Central and Peripheral Mechanisms of Pain in Clinical Knee Osteoarthritis

A thesis submitted to the University of Manchester for the degree of Doctor of Philosophy in the Faculty of Medical and Human Sciences.

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Kayleigh Mason

School of Medicine
Institute of Inflammation and Repair
CONTENTS

LIST OF FIGURES ........................................................................................................... 7

LIST OF TABLES ............................................................................................................. 8

LIST OF EQUATIONS ..................................................................................................... 12

ABBREVIATIONS ........................................................................................................... 13

ABSTRACT ..................................................................................................................... 14

DECLARATION ............................................................................................................... 16

COPYRIGHT STATEMENT ............................................................................................... 16

ACKNOWLEDGEMENTS ................................................................................................. 17

THE AUTHOR’S CONTRIBUTION .................................................................................... 18

PUBLICATION PLAN ..................................................................................................... 18

CHAPTER 1. INTRODUCTION ......................................................................................... 19

1.1. OVERVIEW ............................................................................................................. 19

1.2. PAIN ....................................................................................................................... 19

1.2.1. Definition of Pain ............................................................................................... 19

1.2.2. Organisation of the Somatosensory Nervous System .................................... 20

1.2.3. Pain Processing .................................................................................................. 25

1.2.4. Pain Modulation ................................................................................................. 27

1.2.5. Mechanisms of Sensitisation ......................................................................... 28

1.2.6. Theories of Pain ................................................................................................. 32

1.3. SUMMARY ............................................................................................................. 37

CHAPTER 2. BACKGROUND ........................................................................................... 38

2.1. OVERVIEW ............................................................................................................. 38

2.2. KNEE PAIN ............................................................................................................. 38

2.2.1. Definition of Knee Pain .................................................................................... 38

2.2.2. Epidemiology of Knee Pain ............................................................................ 39

2.2.3. Structure of the Knee ....................................................................................... 43

2.2.4. Knee Osteoarthritis ......................................................................................... 45

2.2.5. Treatment .......................................................................................................... 52

2.2.6. Summary .......................................................................................................... 54

2.3. QUANTITATIVE SENSORY TESTING .................................................................... 54
## Chapter 3. Aims and Objectives ........................................... 80

3.1. Hypotheses ........................................................................... 80
3.2. Objectives ............................................................................. 80

## Chapter 4. Methods ................................................................. 81

4.1. Summary .............................................................................. 81
4.2. Knee Pain Sensitivity Study .................................................. 81
   4.2.1. Study Design ................................................................. 81
   4.2.2. Subjects ......................................................................... 81
   4.2.3. KOPS Recruitment ....................................................... 82
   4.2.4. Study Assessments ....................................................... 85
   4.2.5. Ethics .............................................................................. 96
   4.2.6. Sample Size Determination .......................................... 96
   4.2.7. Data Management ....................................................... 97
   4.2.8. Analysis ......................................................................... 98
4.3. Knee Osteoarthritis Pain Sensitivity Study ............................ 98
   4.3.1. Study Design ................................................................. 98
   4.3.2. Subjects ......................................................................... 98
   4.3.3. KOPS Recruitment ....................................................... 100
   4.3.4. Study Assessments ....................................................... 100
   4.3.5. Ethics .............................................................................. 102
   4.3.6. Sample Size Determination .......................................... 102
   4.3.7. Data Management ....................................................... 102
   4.3.8. Analysis ......................................................................... 102
4.4. Summary of Results Chapters ............................................. 103

## Chapter 5. Reliability of QST Assessments ............................... 104

5.1. Outline ................................................................................ 104
5.2. Introduction ........................................................................ 104
5.3. Aims .................................................................................. 104
5.4. Methods ............................................................................. 104
6.8. CONCLUSION .........................................................................................................................144

CHAPTER 7. DOES QST CHANGE FOLLOWING INTRA-ARTICULAR STEROID THERAPY? .............................................146

7.1. SUMMARY .............................................................................................................................146
7.2. INTRODUCTION ....................................................................................................................146
7.3. AIMS .......................................................................................................................................146
7.4. METHODS .............................................................................................................................147
7.5. STATISTICAL ANALYSIS ......................................................................................................147
7.6. RESULTS ................................................................................................................................148
  7.6.1. Subjects .............................................................................................................................148
  7.6.2. Subject Characteristics ......................................................................................................149
  7.6.3. Pain and QST measures pre- and post-injection ...............................................................150
  7.6.4. QST measures and change in pain ..................................................................................152
  7.6.5. QST measures and responder status ..............................................................................154
  7.6.6. Psychosocial Factors and Change in Pain ......................................................................156
7.7. DISCUSSION ........................................................................................................................157
  7.7.1. Subject Characteristics ......................................................................................................158
  7.7.2. Changes in QST measures following intervention ...........................................................158
  7.7.3. Predictors of change in pain ............................................................................................160
  7.7.4. Strengths and limitations of the present study .................................................................162
7.8. CONCLUSION .......................................................................................................................162

CHAPTER 8. DISCUSSION .........................................................................................................164

8.1. OVERVIEW ...........................................................................................................................164
8.2. MAIN FINDINGS ...................................................................................................................164
8.3. IMPLICATIONS OF FINDINGS ............................................................................................165
8.4. FUTURE RESEARCH ...........................................................................................................166
8.5. SUMMARY ...........................................................................................................................167

REFERENCES ..............................................................................................................................168

APPENDIX I. SYSTEMATIC REVIEW METHODOLOGY .................................................................198

APPENDIX II. KEEPS STUDY DOCUMENTATION ........................................................................200

APPENDIX III. KOPS STUDY DOCUMENTATION ......................................................................215

APPENDIX IV. RANDOMISATION FOR RELIABILITY ASSESSMENTS ....................................220
APPENDIX V.  THE EFFECT OF AGE AND SEX ON ALL OUTCOME MEASURES .......................................................... 223

APPENDIX VI. MEDIATION ANALYSIS .......................................................... 225

APPENDIX VII. MEDIATION ANALYSIS II ..................................................... 233

APPENDIX VIII. QST PREDICTORS OF CHANGE IN PAIN AFTER ADJUSTING FOR BASELINE PAIN ........................................................................ 252

APPENDIX IX. PSYCHOSOCIAL PREDICTORS OF CHANGE IN QST .......... 253

Final word count: 62, 907
LIST OF FIGURES

Figure 1.1 Ascending somatosensory and descending modulatory pathways..............................23
Figure 1.2 The Gate Control Theory (Melzack et al. 1968) ..........................................................33
Figure 1.3 The Neuromatrix of Pain (Melzack et al. 2004).............................................................35
Figure 1.4 The Fear-Avoidance Model (Vlaeyen et al. 2000)........................................................36
Figure 2.1 Prevalence of knee pain, radiographic OA and symptomatic OA in the Framingham Osteoarthritis Study (Nguyen et al. 2011) .................................................................39
Figure 2.2 Structure of the knee ......................................................................................................44
Figure 2.3 Incidence of knee Osteoarthritis in men and women (Oliveria et al. 1995)..................48
Figure 4.1 Study design for the third follow-up of the EPIFUND cohort ......................................82
Figure 4.2 Manchester Coding Schedule (knees shaded) (Hunt et al. 1999) ...............................83
Figure 4.3 Recruitment process......................................................................................................84
Figure 4.4 ACR Coding Schedule (Davies et al. 2009) .................................................................86
Figure 4.5 Location of Tender Points (Chakrabarty et al. 2007) .................................................91
Figure 4.6 Positioning of the equipment used at the knee and forearm ..................................92
Figure 4.7 Sample size calculation using G*Power 3.1.2 software ........................................97
Figure 4.8 TASK Study Design ..................................................................................................99
Figure 6.1 Mediation Model ........................................................................................................117
Figure 6.2 Recruitment flowchart ................................................................................................118
Figure 6.3 The effect of age on mechanical pain sensitivity and allostynia at the knee, mechanical pain threshold at the forearm and the IPQ-Brief coherence item ..........122
Figure 6.4 Scatter plots including predicted values using fractional polynomials of knee pressure pain threshold and HAD depression score with global and knee pain intensity scores .................................................127
Figure 6.5 Mediation model including latent psychosocial mediating variable ..................134
Figure 7.1 Recruitment Flowchart ...............................................................................................149
Figure 7.2  Scatter plot illustrating the association between change in KOOS pain score and baseline wind-up ratio at the control knee with (A) and without (B) influential observations .................................................................154

Figure 7.3  Scatter plot illustrating the association between change in KOOS pain score and baseline mechanical pain threshold at the injected knee .................................................................156

Figure II-1  KEEPS Participant Information Sheet .................................................................200

Figure II-2  KEEPS Appointment Letter ...............................................................................201

Figure II-3  KEEPS Consent Form .........................................................................................202

Figure II-4  KEEPS Study Questionnaire (continued over page) ........................................203

Figure II-5  Standardised QST Instructions ..........................................................................214

Figure III-1  Knee Osteoarthritis Outcome and Injury Score (KOOS) (Roos et al. 1998) ....215

Figure III-2  KOPS Participant Information Sheet .................................................................218

Figure III-3  KOPS Consent Form .........................................................................................219

Figure IV-1  KEEPS Rater Observation Checklist (continued over page) .........................220

Figure IV-2  Random number generator ...............................................................................222

Figure IV-3  Randomisation plan .........................................................................................222

Figure VII-1  Mediation model including latent sensitisation mediating variable ..............234

LIST OF TABLES

Table 1.1  Properties of sensory fibres that transduce nociceptive information..................21

Table 2.1  The Kellgren-Lawrence Radiographic Scale (Kellgren et al. 1957) .....................46

Table 2.2  Sensory modalities detected by peripheral afferents .........................................56

Table 2.3  Studies investigating QST in knee OA subjects .....................................................70

Table 2.4  Studies investigating QST and psychosocial factors in knee OA subjects ............75

Table 2.5  Summary of findings presented in Table 2.3 .......................................................77

Table 4.1  Reports of knee pain using the Manchester manikin coding ............................82
Table 4.2  Characteristics of follow-up responders identified with knee pain (n=565)  ........................................83
Table 4.3  ACR Clinical Classification Criteria for Hand, Knee and Hip OA  ........................................90
Table 4.4  Definitions of somatosensory function for QST measures and tender point  ...........................95
Table 4.5  Summary of questionnaire change scores  ..........................................................103
Table 5.1  QST measures; median and interquartile range for sessions 1 to 3  ......................................106
Table 5.2  Tender Point Counts and Cold Pain Thresholds for each subject at each session  ..................................107
Table 5.3  Intraclass Correlation Coefficients for inter-rater and intra-rater reliability (ICC and 95% CI)  ........................................................................................................................................108
Table 6.1  Characteristics of study subjects  .................................................................................................119
Table 6.2  Range, median and interquartile range of QST measures, psychosocial factors and self-reported pain intensity (n=61)  ........................................................................................................120
Table 6.3  Range, median and interquartile range of QST measures, psychosocial factors and self-reported pain intensity (n=61)  ........................................................................................................121
Table 6.4  The effect of sex on QST, psychosocial factors and pain intensity (Wilcoxon Rank Sum)  ........................................................................................................................................123
Table 6.5  Correlations between self-reported pain intensity and QST measures (Spearman’s Rho)  ........................................................................................................................................124
Table 6.6  Correlations between self-reported pain intensity and psychosocial factors (Spearman’s Rho)  ........................................................................................................................................125
Table 6.7  Association between QST measures, psychosocial factors and self-reported global and knee pain intensity ratings (linear regression)  ........................................................................................................126
Table 6.8  Fractional polynomial transformations (knee pressure pain threshold and HAD depression score)  ........................................................................................................................................127
Table 6.9  Fractional polynomials for pressure pain at the knee and HAD depression (Wald Test)  ........................................................................................................................................128
Table 6.10 Significant results from the Wald Test following regressions of heat pain thresholds against global pain intensity with age interaction terms  ........................................................................................................128
Table 6.11 Significant results from the Wald Test following regressions of QST measures against outcome measures with sex interaction terms (n=61)  ........................................................................................................129
Table 6.12 Results from the backward stepwise regressions (n=61)  ........................................................................................................130
Table 6.13 Correlations between QST measures that are significantly correlated with pain intensity and psychosocial factors (n=61) .................................................................131

Table 6.14 Mediation analysis for tender point count and global pain intensity ...............132

Table 6.15 Mediation analysis for mechanical pain sensitivity at the knee and global pain intensity..............................................................................................................133

Table 6.16 Mediation analysis for mechanical pain sensitivity at the knee and pain intensity at the tested knee ..........................................................................................133

Table 6.17 Mediation analysis for QST measures and global pain intensity including a latent psychosocial mediating variable.................................................................135

Table 6.18 Mediation analysis for QST measures and pain intensity at the tested knee including a latent psychosocial mediating variable.........................................................135

Table 7.1 Subject Characteristics..................................................................................150

Table 7.2 Median scores for baseline and post-injection and mean change values for KOOS pain score, tender point count and QST measures at both knees.........................151

Table 7.3 Mean difference in QST between knees for each visit; one sample T-test........152

Table 7.4 Linear regression of change in pain against baseline QST measures.............153

Table 7.5 Change in pain against baseline wind-up ratio at the control knee: influential observations identified using Cook’s distance >4/32 .........................................................154

Table 7.6 Linear regression of change in pain against baseline wind-up ratio at the control knee: outliers included and removed........................................................................154

Table 7.7 Median values for baseline QST measures by treatment responder status ....155

Table 7.8 Linear regression of change in pain against psychosocial factors...............157

Table I-1 Search strategy used to identify studies presented in Table 2.3......................198

Table V-1 The effect of age on QST, psychosocial factors and pain intensity ...................223

Table V-2 The effect of sex on QST, psychosocial factors and pain intensity ....................224

Table VI-1 Mediation analysis for tender point count and global pain intensity ...........225

Table VI-2 Mediation analysis for mechanical pain sensitivity at the knee and global pain intensity ..............................................................................................................226

Table VI-3 Mediation analysis for allostynia at the knee and global pain intensity (continued over page).................................................................................................227
Table VI-4  Mediation analysis for mechanical pain sensitivity at the forearm and global pain intensity

Table VI-5  Mediation analysis for mechanical pain sensitivity at the knee and pain intensity at the tested knee

Table VI-6  Mediation analysis for allodynia at the knee and pain intensity at the tested knee (continued over page)

Table VI-7  Mediation analysis for mechanical pain sensitivity at the forearm and pain intensity at the tested knee

Table VII-1  Correlations between psychosocial factors that are significantly correlated with pain intensity and QST measures (n=61)

Table VII-2  Mediation analysis for HAD depression and global pain intensity

Table VII-3  Mediation analysis for PCS Rumination and global pain intensity

Table VII-4  Mediation analysis for PCS Magnification and global pain intensity

Table VII-5  Mediation analysis for PCS Helplessness and global pain intensity

Table VII-6  Mediation analysis for PCS Helplessness and pain intensity at the tested knee

Table VII-7  Mediation analysis for IPQ-Brief Consequences and global pain intensity

Table VII-8  Mediation analysis for IPQ-Brief Consequences and pain intensity at the tested knee

Table VII-9  Mediation analysis for IPQ-Brief Timeline and global pain intensity

Table VII-10 Mediation analysis for IPQ-Brief Timeline and pain intensity at the tested knee

Table VII-11 Mediation analysis for IPQ-Brief Treatment Control and global pain intensity

Table VII-12 Mediation analysis for IPQ-Brief Treatment Control and pain intensity at the tested knee

Table VII-13 Mediation analysis for IPQ-Brief Identity and global pain intensity

Table VII-14 Mediation analysis for IPQ-Brief Identity and pain intensity at the tested knee

Table VII-15 Mediation analysis for IPQ-Brief Concern and global pain intensity

Table VII-16 Mediation analysis for IPQ-Brief Concern and pain intensity at the tested knee

Table VII-17 Mediation analysis for IPQ-Brief Emotion and global pain intensity

Table VII-18 Mediation analysis for IPQ-Brief Emotion and pain intensity at the tested knee
Table VII-19 Mediation analysis for HAQ-DI and global pain intensity .................................249
Table VII-20 Mediation analysis for HAQ-DI and pain intensity at the tested knee .................249
Table VII-21 Mediation analysis for psychosocial factors and global pain intensity including a latent sensitisation mediating variable .................................................................250
Table VII-22 Mediation analysis for psychosocial factors and pain intensity at the tested knee including a latent sensitisation mediating variable .........................................................251
Table VIII-1 Linear regression of change in pain against baseline QST measures and baseline pain .....................................................................................................................252
Table IX-1 Screening measures of anxiety and depression as predictors of change in QST ....253
Table IX-2 Screening items of the IPQ-Brief as predictors of change in tender point count and change in QST at the injected knee ........................................................................254
Table IX-3 Screening items of the IPQ-Brief as predictors of change in QST at the contralateral knee .................................................................................................................................255

LIST OF EQUATIONS

Equation 4.1 Standardised score for KOOS subscales (Roos et al. 1998) ...............................101
**ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>ACR</td>
<td>American College of Rheumatology</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>β</td>
<td>β-coefficient</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>CPM</td>
<td>Conditioned pain modulation</td>
</tr>
<tr>
<td>CWP</td>
<td>Chronic widespread pain</td>
</tr>
<tr>
<td>DFNS</td>
<td>Deutschen Forschungsverbund Neuropathischer Schmerz</td>
</tr>
<tr>
<td>DNIC</td>
<td>Diffuse noxious inhibitory control</td>
</tr>
<tr>
<td>EPIFUND</td>
<td>Epidemiology of Functional Disorders (cohort)</td>
</tr>
<tr>
<td>HAD</td>
<td>Hospital Anxiety and Depression Scale</td>
</tr>
<tr>
<td>HAQ-DI</td>
<td>Health Assessment Questionnaire Disability Index</td>
</tr>
<tr>
<td>IPQ-Brief</td>
<td>Illness Perception Questionnaire Brief</td>
</tr>
<tr>
<td>KEEPS</td>
<td>Knee Pain Sensitivity (study)</td>
</tr>
<tr>
<td>KL</td>
<td>Kellgren-Lawrence</td>
</tr>
<tr>
<td>KOOS</td>
<td>Knee Osteoarthritis Outcome and Injury Score</td>
</tr>
<tr>
<td>KOPS</td>
<td>Knee Osteoarthritis Pain Sensitivity (study)</td>
</tr>
<tr>
<td>LTP</td>
<td>Long term potentiation</td>
</tr>
<tr>
<td>mN</td>
<td>Milli-Newton</td>
</tr>
<tr>
<td>NRS</td>
<td>Numeric rating scale</td>
</tr>
<tr>
<td>PCS</td>
<td>Pain Catastrophizing Scale</td>
</tr>
<tr>
<td>OA</td>
<td>Osteoarthritis</td>
</tr>
<tr>
<td>OARSI</td>
<td>Osteoarthritis Research Society International</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>QST</td>
<td>Quantitative sensory testing</td>
</tr>
<tr>
<td>RAPA</td>
<td>Rapid Assessment of Physical Activity</td>
</tr>
<tr>
<td>Rho</td>
<td>Spearman’s rank correlation coefficient</td>
</tr>
<tr>
<td>SF-36</td>
<td>Short Form Health Questionnaire 36</td>
</tr>
<tr>
<td>TASK</td>
<td>Targeting Synovitis in Knee Osteoarthritis (study)</td>
</tr>
<tr>
<td>τ</td>
<td>Kendall’s tau coefficient</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual analogue scale</td>
</tr>
<tr>
<td>WDR</td>
<td>Wide dynamic range</td>
</tr>
<tr>
<td>WOMAC</td>
<td>Western Ontario and McMaster Universities Arthritis Index</td>
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ABSTRACT

Background: Knee pain is a common musculoskeletal complaint with an estimated annual population prevalence of 25% in people aged over 55 years. There are many causes of knee pain though osteoarthritis (OA) is one of the most frequent. Not all people with OA, however, have knee pain. There is discordance between pain intensity and disease severity, the reason for which is unknown. Variation in pain sensitivity may be one possible explanation. Quantitative sensory testing (QST) is a non-invasive technique using non-painful and painful stimuli to assess altered sensitivities in the skin and muscle. Little is known, however, about pain sensitivity in people with knee pain and the role of psychosocial factors in relation to pain sensitivity and pain intensity. Intra-articular steroids are a widely used and effective therapy for knee OA though response to treatment varies in both magnitude and duration of response. Pain sensitivity and/or psychosocial factors may explain some of the variation observed in response to treatment.

Aims: To determine whether (i) greater sensitivity to stimuli is associated with higher levels of pain intensity in a population-based sample with knee pain, and whether those associations are mediated by psychosocial factors, (ii) there are changes in QST following intra-articular steroid injections in patients with symptomatic knee OA, and (iii) whether psychosocial factors and sensitivity to stimuli at baseline predict change in pain following intervention.

Methods: 72 men and women with knee pain were recruited from a population-based cohort. All had QST assessments and completed a range of questionnaire instruments addressing pain intensity and psychosocial factors. QST assessments (including thermal, mechanical, vibration and pressure) were made at the most affected knee and contralateral forearm. Assessments of tender point count, wind-up ratio and diffuse noxious inhibitory control were also performed. Structural equation modelling was used to determine whether associations between QST measures and pain intensity were mediated by a latent psychosocial factor. In a separate open label trial of intra-articular steroid injections, 32 men and women with symptomatic knee OA underwent QST assessments and also completed questionnaires. The assessments were performed at both knees at the baseline visit (prior to injection) and at a post-injection visit 5-15 days later. Changes in QST were assessed using Wilcoxon matched-pairs signed-rank with linear regression used to determine baseline QST predictors of change in pain.

Results: In the observational study, mechanical hyperalgesia (tender point count, mechanical pain sensitivity, and alldynia), illness perceptions, catastrophizing and disability scores were positively associated with higher levels of pain intensity. Mediation analyses revealed stronger associations for the indirect effect including a latent psychosocial mediator between measures of mechanical hyperalgesia and global pain, and stronger associations for the direct effect between measures of mechanical hyperalgesia and knee pain. In the intervention study no changes in QST were observed between visits. However, lower baseline mechanical pain thresholds at the injected knee and illness perceptions predicted response to treatment.

Conclusion: Illness perceptions and mechanical hyperalgesia can be used to identify subjects experiencing higher levels of global and knee pain intensity, and those who were more likely to
respond to intra-articular steroid therapy. Changes in knee pain following intervention with steroid injection are not explained by changes in pain sensitivity.
DECLARATION

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THE AUTHOR’S CONTRIBUTION

**KEEPS Study**

The author designed, submitted and obtained ethics approval for the KEEPS study. The author also recruited 78 of 80 (97.5%) subjects invited to attend a study visit and performed all 72 study assessments. All data collected for this study was entered and cleaned for analysis by the author. All data analyses were completed by the author with guidance from Dr. Mark Lunt.

**KOPS Study**

The author designed, submitted and obtained a substantial amendment to the TASK study protocol to include the KOPS sub-study. The author was part of the TASK study team, but was not involved in the recruitment of subjects and did not attend the screening visits for the TASK study. Members of the study team (Professor Terence O’Neill, Nasimah Maricar and Laura Forsythe) attending the screening visit provided a description of the KOPS sub-study, along with a copy of the KOPS information sheet for the subject to read. These members of the TASK study team also collected the questionnaire data (HAD and IPQ-Brief) used in the analyses for this study at the screening visit, as well as the KOOS pain scores at the baseline and follow-up visits. The author carried out all of the assessments for the KOPS sub-study at the baseline and follow-up visits, including the QST assessments and questionnaire data (HAD and IPQ-Brief collected at follow-up). All data collected for this study was entered and cleaned for analysis by the author. All data analyses were completed by the author with guidance from Dr. Mark Lunt.

**PUBLICATION PLAN**

The findings of the KOPS study were submitted as an abstract and accepted as a poster presentation at the Osteoarthritis Research Society International (OARSI) World Congress in April 2014. A copy of the abstract can be found at:


There are two papers for submission related to this thesis. The first paper will present the KEEPS study (Chapter 6). The second paper will present the KOPS study with an additional 21 participants to those reported in Chapter 7. The papers will be submitted to rheumatology journals with an interest in pain.
CHAPTER 1. INTRODUCTION

1.1. Overview

This chapter provides an overview of the current theories and mechanisms of pain, starting with a description of what pain is and how it can be defined. Chronic pain is a persistent debilitating condition. One way in which chronic pain may differ to acute pain is through altered pain processing. In order to determine where possible differences in pain processing may occur, the structure of the nervous system is outlined with respect to the detection and transmission of painful sensations. The integration and processing of sensory input within the central nervous system (CNS), including the modulation of pain within the brain and the spinal cord, is described. Finally, theories of pain that propose mechanisms by which the sensory, emotional, and/or behavioural components of pain may be altered during chronic pain are explored.

1.2. Pain

1.2.1. Definition of Pain

Pain is a multifaceted experience. It is a result of complex interactions between physiological, social and psychological processes. The International Association for the Study of Pain (IASP) definition of pain is “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (Merskey et al. 1994). This definition incorporates the biological (actual or potential damage) and psychological (unpleasant emotional experience) components of pain.

1.2.1.1. Chronic Pain

Duration is frequently used in classifying pain. Acute pain arises in response to the activation of neurophysiological pathways by noxious stimuli (nociception), such as during surgical incisions (Carr et al. 1999). Acute pain is protective to limit further injury to damaged tissues and usually resolves once healing is complete (Carr et al. 1999). Chronic pain can be defined as “pain which persists beyond the immediate event which precipitated it” (Croft et al. 2010). This definition suggests there could be an insult preceding the development of chronic pain, but this is not always the case. Bonica’s Management of Pain also states that chronic pain “may be elicited by an injury or disease but is likely to be perpetuated by factors that are both pathogenetically and physically remote from the originating cause” (Turk et al. 2009). This definition highlights that the cause of chronic pain becomes less relevant as the pain persists (Turk et al. 2009). The persistence of chronic pain could be related to longer lasting changes in pain processing. For example, some people with chronic widespread pain (CWP) can experience musculoskeletal pain without any discernible underlying pathology, but that does not mean there was no original insult (Clauw et al.
There are other ways of defining pain, such as phenotyping, which is described in the next section.

### 1.2.1.2. Pain Phenotypes

A phenotype is defined as “the observable properties (structural and functional) of an organism” (Rieger et al. 1991). Phenotypes are commonly used in research in order to classify subjects of interest by using observable features, such as those obtained through clinical examination, imaging and/or laboratory results (Felson 2010). However, chronic pain can be difficult to phenotype due to a lack of physical pathology or biochemical markers, and due to fluctuations in pain reports (Dansie et al. 2013).

One problem that arises in epidemiological studies of chronic musculoskeletal pain is the variation in definitions or phenotypes used, as highlighted by McBeth and Jones (2007). Due to a range of time intervals for the presence of pain used in defining new cases, the onset of chronic pain (incidence) is difficult to determine; the prevalence of chronic pain is easier to assess as a subject is asked whether they have pain now (point prevalence) or have experienced it for or within a defined time frame (period prevalence) (McBeth et al. 2007). Another issue within pain research is that the experience of pain is subjective. This makes the assessment of pain difficult as a sensation perceived as painful by one person may not be experienced as painful by another (MacKichan et al. 2008). The severity, chronicity and functional impairment associated with pain or underlying disease can also vary considerably both between and within-person (Creamer et al. 1999a; Wood et al. 2008; Jones et al. 2009). As such, a more objective and repeatable measure of chronic pain is required.

There are currently no objective markers of pain that are routinely used in clinical practice that correlate well with the subjective aspects of pain (Dansie et al. 2013). Instead clinicians rely on detailed self-reports from patients regarding the intensity, location, duration, onset, psychological impact, effect on daily and/or quality of life, and social factors related to their pain (Dansie et al. 2013). In order to understand how chronic pain differs from acute pain, the somatosensory nervous system is outlined in the following section.

### 1.2.2. Organisation of the Somatosensory Nervous System

#### 1.2.2.1. Peripheral Somatosensory Nervous System

The pathways outlined within this section have been investigated in mammals (predominantly rats) and primates, and, where possible, have been validated in humans (Marchand 2008). The somatic nervous system comprises neurons which have specialised sensory receptors (afferents) that respond to specific sensations (modalities) such as visual, auditory, olfactory, gustatory, balance (vestibular system), pressure, noxious sensations (nociception), limb and trunk positions (proprioception), temperature, and itch (Gardner et al. 2000c). The modalities of pressure, itch,
temperature, proprioception and nociception form the somatosensory system as these particular sensations can be felt throughout all of the skin and muscles of the body (i.e. not detected in one anatomical area like visual or auditory stimuli). Sensory afferents provide information about the anatomical location, amplitude and duration of each sensation detected (Compston 2011). Sensations that generate action potentials (a change in voltage across a cell membrane) must pass a certain threshold to be transduced (transmission of a signal within the nervous system). If a stimulus is of sufficient intensity and/or lasts for a long enough period of time, sensory information can be transduced to the spinal cord.

There are four types of sensory afferents in peripheral tissue: Aα, Aβ, Aδ and C fibres. Aα fibres relay information related to muscle sense, while Aβ, Aδ and C fibres can detect different sensory modalities due to the presence of distinct sensory receptors in the cell membranes (Lumpkin et al. 2007). The sensory properties of Aβ, Aδ and C fibres are summarised in Table 1.1.

<table>
<thead>
<tr>
<th>Table 1.1</th>
<th>Properties of sensory fibres that transduce nociceptive information</th>
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<tbody>
<tr>
<td>Property</td>
<td>Aβ Fibres</td>
</tr>
<tr>
<td>Myelination, Diameter and Conduction</td>
<td>Yes</td>
</tr>
<tr>
<td>Receptor types and information transduced</td>
<td>6 to 12 μm</td>
</tr>
<tr>
<td>Mechanoreceptors</td>
<td>35 to 75 m/s</td>
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<tr>
<td>Cutaneous: Meissner’s corpuscle (stroking)</td>
<td>Meissner’s corpuscle (stroking)</td>
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<tr>
<td>Merkel disk (texture)</td>
<td>Merkel disk (texture)</td>
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<tr>
<td>Pacinian corpuscle (vibration)</td>
<td>Pacinian corpuscle (vibration)</td>
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<tr>
<td>Ruffini ending (skin stretch)</td>
<td>Ruffini ending (skin stretch)</td>
</tr>
<tr>
<td>Musculoskeletal: Secondary muscle spindles (muscle stretch)</td>
<td>Secondary muscle spindles (muscle stretch)</td>
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<tr>
<td>Joint capsule mechanoreceptors (joint angle)</td>
<td>Joint capsule mechanoreceptors (joint angle)</td>
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<tr>
<td>Thermoreceptors</td>
<td>Heating (~41°C)</td>
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<tr>
<td>Cooling (~&lt;25°C)</td>
<td>Cool nociceptors (~&gt;45°C)</td>
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<tr>
<td>Heat nociceptors (~&gt;45°C)</td>
<td>Nociceptors</td>
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<tr>
<td>Thermal-mechanical (burning pain)</td>
<td>Thermal-mechanical (burning pain)</td>
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<tr>
<td>Mechanical (pin-prick)</td>
<td>Mechanical (pin-prick)</td>
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<tr>
<td>Synapses with second order neurons in the dorsal horn</td>
<td>Laminae III and IV: proprioceptive</td>
</tr>
<tr>
<td>Lamina V and VI: mostly WDR</td>
<td>Lamina V: mostly WDR</td>
</tr>
</tbody>
</table>


Aα and Aβ fibres are large diameter, fast conducting myelinated afferents that relay information about proprioception (muscle and joint position in space) (Mense et al. 2010). Aβ fibres also respond to pressure, vibration, stretch, and muscle contraction (Vallbo et al. 1979), and also play a
role in nociceptive transmission (Marchand 2008). In some instances of very high threshold stimuli, Aβ fibres may be activated by noxious sensations; for example, a joint positioned at an extreme angle (Djouhri et al. 2004). The gate-control theory of pain proposed that Aβ fibres temporarily block nociceptive transmission from Aδ and C fibres at the spinal cord via interactions with inhibitory interneurons within the dorsal horn (Melzack et al. 1965). This is explored further in in Section 1.2.6.2.

Aδ fibres are also myelinated, but are smaller in diameter than Aα and Aβ afferents and have slower rates of conduction (Vallbo et al. 1979). Aδ fibres are activated by three types of receptor: thermoreceptors, which are sensitive to cooling and painfully hot temperatures; mechanoreceptors, which are sensitive to painful stretch of force; and nociceptors, which respond to burning and pin-prick sensations (Simone et al. 1997). Aδ fibres have small receptive fields which contribute to the sensation of “first pain” characterised as sharp and localised (Giordano 2005).

C fibres are free nerve endings which are responsive to noxious pressure, temperature (including burning pain) and chemical sensations (Basbaum et al. 2000). C fibres are the smallest in diameter, are unmyelinated, and have the slowest conduction velocity (Mense et al. 2010). C fibres have large receptive fields making it difficult to discriminate the modality and location of pain resulting in the sensation of “second pain” (dull burning pain) (Giordano 2005).

Sensory afferents are organised topographically according to the body region they innervate and the position of the dorsal root ganglia (collection of the cell bodies of sensory afferents) at the spinal cord. For example, ascending sensory information from the knees enter the dorsal horn (grey matter) of the spinal cord at the third, fourth and fifth lumbar vertebrae, whereas sensory information from the hands enter the spinal cord between the sixth, seventh and eighth cervical, and first thoracic vertebrae (Keegan et al. 1948). The process by which information is relayed from the periphery through the spinal cord and to higher brain regions is outlined in Sections 1.2.2.2 and 1.2.2.3.

1.2.2.2. Transduction of non-nociceptive somatosensory information

Sensory afferents enter the dorsal horn of the spinal cord, as depicted in Figure 1.1A. The dorsal horn comprises layers, also referred to as laminae, which receive inputs from sensory and motor neurons (D’Mello et al. 2008). Non-nociceptive information from Aα and Aβ fibres synapse with second order proprioceptive neurons within laminae III and IV. The second order neurons ascend via the ipsilateral white matter (dorsal column) of the spinal cord and synapse within the dorsal column of the medulla (see Figure 1.1A) (D’Mello et al. 2008). Neurons from lower body regions are positioned medially within the dorsal column with neurons from upper body regions located more laterally in the dorsal column (Florence et al. 1989). Recent research has suggested that fibres of the same type also ascend within modality-specific clusters that are organised somatotopically (according to body region) (Niu et al. 2013).
Figure 1.1  Ascending somatosensory and descending modulatory pathways

B. Lateral System

C. Medial System

D. Descending System

The pathways displayed in this figure were compiled and adapted from the subsequent references: (Treede et al. 1999; Millan 2002; Suzuki et al. 2004; Ab Aziz et al. 2006; Tracey et al. 2007; D'Mello et al. 2008; Jones et al. 2012). S1 = primary somatosensory cortex; S2 = secondary somatosensory cortex; IC = insular cortex; ACC = anterior cingulate cortex; HTH = hypothalamus; VPL = ventroposterior lateral nucleus; VPM = ventroposterior medial nucleus; VPI = ventroposterior inferior nucleus; VMpo = posterior ventromedial nucleus; ILN = intralaminar nucleus; PC = paracentral nucleus; RF = reticular formation; PAG = periaqueductal gray; RVM = rostral ventromedial medulla; DLPT = dorsolateral pontine tegmentum; PBN = parabrachial nucleus.

A. Shown is a cross-section of the spinal cord receiving input from peripheral afferents (green text and arrows). Afferents enter the dorsal horn (grey matter) of the spinal cord and synapse with second order neurons. These neurons ascend the spinal cord through dorsal column (white matter). Sensory information can ascend via the lateral (B) or medial (C) systems.

B. The lateral system (purple arrows and text) comprises second order neurons from the superficial layers of the dorsal horn and synapse within the VPL, VPM and VPI of the thalamus. Third order neurons from the VPL and VPM project to S1 and neurons from the VPI project to S2 which are associated with processing the strength and location of stimuli.

C. The medial system (arrows and text in black) comprises second order neurons from the deeper layers of the dorsal horn and synapse within the VMpo, ILN and PC of the thalamus and RF of brainstem. Third order projections from the thalamic nuclei synapse within the IC and ACC, which are linked to the PFC, amygdala and HTH. Projections from the RF ascend through the brainstem, synapsing in the PAG and PBN before terminating in the HTH and amygdala. The IC, ACC, PFC, HTH and amygdala are thought to be associated with the affective and motivational components of pain.

D. The descending system (text, arrows and boxes in red) is believed to modulate pain within the brainstem. Descending fibres from the PFC, ACC, amygdala and HTH synapse within the PAG. From here, neurons descend to the RVM and DLPT then modulate signals received at the dorsal horn.
The axons of the neurons located within the dorsal column of the medulla then cross the midline of the spinal cord to the contralateral side of the medulla and ascend to the ventroposterior lateral nucleus of the thalamus where they terminate (see Figure 1.1B) (Rustioni et al. 1979). Thalamic neurons from the ventroposterior lateral nucleus then project to the corresponding body region in the somatosensory cortex (see Figure 1.1B). Non-nociceptive information reaches the somatosensory cortex in the brain via the dorsal column-medial lemniscal pathway (Rustioni et al. 1979). The ascending pathway that relays non-nociceptive information differs to the pathways that relay nociceptive information, which are described in the next section.

1.2.2.3. Transduction of nociceptive somatosensory information

Dorsal Horn

Aδ fibres enter the dorsal horn (Figure 1.1A) and synapse directly with second order neurons in laminae I, II and V (D’Mello et al. 2008). C fibres directly synapse with fibres in laminae I and II (also known as the substantia gelatinosa), and indirectly synapse with second order neurons in lamina V via interneurons (D’Mello et al. 2008). Second order neurons in laminae I and II are mostly nociceptive-specific whereas second order neurons in the deeper layers of the dorsal horn are mostly wide dynamic range (WDR) neurons (Giordano 2005). The latter have large receptive fields and allow for the transmission of non-nociceptive and nociceptive sensations by grading the strength of peripheral inputs (Giordano 2005).

Excitatory and inhibitory interneurons are also present within the dorsal horn and regulate sensory transmission through the spinal cord via interactions with both nociceptive-specific and WDR second order neurons (D’Mello et al. 2008). WDR neurons can also contribute to the process of secondary hyperalgesia (increased sensitivity to stimuli within the area surrounding an insult) via the process of “wind-up”, described further in Section 1.2.5. Second order neurons then cross the midline of the spinal cord and ascend through the anterolateral region of the contralateral white matter through the brainstem before terminating in the thalamus (Figure 1.1B).

Lateral System

The lateral pathway is mostly comprised of nociceptive-specific second order neurons from the superficial layers of the dorsal horn that cross the midline of the spinal cord at the same level as the first order synapses and ascend via the anterolateral column to higher structures via the spinothalamic tract (D’Mello et al. 2008). These neurons enter the thalamus and synapse within the ventroposterior medial, lateral and inferior thalamic nuclei (Figure 1.1B) (Treede et al. 1999; Ab Aziz et al. 2006). Third order neurons from the ventroposterior medial and lateral nuclei then project to the primary somatosensory cortex with third order neurons from the ventroposterior inferior nucleus projecting to the secondary somatosensory cortex to provide information about the strength and location of noxious events (Figure 1.1B). These findings were first characterised in primates using macaques in which lesions in the contralateral dorsal funiculus (targeting
nociceptive inputs) and ipsilateral ventral quadrant (targeting non-nociceptive inputs) of the spinal cord isolated the two ascending pathways (Apkarian et al. 1989). This study identified that the lateral pathway is important for the integration of peripheral inputs for the sensory-discriminative component of pain (Apkarian et al. 1989).

Medial System

The medial pathway feeds into the affective and motivational processing of nociceptive inputs and contains a high proportion of WDR neuron projections from the deeper laminae of the dorsal horn (D’Mello et al. 2008). These neurons are polymodal (respond to a wider range of sensory modalities) and receive both nociceptive and non-nociceptive inputs (D’Mello et al. 2008). A proportion of second order neurons in this pathway synapse directly within the posterior ventromedial and intralaminar nuclei of the thalamus (Ab Aziz et al. 2006). In rats, the neurons ascending via the parabrachial nuclei terminate in the amygdala and hypothalamus, although this finding is yet to be replicated in humans (Petrov et al. 1993). Other second order neurons synapse within the brainstem (reticular formation) and midbrain (periaqueductal gray) (see Figure 1.1C) (Brooks et al. 2005). Projections from these regions synapse within the medial thalamic relay nuclei, such as the intralaminar and paracentral nuclei (see Figure 1.1C) (Ab Aziz et al. 2006).

Summary

The medial and lateral pathways relay the location, modality and intensity of a painful stimulus from the periphery to the brain. How this information is integrated and can be used to form the basis of the perception of pain is described in the next section.

1.2.3. Pain Processing

Third order neurons from the lateral pain pathway synapse within the primary and secondary somatosensory cortices (see Figure 1.1B). This path is thought to encode sensory-discriminative (stimulus location and intensity) and sensory-integrative (usually polymodal inputs) aspects of the pain experience (Treede et al. 1999). Third order neurons from the medial pathway project from the thalamus to the insular and anterior cingulate cortices (involved in processing emotions; see Figure 1.1C) (Brooks et al. 2005). This pathway is involved in the arousal, affective and executive control components of pain (Brown et al. 2008; Brown et al. 2014). However, these components do not always correlate with the intensity of the nociceptive input (Melzack et al. 1968).

Neuroimaging studies have highlighted areas of increased activity during painful stimulation (Derbyshire et al. 1997). A number of cortical regions associated with attention (prefrontal cortex), emotional response (pregenual and anterior cingulate, and insular cortices), motor function (premotor cortex and lentiform nucleus), and sensory integration (thalamus) receive significant
blood flow during laser-evoked potentials (infrared pulses that quickly heat the skin), indicating that sensory integration only forms one part of the pain experience (Derbyshire et al. 1997; Derbyshire et al. 1998). A study by Kulkarni et al. (2007) demonstrated increased glucose metabolism within the cingulate cortex, thalamus and amygdala using positron emission tomography scans of 12 knee osteoarthritis (OA) subjects. The increased metabolism in these regions was observed when subjects were experiencing knee pain compared with experimental pain and no pain conditions, and increased activity was associated with increased emotional salience at the same levels of pain intensity as the experimental pain (Kulkarni et al. 2007). This finding suggests that subjects with chronic pain can have alterations within their pain processing pathways as the cingulate cortex, thalamus, and amygdala are associated with memory, emotion, and sensory integration (Kulkarni et al. 2007).

An important aspect of the experience of pain is the amount of attention paid to a stimulus (Lautenbacher et al. 2007). For example, distraction can reduce the amount of pain perceived in experimental situations. A study of 34 healthy volunteers (16 female; mean age 24.5) who provided pain and unpleasantness ratings (0-100 numeric rating scale; NRS) for a heat stimulus of between 49°C and 53°C at the left forearm (baseline test) were exposed to three test paradigms in a randomised order (Moont et al. 2010). These paradigms included “conditioning” (right hand submerged in 46.5°C water bath for two minutes), “distraction” (counting the number of one, two or three different shapes presented) and “combined” (conditioning and distraction) (Moont et al. 2010). There were significant reductions in pain and unpleasantness ratings for the heat stimulus during the conditioned, distraction and combined tests (Moont et al. 2010). This study also demonstrated that the difference in pain reporting for the combined test (21.2 ± 2.3) was significantly lower than during the conditioning test alone (16.0 ± 2.3) suggesting that the mechanisms for conditioning and distraction are separate (Moont et al. 2010).

The expectation of pain also shapes the experience of it. Unexpected pain is generally perceived as more unpleasant and of greater intensity than expected pain (Carlsson et al. 2006). A recent study of 16 fibromyalgia and 16 OA patients demonstrated that reductions in anticipation in the dorsolateral prefrontal cortex (associated with attention) were associated with higher levels of anxiety (β-coefficient (β) -0.43; p=0.019), depression (β -0.39; p=0.039) and catastrophising (β -0.49; p=0.007), but not with pain (β -0.23; p=0.23) across the patient groups (Brown et al. 2014). However, increased anticipation in the left and right insular cortices (associated with emotional responses) was associated with pain (β 0.56 and 0.40 respectively; p<0.05), with the relationship for the left insular cortex remaining significant after adjusting for anxiety, depression and catastrophising (β 0.66; p=0.001) (Brown et al. 2014). Although the effect was enhanced in the patients with fibromyalgia, this study suggests that common pain pathways exist for both patient subgroups and that they play a role in amplifying pain perception.

