimulus being applied to the knee there is an increased energy requirement by the brain tissues responsible for processing this painful signal.(152) Increased cerebral blood flow occurs as a result of localised neural activity associated with sensory, motor and cognitive processing, termed 'functional hyperaemia'. This increased blood flow is a response by the

brain to deliver increased oxygen and glucose (primary substrates for cellular respiration and metabolism) to the active brain tissue that require them. Oxygenated haemoglobin HbO_2 is diamagnetic meaning that it has no unpaired electrons and has zero magnetic moment thereby making it indistinguishable from brain tissue. However, deoxygenated haemoglobin is paramagnetic having four unpaired electrons and a significant magnetic moment.(152) Paramagnetic substances distort the surrounding magnetic field resulting in a more rapid decay of transverse magnetization (shorter T_2*) Therefore MRI sequences that are sensitive to T_2* show more signal when blood is fully oxygenated and less when the blood is deoxygenated. Under normal conditions oxygenated haemoglobin is converted to deoxygenated haemoglobin at a constant rate within the capillary bed. When neurons with the brain become activated as a result of a painful stimulus the neurons consume more oxygen and glucose with a subsequent increase in the quantity of deoxygenated haemoglobin in circulation. However, the vascular system supplies more oxygenated haemoglobin than is required by the neurons through an over-compensatory increase in cerebral blood flow.(101) This results in a decrease in ratio of deoxygenated haemoglobin to oxygenated haemoglobin within the blood and a corresponding signal loss due to the T2* effects leading to a brighter image on the MRI.(152)

1.12 Literature on BOLD FMRI and OA Pain

Baliki *et al* published one of the first fMRI studies into chronic knee OA pain in 2008. The study recruited five OA patients (age 54-63 years) and seven chronic back pain (CBP) patients (age 29-68 years), and compared the effects of a lidocaine patch on brain activity within the two groups between time point 0 and 2 weeks after lidocaine treatment. The evoked painful stimulus used in the study was a custom-built fMRI compatible device. In

the OA group pressure was applied to the most sensitive part of the painful knee. During each scan, each patient was given six stimulations of pressure/pain of varying intensities (range 2-13 standard units) over 20-45 seconds (mean 32.2+/-15 seconds) with the inter-stimulus interval being set to 30-60 seconds (mean 42.8 +/-16 seconds). In the chronic back pain group patients were not subjected to an experimental evoked stimulus but reported fluctuations in their spontaneous pain. During each session at time point zero and two weeks after the lidocaine patch patients were scanned under two different conditions. Pain rating was assessed using three scans per sessions where subjects reported the intensity of pain using a finger span logging device connected to a computer screen with a moving visual analogue scale (VAS) bar ranging from 0-100. A visual control scan was also conducted where patients used the finger-spanning device to rate the length of a bar moving at approximately their variability in their pain. The pain characteristics of each group were obtained using validated questionnaires. The McGill Pain questionnaire was used in both groups but additionally all chronic back pain patients completed the Neuropathic pain scale questionnaire and all OA patients completed the Western Ontario and McMasters Osteoarthritis Index (WOMAC). Before treatment with the lidocaine patch, painful knee stimulation evoked activity in the bilateral thalamus, secondary somatosensory area (SII), insula, supplementary motor area (SMA), anterior cingulate gyrus (ACG) and medial frontal gyrus and unilaterally in the right putamen and left amygdala. After the second session, following 2 weeks of lidocaine treatment the brain activity map following evoked pressure stimulus to the knee was very similar, however no significant activity was shown in the left amygdala, right putamen and left anterior insula. Significant brain activation was seen in the right ventrolateral orbitofrontal region(154).

Parks *et al* in 2011 published a study looking at evoked and spontaneous pain in a case control study involving chronic knee OA patients and healthy controls using fMRI. Fourteen OA patients (10:4 M:F, age 56.1+/-2.09 years) and nine healthy controls (6:3 M:F, age 46.55+/- 2.6 years) were recruited. All OA patients met the inclusion criteria of fulfilling the American College of Rheumatology criteria for OA, had the disease for at least three months and scored over 30/100 on their VAS scores for pain. Each OA patient was also asked to detail which of their knees was the 'better' and 'worse' knee. No information regarding exclusion criteria or sample calculation was published. The aim of the study was to compare the evoked and spontaneous pain brain activity in OA patients and healthy controls. A custom-made 14mm diameter MRI compatible algometer was used to apply pressure to the most sensitive part of the knee in the OA group and the centre of the knee in the healthy controls. During each scan session four 10-minute minute scan runs of pressure stimulation was applied, (two on each knee, 'worse' and 'better' knee in OA group). Pain rating was conducted using a finger-spanning device, which all participants were trained to use. Spontaneous pain measurement was obtained by asking patients at the start of each scan run to rate their level of pain on a VAS scale of 0-100 in the knee that was about to be stimulated. Therefore. by undertaking this approach, the study design was able to capture evoked pain stimulus brain activity as well as single measurements and readings of brain activity of spontaneous pain. The McGill pain questionnaire and WOMAC questionnaires were used during this study. The results of this study concluded that it is possible to differentiate between evoked pain and spontaneous pain in chronic OA patients. Evoked pain using the algometer activated brain areas associated with acute painful stimuli in healthy subjects. Evoked pain in healthy subjects

activated the bilateral insula, thalamus, basal ganglia (caudate and putamen), amygdala, anterior cingulate gyrus, supplementary motor area, lateral prefrontal cortex, posterior parietal cortex, right secondary somatosensory area, left premotor cortex and periaqueductal gray. The same brain regions were activated in the OA group; however, activity was slightly more widespread. Spontaneous OA pain however, engages the prefrontal limbic regions, which is associated with a more chronic pain state. These regions are involved in emotion and self-assessment. Spontaneous pain regions identified were the medial prefrontal cortex, the orbital prefrontal cortex, bilateral nucleus accumbens and the amygdala. When comparing the 'worse' and 'better' knee in the OA group there was a very small difference between the two in terms of brain activity. There was a slightly increased brain activity in the right lateral prefrontal area in the 'worse' knee than the 'better knee'. The main outcome from this important study was the spontaneous pain engages brain areas distinct from those activated by pressure evoked pain, especially the medial prefrontal limbic structures indicating that spontaneous pain in OA involved more of an emotional state. The amygdala and the periaqueductal gray were also shown to be critical to pain processing working as response modulators. It was shown that the amygdala activity was increased during pain anticipation(155).

Gwilym *et al* published an fMRI study to assess the presence of central sensitisation of pain in 20 patients with hip OA patients and comparing them to 12 healthy controls using thermal and punctate stimuli.(120) With hip OA there is a high incidence of referred pain to the thigh and changes in skin sensitivity at sites away from the joint. These observations led to the authors exploring the possibility of whether altered central processing of nociceptive stimuli was present in these patients with hip OA akin to the alterations seen in patients with neuropathic pain.

Twenty right handed OA patients with right-sided hip OA pain on the waiting list for total hip replacement surgery were recruited. All subjects had primary hip OA and were undergoing their first surgery for their disease. Each OA patient was asked during the screening process if they suffered from referred pain from the hip joint to the thigh. All 20 patients reported this symptom. Patients were excluded if they suffered from any other chronic painful condition, diabetes, neurological or psychiatric disorder. Twelve right-handed healthy controls were recruited and subjects were selected after screening for previous history of arthritis, chronic painful conditions, diabetes, neurological or psychiatric disorders.

Behavioural testing was conducted in all participants with the completion of a number of self-administered questionnaires to assess pain, depression and anxiety. These included the Beck Depression Inventory, Pain Catastrophizing Scale, Tampa Scale for Kinesiophobia, State and Trait Anxiety Index and PainDETECT. Following the completion of the questionnaires, all patients and controls underwent a thermal and punctate QST examination prior to imaging using the standardized protocol from the German Research Network on Neuropathic pain.(107)

The imaging was performed using a 3-Tesla MRI scanner and a whole brain gradient echo-planar imaging sequence was used to obtain BOLD functional images when using the cold thermal and punctate stimulation. For the cold stimulus, an area 5cm distal and 2cm anterior to the right greater trochanter was used as the area for testing on the subjects. A cold stimulus of 12°C was applied for 10 seconds with a 90 second inter-stimulus interval was chosen. This was repeated for eight cycles as part of the thermal protocol. After the cold stimulus was applied for 10 seconds, the temperature returned to 34°C. After the scanning session, subjects were asked to rate if the cold stimulus was painful during the experiment or not. Twelve patients in the hip

OA group and 12 controls underwent thermal testing. Equipment failure with the thermal electrode meant that eight hip OA patients did not undergo this form of testing. For the punctate stimuli testing, 15 stimuli using a 256mN von Frey filament applied the same area over the right greater trochanter was used over a 7-minute testing period. The stimuli were applied in an altered inter stimulus interval which was predetermined using a timing model to coordinate with the event related capture of the BOLD response. All 20 OA patients and 12 healthy controls underwent fMRI testing using the punctate stimulus. All patients underwent a co-registration brain T1 high resolution structural MRI scan to aid in the analysis of the BOLD sequences. Group and subgroup analysis was performed as shown below.

Region of interest analysis was centre around the periaqueductal gray (PAG) as the authors had hypothesised that there was increased activation within the brainstem descending inhibitory region of the PAG in those OA hip patients with referred hip pain secondary to widespread hyperalgesia. Considering the punctate stimulation analysis between the hip OA pain group and the healthy controls there was significantly increased activation in the OA group in the following regions: the ACC, right dorsolateral prefrontal cortex, left middle frontal gyrus and the left lateral occipital cortex. The OA group also reported the punctate stimulus to be significantly sharper compared to the control group ($p=0.028$). Interestingly the study also showed there was an increase in PAG activity in response to punctate stimulation in the referred pain area over the greater trochanter in the OA group compared to the controls ($p<0.05$)

The PainDETECT questionnaire is a validated tool for identifying neuropathic pain like symptoms in OA. The result is a composite score of 0-38 where higher scores are indicative of likely neuropathic pain and lower scores are suggestive of nociceptive pain. A median split of the OA patients PainDETECT scores

allowed the formation of two subgroups; a high PainDETECT group and a low PainDETECT group. There was a significant difference between the high and low PainDETECT groups in terms of how they rated the punctate stimulus. The high PainDETECT group, (those with more neuropathic pain like symptoms) rated the stimulus much sharper than those in the low PainDETECT group (more nociceptive type pain), (mean +/- SD sharpness rating 22.3+/- 16.1 in low PainDETECT group and 48.5+/-25.2 in high PainDETECT group, $p< 0.05$). There was also a significantly increased activity in the PAG in response to the punctate stimuli in the high PainDETECT group compared with the low group.

This study assessed referred pain from hip OA at the level of the greater trochanter. Central sensitisation in OA is identified by lower pressure pain thresholds, widespread hyperalgesia to mechanical stimuli and referred pain and this study confirms these finding in areas of referred pain using a punctate stimulus. In response to the punctate stimulus in the OA group there was increased activation in the PAG compared to the control group, which is associated with clinical hyperalgesia to the stimulus. The authors concluded that the PAG is related to the clinical manifestations of the disease and with its activation within the brainstem it may have a crucial role in the descending inhibition pathways that directly modulate nociceptive processing within the dorsal horn. These changes may play a crucial role in the maintenance of central sensitization and cause the chronicity of pain where central sensitisation is a key finding(120).

1.13 Overall Aims of PhD

This PhD aims to 1) improve the understanding of the pain mechanisms responsible for the development of chronic postoperative pain after TKR surgery, 2) to identify subgroup of knee OA patients that have different preoperative pain characteristics (neuropathic pain/central sensitization), 3) to determine the link between peripheral structural pathology within the knee (BMLs, Hoffa-synovitis and effusion) and patient psychology to neuropathic pain and central sensitization and 4) to identify neural brain imaging biomarkers of central sensitization using fMRI that may predict outcomes following TKR surgery, Figure 1.9.

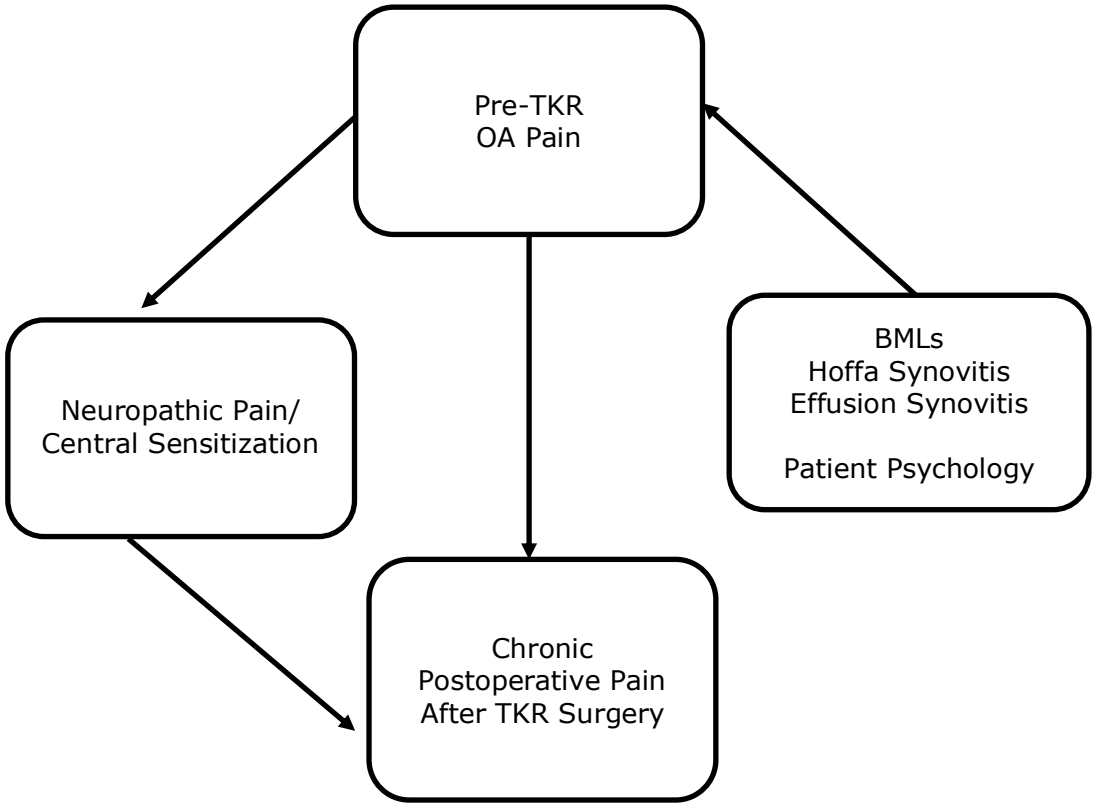


Figure 1.9 Concepts of Thesis to Predict Pain After TKR Surgery

2 Methodology

2.1 Overview and Aims of Each Study

This thesis is based on two main studies both looking into chronic postoperative pain after TKR surgery using the same cohort of 50 pre-TKR OA patients. For the first study which is detailed in Chapters 3 and 4 of this thesis, the main objective was to look specifically at the presence of neuropathic pain in knee OA patients using the PainDETECT questionnaire and its role in influencing patient reported outcomes six months after TKR surgery. In chapter 3, the pain sensitization characteristics of these 50 OA patients with and without neuropathic pain like symptoms are explored using QST and in chapter 4 additional psychological and behavioural traits as well as structural knee MRI changes are examined in the same patients with the aim of determining whether a preoperative neuropathic pain state along with these associated parameters was predictive for the development of chronic postoperative pain six months after TKR surgery.

For the second study which is detailed in Chapters 5 and 6 the objective was to specifically look at central sensitization of pain in knee OA assessed measuring temporal summation of pain in the same cohort. We aimed to assess the neural correlation of temporal summation of pain using functional brain MRI in those OA patients that were central sensitized and identify using knee MRI if any peripheral structural drivers of pain including BMLs or synovitis were driving central sensitization. Using psychological, behavioural and pain related questionnaires we aimed to identify the association of these factors to central sensitization and determine their influence on the development of chronic postoperative pain after TKR surgery. Using novel metal

artefact reduction MRI sequences we aim to assess whether the continued or new presence of BMLs or synovitis may pre present in to patients that continue to report chronic postoperative pain after TKR surgery

All 50 OA patients were invited to take part in this central sensitization functional brain MRI study. Many of the patients were apprehensive and unwilling to undergo a functional brain MRI scan and for that reason only twenty eight out of our 50 patients were included in this additional study described in Chapters 5 and 6.

The reason 50 patients was selected as the number of patients in this study was based on a power calculation conducted in 2013 at the preliminary phase of this study. The study hypothesis in 2013 was based on the assumption that BMLs were the main driver for central sensitization of pain in pre-TKR OA patients and that the failure to resect these during the TKR procedure or the presence of new BMLs around the prosthesis 6 months after TKR surgery may explain a continued sensitization of pain and a chronic postoperative pain state in those patients that continue to report significant pain after surgery. Based on pilot work conducted between 2012 and 2014 the following sample size was performed and submitted to the Medical Research Council for fellowship funding which was successfully awarded.

'In 2001 Felson *et al* conducted the largest published cross sectional study on the association of BMLs and pain in knee OA.(62) His work on 400 patients with knee OA concluded that 78% of patients with painful knee OA had evidence of BML on MRI scans. He also concluded that BMLs were present in 30% of

patients with no pain but with radiological evidence of knee OA on MRI and plain radiographs.

I hypothesize that patients that have the continued presence of BMLs 6 months after total knee replacement surgery, due to incomplete resection of these lesions seen preoperatively, are more likely to lead to postoperative pain. Using these figures would lead to an odds ratio of 2.6 that BMLs are associated with pain.

Therefore the sample size I would need to detect this difference is 20 patients per group with an 80% power and 5% false positive error.

1. Group 1 – 20 patients with no presence of BMLs post op on MAVRIC MRI knee scans.

2. Group 2 – 20 patients with evidence of BMLs post op on MAVRIC MRI knee scans – these could either be new or the continued presence of residual BMLs seen on the pre-operative MRI scan.

The sample size of 50 has also taken into account an expected 10% loss to follow up over the 3 years'.

After the MRC funding was awarded a paper by Neogi *et al* was published stating that synovitis and not BMLs were strongly associated with central sensitization of pain in knee OA.(128) This important study led to further discussion with my supervisors and the MRC and the study was changed to the 2 studies detailed in this thesis, one looking specifically at neuropathic pain with all 50 patients (Chapter 3 and 4) and the other looking at central sensitization using functional brain MRI which included 28 out of the 50 patients. As part of the MRC fellowship, I recruited as many patients as I could with the

financial restrictions of MRI scanning and within the 3 year time frame of the PhD.

In this chapter, generic methods including QST, Knee MRI and MOAKS MRI scoring, that are present in both studies, have been included. However, specific methods relating to each individual study have been included in a methods section within the corresponding chapters.

2.2 Ethical Approvals

The study was approved by the local ethics committee (REC reference: 10/H0408/115) and the University of Nottingham School of Medicine Ethics committee (REC reference:H11122014), all participants gave informed consent, and the procedures were performed according to the Helsinki declaration.

2.3 Quantitative Sensory Testing (QST)

Hand held and cuff algometry was used during the QST assessment to obtain a detailed profile of each individual (both knee OA patients and healthy volunteers) to assess for pain sensitization. Condition pain modulation (CPM) was assessed using cuff algometry and temporal summation of pain (TSP) was assessed with cuff algometry and with a 256mN monofilament. The QST protocols have been established after discussion and approval with our collaborators at the Centre for Sensory-Motor Interaction, a world leading pain centre at The University of Aalborg Denmark, led by Professor Lars Arendt-Nielsen. All protocols are based on previously published methods. Intra-rater reliability assessment results for each of the QST techniques are also described within this section.

2.3.1 Hand Held Pressure Algometry QST Protocol

Pressure-pain thresholds (PPTs) were performed using a hand-held pressure algometer (Somedic AB, Sweden). A 1cm^2 probe

was positioned perpendicular to the skin over the five designated test sites and pressure was applied at 30kPa/s until the subject perceived a change in the stimulus from a pressure to a painful sensation (PPT). At that point subjects were asked to press a button and the pressure stimulus was removed and the PPT value was recorded. PPTs were recorded on side of the affected knee due to be replaced, however the left side was chosen for the healthy controls. Five sites were assessed. Site 1: 3cm medial to mid-point of the medial edge of patella (Fig 2.1). Site 2: 2cm proximal to superior lateral edge of patella. Site 3: 2cm proximal to superior medial edge of patella. Site 4: The tibialis anterior muscle (5cm distal to the tibial tuberosity) was chosen as a distant site to assess for spreading sensitization. Site 5: The extensor carpi radialis longus (ECRL) muscle (5cm distal to the lateral epicondyle of the humerus) was selected as the remote site (arm) to assess for widespread hyperalgesia (14). A 30-s interval between trials at assessment sites was kept. The PPTs were recorded in triplicates and averaged for each site for further analysis. Lower PPTs values indicate increased pain sensitivity.

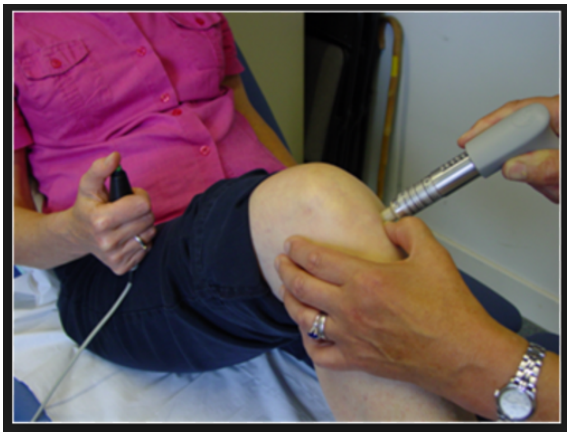


Figure 2.1 – Hand Held QST in practice over the medial joint line of the knee.

Image courtesy of ARUK Pain Centre, Nottingham

Figure 2.1 Hand Held Algometry QST to Assess PPTs

2.3.2 Pin Prick Temporal Summation (TSP)

A weighted 25.6 g von Frey stimulator (Aalborg University, Aalborg, Denmark) was used to assess and induce cutaneous temporal summation of pain. The monofilament was applied directly to the affected knee (5 cm proximal to the centre of patella) in the OA patients or the left knee in the healthy controls. All subjects rated the pain intensity on a VAS. Consecutively, 10 monofilament stimulations were applied repeatedly, to the same site on the subject's knee by the assessor, with a 1-second inter-stimulus interval. Subjects were asked to rate the pain intensity of the first stimulation and the 10^{th} stimulation. Temporal summation was calculated by assessing the difference in the VAS score of the 10^{th} stimulation to the 1^{st} stimulation (14).

2.4 Cuff Pressure Algometry

2.4.1 Cuff Pain Detection and Tolerance Thresholds

A cuff algometer (NociTech and Aalborg University, Denmark) connected to a 13-cm wide single chamber tourniquet cuff (VBM Medizinetechnik GmbH, Sulz, Germany) (Fig. 2.2) was used alongside a computer-controlled air compressor and an electronic 10cm VAS rating system (Aalborg University, Denmark) for cuff algometry assessment (Fig.2.3). The cuff was applied to the lower leg at the level of the gastrocnemius muscle ipsilateral to the affected knee in the knee OA patients and the left side in the controls. The cuff was positioned with a 5cm distance between the upper border of the cuff and the tibial tuberosity.

The cuff was automatically inflated by a computer at the rate of 1 kPa/s until a maximum pressure limit of 100 kPa was reached. The subjects used an electronic VAS to rate their pressure-induced pain intensity and were instructed to press a button to

release the pressure. The VAS signal was sampled at 10 Hz and 0 and 10cm on the scale were defined as 'no pain' and 'maximum pain' respectively. The subjects were all asked to rate the pressure-pain intensity continuously using the electronic VAS with the cuff pain detection threshold (PDT) being defined as the pressure value when the subject rated pain as 1 cm on the electronic VAS (156, 157).The cuff pain tolerance threshold (PTT) was defined as the maximum pressure at the point the subject had to press the release button as a result of the pain intensity being intolerable. Fig 2.4

Figure 2.2 Single Chamber Tourniquet for Cuff Algometry Assessment

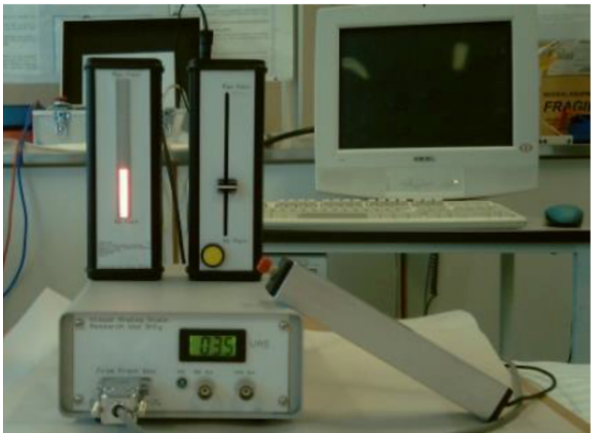


Figure 2.3 Electronic VAS connected to Computer Controlled Air Compressor

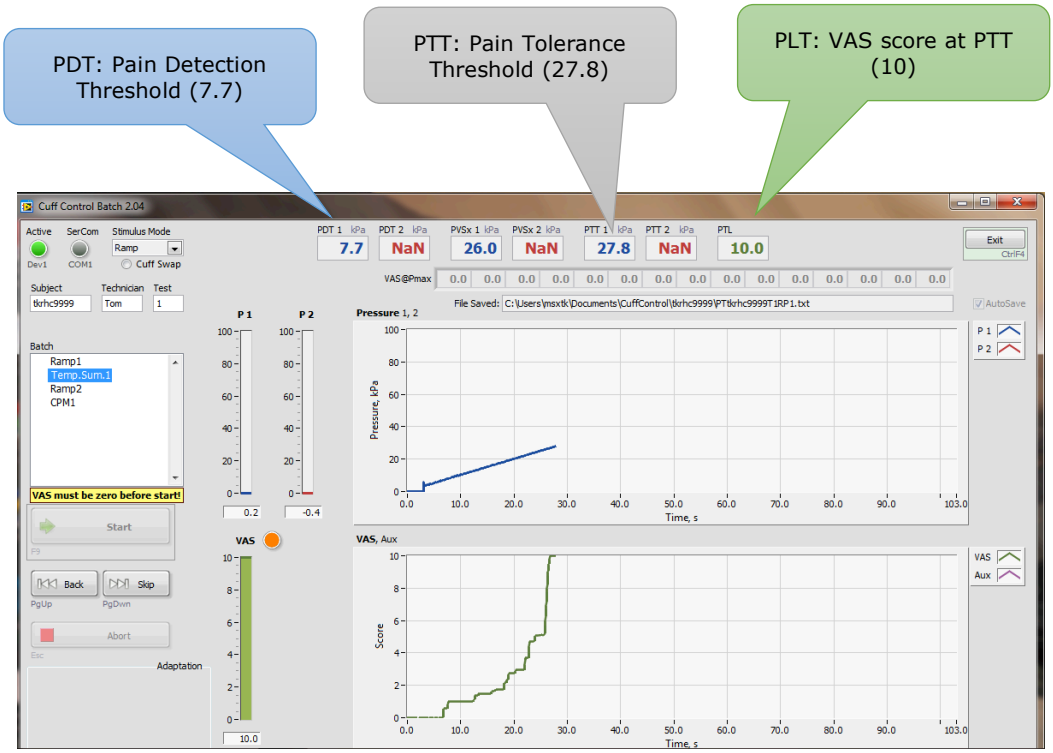


Figure 2.4 Cuff Algometer Showing PDT, PTT and VAS Scores

Figure 2.4 shows cuff algometer in practice with the single chamber cuff being applied to the gastrocnemius muscle, the electronic VAS reader used to the rate the pain and the computer software outlining the subject's PDT (blue), their PTT (grey) and their VAS Pain Score at their PTT.

2.4.2 Cuff Temporal Summation (cuff TSP)

Ten repeated cuff pressure stimulations (1 second duration, 1 second interval) with an intensity equal to PTT were delivered to the lower leg below the affected knee due to be replaced in OA patients and the left side in controls (Figure 2.5). Subjects were asked to rate the pain intensity continuously throughout the 10 pressure cuff stimulations using the electronic VAS and were informed not to return the VAS to zero between cuff stimulations. A constant pressure of 5 kPa was kept between each cuff stimulation to ensure the position of the cuff on the leg did move during the assessment. The VAS score immediately following the individual cuff stimuli was extracted. For the

analysis of TSP the mean VAS score of the 1st to 4th cuff stimulations (VAS-I) was subtracted from the mean VAS score of the 8th to 10th cuff stimulations (VAS II), as previously used in similar studies (137, 157). Based on previous cuff studies facilitated cuff TSP was defined as a cuff TSP score of 1.6 ± 0.2 cm.

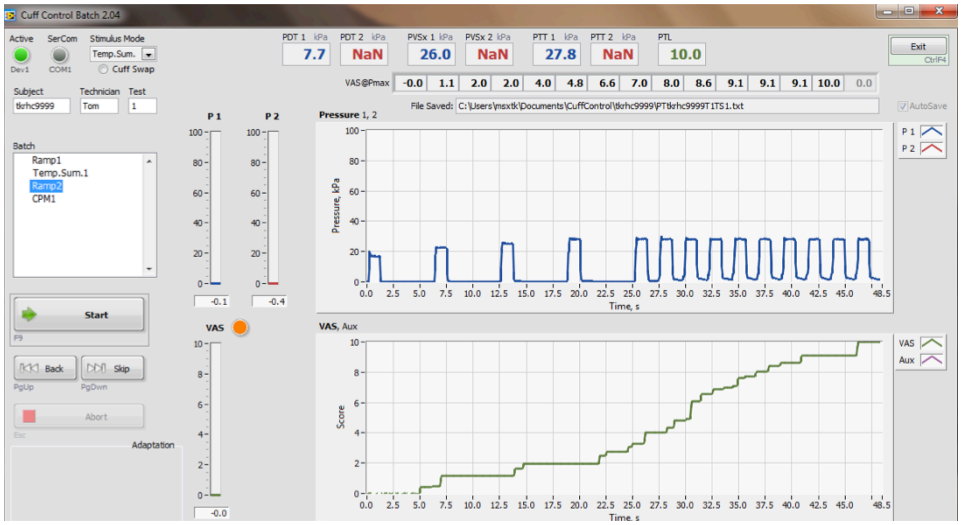


Figure 2.5 Cuff Temporal Summation Paradigm

Figure 2.5 shows cuff algometer in practice assessing TSP by 10x 1 second cuff stimulations set at the subjects PTT. (blue) The subjects digital VAS scores for each of the 10 pressure cuff stimulations recorded in green.

2.4.3 Cuff Condition Pain Modulation (CPM)

Two 13 cm wide cuffs were used to conduct CPM assessment with one cuff on each leg over the gastrocnemius muscles. The painful conditioning cuff stimulus was inflated on the contralateral side (red line in Figure 2.6), with the inflation pressure set equivalent to the subject's PTT. Simultaneous re-assessment of the subject's PDT (blue line in Figure 2.6) was performed with a second cuff on the ipsilateral lower leg (test stimulus). CPM was defined as the difference between the PDT during the conditioning stimulus and the initial trial without it. A CPM score of ≥ 5.5 ± 1.1 kPa was defined as a normal CPM response and a score below this figure was defined as impaired CPM (16).

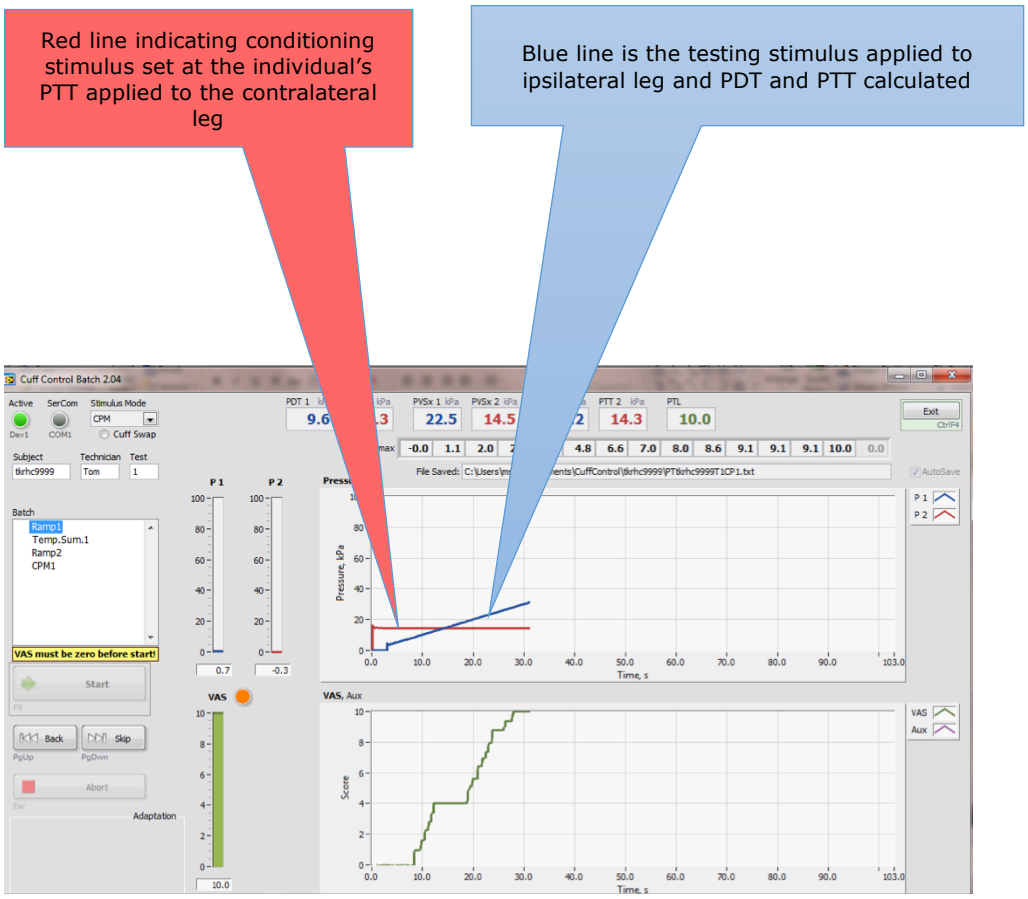


Figure 2.6 Cuff Condition Pain Modulation Paradigm

2.4.4 Intra-reliability for QST Assessments

Ten healthy volunteers recruited to the study were asked if they would participant in a study to assess the test-retest reliability of the quantitative sensory testing (QST) techniques. All QST assessments were performed on each subject and then repeated one week later to assess the intra-reliability of the results. Analysis of intra-rater reliability for the QST assessments was completed using interclass correlation coefficients (ICC) with 95% confidence intervals with SPSS version 23 (SPSS, Inc., Chicago IL). Table 2.1 outlines the intra-rater reliability results showing excellent reliability for the QST assessments.

Table 2.1 Intra-rater Reliability for QST Assessments

QST Test	Rater A 1st Mean [SD]	Rater A 2nd Mean [SD]	Intraclass Correlation	95% CI
Cuff PDT	22.9 [9.4]	25.1 [10.1]	0.948	0.803-0.987
Cuff PTT	43.9 [12.3]	45.2 [10.6]	0.844	0.409-0.961
Pin-Prick TSP	1.4 [1.1]	1.2 [0.92]	0.889	0.580-0.972
Cuff TSP	0.98 [0.60]	1.05 [0.62]	0.890	0.585-0.972
Cuff CPM	2.83 [8.3]	1.64 [7.1]	0.925	0.716-0.981
Mean Knee PPT	585.2 [54.4[	576.5 [70.0]	0.701	0.429-0.925
Tibialis Anterior PPT	537.0 [87.4]	518.3 [74.7]	0.846	0.418-0.961
ECRL PPT	470.4 [50.4]	488.8 [59.1]	0.854	0.447-0.963

2.5 Preoperative Knee MRI and MOAKS MRI Score

All subjects underwent a 3-Telsa knee MRI performed on a 3.0 T system (GE MR 750, GE Healthcare, Waukesha, WI) using an 8-channel phased array transmit-receive knee coil. The knee was scanned in the coronal, sagittal and axial planes using a proton-density fat-suppressed sequence (2.5 mm thickness, spacing 0.3 mm, repetition time (TR) 3321 ms, effective echo time (TE) 41 ms, echo train length (ETL) 7 and pixel bandwidth (BW) 162) (47). MRIs was scored using the semi-quantitative MRI Osteoarthritis Knee Score (Fig 2.7) for severity of Hoffa synovitis (Grade 0-3), effusion size (Grade 0-3) and bone marrow lesions (BML) for all 15 sub-regions of the knee (Score 0-45)(33). The

MOAKS score is a semi-quantitative knee MRI score that has been introduced as an assessment tool that allows identifying pathological features associated with OA and monitor progression of the disease(33, 158). All MRIs were independently graded by one senior musculoskeletal radiologist and one orthopaedic resident trained to complete the MOAKS score. Each observer scored the blinded images independently and repeated the scoring 6 weeks later to assess for inter and intra observer reliability.

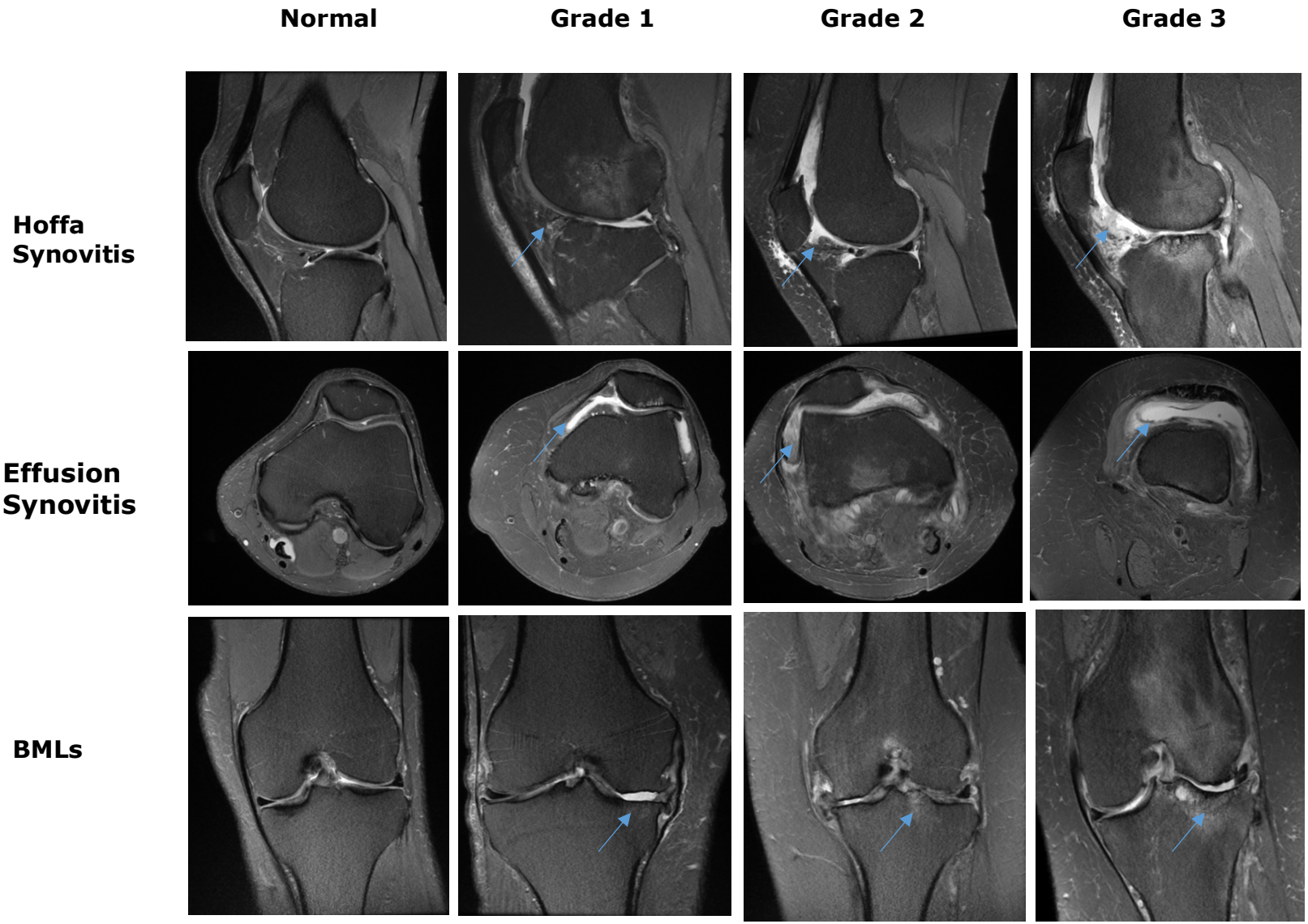


Figure 2.7 MOAKS 3-Tesla MRI Atlas for BMLs, Hoffa and Effusion Synovitis

Blue arrows indicate the different grades of Hoffa Synovitis, Effusion Synovitis or BMLs

2.5.1 Inter and Intra-rater Reliability Data for MOAKS Knee MRI Scores

The intra-rater reliability with a 6-week interval for MOAKS scoring the knee MRI's for BMLs, Hoffa synovitis and effusion size for observer 1 (ICC and 95% CI) were 0.94, (0.84-0.98), 0.96 (0.89-0.99) and 0.98 (0.94-0.99); and observer 2 were 0.97 (0.90-0.99), 0.85, (0.57-0.95) and 0.93 (0.81-0.98). The inter-rater reliability between observer 1 and observer 2 for BMLs, Hoffa synovitis and effusion size was 0.93 (0.78-0.98), 0.82 (0.45-0.94) and 0.92 (0.77-0.97). On occasions when there was disagreement between scores these were each discussed between the observers and the final decision was made by the senior musculoskeletal radiologist.