As previously mentioned, the insular, dorsolateral prefrontal and anterior cingulate cortices are implicated in the sensory and affective components of pain, and in processing fear and aversion demonstrating alterations in pain processing pathways in those with chronic pain. These brain regions form a pain matrix, which influences descending modulatory pathways in the nervous system (Tracey et al. 2007). Alterations in pain processing may arise through facilitatory or
inhibitory mechanisms within this descending modulatory system. This modulation system is described in the following section.

1.2.4. Pain Modulation

A modulatory system is present within the nervous system which regulates the amount of pain perceived. This system contains ascending and descending modulatory pathways (see Figure 1.1D). The descending system receives input from the limbic system and can be affected by an individual's psychological state (interactions between anxiety, depression, attention and other factors), which may subsequently modulate the intensity of pain experienced (Brooks et al. 2005). A study by Villemure and Bushnell (2009) of 14 subjects (5 males) aged 18-28 used heat pain and pleasant and unpleasant odours to distinguish between the effects of attention and emotions on pain. The use of pleasant odours was associated with a reduction in the reporting of pain unpleasantness and decreased activity within the medial thalamus and primary and secondary somatosensory cortices (associated with sensory discrimination and integration), and anterior cingulate cortex (associated with emotional response); the latter region was also associated with increased activity in the periaqueductal gray (Villemure et al. 2009). This study also demonstrated that the co-administration of an odour and heat pain stimulus led to decreased activity within the anterior insular cortex (associated with attention) and was associated with a reduction in pain intensity (Villemure et al. 2009).

Descending efferent fibres from the hypothalamus, anterior cingulate, insular and prefrontal cortices, and amygdala project via the brainstem to the dorsal horn of the spinal cord where peripheral afferents synapse with second order neurons for the transduction of sensory information (Figure 1.1) (Rainville et al. 1997; Tracey et al. 2007). The efferent fibres descend via the periaqueductal gray in the grey matter of the brainstem and synapse with the rostral ventromedial medulla and dorsolateral pontine tegmentum (Fields et al. 1985). The efferents project to and enter the dorsal horn via the dorsolateral funiculus before terminating in the substantia gelatinosa (Fields et al. 1985).

The facilitation or inhibition of primary afferent fibre input in the dorsal horn is thought to be modulated by the release of noradrenaline (rostral ventromedial medulla efferents), serotonin (dorsolateral pontine tegmentum efferents) and/or endogenous opioids (periaqueductal gray) from the synapses of descending efferents (Figure 1.1D) (Dickenson et al. 1981; Rahman et al. 2009). Willer (1977) first demonstrated the opioidergic effect in humans (25 students aged 22-35; 15 males) by recording verbal pain ratings from 0 to 10 for the RIII nociceptive reflex (painful electrical stimulation of the sural nerve in the lower leg generating a reflex which is relayed via the brain stem; baseline average pain rating 6±1) and during four separate test conditions: during an attention test (mental arithmetic for 30 seconds), anticipation of pain (strong electrical stimulation of the sural nerve), heterotopic stimulation (painful electrical stimulation of the contralateral ulnar nerve), and random stimulation (one painful stimulation of the sural nerve without a cue). Higher pain intensities were recorded for the anticipation (7±1.3) and random stimulation tests (9.2±0.4), while reductions in pain intensity were observed during the heterotopic (2.8±0.9) and distraction...
tests (1±0.3) (Willer 1977). Willer et al. (1990) also demonstrated that the pain experienced during the RIII reflex could be inhibited by submerging the contralateral hand into 46.5°C water for two minutes (thermal pressor test); administration of naloxone (an opioid antagonist), and not saline, in a double-blind cross-over trial of 9 participants reversed the inhibitory effects observed and highlighted the inhibitory role of endogenous opioids within the pain modulatory system. However, the role of serotonin and noradrenaline in the descending modulatory pathways in humans remains unclear. Studies in rats have suggested that these two neurotransmitters play a facilitatory role in descending pain modulation in the rostral ventromedial medulla and supraspinal regions, such as the prefrontal and anterior cingulate cortices (Porreca et al. 2002); however, this is yet to be confirmed in humans.

1.2.5. **Mechanisms of Sensitisation**

Sensitisation is an increase in response to repeated stimulation (usually by a noxious event) that can result in a learned behaviour (Kandel 2000). Sensitisation may also arise as a result of altered psychological state, whereby the attention paid to painful signals can be diverted; for example, hypervigilance to pain signals could lead to sensitisation (Lautenbacher et al. 1997). Alterations in descending pain modulatory pathways may also contribute to sensitisation, either by inhibiting opioidergic, or by facilitating descending spinal processes (as described in the previous section), leading to enhanced pain. Amplification of painful and non-painful signals within the nervous system forms the basis of sensitisation in chronic pain, described in further detail in the next sections.

1.2.5.1. **Mechanisms of Peripheral Sensitisation**

Peripheral sensitisation can be defined as “a reduction in threshold and an amplification in the responsiveness of nociceptors that occurs when the peripheral terminals of these high-threshold primary sensory neurons are exposed to inflammatory mediators and damaged tissue” (Latremoliere et al. 2009). Peripheral sensitisation can arise when acute pain related to an insult affects the receptivity of sensory neurons located near to the damaged area (Kidd et al. 2004). For example, peripheral tissue damage can lead to the release of pro- and anti-inflammatory mediators into the local microenvironment, which can activate nociceptors present in the cell membranes of Aδ and C fibres (Schaible et al. 1993).

In those with chronic pain the source of peripheral sensitisation is usually attributed to pathology related to a disease process, but this may not always be the case as previously highlighted (Section 1.2.1.1) (Kramis et al. 1996). Peripheral sensitisation is believed to play a role in people with knee OA. Total knee replacement surgery is thought to alleviate pain in patients with knee OA by removing the damaged joint (the source of pain). A systematic review of pain outcomes following total knee replacement surgery found that between 30% and 85% of patients in 11 studies (n=12,880) reported a favourable outcome following surgery (Beswick et al. 2012).
However, between 8% and 27% of patients reported moderate, severe, or no resolution of pain following surgery suggesting the removal of the diseased knee did not eliminate the pain as anticipated (Beswick et al. 2012). Another recent study of 100 patients undergoing knee replacement surgery identified increased sensitivity to painful pressure stimulation at the forearm pre-operatively was a significant predictor of the presence of worse pain outcomes one year later (Spearman’s rank correlation coefficient (rho) 0.37; p=0.008) (Wylde et al. 2013). The results of these two studies can be interpreted in another way; increased sensitivity to peripheral stimuli in knee OA patients, especially if increased sensitivity is present at a pain-free and distal control site, may be indicative of amplifications within the CNS (Arendt-Nielsen et al. 2010). That is, the increased sensitivity in knee OA patients may be explained by central sensitisation.

1.2.5.2. Mechanisms of Central Sensitisation

Central sensitisation can be defined as “an amplification of neural signalling within the CNS that elicits pain hypersensitivity” (Woolf 2010) and can arise as a result of peripheral sensitisation. There is also evidence emerging suggesting that there are other mechanisms that can contribute to central sensitisation and these are described in the following sections (Schaible et al. 2006).

**Spinal Mechanisms**

Short-term sensitisation can occur via a mechanism of wind-up. If a noxious stimulus is applied repeatedly to one anatomical location, the nociceptive afferents in that area can become more sensitive to nociceptive inputs leading to increased excitability within the CNS (Vierck, Jr. et al. 1997). Mendell and Wall (1965) showed that a 30 volt stimulus lasting 0.5 milliseconds applied to the sural nerve of cats activated C fibres leading to a train of action potentials lasting 8 milliseconds and triggered spontaneous activity in dorsal horn cells; they termed this response “wind-up”. The effect of wind-up was more pronounced following an increase in stimulus frequency to once every three seconds (Mendell et al. 1965).

A series of experiments performed by Woolf (1983) demonstrated the effect of wind-up as a mechanism of central sensitisation in 8 decerebrate rats (removal or damage to the cerebrum or brainstem) via the use of short duration stimuli. Following a noxious thermal insult to the hind paw, the rats exhibited faster paw withdrawal reflexes to lower mechanical stimulation which continued for two hours after the initial insult with thresholds increasing after that and returning to normal 24 hours after the initial insult (Woolf 1983). The study also found increased spontaneous firing of a motor neuron located within the affected leg during the first hour following the insult; the authors interpreted their data as demonstrating that an insult to a peripheral tissue could elicit reversible hypersensitivity within the spinal cord (Woolf 1983). The subsequent heightened response following repeat stimulation peaks approximately half an hour after the start of the test and diminishes over time (from 90 minutes) (Wall et al. 1984). Sensory afferents from deep muscular tissue synapse in lamina III and IV have also been shown to have a prolonged effect on spinal cord sensitisation (Wall et al. 1984).
Short-term sensitisation can in some cases lead to longer lasting sensitisation, also known as long term potentiation (LTP), which involves changes in synaptic plasticity (Kandel 2000). The role of LTP was first investigated in cognitions such as learning and memory in animals, but now has much wider implications (Ji et al. 2003; Lang et al. 2007). One proposed mechanism suggests that LTP increases the success of synaptic transduction rather than the quantity of action potentials transduced (Stevens et al. 1994). Bailey and Chen (1983) provide support for this mechanism as their work focusing on primary afferents indicated that the number of vesicles and the number of active zones present in active synapses are increased for LTP.

There is support for the role of wind-up in humans. C fibres that project into the spinal cord via the anterolateral spinothalamic system can sensitise second order WDR neurons present in the dorsal horn (see Section 1.2.2.3) (Schaible et al. 1993). This may occur after repeated activation at a rate of one or more noxious stimuli per second (Arendt-Nielsen et al. 1995; Eide 2000). This lowers the threshold needed to transduce information via WDR neurons to the thalamus (Bleakman et al. 2006). The assessment of wind-up in humans is termed temporal summation and this term will be used from this point forward. Price and Dubner (1977) demonstrated that Aδ and C fibres contribute to the sensations of first and second pain, respectively, in humans. First pain is typically associated with the onset of an insult as it has a fast onset and provides information about the location, quality and intensity of pain; second pain is poorly localised, has a delayed onset and persists past the original insult and is associated with temporal summation in the CNS (Price et al. 1977). Following 4 applications of a noxious heat stimulus to the hand with a gap of 3 seconds between each application, subjects reported reduced pain intensities for first pain sensations for each subsequent stimulus; however, pain intensities increased for sensations associated with second pain (Price et al. 1977). This suggests that temporal summation in the CNS is mediated by C fibre input.

Studies in patients with chronic pain have revealed that increased sensitivity to temporal summation is associated with higher levels of pain. In a population-based sample of 2126 subjects with knee OA, a 60g von Frey filament was applied to the affected knee and wrist at a rate of one application a second for 30 seconds (Neogi et al. 2013). Subjects provided pain ratings using a NRS (range not provided) following a trial of 4 stimulations and at the end of the 30 second train of stimuli. The presence of temporal summation was determined if the pain rating for the 30 second train exceeded that of the pain rating for the train of 4 stimuli (Neogi et al. 2013). Temporal summation was observed for 877 subjects (41%), with increased sensitivity to temporal summation at the knee (odds ratio (OR) 1.6; 95% confidence interval (CI) 1.4, 1.9) and wrist (OR 1.3; 95% CI 1.1, 1.5) significantly associated with greater pain severity (Neogi et al. 2013). These findings demonstrate generalised changes in pain amplification within the nervous system as increased sensitivity at both the affected and unaffected sites was associated with higher levels of pain severity.

Other studies have utilised thermal stimuli to assess temporal summation. One study of 113 knee OA patients stratified in to one of four groups according to high or low disease severity (assessed using radiographs) and high or low pain severity (Finan et al. 2013b). A sequence of 10 noxious heat stimuli (temperature set to 51°C; rate of 1 pulse per second) were applied at the forearm, with greater pain intensity ratings (0-100) for the final pulse compared with the first pulse used to
determine the presence of temporal summation (Finan et al. 2013b). The highest pain ratings were observed for the high pain and low disease severity group (44.6±33.3) which was significantly higher (p<0.05) than the low pain severity groups (high disease severity 22.3±19.9; low disease severity 30.5±30.6) (Finan et al. 2013b). This study suggests that amplification of pain can occur in the absence of peripheral input (such as underlying disease pathology) and that high pain severity in the group of subjects with high pain ratings for temporal summation at a control site is likely to be due to hypersensitivity within the spinal cord.

There are other mechanisms by which central sensitisation can arise that are not dependent on amplification within the spinal cord. The following section describes changes that may occur within supraspinal regions of the CNS and how this can contribute to chronic pain.

**Supraspinal Mechanisms**

Central sensitisation is not necessarily dependent on peripheral inputs, peripheral sensitisation or temporal summation. Spontaneous neuronal firing in the dorsal horn can enhance receptive field size resulting in an increased responsiveness to primary afferent input (Woolf 1983). However, descending modulation of sensory information sent to the dorsal horn (described in Section 1.2.4) can also influence the amount of pain perceived; this is referred to as the diffuse noxious inhibitory control (DNIC) system (Talbot et al. 1989; Le Bars et al. 1992).

Concomitant painful stimulation of two areas of the body using different test modalities is referred to as heterotopic noxious conditioning stimulation or conditioned pain modulation (CPM) and can be effective in reducing pain via the descending pain system (Edwards et al. 2003). Descending modulation of pain is thought to be impaired if a subject reports more pain during the concurrent application of the test and conditioning stimuli than for the test stimulus alone (Edwards et al. 2003).

Willer et al. (1990) demonstrated in 9 healthy subjects (5 females; age range 23-26 years) that using a thermal pressor test as a conditioning stimulus could inhibit the effect of painful electrical stimulation of the sural nerve, and that this effect was mediated via endogenous opioids as the administration of Naloxone (an opioid antagonist) reversed the inhibitory effect (detailed in Section 1.2.4). Other experimental models of DNIC have demonstrated that inhibitory control of pain is impaired in a number of chronic pain conditions such as fibromyalgia (Kosek et al. 1997; Lautenbacher et al. 1997; Staud et al. 2003; Klauenberg et al. 2008), chronic tension-type headache (Pielsticker et al. 2005), neuropathic pain (Bouhassira et al. 2003; Schwenkreis et al. 2010) and in OA (Kosek et al. 2000; Rahman et al. 2009; Arendt-Nielsen et al. 2010). However, Staud et al. (2003) demonstrated that pain experienced during a sequence of 8 noxious heat stimuli applied to the right hand (53°C with 0.7 second duration and 2 seconds between stimuli), was inhibited in 11 male healthy controls (40.2±16.8 years) during the co-application of a hot pressor test at the left hand (hand submerged in a water bath, set to 47°C in this instance) compared with 22 female pain-free controls (35.8±12 years) and 11 females with fibromyalgia (52.9±6.3 years). This suggests that DNIC may be deficient in women and not in men, and may not be specific to chronic pain; however, women tend to be over-represented in fibromyalgia and the
association with deficient DNIC may be an artefact of the higher proportion of women with the condition (Staud et al. 2003).

A recent systematic review of 30 studies performing CPM assessments in 778 subjects with chronic pain (fibromyalgia, headache, irritable bowel syndrome and arthritis) determined CPM was impaired in chronic pain subjects compared with healthy controls with an effect size of 0.78 (95% CI 0.48, 1.08) (Lewis et al. 2012). One limitation identified by this review was that only 4 studies blinded the assessors to which group the subject belonged to (Lewis et al. 2012). Three of the 30 studies effectively controlled for confounding factors that can influence the results of CPM assessments, such as concomitant pain medications, pain at the time of testing, and menstrual cycle information for females (Lewis et al. 2012). These limitations are important when assessing CPM as women are less sensitive to CPM during ovulation and the use of analgesics or the presence of pain during testing will influence the amount of CPM observed (Popescu et al. 2010). Another limitation identified by Lewis et al. (2012) included the wide range of test protocols that were used including different paradigms for conditioning and test stimuli and pain rating scales; this can influence the comparisons drawn across studies due to the different ascending and descending pathways stimulated and ways in which CPM can be calculated (Matre 2013). However, these findings do suggest that the modulation of nociceptive signals via the DNIC system is impaired in those with chronic pain conditions (Talbot et al. 1989; Li et al. 1999).

Conclusion

Sensitisation can occur either peripherally, centrally or it can arise as a result of both; the current literature suggests that peripheral sensitisation may be important for the initiation of amplification of pain signals within the CNS, and the disruption of descending modulation plays a key role in the maintenance of chronic pain (Meeus et al. 2007). Section 1.2.6 contains an overview of other theories of pain. The section discusses the complexity of pain and that no model completely accounts for all aspects of chronic pain.

1.2.6. Theories of Pain

1.2.6.1. Early Theories of Pain

Prior to the gate-control theory (described in Section 1.2.6.2), pain was considered a wholly sensory event like touch or smell, and the unpleasant aspects of the experience of pain were not accounted for (Melzack et al. 1968). One such theory, the specificity theory by Charles Bell (1868), suggested that different sensory modalities were encoded by separate nerve fibres and those fibres projected to a single pain centre within the brain (Moayedi et al. 2013); this theory stemmed from Rene Descartes’ theory of mind-body dualism in which he described the pathway by which a painful stimulus detected in the periphery reached the brain.
Research into the anatomy of peripheral afferents confirmed the existence of fibre classes that do respond to different sensory modalities. Small diameter fibres can be myelinated or unmyelinated, have slower conduction velocities, and respond to painful stimuli, whereas large diameter fibres are myelinated, have faster conduction velocities, and generally respond to innocuous mechanical stimuli (described further in Section 1.2.2.1) (Gardner et al. 2000c). However, the specificity theory and other theories at the time did not address the psychological aspects of pain, such as the emotional impact or unpleasantness associated with pain (Summers 2000). Those theories focused solely on pathology driving pain, which addresses most aspects of acute pain; however, this does not work well for other pain conditions including chronic pain (Summers 2000). The theories described in the following sections integrate the sensory component of pain with the psychological aspects, which play a key role in the perception of pain.

1.2.6.2. The Gate Control Theory

The gate control theory (Melzack et al. 1965) (see Figure 1.2) built on findings which supported the specificity theory (Bell et al. 1868). The gate control theory proposed that the spinal cord modulated inputs from small and large diameter sensory fibres through a gating mechanism within the substantia gelatinosa (see Figure 1.2 and Section 1.2.2.1).

Figure 1.2 The Gate Control Theory (Melzack et al. 1968)

![Figure 1.2](image)

Figure created from composite of figures 22.2 and 22.3 (Melzack et al. 1968); L represents large diameter fibres; S represents small diameter fibres; SG = substantia gelatinosa; T = central transmission cells; + = excitation; - = inhibition. The theory proposes that large and small fibres synapse within the SG of the dorsal horn and with T cells. Increased activity from small fibres inhibits activity in the SG (closes the gate) while increased activity from large fibres is excitatory, promoting activity in the SG (opens the gate). Neurons from the SG synapse with T cells creating a feedback loop. T cells then project to an action centre (not shown) where sensory-discriminative and motivational-affective processing occur. There are connections between these two regions along with a region for central control (later termed cognitive-evaluative). The integration of information between the sensory-discriminative, motivational-affective and central control processing influence the behaviours arising in response to sensory input (motor mechanisms). The theory also proposed that motivational-affective and central control processing could also influence input at the dorsal horn.

Large and small diameter fibres converged on cells in substantia gelatinosa and on central transmission cells within the dorsal horn. Here, large fibre activity triggered a negative feedback loop through excitation of the inhibitory cells in the substantia gelatinosa on central transmission
cells which “closed the gate” (Melzack et al. 1965). Small fibre activity “opened the gate” by triggering a positive feedback loop through inhibition of the cells in the substantia gelatinosa; due to the gating mechanisms in the substantia gelatinosa, the output from transmission cells did not always reflect the input into the spinal cord (Melzack et al. 1965). Transmission cells then relayed the impulses to the brain where the input was processed and subjected to modulation. That is attention, emotions, and memories impacted on how the sensation was perceived. The theory also suggested that a descending modulatory pathway from the brain may also impact gating in the spinal cord (described further in Section 1.2.4) (Melzack et al. 1968).

This theory provided a simplistic view of the role of the dorsal horn due to the available research at the time of conception. Progress in our understanding of the organisation of the dorsal horn is described in Section 1.2.2.2, with laminae I, III, IV, V and VI also receiving and/or modulating peripheral inputs. Another limitation of the gate-control theory is that it does not account for pain in the absence of peripheral input, such as chronic pain.

Following the gate control theory, Melzack and Casey (1968) proposed that there were three pain components that receive inputs from the dorsal horn, shown in Figure 1.2: (1) the sensory-discriminative component of pain provides the intensity and location of the sensation as well as the modality perceived (for example, noxious heat) (Melzack et al. 1968); (2) the affective-motivational component of pain comprises the unpleasantness and response to pain, and (3) the cognitive-evaluative component comprises the behaviours experienced during pain such as diversion of attention or anxiety (Melzack et al. 1968). By incorporating the gate control theory of pain with these pain components, Melzack proposed the neuromatrix theory of pain (described in the next section) (Melzack 2001).

1.2.6.3. The Neuromatrix of Pain

The neuromatrix of pain proposed a neural network in the brain incorporating the somatosensory cortex (sensory-discriminative component), brainstem and limbic systems (affective-motivational component), and parietal systems (cognitive-evaluative component) that is predetermined genetically and altered over time by sensory inputs (Derbyshire 2000; Melzack 2001). Our current understanding of the sensory-discriminative, affective-motivational and cognitive-evaluative components of pain is described in Sections 1.2.2, 1.2.3 and 1.2.4 respectively.

The neuromatrix of pain suggests that the sensory-discriminative, affective-motivational and cognitive-evaluative components comprise an underlying modifiable pattern for pain (inputs to the neuromatrix; see Figure 1.3) (Melzack 2001). Activation of this underlying pattern provides an explanation as to how pain can be felt without peripheral sensory input, as is the case for some chronic pain conditions as well as phantom limb pain. However, the theory does not provide an explanation as to how these underlying mechanisms can be triggered for those with phantom limb pain or chronic pain (Melzack 2001).
Figure 1.3 The Neuromatrix of Pain (Melzack et al. 2004)

![Neuromatrix Diagram]

Figure reproduced from Melzack and Katz (2004); C = cognitive-evaluative; A = affective-motivational; S = sensory-discriminative. The theory proposes that an underlying modifiable pattern (including sensory inputs, previous experience and stress mechanisms) contribute to a neuromatrix comprising the sensory-discriminative, affective-motivational and cognitive-evaluative components of pain. The integration of inputs and processing in the neuromatrix influences the outputs, such as the perception, behaviours, and stress generated in response to pain.

There are other factors thought to contribute to the neuromatrix including stress, sensory inputs, anxiety, and previous experiences (Figure 1.3). These factors in turn contribute to pain-related perceptions (such as intensity and unpleasantness), further modulation of pain and stress through endogenous systems, and the generation of pain behaviours such as coping and social support (Melzack 2001). The interactions between the inputs and outputs of the neuromatrix shown in Figure 1.3 explain some of the differences in pain reporting, as described in Section 1.2.1.2.

A limitation of the neuromatrix of pain is that it is not a testable model, but a framework designed to improve awareness of the complexity of pain; it does highlight the need to consider multiple brain and body systems when researching pain and incorporates recent biological, psychological, and social findings (Melzack 2001). These factors also form the basis of the biopsychosocial approach to pain, described further in the next section.

1.2.6.4. Biopsychosocial Approach

The biopsychosocial approach was proposed by Engel (1977) to encourage the consideration of biological (e.g. abnormal blood test), psychological (e.g. fear, anxiety, or depression) and social factors (e.g. cultural or socioeconomic) in health care as these factors all contribute to the experience of an illness or disease. The biopsychosocial approach is also more of a theoretical framework than a model that can be directly tested, but it has prompted the inclusion of biological, psychological and social factors associated with chronic pain within research (Lumley et al. 2011). One model derived from the biopsychosocial approach is the fear avoidance model of pain perception proposed by Vlaeyen and Linton (2000). The theory proposes that in the event of a painful injury, the appraisal of whether that injury is threatening determines how the injury is interpreted and dealt with (see Figure 1.4) (Vlaeyen et al. 2000).
The Fear-Avoidance Model (Vlaeyen et al. 2000)

If a painful injury is perceived as non-threatening, no fear will be associated with the injury leading to the continuation of daily activities (confrontation) and rapid recovery (Vlaeyen et al. 2000). If an injury is perceived as threatening it can lead to the development of pain-related fear and hypervigilance to the painful sensation, as well as generating avoidance behaviours such as disability and disuse; this creates a negative feedback loop that could theoretically drive acute pain from an injury to develop into chronic pain (Vlaeyen et al. 2000). Although this model has provided a basis for a number of studies investigating fear-avoidance in relation to chronic musculoskeletal pain conditions, causality between the factors in Figure 1.4 has not yet been established (Leeuw et al. 2007). Another limitation of the fear-avoidance model is that it proposes a basis for the onset and persistence of chronic pain, but does not suggest which factors in the threatening loop should be targeted by interventions (Leeuw et al. 2007).

1.2.6.5. Conclusion

Pain is multifaceted and complex. It is not just a physiological warning system as pain can arise without underlying pathology. The above theories posit that psychological state and social factors can influence pain perception and may explain some of the differences observed in pain reporting. Modifications within the somatosensory nervous system are also described in the gate-control and neuromatrix theories (Melzack et al. 1965; Melzack 2001). This area of research has progressed over the past 40 years (Woollf 2010). Ongoing amplification of signalling in the nervous system can be problematic for people with chronic pain and can explain some of the differences observed in pain reporting, and how the physiological systems underlying these processes may be altered in those with chronic pain.
1.3. Summary

Pain is a complex experience comprised of sensory, affective and cognitive processes that can influence the amount of pain perceived, modulated and reported by individuals experiencing it. There is evidence to suggest that peripheral noxious input does not necessarily result in the transmission of pain due to modulation at the spinal cord (Section 1.2.2.3). Pain signals that do reach supraspinal regions can also be influenced by the amount of attention paid to a stimulus (Section 1.2.3) and modulated by descending facilitatory and/or inhibitory pathways (Section 1.2.4). These pathways are thought to be altered in people with chronic pain. There are multiple theories of pain which try to account for the differences between the experiences of acute and chronic pain through interactions between biological, psychological and social factors (Sections 1.2.5 and 1.2.5). So far, changes within regions of the brain implicated in fear aversion, emotional response and attention, an increase in spinal cord hypersensitivity and a lack of descending modulation of pain have been identified in those with chronic pain. How these factors contribute to the experience of and can be assessed in people with knee pain, a common chronic musculoskeletal pain condition, is described in Chapter 2.
CHAPTER 2. BACKGROUND

2.1. Overview

This chapter provides the rationale for the thesis. Knee pain is a common and disabling condition, particularly in older adults and in women. Other factors which are associated with knee pain include greater psychological distress and poorer physical functioning, but the mechanisms by which these factors contribute to knee pain severity remains unclear. There is a poor relationship between knee pain and the presence of structural markers of knee OA using radiographs, although the association strengthens with greater disease severity. There are also few long-term effective treatments for knee pain with increasing demand for the development of personalised interventions according to the individual needs of a patient. Other mechanisms which may provide an explanation for the discordance between knee pain and underlying OA include altered pain processing, such as peripheral and/or central sensitisation. Quantitative Sensory Testing (QST) is a non-invasive technique that can be used to identify a loss or gain in function within the somatosensory nervous system. The combined role of psychosocial factors and sensitisation with respect to knee pain remains largely unexplored. The identification of mechanisms of sensitisation and/or psychosocial factors which may contribute to knee pain can aid in phenotyping patients and may inform treatment choices in the future.

2.2. Knee Pain

2.2.1. Definition of Knee Pain

There is currently no standardised definition of knee pain. Knee pain is used as a symptom in classification criteria for other conditions such as patellofemoral pain syndrome (Jensen et al. 2007) and knee OA (Altman et al. 1986). A number of observational cohort studies rely on self-reports to determine an estimated proportion of subjects with knee pain (Peat et al. 2004; Thomas et al. 2004; Helmick et al. 2008; Neogi et al. 2009). The use of different definitions of knee pain across studies, or using a classification of underlying disease (such as OA) can impact the prevalence and/or incidence reported by a study. This will also affect the external validity and generalisability to other populations.

There are also differences in patient-reports of knee pain attributable to underlying disease and physician diagnosis. A study of 45 patients with knee pain investigating the level of agreement between patient and physician diagnosis of whether the patient's knee pain was related to OA determined poor agreement with a kappa score of -0.03 (95% CI -0.32, 0.26) (Peat et al. 2005). This suggests that physicians may not be relaying information regarding underlying disease which could impact a patient's perception of their pain; for example, patients who believe their knee pain is attributable to a disease may have differing expectations of how their pain should be managed, or what may be driving their pain, than those who are not informed their pain could be related to knee OA (Peat et al. 2005). Despite this, a recent study demonstrated that the prevalence of self-
reported knee pain and symptomatic knee OA appears to be increasing while the prevalence of underlying OA is decreasing supporting the idea there is a tendency for people to report knee pain whether or not they have underlying disease (described further in the next section; see Figure 2.1) (Nguyen et al. 2011). The following section reviews the estimated prevalence of knee pain in the general population and outlines risk factors for developing pain in the knee.

Figure 2.1 Prevalence of knee pain, radiographic OA and symptomatic OA in the Framingham Osteoarthritis Study (Nguyen et al. 2011)

Figures reproduced from Nguyen et al. (2011). 1983-1985 Original and 1992-1995 Original refer to the prevalence of people with knee pain and OA in both graphs during those follow-up periods of the Framingham Osteoarthritis Study. The cohort was expanded to include the offspring of the original cohort and other residents in Framingham who had not previously participated. The prevalence of knee pain and OA within the later cohort is referred to as 2002-2005 Offspring and Community in both graphs.

2.2.2. Epidemiology of Knee Pain

2.2.2.1. Occurrence of Knee Pain

Chronic musculoskeletal pain is a common complaint, with an estimated global annual incidence of 10% in adults (Goldberg et al. 2011). Knee pain is of particular interest as it is common in older adults with a one year prevalence (number of people with the event of interest in the population under observation over a 12 month period) of 25% in those over 55 (Peat et al. 2001a). A longitudinal population-based study of adults living in Framingham, Massachusetts demonstrated the prevalence of knee pain (p<0.001 for trend; graph A, Figure 2.3) and symptomatic knee OA (p<0.001 for trend; graph B, Figure 2.3) increased at each follow-up after adjusting for age and BMI (Nguyen et al. 2011); the study also reported that the prevalence of radiographic knee OA significantly decreased for women (p=0.036 for trend), but showed a non-significant increase for men (p=0.82 for trend; see graph B, Figure 2.1). The authors suggest that increases in prevalence observed for knee pain and related symptoms, but not for radiographic knee OA may be due to the insensitivity of radiographs for identifying early signs of knee OA and a lack of imaging of the patellofemoral joint (explored further in Section 2.2.4.5) (Nguyen et al. 2011).
The proportion of 3445 responders to a postal survey in Ullensaker, Norway reporting knee pain was 18.6% (95% CI 17.2, 19.9) with the lower back (34.4%; 95% CI 32.7, 36.0), neck (35.7%; 95% CI 34.0, 37.4) and shoulder (34.0%; 95% CI 32.4, 35.7) also commonly reported (Kamaleri et al. 2008a); this study demonstrated that of those reporting knee pain, only 5.1% of women and 11.2% of men reported pain in one knee. The factors outlined previously (age, sex, physical functioning and psychological distress) are also associated with higher levels of knee pain; these relationships are outlined in further detail in the following section.

2.2.2.2. Risk Factors for Knee Pain

Age and Sex

The knee is one of the most common sites of pain and is more common in women with the prevalence rising with age (O'Reilly et al. 1998; Thomas et al. 2004). A population-based study of 4057 adults in Nottingham aged 40-79 reported that 28.7% of responders had knee pain (O'Reilly et al. 1998). The lowest prevalence was observed for the youngest age group (40-49 years; 25.0%) with the prevalence increasing to 36.9% in the oldest age group (70-79 years) (O'Reilly et al. 1998). Another population-based study of 7878 people in North Staffordshire responding to a postal survey established that similar proportions of each age band reported knee pain (35.7% of those aged 50-59, 37.7% of those aged 60-69, 35.4% of those aged 70-79, and 37.6% of the 80 and over age group) (Thomas et al. 2004). The prevalence of pain interference for each age group did increase with age with 56.3%, 66.4%, 71.5% and 86.2% of each age group, respectively, reporting that pain had a greater effect on their lives (Thomas et al. 2004).

There is also a tendency for more women to report knee pain. A population-based sample of 2192 adults in Spain who responded to a postal survey and were subsequently invited to participate in an interview demonstrated that 310 (14.1%) subjects reported knee pain occurring on at least one day in the past month (prevalent knee pain) with 284 (13.0%) reporting knee pain on the day and 153 interviewees (68.6%) were female (Fernandez-Lopez et al. 2008). Figure 2.1 demonstrates that the prevalence of knee pain and symptomatic knee OA is higher for women participating in the Framingham OA cohort at all three time points (Nguyen et al. 2011). The prevalence of radiographic knee OA is also higher in women until the last time point where the prevalence is marginally higher for men (35.4% for men, 35.1% for women) (Nguyen et al. 2011). These findings support that women are more likely to have knee pain than men, and that the prevalence of knee pain increases with age.

Psychological State

An individual’s psychological state, including maladaptive coping skills, comorbid depression and/or anxiety, and pain catastrophising, are associated with higher levels of knee pain with a number of studies investigating the role of the above factors in those with knee pain (Keefe et al. 1990; Creamer et al. 1998; Keefe et al. 2000; Keefe et al. 2010; Somers et al. 2010).
Coping is defined as “purposeful effort to manage or vitiate the negative impact of stress” (Jensen et al. 1991). Patients who have a better understanding of their pain-related feelings, thoughts, fears and stresses, and have some form of social support generally have better coping techniques for their pain (Keefe et al. 2005). One study of 15 knee OA patients awaiting total knee replacement surgery provided with coping skills training and 45 patients receiving standard post-surgical care demonstrated that patients who received training reported significantly lower levels of pain (p=0.017), disability (p=0.023) and catastrophising (p=0.003) at two months post-surgery compared with normal care patients (Riddle et al. 2011). This suggests that although knee replacement surgery targets pathology within the knee, providing a patient with coping strategies can reduce pain severity (Riddle et al. 2011). These findings should be replicated in a larger prospective study to determine any longer term benefits and whether this intervention should be included in pre- and post-surgical care.

Depression is a mood disorder characterised by low self-esteem, change in activity, loss of enjoyment in activities and worthlessness, amongst others (World Health Organization 1992). The influence of depression on knee pain has been the focus of many studies (Geisser et al. 1994; Keefe et al. 2002; Campbell et al. 2003). Anxiety is a disorder generally accompanied by feelings of gastrointestinal discomfort, nervousness and/or dizziness (World Health Organization 1992), and is also associated with pain (Halder et al. 2002; Mallen et al. 2007a; Mallen et al. 2007b). A study of 54 patients with OA (39% with knee OA) who were interviewed and diagnosed by a psychiatrist as having depression, anxiety, or both (40.7% in total) demonstrated the anxiety and depression subscales and total score for the Hospital Anxiety and Depression Scale (HAD) were significantly associated with scores on the McGill Pain Questionnaire (Kendall’s tau coefficient (τ) 0.25, 0.27 and 0.30, respectively; p≤0.01 for all); the depression subscale of the HAD and HAD total score were also significantly associated with the Present Pain Index (τ 0.33; p=0.003) and pain recorded using a visual analogue scale (VAS) (τ 0.27; p=0.005) (Axford et al. 2010).

Pain catastrophising also plays an important role in knee pain. Pain catastrophising is defined as “an exaggerated negative orientation toward noxious stimuli” (Sullivan et al. 1995). A study of 168 subjects with painful knee OA investigated the role of pain catastrophising as a mediator of the relationship between sex and a latent variable comprised of three different pain outcomes (pain intensity, disability and pain behaviour) (Keefe et al. 2000). Women reported significantly higher levels of pain intensity, physical disability and pain behaviours (one way analysis of variance (ANOVA); p<0.05 for all three) with catastrophising identified as a significant partial mediator of the relationship between sex and pain outcomes; catastrophising remained a significant partial mediator of the relationship between sex and pain after controlling for depression (Keefe et al. 2000). Somers et al. (2009b) have demonstrated that higher pain catastrophising is a significant predictor of pain severity (β 0.35; p=0.002) and explained 10% of the variance of pain severity, 20% for psychological disability, and 11% for physical disability in those with knee pain. This study also established that BMI and KL grade accounted for less than 1% of the variance of pain severity and 6% of psychological disability, but does explain 21% of the variance for physical activity when included in a model with pain severity (Somers et al. 2009a). This provides insight into the difference between patients with high pain scores and minimal radiographic changes in the joint and those who have more advanced disease progression with less pain.
Physical Functioning

To date, poorer physical functioning has been characterised as a risk factor for knee pain onset in a prospective cohort of adults aged over 50 (Jinks et al. 2008). Lower levels of physical activity and increased disability are associated with pain in those with knee complaints. 74% (n=1801) of postal survey responders (n=2429) in a prospective population-based cohort aged over 50 reported lower limb disability and pain in several regions, with levels of disability linked to lower levels of physical functioning, and a greater number of pain sites were associated with greater pain severity (Peat et al. 2006). A cross-sectional study of adults aged over 50 also found that knee pain plus other joint pain was associated with low physical functioning and higher levels of psychological distress compared with knee pain alone (Croft et al. 2005). Furthermore, people with severe knee pain are more likely to report higher levels of pain intensity and those with higher pain intensities report higher levels of psychological distress and physical impairment (Peat et al. 2009).

Another population-based study of 819 adults with knee pain who participated in a detailed clinical assessment and demonstrated reduced quadriceps muscle force (β 0.12; p<0.05), tenderness upon patellar palpation (β 0.07; p<0.05), a diminished capacity to stand on one leg for a long period of time (β 0.09; p<0.05), and/or reduced knee flexion (β 0.13; p<0.05) also reported lower physical functioning assessed using the WOMAC after adjusting for age, sex and BMI (Wood et al. 2008). A postal survey of 4057 people aged 40-79 years old living in Nottingham identified that 28.7% reported knee pain with disability was significantly related to the presence of knee pain (p<0.001) (O’Reilly et al. 1998). Another postal survey of 1694 community-dwelling older adults demonstrated a similar prevalence of knee pain (24.0%) with higher disability scores reported by women and older responders using the Health Assessment Questionnaire (Bruce et al. 2003). These findings suggest that knee pain is highly disabling and is related to poorer outcomes (reduced physical functioning and greater psychological distress) in people with knee pain.

Knee pain as a predictor of other painful sites

Isolated knee pain is rare and the development of pain in one site is a predictor of developing additional pain sites as well as reporting a greater impact on daily activities (regression coefficient (β) 0.23; 95% CI 0.22, 0.25), and social activities (β 0.16; 95% CI 0.15, 0.17), and lower levels of physical fitness (β 0.12; 95% CI 0.10, 0.13) after adjusting for age and sex (Kamaleri et al. 2008b). A large cross-sectional study of 5,364 adults aged over 50 responding to a postal survey demonstrated that the presence of knee pain alongside pain in at least one other joint was associated with more severe pain (OR 1.5; 95% CI 1.1, 2.0) and lower levels of physical functioning (OR 1.7; 95% CI 1.3, 2.3) compared with knee pain alone after adjusting for age, sex, body mass index (BMI), depression and whether pain sites are found on both sides of the body (Croft et al. 2005).

There is evidence to suggest that the number of pain sites, rather than site-specific pain, is associated with higher rates of disability and psychological distress. A study of 2445 community-dwelling adults over 18 years old in South East England who responded to a postal questionnaire demonstrated that 45% responders reported chronic musculoskeletal pain, with 12% responders
Reporting pain in a single site and 33% reporting pain in more than one region (Carnes et al. 2007). A population-based study in Ullensaker, Norway of 3179 adults who responded to a postal survey demonstrated that self-reported pain in a single site is uncommon with 16.8% responders reporting pain in one site compared with 53.1% reporting pain in two or more sites, although the proportion reporting pain diminishes for each additional pain site (Kamaleri et al. 2008a). For those reporting knee pain in the past 7 days, 5.1% women and 11.2% men reported pain in only one knee, 32.4% women and 51.7% men reported pain in another 1-3 sites, and 61.4% women and 37.1% men reported pain in 4-9 sites (Kamaleri et al. 2008a). These findings suggest that knee pain may in fact be part of a larger pain continuum where the number of pain sites is of greater importance in terms of levels of physical functioning and impact on daily life than individual sites of pain (Croft et al. 2005).

**Conclusion**

The studies outlined in the previous sections demonstrate that the presence of knee pain is associated with female sex, older age, radiographic OA, psychological distress (including higher levels of anxiety and depression, maladaptive coping strategies and increased pain catastrophising), greater disability and reduced physical functioning. The presence of knee pain is also a predictor of the presence of other regional pain sites, but the mechanism underlying this is yet to be determined. These factors demonstrate the need for targeted and personalised interventions among those with knee pain. The next sections outline the structure of the knee and how underlying disease, such as OA may also contribute to knee pain.

**2.2.3. Structure of the Knee**

The knee is a complex hinge joint comprising three bones; the femur, patella and tibia (see Figure 2.2) (Fairclough et al. 2003). These bones form two articulations: the tibio-femoral joint and the patello-femoral joint. The ends of the femur, tibia and posterior surface of the patella are lined by articular cartilage which helps cushion the joint and enables smooth movement (Buckwalter et al. 2005). Other non-osseous tissues in the knee (including the menisci, collateral and cruciate ligaments, bursae, tendons, and muscle) provide stability and determine the range of movement (Flandry et al. 2011). The knee is primarily a hinge joint, allowing flexion and extension, though some rotation is possible.

The tibiofemoral joint is a bicondylar joint between the distal femur and proximal tibia (see Figure 2.2) (Flandry et al. 2011). The tibial condyles are lined by discs of fibrocartilage (menisci) that aid joint loading. Collateral ligaments connect the lateral and medial condyles of the tibia and femur providing stability (Chhabra et al. 2001). The anterior and posterior cruciate ligaments connect the tibia and femur and also play a role in proprioceptive acuity of the knee (ability to detect where limbs are relative to the body) (Solomonow et al. 2001). The tibiofemoral joint is enclosed within a synovial capsule composed of connective tissue lined with the synovium, which aids joint motion (Tarner et al. 2005) and plays a role in the maintenance of cartilage (lubrication and nutrition).
The patellofemoral joint is formed between the trochlea of the anterior aspect of the distal femur and the patella, which is the largest human sesamoid bone and is located within the quadriceps tendon attached to the femur and tibia. The role of the patella in the patellofemoral joint is to provide support and protection for the anterior aspect of the knee (see Figure 2.2) (Chhabra et al. 2001).

Figure 2.2  Structure of the knee

![Structure of the knee](image)

Source original. MCL = medial collateral ligament; LCL = lateral collateral ligament; PCL = posterior cruciate ligament; ACL = anterior cruciate ligament. Patella is folded down to allow view of tibiofemoral joint.

The knee is highly innervated. Kennedy et al. (1982) describe two nerve bundles; an anterior group including the femoral and common peroneal nerves, and a posterior group consisting of the obturator nerve and articular branch of the tibial nerve. The femoral nerve and saphenous nerve (a branch of the femoral nerve) innervate the anteromedial regions of the knee including the medial tibia, quadriceps muscles (knee extensors), the patellar tendon, anterior cutaneous tissue and the fatty soft-tissues beneath the patella (infrapatellar fat pad) (Gardner 1948; Kennedy et al. 1982). The common peroneal nerve innervates the fibular head, lateral collateral ligament and lateral femoral condyle, with the recurrent peroneal nerve (a branch of the common peroneal nerve) innervating the tibial tuberosity and the infrapatellar fat pad (Gardner 1948; Kennedy et al. 1982). The obturator nerve follows the femoral artery and innervates the posterior and anterior aspects of the medial capsule of the knee and medial femoral condyle (Gardner 1948). The articular branch of the posterior tibial nerve innervates the popliteal plexus from the lateral side of the knee and the cruciate ligaments, and may also innervate the outer regions of the menisci (Kennedy et al. 1982).

Studies of the human knee have highlighted the distribution of sensory afferents within the joint. Sensory afferents located within soft tissue and bony structures include cutaneous (Ruffini endings...
and Pacinian corpuscles) and musculoskeletal (Golgi tendon organs) mechanoreceptors and nociceptors (free nerve endings of Aδ and C fibres; further detail about these receptors is included in Section 1.2.2.1) (Halata et al. 1985; Zimny et al. 1991; Gardner et al. 2000a). Free nerve endings contain receptors which respond to changes in innocuous temperature and to noxious mechanical and thermal sensations (Gardner et al. 2000c) and are located within the joint capsule (near to blood vessels and within the fibrous and synovial layers), infrapatellar fat pad, the surface lining layer of the bone (periosteum) and subchondral patellar plate (Halata et al. 1985; Wojtys et al. 1990; Zimny et al. 1991). Ruffini endings that relay information about skin stretch (Gardner et al. 2000c) have been located within the ligaments and fibrous regions of the joint capsule (Halata et al. 1985; Zimny et al. 1991) with Pacinian corpuscles that detect vibration (Gardner et al. 2000b) located in soft tissues including the periosteum and the outer regions of the menisci (Halata et al. 1985). Golgi tendon organs provide information about limb proprioception (Gardner et al. 2000c) and are present within the medial and lateral collateral ligaments, anterior and posterior cruciate ligaments, and menisci with an increased number of receptors present at the tibial and femoral insertions of the anterior and posterior cruciate ligaments (Zimny et al. 1991).

The knee sustains a great amount of pressure, rotation and loading during normal movement. Alterations in knee joint angulations (Sharma et al. 2001) or increased loading such as in those with physically demanding occupations (Cooper et al. 1994; Vingard 1996; Coggon et al. 2000; Jensen et al. 2000; O’Reilly et al. 2000) or in obese individuals (Felson et al. 1988; Sharma et al. 2000; Coggon et al. 2001; Messier et al. 2005; Niu et al. 2009; Messier 2010; Pena et al. 2010) can enhance the risk of developing arthritis in this joint. Many people with knee pain will also have underlying joint pathology most commonly related to OA. Further information about the pathophysiology and risk factors for knee OA are described in the following sections.

2.2.4. Knee Osteoarthritis

The following section summarises the definition of OA and classification of OA. Details of how degenerative processes in OA can generate pathology in the knee, how to classify different stages of the disease, risk factors for disease progression and treatments currently available for people with knee OA.

2.2.4.1. Definition of Osteoarthritis

OA is the most common form of arthritis worldwide with the knee the most frequently affected joint. The American College of Rheumatology (ACR) define OA as “a heterogeneous group of conditions that lead to joint symptoms and signs which are associated with defective integrity of articular cartilage, in addition to related changes in the underlying bone and at the joint margins” (Altman et al. 1986). OA can affect any joint though the knee is one of the most frequently involved joints. Other joints which may be affected include the hands, feet, hips and spine (Kellgren et al. 1957).
2.2.4.2. Classification of Knee Osteoarthritis

Clinical features of knee OA include pain, stiffness, loss of function and on examination, tenderness around the joint line and crepitus (Cushnaghan et al. 1990; Peat et al. 2001b). OA may be classified by both clinical and radiological criteria. A number of radiographic criteria have been proposed though the most widely used are the Kellgren-Lawrence (KL) radiographic criteria (Kellgren et al. 1957). The scale is graded 0 to 4 and comprises osteophytes, joint space narrowing, and articular cartilage loss (see Table 2.1).

<table>
<thead>
<tr>
<th>Grade</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No findings of radiographic OA</td>
</tr>
<tr>
<td>1</td>
<td>Doubtful JSN. Possible osteophytic lipping</td>
</tr>
<tr>
<td>2</td>
<td>Definite osteophytes and JSN</td>
</tr>
<tr>
<td>3</td>
<td>Moderate multiple osteophytes. Definite JSN. Some sclerosis. Possible deformity of bone contour</td>
</tr>
<tr>
<td>4</td>
<td>Large osteophytes. Marked JSN. Severe sclerosis. Definite deformity of bone contour</td>
</tr>
</tbody>
</table>

Table 2.1 The Kellgren-Lawrence Radiographic Scale (Kellgren et al. 1957)

JSN = Joint Space Narrowing.

The ACR proposed a clinical classification system designed for both experimental and clinical use highlighting key signs and symptoms of knee OA (Altman et al. 1986); the clinical classification criteria include the presence of joint pain plus at least three of the following for knee OA: aged over 50, no palpable warmth, bony enlargement, bony tenderness, crepitus and morning stiffness lasting 30 minutes or less. These classification criteria are frequently used, though there is discordance when considered with radiographic criteria. In a sample of 819 adults aged 50 and over with knee pain, only 33% (n=239) with symptomatic and radiographic knee OA were correctly classified using the ACR clinical classification criteria (sensitivity 41%) (Peat et al. 2001b). This study suggested that only subjects with more severe radiographic grades of OA were correctly identified using the clinical criteria (Peat et al. 2001b). However, the criteria are still frequently used in studies of subjects with knee pain to determine the possibility of underlying disease in the absence of radiographs. Classification of disease influences the reporting of the occurrence of knee OA. Current estimates based on the presence of radiographic OA are presented in the following section.

2.2.4.3. Epidemiology of Knee Osteoarthritis

Occurrence of Knee Osteoarthritis

The latest global burden of disease update from the World Health Organisation (WHO) suggests that OA affects approximately 151.4 million people worldwide with roughly 25% residing in Europe (40.2 million) (Mathers et al. 2008). The estimated prevalence of radiographic knee OA in adults
who are aged over 60 years in the USA is 37.4% (4.3 million) (Dillon et al. 2006). OA in the tibiofemoral joint is more common than in the patellofemoral joint with the medial compartment affected more often (13.7% women and 7.3% men aged over 50 years) than the lateral compartment (6.7% women and 3.6% men) (Lin et al. 2010). Isolated patellofemoral OA affects up to 8% women and 2% men aged 55 or older (Cooper et al. 1992).

A recent systematic review identified 52 studies investigating the impact of the definition of OA used on the estimates of prevalence and incidence; only 7 of the studies (13.5%) provided cumulative and/or annual incidence rates compared with 45 studies (86.5%) providing prevalence estimates (Pereira et al. 2011). There is difficulty in providing a definition for the onset of knee OA, as disease severity observed when a patient first presents to primary care is variable. Therefore it is simpler to determine the number of new cases in a given time period than to quantify the number of patients with knee OA at a single point in time unless they are symptomatic (Symmons et al. 2006). Of the studies investigating incidence in the systematic review previously mentioned, one study demonstrated a cumulative incidence of 27.6% over 12 years for self-reported knee OA while three studies demonstrated cumulative incidences of 12.6%, 12.7% and 15.6% over 4, 5 and 8 years, respectively, for radiographic OA (Pereira et al. 2011). This suggests that the onset of symptoms possibly precedes the onset of radiographic OA (Pereira et al. 2011). A number of risk factors have been identified which are linked with the occurrence of knee OA. The following sections will focus on age, sex, BMI, and biomechanical factors.

**Influence of Age and Sex**

The frequency of knee OA increases with age. In a large population-based cohort of 6585 individuals in Zoetermeer, The Netherlands, who participated in a detailed clinical and radiographic assessment of the knees, there was an increase in the proportion of adults with knee OA with age from 8.7% in men and 12.6% in women for the 45-49 age-band, rising to 24.1% in men and 52.6% in women for those aged 80 years and over (van Saase et al. 1989). Using data from a health maintenance organisation in Massachusetts with approximately 130,000 members the incidence of OA increases by each age decile until age 70-79 years (see Figure 2.3) (Oliveria et al. 1995). OA is more prevalent in women than men over the age of 50 (Felson 1990). A meta-analysis investigating the influence of sex on knee OA occurrence indicated a statistically significant protective risk ratio of 0.63 (95% CI 0.53-0.75) for knee OA in men compared with women (Srikanth et al. 2005). A higher proportion of women in the Zoetermeer study were also found to have knee OA with a sharp increase observed in those over 60 with the proportion of men with knee OA plateauing at age 60 (van Saase et al. 1989). This is comparable with the findings from the Massachusetts health management organisation presented in Figure 2.3 with the incidence of knee OA rising from the 50-59 age band (Oliveria et al. 1995). These findings match those for knee pain with the prevalence of knee OA increasing with age and being more common in women.

Figure 2.3 also demonstrates that the incidence of knee OA is higher in men until the 50-59 age band; a population-based study of 819 people aged 50 and over reporting knee pain within the past year demonstrated a higher proportion of symptomatic men with radiographic OA (245 from 314;
78%) than women (237 from 381; 62.2%) (Peat et al. 2007). However, after further investigation into the x-ray views used, occupational risk factors and participation bias identified the latter as the probable source of the higher proportion of men with radiographic OA due to a high number identified with OA in the patellofemoral joint (Lacey et al. 2008).

Figure 2.3 Incidence of knee Osteoarthritis in men and women (Oliveria et al. 1995)

Body mass Index

BMI is associated with knee OA. A systematic review of 85 prospective cohort and case-control studies identified higher BMI such as being overweight (OR 2.13; 95% CI 1.98, 2.30), or obese (OR 2.89; 95% CI 2.61, 3.20), or being either overweight or obese (OR 3.16; 95% CI 2.78, 3.59) to be risk factors for the onset of knee OA (Blagojevic et al. 2010). Other risk factors identified in this review included injury to the knee (OR 3.48, 95% CI 2.65, 4.57), gender (OR 1.91; 95% CI 1.63, 2.24) and the presence of Heberden’s nodes in distal interphalangeal joints (OR 1.58; 95% CI 1.21, 2.05) (Blagojevic et al. 2010). Smoking was identified as protective with a pooled odds ratio of 0.84 (95% CI 0.74, 0.94) using 8 case-control studies (n=7,047) and 10 cohort studies (n=337,700); however, the pooled odds ratio for the cohort studies only was not significant (OR 0.98; 95% CI 0.86, 1.13) (Blagojevic et al. 2010). This could be due to some studies only using definitions of current or never smoked leading to misclassification.

Biomechanical risk factors

Mechanical factors play an important role in pathogenesis (Felson 2013). Damage to the meniscus within the knee can increase loading at the point of injury; meniscal tears have been linked with the
presence of knee OA in older adults in two large population-based studies (Englund et al. 2007; Englund et al. 2008; Englund 2008), with a meta-analysis of 5 studies also providing a combined odds ratio of 7.4 (95% CI 4.0, 13.7) for the increased risk of knee OA in those who underwent meniscal surgery (Richmond et al. 2013).

Varus and valgus deformity are also significant risk factors for disease progression due to the increase in focal loading within the knee; in a community-based sample of 230 people with knee OA disease progression in the medial compartment at 18 months was significantly associated with baseline varus deformity (OR 4.09; 95% CI 2.20, 7.62) and progression in the lateral compartment was significantly associated with valgus deformity (OR 4.89; 95% CI 2.13, 11.20) after adjusting for age, sex and BMI (Sharma et al. 2001). A meta-analysis of 5 studies investigating previous injury as a risk factor for knee OA resulted in a combined odds ratio of 3.8 (95% CI 2.0, 7.2) (Richmond et al. 2013).

Conclusion

The results from the studies outlined above suggest that older adults, particularly elderly females, and those with high body mass indices have an increased risk of developing knee OA. Features of joint degeneration underlying the signs and symptoms of knee OA in relation to altered physiology and biomechanics are outlined in the following section.

2.2.4.4. Pathophysiology of Knee Osteoarthritis

Studies have established that normal articular repair pathways are impaired in OA (Buckwalter et al. 1998; Martin et al. 2003) such as a reduction in chondrocyte turnover, meniscal pathology, cartilage breakdown, development of osteophytes, subchondral sclerosis (thickening of the bone beneath cartilage) and a resultant increase in inflammatory mediators within the joint (Fahmy et al. 1983; Martin et al. 2003; Tanishi et al. 2009; Dam et al. 2009). The trigger for these is unknown though mechanical factors play a role.

Both inflammation and biomechanical factors contribute to the progression of OA. Although inflammation is more commonly associated with Rheumatoid Arthritis, it is also thought to play a key role localised within osteoarthritic joints as a consequence of degenerative mechanical mechanisms such as increased focal stress (Buckwalter et al. 1998). Pro-inflammatory cytokines, such as Interleukin-1, are released when the synovial membrane becomes inflamed; these mediators influence the release of collagenase (an enzyme which breaks down cartilage) and glycosaminoglycan production (long carbohydrate chains) impacting the stability of cartilage (Baddour et al. 1999). When the normal joint structure is compromised altered biomechanics result in increased loading within the joint and accelerated disease progression.
Associations between structure and pain in knee OA

With the exception of cartilage, the knee is a highly innervated joint (Section 2.2.3) (Halata et al. 1985; Zimny et al. 1991). Although cartilage loss is a hallmark of disease progression, how this degeneration is linked to pain is yet to be discerned as cartilage is aneural (Brandt et al. 2008). It is possible that cartilage loss is indirectly associated with pain through biomechanical alterations, for example, by increasing focal stress through medial (varus deformity) or lateral degeneration (valgus deformity) leading to localised inflammation; this is a potential source of nociception in the osteoarthritic knee (Kidd et al. 2004). Cartilage loss itself appears to be a poor marker of pain severity (Brandt et al. 2008).

Use of magnetic resonance imaging (MRI) to image the knee has resulted in developments in understanding of associations between structure and pain. Evidence from observational studies have demonstrated relationships between pain and the presence of lesions in subchondral bone (bone marrow lesions) and also synovial inflammation (synovitis) (Felson et al. 2001; Zhai et al. 2006; Baker et al. 2008; Attur et al. 2010); both of these regions are highly innervated. In a cross-sectional study of 381 people with knee pain and radiographic OA, 52 with radiographic OA who were without pain, and 25 without radiographic OA or pain, the presence of synovitis (independent of effusions) was associated with the presence of knee pain after adjusting for radiographic disease severity (Hill et al. 2001). An investigation into knee pain using the Tasmanian Older Adult Cohort (prevalence 48%) looked at cartilage and bone abnormalities (identified using MRI scans), with hip and knee radiographs performed to assess radiographic OA (Zhai et al. 2006). Bone marrow lesions (OR 1.72; 95% CI 1.17, 2.52) and cartilage abnormalities in the medial tibial compartment of the knee (OR 2.04; 95% CI 1.06, 3.95) were significantly associated with prevalent knee pain in a multivariable logistic regression including age, sex, BMI, knee extension strength, lateral tibial and femoral chondral defects, medial femoral chondral defects, patellar chondral defects, and hip joint space narrowing; total joint space narrowing at the knee, however, was not significantly correlated with WOMAC pain scores (p=0.07) (Zhai et al. 2006). MRI data from another community-based study of 205 people (80% female) with physician diagnosed knee OA (71 with Kellgren Lawrence grade 2 or 3) demonstrated significant associations between large effusions and pain (OR 9.99; 95% CI 1.28, 149), effusions with stiffness (OR 4.67; 95% CI 1.26, 26.1) and between pain and osteophytes in the patellofemoral joint (OR 2.25; 95% CI 1.06, 4.77) (Kornaat et al. 2006); no other structural findings were associated with pain or stiffness.

A prospective study of 570 individuals with knee OA recruited from a longitudinal population-based cohort investigated the episodic nature of knee pain in OA with structural pathology (synovitis, effusions and bone marrow lesions) using MRI scans taken at 0, 15 and 30 months demonstrated an association between higher severity scores for synovitis (p=0.027 for trend) and effusions (p=0.048 for trend) with worsening knee pain, and a reduction in effusion scores with improvements in pain (p=0.019 for trend) across visits in this study (Zhang et al. 2011). The longitudinal study identified effusion severity as a predictor of changes in knee pain severity over time; this may be due to the associated inflammation and swelling during effusions, but links between these processes and pain intensity are not well established. The advances in imaging techniques have highlighted other pathological features of disease which may be associated with pain, but these require further investigation. As described previously, radiographic imaging remains
the gold standard for diagnosing knee OA (see Section 2.2.4.2); the following section describes the discordance between radiographic signs of knee OA and pain intensity.

2.2.4.5. **Relationship between Radiographic and Symptomatic OA**

The relationship between knee pain and radiographic OA is relatively weak. A community-based study of 745 people with knee pain (54.6% female) demonstrated that higher levels of disability (OR 2.8; 95% CI 1.6, 5.0), pain severity (OR 3.7; 95% CI 2.0, 6.7) and stiffness (OR 3.0; 95% CI 2.0, 4.6) were associated with the presence of radiographic OA after adjusting for age, sex and BMI (Kellgren Lawrence grade 2 or more) (Duncan et al. 2007). However, 236 (31.7%) subjects did not fulfil the criteria for radiographic OA and the study population was limited to those with knee pain so people with radiographic OA who were asymptomatic were not studied. A systematic review by Bedson et al. (2008) demonstrated the proportion of people with radiographic OA who also report knee pain is between 20% and 81% in the studies reviewed while the proportion of people with knee pain who also have radiographic OA ranges from 15% to 76%. The authors highlight that discordance can arise from three sources (Bedson et al. 2008):

(i) the x-ray view(s) used may not be optimal with the patellofemoral joint infrequently imaged; the prevalence of radiographic OA is higher in studies where the patellofemoral joint is imaged;

(ii) different populations studied. Studies including younger adults with knee pain will tend to have a lower prevalence of radiographic OA;

(iii) the definitions of pain and radiographic OA used in studies are variable affecting the generalisability across studies.

The association between knee OA and pain is stronger at higher grades of joint degeneration with a lower proportion of asymptomatic subjects at grade 4; 1032 subjects from two population-based cohorts with knees discordant for pain demonstrated that the risk of consistent knee pain or infrequent knee pain compared with no pain was significantly higher with KL grades 2 (OR 5.5 and 3.0, respectively), 3 (OR 10.0 and 8.6, respectively) and 4 (OR 317 and 42.7, respectively) compared to no radiographic evidence of disease (p<0.001 for both trends) (Neogi et al. 2009). As pain varies in its presence and duration, previous studies have demonstrated conflicting findings between structure and pain; this was one of the first positive studies to show an association between the presence of pain with greater disease severity due to the use of a within-person analysis (Neogi et al. 2009).

People who are asymptomatic for knee OA can be identified if they participate in population-based studies using knee radiographs or other imaging techniques. One study demonstrated the prevalence of radiographic knee OA in a community-based sample of 513 people at 48% (95% CI 38, 59) for men and 56% (95% CI 48, 63) for women in those reporting knee pain, and 15% (95% CI 8, 25) for men and 17% (95% CI 11, 23) for women who do not report knee pain (McAlindon et al. 1992). This study demonstrates it is possible to have radiographic signs of knee OA and also be
asymptomatic for the disease (McAlindon et al. 1992). Those with radiographic knee OA who don’t report pain are also of interest when investigating potential differences in pain processing in those with knee OA; those who have underlying disease may be resilient to the peripheral pain input expected from the disease, although this requires further investigation (Finan et al. 2013b).

**Conclusion**

There is evidence to suggest that knee pain is associated with higher radiographic grades of knee OA (Neogi et al. 2009). Recent advances in imaging techniques are have highlighted other potential sources of pain in the knee that are not visible on x-ray (Zhang et al. 2011). However, there are still cases of knee pain without any discernible signs of underlying pathology. Research into the development and persistence of CWP, the primary symptom of Fibromyalgia, suggests that aberrant pain processing within the central and/or peripheral nervous system plays a key role in the maintenance of chronic pain (Staud 2002). This is of interest as some subjects with Fibromyalgia do not have any discernible musculoskeletal pathology so altered pain processing provides an alternative theory for pain without structural damage (Clauw et al. 2003). This may provide an explanation for those people with knee pain do not have underlying OA, and also presents new targets for interventions used to treat knee pain. The current guidelines for the management of knee OA are outlined in the following section.

2.2.5. **Treatment**

Current treatments for knee OA include non-surgical (pharmacological and non-pharmacological) and surgical interventions. Non-surgical interventions include oral and topical analgesia, anti-inflammatory therapy including oral, topical and intra-articular therapy (steroids), braces, physical activity, and patient education (National Institute for Health and Care Excellence 2014). The aim of these therapies is primarily symptomatic and supportive. Surgical interventions include total or unicompartmental knee arthroplasty (National Joint Registry for England 2013), arthroscopy (Moseley et al. 2002) and osteotomy (Brouwer et al. 2007), with 98% of knee arthroplasty surgeries attributable to OA in the joint (National Joint Registry for England 2013). Currently, no treatments are available that can alter or slow the progression of OA.

The ACR recommends that treatment be adapted to individual patient needs, including a combination of physical therapy, patient education and drug therapies, where appropriate, may be most effective in reducing pain and improving functionality (Hochberg et al. 2012). A systematic review of guidelines for managing knee OA through physical therapy emphasised the importance of patient education, manual therapy, weight loss and biomechanical interventions (wedged insoles and patellar taping in particular) (Larmer et al. 2014). These recommendations were supported by the OARSI guidelines for self-management and non-pharmacological interventions, along with intra-articular steroid injections for those with knee OA (McAlindon et al. 2014).


2.2.5.1. **Intra-articular Steroid Injections**

Intra-articular steroid injections are efficacious in reducing pain in the short term and are believed to be safe with relatively few side effects (Bruce et al. 2004). A Cochrane review of 28 randomised controlled trials (1973 subjects) using intra-articular steroids suggested that steroid injections were effective at reducing pain for up to 4 weeks, though further trials are needed to address longer term benefit (Bellamy et al. 2006).

The mechanism by which steroids reduce pain is still unknown, although it may be related to a reduction in synovitis. Another potential mechanism by which intra-articular steroid injections can provide short-term analgesia is through a reduction in pro-nociceptive mediators within the joint thought to drive peripheral sensitisation (described in Section 1.2.5.1). If true, people with knee OA who are centrally sensitised, may be unlikely to respond to intra-articular steroid injections as localised anti-inflammatory treatment at the knee does not impact amplifications in central pain processing other than by reducing peripheral input (Wooll 2010). There is little evidence to currently support these mechanisms for intra-articular steroid injections, but there is emerging evidence of central sensitisation in subjects reporting poorer outcomes following total knee replacement. Higher levels of pain severity, catastrophising, anxiety and depression, and greater pain sensitivity (all of which are thought to contribute to central sensitisation) are predictors of poor outcome following surgery (Wyde et al. 2007; Sullivan et al. 2009; Wyde et al. 2013); this suggests that while targeting peripheral mechanisms is effective in some people, it is of little benefit to others.

It is also possible that reductions in pain may occur through the placebo effect. The placebo effect can be defined as “any improvement of symptoms or signs following a physically inert intervention” (Tavel 2014); belief that an intervention will be beneficial, either through previous exposure or knowledge of the treatment, can lead to improvements in pain reporting. Studies have also demonstrated that more invasive treatments can incur a greater placebo effect; for example, the size and colour of an oral pill can influence the perceived effectiveness of an intervention (Buckalew et al. 1982), and an injection tends to provide a stronger placebo effect than a pill (Blackwell et al. 1972). Delivering a treatment via an intra-articular injection may increase the likelihood of a patient reporting improvements in their pain and may also enhance the level of pain improvement reported. The Cochrane review by Bellamy et al. (2006) identified four randomised control trials reporting improvements in pain following intra-articular injections of steroid or saline; the studies reported improved pain in 25% (Ravaud et al. 1999) and 71% patients (Friedman et al. 1980) receiving placebo at one week post-injection, 36% at two weeks post-injection (Wright et al. 1960) and 15% at three weeks post-injection (Jones et al. 1996). However, only two studies used a definition of responder status with Jones et al. (1996) defining response as a minimum of 15% improvement in pain while Ravaud et al. (1999) defined response as a minimum of 30% improvement in pain. The review also reported significant improvements in pain recorded using a 100mm VAS in the treated compared with untreated groups at one week post-injection (weighted mean difference -21.91; 95% CI -29.93, -13.89); however, the differences between the groups were not significant at 4 weeks or 6 weeks post-injection (Bellamy et al. 2006). These findings suggest
that the placebo effect may mediate response to treatment in the longer term as there were no significant differences in pain reporting at weeks 4 and 6 post-injection.

2.2.6. Summary

Knee pain affects 25% of older men and women (Peat et al. 2001a). A number of physical and psychological factors, including anxiety, depression, and psychological distress, are linked with increased susceptibility to knee pain. Knee OA can be an underlying cause of knee pain though there is discordance between knee pain and radiographic knee OA, the reasons for which are uncertain. Current models of chronic pain suggest that sensitisation of peripheral afferents and/or central sensory pathways may be contributing mechanisms (described in Section 1.2.5) (Stojanovic 1998). One way to investigate the role of somatosensory function in people with knee pain is to use QST. Current QST assessments and protocols, the strengths and limitations of this method, and studies using QST in subjects with knee OA are discussed in the following section.

2.3. Quantitative Sensory Testing

Altered pain sensitivity has been suggested as a potential mechanism for the variable relationship between pain and underlying disease. There are currently no effective methods of identifying those people with knee pain who would benefit from treatments targeting altered pain processing. Recently, studies of people with chronic musculoskeletal pain have begun using methods, such as QST, that assess sensitivity within the somatosensory nervous system (Pavlakovic et al. 2010). This may help in developing a pain sensitivity phenotype to identify people who could benefit from other treatments, such as those targeting central pain pathways.

QST is a non-invasive psychophysical assessment of cutaneous and deep tissue sensitivity to painful and non-painful stimuli (Pavlakovic et al. 2010). QST can be used to assess a gain in (hypersensitivity) or loss (hyposensitivity) of somatosensory function and is defined by the German Research Network on Neuropathic Pain (Deutschen Forschungsverbund Neuropathischer Schmerz; DFNS) as a “standardized assessment of the somatosensory system comprising all sensory submodalities” (Geber et al. 2009). The next section outlines the different test methodologies which can be used to assess altered sensitivities.

2.3.1. QST Methodologies

Noxious and innocuous pressure, thermal, vibrating and mechanical stimuli can be used to determine changes in the responsiveness of Aβ, Aδ and C fibres (see Table 1.1 in Section 1.2.2.1) (Schaible et al. 2006). Each sensory modality can be assessed using a detection and/or pain threshold by using the methods of limits or levels (Gruener et al. 1994). Using the method of limits involves a continuous application of a sensation of increasing or decreasing intensity, with the
subject indicating when they feel the desired sensation (Shy et al. 2003). The method of levels uses stimuli of fixed intensities applied in ascending or descending order until the subject reports a sensation (Shy et al. 2003). Sensory gain may be characterised by increased sensitivity to stimuli (lower thresholds) with sensory loss characterised by higher detection and pain thresholds.

The psychophysical aspect of QST requires each subject to provide subjective feedback on the sensations felt; as such, the affective and evaluative components of the pain experience are influential in the response to sensory stimuli (Gruener et al. 1994). This is advantageous in comparison with more objective sensory testing (such as laser-evoked potential and nerve conduction studies) as it allows for all aspects of the pain experience to be assessed (described in Section 1.2.5). One disadvantage to using QST is that quantification of sensory gain or loss related to nerve fibre density is not possible. Objective techniques such as skin biopsies for nerve fibre density, sensory evoked potentials and nerve conduction studies can be used to determine the density of small and large sensory afferents (Starr 1978; Kimura 1984; Loseth et al. 2006).

A second disadvantage to using QST is that it is not possible to identify where abnormalities arise within the somatosensory pathway. For example, hyposensitivity to a stimulus could result from a reduction in the number of nociceptive afferents found within the test area (deafferentation; a loss of skin afferents, usually by disruption or damage) so the stimulus is not strong enough to elicit a response, or the subject was not paying attention or was distracted during the testing process (Gruener et al. 1994). Repeated hyposensitivity may indicate sensory deafferentation, but the role of attention cannot be ruled out; thus QST cannot identify which aspect of the somatosensory pathway is affected as it is assessed in its entirety (Gruener et al. 1994). However, some inferences may be made from the results of QST assessments. The following sections outline how the results of different QST assessments can be attributed to mechanisms of sensitisation.

2.3.1.1. Assessments of Peripheral Sensitisation

Hypersensitivity to innocuous and noxious stimuli using the assessments outlined in this section may be indicative of a peripheral mechanism of sensitisation (Binder et al. 2007). For example, peripheral sensitisation can lead to non-innocuous events being transduced as painful (see Section 1.2.5.1). Hendiani et al. (2003) demonstrated significantly lower mechanical pain thresholds at the most painful knee in 28 knee OA subjects (322.7±34.5 grams) compared with either knee for 27 pain-free controls (446.7±0 grams; p<0.001). This sensation is referred to as hyperalgesia, where increased sensitivity to painful sensations is observed. Hyperalgesia and allodynia (hypersensitivity to normally innocuous sensations near to a painful site) can be evaluated using QST (Dyck et al. 1993). Table 1.1 in Section 1.2.2.1 outlines the specialised receptors present on Aβ, Aδ, and C fibres that respond to specific modalities. Although QST assessments are designed to elicit responses from certain fibre populations, there are overlaps in which other fibres and/or receptors may be stimulated. A summary of the predominant fibre types elicited by innocuous (detection) and noxious (pain) sensations is presented in Table 2.2.
Table 2.2  Sensory modalities detected by peripheral afferents

<table>
<thead>
<tr>
<th>Modality</th>
<th>Detection</th>
<th>Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heat</td>
<td>C</td>
<td>Aδ, C</td>
</tr>
<tr>
<td>Cold</td>
<td>Aδ</td>
<td>Aδ, C</td>
</tr>
<tr>
<td>Mechanical</td>
<td>Aβ</td>
<td>---</td>
</tr>
<tr>
<td>Vibration</td>
<td>Aβ</td>
<td>---</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>Aβ</td>
<td>Aδ</td>
</tr>
<tr>
<td>Deep tissue</td>
<td>---</td>
<td>Aβ</td>
</tr>
</tbody>
</table>

The information in this table was compiled and adapted from the following references: (Stojanovic 1998; Pavlakovic et al. 2010).

The term “mechanical” encompasses vibration, and deep tissue and cutaneous sensations. For the purpose of this thesis, a distinction will be made between deep tissue (pressure) and cutaneous (mechanical) stimuli. Pressure pain thresholds, assessed using manual or digital algometers, are used to determine the sensitivity of deep tissue mechanoreceptors on Aβ fibres to noxious stimulation (Table 2.2) (Kosek et al. 1999). Mechanical detection thresholds (assessed using von Frey filaments) are an assessment of larger fibre function (Aβ) with mechanical pain thresholds (assessed using punctate probes) an assessment of cutaneous Aδ fibre mechanoreceptors (Rolke et al. 2006a). Vibration (assessed using a vibrometer or tuning fork) can also be used to assess the response of Aβ fibres in cutaneous tissue or bone (Goldberg et al. 1979). The stimulus response function can be used to assess mechanical hyperalgesia (using punctate probes) and dynamic (moving) and static (fixed) mechanical allodynia (using a brush or cotton bud) in Aβ and Aδ fibres (Magerl et al. 2001). Noxious thermal assessments (assessed using a thermode or water bath) can be used to determine Aδ fibre (cold pain) and C fibre (heat pain) functions (Table 2.2) (Yarnitsky et al. 1991; Yarnitsky et al. 1994).

Altered sensitivities to pain and detection thresholds can provide information about components of the somatosensory system that may be affected by disease pathology. For example, investigations into peripheral neuropathies have demonstrated that thermal and vibratory stimuli can be used to distinguish between losses in Aβ fibres attributed to large fibre neuropathies, and small fibre neuropathies (diminished numbers of Aδ and C afferents) (Dyck et al. 1993). Altered sensitivity to pain thresholds is classified as hyperalgesia or hypoalgesia (diminished sensitivity to painful stimuli) with altered sensitivity to detection thresholds defined as hyper- or hypo-aesthesia.

Studies have also identified that increased sensitivity to stimuli within an affected area (localised) is likely to be related to peripheral sensitisation. For example, testing at the knee in those with knee pain is thought to be related to underlying disease although the evidence for this is limited (see Section 2.3.3). Increased sensitivity at a pain free distal control site could be indicative of central sensitisation (generalised and widespread pain sensitivity) (Arendt-Nielsen et al. 2009). Assessments of central sensitisation are described in the next section.
2.3.1.2. Assessments of Central Sensitisation

There are few effective assessments of central sensitisation with existing methods directed at temporal summation and CPM (Willer et al. 1990; Kosek et al. 2000; Arendt-Nielsen et al. 2010). Tender point counts can also be used as a marker of generalised changes in sensitivity as pain at unaffected distal sites can indicate altered pain processing (Croft et al. 1996). These assessments are described in further detail in the next sections.

Temporal Summation

Temporal summation may be defined as "central spinal mechanism in which repetitive noxious stimulation results in a slow temporal summation that is experienced in humans as increased pain" (Meeus et al. 2007) and can be assessed using trains of mechanical stimuli (generally applied at a rate of one per second) following a single pin-prick of the same weight (Magerl et al. 1998; Rolke et al. 2006a). The presence of temporal summation may be indicative of short-term mechanisms of central sensitisation or alterations in synaptic plasticity within the CNS due to increased sensitivity following repeat stimulation (described in Section 1.2.5).

Conditioned Pain Modulation

The DNIC system involves "the inhibition of wide dynamic range neurons in the dorsal horn of the spinal cord by heterosegmental noxious afferent input" (Fishman et al. 2010). This system can be assessed using a technique called CPM where a noxious stimulus is applied to one part of the body (conditioning stimulus) while concurrently stimulating a separate area (test stimulus). Descending inhibitory modulation is thought to be impaired if a subject reports more or equal pain during the concurrent application of the test and conditioning stimuli than for the test stimulus alone. Descending modulation of sensory information sent to the dorsal horn is thought to be altered in those who suffer from chronic pain; as a result, descending modulatory pathways will not affect experimental noxious stimulation of two body sites (Villanueva 2009). However, altered DNIC mechanisms may be observed if a person is hypervigilant to sensory stimulation (described in Section 1.2.4) (Lautenbacher et al. 1997; Defrin et al. 2010).

Tender Point Count

The presence of widespread hyperalgesia may be indicative of central sensitisation. Unaffected body regions used as control sites have demonstrated abnormal responses to sensory assessment (Bajaj et al. 2001). Tender point counts may be used to indicate widespread mechanical hyperalgesia, and was included in the ACR clinical criteria for Fibromyalgia in 1990 (Wolfe et al. 1990). Assessing the number of tender points a person has involves applying pressure, either manually or with an algometer, to nine bilateral body sites at a rate of 1 kg pressure per second.
until 4 kg pressure is reached or pain is reported (see Section 4.2.4.4 for further details on methodology and test sites) (Chakrabarty et al. 2007).

As well as being an indicator of widespread mechanical hyperalgesia, a high tender point count is also considered a marker of generalised distress; subjects with a high number of tender points do not necessarily fulfil the criteria for CWP (Croft et al. 1996), but do tend to have higher levels of fatigue and depression (Croft et al. 1994). A greater number of tender points are also associated with limited physical functioning (Eggermont et al. 2010) and with poorer quality of life (Croft et al. 1994). For these reasons, tender point counts have been included in studies assessing pain in one or more body regions.

Summary

Heightened responses to temporal summation, a lack of pain inhibition during CPM and a greater number of tender points are thought to be indicative of the presence of central sensitisation in subjects with chronic pain. However, a wide range of study protocols and test equipment exist making comparisons across studies difficult. Standardisation of QST assessments within research is needed. A summary of two QST protocols including thermal, mechanical, vibratory, and pressure methodologies is provided in the next section.

2.3.1.3. QST Protocols

Currently there are two published QST protocols that were originally designed for use in patients with neuropathic pain. The DFNS have published a standardised methodology for QST assessments including thermal detection and pain thresholds, paradoxical heat sensation, mechanical detection and pain thresholds, static and dynamic tactile allodynia, wind-up ratio (an assessment of temporal summation), vibration detection threshold and pressure pain threshold (see Sections 4.2.4.4 and 4.3.4.3 for further detail) (Rolke et al. 2006a). High correlations (Spearman’s rho 0.78-0.97; p<0.001) were observed for test areas on the left and right sides of the body for all QST measures suggesting that using bilateral test sites may reduce between person confounding (Rolke et al. 2006a). Reference figures using this protocol have been outlined providing standard values for bilateral sites on the hands, feet and face of 180 healthy volunteers (Rolke et al. 2006b).

The second protocol was published by Walk et al. (2009) and includes assessments of dynamic mechanical allodynia, vibration and thermal detection thresholds, mechanical, thermal and pressure pain thresholds, and an assessment of temporal summation using mechanical stimuli. This protocol was developed by reviewing the current methodologies used in the assessment of patients with neuropathic pain in order to provide a standardised and more detail assessment of neuropathic pain than is provided by the Rolke et al. (2006a) protocol, which focuses on QST methodology. All assessments outlined above were determined by comparing the sensations elicited at an affected site with those recorded at a pain-free and unaffected site with responses
defined as deficits, allodynic (for detection thresholds), or hyperalgesic (for pain thresholds) (Walk et al. 2009). This protocol also includes the administration of tools and examinations specific to neuropathic pain which may not be appropriate for subjects experiencing chronic musculoskeletal pain; for example, the use of neuropathic pain symptom questionnaires and the determination of test sites at the time of testing (Walk et al. 2009). This protocol is also limited as no reliability testing of the methods, either in subjects with neuropathic pain or pain-free controls, have been reported to date.

There are a number of factors highlighted in both of these protocols which can influence QST results, including the repeatability of assessments, order effects, age and sex. These are described further in the next section.

2.3.2. Factors Affecting Quantitative Sensory Testing

The American Academy of Neurology outlined factors that affect QST such as sex, age, and ethnicity, and recommend that any researcher using QST as a methodology should ensure they are reliable (Shy et al. 2003). The researcher should also generate a set of normalised data using control subjects for the rater, location and equipment, and to standardise test procedures such as the description of the assessments (Shy et al. 2003). Due to the psychophysical nature of this methodology, deviations in the instructions given to subjects are likely to impact the thresholds perceived and reported intensities (Blitz et al. 1968). Another concern with QST is the impact of order-effects: Grone et al. (2012) demonstrated increased sensitivity to mechanical stimuli when applied after thermal stimuli compared with assessing mechanical thresholds first. This suggests that order effects may impact QST measures, but there are currently no studies using randomised ordering of QST measures in subjects with knee OA. The study by Grone et al. (2012) reinforces the recommendations by the American Academy of Neurology (Shy et al. 2003) in obtaining normalised data for the test protocol used as results may differ depending on the order they are given.

Impact of age and sex on QST

There is evidence to suggest that responses to experimental pain stimuli can differ by age and sex (Chakour et al. 1996; Fillingim et al. 2009). A decline in somatosensory functioning with age is observed due to a reduction in nerve fibre density thought to occur by 60 years old (Verdu et al. 2000). This can impact the results of QST as certain modalities may not be detected depending on the type of fibres lost (Gibson et al. 2004). However, the few studies investigating the effect of increasing age have provided inconsistent results for pressure and thermal pain (Gibson et al. 2004).

Women are thought to be more sensitive to experimental pain stimuli than men. A meta-analysis performed to determine the role of sex in QST assessments highlighted that despite studies indicating female sex was associated with increased sensitivity to pain thresholds and pain
tolerance measures, most studies were underpowered to detect a significant difference (Riley III et al. 1998); the meta-analysis demonstrated mean effect sizes of 0.55 for pain thresholds and 0.57 for pain tolerance with the authors recommending that 41 subjects of each sex would provide adequate power (0.70) to detect an effect. Racine et al. (2012a; 2012b) published a two-part systematic review to determine whether the relationship between QST and sex had progressed following the meta-analysis by Riley III and colleagues (1998). The authors demonstrated that healthy females were more sensitive to pressure pain thresholds, thermal tolerance and pressure tolerance than healthy males, but that few differences exist between the sexes for cold pain and ischaemic pain (Racine et al. 2012b). The second part of the review also demonstrated few psychosocial mediators of the relationship between QST and sex with adaptive coping strategies and attention two of the most prominent mediators (Racine et al. 2012a). However, these two reviews have focused on differences in experimental pain sensitivity in healthy men and women and not in those with chronic pain (Racine et al. 2012a).

Role of QST in chronic musculoskeletal pain conditions

The role of QST in chronic pain is not well defined. Twenty three of 26 studies included in a recent review have identified somatosensory abnormalities in subjects with Fibromyalgia, particularly diminished sensitivity to pressure pain thresholds (17 studies) (Dadabhoy et al. 2008). Due to variations in the modalities and methodologies used it is not possible to discern the role of somatosensory functioning within other musculoskeletal conditions and its clinical relevance (Stojanovic 1998; Pavlakovic et al. 2010). QST assessments have been performed in investigations of chronic pain, including knee pain. A summary of the studies published to date using QST in subjects with knee pain is provided in the following section.

2.3.3. Mechanisms of sensitisation in knee pain

A recent systematic review of 41 studies addressed the role of QST in pain phenotyping in subjects with OA (Suokas et al. 2012). This review included studies using subjects with hand, knee and hip OA and thermal, mechanical, pressure, electrical and chemical methodologies; twenty three (56.1%) of the 41 studies included subjects with knee OA (not including those studies which solely used electrical and/or chemical assessments) (Suokas et al. 2012). The authors highlighted the use of pressure pain thresholds in providing different somatosensory profiles for subjects and comparator groups (Suokas et al. 2012). Pressure pain thresholds were significantly lower (indicating increased sensitivity) in OA subjects compared with controls, with standardised mean differences of -1.24 (95% CI -1.54, -0.93) and -0.88 (95% CI -1.11, -0.65) at the affected knee and control sites, respectively (Suokas et al. 2012). Although lower pressure pain thresholds were identified as potential markers of OA, the results for other QST modalities varied and require further investigation. This section provides an updated review of the literature including studies using knee OA subjects as at least one comparator group or as the population of interest, and not including
those studies which only used chemical or electrical assessments (see Appendix I for further details of the search and strategy used).

Demographics

To date, 31 studies (n=4435) have investigated somatosensory function in knee OA subjects using mechanical, pressure, thermal and/or vibratory QST (Table 2.3). Research within this area is increasing with 23 (74.2%) studies published since 2005 with the other 8 (25.8%) studies published between 1989 and 2004. No studies have focused solely on the presence of knee pain without the presence of OA with all 31 studies including subjects with symptomatic knee OA. All studies in Table 2.3 used subjects with confirmation of knee OA (n=3807; 85.8%) with healthy controls (n=508; 11.4%), and samples of subjects with Rheumatoid Arthritis (n=63; 1.5%), Ankylosing Spondylitis (n=18; 0.4%) and OA in other joints (n=39; 0.9%) used as a comparator group in 20 studies.

Sixteen studies used the ACR criteria for classifying knee OA (Altman et al. 1986) with 5 studies recruiting subjects with confirmed knee OA awaiting total knee arthroplasty. One study did not specify how knee OA was confirmed (Keefe et al. 1997) with the other 9 studies using physician diagnosis (3 studies), radiographic OA (2 studies), radiographic OA and knee pain (2 studies), people with OA or at high risk of developing it (1 study) and subjects who underwent revised total knee arthroplasty (1 study). Despite most studies using imaging criteria to determine the presence of OA, all studies in Table 2.3 had at least one comparator group with knee pain.