3 Study 1. Neuropathic Pain in Knee Osteoarthritis

3.1 INTRODUCTION

Knee osteoarthritis (OA) pain has been traditionally attributed to the activation of peripheral nociceptors within the joint or peri-articular structures (159). Significant discordance between radiographic features and knee pain severity (37, 38, 160) has led to researchers investigating the central pain mechanisms with the identification of OA subgroups with different pain phenotypes(2, 14, 16, 17, 105, 133, 161). Up to 34% of OA patients exhibit neuropathic pain like symptoms (162-165) (electric shock sensations (162, 164), burning pain (166) and allodynia (110)) which have been associated with symptoms of central pain facilitation (134, 135). In the US, 3.5 million TKR's are expected to be performed by 2030(167). Worryingly however, up to 20% of patients will develop chronic postoperative pain, (5-13) in spite of objective measures of surgical success which will be a major challenge for health care systems (168). Whether the presence of neuropathic pain like symptoms preoperatively is predictive for chronic postoperative pain after TKR is unknown and requires investigation.

Neuropathic pain is defined as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system".(169) Animal models of OA have demonstrated injury to sensory nerves within subchondral bone (170-172), increased expression of immunoreactivity markers (activating transcription factor-3, ATF-3) within the dorsal root ganglia and spinal microglial activation all suggestive of a neuropathic component (172) . In human OA, increased sensory nerve fibre densities have been seen in the meniscus (173), and meniscal extrusion has been reported in patients with neuropathic pain like symptoms (174) indicating an association between the structural pathology of OA and the development of neuropathic pain.

PainDETECT, like the Doleur Neuropathic 4 (DN4) and the

Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) questionnaires, is a validated self-report questionnaire that has been used in OA patients to evaluate the degree each patient reports the symptoms of neuropathic pain (134-136, 164, 174). Scores range from 0-38 with scores ≥19 indicating 'likely neuropathic pain'. The questionnaire has high sensitivity, specificity and good internal consistency (175) and therefore could be used preoperatively to potentially identify those patients that report persistent pain after TKR.

Quantitative sensory testing (QST) aims at profiling the sensitivity of the pain system (2). Lower pressure pain thresholds (PPTs) assessed distant to the knee, facilitated temporal summation of pain (TSP) and impaired conditioned pain modulation (CPM) have been found as signs of increased pain sensitisation in OA patients compared with controls (105, 137). Preoperative facilitated TSP has been associated with chronic postoperative pain following TKR (17) and total hip replacement (176), indicating the importance of facilitated central pain mechanisms in OA pain.

In this study, it was hypothesised that knee OA patients with severe neuropathic-pain like symptoms before TKR surgery would report higher preoperative knee pain intensity with augmented central pain processing, assessed by widespread pain sensitisation, CPM and TSP, than those OA patients with less neuropathic-pain like symptoms. It was further hypothesised that those patients with severe neuropathic-pain like symptoms and augmented pain processing before TKR are more likely to develop chronic postoperative pain 6 months after TKR surgery.

3.2 METHODS

3.2.1 Study Participants

Fifty patients (mean age 66.4 years [8.3 SD], 60 % women) with chronic knee OA awaiting TKR surgery were recruited from orthopaedic clinics in Nottingham, United Kingdom. These were compared to twenty-two healthy controls (mean age 56.7 years [9.0 SD], 59.1% women) with no symptomatic OA or chronic pain condition. Knee radiographs were obtained for the OA patients (anterior-posterior, lateral and skyline views) as part of their routine preoperative care which were graded using the Kellgren-Lawrence (K-L) system for OA (36). Knee OA patients with associated symptomatic hip OA, psychiatric illness, active cancer, sensory dysfunction, contraindication to MRI or other chronic pain condition e.g. fibromyalgia, rheumatoid arthritis, were excluded at the time of recruitment. All patients were asked not take any analgesic medication 24 hours prior to the assessment. Healthy controls were free of any major medical, neurological or pain related conditions.

3.2.2 Protocol

All subjects completed the self-reported questionnaire PainDETECT to assess for neuropathic pain like symptoms in OA pain. Subjects are asked to record their responses in respect to their pain in the last four weeks. The total score can range from 0 to 38 with a higher score (≥19) indicative of neuropathic pain like symptoms, a score ≤12 representing a nociceptive pain phenotype and a score of (≥13 but ≤18) indicative of a mixed pain phenotype. Subjective knee pain intensity scores were recorded using the visual analogue scale (VAS, 0-10 cm) on the day of assessment. After completion of the PainDETECT questionnaire, QST was performed with the subjects lying on a couch in the supine position in a quiet room. QST data was collected blinded with the examiner unaware of the PainDETECT

questionnaire scores of all the subjects. PPTs were recorded local and distant to the knee. (Figure 3.1) Cuff algometry assessing pain thresholds and tolerance was done on the lower legs (177). Temporal summation of pain (TSP) assessment was based on visual analogue scale (VAS) scores following ten sequential cuff stimulations. Conditioning pain modulation (CPM) was assessed by cuff pain conditioning on one leg and assessment on the contralateral leg. Finally, the degree of temporal summation to cutaneous pin-prick stimulation was assessed.

On average 57 (12.8 to 116) days elapsed between the assessment procedures and TKR. All patients were invited to return for follow up assessment 6-months post TKR surgery to reassess their pain and repeat their QST assessments to determine which patients had developed chronic postoperative pain after TKR surgery. Patients reporting significant postoperative knee pain with a VAS score ≥4 assessed at follow up were defined as having chronic postoperative pain, similar to previous studies (12, 178).

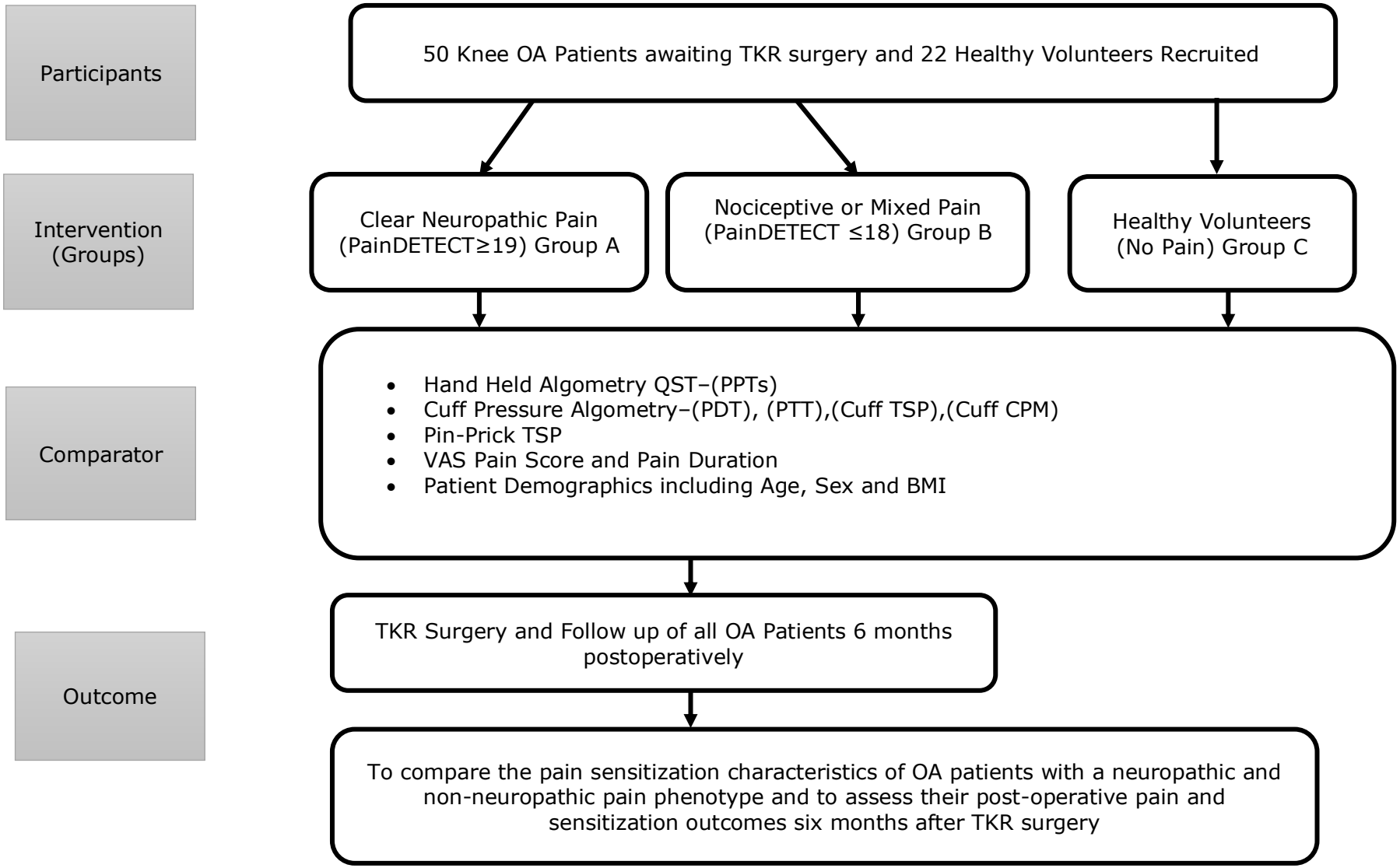


Figure 3.1 Flow Diagram Detailing Study Design

3.2.3 Pressure Algometry

Using a hand-held pressure algometer (Somedic AB, Sweden), PPTs were assessed using a 1 cm^2 probe. A pressure was applied at 30 kPa/s until the subject first perceived a change in the pressure stimulus and it no longer felt like pressure but started to feel painful. At this point the subject pressed a button and the pressure stimulus was removed and the PPT value was recorded. For the OA patients, PPTs were recorded on side of the affected knee due to be replaced, however the left side was chosen for the healthy controls. Five sites were assessed. Site 1: 3 cm medial to mid-point of the medial edge of patella. Site 2: 2 cm proximal to superior lateral edge of patella. Site 3: 2 cm proximal to superior medial edge of patella. Site 4: The tibialis anterior muscle (5 cm distal to the tibial tuberosity) was chosen as a distant site to assess for spreading sensitization. Site 5: The extensor carpi radialis longus (ECRL) muscle (5 cm distal to the lateral epicondyle of the humerus) was selected as the remote site (arm) to assess for widespread hyperalgesia (14). A 30-s interval between trials at assessment sites was kept. The PPTs were recorded in triplicates and averaged for each site for further analysis. Lower PPTs values indicate increased pain sensitivity.

3.2.4 Cuff Pressure Algometry

A cuff algometer (NociTech and Aalborg University, Denmark) connected to a 13-cm wide single chamber tourniquet cuff (VBM Medizinetechnik GmbH, Sulz, Germany) was used alongside a computer-controlled air compressor and an electronic 10 cm VAS rating system (Aalborg University, Denmark) for cuff algometry assessment. The cuff was applied to the lower leg at the level of the gastrocnemius muscle ipsilateral to the affected knee in the knee OA patients and the left side in the controls.

The cuff was positioned with a 5-cm distance between the upper border of the cuff and the tibial tuberosity. The cuff was automatically inflated by a computer at the rate of 1 kPa/s until a maximum pressure limit of 100 kPa was reached. The subjects used an electronic VAS to rate their pressure-induced pain intensity and were instructed to press a button to release the pressure. The VAS signal was sampled at 10 Hz and 0 and 10 cm on the scale were defined as 'no pain' and 'maximum pain' respectively. The subjects were all asked to rate the pressure-pain intensity continuously using the electronic VAS with the cuff pain detection threshold (cPDT) being defined as the pressure value when the subject rated pain as 1 cm on the electronic VAS (156, 157).The cuff pain tolerance threshold (cPTT) was defined as the maximum pressure at the point the subject had to press the release button as a result of the pain intensity being intolerable.

3.2.5 Temporal Pain Summation by Cuff Algometry

Ten repeated cuff pressure stimulations (1 second duration, 1 second interval) with an intensity equal to PTT were delivered to the lower leg below the affected knee due to be replaced in OA patients and the left side in controls. Subjects were asked to rate the pain intensity continuously throughout the 10 pressure cuff stimulations using the electronic VAS and were informed not to return the VAS to zero between cuff stimulations. A constant pressure of 5 kPa was kept between each cuff stimulation to ensure the position of the cuff on the leg did move during the assessment. The VAS score immediately following the individual cuff stimuli was extracted. For the analysis of TSP the mean VAS score of the 1^{st} to 4^{th} cuff stimulations (VAS-I) was subtracted from the mean VAS score of the 8^{th} to 10^{th} cuff stimulations (VAS II), as previously used in similar studies (137, 157). Based

on previous cuff studies facilitated cuff TSP was defined as a cuff TSP score of 1.6 ± 0.2 cm (16).

3.2.6 Conditioning Pain Modulation by Cuff Algometry

Two 13 cm wide cuffs were used to conduct CPM assessment with one cuff on each leg over the gastrocnemius muscles. The painful conditioning cuff stimulus was inflated on the contralateral side, with the inflation pressure set equivalent to the subject's cPTT. Simultaneous re-assessment of the subject's cPDT was performed with a second cuff on the ipsilateral lower leg (test stimulus). CPM was defined as the difference between the cPDT during the conditioning stimulus and the initial trial without it. A CPM score of ≥ 5.5 ± 1.1 kPa was defined as a normal CPM response and a score below this figure was defined as impaired CPM (16).

3.2.7 Cutaneous Temporal Summation of Pain

A weighted 25.6 g von Frey stimulator (Aalborg University, Aalborg, Denmark) was used to assess and induce cutaneous temporal summation of pain. The monofilament was applied directly to the affected knee (5 cm proximal to the centre of patella) in the OA patients or the left knee in the healthy controls. All subjects rated the pain intensity on a VAS. Consecutively, 10 monofilament stimulations were applied repeatedly, to the same site on the subject's knee by the assessor, with a 1-second inter-stimulus interval. Subjects were asked to rate the pain intensity of the first stimulation and the 10^{th} stimulation. Temporal summation was calculated by assessing the difference in the VAS score of the 10^{th} stimulation to the 1^{st} stimulation (14).

3.2.8 Statistical analysis

The OA patients were grouped based on the preoperative PainDETECT score. OA patients with a score ≥19 indicating

neuropathic pain-like symptoms were assigned to Group A, and those with nociceptive or mixed pain based on PainDETECT score <19 were assigned to Group B (179). The healthy controls with no chronic pain condition or osteoarthritis were assigned to Group C.

The data was analysed using Prism 7.0. Parametric data was presented as the mean and standard deviation with median and interquartile ranges (IQR) being expressed for data that was non-parametric. In figures, data are presented as mean and standard error of the mean (SEM). Data were evaluated to determine whether they met the assumption of normality using the D'Agostino-Pearson omnibus normality test. An analysis of variance (ANOVA) with Tukey post hoc tests for normally distributed data, or Kruskal-Wallis ANOVA with Dunn's post hoc tests for the analysis of non-parametric data, was conducted for comparisons of Age, BMI, PPTs, TSP and CPM between Groups A, B and C.

A mixed-model ANOVA was used to assess PPTs, cuff PDT'S cuff PTT, cuff TSP and von Frey induced TSP with group factors (Group A and B) as well as repeated factor time (pre-TKR and post-TKR) for data that was normally distributed. The Wilcoxon Matched Paired Rank Tests for non-parametric data was used to assess pre and post-TKR changes for cuff CPM. Differences in gender distribution were assessed using a chi-square test. Pain Duration and VAS pain scores of the OA patients were assessed between Groups A and B using the Mann Whitney U-Tests and Unpaired t-Test respectively. Association between parameters was assessed by Pearson's correlation for parametric data and Spearman's correlation for non-parametric data. $P < 0.05$ was considered significant. Pre-TKR correlations between pain characteristics and QST measures were assessed using pooled data from all three groups and adjusted for multiple comparisons (Bonferroni). The associations between pre-TKR

and post-TKR pain characteristics were by correlation analysis and significant preoperative factors were used in a linear stepwise regression to identify independent variables.

3.3 RESULTS

3.3.1 Demographic data and pain profiles

Analysis of the demographic data showed no differences in age (ANOVA: F=9.9, p=0.0002) between Group-A and Group-B OA patients (Tukey: p=0.78) but significant differences between Group-A and Group C healthy controls (Tukey p=0.01) and Group-B and Group C (Tukey p=0.0001) were seen (Table 3.1). There were no differences in BMI (Kruskal-Wallis Test: H=10.73 p=0.005) between Group-A and Group-B OA patients (Dunn's: p>0.99) but significant differences were seen between Group-A and Group C (Dunn's: p=0.02) and Group-B and Group-C (Dunn's: p=0.01). All 3 groups had more females present than males, however overall, no significant differences in gender were seen between groups (Chi-Squared Test, p=0.818). Comparing the two OA groups, those OA patients with a neuropathic pain phenotype (Group A) had a longer duration of pain symptoms (Mann Whitney U Test, p<0.02) and higher peak pain VAS scores (Unpaired T-Test, p<0.02). The structural radiological assessment of the knee showed no difference between the OA groups with both groups having a median K-L score of 4 (Table 3.1).

Forty-six patients returned for the re-assessment 6-months post TKR surgery (92% follow up). Regarding the four patients that failed to return; one was excluded from the study due to a fracture which required revision surgery and the other three patients we were unable to contact postoperatively. PainDETECT assessment based on their preoperative pain phenotype showed that 13/15 Group A patients and 33/35 Group B patients

returned for follow up. Group A patients reported higher postoperative VAS pain scores six months after TKR surgery, (4 cm [0.75-7]) compared to Group B patients (0 cm [0-1]), p=0.0003, Mann Whitney U-Test.

Table 3.1 OA Patients and Healthy Control Demographics.

	Group A Neuropathic pain (n=15)	**Group B Non-Neuropathic Pain (n=35)**	**Group C Healthy Controls (n=22)**
PainDetect Score (0-38)	23 (21-27)	10 (6-13)	0 (0-0.25)*
Age (years)	65.1 [8.9]	66.9 [8.0]	56.7 [9.0]*
Male:Female %Female	5:10 66.6%	15:20 57.1%	9:13 59.1%
Body Mass Index	30 (27-33.4)	30 (27-39)	26 (24-28.3)*
Kellgren and Lawrence Radiological Grade Knee OA	4 (3-4)	4 (3-4)	N/A
Pain Duration (months)	61.4 (54.5-86.4)	54.5 (36.4-61.4)*	N/A
Peak pain VAS score (cm) in previous 24 h	6.5 [2.1]	4.7 [2.3]*	N/A

Mean [Standard Deviation] or Median and (IRQ) are used to represent data. Significantly different from the other groups (p<0.05,).*

3.3.2 Pressure Algometry

Pre-TKR assessments: Lower average PPTs around the knee PPT (Fig. 3.2; ANOVA: F =27.1, p<0.0001) were found for Group A (Tukey: p<0.0001) and Group B (Tukey: p<0.0001) compared with Group C. Further, lower PPTs (ANOVA: F=15.0, p<0.001) were found at the tibialis anterior muscle for Group A compared with Group B (Tukey: p<0.02) and Groups C (Tukey: p<0.001) and for Group B compared with Group C (Tukey's:

p<0.03). Assessment of the ECRL muscle showed lower PPTs (ANOVA: F=13.8, p<0.0001) in Group A (Tukey: p<0.0001) and Group B (Tukey: p<0.008) compared to Group C.

Post-TKR assessments: Six months post TKR lower PPTs values were seen over the knee (Fig. 3.2; ANOVA: F=16.0, p<0.0001) comparing Groups A and Group C (Tukey: p<0.0001) and Group B and C (Tukey: p=0.001). Postoperatively, lower PPTs postoperatively were found over the tibialis anterior muscle (ANOVA: F=14.5, p<0.0001) in Group A (Tukey: p<0.0001) and Group B (Tukey: p=0.02) compared with Group C. Significantly lower PPTs were seen over the ECRL muscle (ANOVA: F=11.2, p<0.0001 in Group A patients compared to Group C (Tukey: p<0.0001).However, no differences were seen between Groups B and C indicating normalization of widespread hyperalgesia post TKR surgery in those OA patients with preoperative nociceptive or mixed OA pain.

Comparing pre and post-TKR assessments:

A two-way ANOVA (Group: Group A vs Group B) x (Time: Pre TKR vs Post TKR) was conducted to assess how the mean knee, TA and ECRL PPT scores differed between Groups A and B as a function of TKR surgery. For the mean knee PPTs scores there was a significant main effect of time (pre-post TKR surgery) F(1,96) = 5.32, p=0.02, such that the mean knee PPTs were significantly higher post TKR surgery (M=437.1 SD= 211.9) compared to pre TKR surgery (M=330.3 SD=174.1). There was no significant effect of Group: F(1,96) =1.53, p>0.05 suggesting the mean knee PPTs scores in both groups A and B were similar. There was also no significant interaction effect F(1,96)=0.219, p>0.05.

For the tibialis anterior PPTs, no significant effect of group were seen F(1,96) = 0.5, p>0.05 with similar PPT scores in groups A (M=386.4 SD=212.3) and B (M=356.3 SD=175.6).

There was also no significant effect of time (Pre vs Post TKR) F(1,96)=3.148 p>0.05 or interaction F (1,96) =0.116 , p>0.05.

Assessment of the ECRL PPTs showed a significant main effect of group F (1,96) = 14.77, p<0.001 such that Group A patients (M=261.4, SD 124) had significantly lower ECRL PPTs than Group B patients (M=393.9, SD 162.7). The main effect of time (pre-post TKR surgery) was not significant F(1,96)= 0.264, p>0.05. The interaction effect was also not significant: F (1.96) = 0.203, p>0.05.

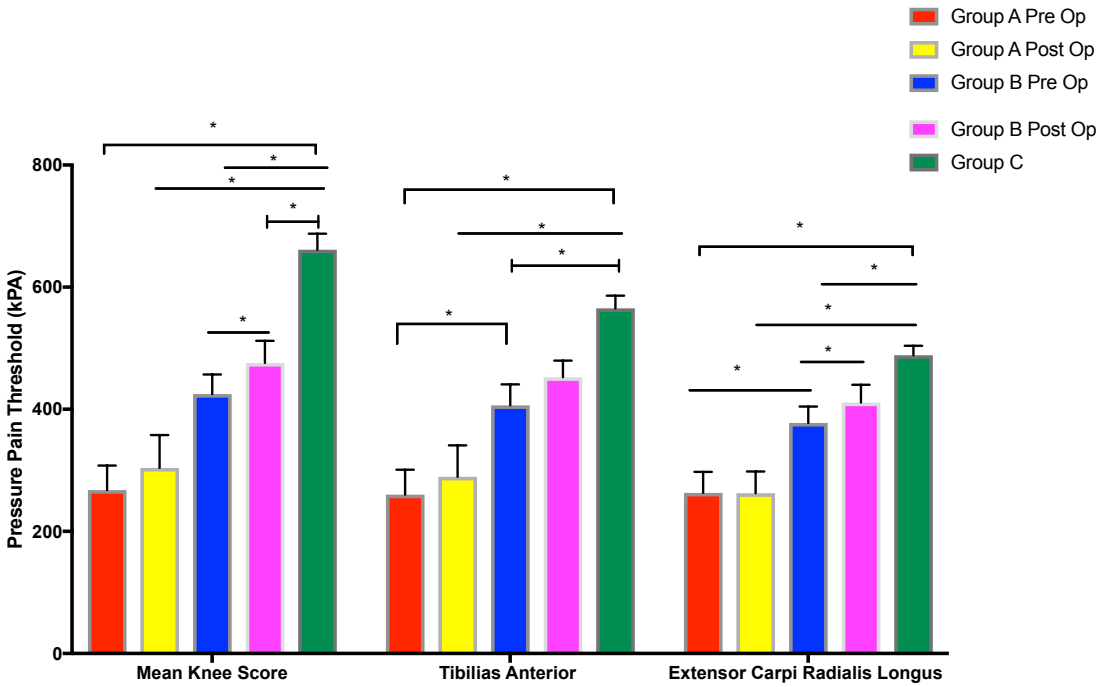


Figure 3.2 Pressure Pain Threshold (PPT) Results

Figure 3.2. Mean (+/-SEM) pressure-pain thresholds (PPTs) assessed using pressure algometry OA patients (Group A, n=15; Group B, n=35) and healthy controls (Group C, n=22). PPTs were assessed on the knee (mean of 3 sites), the tibialis anterior muscle and the on the arm. Pre and 6-month post-TKR PPTs are shown. Significantly different PPTs are illustrated (*), p<0.05).

3.3.3 Cuff Pressure Algometry

Pre-TKR compared with controls: No significant differences in cuff PDTs (Kruskal-Wallis Test: H=0.72 p>0.05) were seen comparing Group A (Dunn's: p>0.05) and Group B (Dunn's: p>0.05) to healthy controls. The PPTs results also were not significantly different (Kruskal-Wallis Test: H=0.44 p>0.05) comparing Group A (Dunn's: p>0.05) and Group B (Dunn's: p>0.05) to healthy controls (Figs 3.3 and 3.4).

Post-TKR compared with controls: Six months post TKR surgery both Group A and Group B OA patients showed no significant differences in postoperative cuff PDT and PTT thresholds to cuff stimulation compared to the healthy controls (cuff PDT: p=0.23; cuff PTT: p=0.50; Kruskal-Wallis Test) (Figs 3.3 and 3.4).

Pre-TKR and Post-TKR in OA patients: No differences were seen in the preoperative cuff PDT (ANOVA: F (1,42) = 2.463, p=0.124) and PTT (ANOVA: F (1,42) = 1.61, p=0.212) scores between Groups A and B (Figs 3.3 and 3.4).

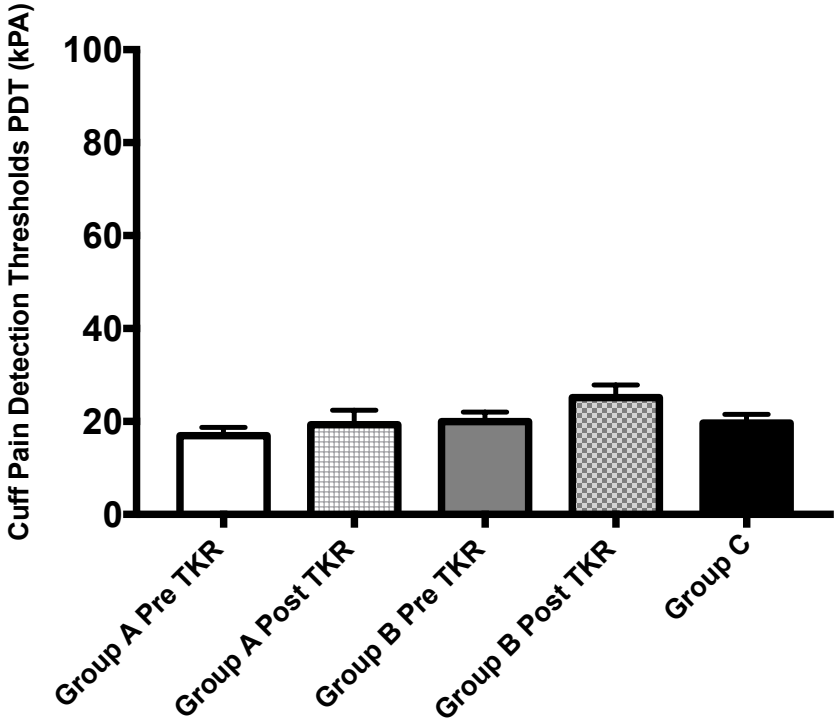


Figure 3.3 Pain Detection Thresholds (PDTs) Pre and Post-TKR

Figure 3.3 Mean (± SEM) cuff Pain Detection Thresholds (PDT) scores for both OA groups (A and B) and Healthy controls (Group C) Pre and Post TKR. (*) p<0.05 was significant

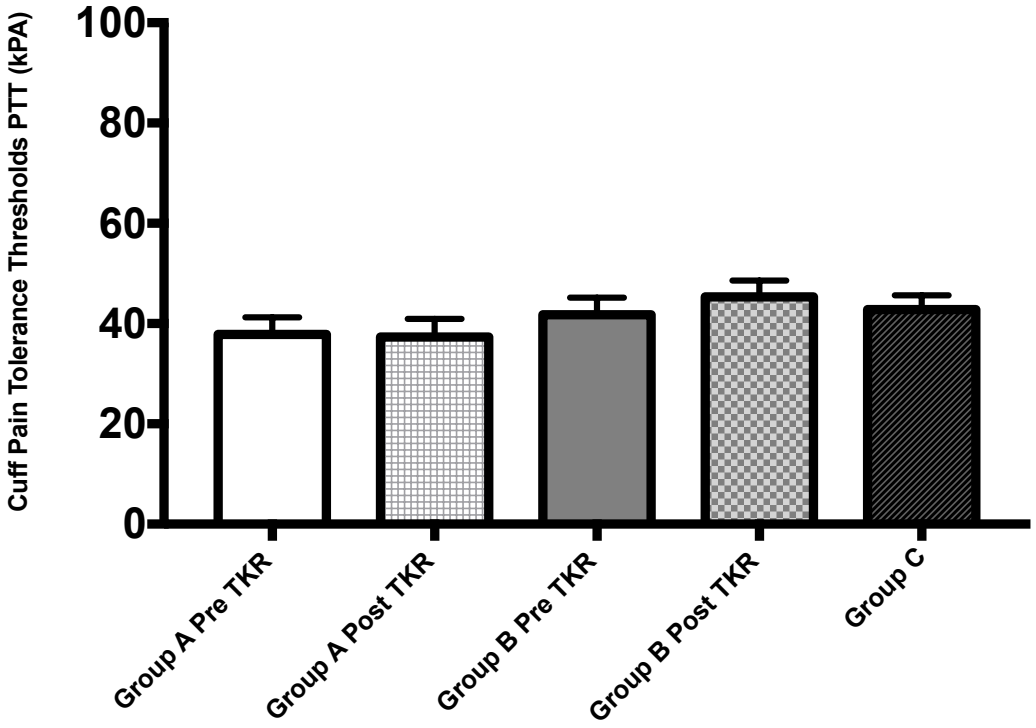


Figure 3.4 Pain Tolerance Thresholds (PTT) Pre and Post-TKR

Figure 3.4. Mean (± SEM) cuff Pain Tolerance Thresholds (PTT) scores for both OA groups (A and B) and Healthy controls (Group C) Pre and Post TKR. (*) p<0.05 was significant.

3.3.4 Temporal Summation of Pain by Cuff Algometry

Pre-TKR compared with controls: Higher cuff TSP scores (Kruskal-Wallis Test: H=10.64 p<0.005) were found in Group A (Dunn's: p<0.01) and Group B (Dunn's: p<0.04) compared to Group C (Figs 3.5 and 3.6).

Post-TKR compared with controls: No significant differences were found comparing the post TKR cuff TSP scores of Group A (Dunn's: p>0.999) or Group B (Dunn's: p=0.784) to Group C (Kruskal-Wallis Test: H=3.26 p=0.197) (Figs 3.5 and 3.6).

Pre-TKR and Post-TKR in OA patients: A two-way ANOVA (Group: Group A vs Group B) x (Time: Pre TKR vs Post TKR) was conducted to assess how the cuff TSP scores differs between Groups A and B as a function of TKR surgery. There was a significant main effect of time (pre-post TKR surgery) $F(1,96) = 8.69$, $p=0.004$, such that the cuff TSP were significantly lower post TKR surgery (M=1.11 SD=1.39) compared to pre TKR surgery (M=2.13 SD=1.75). There was no significant effect of Group: $F(1,96) =0.75$, $p>0.05$ suggesting the cuff TSP scores in both groups A and B were similar. There was also no significant interaction effect $F(1,96)=0$, $p>0.05$(Figs 3.5 and 3.6).

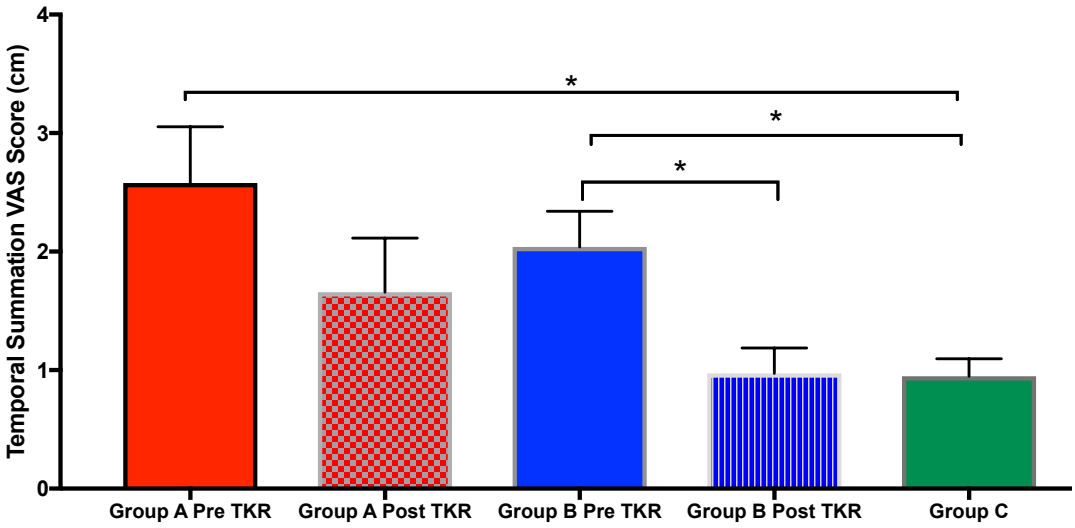


Figure 3.5 Cuff TSP Scores for All Groups Pre and Post-TKR

Figure 3.5. Mean (± SEM) cuff Temporal Pain Summation scores (VASII- VAS I) for both OA groups (A and B) and Healthy Controls Pre and Post TKR. (*) p<0.05 was significant.

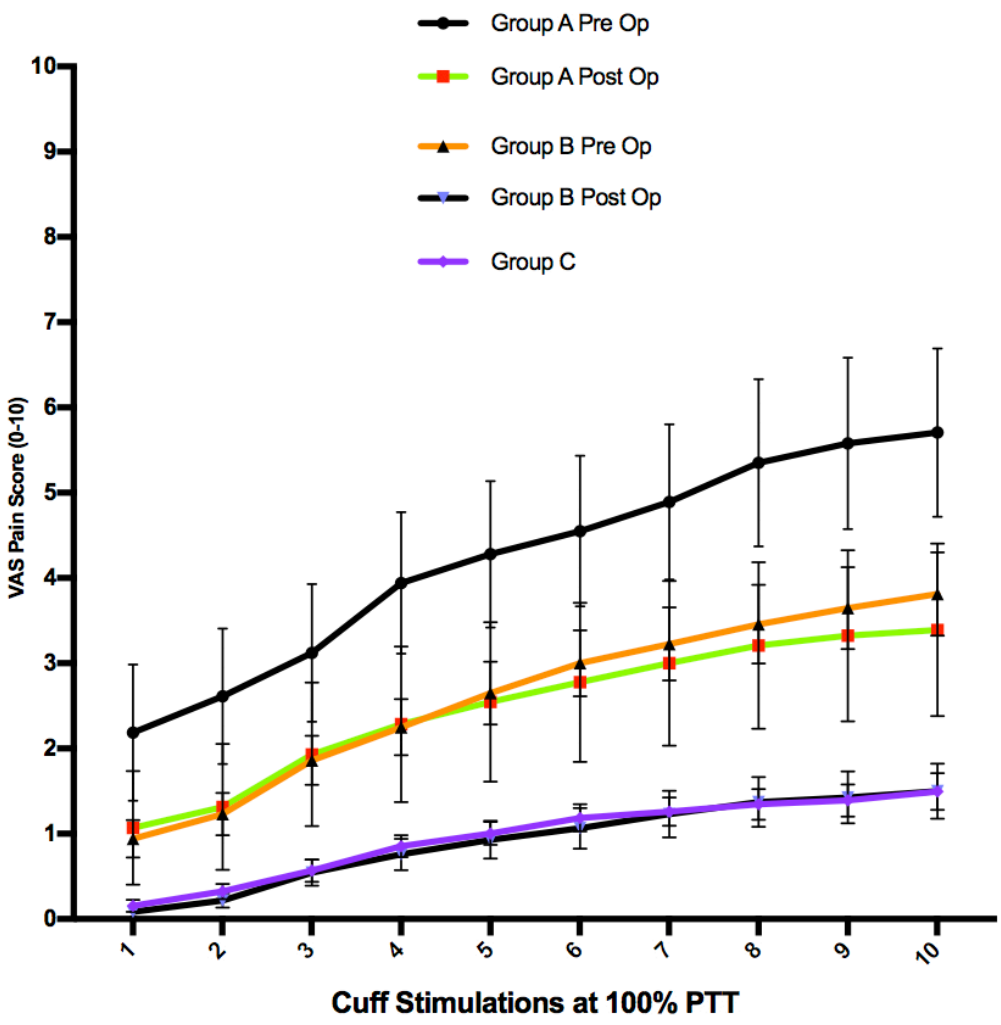


Figure 3.6 Cuff TSP VAS Scores for each of the 10 Stimuli

Figure 3.6 Mean (± SEM) cuff Temporal Pain Summation VAS scores for each of the 10 pressure cuff stimulations set at the subject's individual PTT. Results are displayed for both OA groups A and B pre and post-TKR as well as the healthy controls. (*) p<0.05 was significant

3.3.5 Pin-Prick Temporal Summation of Pain

Pre-TKR compared with controls: Higher preoperative pin-prick TSP VAS scores (Fig.3.7, ANOVA: F=35.7 p<0.0001) were seen in Group A patients compared to Group C controls (p<0.0001) and Group B patients and Group C controls (p=0.0006)

Post-TKR compared with controls: Increased (ANOVA: F= 8.3, p=0.0006) pin-prick TSP VAS scores were seen in Group A

patients post-TKR surgery compared with group C (Tukey's: p=0.02) (Fig 3.7).

Pre-TKR and Post-TKR in OA patients: A two-way ANOVA (Group: Group A vs Group B) x (Time: Pre TKR vs Post TKR) was conducted to assess how the pinprick TSP scores differs between Groups A and B as a function of TKR surgery. There was a significant main effect of time (pre-post TKR surgery) $F(1,96) = 8.82$, $p=0.004$, such that the pinprick induced TSP scores were significantly lower post TKR surgery ($M=2.13$ $SD=2.22$) compared to pre TKR surgery ($M=3.54$ $SD=2.29$). There was no significant effect of Group: $F(1,96) =0.75$, $p>0.05$ with similar pinprick induced TSP scores in both group A (M 3.17 SD 2.31) and B ($M=2.73$ SD 2.31). There was also no significant interaction (Group x Time) effect $F(1,96) =0$, $p>0.05$ (Fig 3.7)

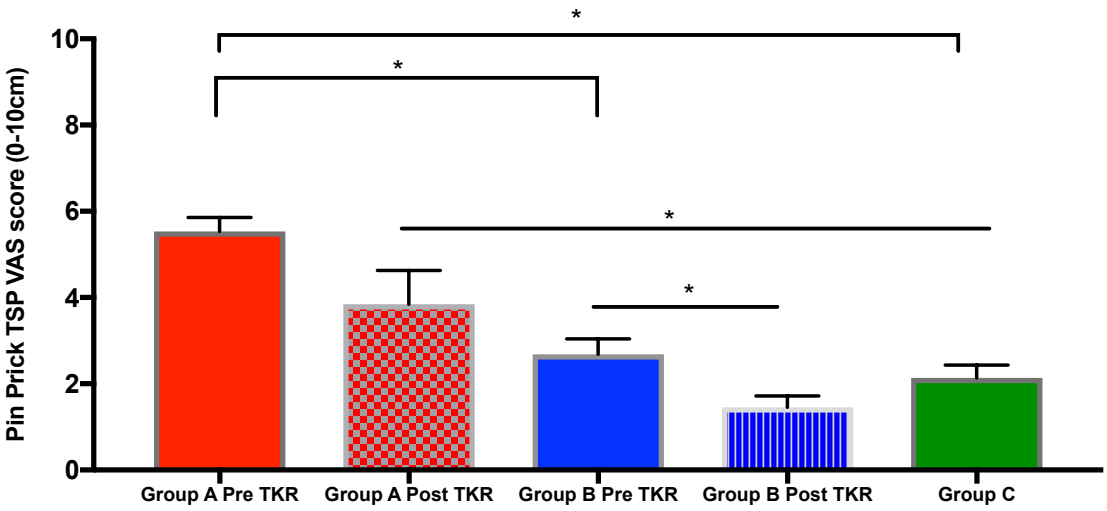


Figure 3.7 Pin-Prick TSP Results: Pre and Post-TKR

Figure 3.7. Mean (± SEM) pin-prick Temporal Summation of pain for both OA Groups (A and B) Pre and Post TKR compared with Healthy Controls (Group C). (*) p<0.05 was significant.

3.3.6 Conditioning Pain Modulation

Pre-TKR compared with controls: Preoperative assessment of conditioning pain modulation showed impaired CPM in Group A patients compared to Group C controls (Dunn's: p=0.012), (Kruskal-Wallis Test: H=8.68, p=0.013) (Fig 3.8).

Pre-TKR and Post-TKR in OA patients: No significant differences were found between the pre TKR CPM results between Group A and Group B OA patients, (Dunn's: p=0.5198) (Kruskal-Wallis Test: H=8.68, p=0.013). Six-months post TKR surgery no significant differences were seen when comparing the pre and post TKR CPM scores of Group A patients (p=0.3804, Wilcoxon) and Group B patients (p=0.4992, Wilcoxon) (Fig 3.8).

Post-TKR compared with controls: Following TKR surgery no significant differences in CPM scores were found between Group A patients and Group C controls (Dunn's: p=0.1687) or Group B patients and Group C controls (Dunn's: p=0.434) (Kruskal-Wallis Test: H=4.09, p=0.129) (Fig 3.8).

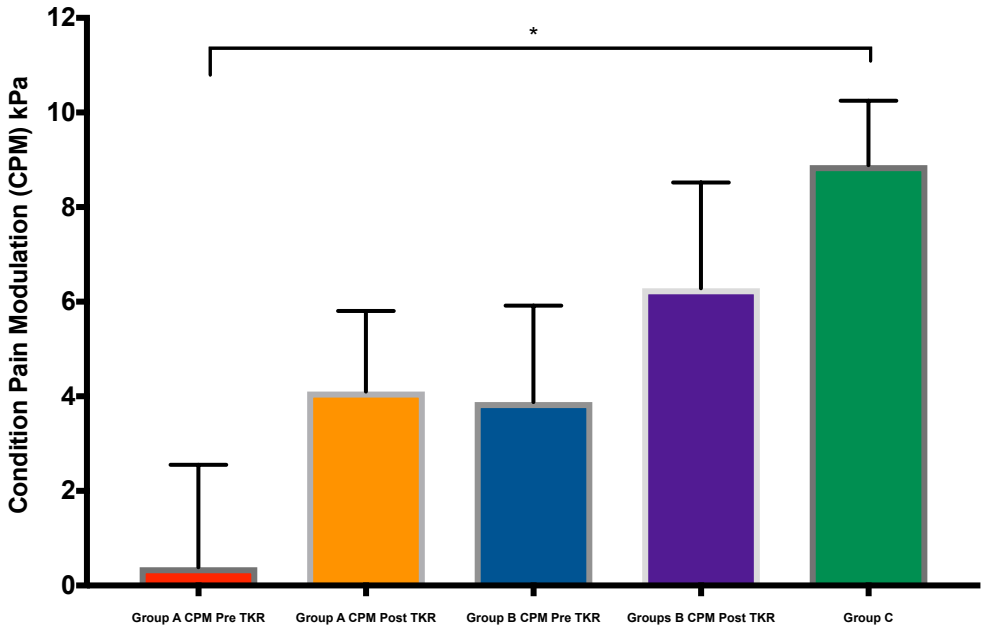


Figure 3.8 Condition Pain Modulation Results: Pre and Post-TKR

Figure 3.8. Mean (± SEM) cuff condition pain modulation (CPM) results for both OA Groups (A and B) Pre and Post TKR compared with Healthy Controls (Group C). (*) p<0.05 was significant.

3.3.7 Incidence of Postoperative Pain after TKR surgery

Fourteen patients (30.4%) were defined as having chronic postoperative pain with eight (53% of group A) originating from Group A and six (17%) from Group B preoperatively. From the 32 responders to TKR surgery (VAS ≤3), 27 (84.4%) originated from Group B and only 5 (15.6%) from Group A.

3.3.8 Pre-TKR correlations between pain characteristics and QST

The preoperative PainDETECT score correlated with OA pain duration (Spearman's R= 0.6519, p<0.0001) and preoperative pain VAS score (Spearman's R= 0.7836, p<0.001).

Table 3.2 outlines the correlations between preoperative pain VAS scores to each of the pre-TKR QST assessments. The strongest correlation was seen between the hand-held algometry mean knee value PPT and preoperative pain VAS score.

Table 3.2 Correlations Preoperative QST Assessments to Preoperative VAS Scores

Preoperative Assessment	Pearson/Spearman's	Correlation (r)	P Value
Mean Knee PPT	Pearson	-0.6792	<0.0001
Tibialis Anterior PPT	Pearson	-0.5251	<0.0001
ECRL PPT	Pearson	-0.5115	<0.0001
Pinprick TSP	Spearman	0.5746	<0.0001
Cuff TSP	Spearman	0.4968	<0.0001
Cuff CPM	Spearman	-0.3403	0.034*
Cuff PDT	Spearman	-0.02078	0.8644
Cuff PTT	Spearman	0.04225	0.7284

Pearson's correlation for parametric data and Spearman's correlation for non-parametric data. p<0.05 considered significant.

3.3.9 Correlations between pre-TKR and post-TKR pain characteristics and QST

Correlation analysis revealed that preoperative PainDETECT (R = 0.397, P = 0.003) (Fig 3.9), VAS (R = 0.413, p = 0.004), mean knee PPT (R = -0.262, p = 0.039) and pinprick TSP (R = 0.343, p = 0.010) were significantly associated with postoperative pain.

A linear stepwise regression, including preoperative significant associated parameters, found that preoperative PainDETECT was only independent factor associated with postoperative pain (crude coefficient: 0.132 (Standard error: 0.46), adjusted coefficient: 0.397 (t = 2.873), p= 0.006).

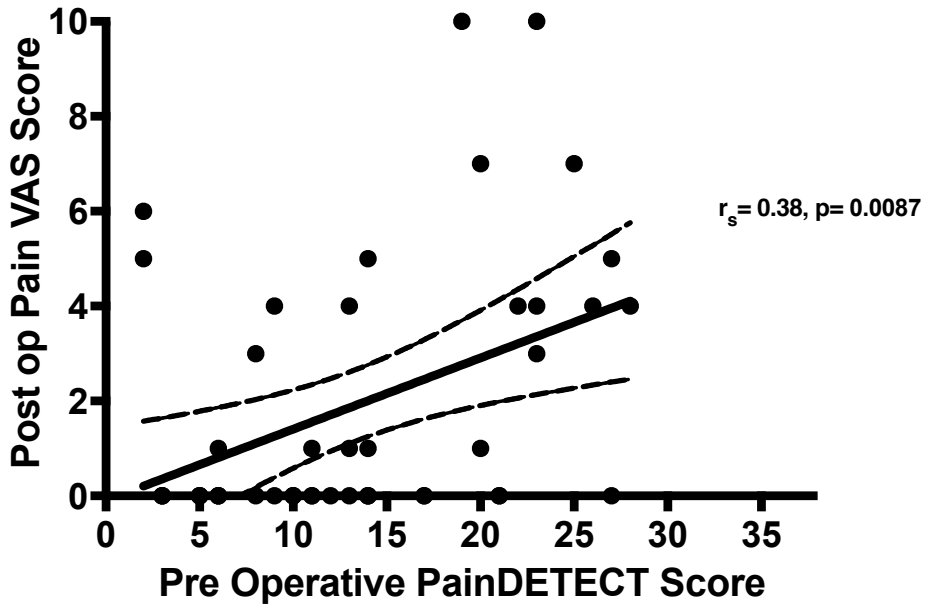


Figure 3.9 Scatter Diagram of Pre-TKR PainDETECT scores to Post-TKR Pain

Figure 3.9. Scatter diagram presenting correlations between preoperative PainDETECT score and postoperative knee pain intensity 6 months after TKR surgery. Dashed line represents 95% CI. (*) p<0.05 was significant.

3.4 DISCUSSION

This study found that knee OA patients with preoperative neuropathic pain like symptoms displayed higher knee pain intensity and duration, widespread hyperalgesia, facilitated TSP, and impaired CPM preoperatively. This group of patients also demonstrated higher postoperative pain intensities post-TKR compared with patients with less neuropathic pain symptoms and continued to have widespread hyperalgesia and facilitated

pin-prick TSP compared with healthy controls. Finally, this study found that preoperative PainDETECT scores independently predicted postoperative pain.

3.4.1 PainDETECT Questionnaire and Knee OA

Neuropathic pain like symptoms (burning, shooting, electric shock like pain and allodynia) have been reported in patients with knee OA (164, 180). Participants with knee OA awaiting TKR surgery in this study demonstrated a range of PainDETECT scores preoperatively however, 30% of OA patients had a PainDETECT score ≥19 suggesting they had features of neuropathic pain. Previous studies assessing pre-TKR OA patients has demonstrated that the percentage of patients with high PainDETECT scores ≥19 ranges from 5.4-34% indicating that our study findings are consistent with previously published data. A high PainDETECT ≥19 is however, not diagnostic of neuropathic pain and the questionnaire can only be used as an assessments tool to identify the symptoms in OA patients that are neuropathic pain-like. Treede *et al* proposed an initial grading system for neuropathic pain(169) which has recently been updated(181) and identified three categories of possible, probable and definite neuropathic pain. Possible neuropathic pain is based on the anatomical distribution of the pain as well as the history from the patient. Probable neuropathic pain is present when there is the presence of measurable sensory deficit in the region that is anatomically neuropathic. A definite grade of neuropathic pain requires the use of diagnostic imaging tests confirming a lesion or disease explaining the neuropathic pain.

3.4.2 Post-TKR Neuropathic Pain Like Symptoms

Neuropathic pain like symptoms have been reported previously in OA patients following TKR surgery, however, the reported estimates vary, ranging from 1-63% (5, 119, 182). Work by

Buvanendran *et al* has shown that six months post TKR surgery the rate of neuropathic pain characteristics was 5% in a prospective series of 120 patients (119) and Wylde *et al* reported the incidence of neuropathic pain characteristics was 6% three to four years after TKR in a retrospective study of 632 patients (5).

3.4.3 Reversal of Widespread Hyperalgesia after TKR surgery

Increasing evidence suggests that preoperative widespread deep tissue hyperalgesia in knee OA patients normalises in pain-free patients who respond well to TKR surgery compared with healthy controls (15, 183). A recent study has shown that OA patients with neuropathic pain like symptoms based on the PainDETECT showed widespread hyperalgesia with lower PPTs, and cold detection thresholds compared to OA patients without neuropathic symptoms (136). In the present study, OA patients with neuropathic pain like symptoms exhibited more widespread hyperalgesia and increased pain sensitivity than those OA patients with a more nociceptive or mixed pain phenotype. Post TKR no significant improvement was seen in the PPTs values at the knee, the tibialis anterior or ECRL muscles in those with neuropathic pain like symptoms unlike those OA patients with a nociceptive or mixed pain phenotype who exhibited significant improvement in their PPTs scores at the knee and the ECRL muscle 6 months post TKR. OA patients with a nociceptive or mixed pain phenotype normalised their PPTs at the ECRL post TKR when compared to healthy controls unlike the OA patients with neuropathic pain like symptoms who demonstrated continued widespread hyperalgesia with increased pain sensitivity over the ECRL muscle compared to the healthy controls. Differences in the PPTs between OA groups exceeded the reported MCID of 114kPa (184) at the knee, the tibialis anterior and ECRL muscles both pre and post-TKR surgery

indicating increased pain sensitivity in those OA patients with a neuropathic pain like phenotype.

3.4.4 Temporal Summation of Pain

Facilitated preoperative temporal summation of pain has been shown to be associated with chronic pain after TKR surgery in knee OA patients (17, 18). This study is the first study to evaluate temporal summation of pain using cuff algometry in OA subgroups based on neuropathic pain like symptoms. From the present study, normalization of TSP occurs in those patients that have nociceptive or mixed pain preoperatively as opposed to those patients that have neuropathic pain like symptoms, who continue to demonstrate facilitated TSP and continued post-operative pain post TKR surgery. Significant correlations were also seen between preoperative cuff TSP score and the self-report PainDETECT questionnaire indicating the association between the questionnaire and the central pain mechanisms in OA.

3.4.5 Conditioning Pain Modulation

Cuff algometry assessment is a valid user independent method of the assessment of pain sensitivity and CPM with several studies showing good reliability of this method of assessment of cuff CPM in healthy controls and chronic pain patients (157, 177, 185, 186). The present study found impaired CPM in those patients with neuropathic pain like symptoms preoperatively based on their high PainDETECT score compared with healthy controls. Studies have shown that an impaired CPM preoperatively is a predictor for the development of chronic post-operative pain and this study complements these findings (187, 188). The current data demonstrate that patients that exhibit neuropathic pain like symptoms preoperatively are a subgroup characterised by impaired CPM and are at risk of developing post-operative pain.

3.4.6 PainDETECT and Central Pain Mechanisms

This study has shown that the PainDETECT questionnaire reflects central pain mechanisms in OA pain. Patients with high PainDETECT scores pre-TKR demonstrated significantly lower PPTs at remote sites away from the knee, indicative of widespread hyperalgesia as well as facilitated TSP and impaired CPM. The correlation of QST measures used to identify the central integrative mechanisms and the PainDETECT questionnaire were also highly significant. Higher preoperative PainDETECT scores were associated with the development of chronic postoperative pain after TKR and this information is supplemented by the significant correlations seen between preoperative VAS pain scores, cuff TSP, mean knee PPTs values and postoperative VAS pain scores. The PainDETECT questionnaire may have an additional role as an added construct to QST measures alongside subjective VAS scores by allowing the identification a subgroup of OA patients with neuropathic pain like symptoms that are more likely to develop chronic postoperative pain after TKR surgery.

Moreton *et al* showed that knee OA patients with high PainDETECT scores demonstrated widespread sensitivity to PPTs (135) and this was complemented by work by Hochman *et al* who showed that 45.6% of eligible OA knee pain cases in their series had at least one sign of sensitised central pain mechanisms on QST assessment (widespread hyperalgesia, facilitated TSP or allodynia) (134). In 20 patients with hip OA awaiting total hip replacement surgery, Gwilym *et al* used functional brain MRI and a reduced version of the German Research Network on Neuropathic Pain (DFNS) QST protocol, to identify he relationship between PainDETECT score and signs of central mechanisms which were sensitized. Hip OA patients with preoperative PainDETECT scores above the sample median score showed significantly higher peri-aqueductal gray (PAG) activity

compared to those with low PainDETECT in response to punctate stimuli. The group with high PainDETECT scores also showed significantly higher pain intensity scores during punctate stimulation (120), indicating higher pain sensitivity. This observation that increased brainstem activation during punctate stimuli may play an important role in the neuropathic pain symptoms in OA (120). Further neuroimaging evidence may help explain the neural correlation of neuropathic pain in knee OA and continued pain after TKR surgery.

Facilitated TSP pre-TKR surgery has been shown to predict poor outcome and postoperative pain 12 months after TKR surgery. The current study did find preoperative TSP to be associated with postoperative pain but TSP was not an independent factor. The present study did find the preoperative PainDETECT scores to be an independent factor that predicts postoperative pain. This therefore suggests that the PainDETECT questionnaire may provide additional value at identifying patients with central changes of pain facilitation in knee OA and can be used as a tool to predict postoperative pain after TKR surgery.

3.4.7 Study Limitations

This explorative study is limited by the small sample size of the knee OA patients and it is important that the results of this study should be interpreted with care. This study did not assess for sensory deficits in knee OA which are diagnostic for neuropathic pain. Further research is required to explore the relationship between pain, neuropathic pain like symptoms identified using the PainDETECT questionnaire and the neurological assessment of sensory deficits in knee OA patients.

3.5 CONCLUSIONS

OA patients with neuropathic pain like symptoms demonstrated preoperative widespread hyperalgesia, facilitated temporal

summation and impaired condition pain modulation and this patient group reported higher postoperative pain intensities after TKR surgery.

As preoperative assessment of neuropathic pain like symptoms in knee OA patients are not undertaken by orthopaedic surgeons this study may aid clinicians in the decision-making process as to whether to embark on TKR surgery for that individual patient based on the likelihood of a successful outcome in terms of pain relief and satisfaction from the procedure. This may lead to improved medical advice being given to OA patients with a stratified treatment approach and ultimately personalised therapy. In future, some patients may be deemed unsuitable for TKR surgery with alternative treatments offered based on their individual sensory profile.

4 Study 2.Psychology, MRI and Neuropathic Pain

4.1 INTRODUCTION

Knee osteoarthritis (OA) pain has traditionally been attributed to localized tissue damage causing 'nociceptive pain'(32). However, increasing evidence suggests that a component of OA pain may be 'neuropathic' in origin with associations to the central pain mechanisms(134, 135, 159, 164, 180). Neuropathic pain is defined as a 'pain arising as a direct consequence of a lesion or disease affecting the somatosensory system'(169). The diagnosis of neuropathic pain is based on medical history and clinical examination with the identification of characteristic neuropathic symptoms (burning and electric shock sensations(163, 164)), somatosensory abnormalities (hyperalgesia, hypoesthesia and allodynia(110, 136)) and ancillary tests including imaging(169). The significant discordance between the radiographic OA severity (assessed by the Kellgren Lawrence score) and knee pain intensity (37) has identified additional OA pathological structures not visualised on conventional radiography but on MRI, including bone marrow lesions (BMLs), synovitis, and joint effusions that are highly correlated with pain(32, 48, 52, 62, 64, 67, 84, 85, 88, 128). These structural pathologies may contribute to the painful symptoms of neuropathic pain. Animal OA models have identified damaged sensory nerves containing neuropeptides in injured knee ligaments(189) the subchondral bone(170-172) and a pan-neuronal marker of nerve injury in the dorsal root ganglia(172). In humans, increased sensory nerve fibre densities have been located in menisci(173) and extrusion of the menisci has been visualised in OA patients with neuropathic pain using MRI(174). Synovitis may be linked to widespread neuronal sensitization in knee OA(128) and BMLs and joint effusion are associated with OA weight-bearing pain(190, 191), however the contribution of these pathologies to neuropathic pain and the associated symptoms is unclear and needs further assessment.

PainDETECT is a valid self-report questionnaire(179) with good internal consistency(175) that has been used to identify patients with neuropathic pain like symptoms in OA(134-136, 192, 193). Scores range from 0 to 38 with higher scores (≥19) indicating a likely neuropathic component (>90% probability)(179). One recent study suggested that PainDETECT was better than the Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS)(194) which is a more traditional neuropathic pain tool at assessing pain quality and the characteristics associated with augmented central pain processing in knee OA(135). Up to 20% of patients who undergo total knee replacement (TKR) surgery for their OA pain develop chronic postoperative pain in spite of objective measures of success.(5-13) Chapter 3 has highlighted that preoperative neuropathic pain like symptoms in knee OA patients are predictive for chronic post-TKR pain. Concurrent psychological abnormalities in OA such as depression, anxiety (195) and pain catastrophizing (196) have also known to be independent predictors of chronic post-TKR pain (10, 197).

The aims of this study were to:

1) determine whether BMLs, synovitis, and joint effusion are potential peripheral drivers for neuropathic pain like symptoms in knee OA,

2) assess the pain, psychological, knee function, and quality of life measures of OA patients with this pain phenotype and,

3) determine if any of those radiological, functional, pain, or psychological factors predicted outcomes six months after TKR surgery.

4.2 METHODS

4.2.1 Study Participants

Fifty OA patients awaiting TKR surgery for chronic knee pain (mean age 66.4 years [8.3 SD], 60% women) were recruited from orthopaedic clinics in Nottingham, United Kingdom. The knee OA patients were compared to twenty-two healthy volunteers (mean age 56.7 years [9.0 SD], 59% women) with no symptomatic OA or chronic pain condition. The patients and volunteers were the same people as studied in Chapter 3. Inclusion criteria for the OA patients specified males and non-pregnant females, aged over the age of 40 years with primary knee OA and awaiting TKR surgery. The patients had to have had no previous knee surgery and were able to give informed consent.

Knee OA patients with associated hip OA, psychiatric illness, active cancer, sensory dysfunction, contraindication to MRI or other chronic pain condition e.g. fibromyalgia, rheumatoid arthritis were excluded at the time of recruitment. Inclusion criteria for the healthy controls specified male and non-pregnant females over the age of 40 years who were able to give informed consent, and were free of any major medical, neurological or pain related conditions. All subjects were asked not take any analgesic medication 24 hours prior to the assessment.

4.2.2 Protocol

All subjects were asked to complete a set of self-reported questionnaires to assess for characteristics for neuropathic pain (PainDETECT), depression (Beck Depression Inventory-II), anxiety (State-Trait Anxiety), pain catastrophizing (Pain Catastrophizing Scale), knee pain and function (Oxford Knee Score), and quality of life (EQ-5D-5L). Subjective knee OA pain

scores were recorded by the Intermittent and Constant Osteoarthritis Pain (ICOAP) questionnaire (Fig 4.1).

After completing questionnaires, all subjects underwent a knee MRI scan to identify the pathological structural changes associated with pain in knee OA, which was scored by two trained observers on two occasions (6 weeks apart) using the semi-quantitative MRI Osteoarthritis Knee Score (MOAKS)(33). Knee radiographs were also taken for the OA patients (anterior-posterior, lateral and skyline views) as part of their routine preoperative care which were graded using the Kellgren-Lawrence (K-L) system for OA (Grades 0-4) (36).

On average 57 (12.8 to 116) days elapsed between the assessment procedures and TKR. Six months after TKR surgery, all OA patients were invited to return for follow up assessment to reassess their pain (ICOAP questionnaire), functional outcome (Oxford Knee Score) and quality of life (EQ-5D-5L) after surgery to determine the outcomes between groups following TKR surgery.

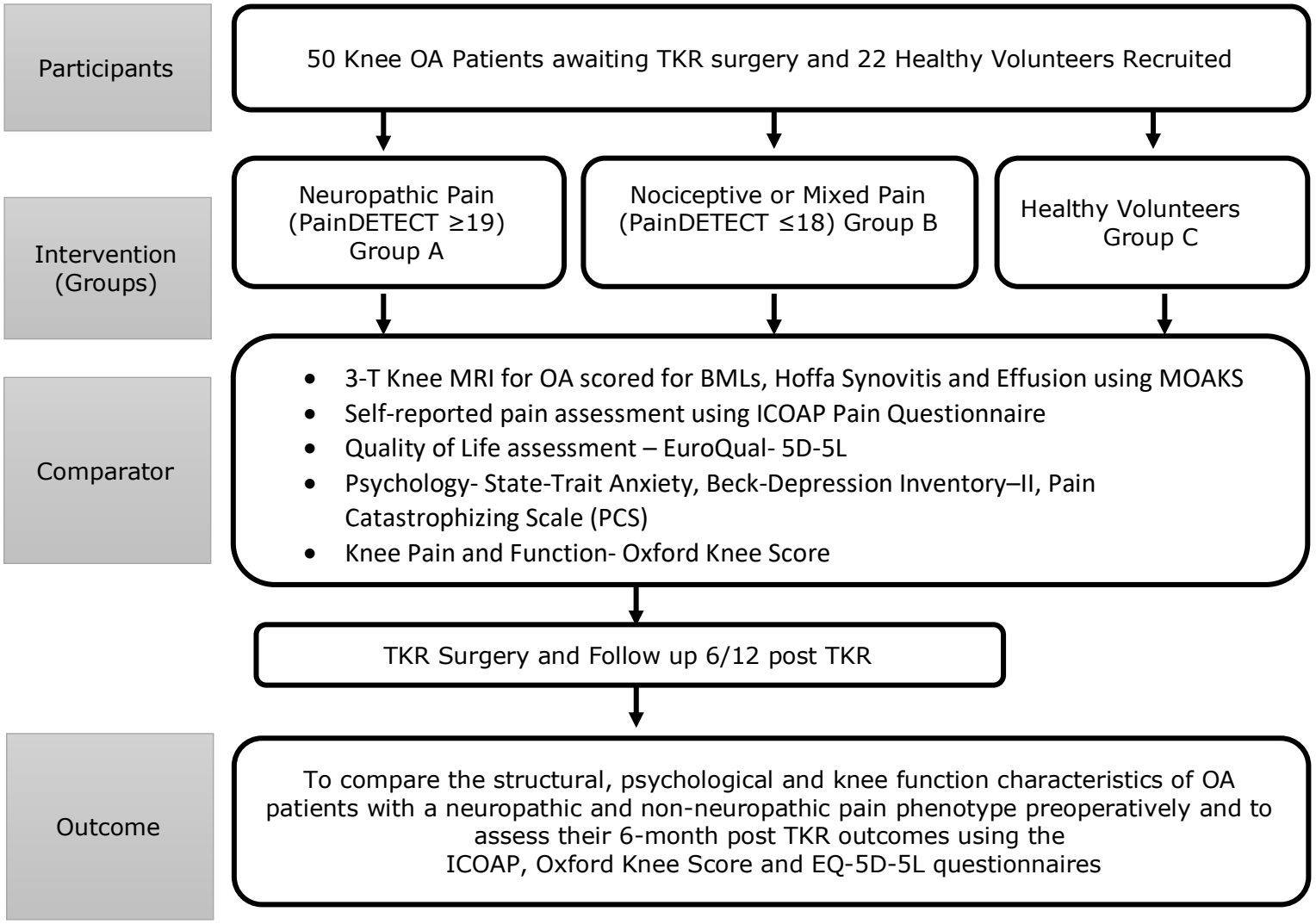


Figure 4.1 Study Flow Diagram Detailing Groups, Interventions and Outcomes

4.2.3 Questionnaires

The PainDETECT questionnaire is a validated self-report questionnaire, which has high sensitivity, specificity and good internal consistency and has been used increasingly to identify neuropathic pain like symptoms in OA studies (134-136, 180, 193). The questionnaire identifies potential neuropathic pain like symptoms and the pattern of pain experienced. Subjects were asked to record their responses in respect to their pain in the last four weeks when completing the self-reported questionnaire. The total score can range from 0 to 38 with a higher score (≥19) indicative of neuropathic pain like symptoms (>90% probability) and the lower score ≤12 as primarily nociceptive. Scores between 13 and 18 indicate a mixed pain pattern (179).

The Intermittent and Constant Osteoarthritis Pain (ICOAP) questionnaire assesses two types of OA pain(198) that were deemed most important by OA focus groups(199). 'Intermittent pain' describes severe but transient pain whereas 'constant pain' describes the continuous dull aching sensation of pain. It has been proposed that the total ICOAP score may be useful as a measure of knee pain severity(198). There are eleven items in the ICOAP questionnaire with five items addressing constant pain and six items assessing intermittent pain(198). The questionnaire can reliably identify pain intensity, as well as the impact of pain on sleep, mood and quality of life with overall scores ranging from 0 (no pain) to 100 (extreme pain)(135, 200). The ICOAP questionnaire has good internal consistency (198), test-retest reliability (200) and construct validity(198) when comparisons have been made to the Western Ontario and McMasters Universities Osteoarthritis (WOMAC) index pain scale(201). The ICOAP

questionnaire has been used successfully as an outcome measure following TKR surgery to assess pain relief associated with the procedure (202) and has been recommended for clinical trials by the Osteoarthritis Research Society International (OARSI)(203).

Spielberger State Trait Anxiety Inventory questionnaire is used to diagnose the levels of anxiety in subjects on the day of assessment (204). This 40 item self-report questionnaire measures both situational (state) and dispositional (trait) anxiety symptoms. All items are rated on a 4-point scale with overall scores ranging from 20-80. Higher scores suggest greater levels of anxiety (204). The questionnaire has been widely used in OA pain studies (120, 205) and also has good reliability (ICC r=.65 to r=.86) and validity in experimental pain studies (206).

The Beck Depression Inventory-II questionnaire is a psychometric test used to assess the severity of depression and has been used extensively to assess depression in OA patients (207-210). This 21-question self-report instrument assesses the presence or severity of depressed mood with each question scored from 0-3 using a four point Likert scale. The overall score ranges from 0-63 with higher scores indicative of severe depression. Scores ranging from 0-13 indicate minimal depression, scores from 14-19 represent mild depression, scores from 20-28 indicate moderate depression, and scores ranging from 29-63 represent severe depression (209, 210).

Pain catastrophizing is used to explain an exaggerated negative perception response to a painful stimulus (211). The Pain Catastrophizing Scale is a 13-item questionnaire where respondents are asked to rate each statement using a 5-point scale (0 = not at all) and 4 (all the time). The pain catastrophizing scale is made up of three subscales which

assess magnification, rumination and helplessness(211). The score ranges from 0-52 with higher scores suggestive of a more pain catastrophizing personality trait.

The Oxford Knee Score is a pain and function questionnaire (212)undertaken by all patients undergoing TKR surgery in the United Kingdom and used by the National Joint Registry (NJR) as a patient reported outcome measure following TKR surgery. The Oxford Knee Score consists of 12 questions that assess pain and function in the knee. Scores range from 0-48 with a higher score indicative of improved knee health with minimal or no pain and good function. A minimum improvement of five points (95% CI 4.4-5.5) has been recently shown to correlate with a clinically relevant improvement in pain and function after TKR surgery (213).

The EQ-5D-5L questionnaire is one of the most widely used patient reported outcome measures in the world and is a standardized assessment of generic health status within a population.(214) This 5-dimension questionnaire is used to assess health status and quality of life (215). The EQ-5D-5L questionnaire has two components: the description of health status and its evaluation. Health status in the description part is made of up five questions, which assess mobility, self-care, subject's usual activities, pain and mood. The respondents self-rate their level of severity for each of the 5 questions with a score from 1-5 for each question. For the evaluation part of the EQ-5D-5L questionnaire the respondents assess their overall health status using a visual analogue scale from 0-100, with poorest health scoring '0' and the best health state scoring '100'.

4.2.4 Pre-surgical Knee MRI Assessment

All subjects underwent a 3-Telsa knee MRI performed on a 3.0 T system (GE MR 750, GE Healthcare, Waukesha, WI)

using an 8-channel phased array transmit-receive knee coil. The knee was scanned in the coronal, sagittal and axial planes using a proton-density fat-suppressed sequence (2.5 mm thickness, spacing 0.3 mm, repetition time (TR) 3321 ms, effective echo time (TE) 41 ms, echo train length (ETL) 7 and pixel bandwidth (BW) 162) (47). MRIs were scored using the semi-quantitative MRI Osteoarthritis Knee Score (MOAKS, Fig. 2.7) for severity of Hoffa synovitis (Grade 0-3), effusion size (Grade 0-3) and bone marrow lesions (BML) for all 15 sub-regions of the knee (Score 0-45)(33) Figure 2.7. The MOAKS score is a semi-quantitative knee MRI score that has been introduced as an assessment tool that allows identification of pathological features associated with OA and can be used to monitor progression of the disease.(33, 158) All MRIs were independently graded by one senior musculoskeletal radiologist and one orthopaedic registrar trained to complete the MOAKS score. Each observer scored the blinded images independently and repeated the scoring 6 weeks later to assess for inter and intra observer reliability (see Chapter 2 Section 2.5.1).

4.2.5 Statistical analysis

The OA patients were sub-grouped based on the degree of preoperative neuropathic pain like symptoms identified using the PainDETECT questionnaire. Group A consisted of those OA patients with a high PainDETECT score ≥19 and Group B consisted of those OA patients with a more nociceptive or mixed pain phenotype with a lower PainDETECT score <19. The healthy controls with no OA or chronic pain position were assigned to Group C.

The data was analysed using Prism 7.0. Parametric data was presented as the mean and standard deviation with median and interquartile ranges (IQR) being expressed for data that

was non-parametric. In figures, the data is presented as the mean and standard error of the mean (SEM). Data normality was assessed using the D'Agostino-Pearson omnibus test. An analysis of variance (ANOVA) with Tukey post hoc tests for normally distributed data or Kruskal-Wallis ANOVA with Dunn's post hoc tests for the analysis of non-parametric data was conducted for preoperative comparisons for MOAKS BMLs, Hoffa Synovitis, Effusion Synovitis, EQ-5D-5L, Pain Catastrophizing Scale, Beck Depression Inventory-II, and State-Trait Anxiety questionnaires between Groups A, B and C. ICOAP pain scores, pain duration and the Oxford Knee Scores of the OA patients were assessed between Groups A and B using the unpaired t-test and Mann Whitney U tests, respectively. Differences in gender distribution were assessed using a chi-square test. Postoperative outcomes using the ICOAP, Oxford Knee Score and EQ-5D-5L six months after TKR surgery were assessed within groups using the Wilcoxon matched-pairs signed rank test and the paired T-test. Post TKR group comparisons of ICOAP, Oxford Knee Score and EQ-5D-5L results were analysed using the Mann Whitney U-Test and unpaired T-Test. Association between parameters was assessed by Pearson's correlation for parametric data and Spearman's correlation for non-parametric data. $P < 0.05$ was considered significant. Pre-TKR correlations between preoperative ICOAP pain scores and MRI MOAKS scores, psychological, pain and behavioural measures were assessed using pooled data from all three groups. The associations between post TKR ICOAP scores and preoperative MRI MOAKS scores, psychological, pain and behavioural measures characteristics were assessed using pooled data from Groups A and B.

Intra and inter-rater reliability for the MOAKS scoring was conducted using SPSS version 23 (SPSS, Inc., Chicago IL).

Reliability was assessed between the two observers and presented using interclass correlation coefficients (ICC) with the 95% confidence intervals.

4.3 RESULTS

4.3.1 Demographic data and preoperative pain profiles

Fifteen OA patients (30%) awaiting TKR surgery had a PainDETECT score of 19 or above indicating a potential neuropathic component to their OA pain (Group A), Table 4.1. Significant differences in age and BMI were seen between the OA groups and the healthy controls, however they were matched for gender (Chi-squared test, $p=0.818$). Group A patients reported significantly higher preoperative ICOAP pain scores compared to Group B (unpaired T-Test, $p<0.02$) and had suffered with OA pain for a considerably longer duration in years (Mann Whitney U Test, $P<0.02$). Radiological analysis of the two OA groups detailed that 49 patients (98%) had a KL Grade 3 or 4 for their knee OA with 53% of patients in Group A and 62% of patients in Group B having the highest Grade 4 changes. No significant differences were seen in K-L Grade between the groups (Mann Whitney U Test $p>0.05$).

Table 4.1 Patient and Healthy Volunteer Demographics

	Group A Neuropathic pain (n=15)	**Group B Non-Neuropathic Pain (n=35)**	**Group C Healthy Volunteers (n=22)**
PainDETECT Score (0-38)	23 (21-27)	10 (6-13)	0 (0-0.25)*
Age (years)	65.1 [8.9]	66.9 [8.0]	56.7 [9.0]*
Male:Female	5:10	15:20	9:13
Body Mass Index (BMI)	30 (27-33.4)	30 (27-39)	26 (24-28.3)*
Pain Duration in Months (Median and Range)	61.4 (54.5-86.4)	54.5 (36.4-61.4)*	N/A
Intermittent and Constant Osteoarthritis Pain Score (ICOAP) (0-100)	65.8 [18.1]	52.1 [16.3]*	N/A
Oxford Knee Score (0-48)	16 [5.3]	23.8 [7.6]*	N/A
Kellegren and Lawrence OA Radiological Grade (1-4) Numbers and (Overall %)	Grade 1 n=0 (0) Grade 2 n=1 (6.7) Grade 3 n=6 (40) Grade 4 n=8 (53.3)	Grade 1 n=0 (0) Grade 2 n=0 (0) Grade 3 n=13 (37.1) Grade 4 n=22 (62.9)	N/A

*Mean [Standard Deviation] or Median and (IRQ) are used to represent data. p<0.05 is significant**

3.2 Preoperative Bone Marrow Lesion, Hoffa Synovitis and Effusion Size scores

The intra-rater reliability with a 6-week interval for MOAKS scoring the knee MRI's for BMLs, Hoffa synovitis and effusion size for observer 1 (ICC and 95% CI) were 0.94, (0.84-0.98), 0.96 (0.89-0.99) and 0.98 (0.94-0.99); and observer 2 were 0.97 (0.90-0.99), 0.85, (0.57-0.95) and 0.93 (0.81-0.98). The inter-rater reliability between observer 1 and observer 2 for BMLs, Hoffa synovitis and effusion size was 0.93 (0.78-0.98), 0.82 (0.45-0.94) and 0.92 (0.77-0.97). On occasions

when there was disagreement between scores these were each discussed between the observers and the final decision was made by the senior musculoskeletal radiologist.

Increased MOAKS BMLs scores (Kruskal-Wallis Test: H=30.18, p<0.0001; Fig. 4.2) were found in Group A (Dunn's: p<0.001) and Group B patients (Dunn's: p<0.001) compared with group C. Increased MOAKS Hoffa synovitis in the knee (ANOVA: F=7.0, p=0.002, Fig. 4.3) was present in Group A (Tukey: P<0.003) and Group B (Tukey: P<0.012) compared with Group C (ANOVA: F=7.0, P=0.002) and increased MOAKS effusion synovitis was visualised in Group A (Dunn's: p<0.001) and Group B (Dunn's: p<0.001) patients compared to Group C (Kruskal-Wallis Test: H=29.24 p<0.0001, Fig. 4.4). No significant differences were detected between Groups A and B OA patients for BMLs, Hoffa Synovitis or effusion size using the MOAKS score.

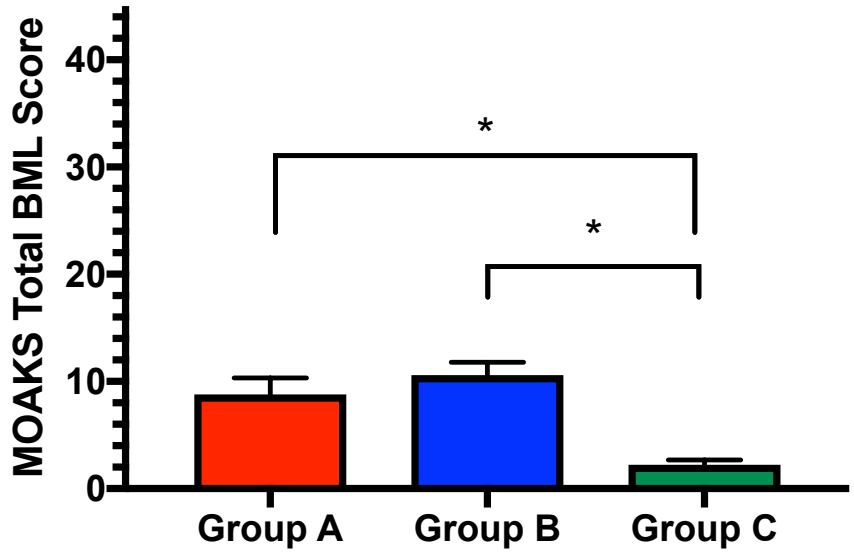


Figure 4.2 MOAKS MRI Total BML Score Results

Figure 4.2. MOAKS MRI Bone Marrow Lesion (BMLs) Scores (0-45) (Mean +/-SEM) for 50 OA patients (Group A, n=15; Group B, n=35) and 22 healthy volunteers (Group C). Difference between groups are indicated (p<0.05). Kruskal-Wallis ANOVA by Ranks Test*

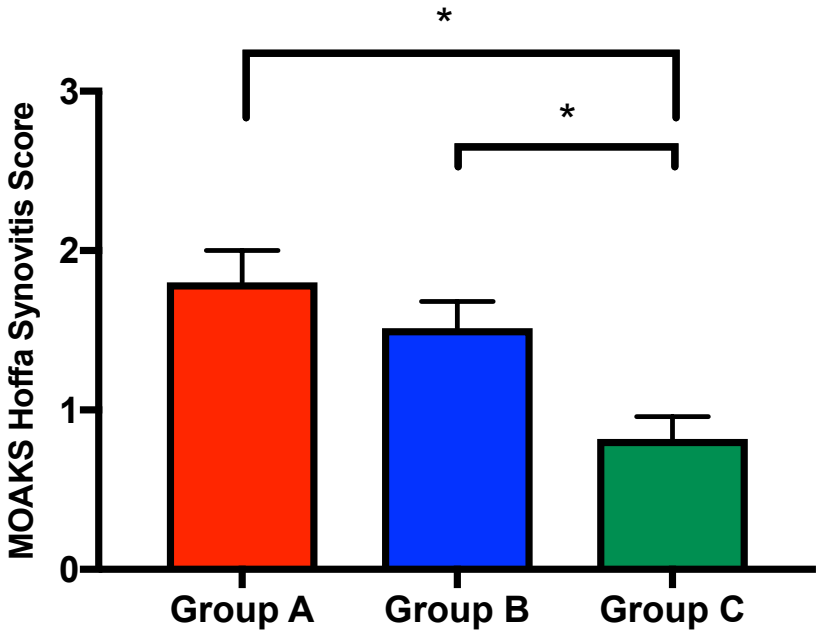


Figure 4.3 MOAKS MRI Hoffa Synovitis Results

Figure 4.3. MOAKS MRI Hoffa Synovitis Scores (0-3) (Mean +/-SEM) for 50 OA patients (Group A, n=15; Group B, n=35) and 22 healthy volunteers (Group C). Difference between groups are indicated (p<0.05) ANOVA*

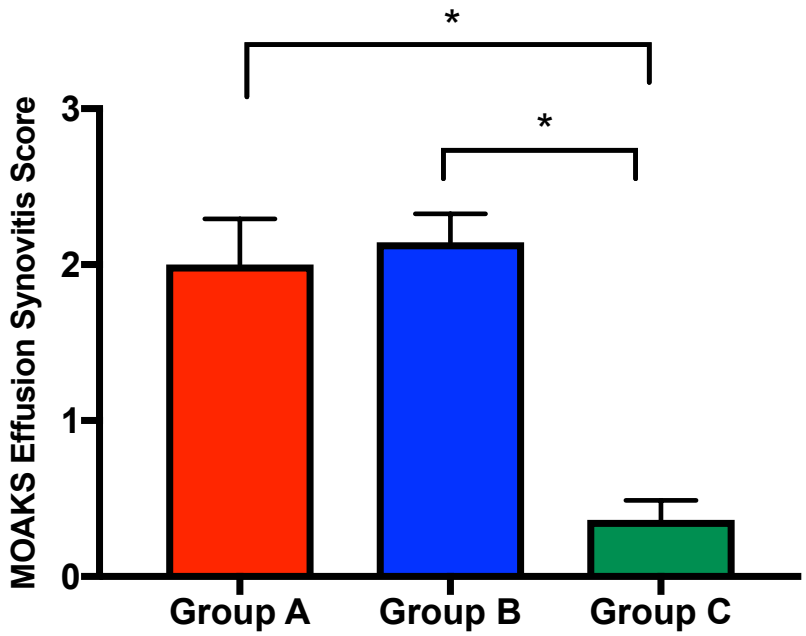


Figure 4.4 MOAKS MRI Effusion Synovitis Results

Figure 4.4 MOAKS MRI Effusion Synovitis Scores (0-3) (Mean +/-SEM) for 50 OA patients (Group A, n=15; Group B, n=35) and 22 healthy volunteers (Group C). Difference between groups are indicated (p<0.05) Kruskal-Wallis ANOVA by Ranks Test*

4.3.2 Preoperative Psychological, Behavioural, and Quality of Life

OA patients in both groups (Group A: Dunn's: $p<0.0001$; Group B: Dunn's: $p<0.0005$) showed higher pain catastrophizing scale scores compared to Group C (Table 4.2; Kruskal-Wallis Test: $H=17.67$, $p<0.0001$). Depression assessed by the Beck Depression Inventory (BDI-II) in OA Group A (Dunn's: $p<0.0001$) and OA Group B (Dunn's: $p<0.0003$) were also higher compared to Group C (Kruskal Wallis Test: $H=26.87$: $p<0.0001$). Group A patients demonstrated significantly higher state anxiety (Kruskal Wallis Test: $H=14.86$, $p<0.0001$) compared to Group B patients (Table 2, Dunn's: $p<0.006$) as well as Group C controls (Dunn's: $p<0.001$). No significant differences were seen between the state anxiety scores of Group B patients and Group C. Trait anxiety scores were also higher in Group A (Tukey: $p<0.0143$) compared with Group C (ANOVA: $F=4.19$, $p<0.02$)

Group A patients with neuropathic pain like symptoms demonstrated significant lower ($p=0.0007$, Unpaired T-Test) Oxford Knee scores pre-TKR surgery compared to Group B patients indicative of significantly worse preoperative knee pain and function Table 4.1.