The youngest mean age of knee OA subjects in all of the studies in Table 2.3 was 52 years and 21 studies had a mean age of above 60 years old. The overall impact of age on QST is not well understood in subjects with knee OA, with varied reports of whether sensitivity increases or decreases and for which modalities. Previous studies have suggested that somatosensory abnormalities tend to increase with age, such as diminished sensitivity, which may be related to a loss of peripheral sensory fibre density with increasing age (Gibson et al. 2004). Despite sensory loss, there are studies that have demonstrated increased sensitivity to both the frequency and intensity of stimuli used (Gibson et al. 2004; Farrell et al. 2007). However, age differences in QST have not been consistently demonstrated in subjects with knee OA. The impact of aging on QST assessments requires further investigation, particularly in those with knee pain as the occurrence of knee pain increases with age (O'Reilly et al. 1998).

A higher proportion of females with knee OA were recruited in 24 studies, with 2 of these studies only recruiting women. An equal proportion of men and women were recruited in 4 studies. Two of 15 studies using a control group of healthy volunteers recruited an equal number of men and women with 9 studies recruiting a higher proportion of women; 2 of these studies only recruited women and the remaining 4 recruited a higher proportion of men than women. A recent systematic review investigating sex differences for QST measures in healthy controls determined a sample size of 41 per sex would be required in order to detect any somatosensory differences between the samples (Racine et al. 2012a). Twenty six (83.9%) of the studies in Table 2.3 do not fulfil this criterion for both sexes which may explain the variation in the effect of sex on QST measures.
Study Design

Cross-sectional study designs were used in 22 studies, with three studies investigating the repeatability of QST measures in knee OA, three randomised control trials (two double-blinded) and two studies using a prospective study design. 19 of the studies also used a case-control design (14 cross-sectional, 3 reliability, and 2 prospective) with 12 studies only using cases (8 cross-sectional, 2 randomised control trials, 1 prospective, and 1 reliability and randomised control trial). Recruitment strategies for these studies to identify subjects with knee OA included: subjects scheduled for total knee arthroplasty (6 studies), outpatient clinics (5 studies), advertisements and outpatient clinics (4 studies) and advertisements (2 studies), with two studies using a community-based sample and one study using hospital records. The remaining 11 studies did not specify how subjects with knee OA were recruited for the study which impacts the external validity of the sample.

Pain Measures

A variety of measures were used to determine pain in knee OA subjects with 13 studies using more than one pain measure. In total, 23 studies used validated measures; 20 of those 23 studies used the pain subscale of the Western Ontario and McMaster (WOMAC) OA Index (Bellamy et al. 1988), 6 studies used the McGill Pain Questionnaire (Melzack et al. 1971), two studies used the Graded Chronic Pain Scale (Von Korff et al. 1992) and one used the Arthritis Impact Measurement Scale (Meenan et al. 1980). 12 studies used 100 mm VAS to determine pain levels in knee OA subjects; of those studies using VAS, 6 assessed current knee pain intensity or severity with three studies assessing pain intensity in the past 24 hours, two studies assessing pain intensity at rest and during physical activity, one study used the Short Form-36 Health Survey and one study assessing pain intensity at rest (Table 2.3). Three of the studies also used dichotomous pain outcomes measures with one study recruiting subjects with mild or moderate knee pain, one study assessing the presence or absence of knee pain and the last study assessing the presence or absence of knee pain on most days in the past month.

The range of pain measures used in these studies influences the comparisons that may be drawn between the studies as the associations with QST measures are variable; this may be due to the use of differing durations, numeric, verbal or Likert rating scales, or the use of validated pain measures. Eight studies demonstrated significant associations between QST measures and pain intensity scores using the WOMAC (pain in the past 48 hours) (Imamura et al. 2008; Shakoor et al. 2012; Wylde et al. 2013; Neogi et al. 2013), a VAS for pain in the previous 24 hours (Arendt-Nielsen et al. 2010; Skou et al. 2013c) and current pain (King et al. 2013; Skou et al. 2013b), and the presence of frequent knee pain in the past month (Neogi et al. 2013). There were also three studies that demonstrated no association between QST measures and current pain assessed using a VAS (Hendiani et al. 2003), WOMAC pain (Creamer et al. 1999a; Finan et al. 2013a) or the McGill Pain Questionnaire (Creamer et al. 1999a). However, the sample sizes of these studies may impact the observed association as there can be wide variability in responses to QST measures.
Of the 11 studies outlined above, only one study with significant associations for increased sensitivity to QST measures and greater pain intensity calculated and achieved their sample size (Shakoor et al. 2012). Two large population-based studies that did not perform sample size calculations and two studies that determined their sample size by exceeding the number of subjects assessed in previous studies also reported positive associations between QST measures and pain intensity (Wylde et al. 2011; Wylde et al. 2013; King et al. 2013; Neogi et al. 2013). But, the associations in these studies were inconsistent as different QST measures were found to be associated with different measures of pain captured over varying time intervals. As such, further research to determine whether QST measures are associated with current or previous levels of pain is needed.

Assessment of Psychosocial Factors

Ten of the studies listed in Table 2.3 also investigated psychosocial factors; these studies are summarised in Table 2.4. Of these ten studies, four studies used psychosocial factors to characterise subjects: Creamer et al. (1998) demonstrated no differences in depression, fatigue, helplessness, self-efficacy, anxiety or quality of life between subjects with medial or generalised knee pain; Kulkarni et al. (2007) found no differences in anxiety, depression or catastrophising across 4 visits for 12 subjects with knee pain; Lee et al. (2011) demonstrated significantly lower physical and social functioning and general health between knee OA subjects and healthy controls; and Neogi et al. (2013) reported 11% of subjects had depressive symptoms and did not report the results of the catastrophising measure, but did adjust for these two factors in the main analyses.

One of the remaining 6 studies investigated associations between psychosocial factors and QST: Finan et al. (2013b) demonstrated significant positive correlations between the anxiety, depression, catastrophising and sleep disturbance scales used and also identified significant associations between higher levels of depression, anxiety and sleep disturbances with increased sensitivity to pressure pain, and higher levels of depression with increased sensitivity to mechanical temporal summation. Another study investigated the associations between levels of disability with anxiety and depression in knee OA subjects with high levels of knee pain intensity who were split into groups according to radiographic severity; the group with KL grade 0 or 1 demonstrated significant correlations between higher levels of disability with higher levels of anxiety and depression (Williams et al. 2004). The group with KL grade 2 and above demonstrated significant correlations between higher levels of disability with higher levels of depression.

The remaining 4 studies investigated the association between psychosocial factors and levels of pain: Creamer et al. (1999a) investigated associations between psychosocial factors and three measures of pain (VAS, McGill Pain Questionnaire and the WOMAC); higher levels of depression, anxiety and fatigue were associated with higher scores on the McGill Pain Questionnaire and higher levels of helplessness and lower levels of self-efficacy (the ability to achieve targets set by yourself) associated with higher scores on both the VAS and the WOMAC; helplessness was identified as the best predictor of all three using stepwise regression modelling (Creamer et al. 1999a). Wideman et al. (2014) demonstrated significant positive correlations between the
catastrophising, depression, and sleep disturbance scales used and demonstrated that higher levels of catastrophising and sleep disturbances were associated with higher levels of knee pain and lower levels of physical functioning.

Two of these 4 studies also investigated associations between QST measures, pain and psychosocial factors: Finan et al. (2013a) observed significant associations between higher levels of positive affect and lower sensitivity to both mechanical temporal summation and daily pain, and between higher levels of negative affect and higher levels of daily pain. Finally, Keefe et al. (1997) found that increased sensitivity to heat pain thresholds and thermal temporal summation, and higher pain intensity and unpleasantness ratings for heat pain thresholds were all correlated with lower levels of self-efficacy.

In summary, there is evidence for the role of psychosocial factors in distinguishing between knee OA and healthy subjects. These measures investigate the emotional and cognitive components of pain (negative affect and low self-efficacy) and were associated with greater pain intensity and sensitivity to QST measures. These findings provide support for the neuromatrix and fear-avoidance theories of pain outlined in Section 1.2.5. However, 8 of the 10 studies described here did not investigate the associations between measures of psychological distress (anxiety, depression, and catastrophising) with both QST measures and pain intensity. This area requires further research.

**Summary of QST Results**

Fourteen QST measures were used across the 31 studies; however, 11 measures were performed in 3 or less studies making interpretation of the results difficult for those measures. Of the remaining three measures (not including reliability studies which are summarised later), pressure pain thresholds were used in 19 studies, mechanical temporal summation was used in 8 studies and 7 studies used heat pain thresholds. The results for these three measures are summarised in the following three paragraphs. Some studies assessed more than one outcome and used multiple QST measures and as such are counted multiple times in the subsequent summaries and Table 2.4.

Of the 19 studies using pressure pain thresholds. Eight studies investigating the associations between this measure and pain determined significant associations between increased sensitivity to pressure pain thresholds with higher levels of pain in knee OA subjects (Table 2.3). Of the 13 studies assessing sensitivity to pressure pain thresholds in people with painful knee OA and other comparator groups, 9 studies reported increased sensitivity in the painful knee OA group compared with healthy controls (6 studies) or knee OA subjects reporting lower or no pain (3 studies). Three of the four remaining studies reported no difference between subjects with knee OA and healthy controls (2 studies) or between knee OA subjects with generalised or medial knee pain (1 study). The final study reported decreased sensitivity to pressure pain thresholds in subjects with painful knee OA compared with subjects with Rheumatoid Arthritis or Ankylosing Spondylitis. These findings suggest that increased sensitivity to pressure pain thresholds in knee OA subjects is
associated with higher pain and can differentiate between knee OA subjects with pain and those without or healthy controls.

Eight studies investigated mechanical temporal summation in subjects with painful knee OA with all 4 studies investigating the association with pain determining that higher sensitivity to mechanical temporal summation was associated with higher levels of pain. Four studies also determined that subjects with painful knee OA were more sensitive to mechanical temporal summation than healthy controls (2 studies) and knee OA subjects with lower levels of pain (2 studies). A final study of subjects with knee OA with and without insomnia did not find a significant difference in sensitivity to mechanical temporal summation between the groups.

Seven studies investigated heat pain thresholds and demonstrated significant associations between increased sensitivity and higher levels of pain (3 studies), lower levels of self-efficacy (1 study), and lower levels of physical functioning (1 study). However, no significant differences in heat pain thresholds were observed for subjects with painful knee OA compared with healthy controls in two studies. This suggests that heat pain thresholds are not effective in distinguishing knee OA subjects from controls, although these findings need to be replicated in other studies.

Only three studies used 5 or more QST assessments (Wylde et al. 2012; King et al. 2013; Skou et al. 2013b). Wylde et al. (2012) and King et al. (2013) included thermal and mechanical detection and pain thresholds in their studies with varying results; Wylde et al. (2012) demonstrated that knee OA subjects were less sensitive than healthy controls for warm, cool and mechanical detection thresholds, whereas King et al. (2013) demonstrated no differences in knee OA and healthy controls for warm detection or heat pain, but did find significant associations between all QST measures and pain intensity ratings. Skou et al. (2013b) included four different assessments of pressure pain and an assessment of CPM in subjects who had undergone a revised total knee replacement; those subjects reporting pain following the revision surgery were significantly more sensitive to all pressure pain conditions and reported more pain during CPM. These studies have highlighted the need for the use of robust QST testing protocols in order to determine which measures are or are not associated with knee pain. The role of thermal and mechanical detection thresholds and CPM in knee OA subjects requires further investigations to determine whether or not they are associated with pain or can differentiate between affected and unaffected individuals.

Eight studies demonstrated significantly higher sensitivity to pain thresholds at control test sites in subjects with painful knee OA compared with healthy controls (5 studies) (Imamura et al. 2008; Lee et al. 2011; Wylde et al. 2012; Wylde et al. 2013; King et al. 2013) or knee OA subjects reporting less pain (3 studies) (Williams et al. 2004; Finan et al. 2013b; Skou et al. 2013b). Six studies also reported significant associations between higher levels of pain intensity and higher sensitivity to pain thresholds at control test sites in subjects with painful knee OA (Keefe et al. 1997; Imamura et al. 2008; Arendt-Nielsen et al. 2010; Wylde et al. 2013; Neogi et al. 2013; King et al. 2013). This suggests that subjects with knee pain may have generalised changes within the nervous system as increased sensitivity to stimuli at pain-free sites could be an indicator of central sensitisation (Bajaj et al. 2001).
In summary, increased sensitivity was reported in 10 of 12 studies investigating the association between QST and higher pain intensity in those with knee OA (Keefe et al. 1997; Creamer et al. 1999a; Gelecek et al. 2006; Imamura et al. 2008; Arendt-Nielsen et al. 2010; Lee et al. 2011; King et al. 2013; Neogi et al. 2013; Wylde et al. 2013; Skou et al. 2013b), with one study reporting diminished sensitivity (Shakoor et al. 2012) and one reporting no association between QST and pain intensity (Hendiani et al. 2003). This suggests that increased sensitivity to QST may also be a marker of greater pain intensity in people with knee pain as well as a marker for sensitisation within the nervous system. Evidence for the associations between CPM, thermal temporal summation, thermal, mechanical and vibration detection, and cold and mechanical pain thresholds is lacking and also requires further investigations.

The findings of the studies described above suggest that pressure pain threshold and mechanical temporal summation are effective in identifying subjects with knee OA compared to a control group, and may be an indicator of pain intensity in those with knee pain. There were 6 studies reporting greater sensitivity to pain thresholds at control sites was associated with higher levels of pain and 8 studies reporting greater sensitivity at control sites for those with painful knee OA compared with healthy controls and knee OA subjects reporting lower levels of pain; this suggests that central sensitisation may be present in subjects with knee pain and supports the use of pain-free control sites in helping to generate a central sensitisation phenotype. However, the findings described previously require further investigation to help determine whether or not QST may be a clinically relevant tool in identifying those people with increased pain intensities and sensitisation within the nervous system. Developing one or more markers of sensitisation could aid in phenotyping people with knee pain as people who are sensitised may need alternate treatment plans to those who are not.

Reliability

Two studies addressed the reliability of QST measures at the knee in people with knee OA and in healthy volunteers. Wylde et al. (2011) assessed both knees and the right forearm of 50 subjects with symptomatic knee OA awaiting total knee replacement and 50 age- and sex-matched healthy controls; assessments were performed one week apart and by the same rater. Pressure pain and heat pain thresholds at the forearm, and index and contralateral knees were the most consistent measures for knee OA subjects with correlation coefficients of 0.86, 0.83 and 0.77 respectively for pressure pain, and 0.86, 0.77 and 0.86 for heat pain; the same measures were also consistent in the control group at the forearm, and right and left knees with correlation coefficients of 0.91, 0.83 and 0.86 respectively for pressure pain and 0.77, 0.85 and 0.79 for heat pain (Wylde et al. 2011). These results indicate little variability in the pressure pain and heat pain methodologies used in the study and the rater had good to very good test-retest reliability across sites for these two measures (Wylde et al. 2011).

Wessel (1995) investigated pressure pain thresholds at the knee in 36 women (18 subjects with knee OA in at least one knee and 18 age-matched controls without knee OA); pressure pain thresholds were performed at 6 test sites on both knees (medial and lateral aspects of the joint line,
medial and lateral ligaments, and vastus medialis and vastus lateralis muscles) on three separate occasions with 5-10 days between each test session. Knee OA subjects had lower mean pressure pain thresholds at all sites on both knees compared with controls; values for analysis of variance indicated reliability in measures at the worst knee in the OA subjects at all test sites (range 0.61-0.91) and all sites on both knees for the control group (range 0.71-0.90), again indicating little variability in pressure pain thresholds and the rater had good to very good test-retest reliability across sites (Wessel 1995). However, this study only assessed reliability in women and further investigations of the reliability of pressure pain thresholds in men are required.

A third study by Tena et al. (2012) investigated the reliability of automated and manual von Frey filaments in assessing mechanical pain thresholds in 30 healthy controls and 28 knee OA subjects who underwent total knee arthroplasty; unlike the aforementioned reliability studies, QST assessments were performed at two distant pain-free control sites (forearm and abdominal wall) rather than at the knee as OA subjects were assessed on the second and third days following total knee arthroplasty. Knee OA subjects were only included in the study if no centrally-acting interventions were administered for post-operative analgesia on the days of assessment as this would impact test results (Tena et al. 2012). Manual von Frey filaments were found to have the lowest reproducibility for intra- and inter-rater assessments (Kappa coefficients 0.24 – 0.64) while the automated filaments were more reliable (Lin coefficients 0.63 - 0.91); however, the automated filament provides a pressure measurement between 0.1 and 1000 grams while the manual filaments are of fixed length with different diameters to produce pressures of 1, 4, 100 and 300 grams so measurement using the manual filaments is less accurate (Tena et al. 2012). A fourth study addressed intra-rater reliability of pressure pain thresholds at the index knee over 48 hours in 38 knee OA subjects participating in a double blind randomised control trial with an intraclass correlation coefficient of 0.98 (Moss et al. 2007).

These four studies demonstrate little variance in pressure pain thresholds at both painful and pain-free test sites in controls and knee OA subjects. Wylde et al. (2011) also demonstrated moderate to good test-retest reliability for other QST measures including heat pain, vibration detection, mechanical pain and light touch thresholds at both knees and forearm test sites of knee OA subjects and controls. However, further reliability studies using the knee as a test site and a larger QST battery are needed to determine whether pressure pain thresholds are the most reliable measure, if other measures are also reliable and to determine the variability of measures at the knee compared with other test sites.

Population-based samples

To date, only two studies have investigated QST with respect to pain intensity in a population-based sample of people with knee pain. King et al. (2013) demonstrated that there are no differences in thermal or mechanical pain thresholds and pain tolerances in people with symptomatic knee OA and high pain severity (n=96) compared with people with knee OA and low pain severity (n=113) and control group without knee pain or knee OA (n=107). However the amount of pain perceived (VAS ratings) for heat pain thresholds at the knee and for heat pain
thresholds and tolerance at both test sites were significantly higher in the high pain severity group. Significant differences in pressure, mechanical and cold pain thresholds were also observed with the high pain severity group more sensitive to all measures at all test sites (King et al. 2013).

Neogi et al. (2013) demonstrated in a community-based sample of 2,126 individuals (61% females) with confirmed knee OA or who were at risk of developing the disease, that after controlling for confounders (age, sex, BMI, race, clinic site, radiographic severity, patellofemoral knee OA, knee injury, depression, catastrophising and analgesic use) there was no association between pressure pain threshold or mechanical temporal summation at the index knee or wrist (control site) with presence or severity of radiographic OA, or the duration of OA. However, increased sensitivity to these measures was associated with pain severity using the WOMAC and the presence of frequent knee pain (Neogi et al. 2013). The authors concluded that the association between sensitivity to stimuli and pain measures indicated that sensitisation was likely to be a trait that subjects were predisposed to develop rather than a state induced by the onset of OA pathology driving peripheral (and subsequently central) sensitisation (Neogi et al. 2013); the authors suggested that identifying markers of susceptibility to sensitisation would provide a target for future treatments. However, this argument proves problematic for managing knee pain in people who are currently sensitised as it suggests that the trait is already established and is unlikely to be altered. Previous studies have demonstrated the potential to reverse peripheral sensitisation through total knee replacements (Wylde et al. 2013) which would suggest that changes in pain sensitivity are plastic, with the potential to alter mechanisms of central sensitisation yet to be established.

In summary, these two studies provide evidence for the role of sensitisation in subjects with symptomatic knee OA as increased sensitivity to stimuli was associated with higher levels of pain. However, neither study fully addresses the role of psychological factors in association with pain or QST measures.

Limitations

These studies also have limitations; all studies provided descriptions of the QST assessments performed but only 16 studies referenced a QST protocol with few studies using the same equipment to assess QST. In total, 18 different test sites were used in the studies either assessed unilaterally or bilaterally; although all but three studies performed QST at the knee, a wide variety of test sites at the knee itself were also used. There are also only four studies which address the reliability of the raters performing QST assessments. These factors impact the generalisability of the results due to the range of test sites, methodologies and equipment used. Generalisability is also difficult for the 10 studies that did not specify the recruitment strategies used for knee OA subjects and for 5 of 15 studies using healthy volunteers that did not specify whether those subjects were free of pain in the affected areas (Gerecz-Simon et al. 1989; Parks et al. 2011; Emerson Kavchak et al. 2012; Tena et al. 2012). Suokas et al. (2012) also recommend a sample size of 45 per group for studies wanting to detect a standardised mean difference of -0.68 (mean difference -1.78 kg/cm²; standard deviation 2.57) in pressure pain thresholds between cases and controls with 90% at the 5% significance level; however, 15 of the 19 case-control studies in Table
2.3 did not fulfil this criteria for the number of cases and/or controls and therefore were likely to be underpowered. Standardised methodologies are required for future studies.

Conclusion

These studies highlight the role of amplified signalling within the nervous system in people with knee pain; pressure pain thresholds and mechanical temporal summation are frequently associated with pain intensity and can also be used to distinguish between people with painful knee OA and comparator groups with little or no pain at the knee. There is a need to use standardised testing protocols of larger QST batteries in order to identify whether associations between pain intensity and other QST measures do exist. Some attempts have been made to identify the association between pain intensity and QST measures with psychosocial factors, but this area requires further development.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Classification</th>
<th>Parameters and Test Site(s)</th>
<th>Design</th>
<th>Recruitment</th>
<th>Comparator Groups</th>
<th>N</th>
<th>Age (mean±SD)</th>
<th>% Pain Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arendt et al. (2010)</td>
<td>ACR criteria</td>
<td>PPT, mTS and CPM (8 sites around the index knee, forearm and leg)</td>
<td>Prospective Case-control</td>
<td>Not specified</td>
<td>Strong/severe knee pain (VAS&gt;6)</td>
<td>24</td>
<td>63.6±1.5</td>
<td>61.7±1.7</td>
<td>61.6±1.6</td>
</tr>
<tr>
<td>Burrows et al. (2014)</td>
<td>Physician diagnosis</td>
<td>PPT (4 upper body all assessed on right hand side and 4 lower body sites on right hand side or index side for OA subjects)</td>
<td>Prospective Case-control</td>
<td>Not specified</td>
<td>Knee OA</td>
<td>11</td>
<td>65.9±10.4</td>
<td>64.3</td>
<td>63.6</td>
</tr>
<tr>
<td>Creamer et al. (1998)</td>
<td>ACR criteria</td>
<td>PPT (3 sites at index knee, 2 forearm sites and thigh)</td>
<td>Prospective Case-only</td>
<td>Outpatient clinics</td>
<td>Knee OA: Generalised pain, Medial pain, Other pain</td>
<td>68</td>
<td>65.7±10.3</td>
<td>64.3±9.9</td>
<td>Not reported</td>
</tr>
<tr>
<td>Creamer et al. (1999a)</td>
<td>ACR criteria</td>
<td>PPT (3 sites at index knee, 2 forearm sites and thigh)</td>
<td>Prospective Case only</td>
<td>Outpatient clinics</td>
<td>Knee OA</td>
<td>68</td>
<td>65.8±10.4</td>
<td>69.1</td>
<td></td>
</tr>
<tr>
<td>Emerson Kavchak et al. (2012)</td>
<td>Physician diagnosis</td>
<td>MDT, allodynia, VDT and PPT (medial aspect of index knee)</td>
<td>Prospective Case-control</td>
<td>Outpatient clinics and adverts</td>
<td>Knee OA subjects</td>
<td>16</td>
<td>52±7</td>
<td>51±7</td>
<td>81</td>
</tr>
<tr>
<td>Finan et al. (2013b)</td>
<td>ACR criteria</td>
<td>PPT (shoulder and index knee), mTS (finger and index knee), tTS (forearm), Cold pressor (hand)</td>
<td>Prospective Case-control</td>
<td>Clinics and adverts</td>
<td>Low pain / low KL grade, Low pain / high KL grade, High pain / low KL grade, High pain / high KL grade</td>
<td>24</td>
<td>62.0±9.29</td>
<td>63.81±8.62</td>
<td>61.6±9.63</td>
</tr>
</tbody>
</table>

N = number; SD = standard deviation; % F = proportion females; ACR = American College of Rheumatology; PPT = pressure pain threshold; mTS = mechanical temporal summation; CPM = conditioned pain modulation; PPTT = pressure pain tolerance threshold; MDT = mechanical detection threshold; VDT = vibration detection threshold; tTS = thermal temporal summation; XS = cross-sectional; VAS = visual analogue scale; KL = Kellgren-Lawrence; WOMAC = Western Ontario and McMaster Universities OA index; MPQ = McGill Pain Questionnaire; ↑ = increased sensitivity; ↓ = decreased sensitivity.
### Table 2.3: Studies investigating QST in knee OA subjects (continued)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Classification</th>
<th>Parameters and Test Site(s)</th>
<th>Design</th>
<th>Recruitment</th>
<th>Comparator Groups</th>
<th>N</th>
<th>Age (mean±SD)</th>
<th>% F</th>
<th>Pain Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finan et al. (2013a)</td>
<td>ACR criteria</td>
<td>tTS (forearm) mTS (index knee and finger)</td>
<td>Case-control</td>
<td>XS</td>
<td>Clinics and adverts</td>
<td>Knee OA Knee OA and insomnia</td>
<td>36</td>
<td>115</td>
<td>67.25±9.99</td>
<td>59.34±8.47</td>
</tr>
<tr>
<td>Gelecek et al. (2006)</td>
<td>ACR criteria</td>
<td>PPT (knee, hip or shoulder; index joint determined by OA classification and one as control site)</td>
<td>Case only</td>
<td>XS</td>
<td>Not specified</td>
<td>OA subjects (24 knee, 8 hip and 31 shoulder)</td>
<td>63</td>
<td>55±10.6</td>
<td>66.7%</td>
<td>GCPS</td>
</tr>
<tr>
<td>Gerecz-Simon et al. (1989)</td>
<td>ACR criteria</td>
<td>PPT (forehead, deltoid, mid forearm, thumb, quadriceps and medial knee joint line, all assessed bilaterally)</td>
<td>Case-control</td>
<td>XS</td>
<td>Not specified</td>
<td>Rheumatoid Arthritis OA Ankylosing Spondylitis Healthy Volunteers</td>
<td>36</td>
<td>36</td>
<td>18</td>
<td>36</td>
</tr>
<tr>
<td>Hendiari et al. (2003)</td>
<td>ACR criteria</td>
<td>MDT and MPT at index knee</td>
<td>Case-control</td>
<td>XS</td>
<td>Outpatient clinics</td>
<td>Rheumatoid Arthritis Knee OA Healthy Volunteers</td>
<td>27</td>
<td>28</td>
<td>27</td>
<td>46.85±2.3</td>
</tr>
<tr>
<td>Imamura et al. (2008)</td>
<td>ACR criteria</td>
<td>PPT (hip, inner thigh, 8 sites at knee, 7 sites at lower back)</td>
<td>Case-control</td>
<td>XS</td>
<td>Patients scheduled for TKA</td>
<td>Knee OA Healthy volunteers</td>
<td>62</td>
<td>22</td>
<td>71.1±6.61</td>
<td>68.95±7.4</td>
</tr>
<tr>
<td>Keefe et al. (1997)</td>
<td>Not specified</td>
<td>HPT, HPTT and tTS (non-dominant forearm)</td>
<td>Case only</td>
<td>XS</td>
<td>Not specified</td>
<td>Knee OA</td>
<td>40</td>
<td>62.48±7.31</td>
<td>52.5%</td>
<td>WOMAC</td>
</tr>
<tr>
<td>King et al. (2013)</td>
<td>ACR criteria</td>
<td>WDT, HPT, HPTT (forearm and index knee) PPT (forearm, index knee, leg, shoulder) mTS, CPT, CPTT (hand)</td>
<td>Case-control</td>
<td>XS</td>
<td>Community-based High WOMAC (≥34) knee OA Low WOMAC (&lt;34) knee OA Healthy volunteers</td>
<td>96</td>
<td>113</td>
<td>107</td>
<td>56.4 (54.8, 58.1) †</td>
<td>58.1 (56.7, 59.5) †</td>
</tr>
</tbody>
</table>

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**Notes:**
- N = number; SD = standard deviation; % F = proportion females; ACR = American College of Rheumatology; tTS = thermal temporal summation; mTS = mechanical temporal summation; PPT = pressure pain threshold; MDT = mechanical detection threshold; MPT = mechanical pain threshold; HPT = heat pain threshold; HPTT = heat pain tolerance threshold; WDT = warm detection threshold; CPT = cold pain threshold; CPTT = cold pain tolerance threshold; XS = cross-sectional; TKA = total knee arthroplasty; WOMAC = Western Ontario and McMaster Universities OA index; * = range (years); † = 95% confidence interval; GCPS = Graded Chronic Pain Scale; VAS = visual analogue scale; AIMS = Arthritis Impact Measurement Scales; ↑ = increased sensitivity; ↓ = decreased sensitivity.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Classification</th>
<th>Parameters and Test Site(s)</th>
<th>Design</th>
<th>Recruitment</th>
<th>Comparator Groups</th>
<th>N</th>
<th>Age (mean±SD)</th>
<th>Pain Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kulkarni et al.</td>
<td>ACR criteria</td>
<td>HPT at index knee</td>
<td>RCT</td>
<td>Case only</td>
<td>Knee OA</td>
<td>12</td>
<td>59.16 (52-67)</td>
<td>Presence or absence of knee pain</td>
<td>HPT condition in knee OA subjects associated with higher metabolism in pain matrix</td>
</tr>
<tr>
<td>Lee et al.</td>
<td>Physician diagnosis</td>
<td>PPT (trapezius and quadriceps muscles, first MCP joint) and HPT (forearm) and Cold pressor (hand)</td>
<td>Case-control</td>
<td>XS</td>
<td>Knee OA and Healthy volunteers</td>
<td>26</td>
<td>56.7 ± 12.0</td>
<td>Bodily pain (SF-36)</td>
<td>↑ PPTs at all sites for OA subjects Mean HPT not different, but ↑ pain ratings for HPT</td>
</tr>
<tr>
<td>Martinez et al.</td>
<td>OA confirmed for TKA surgery</td>
<td>MPT, allodynia, HPT and CPT (both knees and hand)</td>
<td>Prospective</td>
<td>Patients scheduled for TKA surgery</td>
<td>Knee OA</td>
<td>20</td>
<td>69.2 ± 2.1</td>
<td>Pain at rest and during movement (flexion and extension of knee)</td>
<td>↑ MPT and CPT one and four days post-TKA</td>
</tr>
<tr>
<td>Moss et al.</td>
<td>ACR criteria</td>
<td>PPT (medial aspect of index knee)</td>
<td>Double-blind</td>
<td>Case only</td>
<td>Knee OA and Healthy volunteers</td>
<td>38</td>
<td>69.3 ± 11</td>
<td>VAS knee pain</td>
<td>↓ PPT following knee mobilisation and no change in PPT for manual contact or no contact conditions</td>
</tr>
<tr>
<td>Neogi et al.</td>
<td>Presence or at high risk of developing knee OA</td>
<td>PPT (index knee and wrist) and mTS (index knee and wrist)</td>
<td>Case only</td>
<td>Knee OA</td>
<td>Healthy volunteers</td>
<td>2126</td>
<td>68 ± 8</td>
<td>Presence of knee OA</td>
<td>↓ PPT/mTS at both sites with presence of knee OA for frequent knee pain</td>
</tr>
<tr>
<td>Parks et al.</td>
<td>ACR criteria</td>
<td>PPT at index knee</td>
<td>Case-control</td>
<td>XS</td>
<td>Knee OA and Healthy volunteers</td>
<td>14</td>
<td>56.1 ± 2.1</td>
<td>VAS knee pain</td>
<td>No differences in PPT between groups.</td>
</tr>
<tr>
<td>Shakoor et al.</td>
<td>ACR criteria</td>
<td>VDT (first MTP joint, medial and lateral ankle, medial and lateral knee)</td>
<td>Case-control</td>
<td>XS</td>
<td>Knee OA and Healthy volunteers</td>
<td>27</td>
<td>54 ± 12</td>
<td>WOMAC</td>
<td>↓ VDT at all test sites for OA subjects</td>
</tr>
</tbody>
</table>

N = number; SD = standard deviation; % F = proportion females; ACR = American College of Rheumatology; TKA = total knee arthroplasty; HPT = heat pain threshold; PPT = pressure pain threshold; MCP = metacarpophalangeal; MPT = mechanical pain threshold; CPT = cold pain threshold; mTS = mechanical temporal summation; VDT = vibration detection threshold; VAS = visual analogue scale; WOMAC = Western Ontario and McMaster Universities OA index; MPQ = McGill Pain Questionnaire; ICC = intraclass correlation coefficient; ↑ = increased sensitivity; ↓ = decreased sensitivity; SF-36 = Short Form Health Survey; QST = quantitative sensory testing; FMT = foot movement test; RCT = randomised control trial; XS = cross-sectional; SF = Short Form; VDT = vibration detection threshold; RCT = randomised control trial; XS = cross-sectional.
### Table 2.3: Studies investigating QST in knee OA (continued)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Classification</th>
<th>Parameters and Test Site(s)</th>
<th>Design</th>
<th>Recruitment</th>
<th>Comparator Groups</th>
<th>N</th>
<th>Age (mean±SD)</th>
<th>% F</th>
<th>Pain Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shakoor et al. (2012)</td>
<td>ACR criteria</td>
<td>VDT (first MTP joint, medial and lateral ankle, medial and lateral knee)</td>
<td>Case only</td>
<td>XS</td>
<td>Knee OA</td>
<td>58</td>
<td>56±11</td>
<td>74.1</td>
<td>WOMAC</td>
<td>↓ VDT at lateral knee correlated with KL grade and pain ↓ VDT acuity at MTP also correlated with KL grade. Relationship with KL grade persists after adjusting for age, sex and pain at MTP.</td>
</tr>
<tr>
<td>Skou et al. (2013a)</td>
<td>Radiographic and symptomatic knee OA</td>
<td>PPT (8 sites around the index knee and leg) pTS and CPM (most painful knee site and leg)</td>
<td>Case only</td>
<td>XS</td>
<td>Hospital</td>
<td>17</td>
<td>65.1±7.9</td>
<td>23.5</td>
<td>WOMAC</td>
<td>↑ PPT at knee and leg and ↑ pTS pain (assessed using VAS) ↑ pain from the knees and legs significant correlate with peak VAS: peak knee pain in past 24h</td>
</tr>
</tbody>
</table>
### Table 2.3: Studies Investigating QST in Knee OA Subjects (continued)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Classification</th>
<th>Parameters and Test Site(s)</th>
<th>Design</th>
<th>Recruitment</th>
<th>Comparator Groups</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wideman et al. (2014)</td>
<td>ACR criteria</td>
<td>PPT (shoulder and index knee) mTS (finger and index knee)</td>
<td>Case only</td>
<td>XS</td>
<td>Knee OA</td>
<td></td>
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</tr>
<tr>
<td>Williams et al. (2004)</td>
<td>Radiographic knee OA</td>
<td>PPT (9 bilateral sites including medial aspect and anterior tibial regions of both knees)</td>
<td>Case-control</td>
<td>XS</td>
<td>Knee OA and KL&lt;2</td>
<td>↑ PPT associated with higher disability in KL&lt;2 and pain&gt;0 group</td>
</tr>
<tr>
<td></td>
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<tr>
<td>Wylde et al. (2011)</td>
<td>OA confirmed for TKA</td>
<td>MDT, WDT, CDT, PPT and HPT (both knees and right forearm)</td>
<td>Reliability</td>
<td>Case-control</td>
<td>Patients</td>
<td>↓ PPT and HPT at all sites least variable measures for OA (ICCs 0.77-0.86)</td>
</tr>
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</tr>
<tr>
<td>Wylde et al. (2012)</td>
<td>OA confirmed for TKA</td>
<td>MDT, WDT, CDT, PPT and HPT (index or left knee and right forearm)</td>
<td>Case-control</td>
<td>XS</td>
<td>Knee OA</td>
<td>↓ WDT and CDT (knee) for OA subjects ↓ MDT and ↑ PPT (knee and forearm) for 20% to 34% OA subjects</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>Wylde et al. (2013)</td>
<td>OA confirmed for TKA</td>
<td>PPT and HPT (index or left knee and right forearm)</td>
<td>Prospective</td>
<td>Case-control</td>
<td>Patients</td>
<td>↑ PPT at both sites and no difference in HPT for OA subjects compared with controls ↑ forearm PPT (pre-operative) predicts WOMAC; ↑ PPT and HPT at all sites least variable measures for OA (ICCs 0.77-0.86)</td>
</tr>
<tr>
<td>Reference</td>
<td>Parameters and Test Site(s)</td>
<td>Design</td>
<td>Comparator Groups</td>
<td>N</td>
<td>Age; mean years (±SD)</td>
<td>% F</td>
</tr>
<tr>
<td>--------------------</td>
<td>--------------------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Creamer et al. (1998)</td>
<td>PPT (3 sites at index knee, 2 forearm sites and thigh)</td>
<td>Case-control</td>
<td>XS</td>
<td>68</td>
<td>65.7±10.3</td>
<td>35</td>
</tr>
<tr>
<td>Creamer et al. (1999a)</td>
<td>PPT (3 sites at index knee, 2 forearm sites and thigh)</td>
<td>Case only</td>
<td>XS</td>
<td>68</td>
<td>65.8±10.4</td>
<td>74</td>
</tr>
<tr>
<td>Finan et al. (2013b)</td>
<td>PPT (shoulder and index knee), mTS (finger and index knee), tTS (forearm)</td>
<td>Case-control</td>
<td>XS</td>
<td>27</td>
<td>62.04±9.29</td>
<td>68</td>
</tr>
<tr>
<td>Finan et al. (2013a)</td>
<td>tTS (forearm), mTS (index knee and finger)</td>
<td>Case-control</td>
<td>XS</td>
<td>36</td>
<td>67.25±9.99</td>
<td>52</td>
</tr>
<tr>
<td>Keefe et al. (1997)</td>
<td>HPT, HPTT and tTS (non-dominant forearm)</td>
<td>Case only</td>
<td>XS</td>
<td>40</td>
<td>62.48±7.31</td>
<td>31</td>
</tr>
</tbody>
</table>

Note: N = number; SD = standard deviation; % F = proportion females; PPT = pressure pain threshold; mTS = mechanical temporal summation; tTS = thermal temporal summation; HPT = heat pain threshold; HPTT = heat pain tolerance threshold; XS = cross-sectional; KL = Kellgren-Lawrence grade; WOMAC = Western Ontario and McMaster Universities OA index; VAS = Visual Analogue Scale; MPQ = McGill Pain Questionnaire; AIMS = Arthritis Impact Measurement Scales; CES-D = Center for Epidemiologic Studies Depression Scale; STAI = State-Trait Anxiety Inventory; PQOL = Perceived Quality of Life; FSS = Fatigue Severity Scale; RAI = Rheumatology Attitudes Index; ASES = Arthritis Self-Efficacy Scale; PANAS-X = Positive and Negative Affect Schedule; PANAS = Positive and Negative Affect Schedule; POMS = Profile of Mood States; ↑ = higher levels; ↓ = lower levels.
Table 2.4  
Studies investigating QST and psychosocial factors in knee OA subjects (continued)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Parameters and Test Site(s)</th>
<th>Design</th>
<th>Comparator Groups</th>
<th>N</th>
<th>Age; mean years (±SD)</th>
<th>% F</th>
<th>Pain Measures</th>
<th>Psychosocial Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kulkarni et al. (2007)</td>
<td>HPT at index knee</td>
<td>RCT</td>
<td>Case only</td>
<td>12</td>
<td>59.16 (52-67) *</td>
<td>50</td>
<td>Bodily pain</td>
<td>Presence of knee pain</td>
</tr>
<tr>
<td>Lee et al. (2011)</td>
<td>PPT (trapezoius and quadriceps muscles, first MCP joint)</td>
<td>Case-control</td>
<td>XS</td>
<td>26</td>
<td>33</td>
<td>76.9</td>
<td>69.7</td>
<td>Bodily pain (SF-36), General Health (SF-36)</td>
</tr>
<tr>
<td>Neogi et al. (2013)</td>
<td>PPT (index knee and wrist)</td>
<td>Case only</td>
<td>XS</td>
<td>212</td>
<td>68±8</td>
<td>11%</td>
<td>Presence of knee pain</td>
<td>Catastrophising (CSQ), Depression (CES-D)</td>
</tr>
<tr>
<td>Wideman et al. (2014)</td>
<td>PPT (shoulder and index knee)</td>
<td>Case only</td>
<td>XS</td>
<td>107</td>
<td>60.8±10.1</td>
<td>70</td>
<td>Bodily pain</td>
<td>Catastrophising (PCS), Sleep disturbances (PSQI)</td>
</tr>
<tr>
<td>Williams et al. (2004)</td>
<td>PPT (bilateral knee and anterior tibial regions)</td>
<td>Case-control</td>
<td>XS</td>
<td>16</td>
<td>79</td>
<td>59</td>
<td>Bodily pain</td>
<td>Depression (BDI), Anxiety (STAI)</td>
</tr>
</tbody>
</table>

N = number; SD = standard deviation; % F = proportion females; HPT = heat pain threshold; PPT = pressure pain threshold; mTS = mechanical temporal summation; RCT = randomised control trial; XS = cross-sectional; KL = Kellgren-Lawrence grade; SF-36 = Short Form Health Questionnaire 36; WOMAC = Western Ontario and McMaster Universities OA index; HAD = Hospital Anxiety and Depression Scale; CES-D = Center for Epidemiologic Studies Depression Scale; SDQ = children’s emotional and behavioral concerns; STAI = State-Trait Anxiety Inventory; PCS = Pain Catastrophizing Scale; CSQ = Coping Strategies Questionnaire; PSQI = Pittsburgh Sleep Quality Index; POMS = Profile of Mood States; BDI = Beck Depression Inventory; ↑ = higher levels; ↓ = lower levels.
Table 2.5  Summary of findings presented in Table 2.3

<table>
<thead>
<tr>
<th>Reference</th>
<th>Pain measures</th>
<th>Associations with:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arendt-Nielsen et al. (2010)</td>
<td>↑ PPT, mTS</td>
<td>↑ CPM (vs. HV)</td>
</tr>
<tr>
<td>Burrows et al. (2014) †</td>
<td></td>
<td>↓ PPT post-treatment</td>
</tr>
<tr>
<td>Creamer et al. (1998)</td>
<td></td>
<td>--- PPT (OA groups) *</td>
</tr>
<tr>
<td>Creamer et al. (1999a)</td>
<td>↑ PPT</td>
<td>↓ VDT (↑ instability) --- MDT, PPT (Instability)</td>
</tr>
<tr>
<td>Emerson Kavchak et al. (2012)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finan et al. (2013a)</td>
<td></td>
<td>↑ mTS, tTS, cold pressor for high pain, low KL group</td>
</tr>
<tr>
<td>Finan et al. (2013b)</td>
<td>--- tTS, mTS *</td>
<td></td>
</tr>
<tr>
<td>Gelecek et al. (2006)</td>
<td>↑ PPT</td>
<td>↑ PPT (↑ depression &amp; ↑ anxiety)</td>
</tr>
<tr>
<td>Gerecz-Simon et al. (1989)</td>
<td></td>
<td>↓ PPT (vs. RA and AS)</td>
</tr>
<tr>
<td>Hendiani et al. (2003)</td>
<td>--- MDT, MPT</td>
<td>↓ MDT &amp; ↑ MPT (vs. HV)</td>
</tr>
<tr>
<td>Imamura et al. (2008)</td>
<td>↑ PPT</td>
<td>↑ PPT (vs. HV)</td>
</tr>
<tr>
<td>Keefe et al. (1997)</td>
<td></td>
<td>↑ PPT (↑ disability)</td>
</tr>
<tr>
<td>King et al. (2013)</td>
<td>↑ WDT, HPT, HPTT, CPT, CPTT, PPT, mTS</td>
<td>--- WDT, HPT, HPTT, CPT, CPTT (vs. HV)</td>
</tr>
<tr>
<td>Kulkarni et al. (2007)</td>
<td>↑ HPT</td>
<td></td>
</tr>
<tr>
<td>Lee et al. (2011)</td>
<td>↑ HPT</td>
<td>↑ PPT, --- HPT (vs. HV)</td>
</tr>
<tr>
<td>Martinez et al. (2007) †</td>
<td></td>
<td>↑ MPT, CPT post-treatment</td>
</tr>
<tr>
<td>Moss et al. (2007) † ‡</td>
<td></td>
<td>↓ PPT post-treatment --- PPT (reliability)</td>
</tr>
<tr>
<td>Neogi et al. (2013)</td>
<td>↑ PPT, mTS</td>
<td></td>
</tr>
<tr>
<td>Parks et al. (2011)</td>
<td></td>
<td>--- PPT *</td>
</tr>
<tr>
<td>Shakoor et al. (2008)</td>
<td></td>
<td>↓ VDT (vs. HV)</td>
</tr>
<tr>
<td>Shakoor et al. (2012)</td>
<td>↓ VDT</td>
<td></td>
</tr>
<tr>
<td>Skou et al. (2013a)</td>
<td>↑ PPT</td>
<td></td>
</tr>
<tr>
<td>Skou et al. (2013b)</td>
<td></td>
<td>↑ PPT, PPTT, mTS, CPM (vs. OA no pain)</td>
</tr>
<tr>
<td>Takeda &amp; Wessel (1994) †</td>
<td></td>
<td>↓ PPT post-treatment</td>
</tr>
<tr>
<td>Tena et al. (2012) ‡</td>
<td></td>
<td>--- PPT (reliability)</td>
</tr>
<tr>
<td>Wessel (1995) ‡</td>
<td></td>
<td>--- PPT (reliability)</td>
</tr>
<tr>
<td>Wideman et al. (2014)</td>
<td></td>
<td>↑ HPT (↑ physical activity)</td>
</tr>
<tr>
<td>Williams et al. (2004)</td>
<td></td>
<td>↑ PPT, HPT (vs. HV)</td>
</tr>
<tr>
<td>Wylde et al. (2011) ‡</td>
<td></td>
<td>--- CDT, CPT, WDT, MDT, PPT (reliability)</td>
</tr>
<tr>
<td>Wylde et al. (2012)</td>
<td></td>
<td>↓ WDT, CDT, MDT and ↑ PPT (vs. HV)</td>
</tr>
<tr>
<td>Wylde et al. (2013) †</td>
<td>↑ PPT pre-treatment</td>
<td>↑ PPT (vs. HV)</td>
</tr>
</tbody>
</table>

↑ = higher levels for OA group (unless specified); ↓ = lower levels for OA group (unless specified); --- = no difference; * = findings not significant; † = intervention study; ‡ = reliability study; PPT = pressure pain threshold; mTS = mechanical temporal summation; CPM = conditioned pain modulation; HV = healthy volunteers; VDT = vibration detection threshold; MDT = mechanical detection threshold; ITS = thermal temporal summation; KL = Kellgren-Lawrence; RA = Rheumatoid Arthritis; AS = Ankylosing Spondylitis; MPT = mechanical pain threshold; HPTT = heat pain tolerance threshold; CPTT = cold pain tolerance threshold; PPTT = pressure pain tolerance threshold.
2.4. Summary

Knee pain is frequently reported by those aged 50 and over (Peat et al. 2001a). A number of population-based studies investigating knee pain have used postal self-reports to determine the prevalence of knee pain and have identified older age, female sex, psychological distress and diminished physical functioning as risk factors for knee pain (O’Reilly et al. 1998; Peat et al. 2004; Thomas et al. 2004b). The underlying cause of knee pain, however, remains unknown; associations with underlying disease (such as OA) have found that knee pain is associated with higher grades of radiographic disease (Neogi et al. 2009), but few studies have identified key pathological features of disease which are consistently associated with the presence of knee pain (Bedson et al. 2008). Knee pain rarely occurs as a single painful site and is associated with pain in at least one or more body regions (Croft et al. 2005). This suggests knee pain may be one site that contributes to a wider pain disorder due to its associations with poorer psychological and physical outcomes (Kamaleri et al. 2008a; Kamaleri et al. 2008b).