Quality of life EQ-5D-5L index scores were different among groups (Kruskal Wallis Test:$H=47.25$, $p<0.0001$) with Group A ($P<0.0001$) and Group B ($P<0.0001$) OA patients having lower than Group C. The EQ-5D-5L VAS score of health status showed that both Group A ($P<0.0001$) and Group B ($P<0.002$) OA patients had significantly worse preoperative health status scores than Group C (Table 2; ANOVA, $F=11.8$, $p<0.0001$) Table 4.2.

Table 4.2 Psychology and Quality of Life Results

	Group A N= 15	**Group B N= 35**	**Group C N=22**	**Comparison**	**p value**
Pain Catastrophizing Scale (PCS)	16 (9-28)	12 (5-23)	3 (0-9)	A-B A-C B-C	0.3380 0.0002* 0.0054*
Beck Depression Inventory (BDI)	10 (5-16)	5 (2-10)	0 (0-2.25)	A-B A-C B-C	0.1562 <0.0001* 0.0003*
STATE Anxiety	39 (34-45)	29 (24-36)	27 (20.8-32.8)	A-B A-C B-C	0.0062* 0.0005* 0.7966
TRAIT Anxiety	37.7 [11.1]	31.7 [9.8]	28.5 [8.0]	A-B A-C B-C	0.1126 0.0143* 0.4298
EQ-5D-5L Index Score	0.29 (0.21-0.53)	0.63 (0.41-0.70)	1 (1-1)	A-B A-C B-C	0.0009* <0.0001* <0.0001*
EQ-5D-5L VAS Score	59.1 [25.9]	69.2 18.0]	86.9 [8.9]	A-B A-C B-C	0.1598 <0.0001* 0.0017*

*Comparison of OA Patients with (PainDETECT ≥19) with distinct neuropathic pain (Group A) to those with unclear or nociceptive pain (Group B) and healthy volunteers (Group C). Mean [standard deviation] or Median (IQR) values are presented. P-values is based on the Tukey post hoc tests for normally distributed data and Dunn's post-hoc tests for non-normally distributed data. p<0.05 is significant**

4.3.3 Postoperative Follow Up and Pain Outcomes

Six months following TKR surgery, forty-six patients returned for follow up reassessment (92%). One patient was excluded due to a subsequent fracture in the first 2 months following

TKR surgery. We were unable to contact the three remaining patients postoperatively. The final 46 patients consisted of 13/15 Group A patients and 33/35 Group B patients. Group A patients reported significantly higher ICOAP (22.7 [3.25-34.8]) scores post-TKR compared to Group B patients (4.5, [0-14.8], Mann Whitney U-Test, $P<0.01$) indicating a higher subjective constant and intermittent pain in the knee post TKR surgery.

4.3.4 Oxford Knee Score Post-TKR

Both OA groups A and B showed improvement in Oxford Knee Score post-TKR (Group A, $p=0.0002$, Group B, $P<0.0001$, Wilcoxon matched-pairs signed-rank test). The improvement in Oxford Knee Score post-TKR was higher in Group A (18.2 ± 10.5) compared to group B (16.3 ± 8.3), however Group B patients reported overall significantly higher post TKR Oxford Knee Score ($p=0.031$, Mann Whitney U-Test), Table 4.3.

The pre and post TKR results for both OA groups are shown in Figure 4.5

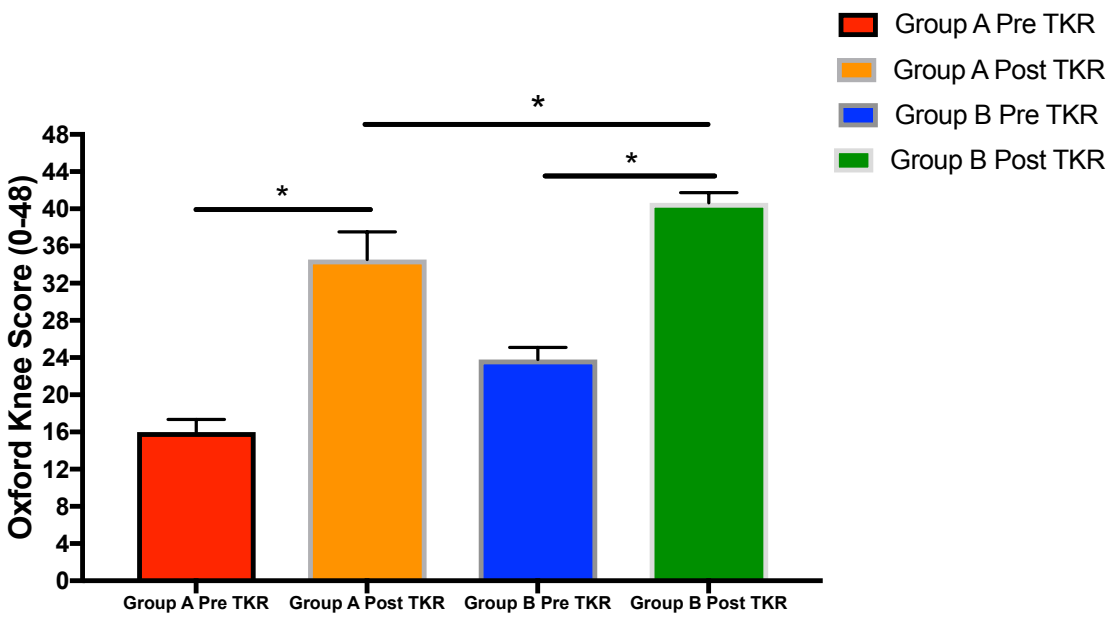


Figure 4.5 Pre and Post-TKR Oxford Knee Scores in Groups A and B

Figure 4.5. Oxford Knee Score results for both OA Groups (Mean +/-SEM) before and 6 months after TKR surgery. Difference between groups are indicated (p<0.05)*

Table 4.3 Post-TKR ICOAP, EQ-5D-5L and Oxford Knee Score Results

	Group A	Group B	P Value
ICOAP	29.5(8.0-41.1)	6.8 (0-15.9)	0.006
EQ-5D-5L Index Score	0.71 (0.60-0.79)	0.809 (0.69-1)	0.026
EQ-5D-5L VAS Score	68.1 (25.3)	82.0 (13.7)	0.021
Oxford Knee Scores	35 (315-43.5)	41 (37-46)	0.031

*Table 4.3. Six-month post-TKR ICOAP, EQ-5D-5L Index and VAS and Oxford Knee Scores in patients with distinct preoperative neuropathic pain (Group A) to those with unclear or nociceptive pain (Group B). Mann Whitney U-Test (median and IQR) for non-parametric data, Unpaired t-test (median and SD) for parametric data. p<0.05 considered significant**

4.3.5 Quality of Life (EQ-5D-5L) Assessment Post TKR

Post-TKR improvement in the EQ-5D-5L index values were seen in both groups (Group A, P<0.0002, Group B, P<0.0001, (Wilcoxon matched-pairs signed-rank test), (Table 4.3). Moreover, the EQ-5D-5L index value scores post-TKR were lower in Group A patients compared to Group B patients (Mann Whitney U-Test, P<0.0256). Post-TKR, Group A (P<0.001) and Group B patients (P<0.0017) had worse overall health assessed using the EQ-5D-5L VAS score compared to Group C (ANOVA: F=11.8, P<0.0001). Post TKR Group B patients significant showed improvement in their EQ-5D-5L VAS (P<0.001) compared to Group A patients who failed to significantly improve post TKR surgery (Paired T-

Test). Significant difference in post TKR EQ-5D-5L VAS score between Groups A and B was demonstrated post-TKR (P=0.0207, Unpaired t-test).

4.3.6 Correlation of Pre-TKR Pain to Psychological and MOAKS scores

Table 4.4 outlines the associations between the specific questionnaires with preoperative knee pain intensity. Significant correlations were seen with Pain Duration (R=0.655, p<0.0001) and questionnaires PainDETECT (R=0.778, p<0.0001), OKS (R=-922, p<0.0001), EQ-5D-5L index (R=-0.844, p<0.0001), EQ-5D-5L VAS (R=-0.607, p<0.0001) and State Anxiety (R=0.484, p<0.0001), Trait Anxiety (R=0.405, p=0.0004), Pain Catastrophizing Scale (R=0.573, p<0.0001), Beck Depression Inventory (R=0.676, p<0.0001), MOAKS BML score (R=0.530, p<0.0001), MOAKS Hoffa Synovitis (R=0.334, p=0.004), and MOAKS Effusion Synovitis (R=0.481, p<0.0001), with the self-reported ICOAP pain score.

Table 4.4 Correlation Pre-TKR ICOAP scores to Psychology, and Knee MRI Results

Preoperative Assessment	**Pearson's/ Spearman's**	**Correlation (r)**	**p Value**
Pain Duration	Pearson's	0.6545	<0.0001
PainDETECT	Pearson's	0.7781	<0.0001
Oxford Knee Score	Pearson's	-0.844	<0.0001
EQ5D-5L Index	Pearson's	-0.6074	<0.0001
EQ-5D-5L VAS	Pearson's	0.484	<0.0001
State Anxiety	Spearman's	0.4047	0.0004
Trait Anxiety	Spearman's	0.5733	<0.0001
Pain Catastrophizing Scale	Pearson's	0.6545	<0.0001
BDI	Spearman's	0.6764	<0.0001
BMLS	Spearman's	0.5296	<0.0001
Hoffa Synovitis	Pearson's	0.3338	0.0042
Effusion Size	Spearman's	0.4808	P<0.0001

Table 4.4. Association between preoperative pain duration and other pain, psychological and behavioural questionnaires and MOAKS MRI scores to OA patients preoperative knee pain intensity (ICOAP) by Pearson's correlation for parametric data and Spearman's correlation for non-parametric data. p<0.05 considered significant.

4.3.7 Correlation of Post-TKR Pain Scores to Pre-TKR Psychology

Table 4.5. describes the correlations between postoperative ICOAP knee pain scores and the self-reported questionnaires assessed prior to TKR surgery with the aim of identifying if any of these pain, psychological or functional parameters are strongly associated with the development of chronic postoperative pain after TKR. Significant correlations were seen between the preoperative PainDETECT (R=0.327, p=0.027), and EQ-5D-5L Index scores (R=-0.381, p=0.009) questionnaires and six-month post TKR knee pain intensity.

Table 4.5 Correlation between Post TKR Pain and Questionnaires and MRI Scores

Preoperative Assessment	Pearson's/ Spearman's	Correlation (r)	p Value
PainDETECT	Spearman's	0.3268	0.0266*
OKS	Spearman's	-0.2296	0.1249
EQ5D-5L Index	Spearman's	-0.3814	0.0089*
EQ-5D-5L VAS	Spearman's	-0.2584	0.0829
STATE Anxiety	Spearman's	0.1726	0.2515
Trait Anxiety	Spearman's	0.1624	0.2810
Pain Catastrophizing Scale	Spearman's	-0.03457	0.8196
BDI	Spearman's	0.2282	0.1271
BMLS	Spearman's	-0.1851	0.2180
Hoffa Synovitis	Spearman's	-0.098	0.5130
Effusion Size	Spearman's	-0.1268	0.4009

Association between preoperative questionnaires, MOAKS Knee MRI scores and postoperative knee pain intensity (ICOAP scores) by Pearson's correlation for parametric data and Spearman's correlation for non-parametric data. $p<0.05$ considered significant.*

4.3.8 Correlation of Pre-TKR PainDETECT Scores to Post-TKR Outcomes.

Significant correlations were seen assessing the preoperative PainDETECT scores for all OA patients to the postoperative ICOAP (R=0.3268, p=0.027), postoperative Oxford Knee Score (R=-0.3626, p=0.013) (Fig 4.6), postoperative EQ-5D-5L Index Score (R=-0.3946, p<0.0001) and postoperative EQ-5D-5L VAS score (R=-0.307, p=0.038).

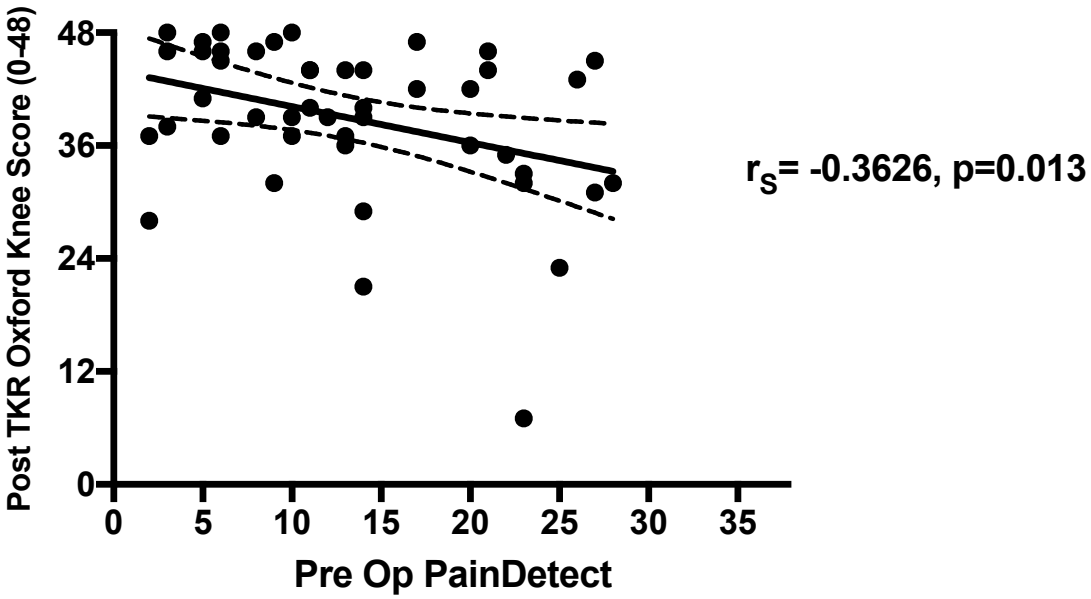


Figure 4.6 Correlation of Pre-TKR PainDETECT score and Post-TKR Oxford Knee Score

Figure 4.6. Scatter diagram presenting correlations between preoperative PainDETECT score and postoperative Oxford Knee Score 6 months after TKR surgery. Dashed line represents 95% CI. (*) P<0.05 was significant.

4.4 DISCUSSION

This study has identified that knee OA patients with preoperative neuropathic pain like symptoms have a less favourable outcome to TKR surgery displaying higher postoperative pain intensity, lower Oxford knee Scores, and lower quality of life scores compared to knee OA patients with a more nociceptive or mixed pain phenotype. Higher

PainDETECT scores and lower EQ-5D-5L index scores preoperatively were predictive for development of chronic postoperative pain after TKR surgery.

4.4.1 Preoperative PainDETECT and Neuropathic Pain

Subgrouping OA patients based on radiological(37, 138) and more recently using pain sensitization assessments(16, 17, 105, 133) has successfully identified subgroups of patients that report differing pain qualities, characteristics and outcomes after TKR surgery(16-18). The PainDETECT questionnaire has been used to identify subgroups of knee OA patients that report symptoms of neuropathic pain(134-136, 174). A recent systematic review suggested that 23% of patients with knee or hip OA have evidence of neuropathic pain(216). Our study is consistent with these finding with 30% of our patients demonstrating significant neuropathic symptoms. The PainDETECT questionnaire used alone is not diagnostic for neuropathic pain and the International Association for the Study of Pain (IASP) has recently developed a grading system for neuropathic pain that has identified three categories of 'possible', 'probable' and 'definite' neuropathic pain(181). 'Possible neuropathic pain' is based on the history and the distribution of pain in a neuro-anatomically plausible region. 'Probably neuropathic pain' is identified when the pain is associated with sensory signs in the same neuro-anatomical distribution and 'definite neuropathic pain' is present when diagnostic tests confirming a lesion or disease within the somatosensory system explain the pain.

4.4.2 Neuropathic pain in OA

Increasing evidence from preclinical models suggests the origin and progression of neuropathic pain in knee OA is

associated with increasing structural damage within the joint. Rabbit models have demonstrated phenotypic changes in peripheral nerves in ligaments containing neuropeptides consistent with peripheral neuropathy.(217) Rodent models have demonstrated increased expression of ATF-3 (activating transcription factor-3) within the dorsal root ganglia, a sensitive pan-neuronal marker of neuronal injury (172) as well as injury to peripheral nerves with subchondral bone(170-172). In humans, the use of MRI in has identified other structures, not visualised on traditional radiography, that are correlated with knee OA pain. BMLs are biomechanically induced lesions which is reflected in finding the histological changes of fibrosis, microfracture and necrosis and are associated with subchondral bone remodelling.(1) and their presence has been strongly associated with knee pain(62, 64, 67, 84), radiographic progression(63), increase cartilage loss(52, 65) and the increased likelihood of TKR surgery. Histological studies observing the subchondral bone in OA has identified increased osteoclastic activity(172) and large reactive osteoblasts(218) within these regions secondary to increased subchondral turnover. Osteoclast induced injury to peripheral nerves within the subchondral bone may be a potential mechanism of nerve damage leading to the development of neuropathic pain and the associated symptoms. A range of osteoclast inhibitors have demonstrated analgesic efficacy in preclinical studies, including bisphosphonates(219), osteoprotegerin(220) and cathepsin K inhibitors(221). In human OA studies an RCT identified single infusion of a bisphosphonate (zoledronate) resulted in significant pain reduction and BMLs(86). Synovitis is inflammation of the synovium and plays a critical role in the development of painful symptoms and disease progression in knee OA(87, 88, 222-224). Synovitis and effusion cause pain

by activation of sensory nerve ending within the synovium, from osteophytes or secondary from the release of prostaglandins, leukotrienes, neuropeptides and cytokines driving inflammation within the joint. Semi-quantitative MRI assessment of synovitis within the Hoffa fat pad region has been associated pain severity(88, 225) and pain fluctuation(84) in knee OA indicating this imaging modality and semi-quantitative scoring of synovitis may be useful in identify OA patients with different pain phenotypes. Our study is consistent with these findings in that the OA patients with pain demonstrated significantly higher overall MOAKS BML, Hoffa synovitis and effusion-synovitis scores compared to pain-free healthy controls. However, for all 3 variables there was no significant difference seen between those OA patients with neuropathic pain like symptoms and those OA patients nociceptive or mixed pain phenotype stratified using the PainDETECT questionnaire. Roubille *et al* found that meniscal extrusion to the strongest risk factor for neuropathic pain in knee OA but showed no difference in BMLs, synovitis membrane thickness or effusion size based on knee OA patients that were stratified using the PainDETECT questionnaire (174) and these findings are consistent with our current study. Both studies had a relatively small sample size and in our study all OA patients had end stage OA awaiting TKR surgery. We therefore speculate that in advanced disease in OA where denuded bone surfaces are abutting one another, alongside BML development and the presence of synovitis both nociceptive and neuropathic pain mechanisms may be active making the discrimination between specific pain mechanisms and the associated structural changes more difficult to entangle using a questionnaire. Contrasting to this, Petersen *et al* found that end-stage OA patients prior to TKR displayed different degrees of synovitis but similar pain

scores, which could indicate that a simple pain phenotyping approach is problematic(138). A larger, longitudinal based study with early and advanced OA patients with differing grades and severity of the disease may help identify MRI structural changes (BMLs, synovitis and effusion size) between pain phenotypes.

4.4.3 Pre-TKR Neuropathic Pain, Psychology and Quality of Life

A recent study has shown that knee OA patients with neuropathic pain like symptoms reported increased knee pain, widespread hyperalgesia, pain sensitivity and more functional impairment than OA patients without these neuropathic symptoms(136) which is consistent with our findings. Progressive pain from knee OA disturbs patients' knee function and associated movement(226) and can result in loss of work and income resulting in significant psychological affects including mood, sleep and quality of life. (24, 227) Knee OA pain is a sensory and emotional experience and a negative affect is a reflection of anxiety and depression which is strongly associated with musculoskeletal pain.(228) We identified significant correlations between preoperative ICOAP pain scores with pain duration, anxiety, depression, pain catastrophizing and quality of life indicating the important association between emotional and psychological parameters and self-reported pain. Pang *et al* reported that knee pain severity has a greater impact on quality of life than other joint symptoms or radiographic severity of OA.(25) Mayer-Roseberg *et al* found that patients with chronic neuropathic pain had significantly impaired quality of life(229) and Valdes *et al* demonstrated neuropathic pain in patients with OA led to impaired quality of life(165) which complements the findings in our study. Preoperative anxiety, depression and pain

catastrophizing have all been reported as psychological traits that are predictive for the development of chronic postoperative pain after TKR surgery.(10, 197) We found that knee OA patients with neuropathic pain like symptoms preoperatively had significantly higher state anxiety compared to knee OA patients without neuropathic symptoms. Work published by Mesci *el al* supports our findings where anxiety and depression scores were also significantly higher in OA patients with a neuropathic pain phenotype.(230) As high preoperative anxiety is linked to the developed of chronic postoperative pain after TKR surgery(9, 10), pharmacological modulation with anxiolytic treatments or with cognitive behavioural therapy may reduce the incidence of postoperative pain in patients with neuropathic pain pre-TKR. Studies have shown treating anxiety can reduced the emotional aspect of musculoskeletal pain(231) but can also improve impaired condition pain modulation which is linked to central sensitization in patients with neuropathic pain(232), thereby potentially improving outcomes for patients post-TKR with this pain phenotype.

4.4.4 Post-TKR Neuropathic Pain, Psychology and Quality of Life

We have identified that patients with preoperative neuropathic pain like symptoms report high postoperative knee pain intensity measured with the ICOAP score ($p=0.006$), lower Oxford Knee Scores ($p=0.0031$) and lower EQ-5D-5L index scores ($p<0.03$) six months post TKR than OA patients without neuropathic symptoms. Preoperative PainDETECT ($r=0.327$, $p<0.03$) scores and EQ-5D-5L index ($r=-0.381$, $p<0.009$) were significant correlated with postoperative pain after TKR surgery.

4.4.5 Limitations

This explorative study is limited by the sample size and as such the MRI findings must be interpreted with care. A larger multicentre study with patients with early and advanced disease will allow conformation of these findings. This study did not assess for sensory deficits and no diagnostic imaging tests were undertaken to confirm a definite diagnosis of neuropathic pain in our patients. Further research is required to explore the relationship between neuropathic pain like symptoms and the neurological assessment of sensory deficits in knee OA patients.

4.5 CONCLUSIONS

The present study demonstrated that a subgroup of patients with knee OA that report neuropathic pain like symptoms experience increased knee pain intensity, anxiety levels, poor knee function and lower quality of life measures prior to TKR surgery. The same patients respond less favourably to TKR surgery with increased knee pain intensity, continued impaired knee function and reduced quality of life.

5 Study 3. Predicting Chronic Postoperative Pain After TKR Using Imaging, QST and Psychology

5.1 INTRODUCTION

Total knee replacement (TKR) surgery is considered a safe, effective surgical intervention to improve pain and function in patients with painful end stage osteoarthritis (OA) of the knee. In the United States, the number of TKR procedures has dramatically increased in recent years from 31.2 per 100,000 person-years in the period of 1971-1976 to 220.9 per 100,000 person years between 2005-2008.(233) Projections of incidence of primary TKR in the USA are expected to further increase by 673% to 3.5 million procedures by 2030(130) due to our ever increasing ageing population and the rising numbers of obesity putting further financial and economic pressure on our already overstretched health care systems in the developed world. Despite significant improvements in implant design, longevity and survival as well as successful surgeon-related outcome measures including infection rates, it is still worrying that up to 20% of patients continue to suffer debilitating chronic postoperative pain after TKR in spite of objective measures of surgical success.(5-13, 20) The potential number of patients suffering with chronic pain after TKR surgery is alarming and improved methods to preoperatively predict which patients will and will not respond to TKR surgery are essential but represent a major challenge and remain an elusive goal for orthopaedic surgeons worldwide.

The mechanisms by which knee OA pathology causes pain remains unclear but involve complex interplay between peripheral, structural and biochemical changes within the joint, pain sensitization within the spinal cord and brain as well as psychosocial factors involving distress, pain catastrophizing, depression and anxiety.(1) Whether post TKR pain is a consequence of new pathological pain mechanisms that are present as a result of the surgery and the prosthesis, or the continuation and persistence of OA pain mechanisms that fail to

resolve post TKR remains uncertain and requires further investigation.

Increasing sensory gain within the pain system is a marker of pain sensitization and recent studies have suggested OA patients with increased pain sensitivity are at higher risk of developing chronic postoperative pain after TKR.(16, 17)

Traditionally knee OA has been considered a non-inflammatory arthritic disease but recent MRI studies have demonstrated significant synovitis with inflammation and effusion within the joint.(45, 60, 84, 87, 88, 138) This imaging modality has also identified structures associated with the pathogenesis of OA not visualised on conventional radiographs but highly associated with pain called subchondral bone marrow lesions (BMLs), which are thought to represent micro-traumatic lesions secondary to mechanical injury and remodelling at the osteochondral junction. Both BMLs and synovitis are richly innervated by nociceptors and have been strongly associated with pain in knee OA.(1) The development of pain sensitization in knee OA has often been attributed to the persistent nociceptive input from the knee driving central neural changes with the brain and spinal cord resulting in pain amplification, widespread hyperalgesia and allodynia or of which are the characteristic hallmarks of central pain facilitation.(2, 14) Recent work by Neogi *et al* has demonstrated the association of synovitis with the widespread pain sensitization in knee OA patients.(128) TKR surgery removes the diseased cartilage and subchondral bone and restores a biomechanical and chemical protective shield between the synovial cavity and the underlying subchondral bone. However, limited resection of the synovium is often undertaken by orthopaedic surgeons during the operation due to the major concerns of developing a postoperative haemarthrosis of the knee due to the high vascularity of the synovial tissue. Knee MRI is not routinely requested by clinicians treating OA patients

undergoing TKR surgery therefore many surgeons are currently unaware of the presence or absence of BMLs in their patients prior to TKR surgery. It is therefore unknown whether residual or new BMLs or the continued presence of intact or regenerative synovitis post TKR may continue to provide the nociceptive drive which contribute to the maintenance of pain sensitization and chronic postoperative pain after surgery. Conventional post TKR MRI of the knee in chronic postoperative pain patients is often limited due to the significant metal artefacts produced from the prosthesis, resulting in signal loss and distortion particularly at higher field strengths. With the introduction of new metal artefact reduction MRI sequences on the 3-Tesla MRI platform significant reductions in susceptibility artefact around metal implant can be observed(47, 147, 234) therefore it may be possible to detect postoperative synovitis and BMLs and to identify their association with postoperative pain and continued pain sensitization. If present, these continued structural abnormalities may act at as therapeutic target and change orthopaedic practice to reduce the overall incidence of postoperative pain after TKR surgery.

Temporal summation of pain (TSP), the perception of increasingly augmented pain evoked by repetitive noxious stimuli (≥0.33Hz) and is a measure of central sensitization.(14, 105, 113, 114, 235) TSP has recently been shown to predict postoperative pain after TKR independent of preoperative knee pain intensity.(17) Understanding the neural mechanisms involved in temporal summation of pain may help explain why up to 20% of patients undergoing TKR surgery develop persistent post-operative pain. Recently, new advances in functional brain MRI (fMRI) has allowed a better understanding of the pain pathways and anatomical alterations seen in OA patients suffering with chronic pain.(120, 154, 236) Functional MRI an imaging modality that could identify the neural

correlation of temporal summation in OA patients using a painful pressure cuff stimulus to characterise the neural signature of central sensitization. Functional MRI may identify imaging biomarkers in the brain in OA patients related to central sensitization of pain and has the ability to detect whether any preoperative brain related changes in response to chronic OA pain normalise in those patients that are pain free after TKR surgery and highlight the functional brain activity in those patients that continue report persist postoperative pain after TKR. Understanding the correlation between the central pain system and the peripheral drivers of pain (BMLs and synovitis) may identify novel therapeutic targets for OA pain and improve the outcome for those patients that currently fail to respond to the surgery.

We conducted a prospective functional brain MRI study in OA patients, pre and 6 months post TKR, compared with an aged matched healthy volunteer group, to identify the neural signature of temporal summation using a novel cuff algometer. The aim of the study was to identify the preoperative biomarkers of pain sensitization in knee OA that possibly predict the development of chronic postoperative pain after TKR.

5.2 METHODS

5.2.1 Study Participants

Twenty-eight patients (mean age 66.9 years [8.4 SD], with chronic knee OA awaiting TKR surgery were recruited from orthopaedic clinics in Nottingham United Kingdom. All knee OA patients met the entry criteria of having predominantly unilateral knee OA pain of sufficient pain intensity to warrant TKR surgery but not having undergone any previous surgery to the joint (See expanded inclusion/exclusion criteria, as same as Chapter 3 and 4 study). These OA patients were compared to seventeen age and sex matched healthy volunteers with no

symptomatic OA or chronic pain condition which were recruited through local advertising. The healthy volunteers were screened to ensure they were not taking any regular analgesic medication or undergoing any alternative therapy for underlying pain. Sample size was based on published functional brain MRI (fMRI) estimates (Napadow *et* al).(237) The study was approved by East Midlands Nottingham ethics committee (REC reference: 10/H0408/115) and the University of Nottingham ethics committee (Ethics Ref:H11122014) and was carried out under the principles of the Declaration of Helsinki and registered on clinicaltrials.gov (NCT03126279). All participants gave informed consent.

All OA patients and healthy volunteers were screened for the following exclusion criteria: hip OA, fibromyalgia, psychiatric illness, active cancer, sensory dysfunctional illnesses chronic pain condition or contraindications to safe MRI scanning. The subjects were requested to not take any analgesic medication 24 hours prior to the initial assessment.

5.2.2 Experimental Design

All subjects were invited to take part in a longitudinal combined brain, knee MRI and behavioural and QST assessment at the University of Nottingham. Subjective knee pain intensity scores for were recorded for each subject using the visual analogue scale (VAS, 0-10 cm) on the day of assessment. The subjects were requested to complete the same set of self-reported questionnaires to assess pain, mood, knee function and quality life as previously described in Chapter 4. After completing the questionnaires, a detailed quantitative sensory testing assessment (QST) was performed. QST was performed with the subjects relaxed in a quiet room in the supine position. QST was performed in full in all subjects as detailed in Chapter 2 and 3.

After completion of the questionnaires and QST assessments all

subjects underwent a brain MRI scan with a structural T1-weighted brain MRI and a nociceptive blood oxygen level dependent (BOLD) functional MRI (fMRI) brain scan at 3-Tesla to identify the neural signature of the central pain mechanisms in knee OA. Five runs of 10 x 1 second stimuli (temporal summation of pain) during fMRI were achieved using cuff inflation applied on the calf muscle ipsilateral to the most affected knee or the left side in healthy volunteers. The stimulation intensity of the cuff pressure was set to each individual's pain tolerance limit (PTT). This was measured at baseline outside the MRI scanner during the QST assessment. The pain intensity change during repeated stimulations was assessed on a numerical rating scale and this was recorded outside of the MRI scanner. All image processing was performed using FSL (FMRIB software library) tools. Models were used to define the pattern of brain activation the $10^{th}>1^{st}$ cuff pressure stimuli (at temporal summation).(14) The group-level analyses were carried out using FSL to compare the brain related activity between OA patients and healthy controls.

After the brain scans were complete all subjects then underwent a 3-Telsa knee scan to identify bone marrow lesions (BMLs) synovitis and effusion size which were scored using the MOAKS MRI score as previously outlined in Chapters 2 and 4.

After all the preoperative questionnaires, QST, knee and brain MRI scan data was collected the knee OA patients were sub-grouped into those that had evidence of facilitated TSP indicative of central sensitization of pain and those OA patients with normal temporal summation. Published TSP cuff algometry cut off values were used to determine the subgroups with TSP: Group A: Knee OA Patients with Facilitated TSP (TSP score ≥1.55+/-0.17, mean+/-SD), Group B: Knee OA Patients with Normal TSP (TSP score <1.55+/-0.17 mean+/-SD). The healthy

volunteers were all assigned to Group C. Comparisons between all knee OA patients and healthy volunteers as well as the knee OA subgroups and healthy volunteers was conducted to help identify the neural correlation of TSP in knee OA and to identify the potential peripheral drivers of pain within the knee joint and psychological parameters of patients potentially driving this central pain facilitation. Six-months after TKR surgery all OA patients were invited to return for follow up assessment to repeat their fMRI brain, assess their self-reported VAS pain scores and pain sensitization characteristics using QST to determine those OA patients who had responded to TKR surgery and those non-responders. All patients also completed a series of questionnaires to assess their pain (ICOAP, Visual Analogue Scale VAS score) knee function (Oxford Knee Score) and quality of life (EQ-5D-5L). Traditional radiography of the prosthesis is routinely used by the orthopaedic surgeon as part of the clinical assessment but especially in all post-operative pain cases. Assessment of the restoration of normal alignment and position of the components is undertaken. However routine radiographs are unable to detect subchondral bone marrow lesions as well as synovitis, which are common causes of pain in the pre-operative state. Conventional MRI of the knee in symptomatic patients with TKR is often limited due to the significant metal artefacts produced, resulting in signal loss and distortion particularly at higher field strengths. Therefore, as part of the postoperative assessment all OA patients underwent a 3-Tesla metal artefact reduction sequence (MARS) knee MRI scan to identify whether the presence of continued or new BMLs, synovitis and effusion size six months after TKR surgery to determine whether the continued or new presence of BMLs, synovitis or effusion is a source of continuous nociceptive input, driving central pain facilitation, leading to chronic postoperative pain and reduced knee satisfaction and function.

5.3 Study Aims

1.To describe the pattern of neural correlates of temporal summation using cuff algometry in knee OA patients and healthy volunteer and compare the differences between groups

2.To identify and compare the brain imaging biomarkers of knee OA patients with evidence of central pain facilitation based on QST to OA patients without central pain facilitation.

3.To understand the association between the painful peripheral knee structural changes in OA including BMLs, synovitis and effusion size and psychological status with central pain facilitation.

4.To determine patient reported outcomes (VAS score, Oxford Knee Score and EQ-5D-5L scores) and functional brain activity in OA patients that have responded and not responded to TKR surgery.

5.To use novel metal artefact reduction MRI sequences to identify whether the continued (or new) presence of residual BMLs within the subchondral bone, synovitis or effusion after TKR surgery are a source of continuous nociceptive input contributing to postoperative pain and altered central pain processing after TKR surgery.

6.To develop a prediction model to identify the preoperative parameters that are associated with the development of chronic postoperative pain after TKR surgery

5.3.1 fMRI protocol with Cuff Temporal Summation Paradigm

The nociceptive pressure pain stimulus used to assess the neural correlation of temporal summation was a cuff algometer (NociTech and Aalborg University, Denmark) connected to a 13-cm wide single chamber tourniquet cuff (VBM Medizinetechnik

GmbH, Sulz, Germany) alongside a computer-controlled air compressor and an electronic 10 cm VAS rating system (Aalborg University, Denmark). The cuff was applied to the gastrocnemius muscle ipsilateral to the affected knee in the knee OA patients and the left side in the volunteers. The cuff was positioned with a 5-cm distance between the upper border of the cuff and the tibial tuberosity. The cuff was automatically inflated by a computer at the rate of 1 kPa/s until a maximum pressure limit of 100 kPa was reached. The subjects used an electronic VAS to rate their pressure induced pain intensity and were instructed to press a button to release the pressure. The VAS signal was sampled at 10 Hz and 0 and 10 cm on the scale were defined as 'no pain' and 'maximum pain' respectively. The subjects were all asked to rate the pressure-pain intensity continuously using the electronic VAS with the cuff pain detection threshold (PDT) being defined as the pressure value when the subject rated pain as 1 cm on the electronic VAS. The cuff pain tolerance threshold (PTT) was defined as the maximum pressure at the point the subject had to press the release button as a result of the pain intensity being intolerable. In case 100 kPa was reached before PTT, 100 kPa was used for further analysis.

Temporal summation of pain was assessed using ten repeated cuff pressure stimulations (1 second duration, 1 second interval) with an intensity equal to PTT which were delivered to the lower leg below the affected knee due to be replaced in OA patients and the left side in the healthy volunteers. Subjects were asked to rate the pain intensity continuously throughout the 10 pressure cuff stimulations using the electronic VAS and were informed not to return the VAS to zero between cuff stimulations. A constant pressure of 5 kPa was kept between each cuff stimulation to ensure the position of the cuff on the leg did move during the assessment. The VAS score immediately following the individual cuff stimuli were extracted. For the

analysis of TSP, the mean VAS score of the 1st-4th cuff stimulations (VAS-I) was subtracted from the mean VAS score of the 8th-10th cuff stimulations (VAS II), as previously used in similar studies. Based on previous cuff studies facilitated cuff TSP was defined as a cuff TSP score of 1.6 ± 0.2 cm. This score was used to define the OA groups: 1) Facilitated TSP Knee OA patients (cuff TSP score ≥ 1.6 ± 0.2 cm) and 2. Normal TSP knee OA patients (<1.6 ± 0.2 cm). This cuff TSP paradigm was repeated within the MRI scanner with 10x1 second nociceptive pressure stimuli being applied whilst simultaneous functional brain imaging was conducted looking for the blood oxygen-level dependent (BOLD) response within the activated brain regions. This stimulus train was repeated 5 times with 40 seconds rest period with no pressure stimulation between each train. (Fig 5.1)

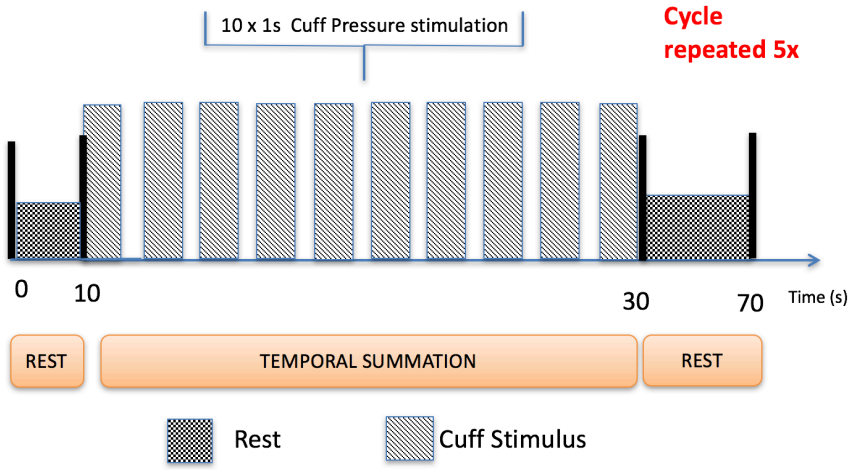


Figure 5.1 fMRI Temporal Summation Paradigm with Cuff Algometer

5.3.2 fMRI Acquisition

All brain imaging MRI data was performed on all subjects using a 3T MRI (Discovery MR750, GE Healthcare) using a 32-channel head coil. The BOLD fMRI data with the knee cuff algometer was generated by140 single-echo echo-planar (EPI) volumes over 4 minutes 40 seconds (TE/TR=32/2000ms, interleaved acquisition,

slice thickness=3.6mm, 35 axial slices parallel to anterior-posterior commissure plane, flip angle=90°, matrix=64x64, field of view=240).For co-registration purposes a T1-weighted anatomical image was acquired for all subjects using a gradient echo sequence (TE/TR=3.324/8.492ms, TI=450ms, slice gap=1mm, field of view=256, matrix=256x256, flip angle=12°).

5.3.3 fMRI Task

Subjects underwent the same temporal summation cuff paradigm inside the scanner that was completed as part of the initial QST with 10x1 second pressure cuff stimulations to the gastrocnemius muscle at the subjects PTT which was assessed outside the scanner. Five blocks of 10 cuff inflations at a rate of 0.5 Hz, with a 40 second rest period between each block were performed in the MRI scanner for BOLD assessment as shown in Fig 5.1. Subjects were instructed to close their eyes for the duration of the scan.

5.4 fMRI Analysis

The fMRI protocol was defined by the Pain Imaging team (Dr Diane Reckziegel) and analysis of the fMRI data was performed by Dr Sarina Iwabuchi guided by Professor Dorothee Auer (Professor of Neuroimaging)

5.4.1 Pre-processing

Quality control assessment was conducted using an in-house process to assess the quality of the raw brain MRI data prior to processing. Five data sets (2 healthy controls and 3 knee OA patients) from the baseline scans and 3 post TKR OA patient scans were excluded due to significant imaging artefacts due to excessive motion or excessive noise in the frequency spectra.(238) A further 2 OA patients were additionally excluded due to the presence of large ventricles which resulted in poor image registration during the pre-processing. After assessment

of quality control was performed at baseline 22 knee OA patients and 15 healthy controls were included and post TKR 19 OA patient's data were deemed suitable (16 in total with both pre and post TKR follow up scans)

Image processing was conducted using FSL 5.0.9 (FMRIB software library. To process the raw data to generate images for comparison, a series of processing steps were performed. These included high pass temporal filtering (0.01-Hz cut-off), interleaved slice timing and motion timing correction, brain extraction and spatial smoothing (5mm FWHM). A T1-weighted structural brain scan was also performed on each of study participants and the functional MRI brain images were registered to the T1-structual images as well and the Montreal Neurological Institute standard template (12 degrees of freedom (DOF)) using FLIRT (FMRI Linear Image Registration Tool (FMRIB).(239, 240) Imaging data was then deionised using independent component analysis and FIX (FMRIB's independent component analysis based X-noiseifier).(241, 242)

5.4.2 General Linear Model

The pre-processed imaging data was entered into a whole-brain General Linear Model (GLM) as implemented in FEAT using FSL. Analysis included 1) a model to assess a change in BOLD response from the 10^{th} > 1^{st} cuff pressure inflation stimulus in knee OA patients and healthy volunteers, 2) the increase in BOLD response related to the self-reported VAS pain score (VAS-BOLD) for each cuff inflation for those OA patients with facilitated TSP, normal TSP and the healthy volunteers and 3) a model to assess the VAS-BOLD response 6 months after TKR surgery in those patients that responded and failed to respond to TKR surgery.