Another possibility is the role of aberrant pain processing in those with knee pain. As approximately one third of people with knee pain have none or mild signs of underlying disease (KL grade 0 or 1) (Nguyen et al. 2011), it is possible that amplification of pain within the nervous system contributes to the discordance between pain intensity and underlying pathology (Finan et al. 2013b). One way to identify the role of aberrant pain processing in people with knee pain is to establish the presence of sensitisation in the nervous system. This can be assessed using QST to determine whether increased sensitivity to stimuli is localised to the affected site (peripheral sensitisation), if increased sensitivity occurs at a pain-free control site (central sensitisation), or if sensitivity to stimuli occurs at all test sites indicating the presence of sensitisation throughout the CNS and peripheral nervous system. Previous studies of QST in subjects with knee pain have identified associations between higher levels of pain intensity and increased sensitivity to pressure pain thresholds and mechanical temporal summation both at the affected knee and at control tests sites. These two measures can also be used to differentiate between subjects with painful knee OA and pain-free controls or subjects with knee OA and lower levels of pain. These findings provide support for the role of sensitisation in people with knee pain; however, the support for the role of other test modalities is limited and further research using a larger test battery is needed.

Higher levels of anxiety, depression and catastrophising are associated with higher levels of pain in subjects with knee OA (Table 2.4), but the relationships between pain intensity, sensitivity to QST measures and these factors have not been thoroughly investigated in people with knee pain. The role of widespread sensitivity, which is an indicator of central sensitisation and is associated with a greater number of pain sites and higher pain intensity, has not yet been determined in subjects with knee pain. The relationship between self-reported pain intensity and QST measures may be mediated by psychosocial factors such as psychological state, beliefs about pain and levels of physical functioning. As a result, there may be important implications for treating pain in those with knee OA, such as the use of intra-articular steroid injections, if mechanisms of peripheral and/or central sensitisation are indicated using QST.

There have been no studies investigating psychosocial factors as mediators of the association between sensitivity to sensory stimuli and self-reported pain intensity in people with knee pain, and
no studies have investigated sensitivity to sensory stimuli and psychosocial factors in relation to changes in pain in knee OA subjects receiving a pharmacological intervention. This project will investigate these two issues with the aims and objectives of the thesis outlined in Chapter 3. Psychological state, beliefs about pain and levels of physical functioning can be investigated in relation to pain intensity using questionnaire instruments with QST able to assess losses or gains in somatosensory function using noxious and innocuous stimulation (outlined in Chapter 4). This project will explore the associations between sensitivity to stimuli using QST and self-reported pain intensity in subjects with knee pain recruited from a prospective population-based cohort (see Section 4.2) and associations between baseline measures of QST and psychological distress with changes in pain in subjects with symptomatic knee OA participating in an uncontrolled open-label clinical trial investigating structural predictors of response to intra-articular steroid therapy (Section 4.3).
CHAPTER 3. AIMS AND OBJECTIVES

3.1. Hypotheses

The hypotheses addressed in this thesis are:

(i) In individuals reporting knee pain, higher levels of pain intensity are associated with greater sensitivity to thermal, pressure, mechanical and vibratory stimuli, and these associations are explained by variation in levels of psychosocial factors.

(ii) Individuals with painful knee OA who experience a decrease in pain following an intra-articular steroid injection are more sensitive to pressure, mechanical and vibratory stimuli at the knee prior to the injection.

3.2. Objectives

To determine whether:

1. levels of pain intensity are correlated with increases in sensitivity to stimuli in community-dwelling adults reporting knee pain.

2. the association between levels of pain intensity and sensitivity to stimuli is moderated by sex and age.

3. any association between increased sensitivity to stimuli and pain intensity is mediated by psychosocial factors including psychological distress, cognitions about pain and lower levels of physical functioning.

4. sensitivity to stimuli changes in subjects with symptomatic knee OA following an intra-articular steroid injection.

5. sensitivity to stimuli prior to the intra-articular steroid injection is associated with (i) change in pain and (ii) response to treatment.

6. psychological state prior to the intra-articular steroid injection is associated with (i) change in pain and (ii) change in sensitivity to stimuli.
CHAPTER 4. METHODS

4.1. Summary

This chapter details the study methods used to address the objectives of the thesis. Subjects from two studies were included; those from a population-based cohort investigating the onset and predictors of CWP (EPIFUND) and, an uncontrolled open label clinical trial of intra-articular steroid therapy in subjects with knee OA (TASK). This chapter describes the design of both studies used to address the thesis objectives, including the recruitment process, assessments performed during a study visit, and sample size calculation. The analysis techniques are summarised and the chapter concludes with a summary signposting the content of subsequent results chapters.

4.2. Knee Pain Sensitivity Study

4.2.1. Study Design

The Knee Pain Sensitivity (KEEPS) study is a cross-sectional study of community-dwelling adults identified as having knee pain in a large cohort study of men and women; the Epidemiology of Functional Disorders (EPIFUND) cohort (see Section 4.2.2.1).

4.2.2. Subjects

4.2.2.1. Epidemiology of Functional Disorders Cohort

EPIFUND is a prospective population-based cohort established in 2001. The cohort is composed of people from three GP practices in the North West of England (Bollington in Cheshire, and Brooklands and Bowland Road in South Manchester). There have been two previous follow-ups of this cohort. The first ran from 2001 (baseline) to 2002 (follow-up) and comprised men and women who were investigated for disturbances in the hypothalamic-pituitary-adrenal (HPA) axis, psychological distress, sleep quality, and socio-economic status as potential risk factors for concurrent and future CWP. The second follow-up ran from 2005 to 2007 and investigated factors in relation to the aetiology of CWP including physical activity, gastrointestinal disturbances, and genetics. A third follow-up of this cohort investigating predictors and occurrence of CWP in men and women using a two-stage clustered sample study design (see Figure 4.1) was completed in 2012. The EPIFUND cohort were first contacted for the third follow-up in January 2011; death and diagnosis of dementia (confirmed using GP records), and change of address (verified by electoral register) since the previous follow-up were checked to minimise erroneous mailings. A baseline questionnaire was mailed to the 2301 remaining members of the cohort (68.1% from 3380 at the previous follow-up) with 1817 (79.0%) returning completed questionnaires. 1320 baseline responders (72.7%) consented to further contact to take part in further assessments. 1785 of the baseline responders (98.2%) were mailed a follow-up questionnaire to investigate the occurrence
of new onset CWP with 1530 (85.7%) returning a completed copy. The baseline and follow-up questionnaires included questions about pain ascertainment including chronicity and body manikins, which were used to identify subjects for the KEEPS study.

Figure 4.1  Study design for the third follow-up of the EPIFUND cohort

Figure 4.1:

Stage 1
Postal survey - Pain assessment

Stage 2
Sub-group assessments

Stage 3
Postal survey

Baseline 0-3 months

Follow-up 12-15 months

10% of the responders to the baseline postal survey were recruited for the sub-group assessments and were stratified into groups according to their pain status.

4.2.3. KEEPS Recruitment

Subjects for this study were recruited from the 1,530 responders to the follow-up questionnaire (Stage 3 in Figure 4.1). Table 4.1 presents the number of people who answered the question “During the past month have you had any ache or pain that has lasted for one day or longer?” and reported knee pain using the Manchester manikin coding schedule (areas 10 and 14; see Figure 4.2) at baseline and follow-up. 1,270 baseline and 1,153 follow-up responders reported symptoms with 577 (45.4%) reporting knee pain at baseline and 565 (49.0%) at follow-up (see Table 4.1). 219 (35.6%) people reported knee pain at both follow-ups. Recruitment for this study began 18 months after the baseline mailing; those reporting knee pain on the follow-up questionnaire (Stage 3 in Figure 4.1) were contacted by telephone for the study.

Table 4.1  Reports of knee pain using the Manchester manikin coding

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n=1270)</th>
<th>Follow-up (n=1153)</th>
<th>Both (n=615)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right knee only</td>
<td>146 (11.5%)</td>
<td>139 (12.1%)</td>
<td>36 (6.7%)</td>
</tr>
<tr>
<td>Left knee only</td>
<td>127 (10.0%)</td>
<td>125 (10.8%)</td>
<td>25 (4.6%)</td>
</tr>
<tr>
<td>Both knees</td>
<td>304 (23.9%)</td>
<td>301 (26.1%)</td>
<td>158 (29.3%)</td>
</tr>
<tr>
<td>Total</td>
<td>577 (45.4%)</td>
<td>565 (49.0%)</td>
<td>219 (35.6%)</td>
</tr>
</tbody>
</table>
Table 4.2 presents the characteristics of the 565 responders to the EPIFUND follow-up questionnaire; 297 (52.6%) were located in South Manchester with a mean age of 59.3 (±9.0), which was significantly lower than the mean age of responders in Bollington (60.9±8.8; p=0.040). There were no significant differences between the sexes for responders in either location. However, there was a significant difference in the deprivation statuses of subjects from each location: 95.6% of responders in South Manchester were classified as being deprived or most deprived compared with 90.3% of responders in Bollington classified as less or least deprived.

Table 4.2 Characteristics of follow-up responders identified with knee pain (n=565)

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>South Manchester</th>
<th>Bollington</th>
<th>p-value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>565</td>
<td>297 (52.6%)</td>
<td>268 (47.4%)</td>
<td>0.223</td>
</tr>
<tr>
<td>Age (±SD)</td>
<td>60.1 (±8.9)</td>
<td>59.3 (±9.0)</td>
<td>60.9 (±8.8)</td>
<td>0.040</td>
</tr>
<tr>
<td>Sex (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>214 (37.9%)</td>
<td>104 (35.0%)</td>
<td>110 (41.0%)</td>
<td>0.140</td>
</tr>
<tr>
<td>Female</td>
<td>351 (62.1%)</td>
<td>193 (65.0%)</td>
<td>158 (59.0%)</td>
<td></td>
</tr>
<tr>
<td>Deprivation Status (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Least</td>
<td>120 (21.2%)</td>
<td>6 (2.0%)</td>
<td>114 (42.5%)</td>
<td>0.000</td>
</tr>
<tr>
<td>Less</td>
<td>133 (23.5%)</td>
<td>5 (1.7%)</td>
<td>128 (47.8%)</td>
<td></td>
</tr>
<tr>
<td>Deprived</td>
<td>94 (16.6%)</td>
<td>71 (23.9%)</td>
<td>23 (8.6%)</td>
<td></td>
</tr>
<tr>
<td>Most</td>
<td>213 (37.7%)</td>
<td>213 (71.7%)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

* = p<0.05 if bold (Significant differences between variables were assessed using independent T-tests (continuous variables) or Chi-squared tests (categorical data)); N = number; SD = standard deviation.
This study used a two-phase telephone recruitment process (see Figure 4.3). If the presence of knee pain was confirmed during the first telephone call, the subject was asked if a copy of the participant information sheet (see Figure II-1, Appendix I) could be mailed to them. If they agreed, a second phone call was made at least one week after the information sheet was mailed. This permitted enough time for the information sheet to be delivered and to give the subject at least 48 hours to read through the information. During the second call, subjects were asked if they had received the information sheet (if not, another was sent) and if they would like to discuss the study further. A description of the study assessments was given. Each subject was asked if they had any questions about the study prior to being invited to make an appointment. An appointment letter, detailing the time, date and location of the appointment (see Figure II-2, Appendix I) was mailed to the subject along with a map providing directions. Subjects were offered appointments at the Bollington Leisure Centre or the Wellcome Trust Clinical Research Facility in Manchester to make travelling to the appointment more convenient; if a subject was unable to travel to either centre they were offered a home visit. In accordance with lone worker policy, two members of the study team undertook home visits to ensure subject and researcher safety, as well as safe transport of study equipment. Appointments lasted a maximum of 90 minutes.

At the appointment, an explanation of the study visit was given including a description of all study assessments and the questionnaire, how long the visit should last, asking any questions the subject may have at any point, and a reminder that participation is entirely voluntary and that the subject may withdraw at any time without giving a reason. If the subject agreed to take part in the study, a copy of the consent form (see Figure II-3, Appendix I) was signed and dated by both the subject and the author at the study visit prior to any study assessments.
4.2.4. Study Assessments

Following consent, subjects were asked to complete a questionnaire assessing current pain including intensity, chronicity, and location (using manikins), psychological distress, cognitions about pain and physical functioning. The instruments are described in Section 4.2.4.1 with details of how items or subscales were scored (see Figure II, Appendix I for questionnaire). Height and weight of each subject was recorded, followed by a joint examination (Section 4.2.4.3) and tender point count (Section 4.2.4.4). QST assessments were performed at the most painful knee (identified at the study visit) and the opposite forearm, if pain-free. If the forearm was identified to be painful, an alternative pain-free site such as the thenar eminence of the opposite hand was assessed. If no pain-free sites were identified, only the most painful knee was assessed. The QST assessments performed in this study include cold and hot pain thresholds, mechanical pain threshold, stimulus response function, wind-up ratio (an assessment of temporal summation), DNIC, vibration detection threshold and pressure pain threshold performed in the order listed. Subjects were randomised in the study database as to whether they received QST assessments at the knee or opposite forearm first.

4.2.4.1. Study Questionnaire

Subjects were asked to complete a survey covering their current pain (intensity, chronicity, and location), psychological distress, cognitions and beliefs about pain, physical activity and levels of disability. Each of the scales detailed in the following section were selected based on previous validation studies assessing construct (the measure accurately assesses the construct of interest), concurrent (correlation between different measures administered at the same time point), and/or predictive validity (previous administration predicts scores at a later date); these are important features of questionnaire development as they allow for inferences to be made from test scores (Messick 1998).

Current Pain

Current pain was ascertained using two items: “During the past month have you had any ache or pain that has lasted for one day or longer?” and “Do you have any such pain today?” scored yes or no. Pain chronicity was assessed using the item “Thinking about this ache or pain, have you been aware of it for more than three months?” also scored yes or no, and pain interference “In the past month, how much has this pain interfered with your daily activities?” scored 0 (no interference) to 10 (unable to carry out activities).

Regions affected by pain

Pain manikins of the front, back, left and right aspects of the body were provided and subjects were asked to shade any current pain or pain felt in the past month. The number of pain sites shaded
were calculated by using the ten quadrants described in the ACR classification criteria for Fibromyalgia (see Figure 4.4) (Wolfe et al. 1990) and the Manchester manikin coding schedule (see Figure 4.2) (Hunt et al. 1999).

Pain Intensity

Pain can be assessed using a VAS or NRS. The advantages to using a VAS or NRS include no cost, rapid assessment time and good test-retest reliability (Hawker et al. 2011). However, these scales only focus on the intensity of pain perceived and don’t address the multidimensional aspects of pain including the affective and cognitive components (Summers 2001). Pain intensity was assessed using the question: “In the past month, on average, how intense was your pain?” Subjects provided a score for each knee and for global pain using an 11 point verbal NRS (0-10) from “no pain” to “pain as bad as it could be”. Subjects reporting no knee pain within the past month at the study visit were subsequently excluded.

Figure 4.4 ACR Coding Schedule (Davies et al. 2009)

Psychological Distress

Psychological distress was assessed using the Hospital and Anxiety Depression (HAD) scale to assess the presence of anxiety or depression. It excludes items that may be related to other mood disorders such as fatigue, headache or dizziness (Zigmond et al. 1983). The HAD is comprised of a subscale for anxiety and for depression, with 7 items in each subscale. Each item is scored from 0
(no symptoms) to 3 (strong indication of symptoms) with each subscale scored 0-21. Scores of 0-7 for each subscale are not considered to be a case of anxiety or depression, with scores of 8-10 being possible cases, and scores above 11 considered to be probable cases as validation studies demonstrated that these cut-off points generated the fewest number of false-positive and false-negative results (Zigmond et al. 1983; Pallant et al. 2005).

Bjelland et al. (2002) performed a literature review to investigate the validity of the HAD scale. The sensitivity (correct classification of cases) and specificity (correct classification of controls) of the anxiety and depression subscales were assessed using studies that had compared the ability of subscales the to identify cases in comparison to diagnoses made by interview (structured or semi-structured); the average sensitivities for anxiety and depression were 0.80 and 0.81 respectively, with specificities of 0.76 and 0.81 if cases are classified using a score of 8 or more (Bjelland et al. 2002). The HAD scale was also assessed for structure validity (whether the individual factors correlate with the construct of interest) using factor analysis in 296 subjects with musculoskeletal pain; these subjects reported higher anxiety and depression scores on the subscales than subjects with coronary heart disease, chronic obstructive pulmonary disease, or cancer, but scored lower on average than psychiatric subjects (Pallant et al. 2005). The Cronbach’s alpha for anxiety (0.83) and depression (0.84) indicate a high level of internal consistency (reliability) for the HAD in these subjects meaning the items for each sub-scale do capture signs of anxiety and depression (Pallant et al. 2005). Both HAD subscales also correlate well with other scales designed to identify depression and anxiety, such as the Beck Depression Index, General Health Questionnaire, and the State Trait Anxiety Index, with correlation coefficients ranging from 0.34-0.83 for anxiety and 0.44-0.81 for depression demonstrating good concurrent validity (Bjelland et al. 2002).

Cognitions and Beliefs about Pain

Cognitions and beliefs about pain were addressed using the Pain Catastrophizing Scale (PCS) and the brief Illness Perception Questionnaire (IPQ-Brief). The PCS is comprised of 13 items each scored 0 (not at all) to 4 (all of the time; range 0-52) used in identifying thoughts and beliefs associated with pain (Sullivan et al. 1995). The scale is split into three categories; rumination (4 items scored from 0-16), magnification (3 items scored from 0-12) and helplessness (6 items scored from 0-24).

A sub-study of the Sullivan et al. (1995) paper addressed the use of the PCS in subjects with nerve entrapment (n=18) and radiculopathy (n=10) undergoing electrodagnostic assessment (electrode stimulation of nerve fibres) who scored <15 or >24 on the scale. Subjects were interviewed for thoughts and beliefs about pain during the procedure and were classified as having catastrophic, coping or neutral thoughts; subjects classified as catastrophisers (scored >24) were more likely to have catastrophic or coping thoughts and reported higher levels of pain, whereas non-catastrophisers predominantly had neutral thoughts, some coping thoughts and reported lower pain (Sullivan et al. 1995). A study investigating the structural validity of the PCS in 215 community-based subjects also assessed whether the PCS could be used to predict whether a subject was from the community-based sample or whether they belonged to a group of 60 chronic pain
outpatients; the total PCS score accurately classified 77.1% of cases, while rumination was the only subscale to have a significant sensitivity of 76.7% (Osman et al. 2000).

The Illness Perception Questionnaire (IPQ) was developed to assess cognitions related to illness and focused on the 5 components of the Common Sense Self-Regulatory Model (Leventhal et al. 1983): identity, cause, timeline, consequences, and cure control (Weinman et al. 1996). This scale included 35 items that could be adapted to include items specific to the illness being assessed. In light of data published addressing construct validity of the IPQ, the scale was modified to improve temporal test-retest reliability and include more items; it was renamed the Revised Illness Perception Questionnaire (IPQ-R) (Moss-Morris et al. 2002). This study used the IPQ-Brief which contains 9 items that address each of the 8 main topics in the IPQ-R scored 0-10 and also includes a qualitative causal question (Broadbent et al. 2006). The first 5 items assess thoughts about the illness (consequences, timeline, personal control, treatment control, identity), items 6 and 8 (concern and emotion) address emotions related to the illness and item 7 (coherence) is related to understanding of the illness (Broadbent et al. 2006). This questionnaire was validated in a study of 90 subjects with acute (n=19) and chronic lower back pain (n=71) with an acceptable internal consistency of 0.72 (Cronbach’s alpha; 95% CI not reported) (Lochting et al. 2013b). The internal consistency of the IPQ-Brief was also found to be acceptable in 84 subjects with acute lower back pain (Cronbach’s alpha 0.73; 95% CI 0.67, 0.83) suggesting that the items do capture subjects’ perceptions about their pain (Hallegraeff et al. 2013).

However, the IPQ-Brief is limited due to the use of one item per construct. van Oort et al. (2011) also identified the potential for misinterpretation of questions in the IPQ-Brief; this could impact the content validity of the IQP-brief due to the use of only 9 items representing each of the constructs in the IQP-R. However, this particular study of 18 older adults used a Dutch translation of the IPQ-Brief with limited validation in that language that may also have impacted the interpretation of questions (Broadbent et al. 2011).

Physical Functioning

Instruments used in the assessment of physical functioning in people with knee pain include the Western Ontario McMaster (WOMAC) Osteoarthritis Index (Bellamy et al. 1988) and Knee Injury and Osteoarthritis Outcome Score (KOOS) (Roos et al. 1998). The WOMAC focuses on symptoms specific to knee OA (Bellamy et al. 1988) while the KOOS is not limited to knee OA and is designed for use in different knee complaints (Roos et al. 1998). These scales not only address current pain intensity and/or severity, they also address the physical impairment associated with knee conditions, with a stiffness scale included in the WOMAC (Bellamy et al. 1988) and the KOOS addressing a wider range of knee symptoms and quality of life (Roos et al. 1998). However, the KOOS and WOMAC are not designed to address the impact of knee pain on general physical activity levels or disability as the KOOS asks for responses about the knee in the past week and the WOMAC for the past 48 hours (Howe et al. 2012).

Levels of physical functioning were determined using the Rapid Assessment of Physical Activity (RAPA) and the Health Assessment Questionnaire Disability Index (HAQ-DI). The RAPA was
developed as a measure of physical exertion in older adults (>50 years old); it contains 9 items rated “yes” or “no”, with 7 items determining levels of physical activity, one item for strength and one item for flexibility (Topolski et al. 2006). The total score for items 1-7 (physical activity; range 0-7) are categorised with a score of 1 classified as sedentary, 2 as underactive, 3 as regular underactive (light activities), 4 as regular underactive and greater than 5 as regular active (Topolski et al. 2006). The score for strength is 1, with a score of 2 for flexibility and 3 for both. An investigation into measures used clinically to assess patient behaviour recommended the use of the RAPA as the main measure of physical activity due to its short administration time and distinction between activity levels (Glasgow et al. 2005).

The Health Assessment Questionnaire (HAQ) is a functional measure that assesses quality of life in the presence of comorbidities in the older population (Bruce et al. 2003). The physical activity subscale of the HAQ was developed over time to become a measure of disability, creating the HAQ-DI (Bruce et al. 2005). The HAQ-DI contains 8 categories to assess disability in daily life; dressing, rising, eating, walking, hygiene, reach, grip and usual activities (Bruce et al. 2005). Each of these categories has 2 or 3 items to assess function and each item is scored from 0 (without any difficulty) to 3 (unable to do); for example, the walking category is assessed by two items addressing difficulty walking on flat ground and ascending five steps (Bruce et al. 2005). The categories are then scored 0-3 according to whether the two or three items per category are scored 0 to 3 for difficulty; there are also 8 items addressing the use of devices and 8 items for requiring assistance for each of the 8 categories (Bruce et al. 2005). If any device or assistance is needed, a category score of 0 or 1 is changed to 2, while category scores of 2 or 3 remain unchanged. The total scores for the categories are summed and then divided by 8 to provide the scores described above (Bruce et al. 2005).

4.2.4.2. Height and Weight

Height was recorded using a Leicester height measure (Seca, United Kingdom) with weight measured using electric scales (Weight Watchers, United Kingdom). BMI was calculated as weight in kilograms, divided by height, in metres, squared.

4.2.4.3. Joint Assessments

A brief musculoskeletal examination was performed to assess subjects for clinical signs of OA. The examinations were developed in accordance with the ACR clinical classification criteria for OA of the hands (Altman et al. 1990), knees (Altman et al. 1986), and hips (Altman et al. 1991) and are listed in Table 4.3.

The ACR clinical criteria were selected because subjects did not have radiographs obtained for these joints as part of the study and the criteria are designed to provide robust definitions of hand, knee, and hip OA for use in research. Subjects were asked at the time of assessment if they had experienced any pain, aching, or stiffness in their hands, knees or hips in the past month, and if
any of these symptoms were present on most days. Subjects were asked about any stiffness in their knees and hips, particularly if they experienced stiffness in the morning and its duration. Subjects were also asked if they had undergone total knee or hip arthroplasty, as this excluded those joints from assessment.

Table 4.3  ACR Clinical Classification Criteria for Hand, Knee and Hip OA

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint pain, aching or stiffness, and three of:</td>
<td>Joint pain, and three of:</td>
<td>Joint pain, and:</td>
<td></td>
</tr>
<tr>
<td>Enlargement ≥2 of 10 joints *</td>
<td>Aged 50+</td>
<td>≤15° internal rotation</td>
<td></td>
</tr>
<tr>
<td>Tissue enlargement in ≥2 distal interphalangeal joints</td>
<td>&lt;30 minutes of stiffness</td>
<td>≤115° flexion</td>
<td></td>
</tr>
<tr>
<td>Swelling in ≤2 metacarpophalangeal joints</td>
<td>Presence of crepitus</td>
<td>Or:</td>
<td></td>
</tr>
<tr>
<td>Deformity in ≥1 of the ten joints</td>
<td>Joint line tenderness</td>
<td>≥15° internal rotation</td>
<td></td>
</tr>
<tr>
<td>Deformity in ≥1 of the ten joints</td>
<td>Bony enlargement</td>
<td>Pain on internal rotation</td>
<td></td>
</tr>
<tr>
<td>Deformity in ≥1 of the ten joints</td>
<td>No palpable warmth</td>
<td>&lt;60 minutes of morning stiffness</td>
<td></td>
</tr>
</tbody>
</table>

*Sensitivity: 94%  Specificity: 87%  Sensitivity: 88%  Specificity: 89%  Sensitivity: 86%  Specificity: 75%

* The ten joints identified by the ACR clinical criteria as being of particular importance are second and third distal and proximal interphalangeal and first carpometacarpal joints of each hand.

The joints of both hands (30 in total) were assessed for deformation, swelling, and bony enlargement. Subjects were asked to indicate if any of the joints felt tender or painful upon palpation. The knee examination included using the dorsum of the hand to detect altered temperature around the knee and fingertip palpation along the joint line to assess for bony tenderness and enlargement. Subjects were then asked to bend their knee twice whilst the assessor determined the presence of crepitus. An assessment for effusion was also performed using the stroke test (Sturgill et al. 2009). Assessment of the hips included a goniometer to measure the angle of maximum internal rotation and flexion of the hips. Subjects were asked to report if either movement felt painful. Based on these assessments, subjects were classified as having OA in the hands, knees and hips.

4.2.4.4. Quantitative Sensory Testing

Tender Point Count

An 18 point tender point count was performed following the ACR protocol for classifying Fibromyalgia (Wolfe et al. 1990). Subjects were asked to rate whether they felt “pressure”, “discomfort”, or “pain” when pressure was applied to the 9 sites on the right and left sides of the body (18 in total) using the locations described by Okifuji et al. (1997) (depicted in Figure 4.5).
Pressure was applied by the assessor using their thumb at a rate of 1 kg per second up to 4 kg unless the subject indicated discomfort or pain (Wolfe et al. 1990). In order to determine the correct pressure was being applied during the tender point examination, the assessor practiced applying pressure with their thumb to an algometer. The number of painful sites was calculated by counting the number of “pain” responses for the 18 sites (Wolfe et al. 1990). The tender point count was included as a measure of widespread sensitivity to determine whether increased sensitivity to sensory stimuli was localised to the knee or if there was an indication of more generalised changes in pain sensitivity.

Figure 4.5  Location of Tender Points (Chakrabarty et al. 2007)

QST Protocol

The QST assessments performed in this study followed the published protocol by the German Research Network on Neuropathic Pain (Rolke et al. 2006a). Although order effects could influence the results of QST assessments, the order of the Rolke et al. (2006a) protocol was used (see Section 2.3.2). Each subject was asked to indicate which of their knees was the most painful and QST was performed at the tibial tuberosity of that knee. The opposite forearm was used as a distant pain-free control site, unless the subject identified their forearm as being painful. Assessments at the forearm were performed two centimetres distal to the lateral epicondyle of the
humerus. Intervals between assessments were observed to minimise sensitisation of the test site. The test sites and equipment used during the assessments are shown in Figure 4.6. The standardised verbal instructions given to participants for each QST measure can be found in Figure II-5, Appendix II. Thermal pain, mechanical pain, stimulus response function, wind-up ratio, vibration detection and pressure pain thresholds were performed bilaterally and in the order above. DNIC was performed following the assessment of wind-up ratio and prior to the assessment of vibration detection threshold at the forearm only. Each assessment and how to determine its overall score is described in detail in the following section.

**Figure 4.6** Positioning of the equipment used at the knee and forearm

![Source original. This image depicts the test sites and equipment used during the assessments. A. Thermode (thermal pain). B. von Frey filament (mechanical detection). C. Punctate probe (mechanical pain). D. Brush, cotton bud and cotton wisp (stimulus response function). E. Tuning fork (vibration detection). F. Algometer (pressure pain).](Image)

**Thermal Pain Thresholds**

Cold and heat pain thresholds were assessed using the TSA 2001-II Thermode (MEDOC, Israel). The thermode was set to a baseline temperature of 32°C, unless a subject indicated this temperature to be uncomfortable; the baseline temperature could be adjusted to suit the subject. The thermode was positioned at the tibial tuberosity of the most painful knee and on the opposite forearm two centimetres distal to the lateral epicondyle of the humerus (shown in image A of Figure 4.6) prior to the cold pain threshold test. The thermode cooled at a rate of 1°C per second from the baseline temperature to the safety cut off point at 0°C, or to the temperature indicated as first painful by the subject pressing a button. The thermode returned to the baseline temperature between tests and the test was repeated twice more, with a minimum of a 5 second interval between each test.

The heat pain threshold was determined in the same manner, with the thermode increasing in temperature at the same rate until 50°C was reached, or the subject pressed the button. This test was also repeated until three measures were obtained. To determine the pain thresholds, the mean temperature was calculated from the three assessments. Diminished sensitivity to thermal stimuli was determined by mean values approaching the limits of the thermode set at 0°C for cold pain or 50°C for heat pain; mean values close to the baseline temperature of 32°C indicate increased sensitivity to thermal stimuli.
**Mechanical Pain Threshold**

Mechanical pain threshold was determined using 7 weighted punctate probes (8 – 512 milli-Newton (mN); MRC Systems GmBH, Germany) applied perpendicularly to the test areas at the knee and forearm (see image C of Figure 4.6) in ascending order. Mechanical pain was determined as the point at which a blunted pin is perceived to be sharp. Subjects were asked to rate if the probe felt “blunt” or “sharp”; once a “sharp” response was recorded, the probes were applied in descending order until the next “blunt” response. A minimum interval of 10 seconds was observed between each probe application. A non-response was recorded if a probe was not described as “sharp” or “blunt” by the subject. The test ended when five of each response was recorded, unless the subject requested the test end sooner. The mechanical pain threshold was calculated by taking the geometric mean of all 10 responses (five blunt, five sharp) with lower mean values indicating increased sensitivity.

**Stimulus Response Function**

The 7 punctate probes used for the mechanical pain and three additional innocuous probes (a paint brush and two different sized cotton buds) were applied in a randomised order to the knee and the forearm (see image D of Figure 4.6; MRC Systems GmBH, Germany). Each probe was applied a total of 5 times. Subjects were asked to rate how painful each probe felt using the same 0 – 100 pain scale as above. A minimum interval of 10 seconds was observed between each probe application. A non-response was recorded if a probe was not rated by the subject. The test ended once 50 responses were recorded, or if the subject requested the test end sooner. The 35 pain scores for the punctate probes and the 15 responses for the innocuous probes were averaged separately to provide a score for mechanical pain sensitivity (punctate probes) and dynamic mechanical allodynia (innocuous probes; referred to allodynia from here) respectively. Higher scores for mechanical pain sensitivity and allodynia both indicated increased sensitivity to stimuli.

**Wind-up Ratio**

Wind-up ratio used the 256 mN punctate probe. Subjects were asked to rate a single application of the probe using a scale of 0 (no pain) up to 100 (worst pain imaginable). After a minimum interval of ten seconds, the same probe was applied ten times at a rate of one per second. The subject was asked to rate how painful the series of applications felt using the 0-100 scale used for the single probe application. The test ended when the ratings for five single and five series of applications of the probe were obtained unless the subject requested the test end sooner. The mean pain scores for the series were divided by the mean pain scores from the single applications of the probe to provide the wind-up ratio. Ratios close to one indicate decreased sensitivity, with larger ratios indicating increased sensitivity to wind-up. It is possible to incur missing data as ratios could not be calculated if subjects rated all probe applications as 0 (no pain). In order to address this issue, the scores were increased by one (range 1-101) to minimise missing data from 0 scores.
Assessment of DNIC involved the use of a conditioning stimulus and a phasic test stimulus applied to contralateral test sites. There is currently no gold standard or widely accepted protocol for assessing DNIC. The protocol used in this study was developed for use in the EPIFUND study by the study team. Based on two previous studies, a mechanical stimulus was used as the test stimulus (Pud et al. 2005) and thermal pain as the conditioning stimulus (Lautenbacher et al. 1997). For this study, the highest value recorded for the heat pain threshold at the forearm, or a maximum temperature of 45.5°C, was used as the conditioning stimulus. A single application of the 256 mN probe followed by a series of ten applications at a rate of one per second after a ten second interval were used as the test stimuli.

For the first test, the thermode was placed at the forearm at the baseline temperature of 32°C for 30 seconds. A single application of the probe was made at the knee ten seconds in to the thirty second conditioning stimulus duration. A series of probe applications were made at the knee during the final ten seconds of the thirty second conditioning stimulus duration. Subjects were asked to rate the single and series of applications at the end of each application using a scale of 0 (no pain) up to 100 (worst pain imaginable). For the second test, the thermode started at the baseline temperature and increased at a rate of 1°C per second to the highest value recorded for the heat pain threshold at the forearm, or 45.5°C. The temperature was maintained at this level for a maximum of 30 seconds. Ten seconds in to the thirty second conditioning stimulus duration, a single and series of probe applications were made at the knee and subjects were asked to rate the single and series of applications using the same 0-100 pain scale described above.

The subject was instructed to press the button used in the thermal tests to end the test at any point. The ratios for DNIC were calculated in a similar manner to the wind-up ratio, including incrementing each score by one (range 1-101) to minimise missing data from 0 scores. The ratio was calculated by dividing the score for the single application by the score for the series of applications for the first test (no heat applied) and doing the same for the scores for the single application and series of applications from the second test (heat applied). The ratio from the first test was then divided by the ratio for the second test to give the score for DNIC. Ratios close to one indicated decreased sensitivity, with larger ratios indicating increased sensitivity to mechanical stimuli during the application of a heat stimulus.

Vibration Detection Threshold

Vibration detection was assessed using a Rydel Seiffer tuning fork (64 Hertz; US Neurologicals, USA). The tuning fork was placed vibrating over the patella of the tested knee and contralateral elbow (see Image E of Figure 4.6). Subjects were asked to indicate if they could feel the vibrations. If they could feel vibrations, the subject was also asked to indicate when the vibrating stopped; a scale of 0 – 8 on the tuning fork was used to score when the subject could no longer feel the vibrations (see image E in Figure 4.6). If a subject could not feel vibrations a score of 0 was recorded. A minimum interval of 10 seconds elapsed between each vibration assessment and the test was repeated twice more unless the subject requested the test end sooner. The mean for the
three tests provides the detection threshold, with lower mean scores indicating a lack of sensitivity to vibration.

**Pressure Pain Thresholds**

Pressure pain thresholds were assessed using an algometer (0 – 10 kg; Pain Diagnostics and Thermography, USA). The algometer was positioned perpendicular to the test sites (see image F of Figure 4.6) and pressure applied at a rate of 1 kg per second up to 10 kg, or when a subject first indicated feeling pain. A minimum interval of one minute was observed between each pressure test. The test was repeated twice more unless the subject requested the test end sooner. The pain threshold was calculated by taking the mean of the three readings with higher mean pressure ratings related to diminished sensitivity. Table 4.4 summarises the range for each QST measure and the interpretation of mean values for this study in terms of a gain or loss of somatosensory function.

<table>
<thead>
<tr>
<th>QST Assessment (Range)</th>
<th>Sensitivity</th>
<th>Change Scores *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tender point count (0 to 18)</td>
<td>Higher count</td>
<td>Lower count</td>
</tr>
<tr>
<td>Cold pain threshold (32°C to 0°C)</td>
<td>Closer to 32°C</td>
<td>Closer to 0°C</td>
</tr>
<tr>
<td>Heat pain threshold (32°C to 50°C)</td>
<td>Closer to 32°C</td>
<td>Closer to 50°C</td>
</tr>
<tr>
<td>Mechanical detection threshold † (0.25mN to 512mN)</td>
<td>Closer to 0.25mN</td>
<td>Closer to 512mN</td>
</tr>
<tr>
<td>Mechanical pain threshold (8mN to 512mN)</td>
<td>Closer to 8mN</td>
<td>Closer to 512mN</td>
</tr>
<tr>
<td>Mechanical pain sensitivity (0 no pain to 100 worst pain)</td>
<td>Closer to 100</td>
<td>Closer to 0</td>
</tr>
<tr>
<td>Allodynia (0 no pain to 100 worst pain)</td>
<td>Closer to 100</td>
<td>Closer to 0</td>
</tr>
<tr>
<td>Wind-up ratio (ratio &gt;1)</td>
<td>&gt;1</td>
<td>1</td>
</tr>
<tr>
<td>DNIC (ratio &gt;1)</td>
<td>&gt;1</td>
<td>1</td>
</tr>
<tr>
<td>Vibration detection threshold (0 to 8)</td>
<td>Closer to 8</td>
<td>Closer to 0</td>
</tr>
<tr>
<td>Pressure pain threshold (0 to 10 kg/cm²)</td>
<td>Closer to 0</td>
<td>Closer to 10</td>
</tr>
</tbody>
</table>

* Used in Knee Osteoarthritis Pain Sensitivity Study (KOPS) only (see Section 4.3.8); sign of the score indicates higher sensitivity at one of the visits.
--- denotes QST assessments not performed in the KOPS study (see Section 4.3.4.3).
† Mechanical detection threshold not performed in KEEP study (see Section 4.2.4.4).
4.2.4.5. Training

I received training in how to perform a tender point examination and all QST assessments from members of the EPIFUND study team (Rosie Duncan, Dr. Matthew Mulvey, and Dr. Deborah Brown). Further details of the training I received are described in Section 5.4.1. For the joint assessments, I was able to attend clinics at Salford Royal NHS Foundation Trust and assess the joints of patients under the supervision of Professor Terence O’Neill. Inter-rater reliability assessments were performed on a convenience sample of 9 pain-free men and women to determine reliability in performing QST assessments between Deborah Brown and the author. The results are described in Section 5.6.

4.2.5. Ethics

The study was submitted to the National Research Ethics Service Committee North West – Cheshire (12/NW/0556) in order to contact the cohort. The study received approval in September 2012 and ran from 8th October 2012 to 22nd March 2013.

4.2.6. Sample Size Determination

The sample size of this study was determined so that an association between tender point count and global pain intensity would have 80% power to detect as statistically significant at the 5% level, given the same size relationship found in the main EPIFUND study. These variables were selected as tender point counts are a measure of generalised distress that correlate well with higher levels of pain intensity (Gupta et al. 2007).

As the outcome measures for this study are continuous and analyses are within-person, the appropriate way to detect an association would be to use linear regression, so the sample size for this study was determined based on this analysis. The appropriate sample size can be determined from the regression coefficient and standard deviations for the variables of interest (Dupont et al. 1998). The β-coefficient for pain intensity regressed against tender point count for members of the EPIFUND cohort who took part in the sub-study assessments is 0.16. The standard deviation for tender point count is 4.5 (0-18 scale) and 2.25 for overall pain intensity (0-10 scale). Entering these values into G*Power 3.1.2 software (Universität Kiel, Germany; see Figure 4.7) provides a sample size of 71 subjects to give 80% power to detect the association as significant at the 5% level.
4.2.7. **Data Management**

All data were entered into a Microsoft Access 2007 database constructed by the database manager for the EPIFUND study. The data entered were limited to the possible range for each variable to minimise erroneous scoring, with any missing observations coded as 9, 99, or 999 depending on the upper limit for the variable. The data were exported into Stata 11.2 software (Stata, USA) for analysis. A data cleaning process was implemented prior to any analyses; this involved identifying all missing data and recoding it appropriately. Missing data are coded as "." in Stata, with ".a" to ".z" as options to categorise missing data. Missing data for this study were categorised as:

- "." for non-response to questionnaire items (not missing at random)
- ".a" if a subject answered "no" to a filter question with subsequent questions not completed (not missing at random)
- ".b" if a subject did not respond to or withdrew from an assessment (not missing at random)

These missing values are classified as not missing at random as there are specific reasons for the data being missing. Items coded as 9, 99 or 999 were recoded to one of the above where
appropriate. Variables were then summarised to ensure the observations fell within the designated ranges and that all data coded 9, 99 or 999 were recoded.