Each model was convolved with the BOLD haemodynamic response function.(243) Group level analysis comparing the OA

patients to the healthy volunteers was carried out using FLAME 1 (mixed effects GLM) in FSL. To investigate whether baseline BOLD response was associated with post-surgical outcome, we also compared baseline data of responders and non-responders where both sets of data were available. Results were thresholded using a familywise error (FWE) corrected threshold of Z>1.96, cluster significance $p<0.05$.

5.5 Quantitative Sensory Testing Assessment

5.5.1 Condition Pain Modulation by Cuff Algometry

The cuff CPM assess the manifestation that a tonic noxious conditioning cuff stimulus applied to the contralateral leg inhibits the noxious test stimulus applied to the affected leg (knee OA) resulting in functional inhibitory pain modulation. (177, 185) Two 13 cm wide cuffs were used to conduct CPM assessment with one cuff on each leg over the gastrocnemius muscles. The painful conditioning cuff stimulus was inflated on the contralateral side, with the inflation pressure set equivalent to the subject's PTT. Simultaneous re-assessment of the subject's PDT was performed with a second cuff on the ipsilateral lower leg (test stimulus). Condition pain modulation was defined as the difference between the PDT during the conditioning stimulus and the initial trial without it. A CPM score of ≥ 5.5 ± 1.1 kPA was defined as a normal CPM response and a score below this figure was defined as impaired CPM. (16)

5.5.2 Cutaneous Temporal Summation of Pain

A weighted 25.6 g monofilament was used to assess and induce cutaneous temporal summation of pain. The monofilament was applied directly to the affected knee (5 cm proximal to the centre of patella) in the OA patients or the left knee in the healthy volunteers. All subjects rated the pain intensity on a VAS. Consecutively, 10 monofilament stimulations were applied

repeatedly to the same site on the subject's knee by the assessor with a 1 second inter-stimulus interval. Subjects were asked to rate the pain intensity of the first stimulation and the 10^{th} stimulation. Temporal summation using a 25.6 g monofilament was calculated by assessing the difference in the VAS score of the 10^{th} stimulation to the 1^{st} stimulation. (14)

5.5.3 Pressure Algometry

Pressure pain thresholds (PPTs) were assessed using hand-held algometry (Somedic AB, Sweden) using a 1 cm^2 probe. A 30kPa/s pressure stimulus was applied until the subject first perceived a change in the pressure stimulus and it no longer felt like pressure but started to feel painful. The subject was asked to press a button at the moment of this change in pressure stimulus and at this point the stimulus was removed at the PPT value was recorded. The PPTs values for the OA patients were recorded on the affected arthritic knee that was due to replaced and for the healthy volunteers the left knee was chosen for assessment. Three testing sites were chosen around the knee. Site 1: 3 cm medial to mid-point of the medial edge of patella. Site 2: 2 cm proximal to superior lateral edge of patella. Site 3: 2 cm proximal to superior medial edge of patella. A further 2 sites were used to assess spreading sensitization distant to the knee (Site 4) and widespread hyperalgesia (Site 5) indicative of central sensitization of pain. These were: Site 4: The tibialis anterior muscle (5 cm distal to the tibial tuberosity). Site 5: The extensor carpi radialis longus muscle (5 cm distal to the lateral epicondyle of the humerus).(14) A 30 second interval between trials at assessment sites was kept. The PPTs were recorded in triplicates and averaged for each site for further analysis. Lower PPTs values indicate increased pain sensitivity.

5.5.4 Questionnaires

All participants were asked to complete the Intermittent and Constant Osteoarthritis Pain Score (ICOAP) (198), PainDETECT (179), Beck Depression Inventory-II (BDI-II) (244), State-Trait Anxiety(204),Pain Catastrophizing Scale(245), Oxford Knee Score(212) and EuroQual EQ-5D-5L (214) questionnaires, Fig 5.2.

The ICOAP questionnaire is a reliable and valid tool used to assess the nature of constant and intermittent pain as well as the impact of pain on sleep, mood and quality of life in patients with knee OA. (202) Eleven questions make up the questionnaire with overall scores ranging from 0 (no pain) to 100 (extreme pain). (198) The PainDETECT questionnaire is a validated self-report questionnaire, used to identify neuropathic pain like symptoms in a range of medical conditions. (175, 179) The questionnaire helps to identify the presence or absence of neuropathic pain like symptoms which have identified in subgroups of knee OA patients. (134, 135, 180) Subjects are asked to record their responses in respect to their pain in the last 4 weeks of time when completing the self-reported questionnaire. The total score can range from 0 to 38 with a higher score (≥19) indicative of neuropathic pain characteristics. (179)

The Beck Depression Inventory (BDI-II) questionnaire is psychometric test used to assess the severity of depression and has been extensively used to assess depression in OA patients. (207-210) This 21-question self-report instrument assesses the presence or severity of depressed mood with each question scored from 0-3 using a 4 point Linkert scale. The overall score ranges from 0-63 with higher scores indicative of severe depression. BDI-II scores ranging from 0-13 indicate minimal depression; scores from 14-19 represent mild depression, scores

from 20-28 indicate moderate depression and scores ranging from 29-63 represent severe depression. (209, 210)

The State Trait Anxiety questionnaire is used to diagnose anxiety and distinguish it from clinical depression. The questionnaire assesses both state (20 questions) and trait (20 questions) anxiety. All items are rated on a 4-point scale with overall scores ranging from 20-80. Higher scores suggest greater levels of anxiety. (204)

The term 'pain catastrophizing' is used to explain an exaggerated negative perception response to a painful stimulus. (211) The Pain Catastrophizing Scale (PCS) is a 13-item questionnaire where respondents are asked to rate each statement using a 5-point scale (0 = not at all) and 4 (all the time). The PCS is made up of 3 subscales which assess magnification, rumination and helplessness. The PCS score ranges from 0-52 with higher scores suggestive of a more pain catastrophizing personality trait. A recent systematic review has suggested that high PCS scores preoperatively in OA patients is an independent predictor to the development of chronic pain after TKR surgery. (197)

The Oxford Knee Score (OKS) is a specifically designed instrument to measure subjective outcome after TKR surgery and is used by National Joint Registry (NJR) in the United Kingdom by all patients undergoing joint replacement surgery. The OKS is made up of 12 questions that assess pain and function in the knee. Scores range from 0-48 with a higher score indicative of improved knee health with minimal or no pain and good function. A minimum improvement of 5 points (95% CI 4.4-5.5) on the OKS has been recently shown to correlate with an improvement in pain and function after TKR surgery. (213)

The EuroQual-5D-5L questionnaire (EQ-5D-5L) is a 5-dimension questionnaire used to assess health status and quality of life in a population. (215) The EQ-5D-5L questionnaire is made up of 2

components; the description of health status and the evaluation. Health status in the description part is made of up 5 questions which assess mobility, self-care, subject's usual activities, pain and mood. The respondents self-rate their level of severity for each of the 5 questions with a score from 1-5 for each question. For the evaluation part of the EQ-5D-5L questionnaire the respondents assess their overall health status using a visual analogue scale from 0-100, with poorest health scoring '0' and the best health state scoring '100'.

5.5.5 Knee MRI acquisition and MRI Osteoarthritis Knee Score (MOAKS)

All subjects underwent a knee MRI which was performed on a 3.0 T system (GE MR 750, GE Healthcare, Waukesha, WI) using an 8-channel phased array transmit-receive knee coil. The knee was scanned in the coronal, sagittal and axial planes using a proton-density fat-suppressed sequence (2.5 mm thickness, spacing 0.3 mm, repetition time (TR) 3321 ms, effective echo time (TE) 41 ms, echo train length (ETL) 7 and pixel bandwidth (BW) 162)

After all the data was completed the knee MRI's were scored by 2 trained observers (one senior musculoskeletal radiologist and one orthopaedic physician using the semi-quantitative MRI Osteoarthritis Knee Score (MOAKS) for the severity of BMLs (score 0-45), effusion size (score 0-3) and Hoffa Synovitis (score 0-3). Each observer scored the blinded images independently and repeated the scoring 6 weeks later to assess for inter and intra observer reliability.

5.5.6 Post TKR Follow Up Assessment

All OA patients were invited to attend the follow up assessment 6 months after their TKR surgery to assess their change in knee pain intensity, knee function and quality of life.

Using QST (PPTs, PDT, PTT, TSP, CPM and pin prick TSP) pain sensitization profiles of the subjects were re-assessed and each OA patient underwent a post TKR fMRI brain scan using the cuff algometer as a pressure stimulus to assess the neural correlation of temporal summation post TKR in OA patients. After the brain imaging was complete the OA patients each underwent a 3-Telsa metal artefact reduction MRI knee scan to image the joint post TKR to assess whether there was the continued presence or new BMLs, synovitis or effusions around the prosthesis postoperatively, Fig 5.2.

After all the data was collected the OA patients were stratified into two groups based on their post TKR VAS pain score (0-10): Responders to TKR surgery (VAS≤3) and Non-Responders to TKR surgery (VAS≥4) based on previously published standards. Analysis of the functional brain activity in response to the 10 sequential cuff pressure stimuli as a measure of TSP was conducted between the Responders and Non-responders to TKR surgery was performed. Further analysis was also conducted assess if there were any neuroimaging pain biomarkers of temporal summation seen preoperatively in those OA patients that failed to respond to TKR surgery and comparison between the postoperative brain activity to the healthy volunteer data set.

5.5.7 Postoperative Metal Artefact Reduction MRI Scan

Six months following TKR, subjects underwent knee MRI at 3.0 Tesla (GE MR750, GE Healthcare, Waukesha, WI) using a 3D multi-acquisition variable-resonance image combination selective (MAVRIC SL®) sequence and an 8-channel phased array transmit-receive knee coil. Images were acquired in coronal, sagittal and axial planes using intermediate weighted (MAVRIC PD) and inversion recovery fat-suppression (MAVRIC STIR) sequences. Image parameters for MAVRIC PD were slice

thickness 4 mm (no gap), repetition time/echo time 3300/7.4 ms, echo train length (ETL) 20, pixel bandwidth 488 Hz/pixel, reconstruction diameter 180 mm, acquisition matrix 320 x 256, flip angle 85 degrees and 0.5 excitations. For MAVRIC STIR, parameters were slice thickness 4 mm (no gap), repetition time/echo time 4300 - 5000/7.0 ms, ETL 20, pixel bandwidth 976 Hz/pixel, reconstruction diameter 180 mm, acquisition matrix 256 x 192, flip angle 75 degrees and 0.5 excitations. The images were scored independently by a senior musculoskeletal radiologist and an orthopaedic physician for postoperative BMLs, effusion synovitis and Hoffa synovitis with both observers blinded to the patient reported outcome measures, questionnaires, QST or fMRI results of the patients. Hoffa synovitis (0-3) and effusion synovitis (0-3) were scored using the standard MOAKS criteria previously described. With a significant proportion of the femoral surface being replaced by the implant along with the large femoral drill tract present in all cases due to intraoperative intramedullary referencing for femoral sizing, the tibial region alone was scored for post TKR BMLs. Six out of the seven MOAKS score tibial sub-regions were used to assess whether BMLs were present post TKR with MAVRIC MRI. The subspinous sub-region region was excluded as the majority of this region was occupied by the tibial stem of the prosthesis in all cases. The standardized MOAKS criteria to score BMLS (0-3) in each of the 6 sub-regions. An overall total MAVIRC post TKR BML was calculated (0-18) for the tibia by summing the individual six sub-regions BML scores with higher scores indicative of increasing BML presence post TKR.

5.5.8 Statistical analysis

The data was analysed using Prism 7.0. Parametric data was presented as the mean and standard deviation with median and interquartile ranges (IQR) being expressed for data that was non-parametric. In figures, data are presented as mean and standard error of the mean (SEM). Data were evaluated to determine whether they met the assumption of normality using the D'Agostino-Pearson omnibus normality test.

Initial analysis was to compare the results of all the preoperative knee OA patients to the healthy volunteers. The unpaired T-Test for age comparison and chi-squared test were used to assess for differences in gender between the 2 groups. Pain duration, ICOAP scores, knee pain intensity VAS scores, PainDETECT and BMI comparisons between the OA patients and healthy volunteers were assessed using the Mann Whitney U-Test. The hand-held algometry QST results and cuff CPM results between OA patients and healthy volunteers were compared using the Unpaired T-test and cuff TSP, pin-prick TSP results between the two groups were assessed using the Mann Whitney U-Test.

Further analysis of the OA patients was conducted as they were sub-grouped into two groups based on the degree of temporal summation of pain (TSP) from their cuff algometry assessment. Published TSP cuff algometry cut off values were used to determine the subgroups with TSP: Group 1: Knee OA Patients with facilitated TSP (TSP score ≥1.55+/-0.17), Group 2: Knee OA Patients with normal TSP (TSP score <1.55+/-0.17). The healthy volunteers with no knee OA or chronic pain condition were all assigned to Group 3.

An analysis of variance (ANOVA) with Tukey post hoc tests for normally distributed data, or Kruskal-Wallis ANOVA with Dunn's post hoc tests for the analysis of non-parametric data, was conducted for comparisons of Age, BMI, PPTs, pin prick and cuff

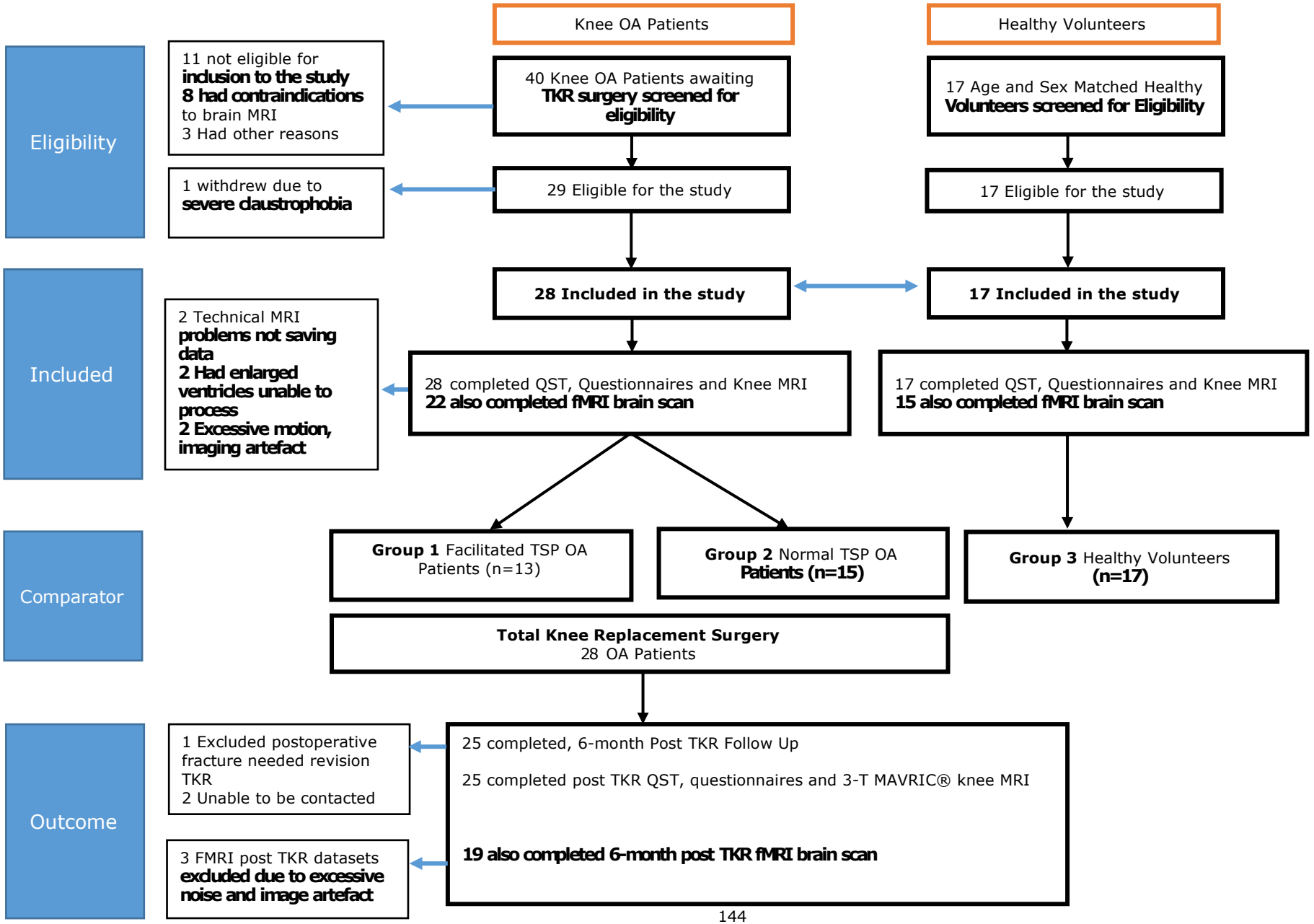
TSP, CPM, MOAKS Hoffa Synovitis, MOAKS effusion synovitis and MOAKS BML scores as well as the questionnaires pain catastrophizing scale, Beck Depression Inventory II, State-Trait Anxiety, Oxford Knee Score and EQ-5D-5L between Groups 1, 2 and 3.

Six months post TKR the outcomes of the OA patients were divided into those that responded (VAS score ≤3) and those that failed to respond (VAS≥4) to TKR surgery. To assess the pain outcome measures between the responders and non-responders the Mann Whitney U-Tests were used to compare the VAS pain ICOAP and PainDETECT scores between the responders and non-responders to TKR surgery. The Oxford Knee scores were assessed using the Mann Whitey U-Test and EQ-5D-5L quality of life assessments were compared using the unpaired T-test.

Assessment in the change in PPT and CPM pre and post-surgery in those responders and non-responders was performed using the paired T-Test for parametric data and the Wilcoxon signed-ranks test for non-parametric data. Three group comparisons between the responders, non-responders and healthy volunteers was performed post TKR for the PPT, TSP and CPM scores using ANOVA when the data was parametric and the Kruskal-Wallis test for non-parametric data.

The post TKR metal artefact reduction MRI scans were assessed with the modified MOAKS scores for tibial BMLs, Hoffa synovitis and effusion synovitis in the responders and non-responders to TKR surgery. The Unpaired T-Test was used to compare Hoffa synovitis and tibia BML scores and the Mann Whitney U-Test was used to assess effusion synovitis differences between the two groups.

Figure 5.2 Study Flow Diagram, Eligibility, Assessment and Outcome



5.6 RESULTS

5.6.1 Demographic Data and Pain Profiles of All Subjects

All 28 OA patients and 17 healthy volunteers completed the preoperative assessment of questionnaires, QST, knee MRI and brain fMRI. Eight fMRI datasets (6 in knee OA group, 2 in heathy volunteer group) were deemed unusable and were excluded due to technical problems with data acquisition, excessive movement artefact or due to the presence of 2 structural brain abnormalities impairing data analysis, Fig 5.2.

Table 5.1 outlines the demographic and pain profile data for the knee OA patients and healthy volunteers. Significant differences were seen comparing BMI ($p=0.0128$), Pain Duration ($p<0.0001$), knee pain intensity VAS scores ($p<0.0001$), ICOAP $p<0.0001$) and PainDETECT scores ($p<0.0001$) Mann Whitney U-Test) between the 2 groups. No significant differences in age ($p>0.05$ unpaired T-Test) or sex ($p=0.789$ Chi-squared test) were seen.

Table 5.1 Patient and Healthy Control Demographics

	All Knee OA Patients (n=28)	**Healthy Controls (n=17)**
Age years (+/- SD)	66.9 [8.4]	62.5 [4.8]
Male:Female (%Female)	11:17 (60.7%)	6:11 (64.7%)
Body Mass Index (BMI)	30 (27.3-33.8)	26 (25.5-29) *
Pain Duration in Years (Median and Range)	2.75 (2-5)	0 (0-0) *
Knee Pain Intensity VAS score (0-10cm) in previous 24 h	5 (4-7)	0 (0-0) *
Intermittent and Constant Osteoarthritis Pain Score (ICOAP)	56.8 (37.6-69.9)	0 (0-0) *
PainDETECT Score (0-38)	13 (8-18.8)	0 (0-0) *

Patient and healthy control demographics. No significant difference in age (unpaired T-Test or sex (Chi-squared test). Significant differences were seen in BMI Pain duration, Knee Pain Intensity, ICOAP and PainDETECT scores (Mann Whitney U-Test), p<0.05 considered significant.*

5.6.2 Subgrouping Knee OA Patient based on Cuff Temporal Summation Scores

Using the cuff algometer the knee OA patients were subgrouped in to those that had facilitated TSP (cuff TSP score ≥ 1.6 ± 0.2 cm) and those that had normal TSP (cuff TSP score < 1.6 ± 0.2 cm) From the 28 OA patients recruited, 13/28 (46.4%) of patients demonstrated evidence of central sensitization of pain evidenced by facilitated TSP on the cuff scores. Table 5.2 outlines the demographic and pain profile data for the OA

patients and healthy volunteers with the OA patients sub-grouped into those that had facilitated TSP and normal TSP based on their cuff algometry scores. Significant differences were seen between the age of the subjects (ANOVA: $F=5.6$, $p=0.007$) with those facilitated TSP OA patients being older than normal TSP OA patients (Tukey's $p=0.035$) and the healthy volunteers (Tukey's: $p=0.0007$). No significant differences were seen assessing sex between all three groups ($p=0.323$, Chi-squared test). The BMI scores results showed significant differences (Kruskal Wallis Test Statistic: 7.0, $p=0.03$) between the facilitated TSP OA patients and the healthy volunteers ($p=0.028$). No significant difference between the 2 OA groups were seen in terms of pain duration ($p=0.2102$) Mann Whitney U-Test, knee pain intensity VAS score ($p=0.086$), Unpaired T-Test, ICOAP scores ($p=0.939$), Unpaired T-test and PainDETECT scores ($p=0.364$) Unpaired T-Test).

Table 5.2 Facilitated and Normal TSP OA Patients and Healthy Control Demographics.

	Group 1: Facilitated TSP OA Patients (n=13)	Group 2: Normal TSP OA Patients (n=15)	Group 3: Healthy Volunteers (n=17)
Age years (+/- SD)	70.5 [6.1]	63.9 [9.0]	62.5 [4.8]*
Male:Female (% Female)	7:6 (46.2%)	4:11 (73.3%)	6:11 (64.7%)
Body Mass Index (BMI)	31 (29.5-33.5)	28 (27-35)	26 (25.5-29)*
Pain Duration in Years (Median and Range)	2 (2-5.5)	3 (2-5)	N/A
Knee VAS Pain score(0-10cm)	6 (1.7)	4.7 (2.0)	N/A
Intermittent and Constant Osteoarthritis Pain Score (ICOAP)	56.7 (15.6)	57.2 (22.7)	N/A
PainDETECT Score (0-38)	12.0 (7.5)	14.7 (7.7)	N/A

**p<0.05 indicating significant differences between Group 3 Healthy Volunteers and Knee OA Patients Gr oups 1 and 2*

5.6.3 Preoperative Brain fMRI TSP BOLD Results – All OA Patients vs Healthy Volunteers

Figure 5.3 shows the TSP BOLD fMRI results of the healthy volunteers and all the knee OA patients assessing the pain related brain activity comparing the 10^{th}>1st cuff stimulations to identify the brain activity related signal increase in response to repeated cuff pressure stimuli. The healthy volunteers with no chronic knee pain demonstrated very little change in BOLD level over the temporal summation protocol with prefrontal activations seen with in inferior frontal gyrus. The knee OA patients demonstrated significantly different brain related pain activity predominantly within the default mode network (DMN) brain regions including the medial prefrontal cortex, posterior cingulate cortex and inferior parietal lobe. The DMN is a group of networking brain regions whose activity is highly synchronised and distinct from other networks within the brain. The DMN is most commonly active when the person is not focussed on the outside world and the brain is in a state of wakeful rest for example when you are mind wondering or day dreaming.(246) The DMN is also active when people are thinking about themselves or others or at times of remembering past events or planning for the future.(247) These brain regions in the DMN are activated by 'default' when the person is not involved in a task. Figure 5.4 highlights the significant differences in brain activity to TSP between the healthy volunteers and knee OA patients. The increased activity in the DMN is clearly visualised in chronic knee OA (Figs 5.3 and 5.4) patients and is most likely to represent a state of less deactivation of the ascending painful signals from the knee seen in a chronic pain state.

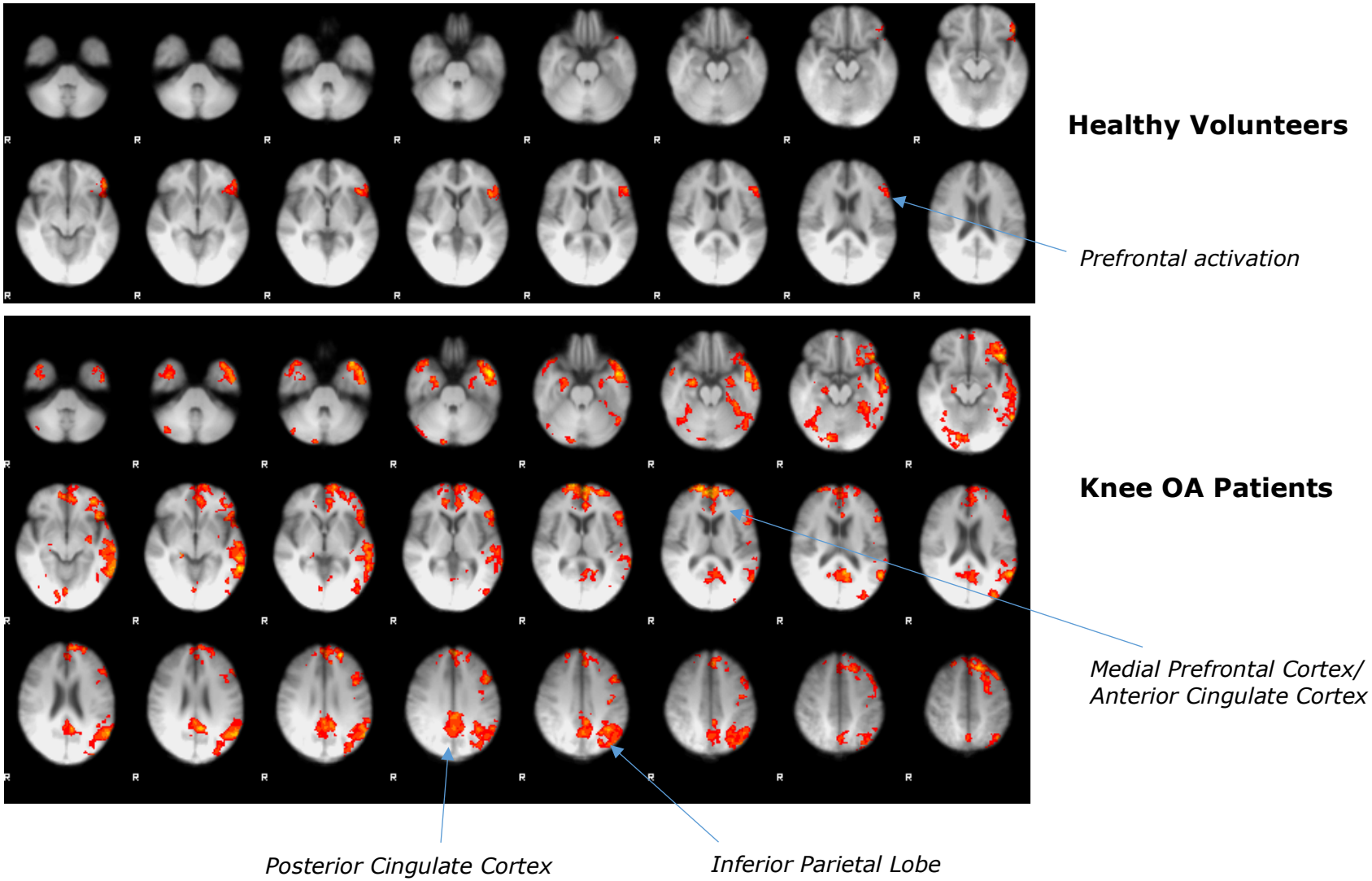


Figure 5.3 fMRI TSP BOLD Effects Results Pre TKR OA Patients and Healthy Volunteers

Figure 5.3 TSP BOLD fMRI *changes of the contrast $10^{th}>1^{st}$ cuff stimulation with cuff pressure algometer comparing the knee OA patients and healthy volunteers. (One sample T-Test per group $p<0.05$). Knee OA patients demonstrate significantly increased activation within the default mode network (DMN) which is composed of the medial prefrontal cortex, anterior cingulate cortex, posterior cingulate cortex and inferior parietal lobe.*

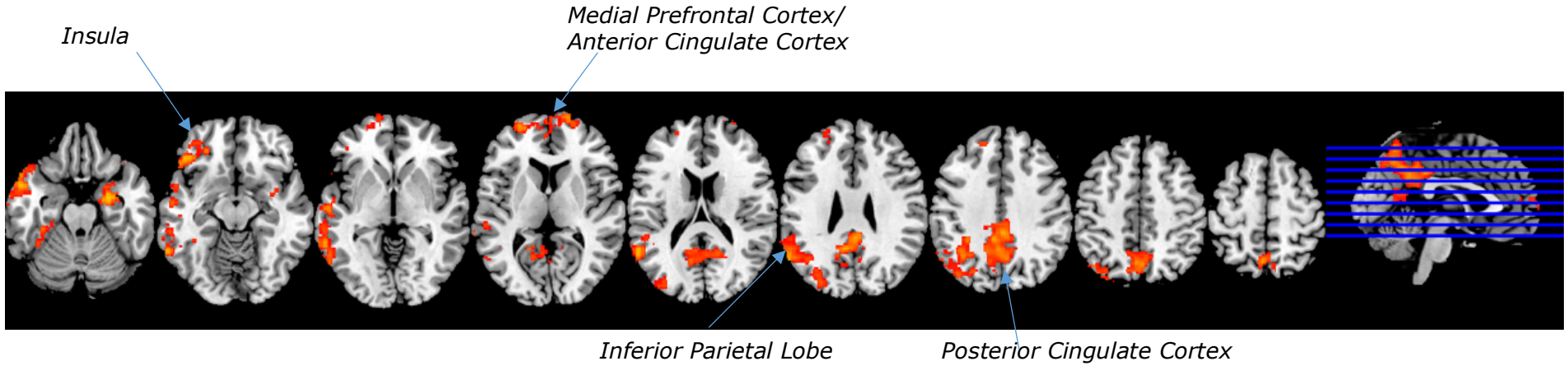


Figure 5.4 Overall Significant Differences in BOLD Brain Activity Between OA Patients and Healthy Volunteers

Figure 5.4 Significant Differences in fMRI *brain activity between knee OA Patients> Healthy volunteers showing relatively higher pain related brain activity to temporal summation protocol with cuff pressure stimulation in OA patients in the DMN. Areas highlighted in orange show the areas of significant activation in the OA patients compared to the healthy volunteers (p<0.05).*

Raichle in 2015 published a review article on the DMN and highlighted the brain map of the DMN regions.(248) Figure 5.5 outlines the brain regions of the DMN visualised using fMRI and this map clearly shows that the same brain regions of the DMN are activated in knee OA patients (Figs 5.3 and 5.4) with chronic pain.

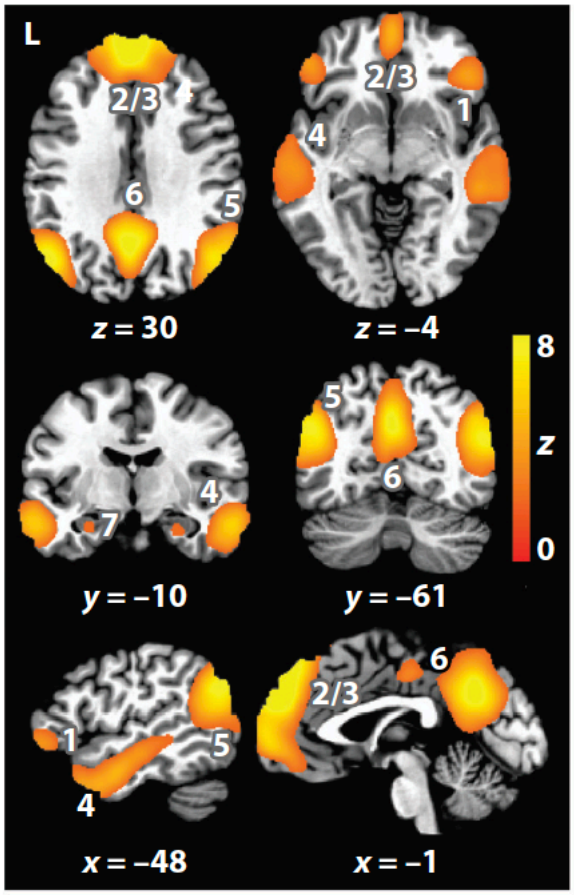


Figure 5.5 Brain Map of the Human Default Mode Network (DMN)

Figure 5.5 outlines the significant cluster of brain activation of the human brain DMN. Significant clusters include 1. Orbital frontal cortex, 2/3. Medial prefrontal cortex/anterior cingulate cortex, 4 lateral temporal cortex, 5. Inferior parietal lobe, 6. Posterior cingulate cortex, 7 hippocampal/parahippocampal cortex (z>2.1, corrected p<0.05) Figure from Raichle et al 2015(248)

5.6.4 Pattern of VAS-BOLD fMRI Correlation in Facilitated TSP, Normal TSP Knee OA Patients and Healthy Volunteers

Comparisons were then made assessing the correlation of the fMRI brain response to cuff algometer pressures alongside the associated pain perception (VAS) in those OA patients that had facilitated TSP, OA patients with normal TSP and the healthy volunteers. For this analysis, the BOLD fMRI brain response related to each individual's VAS pain score (VAS-BOLD) for the 10 cuff stimuli was conducted to identify the neural correlation of TSP related to pain perception. Figure 5.6 shows the one sample T-Tests results for each group. Healthy volunteers with no chronic pain and a low TSP VAS score (mean=0.81, SD=0.73) showed VAS-BOLD correlation within the bilateral insula. Knee OA patients in chronic pain but with normal cuff TSP scores (mean=0.71, SD=0.38) showed no VAS-BOLD correlation, whereas the knee OA patients with chronic pain and facilitated TSP (mean=3.69, SD=1.70) showed significant activation within the right S2 region that corresponds with VAS scores during TSP.

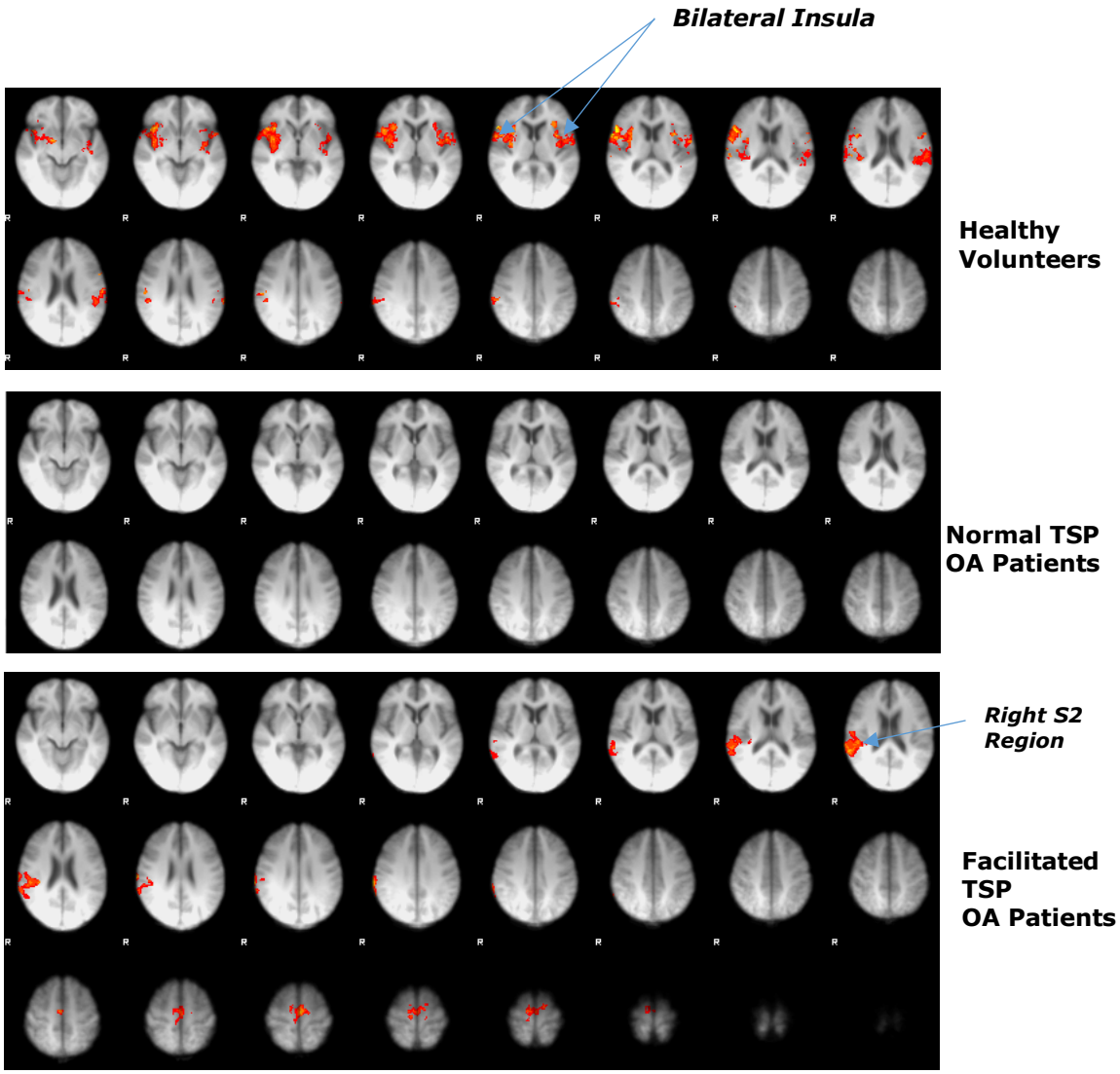


Figure 5.6 VAS-BOLD fMRI Brain Activity Results

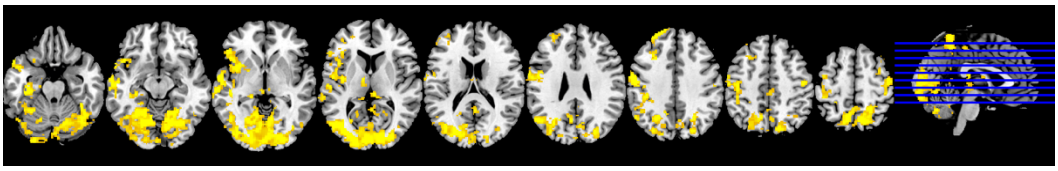
Figure 5.6 – VAS-BOLD related brain activity to cuff algometry pressure stimulation to determine the behavioural correlates of temporal summation which induce pain sensitization. Assessment of the 10^{th}>1^{st} cuff stimuli pressure for the healthy volunteers, normal TSP OA patients and facilitated TSP OA patients. One sample T-Test in each group. Bilateral Insula activation seen in healthy volunteers and right S2 activation in the facilitated TSP OA patients.

5.6.5 Comparative Analysis of Pain Perception by VAS-BOLD Changes between Groups

No significant differences were found in brain regions encoding pain intensity in a temporal summation pain stimulation paradigm between knee OA patients not showing behavioural

TSP and pain free healthy controls. VAS-BOLD related brain activity between the normal TSP OA patients and healthy volunteers showed similar regions of activation (DMN, visual cortex, insula) when correlated with the subjective VAS scores suggesting that pain perception is linked to neural brain related activity in both healthy volunteers and normal TSP OA patients, Fig 5.7**.**

Normal TSP> facilitated TSP Comparison



Healthy Volunteer> Facilitated TSP OA Comparison

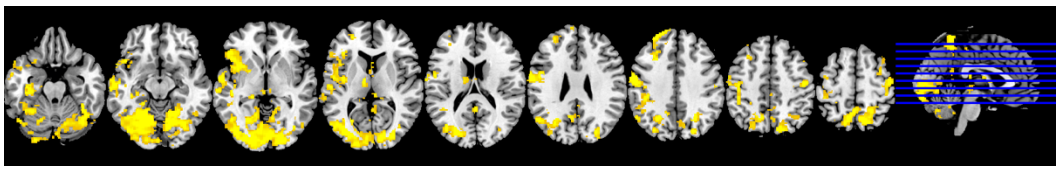
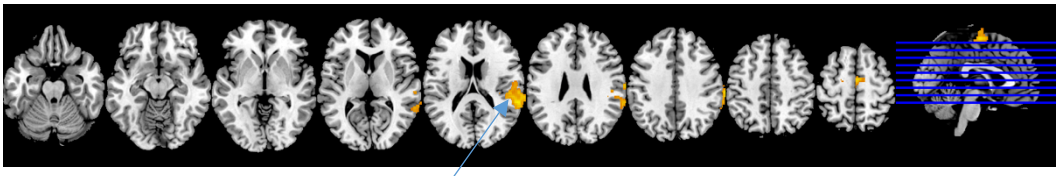


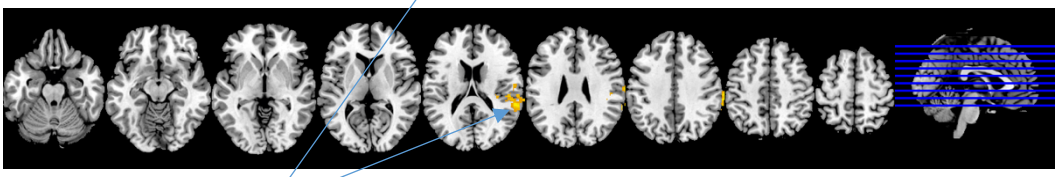
Figure 5.7 Pain Perception (VAS-BOLD) Activity Comparing Normal TSP OA Patients and Healthy Volunteers

Facilitated TSP OA patients demonstrated altered pain perception compared with heathy volunteers and normal TSP OA patients with significant discordance between the subjective VAS scores and the degree of BOLD related brain activity, Fig 5.8. The pattern of VAS-BOLD activity in the facilitated TSP OA Patients was significantly different to that of the normal TSP OA patients as well as the healthy controls with brain activity within the somatosensory region S2 being identified preoperatively in this subgroup of patients with evidence of central sensitization, suggesting that in facilitated TSP OA patients there is an alteration in preoperative pain perception.