4.2.8. Analysis

Descriptive statistics were used to summarise variables with the median and inter-quartile range (IQR) for non-normal continuous variables and percentages for categorical variables. Spearman’s correlations were used to determine associations between pain intensity (global or at the tested knee) and QST, and for QST measures with psychosocial factors. Linear regression was used to determine whether pain intensity (dependent variable) was significantly predicted by QST measures or psychosocial factors (independent variables). The Kruskal-Wallis test was used to determine whether the independent variables or dependent variables differed across four age bands (40-49, 50-59, 60-69 and 70+). Wilcoxon rank sum was used to detect whether the independent and dependent variables differed by sex. Whether age and sex can explain variations in the association between pain intensity and the dependent variables was determined by adjusting for these variables in linear regressions. Associations between the independent variables (QST and psychosocial factors) were also explored using correlation coefficients. QST measures which were correlated with pain intensity, and psychosocial factors that were correlated with QST measures, were explored using mediation analysis. Mediation analysis was used to determine whether associations between pain intensity and QST measures were explained to some extent by psychosocial factors. Further details of analyses are presented in Chapter 6. All analyses were performed using Stata 12.0 software (Stata, USA).

4.3. Knee Osteoarthritis Pain Sensitivity Study

4.3.1. Study Design

The Knee Osteoarthritis Pain Sensitivity (KOPS) study is a sub-study nested within an uncontrolled open label intra-articular steroid injection trial.

4.3.2. Subjects

4.3.2.1. Targeting Synovitis in Knee Osteoarthritis Study

The Targeting Synovitis in Knee Osteoarthritis (TASK) study is an uncontrolled open label trial in subjects with symptomatic knee OA investigating structural changes and pain in the knee following a steroid injection. Two hundred subjects with symptomatic knee OA completed the study. Subjects for the TASK study were recruited from a number of sources, including mailings from general practitioners within Greater Manchester to subjects with knee pain, referrals from community care teams and physiotherapists, posters placed in hospital rheumatology and orthopaedic clinics, and
Each subject recruited into the TASK study attended a minimum of three visits; screening, baseline and post-injection. Subjects were screened for eligibility with those eligible (see 4.3.2.1) and who consented to take part attending a baseline visit to receive an intra-articular injection of 80 mg DepoMedrone. Those who responded to the treatment at follow up after 1-2 weeks (defined using the OARSI responder criteria; see section 4.3.4.1) were followed by regular telephone calls (2-4 weekly) and asked to attend a final visit when their pain score returned to within 20% of their baseline score, or if the pain did not recur to return for a final visit at 6 months post-injection. Those who did not respond following the injection were not subsequently followed up. The study design and assessments performed at each visit are shown in Figure 4.8. Subjects completed a number of questionnaires at each visit. The HAD scale and IPQ-Brief (see Section 4.2.4.1) were administered at the screening visit. The Knee Osteoarthritis Outcome and Injury score (KOOS) was administered at each of the visits (see Figure III-1, Appendix III), as well as VAS for pain, activity and wellness. A VAS for global change in pain was administered at each of the follow-up assessments.

Figure 4.8 TASK Study Design

This image depicts the study visits and assessments performed for the TASK study. Items prefaced by “sub-study” refer to the Knee Osteoarthritis Pain Sensitivity study. eGFR = estimated glomerular filtration rate; MRI = magnetic resonance imaging.

4.3.2.2. Inclusion and Exclusion Criteria

Men or women aged 40 years or older with at least grade II radiographic or grade II arthroscopic signs of OA, or significant signs of OA on MRI, were eligible for the TASK study. Subjects were also included if they reported moderate knee pain lasting for 48 hours within the past fortnight and scored 7 or more on the KOOS pain scale (see Section 4.3.4.1). Other exclusion criteria included the presence of secondary or inflammatory arthritis, pregnancy, systemic infections, metal implants that are contraindicated for MRI scans, a steroid injection within the past 3 months or knee surgery within the past 6 months, systemic infection, and hypersensitivity to the study drug. Any subjects who were unable to attend all study visits within the between-visit windows or did not fully understand the requirements of the study were not eligible.
4.3.3. **KOPS Recruitment**

All subjects who attended a screening appointment for the TASK study between 8\textsuperscript{th} November 2011 and 7\textsuperscript{th} May 2013 were invited to participate in KOPS. A verbal description of the KOPS study and a copy of the information sheet (see Figure III-2, Appendix III) were given to all subjects during the screening visit. Subjects attending a baseline visit for TASK who were interested in taking part in KOPS were given a detailed description of all assessments and duration and encouraged to ask any questions prior to consenting to participate. The consent form is shown in Figure III-3, Appendix III.

4.3.4. **Study Assessments**

Assessments were performed at Salford Royal NHS Foundation Trust. Assessments lasted for a maximum of 45 minutes at the baseline and follow-up study visits.

4.3.4.1. **Study Questionnaires**

The HAD and IPQ-Brief (see Section 4.2.4.1) were completed at the screening visit for the main study and were collected at the follow-up visit for this study (see Figure 4.8). The Knee Osteoarthritis Outcome and Injury Score (KOOS) was completed at all study visits (see Figure 4.8) and was used to determine changes in pain between the baseline and post-injection visits in this study.

*Current Pain*

The KOOS was developed as a measure of symptoms and function following intervention for knee problems (Roos et al. 1998). There are 5 subscales (42 items in total each scored 0-4) comprising pain (9 items), symptoms (7 items), daily activities (17 items), sport and recreation (5 items), and quality of life (4 items) (Roos et al. 1998). Once a total score for each subscale was obtained, values were standardised to a 0 to 100 scale (see Equation 4.1) where 0 represents the poorest outcome and 100 represents no knee related issues. This study used the pain subscale only to determine whether knee-specific changes were observed following treatment with an intra-articular steroid injection; a recent review demonstrated the KOOS to be effective in detecting changes in pain, symptoms and/or physical functioning following total knee replacement surgery, physical therapy or intra-articular hyaluronic acid injections despite the short recall period of one week for each item (Collins et al. 2011).
Equation 4.1  Standardised score for KOOS subscales (Roos et al. 1998)

\[
100 - \frac{(Patient \ Score \times \ 100)}{Maximum \ subscale \ score}
\]

4.3.4.2.  Responder Criteria

Clinical responder criteria for clinical trials involving subjects with OA were proposed by the OMERACT-OARSI initiative (Pham et al. 2003). The criteria define responders in two ways; an improvement in pain or function of >50% or a change in score of ≥20 using an instrument using a 0-100 scale (such as the KOOS pain scale), or ≥20% improvement and ≥10 change in score in at least two of pain, function, or global assessment (Pham et al. 2003). Responders and non-responders in this study were defined using these criteria.

4.3.4.3.  Quantitative Sensory Testing

Mechanical detection and pain, stimulus response function, wind-up ratio, vibration detection, and pressure pain assessments were made at the tibial tuberosity on both knees (see Section 4.2.4.4 and the following section for mechanical detection threshold). Mechanical detection threshold was included in this study as thermal thresholds were not assessed. A tender point count was also performed as a measure of widespread sensitivity (see Section 4.2.4.4). Assessments were made at baseline prior to the injection and at the follow-up visit 5-15 days later.

Mechanical Detection Threshold

Mechanical detection threshold was determined using 12 von Frey filaments (0.25-512 mN; MARSTOCKnervtest, Germany) applied to the tibial tuberosity of both knees in descending order starting with the 16 mN filament (see image B of Figure 4.6 for probe application). Mechanical detection was determined as the point at which fine hairs (von Frey filaments) can no longer be felt. Subjects were asked to indicate if they could feel the filament by saying “yes”; once a non-response was recorded (the subject did not acknowledge feeling a filament after one was applied), the filaments were applied in ascending order until the next “yes” response. The test ended when a total of 5 ascending and 5 descending series were recorded, unless the subject requested the test end sooner. The mechanical detection threshold was calculated by taking the geometric mean for all 10 responses (five felt, five not felt) with lighter weights indicating increased sensitivity to light touch.
4.3.5. Ethics

The TASK study was submitted to the Leicestershire, Northamptonshire and Rutland Research Ethics Committee (09/H0402/107) and received approval in January 2010. The study is included in the European Union Drug Regulating Authorities Clinical Trials database (2009-015849-22) and the International Standard Randomised Controlled Trial Number register (07329370). A substantial amendment was submitted to the same Research Ethics Committee to include the KOPS sub-study. The substantial amendment was approved in November 2011, with the first sub-study subject assessed in February 2012 and the last in June 2013. Subjects in the TASK study between November 2011 and February 2012 were not eligible for the KOPS study as their screening visits and consent forms were completed prior to approval for the substantial amendment which included a version change to the consent form and information sheet for TASK.

4.3.6. Sample Size Determination

There are no existing data for the use of QST with knee OA subjects receiving an intra-articular steroid injection on which to base a sample size calculation for this study. A meta-analysis investigating differences in pain tolerance and pain thresholds between the sexes demonstrated small effect sizes of 0.57 and 0.55 respectively (Riley III et al. 1998); the authors suggested that 41 subjects of each sex provides sufficient power (0.70) to detect a difference in pain thresholds with an effect size of 0.55. As the present study is designed to assess the feasibility of QST measures in subjects with symptomatic knee OA, a target of 50 fully evaluable subjects from the TASK study was considered appropriate.

4.3.7. Data Management

Demographic data obtained during the recruitment process and data from screening visits were entered into a Microsoft Access 2007 database by members of the TASK study team. The study database was constructed by the database manager for the TASK study in the same manner as described in Section 4.2.7, using the same data cleaning technique and coding of missing data.

4.3.8. Analysis

Subject characteristics, change in KOOS pain score, time between study visits, number of right or left knees injected, and pain present in the control knee are presented in Chapter 7. Significant differences between variables were assessed using independent T-tests (continuous variables) or Chi-squared tests (categorical data). Changes in QST measures between baseline and follow-up were assessed using Wilcoxon rank sum and independent T-tests. Associations between baseline QST and change in QST with change in KOOS pain score were assessed using linear modelling. Associations between the HAD subscales or IPQ-Brief items at screening with change in QST and
change in pain were also assessed with linear modelling. Table 4.5 presents the interpretation of direction of change for the questionnaire change scores (KOOS pain scale, HAD and IPQ-Brief). All analyses were performed using Stata 11.2 software (Stata, USA).

<table>
<thead>
<tr>
<th>Questionnaire (Range)</th>
<th>Change scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>KOOS pain score (0-100 worst to best)</td>
<td>Positive Negative</td>
</tr>
<tr>
<td>HAD subscales (0-21 best to worst)</td>
<td>Negative Positive</td>
</tr>
<tr>
<td>IPQ-Brief subscales (0-10 best to worst)</td>
<td>Negative Positive</td>
</tr>
</tbody>
</table>

KOOS = Knee Osteoarthritis Outcome and Injury Score; HAD = Hospital Anxiety and Depression Scale; IPQ-Brief = Brief Illness Perception Questionnaire Brief.

4.4. Summary of Results Chapters

Prior to undertaking fieldwork for the study, reliability of the QST assessments was assessed in a sample of healthy volunteers. The description of the study undertaken, results and analysis of this study are presented in Chapter 5. Chapter 6 summarises the main results from the KEEPS study and Chapter 7 the main results from the KOPS study. Chapter 8 summarises the main findings of the studies and discusses how they compare with previous literature and their clinical and research implications. Suggestions for future studies are discussed.
CHAPTER 5. RELIABILITY OF QST ASSESSMENTS

5.1. Outline

This chapter outlines the evaluation of intra- and inter-rater reliability of the battery of QST assessments used in this thesis. This study was performed to determine the reliability of one rater (the author) in performing QST assessments. A convenience sample of 9 men and women participated in three testing sessions. During these sessions a battery of QST assessments were administered to all subjects. Two sessions were conducted on the same day by different raters (A and B) to address inter-rater reliability, with a third session performed one week later by rater A to determine intra-rater reliability. Analysis suggested that QST assessments performed by rater A were consistent over time, and that QST assessments performed by raters A and B on the same day were also reliable.

5.2. Introduction

Reliability of clinical testing is important within research as it provides information about how a measure varies when assessed by the same or different individuals and at different time points. Inter-rater reliability is a measure of reliability between raters, while intra-rater reliability is a measure of a single rater's reliability over repeated measurements. Establishing the reliability of QST measures and raters is important in interpreting results of studies which report them.

5.3. Aims

The aims of this study were to determine (i) the inter-rater reliability, and (ii) the intra-rater reliability of the battery of QST assessments which were used in the two studies outlined in the thesis.

5.4. Methods

5.4.1. Training

As part of her training, the author observed QST tests on subjects taking part in a separate study and also performed tests in these subjects under supervision. The assessments included QST assessments at the hand and foot. Pressure pain thresholds were not assessed in the test subjects and additional training provided for this assessment. Three of the KEEPS study visits were observed by James Anderson (member of the EPIFUND study team) to ensure protocol adherence (See Figure IV, Appendix IV).
5.4.2. **Subjects**

A convenience sample of 9 pain-free subjects consisting of members of the EPIFUND and TASK study teams and PhD students from the Institute of Inflammation and Repair at the University of Manchester were recruited.

5.4.3. **Inter-rater Reliability**

All subjects were assessed on two occasions on the same day; rater A (the author) assessed the subjects in the morning (session 1), with rater B (Deborah Brown) assessing the subjects in the afternoon of the same day (session 2). Rater B received the same training as the author. A minimum break of one hour was observed between assessments to minimise sensitisation of the test sites and to reduce subject recall between the sessions (an effect of repeat testing). A tender point count was performed first, followed by thermal and mechanical pain thresholds, wind-up ratio, vibration detection and pressure pain thresholds (see Section 4.2.4.4). The testing sessions lasted 15 minutes for each subject. As all subjects were pain free, they were randomised as to which knee would be tested. A random number generator (www.random.org/; Figure IV, Appendix IV) was used to select a seed number between 1 and 10,000. The seed number was then entered into a randomisation website (http://www.randomization.com; Figure IV, Appendix IV).

5.4.4. **Intra-rater Reliability**

All subjects were asked to attend a second assessment session one week later at which time rater A performed all assessments. The QST battery and order of tests described in the previous section was used in the repeat sessions. One subject was unable to attend the last session, with a total of 8 participants then who contributed data to the analysis.

5.5. **Analysis**

Intraclass correlation coefficients (ICCs) were selected as the method of analysis as each QST variable is continuous; information on how to score each QST measure can be found in Section 4.2.4.4. ICCs are a measure of agreement and do not require observations to be ordered, as would be the case for Pearson’s product moment correlation coefficient; however, ICCs are dependent on the scale of the measures used and the impact of the size of errors are not assessed (Bland et al. 1990). Alternative measures of agreement include the Pearson’s product moment correlation coefficient and Cohen’s kappa coefficient. These measures were not appropriate for determining agreement in this study as Pearson’s product moment correlation coefficient assumes data were normally distributed and Cohen’s kappa coefficient is used to calculate reliability between categorical data (Bland et al. 1990). Session 1 was compared with session 2 (inter-rater reliability).
and with session 3 (intra-rater reliability) so ICCs for reliability could be calculated. ICCs provide values between 0 (perfect disagreement) and 1 (perfect agreement) (Munro 2005). Due to the limited sample size used in the present study and the skewed distribution of mechanical pain thresholds (7 probes doubling in weight from 8 to 512 mN) and wind-up ratio (maximum range 1-101), the results for these variables are presented after logarithmic transformation. Coefficients of 0.00-0.24, 0.25-0.49, 0.50-0.69, 0.70-0.89 and 0.90-1.00 were interpreted as indicating none or little, low, moderate, high and very high ICCs respectively. Analyses were performed using Stata 11.2 software (Stata, USA).

5.6. Results

5.6.1. Subject Characteristics

Five men and four women (median age 25, range 22-45) without musculoskeletal pain completed the first two testing sessions. One subject (male, aged 25) was unable to attend the third session.

5.6.2. QST Measures

The median and IQR for each QST measure for the three testing sessions are presented in Table 5.1. The median score for tender point count was higher in session 2 (4) conducted by rater B than in either session conducted by rater A (0 for both sessions 1 and 3; Wilcoxon signed rank test p=0.0561 and p=0.2467, respectively). While the median values for cold pain thresholds were 0 for all three sessions, the IQRs were wider for sessions 1 and 3 (0-1.8 and 0-2.7, respectively) performed by rater A than for rater B in session 2 (0-0.2; Table 5.1).

<table>
<thead>
<tr>
<th>Table 5.1</th>
<th>QST measures; median and interquartile range for sessions 1 to 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable (Range)</td>
<td>Session 1 Rater A (n=9)</td>
</tr>
<tr>
<td>Tender point count (0-18)</td>
<td>0 (0-0)</td>
</tr>
<tr>
<td>Cold pain (0-32.0°C)</td>
<td>0 (0-1.8)</td>
</tr>
<tr>
<td>Heat pain (32.0-50°C)</td>
<td>47.3 (45.1-49.0)</td>
</tr>
<tr>
<td>Mechanical pain (0.0-2.71) †</td>
<td>2.2 (1.5-2.3)</td>
</tr>
<tr>
<td>Wind-up ratio (0.0-2.0) †</td>
<td>0.3 (0.2-0.4)</td>
</tr>
<tr>
<td>Vibration Detection (0-8)</td>
<td>5.3 (4.7-6.0)</td>
</tr>
<tr>
<td>Pressure pain (0.0-10.0 kg/cm²)</td>
<td>8.0 (6.8-8.8)</td>
</tr>
</tbody>
</table>

† Logarithmic transformations.
5.6.3. Intra-rater and Inter-rater Reliability

The ICCs for tender point count and cold pain threshold could not be determined as a large number of 0 scores were reported (17 for tender point and 18 for cold pain from 26 assessments). The results of the tender point count and cold pain thresholds are shown in Table 5.2. The median tender point count was highest for session 2, which was performed by rater B. As can be seen from Table 5.2, 5 subjects reported pain upon palpation at 4 or more sites during session 2, two of which fulfilled the tender point count criteria for Fibromyalgia (11 tender points) even though they reported no concomitant pain (Wolfe et al. 1990). The participants in this study with a cold pain threshold of 0°C reached the limit of the thermode and had not reported pain which provides an explanation for the high proportion of 0 scores reported for this measure (Table 5.2). Table 5.2 also shows that one subject reported elevated sensitivity to cold pain during sessions 1 and 2 (20.2°C and 24.4°C, respectively). However, this same subject (number 8) reported pain at a lower temperature during session 3. Although the results for this participant were unusual, there were no significant differences between sessions (inter-rater p=0.9581; intra-rater p=0.8113; sessions 2 and 3 p=0.6329). These individual observations explain some of the differences in median values and greater variation observed between the testing sessions for tender point count and cold pain thresholds.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Tender Point Counts</th>
<th>Session</th>
<th>Cold Pain Thresholds</th>
<th>Session</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>---</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>8</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>4</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>6</td>
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<tr>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>13</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>9</td>
<td>2</td>
<td>11</td>
<td>2</td>
<td>9</td>
</tr>
</tbody>
</table>

ICCs for wind-up, vibration detection threshold, and heat, mechanical, and pressure pain thresholds are shown in Table 5.3. With the exception of the low value observed for inter-rater vibration detection threshold (0.381), all ICCs were moderate to high. Moderate ICCs were observed for inter-rater and intra-rater measures of mechanical pain (0.599 and 0.637, respectively) and wind-up ratio (0.661 and 0.672, respectively). The intra-rater ICC for vibration
detection (0.690) was moderate with high ICCs observed for inter-rater and intra-rater measures of pressure pain (0.768 and 0.861, respectively) and heat pain (0.803 and 0.710, respectively).

### Table 5.3 Intraclass Correlation Coefficients for inter-rater and intra-rater reliability (ICC and 95% CI)

<table>
<thead>
<tr>
<th>Threshold</th>
<th>Inter-rater</th>
<th>95% CI</th>
<th>Intra-rater</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heat pain</td>
<td>0.803</td>
<td>0.56-1.04</td>
<td>0.710</td>
<td>0.36-1.06</td>
</tr>
<tr>
<td>Mechanical pain †</td>
<td>0.599</td>
<td>0.17-1.03</td>
<td>0.637</td>
<td>0.22-1.06</td>
</tr>
<tr>
<td>Wind-up †</td>
<td>0.661</td>
<td>0.28-1.04</td>
<td>0.672</td>
<td>0.29-1.05</td>
</tr>
<tr>
<td>Vibration detection</td>
<td>0.381</td>
<td>0.00-0.96</td>
<td>0.690</td>
<td>0.32-1.05</td>
</tr>
<tr>
<td>Pressure pain</td>
<td>0.768</td>
<td>0.49-1.04</td>
<td>0.861</td>
<td>0.68-1.04</td>
</tr>
</tbody>
</table>

† Logarithmic transformations. CI = confidence interval.

### 5.7. Discussion

The ICCs for the reliability of QST assessments in the present study demonstrate good inter- and intra-rater reliability for heat, mechanical and pressure pain thresholds, and wind-up ratio. Good intra-rater reliability was also observed for vibration detection threshold, but not for inter-rater reliability of this measure (ICC 0.381). Assessments of heat pain and pressure pain thresholds were the most reliable with intra-rater ICCs 0.710 and 0.861, and inter-rater ICCs 0.803 and 0.768, respectively.

### 5.7.1. Inter-rater Reliability

The findings of the present study suggest that QST measures performed by rater B were consistent with measures performed by rater A on the same day, with the exception of vibration detection threshold. The ICC for inter-rater vibration detection was low (0.381), though intra-rater reliability was good. This is likely due to the higher median score observed for rater B (7.0; IQR 6.0-7.0) than for either session conducted by rater A (session 1 5.3, IQR 4.7-6.0; session 3 5.0, IQR 4.0-5.8). It is possible in QST testing for differences to arise between raters for vibration detection because of the scale used to assess the threshold. It relies upon the crossing over of two triangles and reading the output at the moment the subject indicates the lack of sensation. There were two sets of triangles (filled and not filled) present on the tuning fork used to assess vibration detection. Differences between raters in the interpretation at which point the triangles were crossing, or which set of triangles were used for the reading, may have contributed to low intra-rater reliability. One way to address this issue in future studies would be to specify which set of triangles the assessors should use to make the reading and what to do in the likely event of a measurement occurring between two points on the scale. Both assessors, however, in the present study used the same filled set of triangles.
There are no previous studies investigating the inter-rater reliability of tender point counts in healthy controls. The median and IQR for tender point count in the present study was larger for rater B (4, IQR 0-11) than either session conducted by rater A (0, IQR 0-0 and 0, IQR 0-2; see Table 5.1), suggesting a difference in the pressure applied by the two assessors. A previous study of 15 subjects with fibromyalgia demonstrated good reliability for tender point counts assessed using an algometer (kappa 0.62; p<0.001) and by digital palpation (kappa 0.51; p<0.001) with a greater number of tender points identified using an algometer (Cott et al. 1992). Both raters in the present study used digital palpation and it is possible for the raters to be applying more or less pressure at a faster or slower rate than the other which could lead to differences in the reporting of tender points. One way to reduce this variability would be to use an algometer in future studies to minimise differences between raters.

There are also no previous studies investigating the inter-rater reliability of the other QST measures that were assessed in the present study (wind-up ratio, vibration detection or cold, heat, pressure and mechanical pain thresholds) in healthy controls or in subjects with knee OA. The DFNS, who published the protocol used in this study, have published results of inter- and intra-rater reliability testing for the test protocol at a painful site and at a control site in 60 subjects (37 males; 56.4±1.9 years) with sensory disturbances (Geber et al. 2011). The subjects were recruited from 4 centres (n=15 at each) and participated in 4 sessions performed by two different assessors over two days to determine reliability, one assessor performing both of the morning or both of the afternoon sessions, and two assessors performing sessions on the same day (Geber et al. 2011). Pearson’s product-moment correlation coefficients of 0.812, 0.871, 0.843, 0.795, 0.556, and 0.886 were observed for the inter-rater reliability of cold, heat, pressure and mechanical pain thresholds, wind-up ratio and vibration detection thresholds, respectively (Geber et al. 2011). Wind-up ratio was the least reliable measure though the authors did not take account of missing data (Geber et al. 2011). The same study also demonstrated significant correlations between testing in the morning compared with the afternoon (correlation coefficients of 0.558-0.868) (Geber et al. 2011) despite previous studies suggesting time of day may influence test results (Gruener et al. 1994).

5.7.2. Intra-rater Reliability

In the present study, reliability of QST measures performed by rater A was moderate or high (see Table 5.3). Although ICCs could not be determined, the scores for tender point count and cold pain threshold were similar suggesting that rater A performed these assessments reliably.

Two previous studies investigating the intra-rater reliability of QST measures at the knee in healthy volunteers support the findings presented in this chapter (Wessel 1995; Wylde et al. 2011). Wessel (1995) investigated pressure pain thresholds at the knee in 36 women (18 subjects with knee OA in at least one knee and 18 age-matched controls without knee OA). Pressure pain thresholds were performed at 6 test sites on both knees (medial and lateral aspects of the joint line, medial and lateral ligaments, and vastus medialis and vastus lateralis muscles) on three separate occasions with 5 to 10 days between each test session. Knee OA subjects had lower mean pressure pain thresholds at all sites on both knees compared with controls (Wessel 1995). Results indicated,
consistent with findings in this thesis, good reliability for pressure pain thresholds at the worst knee in the OA patients at all test sites (range 0.61-0.91) and all sites on both knees for the control group (range 0.71-0.90) (Wessel 1995). Wessel (1995) also demonstrated that despite the difference in pressure pain thresholds between the groups, reliability was similar for those with and without OA (Wessel 1995). However, the study assessed the reliability of pressure pain thresholds in women only with no data in men (Wessel 1995).

Wylde et al. (2011) assessed intra-rater reliability of QST assessments performed one week apart by a single rater at both knees and the right forearm of 50 subjects with symptomatic knee OA awaiting total knee replacement and 50 age- and sex-matched healthy controls. Consistent with the results reported in this chapter, high and very high ICCs were observed for pressure pain and heat pain thresholds at the forearm and right and left knees in the control group (ICCs of 0.91, 0.83 and 0.86 respectively for pressure pain and 0.77, 0.85 and 0.79, respectively for heat pain) (Wylde et al. 2011). High and very high ICCs were also observed for pressure pain and heat pain thresholds at the index and contralateral knees and at the forearm for knee OA subjects (ICCs of 0.86, 0.83 and 0.77, respectively for pressure pain and 0.86, 0.77 and 0.86, respectively for heat pain) (Wylde et al. 2011).

The ICCs for mechanical, warm and cool detection thresholds were, however, more variable than the pain thresholds in both knee OA and healthy subjects, and ranged between little and high reliability (ICCs between 0.20 and 0.79) (Wylde et al. 2011). Due to the psychophysical nature of QST assessments, one possibility for the wide range of ICCs observed for detection thresholds in knee OA and healthy subjects is that recognition of the first sensation (warming, cooling or light touch) could be influenced by fatigue or alterations in attention (Geber et al. 2011). There is some evidence to suggest that the method of limits (reaction time to a sensation, such as thermode heating or cooling) is demanding and can lead to fatigue over multiple trials, whereas the method of levels (sensation felt at a specific stimulus intensity, such as the individual filaments used for light touch) is susceptible to disturbances in attention due to longer administration times (Dyck et al. 1993). It is likely these factors contributed to some of the variation observed in detection thresholds in the study by Wylde et al. (2011).

Two other studies also reported the reliability of QST measures in subjects with knee OA. Tena et al. (2012) demonstrated low intra- and inter-rater reliability for manual von Frey filaments (Kappa coefficients 0.24 – 0.64) compared with automated filaments (Lin coefficients 0.63 - 0.91) for mechanical pain thresholds in 30 healthy controls and 28 knee OA patients who underwent total knee arthroplasty. This difference may have arisen as a result of technical artefact as the automated filament provided a pressure measurement between 0.1 and 1000 grams while the manual filaments are of fixed length with different diameters to produce pressures of 1, 4, 100 and 300 grams (Tena et al. 2012). As such, measurement using the manual filaments is less precise. However, these assessments were performed at two distant pain-free control sites (forearm and abdominal wall) with the reliability of manual and automated measures of mechanical pain thresholds at knee still unknown (Tena et al. 2012). Moss et al. (2007) demonstrated very high intra-rater reliability (ICC 0.98) for pressure pain thresholds at the index knee over 48 hours in 38 knee OA patients participating in a double blind randomised control trial which is consistent with the findings of the previous studies (Wessel 1995; Wylde et al. 2011).
Intra-rater reliability was also investigated at a painful site and at a control site in 60 subjects with sensory disturbances using the DFNS protocol (results of inter-rater reliability described in Section 5.7.1) (Geber et al. 2011). Pearson’s product-moment correlation coefficients of 0.855, 0.881, 0.881, 0.802, 0.671 and 0.932 were observed for the intra-rater reliability of cold, heat, pressure and mechanical pain thresholds, wind-up ratio and vibration detection thresholds, respectively (Geber et al. 2011).

The findings of the above studies suggest that heat and pressure pain thresholds were reliable in both healthy controls and subjects with knee OA despite significant differences between the thresholds for each group. These measures were also more reliable than detection thresholds which may be influenced by external factors, such as alterations in attention or fatigue during testing. The role of these factors in QST reliability in subjects with musculoskeletal pain remains unknown.

5.7.3. Strengths and Limitations

The study samples (Chapter 6 and Chapter 7) reported in this thesis were older than the subjects in whom reliability was tested. Also, unlike the study samples they had no knee pain, potentially limiting the application of the findings reported in this chapter to this group. Geber et al. (2011) demonstrated significantly higher reliability at test sites where subjects were experiencing pain than at pain-free control sites using the same test protocol for both inter-rater (mean correlations of 0.83 and 0.71 for the painful and non-painful sites, respectively; p<0.01) and intra-rater reliability (0.86 and 0.79 at the painful and non-painful sites, respectively; p<0.001). Wylde et al. (2011) and Wessel et al. (1995) also demonstrated that the reliability of measures for both groups was good even though knee OA subjects were more sensitive to QST measures at all test sites than the control subjects. These findings suggest that in relation to the presence of knee pain that reliability is likely to be at least as good as reported in this chapter.

It is possible that the time between intra-rater assessments influenced the results. For example, the IQR for cold pain threshold was narrower for session 2 than for the other two sessions which may be due to carryover effects (described in the next paragraph). However, performing three reliability sessions in one day may increase subject recall of test procedures and introduce bias of repeat testing. As the same items of equipment were used in all three testing sessions, it is unlikely that differences in responses are attributable to the instruments used. Variations in observers may arise if the application of the instruments differs between the two raters, but the raters for the present study received the same training, followed the same procedures, and gave the same verbal instructions to subjects (script received in training) in order to minimise these effects.

It is possible that carryover effects (learning how to perform the tests in the first trial may impact performance in subsequent trials), due to the short time between sessions 1 and 2 and/or three administrations within a one-week timeframe, may account for some of the variations observed in the data. There are, however, currently no data investigating the role of carryover effects in QST reliability. Another possibility is observer effect where subjects, either consciously or unconsciously,
alter their responses upon repeat testing due to the fact they are participating in a trial rather than responding to actual change. One way to control for this in studies is to remove the researcher from the testing and provide a neutral environment for subjects so they become less aware of their participation in a study (Silman et al. 2002), though this was not possible in the present study.

Lastly, although the sample tested was small and the coefficients of association had wide CIs for each measure, having comparable coefficients for heat and pressure pain thresholds to two larger samples of healthy controls and subjects with knee OA also tested at the knee indicates low variability in these two measures. A larger sample of subjects with knee pain would provide better precision of the reliability of QST measures at the knee and should also include a pain-free distant control test site.

5.8. Conclusion

In this small study using pain-free volunteers, inter- and intra-rater reliability were good for a battery of QST measures including wind-up ratio, vibration detection, and heat, mechanical and pressure pain thresholds. Assessment of vibration detection, in contrast, showed poor inter-rater reliability. The lack of variability in cold pain threshold and tender point count in the sample used for reliability testing makes estimating reliability difficult.
CHAPTER 6. ARE PSYCHOSOCIAL FACTORS AND QST ASSOCIATED WITH SELF-REPORTED PAIN INTENSITY?

6.1. Outline

This chapter provides the characteristics for the 72 subjects recruited for the present study from the EPIFUND cohort. The subjects completed a questionnaire addressing psychosocial factors and underwent QST assessments at the most painful knee and opposite forearm, if pain-free. The aim of the present study was to determine whether QST measures and psychosocial factors were associated with both global pain intensity and pain intensity at the tested knee. Three variables (mechanical pain sensitivity at the knee and forearm, and allodynia at the knee) were identified as significant predictors of both global and knee pain intensity. Tender point count was also identified as a significant predictor of global pain intensity. Psychosocial factors significantly correlated with the QST predictors were modelled as mediating variables in structural equation models; loading the significant psychosocial factors on to a single latent mediator within the model explained a higher proportion of the total mediated effect than any single psychosocial factor modelled as a mediator. The results are presented and discussed below.

6.2. Introduction

To date, there have been no studies that have investigated psychosocial factors as mediators of the relationship between somatosensory functioning and self-reported pain intensity in a population-based sample with knee pain. There have been two population-based studies of somatosensory functioning in people with knee OA: one study demonstrated that increased sensitivity to pressure pain and mechanical temporal summation at the knee and wrist were significantly associated with the presence of frequent knee pain and higher levels of pain intensity (Neogi 2013). The second study demonstrated that subjects reporting a greater number of symptoms related to knee OA had comparable heat and cold pain thresholds with pain-free controls and knee OA subjects with a lower symptom count (King et al. 2013). However, those with a greater symptom count perceived higher pain intensities during somatosensory testing compared with the pain-free controls (King et al. 2013). These studies suggest that underlying pathology and a greater number of knee-related symptoms have little association with somatosensory functioning, but that pain severity is related to increased sensitivity to QST. However, these studies fail to address the impact of psychosocial factors on the association between somatosensory functioning with localised and global pain intensities. Psychosocial factors are important in the perception of pain as higher levels of depression (Axford et al. 2010), greater pain catastrophizing (Somers et al. 2009), and lower levels of physical functioning (Jinks et al. 2008) are associated with more severe pain in those with knee pain. The present study examined the impact of psychosocial factors as mediators of the relationship between QST measures and self-reported pain intensity.
6.3. Aims

This aims of the analyses presented in this chapter are to determine whether

(i) levels of pain intensity were associated with sensitivity to stimuli.

(ii) the association between levels of pain intensity and sensitivity to stimuli is moderated by age and sex.

(iii) the association between levels of pain intensity and sensitivity to stimuli is mediated by psychosocial factors.

6.4. Methods

Subjects in the EPIFUND cohort who were identified as having knee pain in the most recent follow-up survey, using the Manchester manikin coding schedule, were contacted and recruited for this cross-sectional sub-study. Self-reported pain intensities for both global pain and at the most painful knee were collected during the study visit. Subjects completed a survey that included items related to psychological distress (HAD), cognitions about pain (PCS and IPQ-Brief) and physical functioning (RAPA and HAQ-DI). An examination of a subject’s hands, knees and hips were performed to assess the presence of clinical OA in these joints using the ACR criteria (Altman et al. 1986; Altman et al. 1990; Altman et al. 1991). A tender point count was then performed followed by QST measures at the most painful knee and opposite forearm (if pain-free). Further details of the sub-study survey and assessments can be found in Section 4.2.4.

6.5. Statistical Analysis

The proportion of responders to the questionnaires mailed as part of the third follow-up of the EPIFUND cohort who reported knee pain using the Manchester manikin coding schedule are presented. Further details about the recruitment process for the present study can be found in Section 4.2.3. The median and IQR are presented for age, BMI, manikin pain count, QST measures, psychosocial factors and self-reported pain intensity (continuous variables), with proportions shown for sex, location of study visit, deprivation status by home address postcode and ACR clinical criteria (categorical variables).

Subjects were categorised according to the following age bands: 40-49 years, 50-59 years, 60-69 years, and 70 years and above. The median age band (60-69) was set as the reference category. The Kruskal-Wallis test is a non-parametric assessment of whether the distribution of a particular variable differs between two or more groups. In this instance, because the variables were not normally distributed, it was used to assess for any differences in QST measures, psychosocial factors and self-reported pain intensities across the four age bands. The Kruskal-Wallis test provides a p-value for the significance of the differences between the groups, but does not indicate
what the differences between the groups may be. The median values for variables that differed significantly across the age-bands are presented.

The most prevalent sex (female) was selected as the reference category in the analyses described here. The Wilcoxon Rank Sum test is non-parametric and assesses the ranks of observations for one variable when split according to two groups. A significant result indicates the sum of the ranks for one group is higher than for the other and hence the values of the variable tend to be higher for that group. The median values in men and women are presented for variables that differed significantly between the sexes.

Spearman's rho, a non-parametric test of correlation between variables, was used to determine the presence of significant associations between self-reported pain intensity (globally and at the knee tested) with (i) all QST measures, and (ii) psychosocial factors. All variables with p-values of less than 0.1, whether for global or knee pain intensity, were included as predictors in regression models. Linear regressions are used to determine if the outcome measure is linearly associated with the independent variable. The univariate linear regression model assumes that $y = \beta_0 + \beta_1 x + \epsilon$, where $x$ is the predictor variable, $y$ is the outcome variable, $\epsilon$ is a normally distributed error term with mean 0, $\beta_1$ is the expected change in the dependent variable ($y$) per unit change in the independent variable ($x$), and $\beta_0$ is the y-axis intercept value (the value $y$ takes when $x=0$). $\beta_1$ (referred to as $\beta$-coefficient from this point) and 95% CIs from regression analyses performed in this chapter are presented. The impact of age and sex on the associations between QST and pain intensity, and the associations between psychosocial factors and pain intensity, were investigated using multivariate linear regressions by adding sex or age categories (40-49 years, 50-59 years, 60-69 years, and 70 years and above) and terms for their interaction with the independent variable.

For the variables which were significantly correlated with the outcome but did not show a significant linear association in the regression model, polynomials were used to identify the best-fitting transformations of the predictor variables. Polynomials allow for a non-linear association between predictor and outcome variables by including terms for the square of the predictor variable, its cube, and so on (Schmidt et al. 2013). For this analysis the two best fitting fractional polynomial terms for each variable were used. A Wald test can assess the impact of multiple parameters added to a model and was used to determine the joint impact of the two fractional polynomial transformations on the association between the outcome and predictor variables. Linear predictions were performed following regression analyses to generate a new variable containing only the predicted values for each observed pain intensity score ($y$) based on the fractional polynomials generated for the independent variables. Predicted values for pain intensity were generated using the linear predictor of the regression equation ($y = \beta_0 + \beta_1 x$) by entering each value for the transformed predictor variable ($x$) in combination with the $\beta$-coefficient and intercept ($\beta_0$) generated by the regression. Scatter plots were used to illustrate the relationship between self-reported pain intensity and predictor variables where the association between the two variables was not linear (original data displayed as points) with a line fit for the values generated by linear prediction (line with 95% CI).

Stepwise modelling is an exploratory technique used to identify which predictor variables make independent statistically significant contributions to a model; in the present study, the predictor
variables were QST measures at the knee and forearm, and psychosocial factors. Although all predictor variables can be included in a stepwise model, only variables that reach a particular significance level were kept to reduce the risk of false positives. Forward and backward stepwise models can be used; the forward method allows each variable added to the regression to be assessed as a statistically significant predictor of the outcome measure. At each stage, the most significant predictor was added to the model, until no further predictors were significant at the 5% level. The backward technique includes all variables of interest in the first regression and then excludes variables that were not significant predictors (p>0.05) of the outcome measure from the model. Using the forwards or backwards method, variables were excluded if they were not statistically significant predictors. Interactions between the predictors (QST measures and psychosocial factors) and age-group and sex were also included in the stepwise models to determine whether the effect of the predictors varied with age and sex.

### 6.5.1. Assessing the extent to which the association between pain intensity and sensitivity to QST is mediated by psychosocial factors

Mediation analysis is used to determine the effect of a variable (mediator) that is associated with both the independent and dependent variables in an analysis. This relationship is directional; using linear regressions the mediator variable is a predictor of the dependent variable while the independent variable is causally associated with the dependent and mediator variables. Baron and Kenny (Baron et al. 1986) outlined four steps to mediation analysis using linear regression, described below.

(i) an association exists between the independent and dependent variables (total effect);

(ii) an association exists between the independent and mediator variables;

(iii) when adjusting for the independent variable, the mediator variable is associated with the dependent variable (indirect effect);

(iv) when adjusting for the mediator variable, the dependent variable is no longer associated with the dependent variable (direct effect= 0).

The $\beta$-coefficient for the total effect is the sum of the $\beta$-coefficient for the direct effect and the product of the $\beta$-coefficients forming the indirect effect. However, these steps are limited by the fact mediation can still occur without all of the above criteria being met.; for example, step (iv) is only met in the case of full mediation (when the $\beta$-coefficient for the indirect effect described in step (iii) is equal to the total effect and the $\beta$-coefficient for the direct effect is approximately zero). It is possible to incur partial mediation if step (iv) is not met (Hayes 2009).

One method of mediation analysis is structural equation modelling (SEM); SEM is a combination of structural models (using linear regression or path analysis) and measurement models (using factor analysis) designed to assess associations between observed and latent variables in one model.
Latent variables cannot be directly observed, but can be modelled using observed variables; for example, depression was not directly observed in the present study but can be modelled as a latent variable using the seven items forming the HAD depression subscale. However, latent variables were not used in the analysis of the present study as the composite scores for the subscales of the PCS, HAD, RAPA and HAQ-DI were added into the model as mediating variables. These variables can be treated as observed continuous variables as they have been validated as good proxies for the latent psychosocial variables of interest. The use of composite scores for measures of catastrophising, anxiety, depression, physical activity and levels of disability respectively is well established in the literature (see Section 4.2.4.4 for further details on these measures).

Some of the benefits in using SEM over the Baron and Kenny steps are the inclusion of latent variables and inclusion of error terms for all variables in the model (Hayes 2009). Figure 6.1 below demonstrates the models constructed to analyse the effect of psychosocial factors on the relationship between QST and self-reported global and knee pain intensities. The total effect of QST on self-reported pain intensity can be obtained by using linear regression. The total effect is then split into the direct effect (path c between QST and pain intensity) and the indirect effect (path a and path b) via the mediating variable to determine the impact that the mediating variable has on the total effect.

**Figure 6.1  Mediation Model**

This figure represents a mediation model. The direct effect is represented by path c between the independent and dependent variables. The indirect path is represented by path a between the independent and mediator variables, and path b between the mediator and dependent variables.

Mediation analyses were only performed for psychosocial factors that were significantly correlated with QST variables (using Spearman’s rho) and for QST variables that were significantly correlated with either global or knee pain intensity (using Spearman’s rho) to address the main aim of the present study (see Section 3.1.). The total effect mediated was calculated by dividing the product of the β-coefficients forming the indirect effect (path a x path b) by the β-coefficient for the total effect to determine the proportion of the total effect that was explained by the inclusion of the mediating variable in the model. Only models with indirect effects significantly greater than zero were considered to have significant mediation via the psychosocial factor entered into that model.
6.6. **Results**

6.6.1. **Subjects**

The subjects for the present study were recruited from the third follow-up of the EPIFUND cohort (see Sections 4.2.2, 4.2.3 and Figure 6.2 below). Of the 565 responders identified with knee pain from the EPIFUND follow-up questionnaire, 299 (52.9%) were not contacted for the present study: 198 responders (35.0%) did not consent to further contact, 5 (0.9%) had moved away from the area and 96 (17.0%) either participated in the sub-study for the third follow-up of the EPIFUND cohort or declined further contact during the telephone screening for the EPIFUND sub-study.

**Figure 6.2** **Recruitment flowchart**

![Recruitment flowchart](image)

This figure details the recruitment process and proportion of subjects who did not participate in the present study.

*Withdrawn: 5 (1.9%) no knee pain, 2 (0.7%) unable to complete assessments, 1 (0.4%) bilateral TKR.*
Of the 266 remaining people, 213 (80.1%) received a first telephone call and 53 people (19.9%) were not contacted as the sample size for the study was achieved. One hundred and thirty three people (50.0%) agreed to the information sheet being mailed to them and received a second phone call at least one week after the information sheet had been mailed. Of the 133 receiving a second phone call, 91 people (34.2%) agreed to participate in the study. Eighty subjects (30.1%) did attend appointments with 11 subjects (4.1%) not attending the study appointment. In total, 72 subjects (27.1%) completed the study. Eight subjects (3.0%) were withdrawn from the study during the appointment. Five subjects (1.9%) reported they had not experienced knee pain in the 30 days preceding the study visit and were withdrawn from the study assessments. Reasons for the other three withdrawals included two subjects who withdrew from assessments due to concomitant pain conditions (Rheumatoid Arthritis and Addison’s disease), and one subject with bilateral knee replacements.

6.6.2. Subject Characteristics

Of 72 subjects who took part, a median age of 64 (IQR 57.5-69 years) was observed with 43 (59%) women completing the study (see Table 6.1). The median BMI for subjects was 28.0 kg / m² with 58 (80.6%) subjects classified as overweight (BMI of 25-30) or obese (BMI of >30-34.9) (World Health Organization 2000). Thirty two (44.4%) subjects met the ACR criteria for hand OA, 12 (16.7%) met the ACR criteria for hip OA at one or both hips, and 47 (65.3%) met the ACR criteria for knee OA at one or both knees. The median number of pain sites determined using the ACR and Manchester manikin coding schedules were 4 (IQR 2-6.5) and 7 (IQR 4-11) respectively. Few subjects reported single site pain with 56 (77.8%) reporting more than one site using the ACR coding schedule and 60 (83.3%) reporting more than one site using the Manchester coding schedule.

Table 6.1 Characteristics of study subjects

<table>
<thead>
<tr>
<th>Variables (Possible range)</th>
<th>Total (n=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females (%)</td>
<td>43 (59.7%)</td>
</tr>
<tr>
<td>Age (41-76 years; median (IQR))</td>
<td>64.0 (57.5-69.0)</td>
</tr>
<tr>
<td>BMI (21-48.9 kg / m²; median (IQR))</td>
<td>28.0 (26.1-30.9)</td>
</tr>
<tr>
<td>ACR Clinical Criteria (%)</td>
<td></td>
</tr>
<tr>
<td>Hand Osteoarthritis</td>
<td>32 (44.4%)</td>
</tr>
<tr>
<td>Hip Osteoarthritis</td>
<td>12 (16.7%)</td>
</tr>
<tr>
<td>Knee Osteoarthritis</td>
<td>47 (65.3%)</td>
</tr>
<tr>
<td>Manikin Pain Count (median(IQR); n=68)</td>
<td></td>
</tr>
<tr>
<td>ACR coding schedule (0-10)</td>
<td>4.0 (2.0-6.5)</td>
</tr>
<tr>
<td>Manchester coding schedule (0-29)</td>
<td>7.0 (4.0-11.0)</td>
</tr>
</tbody>
</table>

IQR = interquartile range; BMI = Body Mass Index; kg / m² = kilograms per metre squared; ACR = American College of Rheumatology.
There were 11 subjects (4 males, 7 females) with one or more observations missing. Six subjects withdrew from knee and/or forearm QST assessments, three subjects had incomplete questionnaire data and 2 subjects withdrew from assessments and had incomplete questionnaire data. These subjects were excluded from further analysis leaving 61 subjects. Multiple imputation was considered in the analysis of this study to minimise selection bias when using a non-random sample. However, the sample in this study was too small to produce a reliable imputation model.

Subjects in the present study reported a median of 0 tender points, with no subjects meeting the criteria for fibromyalgia (11 tender points; Table 6.2) (Wolfe et al. 1990). Wind-up ratios at both test sites were similar, with ratios greater than one indicating higher pain following the temporal stimuli. The median values for heat pain, mechanical pain sensitivity and dynamic mechanical allodynia were similar at both test sites with subjects marginally more sensitive to cold pain, mechanical pain, vibration detection, and pressure pain thresholds at forearm than at knee.

Table 6.2 Range, median and interquartile range of QST measures, psychosocial factors and self-reported pain intensity (n=61)

<table>
<thead>
<tr>
<th>Variable (possible range)</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Central QST</strong></td>
<td></td>
</tr>
<tr>
<td>Tender point (0-18)</td>
<td>0 (0-2.0)</td>
</tr>
<tr>
<td>Knee wind-up (≥1)</td>
<td>2 (1.4-2.7)</td>
</tr>
<tr>
<td>Forearm wind-up (≥1)</td>
<td>1.9 (1.4-2.5)</td>
</tr>
<tr>
<td>DNIC (≥0.1)</td>
<td>1 (0.8-1.5)</td>
</tr>
<tr>
<td><strong>Knee QST</strong></td>
<td></td>
</tr>
<tr>
<td>Cold pain (0-32.0°C)</td>
<td>0 (0-0.8)</td>
</tr>
<tr>
<td>Heat pain (32.0-50°C)</td>
<td>48.3 (45.3-50)</td>
</tr>
<tr>
<td>Mechanical pain (0-512 mN)</td>
<td>90.5 (42.2-174.2)</td>
</tr>
<tr>
<td>MPS (0-100 NRS)</td>
<td>2.5 (0.9-6.0)</td>
</tr>
<tr>
<td>Allodynia (0-100 NRS)</td>
<td>0 (0-1.0)</td>
</tr>
<tr>
<td>Vibration (0-8)</td>
<td>4.3 (3.3-5.3)</td>
</tr>
<tr>
<td>Pressure pain (0-10 kg/cm²)</td>
<td>5.6 (3.4-7.3)</td>
</tr>
<tr>
<td><strong>Forearm QST</strong></td>
<td></td>
</tr>
<tr>
<td>Cold pain (0-32.0°C)</td>
<td>1.3 (0-14.3)</td>
</tr>
<tr>
<td>Heat pain (32.0-50°C)</td>
<td>47.0 (45.1-48.6)</td>
</tr>
<tr>
<td>Mechanical pain (0-512 mN)</td>
<td>45.3 (21.1-105.0)</td>
</tr>
<tr>
<td>MPS (0-100 NRS)</td>
<td>3.0 (0-9.7)</td>
</tr>
<tr>
<td>Allodynia (0-100 NRS)</td>
<td>0 (0-0.2)</td>
</tr>
<tr>
<td>Vibration (0-8)</td>
<td>6 (5.3-6.7)</td>
</tr>
<tr>
<td>Pressure pain (0-10 kg/cm²)</td>
<td>3.7 (2.6-5.1)</td>
</tr>
</tbody>
</table>

IQR = interquartile range; DNIC = diffuse noxious inhibitory control; MPS = mechanical pain sensitivity; NRS = numeric rating scale.
The medians and IQRs were the same for both self-reported pain intensity outcome measures (Table 6.3). Few subjects were classified as a possible (scored 8-10) or a probable (scored greater than 11) case for anxiety (12 and 7 subjects, respectively) or depression (8 and 3 subjects, respectively). The median scores for the subscales of the PCS were 3 (IQR 1-6), 1 (IQR 1-3) and 3 (IQR 2-5) for the rumination, magnification and helplessness subscales, respectively. In relation to the range of the individual items of the IPQ-Brief, scores nearer to 10 for timeline (pain continuity) indicate that subjects believe their pain is more long-lasting than acute, with scores nearer to 10 for both control items indicating they do not believe they have much control of their pain or that treatment will help. For all other items, scores nearer to 0 indicate that their current pain has little impact on them emotionally (emotion) or the number of symptoms experienced (identity), their understanding of the disease (coherence), and doesn’t cause them much concern. Subjects in the present study also reported moderate levels of physical activity using the RAPA with a median disability score of 0 using the HAQ-DI.

Table 6.3  Range, median and interquartile range of QST measures, psychosocial factors and self-reported pain intensity (n=61)

<table>
<thead>
<tr>
<th>Variable (possible range)</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-reported pain intensity</td>
<td></td>
</tr>
<tr>
<td>Global pain (0-10 NRS)</td>
<td>5.0 (3.0-7.0)</td>
</tr>
<tr>
<td>Knee pain (0-10 NRS)</td>
<td>5.0 (3.0-7.0)</td>
</tr>
<tr>
<td>HAD (0-21 sub-scale)</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>3.0 (1.0-6.0)</td>
</tr>
<tr>
<td>Depression</td>
<td>5.0 (2.0-8.0)</td>
</tr>
<tr>
<td>Pain Catastrophizing Scale</td>
<td></td>
</tr>
<tr>
<td>Rumination (4 items; 0-16)</td>
<td>3.0 (1.0-2.0)</td>
</tr>
<tr>
<td>Magnification (3 items; 0-12)</td>
<td>1.0 (1.0-3.0)</td>
</tr>
<tr>
<td>Helplessness (6 items; 0-24)</td>
<td>3.0 (2.0-5.0)</td>
</tr>
<tr>
<td>IPQ-Brief (0-10 NRS per item)</td>
<td></td>
</tr>
<tr>
<td>Consequences</td>
<td>3.0 (2.0-5.0)</td>
</tr>
<tr>
<td>Timeline</td>
<td>8.0 (4.0-10.0)</td>
</tr>
<tr>
<td>Personal Control</td>
<td>5.0 (3.0-7.0)</td>
</tr>
<tr>
<td>Treatment Control</td>
<td>5.0 (2.0-7.0)</td>
</tr>
<tr>
<td>Identity</td>
<td>2.0 (1.0-4.0)</td>
</tr>
<tr>
<td>Concern</td>
<td>4.0 (2.0-7.0)</td>
</tr>
<tr>
<td>Coherence</td>
<td>2.0 (1.0-5.0)</td>
</tr>
<tr>
<td>Emotion</td>
<td>3.0 (1.0-4.0)</td>
</tr>
<tr>
<td>Physical Functioning</td>
<td></td>
</tr>
<tr>
<td>RAPA (7 items; 0-7)</td>
<td>4.0 (4.0-5.0)</td>
</tr>
<tr>
<td>HAQ-DI (composite score; 0-3)</td>
<td>0 (0-1.0)</td>
</tr>
</tbody>
</table>

IQR = interquartile range; HAD = Hospital Anxiety and Depression Scale; IPQ-Brief = Illness Perception Questionnaire Brief; RAPA = Rapid Assessment of Physical Activity Scale; HAQ-DI = Health Assessment Questionnaire Disability Index.
For all analyses detailed below, the outcome (or dependent) measures are the scores for global pain intensity and pain intensity at the tested knee. Central (tender point, wind-up and DNIC) and peripheral (knee and forearm) measures of QST and psychosocial factors (see Section 4.2.4) are used as predictor (independent) variables. Analyses comparing global pain intensity, pain intensity at the tested knee, central and peripheral (knee and forearm) QST measures, and psychosocial factors were performed on subjects with full datasets (n=61).

### 6.6.3. Influence of age and sex on QST and psychosocial factors

Four variables differed significantly between the age bands; mechanical pain sensitivity and allodynia at the knee, mechanical pain threshold at the forearm, and the coherence item of the IPQ-Brief. The scores for mechanical pain sensitivity and allodynia at the knee both increase with age (p=0.0335 and p=0.001, respectively), whereas younger subjects reported higher median scores on the coherence item of the IPQ-Brief indicating a poorer level of understanding of their knee pain (p=0.0264; Figure 6.3). The scores for mechanical pain threshold at the forearm do not follow an age-related trend (p=0.0304) with median thresholds highest in the 50-59 age band, but this is impacted by the large range observed for this group. No other variables differed by age (presented in Table V-1, Appendix V).

**Figure 6.3** The effect of age on mechanical pain sensitivity and allodynia at the knee, mechanical pain threshold at the forearm and the IPQ-Brief coherence item

The boxplots in this figure demonstrate the differences by age group for (clockwise from top left): knee mechanical pain sensitivity, knee allodynia, the coherence item of the Illness Perception Questionnaire Brief (IPQ-Brief) and forearm mechanical pain threshold.
Seven variables differed by sex; tender point count, heat pain and mechanical pain sensitivity at the knee, allodynia at the forearm, pressure pain at both test sites, and the personal control item of the IPQ-Brief (Table 6.4). Men were less sensitive than women for tender point count, heat pain at the knee, pressure pain at both test sites and for mechanical pain sensitivity at the knee (Table 6.4). Men also had a higher median score for the personal control item of the IPQ-Brief indicating a lower perceived level of control over their illness. Men were also more sensitive to allodynia at the forearm; although the medians for both sexes are the same, men have a larger interquartile range (0-1) compared to women (Table 6.4). No other variables differed by sex (presented in Table V-2, Appendix V).

### Table 6.4 The effect of sex on QST, psychosocial factors and pain intensity (Wilcoxon Rank Sum)

<table>
<thead>
<tr>
<th>Variable (range)</th>
<th>Total (n=61)</th>
<th>Female (n=36)</th>
<th>Male (n=25)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tender Point</td>
<td>Median</td>
<td>IQR</td>
<td>Median</td>
<td>IQR</td>
</tr>
<tr>
<td>Knee HPT (32-50°C)</td>
<td>0</td>
<td>0-2.0</td>
<td>1.0</td>
<td>0-2.5</td>
</tr>
<tr>
<td>Knee MPS</td>
<td>48.3</td>
<td>45.3-50.0</td>
<td>47.6</td>
<td>45.0-49.6</td>
</tr>
<tr>
<td>Knee PPT (0-10kg/cm²)</td>
<td>2.5</td>
<td>0.9-6.0</td>
<td>1.9</td>
<td>0.6-5.4</td>
</tr>
<tr>
<td>Forearm Allodynia</td>
<td>5.6</td>
<td>3.4-7.3</td>
<td>3.9</td>
<td>3.2-6.0</td>
</tr>
<tr>
<td>Forearm PPT (0-10kg/cm²)</td>
<td>0</td>
<td>0-0.2</td>
<td>0</td>
<td>0-0</td>
</tr>
<tr>
<td>IPQ-Brief Personal Control (0-10 NRS)</td>
<td>5.0</td>
<td>3.0-7.0</td>
<td>4.0</td>
<td>2.0-7.0</td>
</tr>
</tbody>
</table>

* p<0.05 if bold; HPT = heat pain threshold; MPS = mechanical pain sensitivity; PPT = pressure pain threshold; IPQ-Brief = Illness Perception Questionnaire Brief; NRS = numeric rating scale.

### 6.6.4. Factors affecting self-reported pain intensity

#### 6.6.4.1. Relationship between QST, psychosocial factors and pain

Four QST measures were significantly correlated with one or both pain intensity outcome measures, with higher scores for mechanical pain sensitivity at both test sites and allodynia at the knee significantly correlated with higher levels of global and knee pain intensity and a greater number of tender points significantly correlated with higher levels of global pain intensity (Table 6.5). The correlation between increased sensitivity to pressure pain at the knee and higher global pain intensity was approaching significance (p=0.0869), but no other QST measures were significantly correlated with either pain intensity measure.
Table 6.5 Correlations between self-reported pain intensity and QST measures (Spearman’s Rho)

<table>
<thead>
<tr>
<th>QST Measures</th>
<th>Global Pain *</th>
<th>Knee Pain *</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Central QST</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tender point</td>
<td>0.3364</td>
<td>0.1811</td>
</tr>
<tr>
<td>Knee wind-up</td>
<td>-0.0608</td>
<td>-0.1034</td>
</tr>
<tr>
<td>Forearm wind-up</td>
<td>0.097</td>
<td>0.1433</td>
</tr>
<tr>
<td>DNIC</td>
<td>-0.0793</td>
<td>0.1476</td>
</tr>
<tr>
<td><strong>Knee QST</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cold pain</td>
<td>0.1948</td>
<td>0.2430</td>
</tr>
<tr>
<td>Heat pain</td>
<td>-0.0731</td>
<td>0.0153</td>
</tr>
<tr>
<td>Mechanical pain</td>
<td>0.0844</td>
<td>0.1146</td>
</tr>
<tr>
<td>MPS</td>
<td><strong>0.3366</strong></td>
<td><strong>0.3350</strong></td>
</tr>
<tr>
<td>Allodynia</td>
<td><strong>0.3336</strong></td>
<td><strong>0.4358</strong></td>
</tr>
<tr>
<td>Vibration</td>
<td>0.0169</td>
<td>-0.0929</td>
</tr>
<tr>
<td>Pressure pain</td>
<td>-0.2211</td>
<td>-0.1443</td>
</tr>
<tr>
<td><strong>Forearm QST</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cold pain</td>
<td>-0.076</td>
<td>-0.0396</td>
</tr>
<tr>
<td>Heat pain</td>
<td>-0.1429</td>
<td>-0.0385</td>
</tr>
<tr>
<td>Mechanical pain</td>
<td>-0.0364</td>
<td>-0.0379</td>
</tr>
<tr>
<td>MPS</td>
<td><strong>0.3319</strong></td>
<td><strong>0.3333</strong></td>
</tr>
<tr>
<td>Allodynia</td>
<td>0.2413</td>
<td>0.1949</td>
</tr>
<tr>
<td>Vibration</td>
<td>-0.0049</td>
<td>-0.1158</td>
</tr>
<tr>
<td>Pressure pain</td>
<td>-0.1852</td>
<td>-0.1183</td>
</tr>
</tbody>
</table>

* p<0.05 if bold and 0.05≤p<0.1 if in italics. DNIC = diffuse noxious inhibitory control; MPS = mechanical pain sensitivity.

Eight psychosocial factors were significantly correlated with global pain intensity and pain intensity at the tested knee: helplessness subscale of the PCS, consequences, timeline, treatment control, identity, concern and emotion items from the IPQ-Brief, and HAQ-DI score (Table 6.6). The rumination and magnification subscales of the PCS also significantly correlated with global pain intensity and HAD depression with tested knee pain intensity (Table 6.6). Higher scores for all items except treatment control (scored inversely so lower scores indicate treatment is helpful) are significantly correlated with higher levels of pain intensity; this suggests that subjects with higher levels of global and knee pain experience higher levels of disability (HAQ-DI), have more catastrophic thoughts about their pain (PCS), believe that their pain has a substantial impact on their life (consequences) and that it will continue to do so (timeline), do not believe treatment can help with their pain (treatment control) and also report greater emotional impact and concern related to their pain (Table 6.6). The correlation between higher scores for HAD depression and global pain intensity was approaching significance (p= 0.0796), but no other psychosocial factors were significantly correlated with pain intensity.
The QST measures and psychosocial factors correlated with global and knee pain intensity (p-value less than 0.1) were included in regression models. Pressure pain threshold at the knee and the depression subscale of the HAD were no longer significantly associated when regressed against global and knee pain intensity scores (Table 6.7). All other variables remained significantly associated with self-reported pain intensity. Pressure pain at the knee and depression subscale of the HAD were investigated further. Transformations were carried out using fractional polynomials to determine the two best fitting transformations of the data when regressed against global pain and knee pain intensity (Table 6.8).

Scatter plots were used to illustrate the non-linear relationships between self-reported knee and global pain intensities with knee pressure pain threshold and the depression subscale of the HAD, with the effect of the fractional polynomial transformations on the independent variables also shown (Figure 6.4). The plots show the values for pain intensity plotted against either the total score for the HAD depression subscale or the median pressure pain threshold for each subject (green dots). The grey band represents the CI for the predicted values for global pain and knee pain intensities.
when regressed against the transformed values for pressure pain threshold at the knee and the HAD depression subscale. The fit of the fractional polynomial transformations for the same predicted values for global pain and knee pain intensities (as used for the CIs) is represented by the blue line. It is possible to determine from the scatter plot below (Figure 6.4) that the observation at (1, 6) for knee pressure pain threshold and global pain intensity respectively, does not fit the curve and therefore impacts the fit of the data (p=0.0676; Table 6.9).

Table 6.7 Association between QST measures, psychosocial factors and self-reported global and knee pain intensity ratings (linear regression)

<table>
<thead>
<tr>
<th></th>
<th>Global Pain</th>
<th>Knee Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>95% CI *</td>
</tr>
<tr>
<td><strong>Central QST</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tender point</td>
<td>0.4666</td>
<td>0.1733, 0.7599</td>
</tr>
<tr>
<td><strong>Knee QST</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPS</td>
<td>0.1243</td>
<td>0.0467, 0.202</td>
</tr>
<tr>
<td>Allodynia</td>
<td>0.3310</td>
<td>0.0208, 0.6412</td>
</tr>
<tr>
<td>Pressure pain</td>
<td>-0.2186</td>
<td>-0.4916, 0.054</td>
</tr>
<tr>
<td><strong>Forearm QST</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPS</td>
<td>0.0721</td>
<td>0.0033, 0.1408</td>
</tr>
<tr>
<td><strong>Hospital Anxiety and Depression Scale</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>0.1273</td>
<td>-0.0742, 0.3289</td>
</tr>
<tr>
<td><strong>Pain Catastrophizing Scale</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rumination</td>
<td>0.3517</td>
<td>0.1622, 0.5412</td>
</tr>
<tr>
<td>Magnification</td>
<td>0.3963</td>
<td>0.0762, 0.7164</td>
</tr>
<tr>
<td>Helplessness</td>
<td>0.4295</td>
<td>0.2497, 0.6093</td>
</tr>
<tr>
<td><strong>Illness Perception Questionnaire Brief</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consequences</td>
<td>0.6222</td>
<td>0.3999, 0.8444</td>
</tr>
<tr>
<td>Timeline</td>
<td>0.2858</td>
<td>0.0861, 0.4856</td>
</tr>
<tr>
<td>Treatment Control</td>
<td>-0.2604</td>
<td>-0.4726, -0.0482</td>
</tr>
<tr>
<td>Identity</td>
<td>0.3371</td>
<td>0.0847, 0.5895</td>
</tr>
<tr>
<td>Concern</td>
<td>0.4993</td>
<td>0.3176, 0.6810</td>
</tr>
<tr>
<td>Emotion</td>
<td>0.3173</td>
<td>0.0729, 0.5617</td>
</tr>
<tr>
<td><strong>Physical Functioning</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAQ-DI</td>
<td>0.1434</td>
<td>0.0385, 0.2483</td>
</tr>
</tbody>
</table>

β = β-coefficient; CI = confidence interval; * p<0.05 if bold. MPS = mechanical pain sensitivity; HAQ-DI = Health Assessment Questionnaire Disability Index.
Table 6.8  Fractional polynomial transformations (knee pressure pain threshold and HAD depression score)

<table>
<thead>
<tr>
<th></th>
<th>Global Pain</th>
<th>Knee Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Knee pressure pain</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polynomial 1</td>
<td>$(\text{var}1)^2 - 0.03332883$</td>
<td>$(\text{var}1)^{0.5} - 0.4272725741$</td>
</tr>
<tr>
<td>Polynomial 2</td>
<td>$(\text{var}1)^{-1} - 0.1825618526$</td>
<td>ln(var1) - 1.700666245</td>
</tr>
<tr>
<td><strong>HAD Depression †</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polynomial 1</td>
<td>ln(X) + 0.6997261517</td>
<td>ln(X) + 0.6997261517</td>
</tr>
<tr>
<td>Polynomial 2</td>
<td>ln(X)-0.48961666873 - 0.7047845852</td>
<td>(X)0.5 - 0.7047845852</td>
</tr>
</tbody>
</table>

HAD = Hospital Anxiety and Depression Scale; † $X = (\text{var}2 + 1) / 10$; var1 represents knee pressure pain threshold and var2 represents HAD depression score.

Figure 6.4  Scatter plots including predicted values using fractional polynomials of knee pressure pain threshold and HAD depression score with global and knee pain intensity scores

The scatter plots above depict the non-linear associations for knee pressure pain threshold and the depression subscale of the Hospital Anxiety and Depression Scale (HAD) with global pain intensity (top row, respectively), and for knee pressure pain threshold and HAD depression subscale with knee pain intensity (bottom row, respectively). CI = confidence interval.
Fractional polynomials for pressure pain at the knee and HAD depression (Wald Test)

<table>
<thead>
<tr>
<th></th>
<th>Global Pain</th>
<th>Knee Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F value</td>
<td>p-value *</td>
</tr>
<tr>
<td>Knee PPT</td>
<td>2.82</td>
<td>0.0676</td>
</tr>
<tr>
<td>HAD Depression</td>
<td>4.29</td>
<td><strong>0.0182</strong></td>
</tr>
</tbody>
</table>

* p<0.05 if bold; PPT = pressure pain threshold; HAD = Hospital Anxiety and Depression Scale.

6.6.4.2. Differences between age groups and sexes in the association between pain and its predictors

Linear regressions were performed to determine if the associations between global or knee pain intensity and QST measures were affected when the interaction between age the independent variable was included. The inclusion of the interaction with age in the regression did not impact the associations between QST measures and either pain intensity measure. However, the Wald test performed following the regressions indicated that the addition of the interactions with heat pain thresholds at both sites for global pain intensity was significant (p=0.0275 for the knee and p=0.0679 for the forearm). Increased sensitivity for both heat pain thresholds was significantly associated with global pain intensity only in the 70+ age band (Table 6.10). Linear regressions were also performed to determine if the associations between global or knee pain intensity with psychosocial factors were affected by age. However, age was not found to have an impact on the associations between pain intensity and psychosocial factors (p≥0.1384 for global pain and p≥0.2034 for knee pain).

<table>
<thead>
<tr>
<th>Age bands</th>
<th>n</th>
<th>β</th>
<th>95% CI *</th>
<th>β</th>
<th>95% CI *</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-49</td>
<td>9</td>
<td>0.2062</td>
<td>-0.1670, 0.5793</td>
<td>0.3060</td>
<td>-0.899, 0.7020</td>
</tr>
<tr>
<td>50-59</td>
<td>12</td>
<td>-0.0337</td>
<td>-0.6387, 0.5713</td>
<td>-0.0357</td>
<td>-0.3643, 0.2929</td>
</tr>
<tr>
<td>60-69</td>
<td>27</td>
<td>0.0847</td>
<td>-0.1397, 0.309</td>
<td>-0.0364</td>
<td>-0.2800, 0.2071</td>
</tr>
<tr>
<td>70+</td>
<td>13</td>
<td>-1.0542</td>
<td><strong>-1.8011, -0.3073</strong></td>
<td>-0.3378</td>
<td><strong>-0.6316, -0.0440</strong></td>
</tr>
</tbody>
</table>

HPT = heat pain threshold; β = β-coefficient; CI = Confidence Interval; * p<0.05 if bold.

Linear regressions were performed to determine if the relationships between global or knee pain intensity with QST measures differed between men and women. The inclusion of the interaction with sex in the regression did not impact the associations between QST measures and either pain intensity measure; however, the Wald test identified that the association between global pain, and
wind-up ratio at the knee differed between men and women, as did the association between pain intensity at the tested knee and both DNIC and heat pain threshold at the forearm (Table 6.11). Global pain intensity increased with increasing wind-up ratio in females (p=0.082) but decreased in males (p=0.088; Table 6.11). Women also reported that knee pain intensity increased significantly with increasing DNIC, the association being non-significant in men. Men did report that knee pain intensity decreased significantly with increasing heat pain thresholds, this effect not being seen in women (Table 6.11). Sex does not impact the associations between psychosocial factors and either measure of pain intensity (p≥0.2720 for global pain and p≥0.1418 for knee pain).

Table 6.11

<table>
<thead>
<tr>
<th>Sex</th>
<th>Global pain &amp; Knee WUR</th>
<th>Knee pain &amp; DNIC</th>
<th>Knee pain &amp; Forearm HPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>36</td>
<td>0.3635</td>
<td>0.1962</td>
</tr>
<tr>
<td></td>
<td>-0.0476, 0.7747</td>
<td>0.0474, 0.3450</td>
<td>-0.923, 0.2363</td>
</tr>
<tr>
<td>Male</td>
<td>25</td>
<td>-0.6481</td>
<td>-0.0660</td>
</tr>
<tr>
<td></td>
<td>-1.3954, 0.0991</td>
<td>-0.3341, 0.1022</td>
<td>-0.4879, -0.0040</td>
</tr>
</tbody>
</table>

WUR = wind-up ratio; DNIC = diffuse noxious inhibitory control; HPT = heat pain threshold; β = β-coefficient; CI = confidence interval; * p<0.05 if bold.

6.6.4.3. Determining the best model for the relationship between QST, measures of distress, beliefs and behaviour, and pain

Stepwise regressions were performed to determine which variables provided the best overall model for predicting global pain intensity and pain intensity at the tested knee (see Table 6.12). All QST measures were included in a stepwise regression with global pain intensity. Tender point count and knee mechanical pain sensitivity were identified as significant predictors of global pain intensity at the 5% level and were kept in the model. The same steps were performed for all psychosocial factors, with the consequences item of the IPQ-Brief identified as the best predictor of global pain intensity. A stepwise regression was then performed including the consequences item of the IPQ-Brief, tender point count and knee mechanical pain sensitivity with global pain intensity. The consequences item and knee mechanical pain sensitivity remained significant following this regression (see Table 6.12).

Following the same steps as above, mechanical pain sensitivity and mechanical pain threshold at the knee, the consequences item of the IPQ-Brief and the rumination subscale of the PCS were identified as significant predictors of pain intensity at the tested knee. The consequences item of the IPQ-Brief has an R² of 0.3471 for global pain intensity and an R² of 0.2878 for knee pain intensity. This suggests that beliefs regarding the impact knee pain has on a subject’s life is consistently the best predictor of self-reported pain intensity both at the knee and globally.
Table 6.12  Results from the backward stepwise regressions (n=61)

<table>
<thead>
<tr>
<th>Predictor Variables</th>
<th>β</th>
<th>95% CI *</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global Pain Intensity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee MPS</td>
<td>0.0741</td>
<td>0.0050, 0.1433</td>
<td>0.3951</td>
</tr>
<tr>
<td>IPQ Consequences</td>
<td>0.5498</td>
<td>0.3237, 0.7760</td>
<td></td>
</tr>
<tr>
<td>Knee Pain Intensity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee MPT</td>
<td>0.0037</td>
<td>0.0004, 0.0070</td>
<td>0.4834</td>
</tr>
<tr>
<td>Knee MPS</td>
<td>0.1049</td>
<td>0.0422, 0.1676</td>
<td></td>
</tr>
<tr>
<td>IPQ Consequences</td>
<td>0.5880</td>
<td>0.3505, 0.8255</td>
<td></td>
</tr>
<tr>
<td>PCS Rumination</td>
<td>-0.2037</td>
<td>-0.3793, -0.0281</td>
<td></td>
</tr>
</tbody>
</table>

β = β-coefficient; CI = confidence interval; R² = coefficient of determination; * p<0.05 if bold; MPS = mechanical pain sensitivity; IPQ-Brief = Illness Perception Questionnaire Brief; MPT = mechanical pain threshold; PCS = Pain Catastrophizing Scale.

Age and sex were also added as categorical variables to the stepwise regression models to determine if the model fit could be improved by controlling for age or sex and to assess if other variables should be added or removed from the models for global pain and tested knee pain intensity. Age and sex did not affect the predictor variables identified for either outcome measure. However, the addition of age and sex did improve the fit of each model with age having the largest impact on improving the fit of the models. Variables transformed using fractional polynomials were also included in stepwise regressions to determine if the transformations improved the model, but they did not affect the variables in the final model or affect the model fit.

### 6.6.4.4. Determining psychosocial mediators of the relationship between QST and pain intensity

Mediation analyses were performed using the model depicted in Figure 6.1. QST measures which significantly correlated with global pain intensity or pain intensity for the tested knee were used as the independent variables in this model with seven correlations identified; tender point count with global pain intensity, mechanical pain sensitivity at the knee and at the forearm with global and knee pain intensity, and allodynia at the knee with global and knee pain intensity (Table 6.5). Psychosocial factors which significantly correlated with tender point count, mechanical pain sensitivity at the knee and forearm, and allodynia at the knee were identified as variables which would be entered into each model as the mediating variable (Table 6.13). A total of 52 mediation models were constructed with 10 mediating variables identified for the model for tender point count and global pain intensity, 7 mediators for mechanical pain sensitivity at the knee and both pain intensity measures, 9 mediators for allostynia at the knee and both pain intensity measures, and 5 mediators for mechanical pain sensitivity at the forearm and both pain intensity measures.
Table 6.13 Correlations between QST measures that are significantly correlated with pain intensity and psychosocial factors (n=61)

<table>
<thead>
<tr>
<th></th>
<th>Tender point *</th>
<th>Knee MPS *</th>
<th>Knee Allodynia *</th>
<th>Forearm MPS *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital Anxiety and Depression Scale</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.1173</td>
<td>0.1251</td>
<td>0.2332</td>
<td>0.0498</td>
</tr>
<tr>
<td>Depression</td>
<td>0.1776</td>
<td>0.1539</td>
<td><strong>0.2994</strong></td>
<td>0.0275</td>
</tr>
<tr>
<td>Pain Catastrophizing Scale</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ruminating</td>
<td><strong>0.2654</strong></td>
<td>0.2117</td>
<td>0.3120</td>
<td>0.1165</td>
</tr>
<tr>
<td>Magnification</td>
<td><strong>0.4011</strong></td>
<td><strong>0.3374</strong></td>
<td>0.3550</td>
<td><strong>0.2850</strong></td>
</tr>
<tr>
<td>Helplessness</td>
<td><strong>0.3303</strong></td>
<td>0.3946</td>
<td>0.3548</td>
<td>0.2259</td>
</tr>
<tr>
<td>Illness Perception Questionnaire Brief</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consequences</td>
<td>0.4524</td>
<td>0.3833</td>
<td>0.3237</td>
<td>0.2839</td>
</tr>
<tr>
<td>Timeline</td>
<td>0.3227</td>
<td>0.3820</td>
<td>0.2778</td>
<td><strong>0.2700</strong></td>
</tr>
<tr>
<td>Personal Control</td>
<td>-0.1248</td>
<td>0.0885</td>
<td>0.1257</td>
<td>0.0255</td>
</tr>
<tr>
<td>Treatment Control</td>
<td>-0.2300</td>
<td>-0.1237</td>
<td>0.0348</td>
<td><strong>-0.3002</strong></td>
</tr>
<tr>
<td>Identity</td>
<td><strong>0.4325</strong></td>
<td><strong>0.2777</strong></td>
<td>0.1980</td>
<td>0.2361</td>
</tr>
<tr>
<td>Concern</td>
<td><strong>0.4447</strong></td>
<td><strong>0.3676</strong></td>
<td><strong>0.2801</strong></td>
<td><strong>0.2911</strong></td>
</tr>
<tr>
<td>Coherence</td>
<td>-0.1955</td>
<td>0.0029</td>
<td>-0.1074</td>
<td>0.0577</td>
</tr>
<tr>
<td>Emotion</td>
<td><strong>0.4064</strong></td>
<td><strong>0.3185</strong></td>
<td><strong>0.3391</strong></td>
<td>0.1652</td>
</tr>
<tr>
<td>Physical Functioning</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAPA</td>
<td>-0.3110</td>
<td>-0.1339</td>
<td>-0.0600</td>
<td>-0.0839</td>
</tr>
<tr>
<td>HAQ-DI</td>
<td><strong>0.4883</strong></td>
<td>0.2453</td>
<td><strong>0.3818</strong></td>
<td>0.1222</td>
</tr>
</tbody>
</table>

*p<0.05 if bold. MPS = mechanical pain sensitivity; RAPA = Rapid Assessment of Physical Activity Scale; HAQ-DI = Health Assessment Questionnaire Disability Index.

Knee mechanical pain sensitivity was also identified as a predictor of pain intensity at the tested knee using stepwise regression modelling along with mechanical pain sensitivity at the knee, the consequence item of the IPQ-Brief and the rumination subscale of the PCS (Table 6.12). Knee mechanical pain threshold could only be an independent variable in the model above when adjusting for the other variables identified in the stepwise model as it is not univariately significantly correlated with knee pain intensity (rho 0.1146; Table 6.5). However, only one psychosocial factor (RAPA) was significantly correlated with knee mechanical pain threshold (rho 0.2604) and was not significantly correlated with knee pain intensity (rho -0.058; Table 6.5). As a result, knee mechanical pain threshold was not included as an independent variable in a mediation analysis.

Complete mediation was not observed for any of the 52 models; however, 9 models demonstrated significant partial mediation, with Z-scores of 1.96 or greater for the indirect effect. The results of the mediation analyses performed for tender point count and global pain intensity are shown in Table 6.14.
The indirect effects shown in Table 6.14 have stronger associations with the outcome measures than the association observed for the direct effect. However, there are other factors thought to influence QST measures and pain intensity which are not included in the present model. As such, the proportion of the total mediated effect provides an indication of the strength of the indirect effect in the models tested. Four psychosocial factors were identified as significant mediators of the relationship between increased global pain intensity and higher tender point count: higher scores for concern about pain and consequences (lower understanding of pain) items of the IPQ-Brief account for 59.71% and 57.42% of the total effect of tender point count on global pain intensity, while higher scores for helplessness and rumination in relation to pain account for 56.43% and 34.12%, respectively.

Higher scores for concern, consequences and helplessness were also identified as significant mediators of the relationship between higher scores for mechanical pain sensitivity at the knee and higher global pain intensity scores; the inclusion of concern, consequences and helplessness variables in the model accounted for 44.65%, 40.39% and 39.50% of the total effect respectively (Table 6.15). Similarly, higher scores for concern and consequences accounted for 30.47% and 29.46% of the total effect respectively in a model where higher scores for mechanical pain
sensitivity at the knee is associated with higher levels of pain intensity at the same knee (Table 6.16). Results of the mediation analyses for the other 43 models can be found in Appendix VI.

### Table 6.15  Mediation analysis for mechanical pain sensitivity at the knee and global pain intensity

<table>
<thead>
<tr>
<th></th>
<th>β-coefficient</th>
<th>95% CI *</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Effect</td>
<td>0.1243</td>
<td>0.0495, 0.1991</td>
<td>0.0382</td>
<td>3.26</td>
<td>----</td>
</tr>
<tr>
<td><strong>IPQ-Brief Concern</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Path a</td>
<td>0.1268</td>
<td>0.0379, 0.2158</td>
<td>0.0454</td>
<td>2.79</td>
<td>44.65%</td>
</tr>
<tr>
<td>Path b</td>
<td>0.4378</td>
<td>0.2576, 0.6179</td>
<td>0.0919</td>
<td>4.76</td>
<td></td>
</tr>
<tr>
<td>Path c (Direct Effect)</td>
<td>0.0687</td>
<td>0.0009, 0.1366</td>
<td>0.0346</td>
<td>1.99</td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0555</td>
<td>0.0104, 0.1007</td>
<td>0.0230</td>
<td>2.41</td>
<td></td>
</tr>
<tr>
<td><strong>IPQ-Brief Consequences</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Path a</td>
<td>0.0912</td>
<td>0.0180, 0.1645</td>
<td>0.0374</td>
<td>2.44</td>
<td>40.39%</td>
</tr>
<tr>
<td>Path b</td>
<td>0.5498</td>
<td>0.3339, 0.7658</td>
<td>0.1102</td>
<td>4.99</td>
<td></td>
</tr>
<tr>
<td>Path c (Direct Effect)</td>
<td>0.0741</td>
<td>0.0081, 0.1401</td>
<td>0.0337</td>
<td>2.20</td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0502</td>
<td>0.0053, 0.0950</td>
<td>0.0229</td>
<td>2.19</td>
<td></td>
</tr>
<tr>
<td><strong>PCS Helplessness</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Path a</td>
<td>0.1343</td>
<td>0.0405, 0.2281</td>
<td>0.0479</td>
<td>2.81</td>
<td>39.50%</td>
</tr>
<tr>
<td>Path b</td>
<td>0.3655</td>
<td>0.1878, 0.5433</td>
<td>0.0907</td>
<td>4.03</td>
<td></td>
</tr>
<tr>
<td>Path c (Direct Effect)</td>
<td>0.0752</td>
<td>0.0046, 0.1458</td>
<td>0.0360</td>
<td>2.09</td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0491</td>
<td>0.0073, 0.0909</td>
<td>0.0213</td>
<td>2.30</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; * p<0.05 if bold. SE = standard error; Z = Z-score; IPQ-Brief = Illness Perception Questionnaire Brief; PCS = Pain Catastrophizing Scale.

### Table 6.16  Mediation analysis for mechanical pain sensitivity at the knee and pain intensity at the tested knee

<table>
<thead>
<tr>
<th></th>
<th>β-coefficient</th>
<th>95% CI *</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Effect</td>
<td>0.1290</td>
<td>0.0623, 0.1956</td>
<td>0.0340</td>
<td>3.79</td>
<td>----</td>
</tr>
<tr>
<td><strong>IPQ-Brief Consequences</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Path a</td>
<td>0.0912</td>
<td>0.0180, 0.1645</td>
<td>0.0374</td>
<td>2.44</td>
<td>30.47%</td>
</tr>
<tr>
<td>Path b</td>
<td>0.4307</td>
<td>0.2294, 0.6319</td>
<td>0.1027</td>
<td>4.19</td>
<td></td>
</tr>
<tr>
<td>Path c (Direct Effect)</td>
<td>0.0897</td>
<td>0.0282, 0.1512</td>
<td>0.0314</td>
<td>2.86</td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0393</td>
<td>0.0028, 0.0758</td>
<td>0.0186</td>
<td>2.11</td>
<td></td>
</tr>
<tr>
<td><strong>IPQ-Brief Concern</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Path a</td>
<td>0.1268</td>
<td>0.0379, 0.2158</td>
<td>0.0454</td>
<td>2.79</td>
<td>29.46%</td>
</tr>
<tr>
<td>Path b</td>
<td>0.2996</td>
<td>0.1272, 0.4720</td>
<td>0.0880</td>
<td>3.41</td>
<td></td>
</tr>
<tr>
<td>Path c (Direct Effect)</td>
<td>0.0910</td>
<td>0.0261, 0.1559</td>
<td>0.0331</td>
<td>2.75</td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0380</td>
<td>0.0035, 0.0725</td>
<td>0.0176</td>
<td>2.16</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; * p<0.05 if bold. SE = standard error; Z = Z-score; IPQ-Brief = Illness Perception Questionnaire Brief.
The total proportion of mediated effect explained by the psychosocial factors added to each model totals more than 100% (including the non-significant mediating factors in Appendix VI). This finding suggests there may be a latent variable that correlates with each of the psychosocial factors. New models were constructed to include all psychosocial factors significantly correlated with each QST measure (as identified in Table 6.13) loading on to a single latent mediator (depicted in Figure 6.5). The variance of the latent mediator is undefined in the model; therefore the regression coefficient for path b is uninterpretable and is constrained to 1.0 (not included in Table 6.17 or Table 6.18). The models including a latent mediating variable for forearm mechanical pain sensitivity with global pain intensity and with pain intensity at the tested knee did not converge and are not presented.

**Figure 6.5** Mediation model including latent psychosocial mediating variable

![Diagram showing mediation model]

This figure depicts the mediation model constructed to include the individual psychosocial factors identified in Table 6.13 loading on to a latent mediator. Path c represents the direct effect between the independent and dependent variables. Paths a and b represent the indirect path between the independent and mediator variables (path a), and between the mediator and dependent variables (path b). ε = error term; QST = quantitative sensory testing.