Facilitated TSP OA >Healthy Volunteers Comparison



Facilitated TSP OA > Normal TSP OA Patients Comparison



Right S2 Activation

Figure 5.8 Pain Perception (VAS-BOLD) Activity Comparing Facilitated TSP OA Patients and Healthy Volunteers

5.7 Preoperative MOAKS MRI Scores Results

Knee OA patients with evidence of facilitated TSP showed significantly higher MOAKS MRI Hoffa Synovitis scores (Kruskal Wallis Test Statistic: 15.2, p=0.0005) than those OA patients with normal TSP (p=0.0064) and healthy volunteers (p=0.0007). (Fig 5.8) There was no significant difference between the MOAKS Hoffa synovitis scores of the normal TSP OA patients and the healthy volunteers, Fig 5.9.

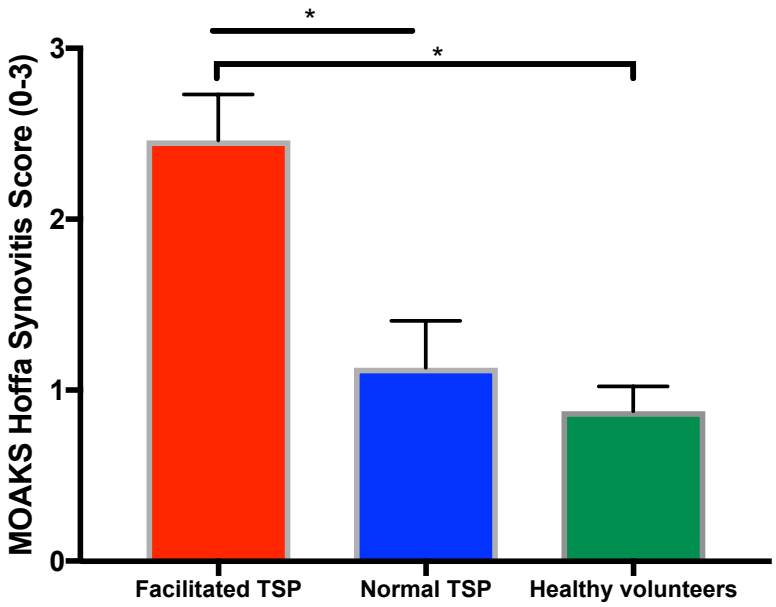


Figure 5.9 MOAKS Hoffa Synovitis Scores Grouped by Cuff TSP Scores

Comparing the subchondral BML MOAKS MRI scores between the three groups demonstrated significant differences (Kruskal Wallis Test Statistic: 18.5. $p<0.0001$) between the healthy volunteers and the facilitated TSP OA group ($p=0.0007$) and normal TSP OA group ($p=0.0008$). No significant differences were seen between the OA groups. Fig 5.10

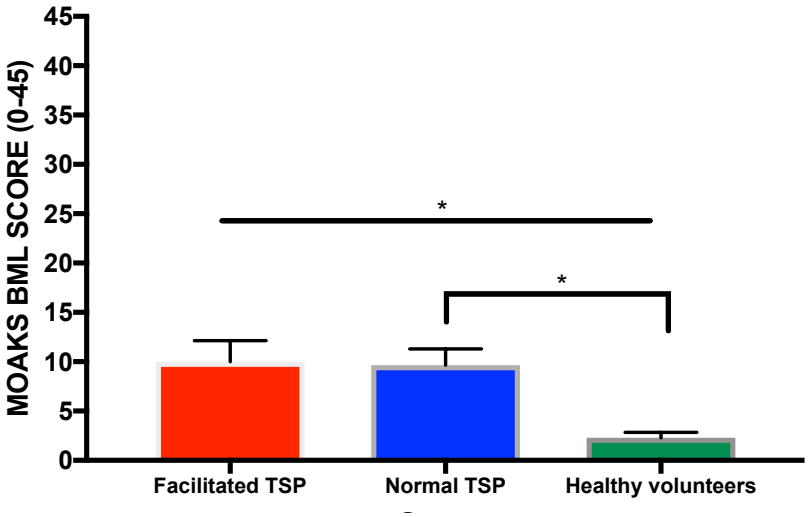


Figure 5.10 MOAKS Total BML Scores Grouped by Cuff TSP Scores

Significant difference in MOAKS MRI Effusion-Synovitis Scores (ANOVA: $F=32.2$, $p<0.0001$) were seen between the healthy volunteers and facilitated TSP OA patients ($p<0.0001$) and normal TSP OA patients ($p<0.0001$). Fig 5.11 No significant differences were seen between the OA groups.

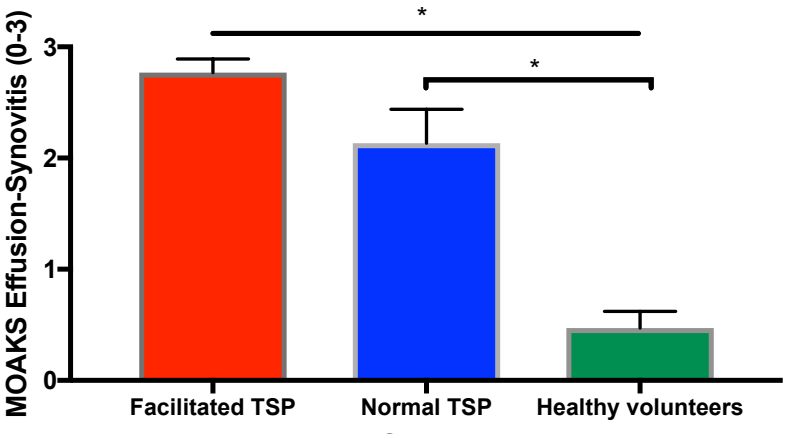


Figure 5.11 MOAKS Effusion Synovitis Scores Grouped by Cuff TSP Scores

5.7.1 Pre-TKR Hand Held Algometry QST Results

Assessment of the pre-TKR PPTs of all the OA patients grouped together and comparing them to the healthy volunteers showed significantly lower PPTs not just at the knee (MJL, SMP, SLP and Mean Knee Score) ($p<0.0001$), but also over the Tibialis Anterior muscle ($p<0.0001$) and Extensor carpi Radialis Longus Muscle (ECRL) ($p<0.0001$). (Unpaired T-Tests) Fig 5.12

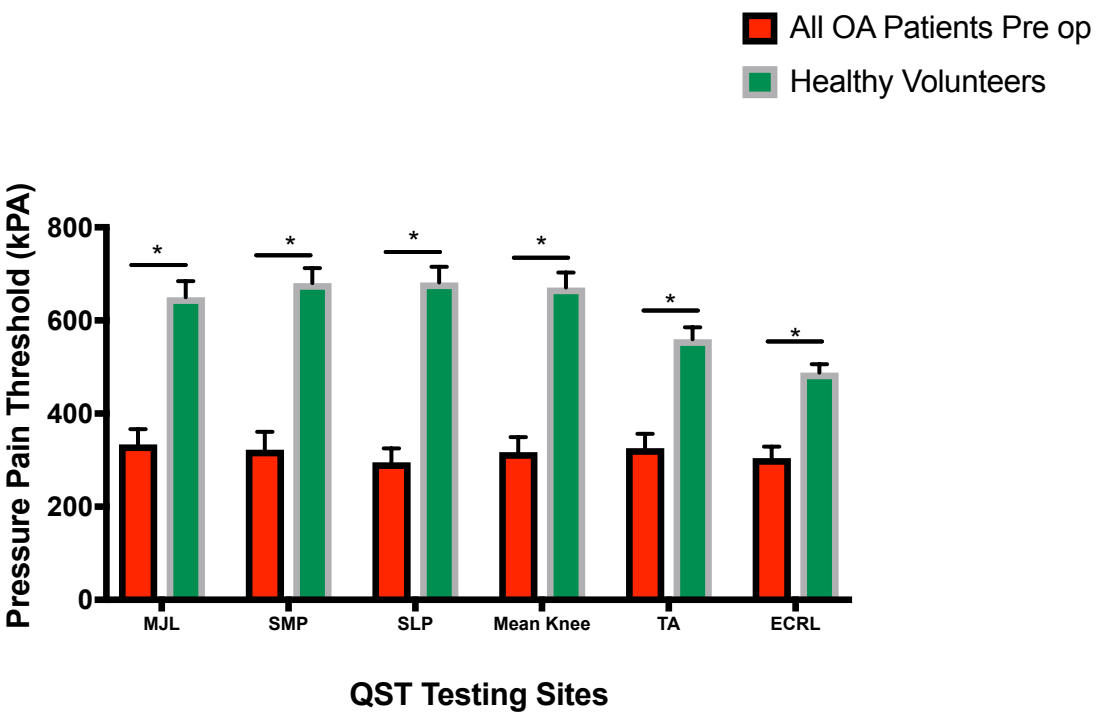


Figure 5.12 Hand-Held QST Results. All OA Patients and Healthy Volunteers

Lower PPTs over the medial joint line (MJL) of the knee (ANOVA: $F=22.0$, $p<0.0001$) were seen in the facilitated TSP OA patients ($P<0.0001$) and normal TSP OA patients ($p<0.0001$) compared to the healthy volunteers, Fig 5.13. Lower PPTs over the superiomedial patella (SMP) were also seen (Kruskal Wallis Test Statistic: 23.4, $P<0.0001$) between facilitated TSP OA patients ($p<0.0001$) and normal TSP OA patients($p=0.0007$) compared to heathy volunteers. The superior-lateral patella region was also assessed and lower PPTs were also seen (ANOVA, $F=37.6$, $p<0.0001$) in the facilitated TSP OA patients and normal TSP

patients to the healthy volunteers. The 3 knee sites were averaged to generate a mean knee score which demonstrated significant differences in the PPTs values (ANOVA: $F=31.1$ $p<0.0001$) between the facilitated TSP OA patients ($p<0.0001$) and the normal TSP ($p<0.0001$) to the healthy volunteers. Lower PPTs were seen in sites distant from the knee with significant differences in PPTs over the Tibialis Anterior muscle (TA) (Kruskal Wallis Test Statistic: 19.7, $p<0.0001$) comparing the facilitated TSP OA patients ($p=0.002$) and normal TSP OA patients ($p=0.001$) to the healthy volunteers. Facilitated TSP OA patients demonstrated evidence of widespread hyperalgesia characteristic of central sensitization by having significantly lower PPTs over a remote body site at the Extensor Carpi Radialis Longus (ECRL) muscle (ANOVA: $F=20.2$, $p<0.0001$) than normal TSP OA patients ($P=0.0011$) or healthy volunteers ($p<0.0001$). Significant differences were also seen between normal TSP OA patients and healthy volunteers ($p=0.0005$).

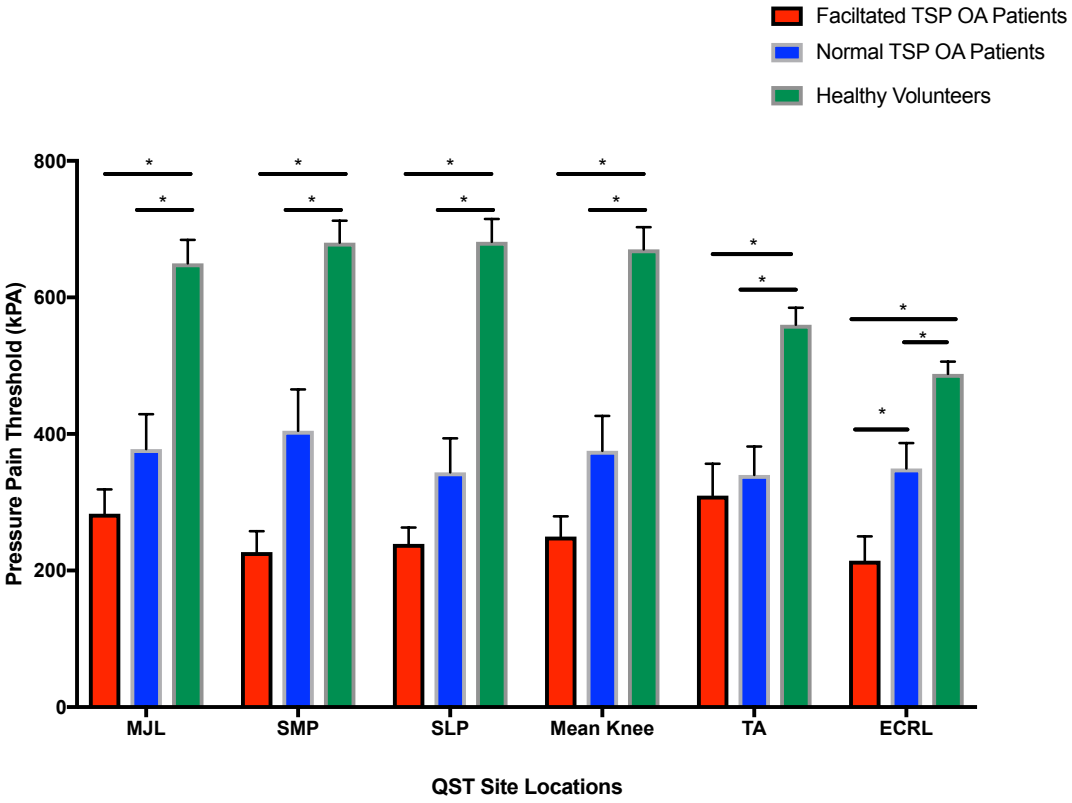


Figure 5.13 Hand Held Algometry QST Results Grouped by Cuff TSP Scores

Figure 5.13 Key: MJL (medial joint line), SMP (superior-medial patella). SLP (superior-lateral patella), TA (Tibialis Anterior Muscle) and ECRL (Extensor Carpi Radialis Longus Muscle). p<0.05 considered significant.*

5.7.2 Preoperative Cuff TSP Results

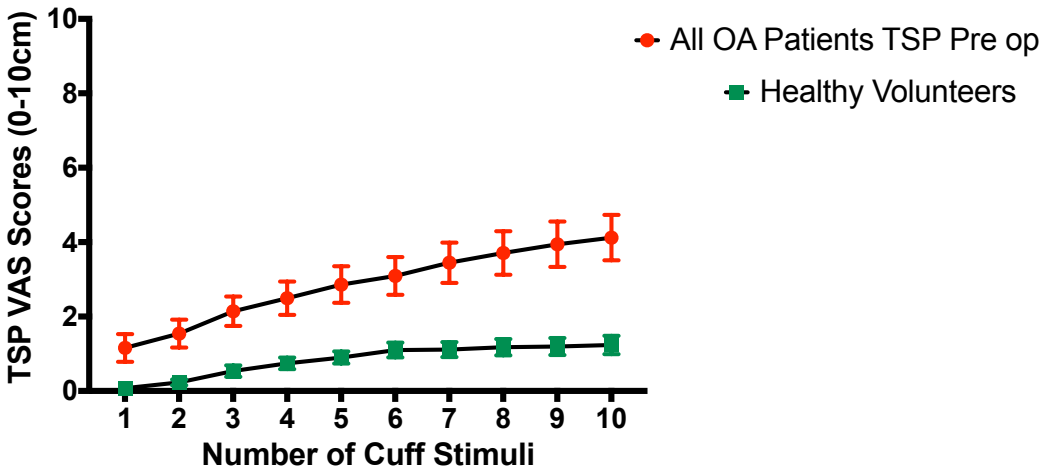


Figure 5.14 Cuff TSP Scores for Each Stimuli OA Patients and Volunteers

Figure 5.14 outlines the TSP VAS scores (mean+/-SEM) for each of the 10 cuff pressure stimulations comparing all OA patients together pre-TKR and all healthy volunteers. End-stage knee OA patients awaiting TKR surgery demonstrated facilitated TSP compared to healthy volunteers with their VASII-VASI TSP scores equalling (2.1+/-1.9) scores which exceeds the published thresholds of TSP score >1.55+/-0.17(16), indicating facilitated TSP and central sensitization of pain. Significant differences in the cuff TSP VAS II-VAS I scores were seen comparing all OA patients to the healthy volunteers (p=0.0088), Mann Whitney U-Test.

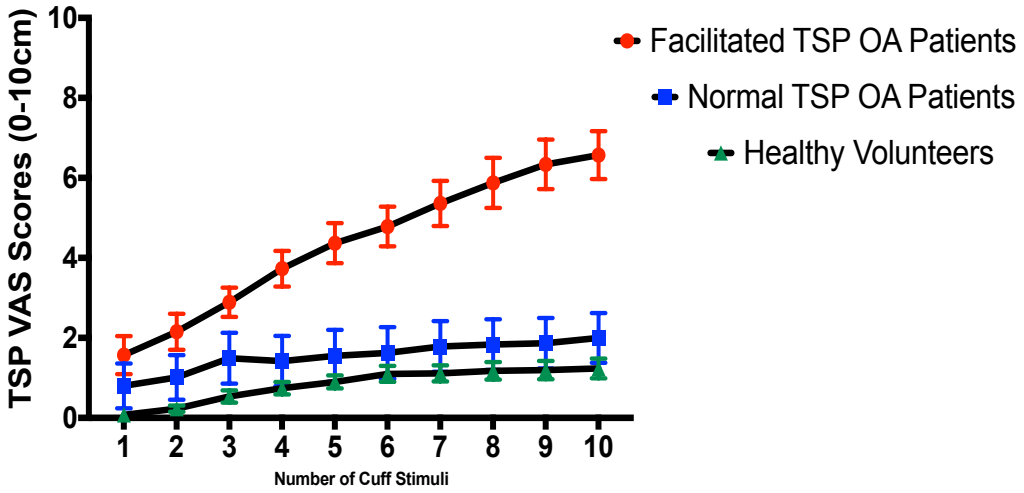


Figure 5.15 Cuff TSP Scores for Each Stimuli 3 Group Results

Figure 5.15 shows the TSP VAS scores (mean+/-SEM) for each of the 10 cuff stimulations between the OA patients now sub-grouped into those that had facilitated TSP, normal TSP and the healthy volunteers. Significant differences in TSP VAS Score (VASII-VASI) were seen (Kruskal Wallis Test Statistic: 25.5, p<0.0001) between facilitated TSP OA patients and normal TSP OA patients (p<0.0001) and facilitated TSP OA patients and healthy volunteers (p<0.0001). Fig 5.15

The analysis of the functional brain MRI paradigm assesses the TSP with the cuff algometer and for analysis the TSP effect was

assessed comparing the difference in neural brain activity of the 10th cuff stimulus to the 1st cuff stimulus. For that reason, the cuff algometry TSP results are also presented comparing the TSP VAS score of the 10th cuff stimulation to the 1st cuff stimulation. Similar results were seen to the VASII-VAS I results described above with the OA patients having significant higher (3.0, [2.4], mean +/-[SD]) cuff TSP difference scores (10th-1st cuff stimulus) than the healthy volunteers (1.2, [1.0], mean +/-[SD]), Unpaired T-Test (p=0.0057). Those OA patients with facilitated TSP also demonstrated significantly higher facilitated TSP scores when the analysis was between the 10th and 1st VAS score (ANOVA: F=38.0, p<0.0001) than normal TSP patients (p<0.0001) and healthy volunteers (p<0.0001). Fig 5.16

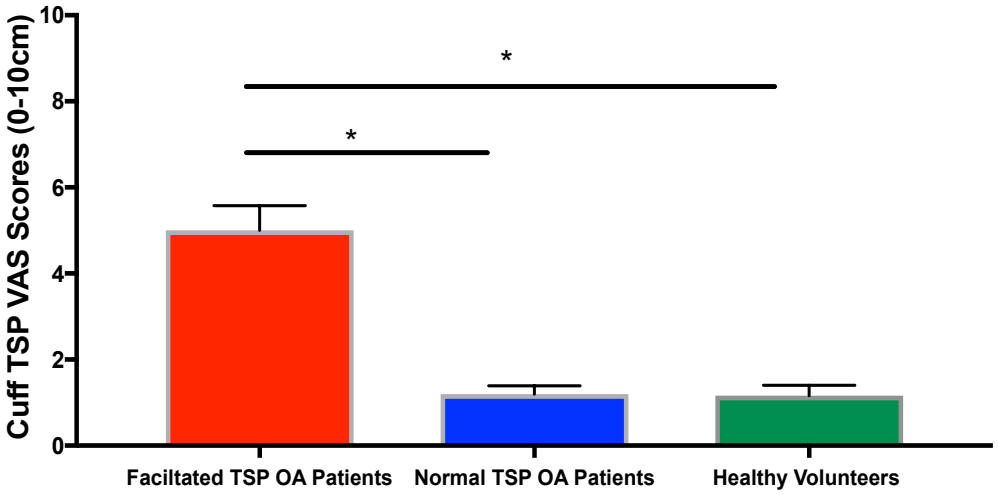


Figure 5.16 Cuff TSP Comparing (10th-1st stimuli) VAS Scores for fMRI Paradigm

Figure 5.16. Mean +/-SEM of the cuff TSP scores comparing the 10th-1st cuff stimuli VAS scores of those OA patients that are centrally sensitized indicative of facilitated TSP, those that are just peripherally sensitized indicative of normal TSP and the healthy volunteer. p<0.05 considered significant.*

5.7.3 Cutaneous Pin Prick TSP Assessment (10^{th}–1^{st})

Using the 25.6g monofilament patients with knee OA demonstrated significantly higher TSP scores than healthy volunteers (p=0.0001, Mann Whitney U-Test), Fig 5.17. Subgrouping the OA patients into facilitated TSP and normal TSP based on the cuff VAS II-VAS I demonstrated that the OA patients with facilitated TSP (P=0.0007) as well as the normal TSP (0.0117) had significantly higher pin prick TSP VAS scores than the healthy volunteers. (ANOVA: F=9.0, p=0.0005). Fig 5.18

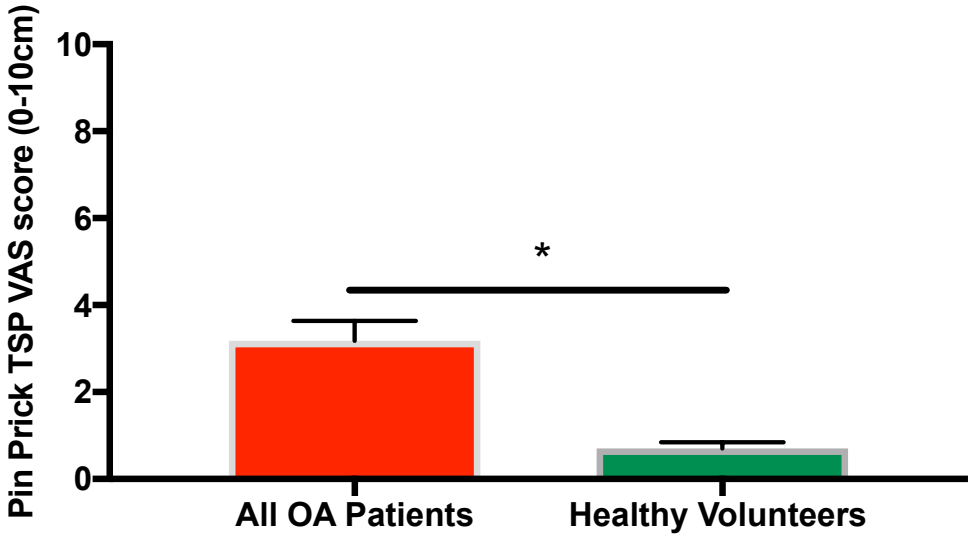


Figure 5.17 Pin-Prick TSP Scores OA Patients and Volunteers

Figure 5.17. Mean +/- SEM pin prick TSP scores comparing all OA patients to healthy volunteers. P<0.05 considered significant.*

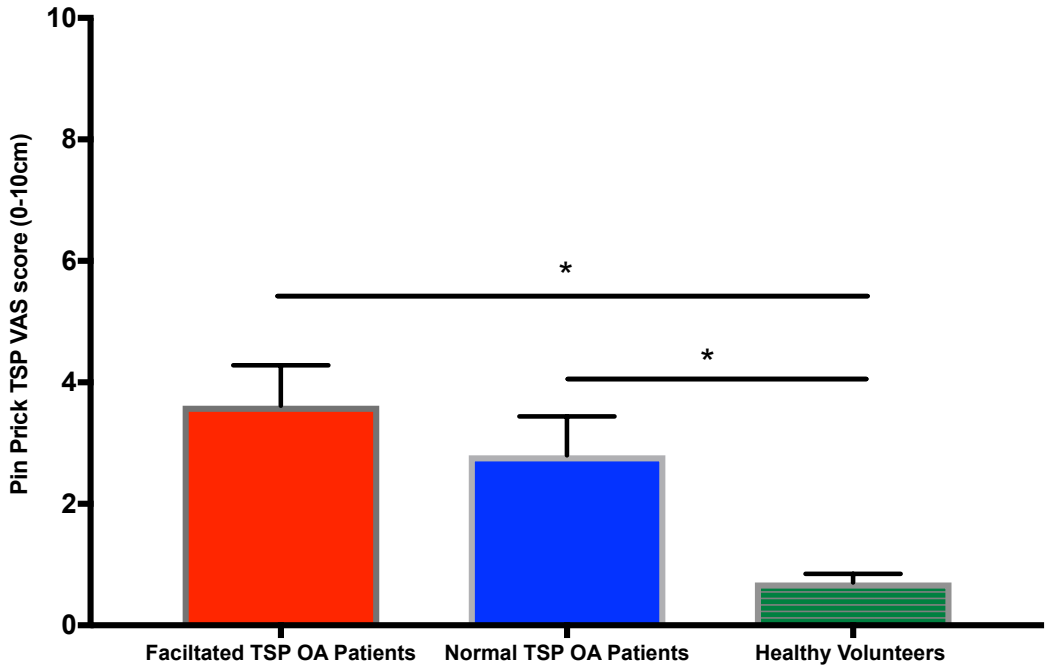


Figure 5.18 Pin-Prick TSP Scores between sub-grouped OA patients and volunteers

Figure 5.18. Mean +/- SEM pin prick TSP scores comparing all knee OA patients with facilitated TSP, those with normal TSP scores and healthy volunteers. P<0.05 considered significant*

5.7.4 Preoperative Cuff Condition Pain Modulation results

Knee OA patients awaiting TKR surgery demonstrated significantly impaired CPM scores to heathy volunteers (p=0.0042), Unpaired T-Test. Fig 5.19

Analysis of the CPM scores of OA patients sub-grouped into those that had facilitated TSP and normal TSP scores showed that that those knee OA patients with facilitated TSP had significantly impaired CPM results (Kruskal Wallis Test Statistic:7.3, p=0.0262) compared to healthy volunteers (p=0.037). Fig 5.20

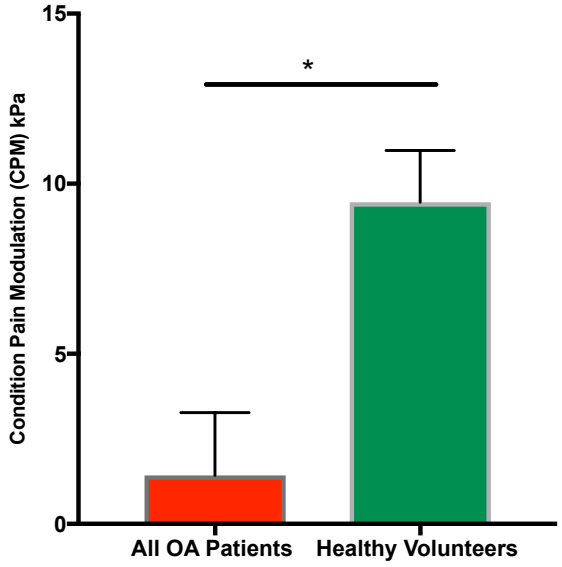


Figure 5.19 Pre-TKR CPM Results of OA Patients and Volunteers

Figure 5.19. Mean +/-SEM CPM scores between OA patients and healthy volunteers. P<0.05 considered significant*

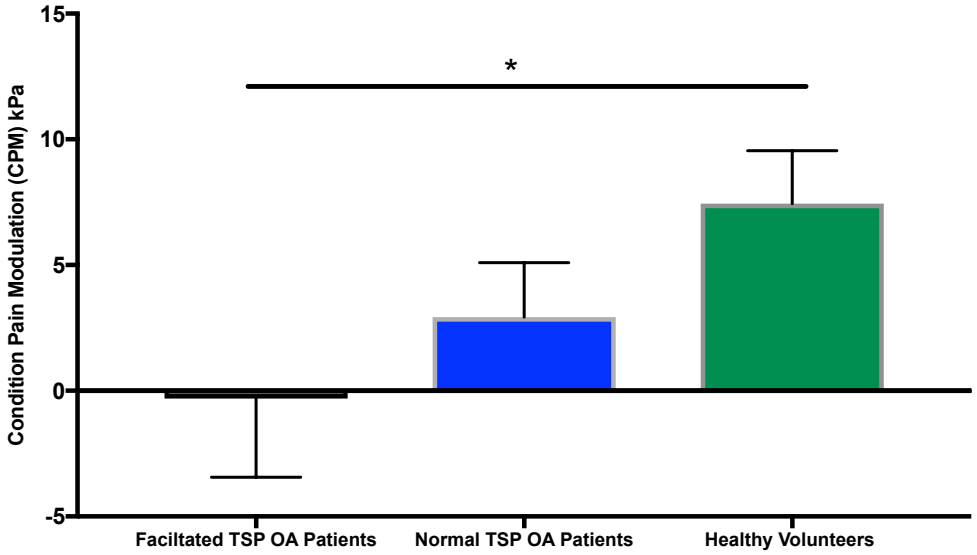


Figure 5.20 Pre-TKR CPM Results OA Patients Sub-grouped and Volunteers

Figure 5.20. Mean +/-SEM CPM scores between OA patients with facilitated TSP, Normal TSP and healthy volunteers. P<0.05 considered significant*

Table 5.3 Pre-TKR Psychology, Knee Function and Quality of Life Results

	Facilitated TSP OA Patients	Normal TSP OA Patients	Healthy Controls	ANOVA/ KW Test	F or H Statistic	P Value	Comparison	p values
Pain Catastrophizing Scale (PCS)	9 (2-29.5)	15 (5-20)	2 (0-8.5)	KW Test	8.811	0.0122	A-B A-C B-C	>0.9999 0.0598 0.0212*
Rumination (PCS)	4 (0.5-11.5)	5 (3-10)	0 (0-4)	KW Test	9.679	0.0079	A-B A-C B-C	>0.9999 0.1154 0.0079*
Beck Depression Inventory (BDI)	7 (2.5-10.5)	6 (3-14)	0 (0-2.5)	KW Test	15.37	0.0005	A-B A-C B-C	>0.9999 0.0038* 0.0017*
STATE Anxiety	36.1 [12.9]	32.7 [11.1]	26.4 [6.5]	ANOVA	3.5	0.1429	A-B A-C B-C	0.6670 0.0367* 0.2014
TRAIT Anxiety	31 (23-46)	33 (25-42)	25 (20.5-32)	KW TEST	5.66	0.0590	A-B A-C B-C	>0.9999 0.1813 0.0945
Oxford Knee Score	20 (17-28)	24 (16.5-31.5)	48 (47-48)	KW TEST	28.33	<0.0001	A-B A-C B-C	>0.9999 <0.0001* <0.0001*
EQ-5D-5L Index Score	0.49(0.25-0.64)	0.53 (0.20-0.65)	1 (0.92-1)	KW TEST	29.36	<0.0001	A-B A-C B-C	>0.9999 <0.0001* <0.0001*
EQ-5D-5L VAS Score	70.5 [15.1]	65.3 [23.0]	88.6 [9.5]	ANOVA	8.656	0.0007	A-B A-C B-C	0.6888 0.0141* 0.0008*

ANOVA or Kruskall Wallis Test. Mean [standard deviation] or Median (IQR) values are presented. P-values are based on the Tukey's post hoc tests for normally distributed data and Dunn's post-hoc tests for non-normally distributed data. p<0.05 is significant

5.7.5 Preoperative Psychological, Knee Function and Quality of Life Assessment Results

Table 5.3 outlines the behavioural psychological, knee function and quality of life assessment in knee OA patients prior to TKR surgery that had facilitated TSP, those that had normal TSP and and the healthy volunteers. Significant differences in the total pain catastrophizing scale scores as well as the 'rumination' sub-score of the pain catastrophizing scale were seen between the normal TSP OA patients and healthy volunteers. The OA patients also exhibited significantly higher levels of clinical depression compared to the healthy volunteers assessed using the BDI-II questionnaire.

STATE anxiety was seen to significantly higher in the facilitated TSP patients compared to the healthy volunteers ($p=0.0367$) and both OA subgroups demonstrated significant worse quality of life assessment measures compared to the healthy volunteers ($p<0.0001$). The Oxford knee scores which are a measure of knee pain and function were also significantly lower indicating worse knee pain and overall function of the joint in the OA patients compared to the healthy volunteers ($p<0.0001$).

5.7.6 Follow up six months post-TKR surgery

Twenty five out of the 28 OA patient returned for post-TKR follow up 6 months after their surgery (89.2%). One patient was excluded at the follow up stage as 1 month after her TKR operation she had a fall and suffered a peri-prosthetic fracture that required a revision TKR procedure. The final 2 patients were lost to follow up. All 25 patients underwent the postoperative QST assessment using hand held pressure algometry to assess PPTs, Cuff algometry (PDT, PTT, TSP and CPM) and cutaneous pin prick TSP assessment as well as completion of the ICOAP,

VAS score, Oxford Knee Scores and EQ-5D-5L quality of life questionnaires. All subjects underwent a 3-Tesla MAVRIC® metal artefact reduction MRI scan. Twenty-two knee OA patients underwent a preoperative fMRI brain scan and 19 out of these 22 patients completed the post TKR fMRI scan for comparative analysis. Three post-TKR patient datasets were deemed unusable due to excessive motion during the scan acquisition.

5.7.7 Responders and Non-Responders to TKR Surgery and Pain Outcomes

The primary outcome measure was defined as chronic knee pain six months after TKR surgery. Patients reporting significant postoperative knee pain with a knee pain intensity VAS score > 3 on a numeric rating scale assessed at follow up were defined as being in chronic postoperative pain, similar to previous studies (12, 178) and categorised as non-responders to TKR surgery. Responders to TKR surgery were defined as those OA patients with a knee pain intensity VAS score of ≤3 on a numeric rating scale 6 months after TKR surgery. From the 25 knee OA patients that returned for follow up 6 months after TKR surgery seventeen patients (68%) were classified as responders to TKR surgery with a mean [SD] post TKR knee pain intensity VAS score of 0.12 [0.33] and 8 were non responders with a mean [SD] post TKR knee pain intensity VAS scores of 4.3 [0.46] which is higher than the reported literature.(5-13) Statistically significant differences in the knee pain intensity post-TKR VAS scores were seen between the responders and non-responders to TKR surgery ($p<0.0001$), Mann Whitney U-Test. The non-responders to TKR surgery showed significantly higher ($p=0.0004$) post-TKR ICOAP scores (25, (12.5-37.5), median and IQR) compared to the responders to TKR (0, (0-5.6), Mann Whitney U-Test. Post-TKR PainDETECT scores were also significantly different between the responders (median and IQR, (2, (0-4.5)) and non-responders

(7, (2.5-17.5) (P=0.027), Mann Whitney U-Test.

5.7.8 VAS-BOLD fMRI Results between Responders and Non-Responders to TKR Surgery

Figure 5.21 highlights the VAS-BOLD fMRI results identifying areas of brain activation associated with subjective VAS pain intensity scores assessed using the cuff algometer in responders and non-responders to TKR surgery. Responders (shown in blue regions) demonstrated similar brain activation to the TSP paradigm post TKR as the healthy volunteers with activation predominately in the prefrontal regions suggesting some degree of normalization of pain and pain perception post-surgery which correlated with their subjective VAS scores reported. This is in contrast to the non-responders (shown in red) who continue to report subjectively persistent postoperative pain and demonstrate continued brain activity in the S2 region as well as activation in the sensorimotor and supramargial gyrus regions post TKR. This area of activity of interest at it was the same region that was identified in those preoperative knee OA patients we had identified that were centrally sensitized with facilitated TSP based on their cuff algometry scores.

These results suggest that continued graded neural brain activity in the S2 region may be an important imaging biomarker for chronic post-TKR pain and is activated in response to facilitated TSP.

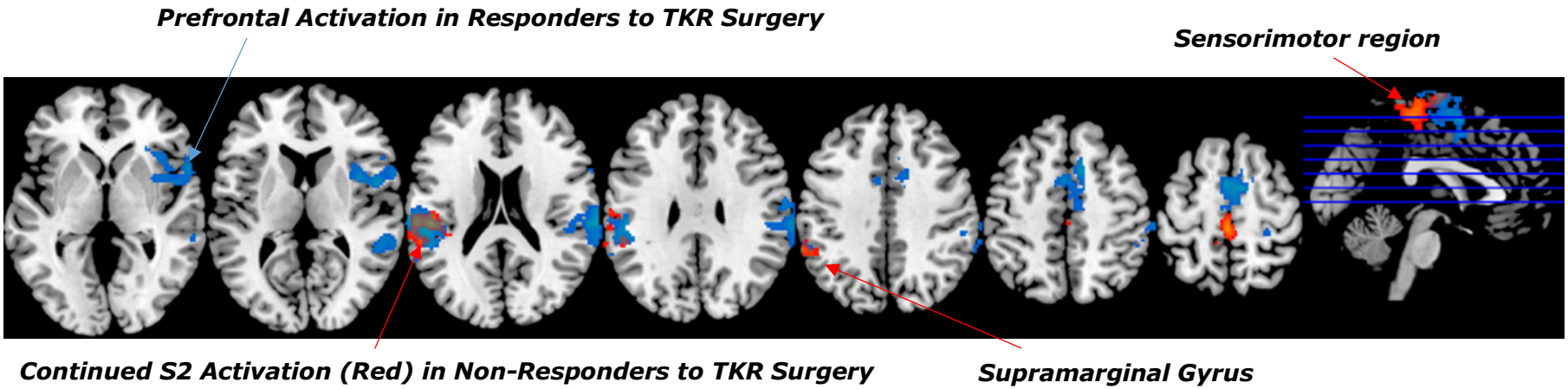


Figure 5.21 fMRI Results Responders (shown in blue) and Non-Responders (red) to TKR Surgery

Figure 5.21. VAS-BOLD fMRI *results Six months post TKR in those Responders (VAS≤3) or Non-responders (VAS≥4) in respect to knee pain intensity using the TSP Cuff paradigm. Responders (shown in blue appear to normalise their brain activity post TKR with predominant activation within the prefrontal cortex, similar to the healthy volunteers as seen in Figure 5.6. However, non-responders to TKR surgery (shown in red) who report persistent pain following surgery continue to show brain activation within the S2 regions which is similar to those preoperative OA patients with facilitated TSP.*

5.7.9 Baseline Pre-TKR fMRI Differences Between Responders and Non-Responders to TKR surgery

Figure 5.22 demonstrates the baseline preoperative VAS-BOLD TSP changes in the brain in those OA patients that responded and failed to respond to TKR surgery. The yellow regions demonstrate the (Non-responders>Responders) comparison clearly identifying that those OA patients that fail to respond to TKR surgery demonstrate preoperative activation in the S2 region which we have also shown continues to be activated post-TKR in this subgroup. The blue brain regions demonstrate the (Responders>Non-responders) comparison and demonstrate preoperative activation within the DMN regions as well as the cerebellum and occipital lobes. These results appear to suggest the preoperative correlated activation within the S2 regions with pain severity reported in response to a TSP cuff challenge paradigm may be an imaging biomarker for the prediction of chronic postoperative pain following TKR surgery.

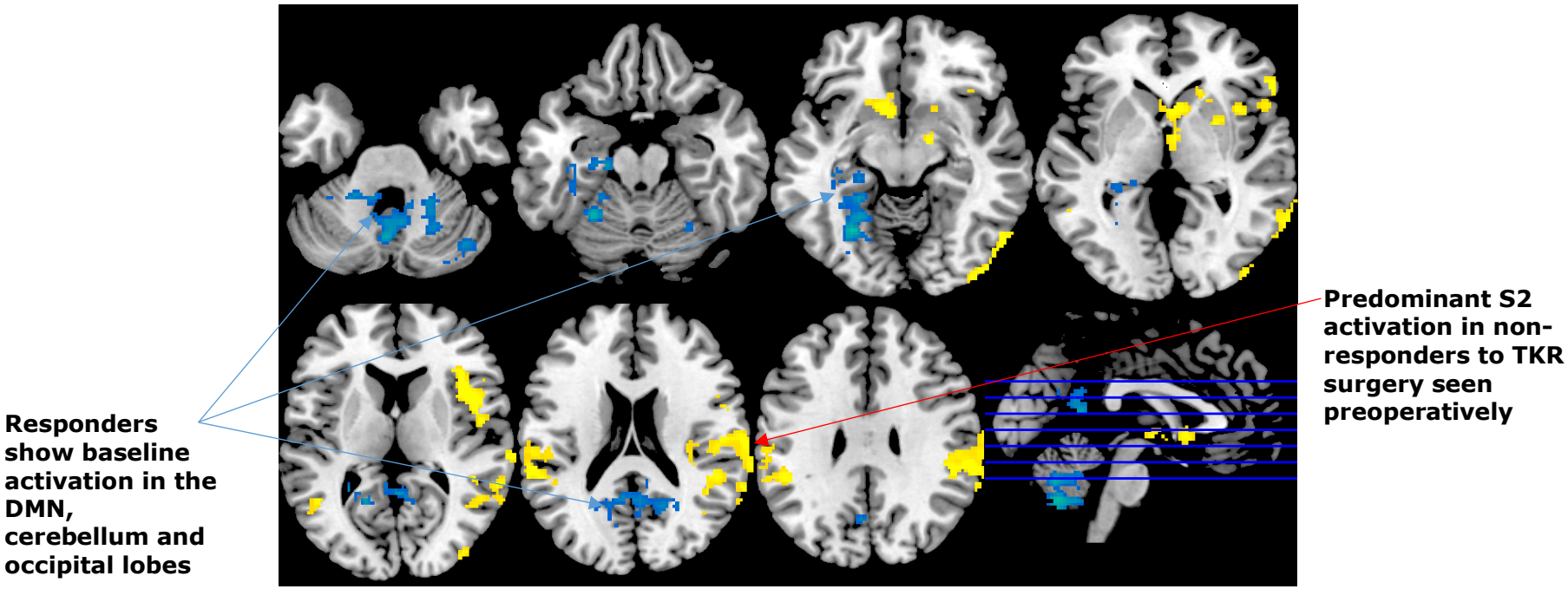


Figure 5.22 Baseline Pre TKR VAS-BOLD fMRI Results of Responders (blue) and Non-Responders to TKR (yellow)

5.7.10 Baseline Pre-TKR PPTs Results Between Responders and Non-Responders to TKR Surgery

After the identification of the responders and non-responders to TKR surgery, retrospective assessment of the pre TKR PPTs of those subgroups was conducted to identify if there was any underlying preoperative difference in pain sensitivity profiles assessed by PPTs between those OA patients that responded and those that failed to respond to TKR surgery. No significant differences were seen in pre-TKR PPTs results between the responders and non-responders to TKR surgery, Knee (MJL: $p=0.2352$, SMP: $p=0.2540$, mean knee: $p=0.0017$ Unpaired T-Tests, (SLP: $p=0.4086$, Mann Whitney U-Test), distant sites (TA: $p=0.4033$, Unpaired t-Test) and remote sites (ECRL: $p=0.6639$, Unpaired T-test), Fig 5.23.

5.7.11 Change in PPTs in Responders After TKR Surgery

OA patients that responded to TKR surgery showed significant improvement in the PPTs scores pre and post TKR surgery. Improvements in all testing sites at the knee joint (MJL: $p=0.0035$, SMP $p=0.0086$, Mean Knee: $p=0.0017$, Paired T-Tests and SLP: $p<0.0001$, Wilcoxon Signed Ranks Test) at distant sites (TA: $p=0.0064$, Wilcoxon Signed Ranks Test) and remote sites (ECRL: $p=0.0018$, Paired T-Test) were seen in this subgroup after TKR surgery, Fig 5.23.

5.7.12 Change in PPTs in Non-Responders After TKR Surgery

Non-responders showed no significant improvement in PPTs after TKR surgery at the knee (MLJ: $p=0.5216$, SLP: $p=0.3767$, Paired T-Tests and SMP: $p=0.4609$ and Mean Knee: $p=0.8438$, Wilcoxon Signed Ranks Test) or at distant knee sites (TA:

p=0.4033, Paired T-test) or remote sites (ECRL: p=0.5241), Fig 5.23.

5.7.13 Post TKR PPTs Results at the Knee Compared to Healthy Volunteers

Comparison of post-TKR PPTs results between the responders and non-responders to the healthy volunteers can determine whether the increased pain sensitivity seen in OA patients prior to TKR surgery has normalised after the operation. At the knee, significant differences were seen between the non-responders post-TKR PPTs results to the healthy volunteers but no differences were seen comparing post TKR PPTs in the responders to the volunteers: MJL: (ANOVA: F=7.0, p=0.0026, non-responders vs healthy volunteers p=0.0018, responders vs healthy volunteers p=0.229), SMP: (Kruskal Wallis Test Statistic= 12.5, p=0.002, non-responders vs healthy volunteers p=0.0018, responders vs healthy volunteers p=0.1035), SLP: (ANOVA: F=9.7, p=0.0004, non-responders vs healthy volunteers p=0.0003, responders vs healthy volunteers p=0.009 and mean knee: (Kruskal Wallis Test statistic = 11.2, p=0.004, non-responders vs healthy volunteers P=0.0028, responders vs healthy volunteers p=0.2558), Fig 5.23.

5.7.14 Post TKR PPTs Results at Distant and Remote Sites Compared to Healthy Volunteers

Non-responders to TKR surgery continue to demonstrate evidence of continued central pain facilitation post TKR displaying significant differences in the PPTs recorded at distant sites to the knee and at remote sites. This is in contrast to the responders to TKR surgery who demonstrate normalization of central sensitization post TKR surgery evidenced with no significant difference in PPTs at distant and remote sites to the healthy volunteers: TA (Kruskal Wallis Test statistic = 7.5, p=0.002 non-responders vs healthy volunteers p=0.002,

responders vs healthy volunteers p=0.404), ECRL (ANOVA: F=3.0, p=0.06, non-responders vs healthy volunteers p=0.047, responders vs healthy volunteers p=0.590), Fig 5.23.

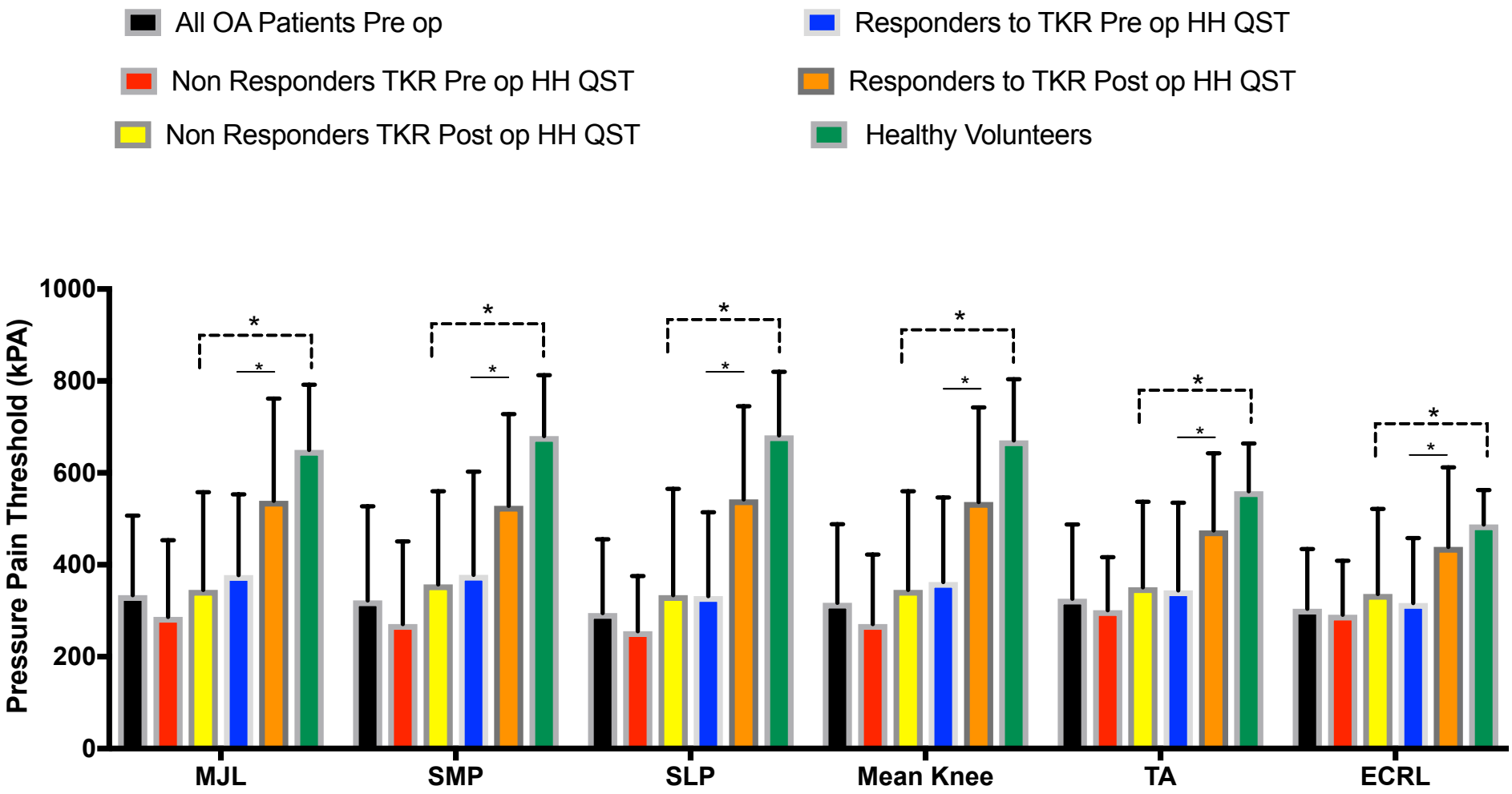


Figure 5.23 Hand Held (HH) Algometry PPTs Results Pre and Post-TKR with Healthy Volunteers

Key: MJL (medial joint line), SMP (superior-medial patella). SLP (superior-lateral patella), TA (Tibialis Anterior Muscle) and ECRL (Extensor Carpi Radialis Longus Muscle). p<0.05 considered significant.*

5.8 Condition Pain Modulation (CPM) Post TKR Responder, Non-Responders and Healthy Volunteers

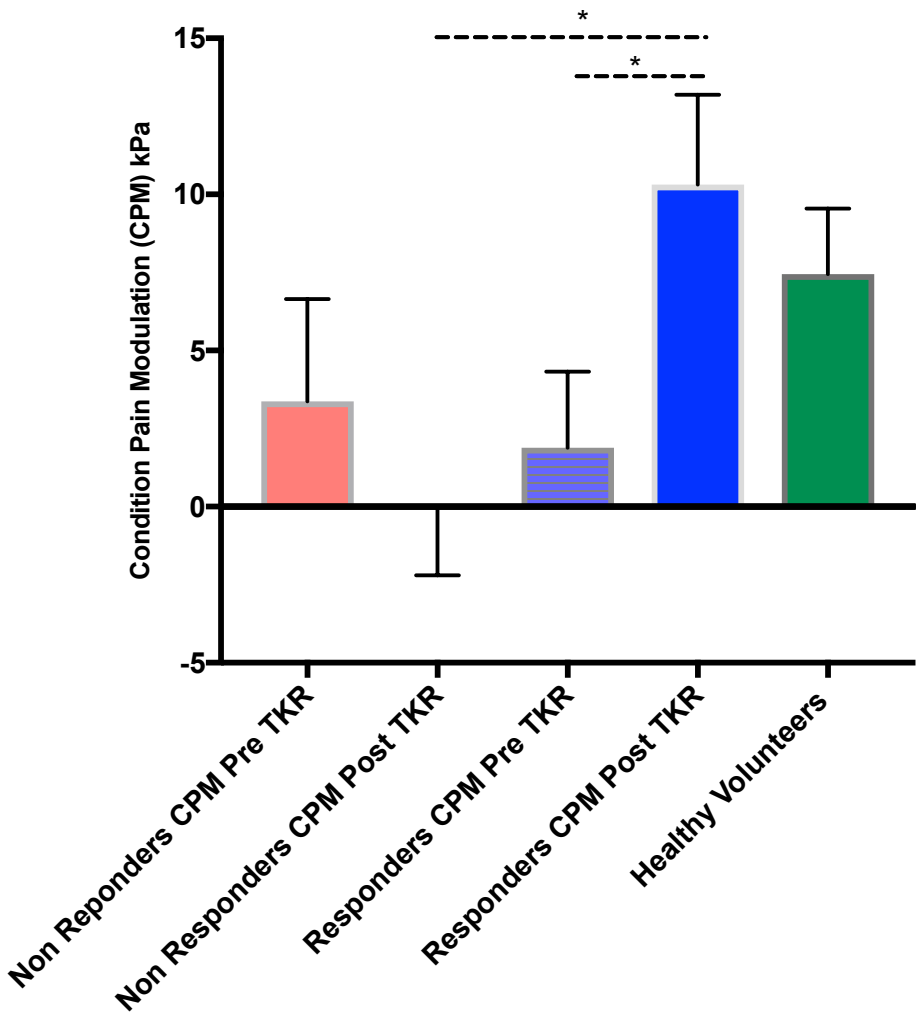


Figure 5.24 CPM results Responders and Non-Responders to TKR Surgery

Responders to TKR show significant improvement in the CPM following TKR surgery, (p=0.0395, Wilcoxon Signed Rank Test). (Fig. 5.16) Prior to TKR surgery both the responders (1.88 [10.1], mean and SD) and non-responders (3.38 [9.3], mean and SD) demonstrated impaired CPM when referenced against previously published cut off values for cuff algometry CPM (impaired CPM cuff <5.5 ± 1.1kPa). (16)

Post TKR the responders showed significant improvement in CPM score (10.3 [11.9] mean and SD) as opposed to the non-responders who in our series have further impairment in their

CPM scores post TKR (-0.03 [6.1] mean and SD). Assessment of the post TKR CPM scores of the two operated groups and the healthy volunteers showed significant differences (Kruskal Wallis Test statistic = 7.3, P=0.026,) between the responders and non-responders (p=0.0298) but no significant differences between the healthy volunteers and non-responders (p=0.0056) or the healthy volunteers and responders to TKR surgery (p>0.9999), Fig 5.24.

5.8.1 Cuff TSP Results in Responders and Non-Responders to TKR Surgery

Figure 5.25 outline the TSP VAS scores (mean +/-SEM) for each of the cuff pressure stimulations (1-10) set at the individuals pain tolerance thresholds (PTT). The graph clearly shows that responders to TKR normalise their TSP post TKR with similar TSP VAS scores recorded for the healthy volunteers, Figures 5.25 and 5.26. Knee OA patients that fail to respond to TKR surgery continue to demonstrate facilitated TSP, a marker of persistent central sensitization 6 months post TKR surgery as shown in Fig 5.26. Significant differences in post TKR cuff TSP scores were seen comparing non-responders to responders and healthy volunteers (Kruskal-Wallis Test, p=0.0018, non-responders vs responders, p=0.002, Fig 5.26.

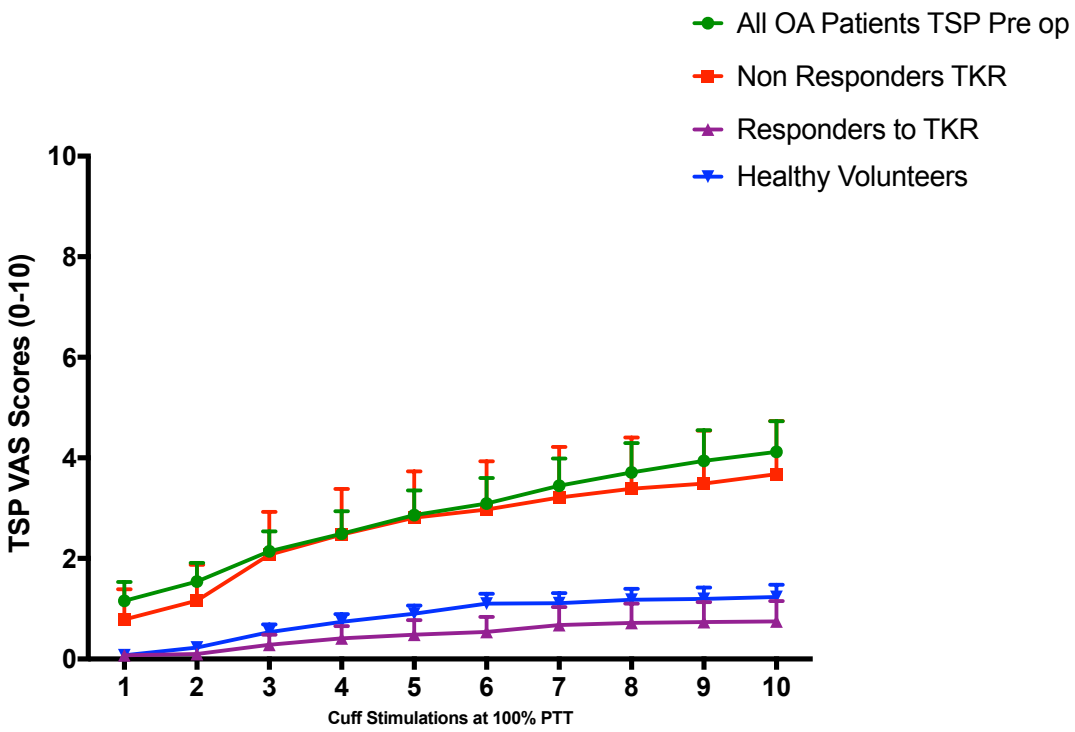


Figure 5.25 Cuff TSP VAS Scores in Responders and Non-Responders to TKR

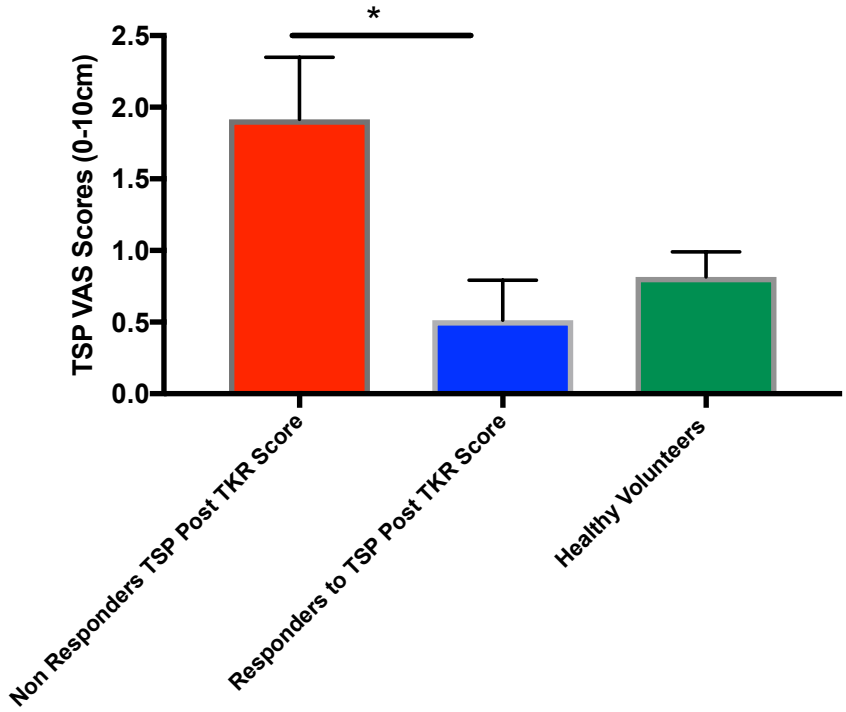


Figure 5.26 TSP Results Post TKR in Responders and Non-Responders

5.8.2 Post TKR Knee Pain and Quality of Life Outcomes

Significant differences were seen in the post TKR Oxford Knee Scores (p=0.0008, Mann Whitney U-=Test) between the responders (44, (40-47), median and IQR) and non-responders (34.5, (32-38.5)) with the responders to TKR showing greater overall improvement in their knee pain and function after TKR surgery. Overall health assessed by the EQ-5D-5L index questionnaires post TKR showed that responders to TKR had significant improved overall self-reported health status (0.85 [0.16] mean and SD) compared to non-responders to TKR (0.71 [0.12]), (p=0.0033), Unpaired T-Test. No significant differences were seen in the evaluation (EQ-5D-5L VAS) questionnaire between responders and non-responders after TKR surgery, Unpaired T-Test.

5.8.3 MAVRIC Post TKR Knee MRI Scan results

All 25 patients who returned for follow up assessment underwent a MAVRIC 3-Tesla knee MRI scan. Post TKR tibial BML MOAKS scores were significantly higher in the non-responders to TKR surgery (7.13 [2.2], mean and SD) compared to responders (1, [1.1], mean and SD), p<0.0001, Unpaired T-Test, Fig 5.27. The medial anterior sub-region of the tibia was the commonest region for the largest BMLs seen post TKR. Non-responders to TKR also showed significantly higher post TKR MOAKS effusion synovitis scores (2.5 (2-3), median and IQR) than the responders (1, (0-1) median and IQR), p=0.0007, Mann Whitney U-Test, Fig 5.25. MOAKS Hoffa synovitis scores were significantly greater in the non-responders to TKR surgery (2.5, [0.76], mean and SD) compared to the responders (0.75 [0.77], mean and SD), p<0.0001, Unpaired T-Test, Fig 5.27. The use of a MAVRIC, a novel metal artefact reduction knee MRI sequence has identified for the first time the presence of post TKR BMLs, effusion synovitis and Hoffa synovitis which are

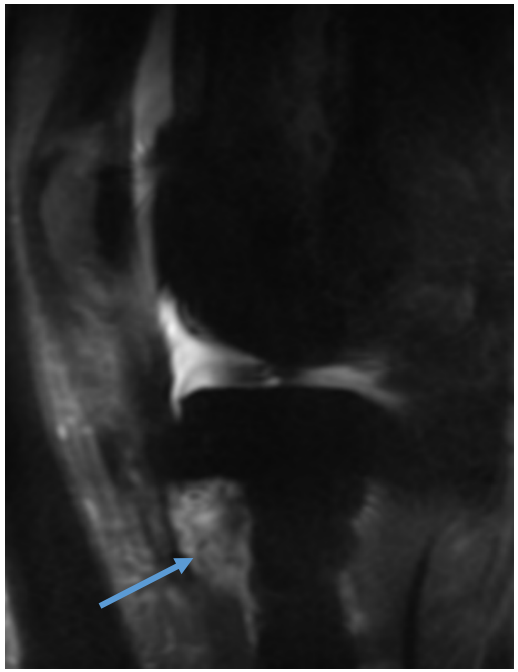
known peripheral drivers of pain. These results show that the continued or new presence of these structural pathologies in OA may be sources of continuous nociceptive input contributing significantly to postoperative pain, dissatisfaction and maintaining central pain processing after TKR surgery.

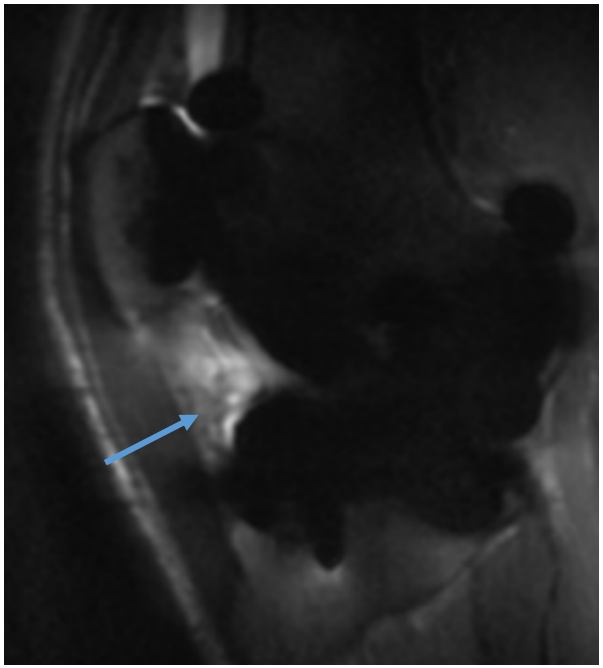
5.8.4 Inter-rater Reliability results of MAVRIC MRI Scoring

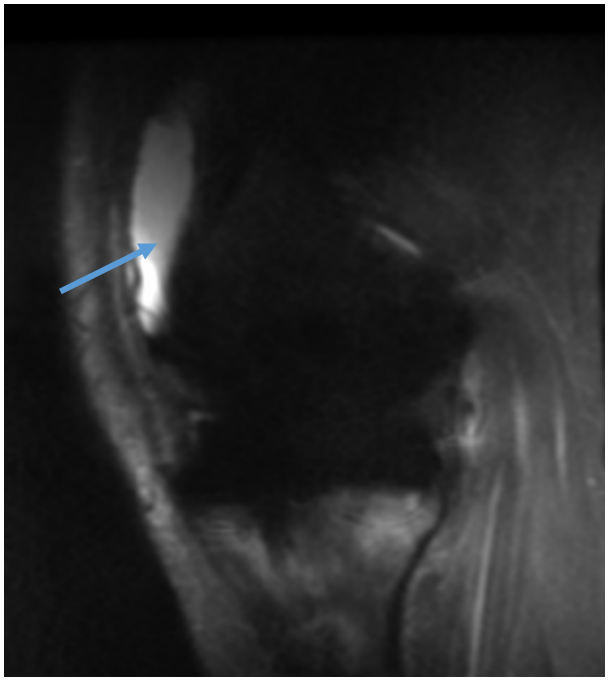
The MAVRIC post TKR MRI scans were scored by 2 observers, one an orthopaedic physician trained to complete the MAVRIC scores and a senior, experienced consultant musculoskeletal radiologist. The same MOAKS MRI scoring criteria were used to assess for BMLs (within the tibia post TKR) as well as effusion synovitis and Hoffa synovitis. Ten MRI data sets were chosen at random to assess for inter-rater reliability between the 2 observers.

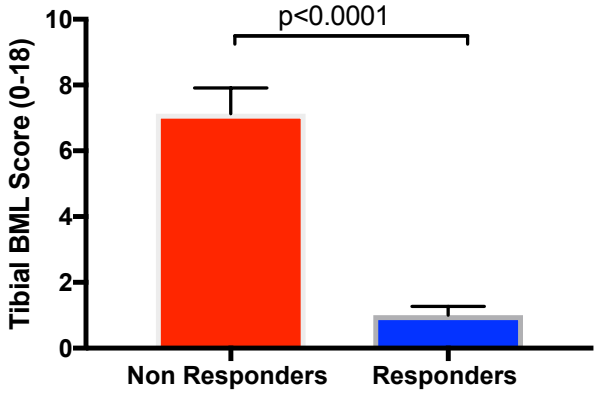
The tibial MAVRIC BML interclass co-efficient (ICC) between the 2 observers was 0.962 (95% CI 0.851-0.99), the effusion synovitis ICC was 0.921 (95% CI 0.701-0.980) and the Hoffa synovitis ICC was 0.851 (0.444-0.962) demonstrating excellent agreement between the 2 observers. In cases where there was disagreement between the scores the senior musculoskeletal radiologist decided the final outcome.

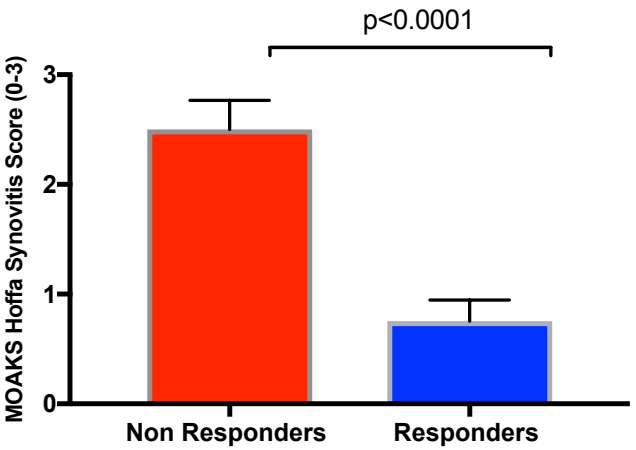
Figure 5.27 Post TKR BML, Hoffa Synovitis and Effusion Synovitis MAVRIC MRI Images and Scores

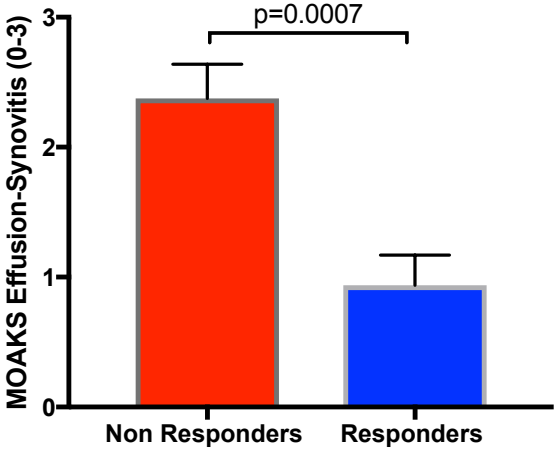












5.9 Statistical Analysis for Predictive Model for post-TKR Pain

One of the study aims was to develop a predictive model to understand if baseline variables were predictive for a successful or poor outcome six months following TKR surgery. The outcome variable was whether the patients had a good (responder) or poor (non-responder and still in pain post-operatively) outcome. The study was underpowered to utilise a logistic regression model with outcome coded as responder (post-operative VAS = 0 or 1) or not (post-operative VAS ≥ 4). Note, no patients reported a post-operative VAS score of 2 or 3. Accordingly, a linear regression model was utilised with the dependent variable (outcome) being the post-operative VAS score as a continuous variable similar to other studies.(12, 178, 249, 250) A Shapiro Wilks test was used to determine whether the VAS data were normally distributed.

5.9.1 Unpaired Analysis

Due to the large dataset (i.e. many risk factors measures), initially unpaired analyses of the risk factors (comparing OA patients who responded (no/minimal pain) with those who non-responded (chronic pain) was undertaken. This would identify risk factors most likely to be important in the predictive model.

A Shapiro Wilks test was used to determine whether continuous data (risk factors) were normally distributed. Where the data met parametric assumptions (e.g. continuous variable, Normal distribution, independent, interval, homogenous), a Levene's test was used to determine whether the variance in the two groups was equal or not, and then the corresponding independent t-test was used to assess differences between the patients with a good outcome (responders) and those with a poor outcome (non-responders in chronic pain). This was true

for the variables 'age' and 'BMI' with the results suggesting older and obese patients are more likely to develop chronic pain after TKR surgery, Table 5.4).

Where data were categorical (usually ordinal) or scale or did not meet parametric assumptions (e.g. not normal distribution), chi squared test was used to assess differences between the patients with a good outcome (responders) and those with a poor outcome (non-responders in chronic pain), Table 5.5 and 5.6.

The unpaired analyses showed that there were statistically significant differences between groups (responders and non-responders) for the TSP 2nd cuff pressure ($p=0.008$, Table 5.6. This is likely due to the small sample size (i.e. Type II error indicating a false negative result). Nevertheless, other data showed trends. For example, older and obese patients were less likely to do well following TKR surgery. (See Tables 5.4, 5.5 and 5.6).

Variable	Shapiro Wilks test (ie Normal if >0.05)	Levene's test (ie equal variance if >0.05)	unpaired T-Test equal variance	Responders (mean)	Non-Responders (mean)	Notes
Age	0.753	0.960	0.212	66.2 years	70.3 years	*Older patients less likely to do well*
BMI	0.226	0.350	0.645	29.6 kg/m2	30.5 kg/m2	*Obese patients less likely to do well*

Table 5.4 Results of unpaired T-Test for Age and BMI (Parametric)

Variable	chi square p value:	Responders %	Non-Responders %	Relative Risk	Responders (mean)	Non-Responders (mean)	Notes
Sex M-Male F-Female	0.424	62.5%F; 77.8%M	37.5%F; 22.2%M	1.7	-	-	M more likely to do well; F 1.7x more likely to have poor outcome
Cuff TSP Scores (VAS II-I)	0.318	58% High TSP 77% Low TSP	42% High TSP; 23% Low TSP	1.8	2.00	2.26	Low TSP are more likely to do well; if High TSP 1.8x more likely to have poor outcome
VAS pain Score	0.228	61% high (≥4) 86% low (≤3)	39% high (≥4 14% low (≤3)	2.7	4.82	6.25	If high score 2.7x more likely to have poor outcome
Cuff CPM Score	0.144	59% ≤5.5 (low) 88% >5.5 (high)	41% ≤5.5 (low) 12% >5.5 (high)	3.3	1.9	3.4	If have low score 3.3x more likely poor outcome

Table 5.5 Summary of unpaired analyses results for categorical variables

Variable	chi square p value:	Shapiro Wilk (ie Normal if >0.05)	Responders (mean)	Non-responders (mean)	Notes
Pain Duration	0.370	0.003	3.71 years	3.22 years	Less pain duration, do less well
PainDETECT Score	0.089	-	11.0	15.4	*Higher score associated with pain/poor outcome*
ICOAP Score (0-49 low and 50+ high)	0.073	-	54.8	56.5	*Higher score associated with pain/poor outcome*
Pain Catastrophizing Scale	0.113	-	14.6	12.1	
Beck Depression Inventory II	0.157	-	7.8	9.0	
STATE anxiety	0.122	-	31.9	35.6	
Trait Anxiety	0.054	-	30.6	38.4	*Higher score associated with poor outcome*
PDT	0.115	-	22.0	13.2	*Lower score associated with poor outcome*
PTT	0.144	-	44.2	39.9	
Pin-prick TSP	0.116	-	2.3	4.5	
Medial Joint Line PPT	0.144	-	365.1	286.5	
Superiomedial Patella PPT	0.115	-	365.0	271.1	
Superiolateral Patella PPT	0.115	-	322.8	255.3	
Mean Knee PPT	0.144	-	350.9	271.0	*Lower score associated with poor outcome*
Tibialis Anterior PPT	0.158	-	341.8	301.1	

ECRL PPT	0.089	-	304.7	291.2	Lower score associated with poor outcome
MOAKS BML Score	0.436	-	11.1	7.3	
MOAKS Hoffa Synovitis	0.412	-	1.9	1.6	
MOAKS Effusion Synovitis	0.084	-	2.7	1.9	Lower score associated with poor outcome
Oxford Knee Score	0.379	-	23.5	21.8	
EQ-5D-5L VAS Score	0.293	-	72.8	70.6	
TSP Cuff 1st Cuff Pressure	0.075	0.000	0.829	2.225	
TSP Cuff 2nd Cuff Pressure	0.008	0.000	0.988	3.088	Patients with higher initial scores do less well
TSP Cuff 3rd Cuff Pressure	0.057	0.003	1.624	3.600	
TSP Cuff 4th Cuff Pressure	0.073	0.005	1.906	3.988	
TSP Cuff 5th Cuff Pressure	0.125	0.020	2.241	4.463	
TSP Cuff 6th Cuff Pressure	0.068	0.043	2.482	4.638	
TSP Cuff 7th Cuff Pressure	0.097	0.038	2.853	4.938	
TSP Cuff 8th Cuff Pressure	0.115	0.025	3.129	5.275	
TSP Cuff 9th Cuff Pressure	0.214	0.021	3.335	5.500	
TSP Cuff 10th Cuff Pressure	0.125	0.025	3.541	5.663	
TSP Cuff 10th-1st Pressure	0.097	0.030	2.712	3.438	
TSP Cuff VAS I mean	0.073	0.000	1.338	3.228	
TSP Cuff VAS II mean	0.144	0.026	3.335	5.480	
TSP Cuff VAS II-VAS I	0.144	0.003	1.999	2.256	

Table 5.6 Summary of unpaired analyses results for non-parametric variables

5.9.2 Model reduction:

Key risk factors for chronic postoperative pain after TKR based on the clinical literature (5, 7, 10, 12, 13, 16-18, 20, 197, 251, 252) the unpaired analysis and the results from Chapters 3 and 4 were put into a linear regression model, with post-operative VAS score as the outcome variable on an entry method. Model reduction was used to determine the optimal fit model. That is, variables that were not statistically significant and/or had a small effect size were removed from the model one by one to determine the most important predictor variables for post-operative pain outcome. Two separate predictive models have been developed from the results of this study. One includes the brain imaging Z-scores from the fMRI data set for the left S2 and right S2 brain regions and another model which is more transferable to standard clinical practice which includes a series of pain questionnaires and standard QST measurements without MRI imaging. Model I shown in Table 5.7 using sixteen independent preoperative variables including the brain S2 region Z-scores, patient demographics (age, sex and BMI), pain and psychological questionnaires (pain duration in years, ICOAP, PainDETECT, Pain Catastrophizing Scale, and State anxiety) and QST scores (pin-prick TSP, CPM, PTT, ECRL PPT and Cuff TSP VAS I scores). Preliminary unpaired analysis identified that the conventional assessment of cuff TSP (VAS II-VAS I) was not a significant predictor of chronic postoperative pain, however the VAS I scores demonstrated a trend of significance ($p=0.073$, Table 5.6) and were included in the model. With our TSP paradigm having 10 sequential cuff pressure stimulations to the gastrocnemius muscle ipsilateral to the affected OA knee with a 1 second inter-stimulus interval it is clear an increase in VAS response between the 1st and 4th cuff pressure stimulus is present, especially in those OA patients with facilitated TSP, Fig

5.13. Model I with the sixteen significant independent variables is 99.7%, $p<0.001$ (adjusted R^2 =0.997) predictive for chronic pain six months after TKR surgery.

Model II uses sex, pain questionnaires (ICOAP, Pain Catastrophizing Scale and PainDETECT) and QST (pin-prick TSP, PTT and cuff TSP VAS I score) to identify those OA patients preoperatively that are at most risk of developing chronic postoperative pain six months after TKR surgery. This model with seven independent variables is more reproducible by orthopaedic surgeons as it does not include any brain imaging data. Model II with the associated variables is 55.8% predictive of chronic postoperative pain after TKR surgery (adjusted R^2= 0.558, p=0.002), Table 5.8.

Given the small data set in this study the multiple regression models must be interpreted with caution, however many of study participants completed the full study (89.2%) and were included in the postoperative follow up analysis, which is a major strength. This is the first study to use a multi-modal assessment including demographics, pain and psychological questionnaires, knee and brain MRI and QST to predict outcome following TKR surgery and it is hoped that this exploratory study will lead to much larger clinical trials into OA pain to identify those patients most likely to develop chronic postoperative pain.

Table 5.7 Preoperative Predictive Model I for Chronic Postoperative Pain after TKR Surgery

Model: Adjusted R^2 99.7%, P<0.001					
Coefficients [a]					
	Unstandardized Coefficients		**Standardized Coefficients**	**t**	**Significance**
MODEL	**B**	**Standard Error**	**ß**		
Age	0.029	0.0006	0.108	4.922	***0.016***
Sex	3.128	0.144	0.761	21.676	***<0.001***
BMI	0.518	0.020	1.068	26.526	***<0.001***
Pain Duration	-0.442	0.036	-0.471	-12.150	***0.001***
MOAKS Hoffa Synovitis	-1.448	0.063	-0.796	-22.947	***<0.001***
MOAKS BMLs	0.029	0.007	0.110	4.020	***0.028***
Pin-Prick TSP	2.353	0.106	0.588	22.161	***<0.001***
CPM	-0.975	0.101	-0.244	-9.607	***0.002***
ECRL PPT	0.001	0.000	0.073	3.645	***0.036***
PTT	0.045	0.004	0.517	12.226	***0.001***
Cuff TSP VAS I Score	0.885	0.060	0.698	14.774	***0.001***
ICOAP	-1.099	0.123	-0.268	-0.8931	***0.003***
Pain Catastrophizing Scale	-0.130	0.004	-0.807	-28.804	***<0.001***
PainDETECT	-3.278	0.128	-0.669	-25.648	***<0.001***
STATE Anxiety	-0.043	0.004	-0.263	-10.438	***0.002***
Brain Left S2/Right S2	-0.349	0.084	-0.131	-4.169	***0.025***

a. Dependent Variable: Follow Up VAS Pain Score (0-10cm) Six Months after TKR Surgery

Table 5.7 Outlines the independent variables used in model I to predict outcome (Postoperative Pain after TKR Surgery).

Key: BMI (body mass index). MOAKS MRI Osteoarthritis Knee Score), BMLs (Bone Marrow Lesions), TSP (Temporal Summation of Pain), CPM (Condition Pain Modulation), ECRL PPT (Extensor Carpi Radialis Longus Pressure Pain Threshold, PTT (Pain Tolerance Threshold), Cuff TSP VAS I Score (mean VAS Score of 1st to 4th cuff pressure stimulations), ICOAP (Intermittent and Constant Osteoarthritis Pain Score). Brain Left S2/Right S2 – sum of the Z scores of the S2 brain region right and left seen during functional MRI experiment.

Table 5.8 Preoperative Predictive Model II for Chronic Postoperative Pain after TKR Surgery

Model: Adjusted R^2 55.8%, P=0.002					
Coefficients [a]					
	Unstandardized Coefficients		**Standardized Coefficients**	**t**	**Significance**
MODEL	**B**	**Standard Error**	**ß**		
Sex	2.766	0.860	0.677	3.214	***0.005***
ICOAP	1.979	0.717	0.484	2.762	***0.013***
Pain Catastrophizing Scale	-0.085	0.027	-0.529	-3.192	***0.005***
PainDETECT	-2.000	0.869	-0.408	-2.302	***0.034***
Pin-Prick TSP	3.429	0.747	0.856	4.592	***<0.001***
Cuff TSP VAS I Score	0.498	0.150	0.529	3.331	***0.004***
PTT	0.066	0.021	0.705	3.149	***0.006***

a. Dependent Variable: Follow Up VAS Pain Score (0-10cm) Six Months after TKR Surgery

Table 5.8 Outlines the independent variables used in model II to predict outcome (Postoperative Pain after TKR Surgery). (Without Brain data)

Key: ICOAP (Intermittent and Constant Osteoarthritis Pain Score), TSP (Temporal Summation of Pain), PTT (Pain Tolerance Threshold), Cuff TSP VAS I Score (mean VAS Score of 1st to 4th cuff pressure stimulations)

5.10 DISCUSSION

This study has found that knee OA patients with evidence of central sensitization (facilitated TSP) assessed using cuff algometry have altered preoperative pain perception highlighted by increased VAS-BOLD related neural brain activity within the S2 region. The same S2 brain region continues to show activation in those OA patients that develop chronic postoperative pain after TKR surgery and are classified as non-responders to the surgical intervention. The baseline pre-TKR brain activity of those patients that fail to respond to TKR surgery also highlight the presence of the S2 brain region thereby identifying this region as a potential neural imaging biomarker of central sensitization in knee OA patients that are at higher risk of developing chronic postoperative pain.

Our study has identified that knee OA patients with facilitated TSP pre-TKR display widespread hyperalgesia assessed using hand held algometry as well as significantly increased MOAKS Hoffa-synovitis scores compared to OA patients without facilitated TSP therefore identifying a possible association between a peripheral driver of OA pain (synovitis) and the development of central sensitization in knee OA. This work complements work undertaken by Neogi *et al* who described the association of synovitis and central sensitization by identifying widespread hyperalgesia in OA patients with worsening synovitis in the knee.(128) Our study linking the central and peripheral drivers of knee OA pain to predict outcomes after TKR surgery has identified that inflammation within the synovium assessed using MRI may be driving the central neural changes within the spinal cord and brain leading to central sensitization of the nervous system and a chronic pain state. Compared with OA patients without facilitated TSP, patients with facilitated TSP also

demonstrated increased STATE anxiety preoperatively compared to our healthy volunteers.

Six months following TKR surgery those patients that developed postoperative pain demonstrated the continued or new presence of subchondral BMLs in the tibia, as well as more severe grades of Hoffa synovitis and effusions synovitis around the knee compared to those OA patients that responded to TKR surgery without postoperative pain. As postoperative knee MRI scans post TKR are rarely undertaken by orthopaedic surgeons worldwide as a result of the significant in plane metal artefacts visualised using conventional MRI sequences ,we have, with the use of metal artefact reduction MRI sequences been able to identify the continued or new presence of painful peripheral structures in the knee around the prosthesis including postoperative BMLs, Hoffa synovitis and effusions that may maintain central sensitization post TKR leading to a chronic postoperative pain state. This study is the first to identify the link between the peripheral and central drivers of preoperative knee OA pain identifying neural imaging biomarker in the brain and well as a continued peripheral stimulus post-surgery in those OA patients that fail to respond to surgery.

5.10.1 Synovitis and Central Sensitization

OA is commonly considered a disease due to damage within the joint as a result of mechanical stress during movement and weight bearing. However, the subjective pain experience reported by patients is not linearly related to the degree of structural damage when assessed by conventional radiology using plain radiographs. Neogi *et al* undertook a prospective cohort study and identified that inflammation as evidenced by synovitis or effusion within the knee was associated with widespread pain sensitization in knee OA. The authors also assessed the association between the presence of BMLs and

widespread hyperalgesia using hand held pressure algometry and identified that BMLs did not appear to contribute to central sensitization suggesting that inflammation, evidenced by the presence of synovitis in the knee may be the underlying peripheral driver of pain that contribute to the development and maintenance of central sensitization of pain in knee OA.(128) Our study complements these finding with those preoperative knee OA patients with central sensitization (facilitated TSP scores) having higher MRI MOAKS grades of Hoffa synovitis within the knee joint. There were no significant differences in the preoperative MOAKS BML scores between those OA that had central sensitization (facilitated TSP) and those that were not centrally sensitized (normal TSP).

Inflammatory cytokines produced by inflamed synovium within the joint are associated with degradation of cartilage and play an important role as mediators of pain generation.(89) In patients without knee OA there is a careful balance between the pro and anti-inflammatory cytokines maintain cartilage stability without the degeneration of pain. Yusuf *et al* conducted a systematic review in 2011 and concluded that synovitis in the knee is strongly associated with knee OA pain.(253) Specific pro-inflammatory cytokines, such as IL-1β, IL-6, IL-17 and TNF-alpha have been shown to sensitize peripheral nociceptors(89) and the continued presence of these pro-inflammatory mediators may be the potential cause of central sensitization in knee OA. In early and advanced OA, serological levels of IL-2, IL-4 and IL-10 have been identified in patients(254) and in another study the synovial fluid levels of IL-6 and TNF-alpha were associated with chronic postoperative pain after TKR surgery.(255) We have also demonstrated that the continued presence of Hoffa synovitis or effusions within the knee joint is more prominent in this patients that continue to experience chronic postoperative pain after TKR surgery. Synovitis therefore

with the release of pro-inflammatory cytokines may be one of the currently underestimated peripheral sources of pain, maintaining central sensitization post TKR leading to a chronic pain state. Potentially, early targeting of synovitis in OA may prevent the development of central sensitization and more radical resection of the synovium during TKR surgery may reduce the incidence of chronic postoperative pain after TKR surgery.

5.10.2 Reversal of Central Sensitization of Pain in Responders after TKR Surgery

Increasing evidence suggests that preoperative widespread deep tissue hyperalgesia, assessed using hand held algometry QST, normalise in those OA patients that are pain free following TKR surgery.(15, 183) Our study complements these finding with those OA patients that respond to TKR surgery (VAS score ≤3) normalising there PPTs scores six months after surgery when compared to an age and sex matched healthy control cohort. In contrast, those patients that continue to report subjective chronic postoperative pain six months following TKR surgery (VAS score ≥4) demonstrate no significant improvement in the PPTs scores post TKR. When comparing these non–responders to TKR surgery to the aged and sex matched healthy controls there remains a significant difference in the PPTs scores at the knee, a distant site (tibialis anterior) and a remote site (ECRL) therefore indicating continued localised (knee) and widespread spread hyperalgesia post-surgery in this subgroup of patients.

The present study has identified knee OA have an impaired CPM response prior to TKR surgery compared with healthy volunteers. However, in those patients that are pain free and report a successful outcome following surgery they normalise their CPM response with similar responses to the age and sex matched, pain free healthy volunteers. The non-responders to

surgery continue to demonstrate an impaired CPM response six months post TKR surgery which supports the findings that this subgroup of patients continue to be centrally sensitized following surgery. Preoperative impaired CPM response has been suggested to be predictive in determining which patients developing chronic postoperative pain(187, 188) and a recent study in knee OA have identified a subgroup of patients with preoperative facilitated TSP and impaired CPM that continue to experience chronic postoperative pain following TKR surgery compared with other knee OA patients with other preoperative sensory profiles.(16) Preoperative facilitated TSP has been recently shown to be predictive for chronic postoperative pain after TKR.(17) This study has identified that those patients that continue to report chronic postoperative pain remain sensitized with facilitated TSP after TKR surgery. We have identified the S2 somatosensory brain region as a potential imaging biomarker of TSP using the TSP cuff paradigm whilst simultaneously performing functional brain imaging, however further research in this field is required to confirm our findings.

5.10.3 Post TKR MRI and Continued Peripheral Drivers of Pain

This study is the first study to identify the presence of BMLs six months following TKR surgery in the tibia in close proximity to the prosthesis. As BMLs are strongly associated with pain in OA it is possible that the continued of new presence of these lesions may be linked to the continuation of pain post TKR surgery. In the US, subchondroplasty is being trialled in certain centres where cement is infiltrated into these MRI detected BMLs to help with OA pain and prevent progression of cartilage degradation.(256, 257) It is hypothesised that the exothermic cement setting process destroys any nerves fibres within the subchondral BMLs which have the potential to cause pain.

Whether this treatment modality has the potential to treat postoperative BMLs in patients that are in continued pain following surgery is unknown and future work in this field is required.

We have also been able identify the presence of significant synovitis and effusions in patients post TKR. Synovitis and the associated inflammatory cytokine response is a known peripheral nociceptive driver of pain but the continued presence of synovitis and large effusions post TKR may be maintaining pain and sensitization following surgery. Radical surgical resection of the synovium during TKR procedures may reduce the incidence of postoperative synovitis and post TKR pain and future trials to assess this are required.

5.11 CONCLUSION

This study has identified that preoperative facilitated TSP seen in a subgroup of OA may be driven by high grades of Hoffa synovitis within the knee joint. Therefore, potential therapeutic treatments to reduce synovitis may reduce central sensitization and improve outcomes for those patients undergoing TKR surgery.

This study has also highlighted, that patients with facilitated TSP have brain activation within the S2 region, which continues to be present in those patients that fail to respond to TKR and whom develop chronic postoperative pain. Post TKR peripheral nociceptive structures like BMLs, synovitis and effusions postoperatively may be a continued nociceptive driver of pain, maintaining central sensitization leading to a chronic pain following surgery. These novel findings may aid the development of new pharmaceutical or surgical techniques that could reduce the incidence of chronic postoperative pain after TKR.

6 Challenges Encountered During PhD

Much my first year of my PhD was spent on the set up and design of this clinical study including ethical applications and approvals, QST training at the Centre for Sensorimotor interaction (SMI) in Denmark as well as finalising the imaging protocols for the knee and functional brain imaging sections of this large study. In May 2015, my supervisors and myself were able to secure an international collaboration with the Professor Lars Arendt-Nielsen at the Centre for Sensorimotor interaction (SMI) at the University of Aalborg, Denmark to use their cuff algometry in my QST assessment and for it to be used as a painful stimulus for our functional MRI study.

Prior to the decision to use the cuff algometer in this study, I had spent the first 6 months of my PhD working with Professor Donal McNally (Professor of Medical Engineering) and Mr Mark Parry in the School of Engineering, The University of Nottingham working on the development of an MRI compatible pneumatic knee compression device (Figure 6.1)

Figure 6.1 Pilot Testing of Pneumatic Knee Compression Device

Problems were encountered when using the device in a pilot study, which resulted in us looking at alternative pain stimuli for the fMRI study. Ethical approval was obtained prior to testing the device on any healthy subjects. Preliminary testing was

performed outside the MRI scanner to assess the feasibility of the device. Even at high pressures set using air compressor, the device (20 bar) was unable to cause significant compression of the knee to generate any pain in a healthy subject. Pilot testing on 5 subjects showed that the pain generated using the device was ischaemic in nature with some subjects describing severe cramp like symptoms and pins and needles for a few minutes after testing. Even at the maximum compression limits of the device we were only able to stimulate visual analogue pain scores in healthy subjects of between 1 or 2cm out 10 on the VAS scale. For these reasons, the pneumatic knee compression device was deemed unsuitable for this study and the cuff algometer from Denmark was used which has proved much more reliable and successful.

7 Overall Conclusion and Future Work

The work presented in this thesis highlights the growing trend and severity of chronic pain following primary TKR surgery. This thesis has identified preoperative neuropathic pain like symptoms and pain sensitization characteristics can predict the development of post-operative pain following TKR surgery. A multi-model approach has been used including QST, MRI and psychology and has identified synovitis as a potential driver of central sensitization in knee OA and the presence synovitis and BMLs post TKR may explain continued sensitization and chronic postoperative pain after TKR surgery. The work has also identified a preoperative brain imaging biomarker of pain (S2) that may also predict pain after TKR surgery.

The focus of future work should be on improving the preoperative screening for all knee OA patients with an individualized medical approach for those patients with neuropathic pain like symptoms or central sensitization pre TKR and therefore most at risk of developing chronic postoperative pain. In the UK, orthopaedic surgeons are expected to report all their patient reported outcomes on the National Joint Registry and with the continued financial restraints within our already overstretched National Health Service (NHS) it is essential that all surgeons listing patients for TKR surgery must select only those patients that are likely to report significant improvement in pain and function following the operation. Improved screening of preoperative neuropathic pain with the PainDETECT questionnaire or bedside assessment of central sensitization with a von Frey filament may help identify those patients most at risk of developing chronic postoperative pain. A multi-disciplinary approach to these high-risk patients should then be undertaken, with orthopaedic surgeons, pain specialists, psychologists and the patient's general practitioner working together to reduce the

patients preoperative pain sensitization or neuropathic symptoms before considering any form of surgery.

This work has identified synovitis to be the most likely peripheral driver of central sensitization and therefore future studies assessing whether radical synovectomy during TKR surgery can reduce central sensitization and improve outcomes following surgery is required. Postoperative BMLs have been identified in this thesis in the tibia post TKR and with randomized controlled trials demonstrating the beneficial effects of bisphosphonates on BML size and pain in arthritis patients, future work should be conducted to assess the benefit of bisphosphonate therapy on postoperative BML size and pain in those patients with BMLs and in chronic pain after TKR surgery. Postoperative synovitis and BMLs may be future therapeutic targets to help alleviate the pain following TKR surgery.

Larger fMRI studies with OA patients with and without facilitated TSP and with impaired CPM responses would allow for a more comprehensive neural understanding of central sensitization in knee OA and future studies should assess the neural brain activity of those OA patients with neuropathic pain like symptoms. It is hoped that with this strategy we can better select our OA patients undergoing TKR surgery and reduce the incidence of chronic postoperative pain after TKR surgery.

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9 Appendices

9.1 Ethics Approval for NHS Patients

NHS
Health Research Authority

NRES Committee East Midlands - Nottingham 2
Royal Standard Place
Nottingham
NG1 6FS

Tel: 0115 8839435

26 November 2014

Professor Dorothee P Auer
Clinical Professor
University of Nottingham
Division of Academic Radiology
B Floor, West Block, QMC Campus
Derby Road, Nottingham
NG7 2UH

Dear Professor Auer

Study title:	**Imaging to Understand Pain in Osteoarthritis**
REC reference:	**10/H0408/115**
Protocol number:	**10093**
Amendment date:	**20 October 2014**
IRAS project ID:	**57467**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Discussion

There were no ethical issues raised.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Notice of Substantial Amendment (non-CTIMP)		20 October 2014
Participant information sheet (PIS)	1.8	14 October 2014
Research protocol or project proposal	2.0	14 October 2014
Validated questionnaire [Oxford Knee Score Questionnaire]	1.0	14 October 2014
Validated questionnaire [Intermittent and Constant Osteoarthritis Pain Score]	1.0	14 October 2014
Validated questionnaire [EQ5-D Questionnaire]	1.0	14 October 2014
Validated questionnaire [Visual Analogue Scale Question]	1.0	14 October 2014

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

10/H0408/115:	**Please quote this number on all correspondence**

Yours sincerely

PP

Dr Frances Game
Chair

E-mail: NRESCommittee.EastMidlands-Nottingham2@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Dr Marie Koufali, Nottingham University Hospitals NHS Trust*
Mr Cartledge Paul

9.2 University of Nottingham Ethics Approval for Healthy Volunteers

Direct line/e-mail
+44 (0) 115 8232561
Louise.Sabir@nottingham.ac.uk

Faculty of Medicine and Health Sciences

Research Ethics Committee
School of Medicine Education Centre
B Floor, Medical School
Queen's Medical Centre Campus
Nottingham University Hospitals
Nottingham
NG7 2UH

22nd December 2014

Mr Thomas Kurien
MRC Clinical Research Training Fellow/PhD Student
Division of Rheumatology Orthopaedics & Dermatology
School of Medicine
C Floor, West Block
QMC Campus
Nottingham University Hospitals
Nottingham
NG7 2UH

Dear Thomas

Ethics Reference No: H11122014 SoM ROD RIC PhD
Study Title: In-vivo testing of MRI compatible Knee Compression Device (KCD) for dynamic MR image acquisition
Short Title: Knee OA study.
Chief Researcher/Academic Supervisor: Professor Dorothee Auer, Professor of Neuroimaging, Professor Brigitte Scammell, Professor of Orthopaedic Sciences, School of Medicine.
Other key researchers/student: Mr Thomas Kurien, MRC Clinical Research Training Fellow, PhD Student, Dr Richard Pearson, Senior Research Fellow, School of Medicine, Professor Donal McNally, Professor of Engineering, Mr Mark Parry,Biomechanics Laboratory Manager, School of Engineering.
Duration of Study: 12/2014-03/2015 4mths **No of Subjects:** 10 (+18 yrs)

Thank you for you letter dated dd/mm/yy responding to the issues raised by the Committee and the following documents were received:

KCD Study:
- FMHS REC Application Form, version 1.0 Date: 02/12/201
- KCD Study Protocol Final Version 1.0 Date: 02/12/2014
- Recruitment Poster Final Version 1.0 02/12/2014
- Participant Information Sheet Final Version 1.0 date 02/12/2014
- Consent Form Final Version 1.0: 02/12/14
- HRA NRES approval letter for parallel/related patient study ref 10/H0408/115 dated 6 November 2014.

These have been reviewed and are satisfactory and the study is approved.

Approval is given on the understanding that the Conditions of Approval set out below are followed.

1. You must follow the protocol agreed and inform the Committee of any changes using a notification of amendment form (please request a form).

2. You must notify the Chair of any serious or unexpected event.

3. This study is approved for the period of active recruitment requested. The Committee also provides a further 5 year approval for any necessary work to be performed on the study which may arise in the process of publication and peer review.

4. An End of Project Progress Report is completed and returned when the study has finished (Please request a form).

Yours sincerely

Dr Clodagh Dugdale
Chair, Faculty of Medicine & Health Sciences Research Ethics Committee

9.3 Study Questionnaire Booklet

The University of Nottingham

Knee Osteoarthritis Pain Questionnaire

A study enquiring about the Pain in Your Worst Affected Knee

For assistance or any queries, please contact the research team:

Tel: 01158231113

E-mail: Thomas.kurien@nottingham.ac.uk

For office use only:

Participant ID Number								
Return date	D	D	M	M	Y	Y	Y	Y

Please complete this questionnaire enquiring about the pain in the worst knee that you are having your operation on. If one or both of your knees cause you a problem, please complete the questionnaire for your worst knee. It will take 20-30 minutes.

Background Information Section

How old are you today? ……years

Are you:	Male ☐	Female ☐
How tall are you:	. . . ft, . . . inches, or	. . . . . cm
How much do you weigh:	. . . st, . . . lb, or	. . . . . kg

Do you have activity related joint pain in one or both knee(s)? ☐ Yes ☐ No

Do you have morning stiffness in one or both knee(s)? ☐ Yes ☐ No

If yes, does this morning knee stiffness last for **more than** 30 minutes? ☐ Yes ☐ No ☐ Not applicable

Have ever had knee joint replacement in one or both knee(s)? ☐ Yes ☐ No

Have you ever had surgery/arthroscopy for ligament or meniscal repair in one or both knee(s)? ☐ Yes ☐ No

Do you have a current significant knee injury (for example, one that you have sought medical treatment for)? ☐ Yes ☐ No

Please list your current Medications

_____

Questionnaire Section

Answer every question by ticking the appropriate box, only one box for each question.

A Measure of Intermittent and Constant Pain in your Knee

Constant Pain

*'For each of the following questions, please select the response that best describes on average your **CONSTANT Knee Pain** in the **PAST WEEK' (Questions 1-10)***

1. In the past week, how intense has your **constant knee pain** been?

Not at all	Mildly	Moderately	Severely	Extremely
☐	☐	☐	☐	☐

2. In the past week, how much has your **constant knee pain** affected your sleep?

Not at all	Mildly	Moderately	Severely	Extremely
☐	☐	☐	☐	☐

3 In the past week, how much has your **constant knee pain** affected your quality of life?

Not at all	Mildly	Moderately	Severely	Extremely
☐	☐	☐	☐	☐

4. In the past week, how frustrated or annoyed have you been by your **constant knee pain**?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

5. In the past week, how upset or worried have you been by your **constant knee pain**?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

'Pain That Comes and Goes'

*'For each of the following questions, please select the response that best describes on average your **KNEE PAIN THAT COMES AND GOES** in the **PAST WEEK'***

6. In the past week, how intense has your most severe **knee pain that comes and goes** been?

Not at all	Mildly	Moderately	Severely	Extremely
☐	☐	☐	☐	☐

7. In the past week, how frequently has this **knee pain that come and goes** occurred?

Not at all	Mildly	Moderately	Severely	Extremely
☐	☐	☐	☐	☐

8. In the past week, how much has your **knee pain that comes and goes affected** your sleep?

Not at all	Mildly	Moderately	Severely	Extremely
☐	☐	☐	☐	☐

9. In the past week, how frustrated or annoyed have you been by your **knee pain that comes and goes**?

Not at all	Mildly	Moderately	Severely	Extremely
☐	☐	☐	☐	☐

10. In the past week, how upset or worried have you been by your **knee pain that comes and goes?**

Not at all	Mildly	Moderately	Severely	Extremely
☐	☐	☐	☐	☐

Problems with your knee during the past 4 weeks…
(Questions 11-22)

Tick (✓) one box for every question.

11. During the past 4 weeks… How would you describe the pain you usually have from your knee

None	Very mild	Mild	Moderate	Severe
☐	☐	☐	☐	☐

12. During the past 4 weeks… Have you had any trouble with washing and drying yourself (all over) because of your knee?

No trouble at all	Very little trouble	Moderate trouble	Extreme difficulty	Impossible to do
☐	☐	☐	☐	☐

13. During the past 4 weeks… Have you had any trouble getting in and out of a car or using public transport because of your knee? (Whichever you tend to use)

No trouble at all	Very little trouble	Moderate trouble	Extreme difficulty	Impossible to do
☐	☐	☐	☐	☐

14. During the past 4 weeks… For how long have you been able to walk before pain from your knee becomes **severe**? (With or without a stick)

No pain/ More than 30 minutes	16 to 30 minutes	5 to 15 minutes	Around the house only	Not at all/ pain severe when walking
☐	☐	☐	☐	☐

15. During the past 4 weeks… After a meal (sat at a table), how painful has it been for you to stand up from a chair because of your knee?

Not at all painful	Slightly painful	Moderately painful	Very painful	Unbearable

☐	☐	☐	☐	☐

16.	During the past 4 weeks… Have you been limping when walking, because of your knee?

Rarely/ never	Sometimes, or just at first	Often, not just at first	Most of the time	All of the time
☐	☐	☐	☐	☐

17.	During the past 4 weeks… Could you kneel down and get up again afterwards?

Yes, easily	With little difficulty	With moderate difficulty	With extreme difficulty	No, impossible
☐	☐	☐	☐	☐

18.	During the past 4 weeks… Have you been troubled by pain from your knee in bed at night?

No nights	Only 1 or 2 nights	Some nights	Most nights	Every night
☐	☐	☐	☐	☐

19.	During the past 4 weeks… How much has pain from your knee interfered with your usual work (Including housework)?

Not at all	A little bit	Moderately	Greatly	Totally
☐	☐	☐	☐	☐

20. During the past 4 weeks… Have you ever felt that your knee might suddenly give way or let you down?

Rarely/Never	Sometimes	Often	Most of the time	All of the time
☐	☐	☐	☐	☐

21. During the past 4 weeks… Could you do the household shopping on your own?

Yes, easily	With difficulty	Moderate difficulty	Extreme difficulty	No impossible
☐	☐	☐	☐	☐

22. During the past 4 weeks…Could you walk down a flight of stairs?

Yes, easily	With difficulty	Moderate difficulty	Extreme difficulty	No impossible
☐	☐	☐	☐	☐

Your general health today *(Questions 23-27)*

Under each heading, please tick the ONE box that best describes your health **TODAY**

23. MOBILITY

I have no problems in walking about ☐

I have slight problems in walking about ☐

I have moderate problems in walking about ☐

I have severe problems in walking about ☐

I am unable to walk about ☐

24. SELF-CARE

I have no problems washing or dressing myself ☐
I have slight problems washing or dressing myself ☐
I have moderate problems washing or dressing myself ☐
I have severe problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

25. USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ☐
I have slight problems doing my usual activities ☐
I have moderate problems doing my usual activities ☐
I have severe problems doing my usual activities ☐
I am unable to do my usual activities ☐

26. PAIN / DISCOMFORT

I have no pain or discomfort ☐
I have slight pain or discomfort ☐
I have moderate pain or discomfort ☐
I have severe pain or discomfort ☐
I have extreme pain or discomfort ☐

27. ANXIETY / DEPRESSION

I am not anxious or depressed ☐
I am slightly anxious or depressed ☐
I am moderately anxious or depressed ☐
I am severely anxious or depressed ☐
I am extremely anxious or depressed ☐

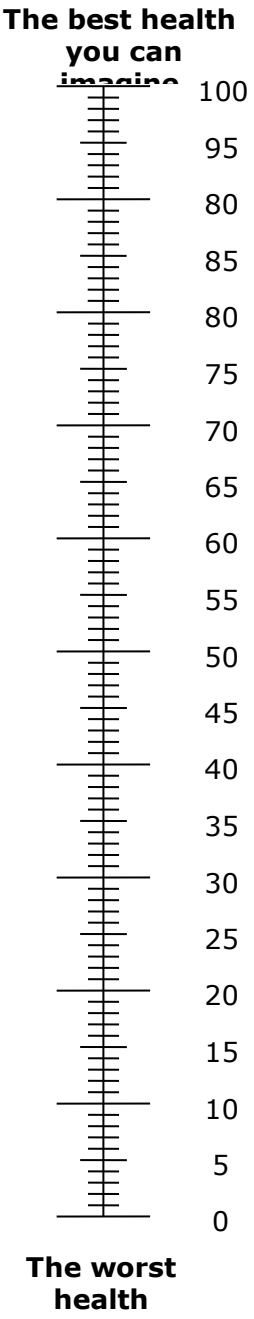
We would like to know how good or bad your health is **TODAY**. This scale is numbered from **0** to **100**.

- **100** means the best health you can imagine.
- **0** means the worst health you can imagine.

- Mark an X on the scale to indicate how your health is **TODAY**.

- Now, please write the number you marked on the scale in the box below.

28.	YOUR HEALTH TODAY	**=**	



You Mood and Feelings *(Questions 29-50)*

Under each heading, please tick the ONE box that best describes your mood **TODAY**

29. SADNESS

I do not feel sad ☐
I feel sad much of the time ☐
I feel sad all of the time ☐
I am so sad or unhappy that I can't stand it ☐

30. PESSIMISM

I am not discouraged about my future ☐
I feel more discouraged about my future than I used to be ☐
I do not expect things to work out for me ☐
I feel my future is hopeless and will only get worse ☐

31. PAST FAILURES

I do not feel like I am a failure ☐
I have failed more than I should have ☐
As I look back, I see a lot of failures ☐
I feel I am a total failure as a person ☐

32. PAIN / DISCOMFORT

I have no pain or discomfort ☐
I have slight pain or discomfort ☐
I have moderate pain or discomfort ☐
I have severe pain or discomfort ☐
I have extreme pain or discomfort ☐

33. LOSS OF PLEASURE

I get as much pleasure as I ever did from the things I enjoy ☐
I don't enjoy things as much as I used to ☐
I get very little pleasure from the things I used to enjoy ☐
I can't get any pleasure from the things I used to enjoy ☐

34. GUILTY FEELINGS

I don't feel particularly guilty ☐
I feel guilty over many things I have done or should have done ☐
I feel quite guilty most of the time ☐
I feel guilty all of the time ☐

35. PUNISHMENT FEELINGS

I do not feel I am being punished ☐
I feel I may be punished ☐
I expect to be punished ☐
I feel I am being punished ☐

36. SELF DISLIKE

I feel the same about myself as ever ☐
I have lost confidence in myself ☐
I am disappointed in myself ☐
I dislike myself ☐

37. SELF CRITICALNESS

I don't criticize or blame myself more than usual ☐
I am more critical of myself than I used to be ☐
I am disappointed in myself ☐
I dislike myself ☐

38. SUICIDAL THOUGHTS OR WISHES

I don't have any thoughts of killing myself ☐
I have thoughts of killing myself, but I would not carry them out ☐
I would like to kill myself ☐
I would like to kill myself if I had the chance ☐

39. CRYING

I don't cry anymore than I used to ☐
I cry more than I used to ☐
I cry over every little thing ☐
I feel like crying, but I can't ☐

40. AGITATION

I am no more restless or wound up than normal ☐
I feel more restless or wound up than usual ☐
I am so restless or agitated that it's hard to stay still ☐
I am so restless or agitated that I have to keep moving or doing something ☐

41. LOSS OF INTEREST

I have not lost interest in other people or activities ☐
I am less interested in other people or things than before ☐
I have lost most of my interest in other people or things ☐
It's hard to get interested in anything ☐

42. INDECISIVENESS

I make decisions about as well as ever ☐
I find it more difficult to make decisions than usual ☐
I have much greater difficulty in making decisions than I used to ☐
I have trouble making decisions ☐

43. WORTHLESSNESS	
I do not feel I am worthless	☐
I don't consider myself as worthwhile and useful as I used to	☐
I have much greater difficulty in making decisions than I used to.	☐
I feel utterly worth	☐
44. LOSS OF ENERGY	
I am not discouraged about my future	☐
I feel more discouraged about my future than I used to be	☐
I do not expect things to work out for me	☐
I feel my future is hopeless and will only get worse	☐
45. CHANGES IN SLEEP PATTERN	
I have not experienced any change in my sleeping pattern	☐
I sleep somewhat more than normal	☐
I sleep somewhat less than normal	☐
I sleep a lot more than normal	☐
I sleep a lot less than normal	☐
I am less interested in other people or things than before	☐
I have lost most of my interest in other people or things	☐
46. IRRITABILITY	
I am no more irritable than usual	☐
I am more irritable than usual	☐
I am much more irritable than usual	☐
I am irritable all the time	☐

47. CHANGES IN APPETITE	
I have not experienced any change in my appetite	☐
I appetite somewhat less than usual	☐
I appetite somewhat greater than usual	☐
I appetite is much less than before	☐
I appetite is much greater than usual	☐
I have no appetite at all	☐
I crave food all the time	☐

48. CONCENTRATION DIFFICULTIES	
I can concentrate as well as ever	☐
I can't concentrate as well as usual	☐
It's hard to keep my to keep my mind on anything for very long	☐
I find I can't concentrate on anything	☐

49. TIREDNESS OR FATIGUE	
I am no more tired or fatigues than usual	☐
I get more tired or fatigued more easily than usual	☐
I am too tired or fatigued to do a lot of the things I used to do	☐
I am too tired or fatigues to do most of the things I used to do	☐

50. LOSS OF INTEREST IN SEX	
I have not noticed any recent change in my interest in sex	☐
I am less interested in sex than I used to be	☐
I am much less interested in sex now	☐
I have lost interest in sex completely	☐

Pain in your Knee *(Questions 51-53)*

Please circle (**o**) one box for every question.

51. How would you assess your pain **NOW**, at this moment

0	1	2	3	4	5	6	7	8	9	10
None	→									Max

52. How strong was the **STRONGEST** pain in the last 4 weeks?

0	1	2	3	4	5	6	7	8	9	10
None	→									Max

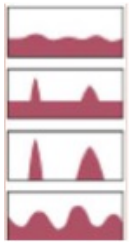
53. How strong was the pain during the past 4 weeks on **AVERAGE?**

0	1	2	3	4	5	6	7	8	9	10
None	→									Max

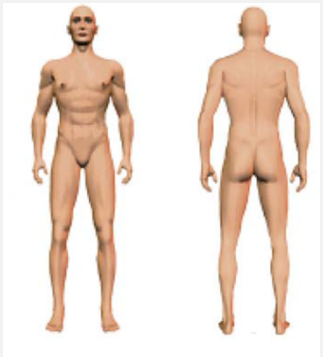
54. Picture description of pain

Please look at the picture with the graphs and **tick ONE box** that best describes the course of your pain?

Persistent pain with fluctuations	☐
Persistent pain with pain attacks	☐
Pain attacks without pain between them	☐
Pain attacks with pain between them	☐



55. Please mark your main areas of pain



56. Does your pain radiate to other regions of your body. **Yes/No**
If it does please **draw an arrow** on the pictures above in the direction in which your pain radiates?

Under each question, please tick the ONE box that best describes your symptoms **TODAY**? *(Questions 57-63)*

57. Do you suffer from a burning sensation (e.g stinging nettles) in the

	marked areas?				
Never ☐	Hardly noticed ☐	Strongly ☐	Moderately ☐	Strongly ☐	Very Strongly ☐

58.	Do you have a tingling or prickling sensation in the area of your pain (like crawling ants or electrical tingling)?				
Never ☐	Hardly noticed ☐	Strongly ☐	Moderately ☐	Strongly ☐	Very Strongly ☐

59.	Is light touching (clothing, a blanket) in the area painful?				
Never ☐	Hardly noticed ☐	Strongly ☐	Moderately ☐	Strongly ☐	Very Strongly ☐

60.	Do you have sudden pain attacks in the area of your pain, like electric shocks?				
Never ☐	Hardly noticed ☐	Strongly ☐	Moderately ☐	Strongly ☐	Very Strongly ☐

61.	Is cold or heat (bath water) in this area occasionally painful?				
Never ☐	Hardly noticed ☐	Strongly ☐	Moderately ☐	Strongly ☐	Very Strongly ☐

62.	Do you suffer from a sensation of numbness in the areas that you marked?				
Never ☐	Hardly noticed ☐	Strongly ☐	Moderately ☐	Strongly ☐	Very Strongly ☐

63.	Does slight pressure in this area, e.g with a finger, trigger pain?				
Never ☐	Hardly noticed ☐	Strongly ☐	Moderately ☐	Strongly ☐	Very Strongly ☐

How Anxious are you *(Questions 64-83)*

A number of statements which people have used to describe themselves are given below. Read the statements below and then tick the appropriate box that indicates how you feel **RIGHT NOW AT THIS MOMENT.** There are no right or wrong answers. Do not spend too much time on each statement, but give the answer which seems to describe your present feelings best.

64. I feel calm			
Not at all ☐	Somewhat ☐	Moderately so ☐	Very much so ☐
65. I feel secure			
Not at all ☐	Somewhat ☐	Moderately so ☐	Very much so ☐
66. I am tense			
Not at all ☐	Somewhat ☐	Moderately so ☐	Very much so ☐
67. I feel strained			
Not at all ☐	Somewhat ☐	Moderately so ☐	Very much so ☐
68. I feel at ease			
Not at all ☐	Somewhat ☐	Moderately so ☐	Very much so ☐
69. I feel upset			
Not at all ☐	Somewhat ☐	Moderately so ☐	Very much so ☐
70. I am presently worrying over possible misfortunes			
Not at all ☐	Somewhat ☐	Moderately so ☐	Very much so ☐
71. I feel satisfied			
Not at all ☐	Somewhat ☐	Moderately so ☐	Very much so ☐
72. I feel frightened			
Not at all ☐	Somewhat ☐	Moderately so ☐	Very much so ☐
73. I feel comfortable			
Not at all ☐	Somewhat ☐	Moderately so ☐	Very much so ☐
74. I feel self-confident			
Not at all ☐	Somewhat ☐	Moderately so ☐	Very much so ☐

75.	I feel nervous		
Not at all ☐	Somewhat ☐	Moderately so ☐	Very much so ☐

76.	I am jittery		
Not at all ☐	Somewhat ☐	Moderately so ☐	Very much so ☐

77.	I feel indecisive		
Not at all ☐	Somewhat ☐	Moderately so ☐	Very much so ☐

78.	I am relaxed		
Not at all ☐	Somewhat ☐	Moderately so ☐	Very much so ☐

79.	I feel content		
Not at all ☐	Somewhat ☐	Moderately so ☐	Very much so ☐

80.	I am worried		
Not at all ☐	Somewhat ☐	Moderately so ☐	Very much so ☐

81.	I feel confused		
Not at all ☐	Somewhat ☐	Moderately so ☐	Very much so ☐

82.	I feel steady		
Not at all ☐	Somewhat ☐	Moderately so ☐	Very much so ☐

83.	I feel pleasant		
Not at all ☐	Somewhat ☐	Moderately so ☐	Very much so ☐

General Anxiety, Mood and beliefs *(Questions 84-103)*

A number of statements which people have used to describe themselves are given below. Read the statements below and then tick the appropriate box that indicates how you feel **GENERALLY.** There are no right or wrong answers. Do not spend too much time on each statement, but give the answer which seems to describe your present feelings best. This is

84.	I feel pleasant		
Not at all ☐	Somewhat ☐	Moderately so ☐	Very much so ☐

85.	I feel nervous and restless		
Not at all ☐	Somewhat ☐	Moderately so ☐	Very much so ☐

86.	I feel satisfied with myself		
Not at all ☐	Somewhat ☐	Moderately so ☐	Very much so ☐
87.	I wish I could be as happy as others seem to be		
Not at all ☐	Somewhat ☐	Moderately so ☐	Very much so ☐
88.	I feel like I am a failure		
Not at all ☐	Somewhat ☐	Moderately so ☐	Very much so ☐
89.	I feel rested		
Not at all ☐	Somewhat ☐	Moderately so ☐	Very much so ☐
90.	I am calm cool and collected		
Not at all ☐	Somewhat ☐	Moderately so ☐	Very much so ☐
91.	I feel that difficulties are piling up so that I cant overcome them		
Not at all ☐	Somewhat ☐	Moderately so ☐	Very much so ☐
92.	I worry too much over something that doesn't matter		
Not at all ☐	Somewhat ☐	Moderately so ☐	Very much so ☐
93.	I am happy		
Not at all ☐	Somewhat ☐	Moderately so ☐	Very much so ☐
94.	I have disturbing thoughts		
Not at all ☐	Somewhat ☐	Moderately so ☐	Very much so ☐
95.	I lack self confidence		
Not at all ☐	Somewhat ☐	Moderately so ☐	Very much so ☐
96.	I feel secure		
Not at all ☐	Somewhat ☐	Moderately so ☐	Very much so ☐
97.	I make decisions easily		
Not at all ☐	Somewhat ☐	Moderately so ☐	Very much so ☐
98.	I feel inadequate		
Not at all ☐	Somewhat ☐	Moderately so ☐	Very much so ☐
99.	I am content		
Not at all ☐	Somewhat ☐	Moderately so ☐	Very much so ☐
100.	Some unimportant thought runs through my mind and bothers me		

Not at all	Somewhat	Moderately so	Very much so
☐	☐	☐	☐
101.	I take disappointments so keenly that I can't put them out of my mind		
Not at all	Somewhat	Moderately so	Very much so
☐	☐	☐	☐
102.	I am a steady person		
Not at all	Somewhat	Moderately so	Very much so
☐	☐	☐	☐
103.	I get in a state of tension or turmoil as I think over my recent concerns and interests		
Not at all	Somewhat	Moderately so	Very much so
☐	☐	☐	☐

Thoughts about the Pain and the Interpretation of Pain (PCS)
(Questions104-117)

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

We are interested in the types of ***thoughts and feelings that you have when you are in pain***. Listed below are 13 statements describing different thoughts and feelings that may be associated with pain. Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain. Place you answer in the box next to each question using the scale below.

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

104-117	***WHEN I AM IN PAIN……***	
I worry, all the time about when the pain will end		☐
I feel I can't go on		☐
It is terrible and I think it will never get any better		☐
It is awful and I feel that it overwhelms me		☐
I feel I can't stand it anymore		☐
I become afraid that the pain will get worse		☐
I keep thinking of other painful events		☐
I anxiously want the pain to go away		☐
I can't seem to keep it out of my mind		☐
I keep thinking about how much it hurts		☐
I keep thinking about how badly I want to stop the pain		☐
There is nothing I can do to reduce the intensity of the pain		☐
I wonder whether something serious may happen		☐

Please provide your GP's name and address if you wish us to contact him/her about your answers to the questionnaire
Your GP's Name and Address

Thank you very much for completing this questionnaire

Please return the questionnaire when you meet us again for your MRI scan and sensory testing. We look forward to seeing you and thank-you again for contributing significantly to Arthritis Pain Research.

If you have any queries, please contact:

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9.4 MOAKS MRI Score Sheet

BML & Cysts; 0 = none, 1 = <33%, 2 = 33-66%, 3 = >66% Sequences PD Axial, Coronal and Saggital Planes

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
	Patella		Femur						Tibia						
Subregion	Medial Patella	Lateral Patella	Medial Trochlea	Lateral Trochlea	Medial Central	Lateral Central	Medial Posterior	Lateral Posterior	Medial Anterior	Medial Central	Medial Posterior	Lateral Anterior	Lateral Central	Lateral Posterior	Subspinous Subregion (SS)

Cartilage; 0 = none, 1 = <10%, 2 = 10-75%, 3 = >75% PD images but in MOAKS paper no set criteria, we will do T2 Map
Partial Thickness Loss

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
	Patella		Femur						Tibia						
Subregion	Medial Patella	Lateral Patella	Medial Trochlea	Lateral Trochlea	Medial Central	Lateral Central	Medial Posterior	Lateral Posterior	Medial Anterior	Medial Central	Medial Posterior	Lateral Anterior	Lateral Central	Lateral Posterior	Subspinous Subregion (SS)

Osteophytes; 0 = none, 1 = small, 2 = medium, 3 = large T1 images better than PD

	1	2	3	4	5	6	7	8	9	10	11	12
	Patella				Femur						Tibia	
Subregion	Patella Superior *(Sagital)*	Patella Inferior (Sagital)	Patella Medial *(Axial)*	Patella Inferior *(Axial)*	Anterior Femur Trochlea Medial *(Sagittal/ Axial)*	Anterior Femur Trochlea Lateral *(Sagittal/Axial)*	Central Femur Medial *(Coronal)*	Central Femur Lateral *(Coronal)*	Posterior Femur Medial (Sagittal/Axial)	Posterior Femur Lateral (Sagittal/Axial)	Tibia Medial *(Coronal)*	Tibia Lateral (Coronal)

Hoffa-synovitis PDw scan or T2 map			
0 = normal	1 = mild	2 = moderate	3 = severe

Effusion Size PDw scan or T2 Map			
0 = physiological amount	1 = small	2 = medium	3 = large

Meniscus Extrusion; 0 = <2 mm, 1 = 2-2.9 mm, 2 = 3-4.9 mm, 3 = > 5 mm			
Medial Meniscus: Medial (coronal image)	Medial meniscus: Anterior (sagittal image)	Lateral Meniscus: Lateral (coronal image)	Lateral Meniscus: Anterior (sagittal image)
PD FS Images			

Meniscus Morphology PD FS images					
Medial Meniscus anterior horn	Medial Meniscus body	Medial Meniscus posterior horn	Lateral Meniscus anterior horn	Lateral Meniscus body	Lateral Meniscus posterior horn
Vertical tear; Y/N					
Horizontal tear; Y/N					
Radial tear; Y/N					
Complex tear; Y/N					
Root tear (posterior horn); Y/N					
Partial maceration; Y/N					
Progressive Partial maceration; Y/N					
Complete maceration; Y/N					
Meniscal cyst; Y/N					
Meniscal hypertrophy; Y/N					

Ligaments and Tendon C/A/S PD images		
0 = normal, 1 = complete tear		0 = no signal abnormality, 1 = signal abnormality present
Anterior cruciate Ligament (ACL)	Posterior Cruciate Ligament (PCL)	Patellar Tendon

Peri-Articular Features PD or T2 Images Abscent(0)/Present(1)								
Pes anserine bursitis	Iliotibian band (ITB)	Popliteal cyst	Infrapatellar bursa signal	Prepatellar bursa signal	Gan cyst assc w/ tibfib jt	Gan cyst assc w/ ACL or PCL	Gan cyst assc w/ other	Loose Bodies