The inclusion of a latent variable in the mediation models instead of individual psychosocial factors accounted for 75.27%, 52.13% and 63.44% of the total effect of tender point count, knee mechanical pain sensitivity and knee allodynia respectively on global pain intensity (Table 6.17). The proportion of the total mediated effect for the latent variable in each of these models exceeded the proportion of any single psychosocial factor in the previous models (Table 6.14, Table 6.15 and Table 6.16, and Appendix VI, Table VI-2, Table VI-3 and Table VI-4). These findings suggest that a combination of psychosocial factors and diffuse mechanical hyperalgesia could be markers of increased global pain intensity.
Table 6.17  Mediation analysis for QST measures and global pain intensity including a latent psychosocial mediating variable

<table>
<thead>
<tr>
<th>Exogenous: Tender Point</th>
<th>Coefficient</th>
<th>95% CI</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Effect</td>
<td>0.4666</td>
<td>0.1841, 0.7492</td>
<td>0.1442</td>
<td>3.24</td>
<td>----</td>
</tr>
<tr>
<td>Indirect Effect (path a x b)</td>
<td>0.3512</td>
<td>0.1326, 0.5698</td>
<td>0.1115</td>
<td>3.15</td>
<td>75.27%</td>
</tr>
<tr>
<td>Direct Effect (path c)</td>
<td>0.1154</td>
<td>-0.1765, 0.4073</td>
<td>0.1489</td>
<td>0.77</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exogenous: Knee MPS</th>
<th>Coefficient</th>
<th>95% CI</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Effect</td>
<td>0.1243</td>
<td>0.0495, 0.1991</td>
<td>0.0382</td>
<td>3.26</td>
<td>----</td>
</tr>
<tr>
<td>Indirect Effect (path a x b)</td>
<td>0.0648</td>
<td>0.0147, 0.1149</td>
<td>0.0256</td>
<td>2.54</td>
<td>52.13%</td>
</tr>
<tr>
<td>Direct Effect (path c)</td>
<td>0.0594</td>
<td>-0.0094, 0.1282</td>
<td>0.0351</td>
<td>1.69</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exogenous: Knee Allodynia</th>
<th>Coefficient</th>
<th>95% CI</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Effect</td>
<td>0.3310</td>
<td>0.0322, 0.6298</td>
<td>0.1525</td>
<td>2.17</td>
<td>----</td>
</tr>
<tr>
<td>Indirect Effect (path a x b)</td>
<td>0.21</td>
<td>0.0143, 0.4057</td>
<td>0.0999</td>
<td>2.1</td>
<td>63.44%</td>
</tr>
<tr>
<td>Direct Effect (path c)</td>
<td>0.121</td>
<td>-0.1411, 0.3831</td>
<td>0.1337</td>
<td>0.9</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; * p<0.05 if bold. SE = standard error; Z = Z-score; MPS = mechanical pain sensitivity.

Table 6.18  Mediation analysis for QST measures and pain intensity at the tested knee including a latent psychosocial mediating variable

<table>
<thead>
<tr>
<th>Exogenous: Knee MPS</th>
<th>Coefficient</th>
<th>95% CI</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Effect</td>
<td>0.1290</td>
<td>0.0623, 0.1956</td>
<td>0.0340</td>
<td>3.79</td>
<td>----</td>
</tr>
<tr>
<td>Indirect Effect (path a x b)</td>
<td>0.045</td>
<td>0.0062, 0.0838</td>
<td>0.0198</td>
<td>2.27</td>
<td>34.88%</td>
</tr>
<tr>
<td>Direct Effect (path c)</td>
<td>0.084</td>
<td>0.0182, 0.1498</td>
<td>0.0336</td>
<td>2.5</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exogenous: Knee Allodynia</th>
<th>Coefficient</th>
<th>95% CI</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Effect</td>
<td>0.4341</td>
<td>0.1722, 0.6960</td>
<td>0.1336</td>
<td>3.25</td>
<td>----</td>
</tr>
<tr>
<td>Indirect Effect (path a x b)</td>
<td>0.1319</td>
<td>-0.0047, 0.2684</td>
<td>0.0697</td>
<td>1.89</td>
<td>30.38%</td>
</tr>
<tr>
<td>Direct Effect (path c)</td>
<td>0.3022</td>
<td>0.0492, 0.5553</td>
<td>0.1291</td>
<td>2.34</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; * p<0.05 if bold, 0.05≤p<0.1 if in italics. SE = standard error; Z = Z-score; MPS = mechanical pain sensitivity.

The latent variable for knee mechanical pain sensitivity and knee allodynia on pain intensity at the tested knee accounted for 34.88% and 30.38% of the total effect respectively (see Table 6.18). Significant partial mediation was observed for mechanical pain sensitivity at the knee with the inclusion of the latent variable. However, the latent variable included in the mediation model for knee allodynia was not a partial mediator of the association with pain intensity at the tested knee (see Table 6.18). While the proportion of the total mediated effect for the latent variable in the models exceeded the proportions observed in the previous models (see Table 6.16 and Appendix...
VI, Table VI-5, Table VI-6 and Table VI-7), neither proportion exceeded 35% indicating the sensitivity to mechanical stimuli at the knee explains a significantly greater proportion of the association with knee pain. These findings suggest that the presence of localised mechanical hyperalgesia may be a marker of pain intensity at the tested knee.

The results presented for the mediation model depicted in Figure 6.5 provides one possible mechanism for the relationship between QST measures and self-reported pain intensity. Higher levels of pain intensity are associated with higher levels of psychosocial distress; it is also possible that those associations may be mediated by sensitivity to pain (assessed using QST measures). This alternative mechanism was explored (detailed in Appendix VII) and showed that the associations between psychosocial factors and self-reported pain intensity were not mediated by QST measures.

### 6.7. Discussion

The analyses presented in this chapter demonstrate that hypersensitivity to mechanical assessments both locally (mechanical pain sensitivity and allodynia at knee) and distally (forearm mechanical pain sensitivity) were associated with higher levels of self-reported pain intensity at the tested knee and globally. An increased number of tender points were also significantly associated with higher levels of global pain intensity. Both pain intensity measures were correlated with six illness perceptions including consequences, timeline, treatment control, identity, concern and emotion, as well as the helplessness subscale of the PCS and the HAQ-DI. Global pain intensity was also correlated with the rumination and magnification subscales of the PCS while pain intensity at the tested knee was correlated with depression. Pain intensity at the tested knee and global pain intensity were highly correlated with one another (rho = 0.583) which explains why some factors were correlated with both of them.

#### 6.7.1. Subject Characteristics

The subjects recruited into the present study were representative of the source population (EPIFUND cohort). The proportion of women in the present study (59.7%) was comparable to the 565 responders of the EPIFUND cohort follow-up mailing identified as having knee pain using the Manchester manikin coding (62.1%; Table 4.2). The average age of 60.1 years (±8.9) for the EPIFUND cohort follow-up responders with knee pain (see Table 4.2) was similar to the average age of subjects in the present study (62.5 ± 9.0). There were noteworthy differences between the source population and the subjects in the present study. The proportion of people aged over 60 with knee pain in the follow-up survey (53.8%) was notably lower than in the present study (69.4%). Also, 79% of subjects in the present study were recruited from one part of the recruitment area (Bollington) compared to 47% in the EPIFUND cohort (Table 4.2). The socioeconomic status (categorised as least deprived, less deprived, deprived and most deprived) of subjects in Bollington differed to those in South Manchester. Fifty four subjects (75%) in the present study were
categorised as less or least deprived compared to 54% in the EPIFUND cohort (Table 4.2), with 53 of the 54 subjects categorised as less or least deprived residing in Bollington. As such, the sample in the present study was not representative of the EPIFUND cohort with regards to socioeconomic status.

The characteristics for subjects in the present study were also comparable with other population-based studies. A study in Spain demonstrated that of 218 people aged 40 and over with prevalent knee pain responding to a postal survey and subsequently interviewed, 162 (74.31%) were female and 173 (79.36%) subjects were aged over 60 (Fernandez-Lopez et al. 2008) indicating a higher prevalence of knee pain in older people and in women. The present study demonstrated that 75% of subjects were overweight or obese; this is consistent with the increased risk of being overweight or obese in knee OA subjects (OR 3.16; 95% CI 2.78, 3.59) (Blagojevic et al. 2010). The present study also demonstrated that few subjects report pain solely in the tested knee with 56 (77.8%) and 60 (83.3%) of subjects reporting pain in at least one other body region using the ACR and Manchester manikin coding schedules, respectively. This supports the findings of Kamaleri et al. (2008a) and Croft et al. (2005) who reported that in excess of 75% of subjects reported the presence of pain at the knee and at least one other site.

6.7.2. The influence of age and sex on QST, psychosocial factors and pain

The influence of age

A significant increase in mechanical pain sensitivity and alldynia at the knee and decreasing median coherence scores (with lower scores indicating greater coherence) were observed across the age bands with the highest median scores observed in the 70+ group. Age also influenced mechanical pain thresholds at the forearm, but it did not follow a linear pattern. Reduced sensitivity was observed for the 50-59 age band compared with the others, but this was likely to be due to the wide range observed for forearm mechanical pain threshold in this age band (13.7–512 mN). Age was also shown to significantly moderate the associations between heat pain thresholds at the knee and forearm with global pain intensity in the 70+ age band.

Only one previous study investigated age differences by assessing pressure pain thresholds and tolerances before and after resistance exercises in 11 subjects with knee OA (65.9±10.4 years), 11 age-matched healthy controls (61.3±8.2 years) and 11 younger healthy controls (25.0±4.9 years) (Burrows et al. 2014). Despite significant improvements in pressure pain thresholds following the resistance exercise, no differences were observed between groups for pressure pain thresholds or tolerances (Burrows et al. 2014).

There were only 12 subjects within the 50-59 age band in the present study, with the 60-69 age band over-represented (n=27). As such, the finding for forearm mechanical pain threshold was likely due to the wider range of observations for the 50-59 age-band rather than a true effect. There were also overlaps in the 95% CIs reported for each age band and there was no overall age-
related trend observed for the associations between heat pain thresholds and global pain intensity. A decline in somatosensory functioning with age is thought to occur, but studies have not provided consistent results for pressure and thermal pain thresholds (Gibson et al. 2004). Future studies investigating whether age does moderate the association between QST measures and pain intensity should be performed.

The influence of sex

The present study identified women were more sensitive than men for tender point count, heat pain at the knee, pressure pain at both test sites and for mechanical pain sensitivity at the knee. Men scored higher for the personal control item of the IPQ-Brief (indicating a lower level of control) and had marginally higher sensitivity to allodynia at the forearm. There were also sex differences observed for the associations between global pain and wind-up ratio at the knee, and pain intensity at the tested knee with DNIC and heat pain threshold at the forearm. Females tended to be more sensitive to wind-up, DNIC and forearm heat pain thresholds at higher pain intensities while men demonstrated a tendency to be more sensitive for these measures at lower pain intensities. However, it is possible the sex differences for the associations previously described were due to opposing trends observed for men and women.

One previous study investigated sex differences for QST measures in subjects with knee OA (Gerecz-Simon et al. 1989), with another study investigating sex as a predictor of walking distance and pain (Wideman et al. 2014). Gerecz-Simon et al. (1989) demonstrated significantly lower pressure pain thresholds for women at 6 bilateral test sites (forehead, deltoid, mid-forearm, thumb, quadriceps and medial knee joint line) in a study of 126 subjects with rheumatoid arthritis (n=36; 50% male), OA (n=36; 50% male), ankylosing spondylitis (n=18; 100% male) and pain-free controls (n=36; 50% male) (Gerecz-Simon et al. 1989). Two studies adjusted for sex in the analyses although this had no impact on the reported results (King et al. 2013; Neogi et al. 2013). One issue with investigating sex differences is that women tend to be over-represented in studies of knee OA, with 24 (77.4%) of 31 studies in Table 2.3 using a greater proportion of women, 4 studies (12.9%) using an equal proportion and 3 studies (9.7%) using a greater proportion of men.

Although the present study identified sex differences, this exploratory analysis also identified overlaps in the interquartile ranges and 95% CIs for all variables and associations that differed by sex in the present study. This is likely due to a lack of power to detect sex differences among the 36 women and 25 men in the study sample. A meta-analysis by Riley III et al. (1998) recommended a sample size of 41 per group to investigate sex differences in QST measures for healthy subjects. A recent systematic review providing an update on sex differences in QST also reported mixed results and suggested that experimental pain models may not demonstrate consistent sex differences due to the laboratory settings used (Racine et al. 2012b).
6.7.3. Factors associated with pain intensity

QST predictors of pain intensity

In the present study, a greater number of tender points were significantly associated with higher levels of global pain intensity. Increased sensitivity to mechanical pain sensitivity at the knee and forearm, and allodynia at the knee were identified as predictors of global pain intensity and pain intensity at the tested knee.

Only two previous studies have investigated QST measures with respect to pain intensity in a population-based sample of people with knee pain (King et al. 2013; Neogi et al. 2013). Neogi et al. (2013) demonstrated significant associations between pressure pain thresholds and mechanical temporal summation with two measures of pain (the presence of frequent knee pain and WOMAC knee pain severity) that persisted after controlling for confounders (age, sex, BMI, race, clinic site, radiographic severity, patellofemoral knee OA, knee injury, depression, catastrophising and analgesic use) in a study of 2126 community-dwelling older adults. However, no associations were observed for the presence or severity of radiographic OA at the knee with QST measures. The findings of the present study support the findings of Neogi et al. (2013) with significant associations observed between mechanical assessments and pain. The authors of the study suggested their findings reflected the presence of a predisposition to sensitisation (inherent trait) rather than the development of sensitisation (state induced by osteoarthritic pathology) (Neogi et al. 2013).

However, this explanation does not address the possibility of reversing sensitisation as shown following total joint replacements (Beswick et al. 2012; Wylde et al. 2013). Plasticity within the nervous system could be a future target for intervention, particularly for the reversal of altered pain processing pathways through interventions such as coping skills training (France et al. 2004).

A recent study demonstrated that subjects with severe radiographic disease (KL grade 3 or 4) who report mild pain do report significantly lower pain scores (0-100 NRS) to mechanical temporal summation at the finger (24.5±18.3 vs. 44.3±30.4), thermal temporal summation at the forearm (63.7±21.5 vs. 83.7±18.5) and cold pressor tests (68.8±16.9 vs. 75.7±22.5) compared with subjects with mild radiographic disease (KL grade 1 or 2) and more severe pain (Finan et al. 2013b). These subjects also have higher pressure pain thresholds at the quadriceps in comparison with the subjects with milder disease and higher pain (616±225 vs. 439±228.2 kPA, respectively) (Finan et al. 2013b). These findings indicate there may be amplifications within central pain processing pathways in subjects with high pain and milder disease that are not observed for subjects with severe disease and low pain, suggesting a predisposition to sensitisation as suggested by Neogi et al. (2013). However, the same study investigated two other groups (high pain with severe disease and low pain with milder disease) and observed similar trends for the two groups with high pain, and for the two groups with low pain suggesting underlying disease also contributes to pain reporting in some people (Finan et al. 2013b).

King et al. (2013) demonstrated that there were no differences in thermal or mechanical pain thresholds and pain tolerances in a population-based sample of people with knee OA (n=96) reporting a high number of symptoms compared with a group (n=113) with a low number of symptoms related to knee OA, and a pain-free control group (n=107). However, the amount of pain
perceived (assessed using VAS ratings) for heat pain thresholds at the knee (28.6, 95% CI 23.6, 33.5) and forearm (27.6, 95% CI 22.8, 32.5) were significantly higher (p<0.01) in the high symptom count group compared with the low symptom count group (knee 18.9, 95% CI 14.7, 23.0; forearm 17.9, 95% CI 13.8, 22.1) and healthy controls (knee 19.5, 95% CI 14.7, 23.0; forearm 19.6, 95% CI 15.3, 23.9) (King et al. 2013). Significant differences in pressure, mechanical and cold pain thresholds were also observed with the high pain severity group more sensitive to all measures at all test sites (King et al. 2013). This study focused on pain intensity and increased number of symptoms to stratify subjects and did not include measures of pain-related beliefs or psychological distress, although the high symptom count group scored significantly higher (p<0.01) for disability (57.2, 95% CI 53.1, 61.2) compared with the low symptom count (24.9, 95% CI 21.5, 28.3) and control groups (4.9, 95% CI 1.4, 8.6).

The assessments of mechanical pain sensitivity and allodynia in the present study differ to pain thresholds as these measures require subjects to quantify how much pain they perceive during testing. Providing pain ratings (compared with indicating when a stimulus first feels painful) elicits different aspects of pain processing and may be influenced by other qualities of pain, such as the intensity and unpleasantness experienced during testing (Keefe et al. 1997). Pain thresholds in the Rolke et al. (2006a) protocol were determined by subjects indicating the first sensation of pain for cold, heat, mechanical and pressure stimuli and did not include pain ratings of the thresholds. Both the neuromatrix of pain and the fear-avoidance model suggest that the integration of negative emotional and cognitive processes during the experience of pain can exacerbate the experience of pain (Vlaeyen et al. 2000; Melzack 2001). Future studies using the DFNS protocol should consider the inclusion of pain ratings during testing in the same way as the study by King et al. (2013).

**Psychosocial predictors of self-reported pain intensity**

Higher levels of helplessness and disability, and stronger beliefs about pain such as greater concern, the effect pain has on life (consequences), how long pain will continue (timeline), the number of pain-related symptoms (identity), and the emotional impact of pain (emotion) were significantly associated with both measures of pain intensity. The rumination item of the PCS and consequences item of the IPQ-Brief were also identified as two of the best predictors of knee pain intensity with the consequences item also one of the best predictors of global pain intensity. No previous studies have investigated the role of illness perceptions in people with knee pain, either in relation to underlying disease or pain intensity meaning the findings of the present study were novel.

The findings of the present study were consistent with clinical samples of knee OA subjects. Previous studies have demonstrated that higher levels of depression and lower levels of physical functioning were observed for subjects with painful knee OA (Wideman et al. 2014), with higher levels of anxiety, depression, sleep disturbances, catastrophising and helplessness associated with higher knee pain intensities (Creamer et al. 1999a; Finan et al. 2013a). Higher levels of anxiety and depression were also associated with higher levels of disability and higher levels of negative affect were associated with higher daily pain ratings (Keefe et al. 1997). Finan et al. (2013b) also
demonstrated significant differences in pain catastrophising (20.9±12.1 vs. 8.5±7.3), anxiety (35.8±11.6 vs. 28.3±7.7) and depression (15.4±9.5 vs. 6.9±6.5) for subjects with high pain and milder disease compared with subjects with low pain and severe disease, respectively.

The previous studies used clinical samples of subjects with knee OA (Keefe et al. 1997; Creamer et al. 1999a; Finan et al. 2013b; Wideman et al. 2014), while the present study demonstrates that these findings are also applicable to population-based samples with knee pain, regardless of radiographic disease progression. This suggests that structural progression, while an important clinical marker of disease, has little bearing on the relationship between pain intensity and psychosocial factors, such as catastrophising, sleep disturbances, negative affect, anxiety, or depression, in those with knee pain.

The findings of the present study support two theories of pain: the neuromatrix of pain (Melzack 2001) and the fear-avoidance model (Vlaeyen et al. 2000). The neuromatrix of pain proposes sensory input can be augmented by the affective and cognitive components of pain processing within the brain (Melzack 2001). The present study provides support for the hypothesis as psychosocial factors including pain catastrophising and illness perceptions were associated with higher levels of pain intensity globally and at the knee. The fear-avoidance model posits that negative affect can influence pain catastrophising and drive fear associated with pain, which can lead to the development of a negative feedback loop including lower physical functioning, higher levels of disability, and depression (Vlaeyen et al. 2000). The present study also provides support for parts of the fear-avoidance model with associations observed for higher levels of self-reported global and knee pain intensities with illness perceptions and pain catastrophising.

Psychosocial mediators of the relationship between QST and pain intensity

Individual psychosocial factors, including the consequences and concern items of the IPQ-Brief and the rumination subscale of the PCS, were significant partial mediators of association between measures of mechanical hyperalgesia and self-reported pain intensity. Only one previous study investigated pain catastrophising as a mediating factor for the association between sex and a latent pain-related outcome measure comprising observed measures of pain intensity, disability and pain behaviour in 168 subjects with knee OA (96 females; 61.1±10.6 years) (Keefe et al. 2000a). Significant sex differences were observed for pain intensity, disability and pain behaviour with women consistently reporting higher levels for each (Keefe et al. 2000a). A significant direct effect was observed for sex and the latent pain-related outcomes variable with catastrophising a significant partial mediator of that association when added into the model; the effect of catastrophising as a partial mediator remained significant after controlling for depression in the model (Keefe et al. 2000a). These findings demonstrated that women are more likely than men to report pain, and that relationship is to some degree explained by catastrophizing (Keefe et al. 2000a).
6.7.4. **Strengths of the present study**

Three novel findings were identified by the present study:

(i) illness perceptions and mechanical hyperalgesia were strongly associated with self-reported global and knee pain intensities;

(ii) stronger associations were observed for the indirect effect compared with the direct effect when psychosocial factors modelled as a latent variable were included as mediators of the associations between measures of mechanical hyperalgesia (tender point count, knee mechanical pain sensitivity and knee allodynia) and global pain intensity;

(iii) stronger associations were observed for the direct effect compared with the indirect effect when psychosocial factors modelled as a latent variable were included as mediators of the associations between measures of mechanical hyperalgesia at the knee (mechanical pain sensitivity and allodynia) and pain intensity at the tested knee.

A strength of the present study is the use of structural equation modelling to address the impact of psychosocial factors on the relationship between greater pain sensitivity (assessed using QST) and higher levels of pain intensity, both globally and at the tested knee. No other studies of community-dwelling adults with knee pain have investigated both somatosensory and psychosocial factors in relation to global pain intensity and knee pain intensity. Structural equation modelling also enables latent variables to be modelled from observed values and the inclusion of error terms for all variables within the model (Hayes 2009). This provides an opportunity to apply a theoretical model to the data collected. The associations between QST measures, psychosocial factors and pain intensity have not previously been modelled in this way, and as such the relationship between these factors was unclear.

Another strength of the present study was that the findings supported previous research in subjects with knee OA typically recruited through primary or secondary care. Community-based samples tend to be more representative of people with knee pain in the general population, whereas samples of clinical populations tend to be more distressed with worse overall health outcomes (Arden 2008). Previous studies have also identified deep tissue hyperalgesia (increased sensitivity to pressure pain thresholds) as a way of distinguishing subjects with painful knee OA from healthy controls (Wessel 1995; Imamura et al. 2008; Lee et al. 2011; Wylde et al. 2011; Wylde et al. 2012; Wylde et al. 2013) and from subjects with knee OA reporting lower or no pain (Williams et al. 2004; Finan et al. 2013b; Skou et al. 2013b). However, this study determined that within-person, mechanical hyperalgesia was an indicator of higher levels of self-reported pain. This is a novel finding and demonstrates the need for future studies to include mechanical measures in their test batteries.

The findings of this study also provide support for the theories of pain outlined in Chapter 1. The neuromatrix of pain proposes sensory input can be augmented by the affective and cognitive components of pain processing within the brain (Melzack 2001). This is similar to the fear-avoidance model which suggests that negative illness beliefs, pain catastrophising and higher
levels of disability all contribute to a negative feedback loop, which may contribute to the persistence of chronic pain (Vlaeyen et al. 2000). The present study demonstrated stronger associations for the indirect effect between mechanical hyperalgesia and global pain intensity via a latent psychosocial mediator than for the direct effect. This suggests the factors contributing to the latent psychosocial mediator, such as illness perceptions and pain catastrophising, contributed more to the levels of global pain intensity observed than mechanical hyperalgesia.

The presence of hyperalgesia is thought to be indicative of amplifications within the CNS, also known as central sensitisation (Woolf 2010). The associations between higher tender point counts and the presence of mechanical hyperalgesia at both the knee and at a pain-free control site with self-reported pain intensities globally and at the knee suggest more generalised changes in pain processing, such as central sensitisation. The role of sensitisation is also supported by the stronger associations observed for the direct effect of knee pain intensity with both mechanical pain sensitivity and allodynia at the knee suggesting peripheral input at the knee reflects higher levels of pain reported for the same site. While this finding may be interpreted as evidence for the presence of peripheral sensitisation, it is more likely to be an artefact of central sensitisation due to the presence of mechanical hyperalgesia at sites outside of the knee which are also strongly associated with global pain intensity.

6.7.5. Limitations of the present study

There are a number of limitations for the present study. Firstly, all of the associations observed were cross-sectional. While the present study provides insight into the associations between QST measures, psychosocial factors and pain intensity cross-sectionally, it is not known whether mechanical hyperalgesia or illness perceptions can be used to predict likelihood of developing severe pain at subsequent time points. This requires further investigation as predictors of pain intensity may be used as a clinical tool to aid with the development of personalised treatment plans for people with knee pain.

A second limitation is the findings of the exploratory analyses performed to determine the impact of age and sex on pain intensity, QST measures, or psychosocial factors, or as moderators of the relationship between pain intensity and QST measures or psychosocial factors. Age and sex differences were observed in the present study, but those differences were small and the interquartile ranges for all variables overlapped with the other age bands or opposite sex. While the present study was not designed or sized to answer those questions, it demonstrated sex and/or age may impact the associations between pain intensity and QST measures and that there were no effects observed for the associations between psychosocial factors and pain intensity.

Another limitation with the present study is the definitions of global and knee pain intensity used. This was the first study to include self-reported levels of global and knee pain intensity over the past month. However, these measures of pain intensity may not correlate well with current QST assessments because they were not reflective of pain intensity at the time of testing. Knee pain is rarely continuously present and it fluctuates in occurrence and duration, which may also influence
pain reporting (Bellamy et al. 1990). The results of previous studies investigating associations between knee pain intensity and sensitivity to QST have also varied: eight studies demonstrated significant associations between QST measures and pain intensity scores using the WOMAC (pain in the past week) (Imamura et al. 2008; Shakoor et al. 2012; Wylde et al. 2013; Neogi et al. 2013), VAS for pain in the previous 24 hours (Arendt-Nielsen et al. 2010; Skou et al. 2013a) and current pain (King et al. 2013; Skou et al. 2013b), and the presence of frequent knee pain in the past month (Neogi et al. 2013). There were also three studies that demonstrated no association between QST measures and WOMAC pain (Creamer et al. 1999a; Finan et al. 2013a) or the McGill Pain Questionnaire (Creamer et al. 1999a). Future studies investigating the association between QST measures and pain intensity should consider the use of multiple pain measures to address current and recent pain intensities.

Of the 11 studies outlined above, only one study with significant associations for increased sensitivity to QST measures and greater pain intensity calculated and achieved their sample size (Shakoor et al. 2012). Two large population-based studies (n=2126 and n=316) did not perform sample size calculations (Neogi et al. 2013; King et al. 2013) and two studies determined their sample size by exceeding the number of subjects assessed in previous studies (n=100 and n=101) (Wylde et al. 2011; Wylde et al. 2013). All four studies also reported positive associations between QST measures and pain intensity. But, the associations in these studies were inconsistent as different QST measures were found to be associated with measures of pain captured over varying time intervals. It is difficult to draw conclusions from the current literature investigating the role of QST measures in subjects with knee OA due to a lack of consensus surrounding outcome measures, QST protocols, and which QST measures should be assessed. These issues must be addressed in order to provide robust evidence for the use of QST as a viable clinical tool. As such, QST measures are unlikely to be used clinically as a more objective measure of pain or sensitisation until a conclusion is drawn on whether QST measures reflect current levels of pain or to what extent they may reflect sensitisation in subjects with knee OA.

6.8. Conclusion

Mechanical hyperalgesia and pain-related beliefs are significant predictors of global pain and knee pain intensities in the past month in a population-based sample of people with knee pain. Stronger associations were observed for the indirect effect than the direct effect when a latent psychosocial mediator was included in the model for the association between QST measures and global pain intensity. This suggests that psychosocial factors, particularly illness perceptions, were driving self-reported global pain intensity levels more than peripheral somatosensory functioning in people with knee pain. Conversely, stronger associations were observed for the direct effect than the indirect effect between knee mechanical pain sensitivity and knee allodynia with self-reported pain intensity at the tested knee when the latent mediator was included. This suggests that peripheral somatosensory input at the knee does reflect self-reported pain intensity during the past month with the latent psychosocial mediator also contributing significantly to the model. These findings provide new insights into the mechanisms which may account for some of the discordance between radiographic OA and knee pain.
Future studies should also include repeat QST measures to determine whether QST and psychosocial factors alter according to the pain currently felt by the subject. Inclusion of radiographic confirmation of knee OA would also allow for disease severity to be investigated as a confounding factor of the relationships between pain intensity, psychosocial factors and somatosensory function.
CHAPTER 7. DOES QST CHANGE FOLLOWING INTRA-ARTICULAR STEROID THERAPY?

7.1. Summary

This chapter provides the characteristics for the 32 men and women (median age 61.5 years) from the TASK study who underwent QST assessments at the injected and contralateral knees at the baseline and post-injection study visits. The aim of the present study was to determine whether QST measures change following treatment. Detailed methods were described in Chapter 4 with methods for the analyses in this chapter presented in Section 7.5. No significant changes in QST measures were observed between the study visits or between knees following an intra-articular steroid injection in subjects with knee OA. However, increased sensitivity to mechanical pain threshold was associated with response to treatment with higher levels of personal control, treatment control and coherence significantly associated with diminished pain.

7.2. Introduction

The efficacy of intra-articular steroid therapy in the management of knee OA is well established, although response to treatment including duration of response varies substantially (Bellamy et al. 2006). There are few data concerning factors linked with response to treatment for intra-articular steroid injections in subjects with knee OA (Maricar et al. 2013) and to date, there have been no studies that have investigated the associations between QST and intra-articular steroid injections in subjects with symptomatic knee OA. There are data which look at the association between QST and treatment response in knee OA including the effect of (i) total knee replacement (Wylde et al. 2013), (ii) acupuncture (Takeda et al. 1994) (iii) knee mobilisation (Moss et al. 2007) and (iv) resistance exercise (Burrows et al. 2014) on pain. Diminished sensitivity to pressure pain was observed following the knee mobilisation (Moss et al. 2007), resistance exercise (Burrows et al. 2014), and acupuncture interventions (Takeda et al. 1994), while lower baseline pressure pain thresholds at the forearm were predictive of higher pain levels one year after total knee replacement surgery (Wylde et al. 2013). Only the latter study, however, investigated baseline QST measures as predictors of a change in pain following an intervention. None of the studies addressed the potential role of psychosocial factors.

7.3. Aims

This aims of the analyses presented in this chapter are to determine whether:

(i) sensitivity to stimuli, as assessed using QST, changes following intra-articular steroid therapy;
(ii) sensitivity to stimuli prior to the injection is associated with change in pain following intra-articular steroid therapy;

(iii) baseline psychosocial factors were associated with changes in pain or sensitivity.

7.4. Methods

Detailed methods are provided in Chapter 4. Subjects with symptomatic knee OA attending screening visits for the TASK study (an uncontrolled clinical trial of intra-articular steroid therapy) between 8th November 2011 and 7th May 2013 were provided with the information sheet for the sub-study. At the baseline visit for the TASK study, subjects who consented to take part in the sub-study underwent QST assessments at the injected and contralateral knees prior to receiving the injection. Also prior to the injection, a tender point examination was performed followed by QST assessments including mechanical detection and pain thresholds, mechanical pain sensitivity, dynamic mechanical allodynia, wind-up ratio, vibration detection threshold and pressure pain threshold (see Sections 4.2.4.4 and 4.3.4.3 for further details). The same assessments were performed at the post-injection visit 5 to 15 days following the injection. Information about psychosocial factors and pain were obtained from questionnaires administered as part of the main TASK study at screening, baseline and/or the post injection visit. These included the HAD and IPQ-Brief questionnaires and the KOOS pain scale

7.5. Statistical Analysis

The proportions of subjects screened and subsequently recruited for the TASK study during the data collection period for this sub-study (first to last screening: 8th November 2011 to 7th May 2013) were calculated. Proportions were also calculated for categorical demographic variables such as response to treatment, knee injected and the presence of pain in the contralateral knee. The median and IQR for continuous data were calculated including age, number of days between each study visit, baseline, post-injection and change in KOOS pain subscale scores and QST measures, and screening, post-injection and change in psychosocial factors. The Wilcoxon signed-rank test was used to determine if any within-person changes were observed for tender point count and QST measures at each knee following the intra-articular steroid therapy. The Wilcoxon rank-sum test was used to determine whether baseline QST measures at both knees and tender point count differed for subsequent treatment responders and non-responders.

Within-person differences in tender point count and for QST between knees (contralateral minus injected scores for baseline and post-injection visits) were assessed using one-sample t-tests. Linear regression (described in Section 6.5) was used to determine whether screening psychosocial factors could predict change in QST. In the analyses, change scores for tender point count and QST measures at both knees (outcomes) were regressed on the screening scores for the anxiety and depression subscales of the HAD and the 8 items of the IPQ-Brief (predictors).
Linear regression was also used to determine whether screening psychosocial factors were linked with change in pain. The change in score for the KOOS pain subscale was regressed on the screening scores for the HAD subscales and IPQ-Brief, and against tender point count and QST measures at baseline for all models. A Cook-Weisberg test was performed to detect linear forms of heteroscedasticity. Heteroscedasticity is a change in variance as the value of the independent variables changes, whereas homoscedasticity occurs when the variance is stable as the value of the predictor changes (Cook et al. 1983). The Cook-Weisberg test compares the null hypothesis that error variances were constant (indicating homoscedasticity) against the alternative that the variance changes as the independent variable increases or decreases; large Chi\(^2\) values for this test indicate heteroscedasticity.

Cook’s distance was used to test whether significant associations could be explained by individual outlying observations (Cook 1977); an observation with high leverage (difference between the value of an observation in a given variable and the sample mean for that variable) and/or high residual values (difference between the observed outcome and the expected value generated by the regression line) can influence the significance of an association. Cook’s distance combines these two measures to identify influential observations that may impact the results from a regression analysis (Cook 1977). For this reason, observations with a Cook’s distance of 4/n or greater \((n=32\text{ in the present study})\) were excluded from the analysis to determine the effect on the regression.

7.6. Results

7.6.1. Subjects

Eighty subjects were recruited from the TASK study during the data collection period for the present study. Twenty nine subjects (36.3%) were deemed ineligible for the TASK study with a lack of visible effusion at the index knee the most common reason for ineligibility \((n=14; 17.5\%)\). The remaining 51 \((subjects 63.8\%)\) were entered into the study with three \((3.8\%)\) withdrawn prior to the baseline visit for the study. Of the 48 subjects \((60\%)\) who attended the baseline visit, 37 \((46.3\%)\) completed assessments for the present study with the 11 subjects \((13.8\%)\) not assessed declining the invitation. In total, 32 subjects \((40\%)\) completed assessments at the post-injection visit. Five subjects \((6.3\%)\) were withdrawn following the baseline sub-study assessments; 1 \((subject 1.3\%)\) was withdrawn as they had recently received an intra-articular steroid injection to the contralateral knee, 1 subject \((1.3\%)\) withdrew prior to receiving the injection, and 1 subject \((1.3\%)\) withdrew due to experiencing claustrophobia during the baseline MRI scan. A further 2 subjects \((2.5\%)\) were unable to complete the post-injection assessments.
7.6.2. **Subject Characteristics**

The median age of the 32 subjects who contributed both baseline and follow up data was 61.5 (IQR 54.5-72.5 years) with 21 women (65.6%) completing the study (Table 7.1). The median time from screening to the post-injection visit was 46.3 days (±15.3) with a median of 7.5 days (IQR 7-10) between the baseline and post-injection visits. The right knee was the more frequently injected knee with 20 subjects (62.5%) reporting more severe pain scores, a greater number of symptoms, and/or having higher grades of radiographic disease for that knee. There were 11 subjects (34.4%; 5 males, 6 females) with at least one observation missing. Seven subjects (21.9%) did not complete all screening or post-injection visit questionnaire items: two subjects did not have QST assessments at the contralateral knee at baseline and at the post-injection visit, one subject had incomplete baseline QST assessments and one subject had incomplete baseline QST assessments and incomplete screening questionnaire data.

The median scores for the anxiety (6, IQR 3-9) and depression (4, IQR 2-8) subscales of the HAD were below the cut-off point for a possible case of anxiety or depression (≤7; see Table 7.1).
However, 4 subjects did fulfil the criteria for a possible case of anxiety (score ≥8 and ≤10) with 2 subjects as possible cases for depression. Twelve subjects also met the criteria as a probable case of anxiety (score ≥11) with 9 probable cases of depression also identified. In relation to the IPQ-Brief, the highest median scores were reported for the timeline (9.5, IQR 8-10), identity (7, IQR 5-9) and concern (8, IQR 5-10) items of the IPQ-Brief indicating subjects believe their pain will continue for a long time, they were experiencing a greater number of symptoms related to their pain and they were more concerned about their pain, respectively. A low median score for the coherence item (0.5, IQR 0-4) indicates subjects were reporting a greater understanding of their pain, while a low median score for treatment control (2, IQR 0-5) indicates they believe treatment will help to reduce their pain.

### Table 7.1 Subject Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females (%)</td>
<td>21 (65.6%)</td>
</tr>
<tr>
<td>Age (years; median (IQR))</td>
<td>61.5 (54.5-72.5)</td>
</tr>
<tr>
<td>Right knee injected (%)</td>
<td>20 (62.5%)</td>
</tr>
<tr>
<td>Pain in opposite knee (%)</td>
<td>14 (43.8%)</td>
</tr>
<tr>
<td>Treatment Responders (%)</td>
<td>21 (65.6%)</td>
</tr>
<tr>
<td>Screening HAD (0-21 sub-scales)</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td>Anxiety (1-17)</td>
<td>6.0 (3.0-9.0)</td>
</tr>
<tr>
<td>Depression (1 to 15)</td>
<td>4.0 (2.0-8.0)</td>
</tr>
<tr>
<td>Screening IPQ-Brief (0-10 scale per item)</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td>Consequences (1-10)</td>
<td>6.0 (3.0-8.0)</td>
</tr>
<tr>
<td>Timeline (2-10)</td>
<td>9.5 (8.0-10.0)</td>
</tr>
<tr>
<td>Personal Control (0-10)</td>
<td>5.0 (2.0-7.0)</td>
</tr>
<tr>
<td>Treatment Control (0-6)</td>
<td>2.0 (0-5.0)</td>
</tr>
<tr>
<td>Identity (1-10)</td>
<td>7.0 (5.0-9.0)</td>
</tr>
<tr>
<td>Concern (3-10)</td>
<td>8.0 (5.0-10.0)</td>
</tr>
<tr>
<td>Coherence (0-6)</td>
<td>0.5 (0-4.0)</td>
</tr>
<tr>
<td>Emotion (0-10)</td>
<td>5.0 (2.0-6.0)</td>
</tr>
<tr>
<td>Time between visits (days)</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td>Screening to Baseline (7-79)</td>
<td>37 (23-49)</td>
</tr>
<tr>
<td>Baseline to Week One (6-16)</td>
<td>7.5 (7-14)</td>
</tr>
<tr>
<td>Screening to Week One (21-88)</td>
<td>46 (35-57)</td>
</tr>
</tbody>
</table>

IQR = interquartile range; HAD = Hospital Anxiety and Depression scale; IPQ = Illness Perception Questionnaire Brief.

#### 7.6.3 Pain and QST measures pre- and post-injection

The median values for the KOOS pain scale and QST measures at baseline and follow up at the index and contralateral knees, and also mean changes in these variables between baseline and follow up are shown in Table 7.2. The scores for tender point count and each QST measure at
Baseline and post-injection visit were not normally distributed; the distribution was determined by plotting histograms of each variable. The KOOS pain scores at both visits were normally distributed as were the change scores for each variable (post-injection visit minus baseline). The median KOOS pain subscale score was higher at the post-injection visit (68.8, IQR 50.0-87.5 compared with 43.8, IQR 32.8-56.3) indicating a significant improvement in pain following the injection (p<0.001; Table 7.2). The median score for wind-up ratio exceeds 1.0 at both knees and for both visits indicating that subjects reported higher pain following the train of stimuli compared with the single application.

### Table 7.2 Median scores for baseline and post-injection and mean change values for KOOS pain score, tender point count and QST measures at both knees

<table>
<thead>
<tr>
<th>Variable (Range)</th>
<th>Baseline (IQR)</th>
<th>Post-injection (IQR)</th>
<th>Change (±SD)*</th>
<th>p-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>KOOS Pain Score (0-100)</td>
<td>43.8 (32.8-56.3)</td>
<td>68.8 (50.0-87.5)</td>
<td>23.6 (±23.0)</td>
<td>0.0000</td>
</tr>
<tr>
<td>Tender point count (0-18)</td>
<td>0.5 (0-2.0)</td>
<td>0 (0-2.0)</td>
<td>0.03 (±2.3)</td>
<td>0.6734</td>
</tr>
<tr>
<td>Injected knee</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDT (0-512 mN)</td>
<td>5.9 (1.4-17.2)</td>
<td>8.0 (1.9-13.5)</td>
<td>-8.73 (±69.5)</td>
<td>0.7014</td>
</tr>
<tr>
<td>MPT (0-512 mN)</td>
<td>64 (39.5-111.7)</td>
<td>42.2 (25.1-111.4)</td>
<td>-16.9 (±60.1)</td>
<td>0.1722</td>
</tr>
<tr>
<td>MPS (0-100 NRS)</td>
<td>3.8 (1.2-9.6)</td>
<td>2.9 (0.7-7.6)</td>
<td>-1.81 (±6.2)</td>
<td>0.0888</td>
</tr>
<tr>
<td>Allodynia (0-100 NRS)</td>
<td>0 (0-0.7)</td>
<td>0 (0-0.6)</td>
<td>0.42 (±2.1)</td>
<td>0.7939</td>
</tr>
<tr>
<td>Wind-up ratio (≥1)</td>
<td>2.6 (1.7-4.2)</td>
<td>2.2 (1.6-3.0)</td>
<td>-0.29 (±2.0)</td>
<td>0.3939</td>
</tr>
<tr>
<td>Vibration detection (0-8)</td>
<td>3.3 (2.3-4.7)</td>
<td>3 (1.5-4.3)</td>
<td>-0.51 (±1.9)</td>
<td>0.1074</td>
</tr>
<tr>
<td>Pressure pain (0-10 kg/cm²)</td>
<td>4.5 (3.1-6.1)</td>
<td>4.3 (2.8-6.1)</td>
<td>-0.32 (±1.5)</td>
<td>0.2617</td>
</tr>
<tr>
<td>Contralateral knee</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDT (0-512 mN)</td>
<td>4.0 (1.2-12.1)</td>
<td>4.0 (1.9-9.2)</td>
<td>-4.60 (±34.5)</td>
<td>0.8774</td>
</tr>
<tr>
<td>MPT (0-512 mN)</td>
<td>73.7 (32.0-157.6)</td>
<td>61.9 (32.0-128.0)</td>
<td>-9.30 (±61.4)</td>
<td>0.4715</td>
</tr>
<tr>
<td>MPS (0-100 NRS)</td>
<td>2.5 (1.1-5.3)</td>
<td>2.4 (0.9-3.8)</td>
<td>-0.05 (±3.8)</td>
<td>0.4106</td>
</tr>
<tr>
<td>Allodynia (0-100 NRS)</td>
<td>0 (0-0.3)</td>
<td>0 (0-0.3)</td>
<td>-0.10 (±1.8)</td>
<td>0.9366</td>
</tr>
<tr>
<td>Wind-up ratio (≥1)</td>
<td>2.3 (1.7-3.5)</td>
<td>2.1 (1.7-3.4)</td>
<td>-0.63 (±2.1)</td>
<td>0.3638</td>
</tr>
<tr>
<td>Vibration detection (0-8)</td>
<td>3.7 (1.7-4.7)</td>
<td>3.3 (2.3-4.3)</td>
<td>-0.09 (±1.7)</td>
<td>0.2511</td>
</tr>
<tr>
<td>Pressure pain (0-10 kg/cm²)</td>
<td>4.6 (3.3-6.5)</td>
<td>4.1 (3.2-5.9)</td>
<td>-0.28 (±1.1)</td>
<td>0.1985</td>
</tr>
</tbody>
</table>

IQR = interquartile range; SD = standard deviation; * Negative change scores for MDT, MPT and pressure pain, and positive change scores for tender point, MPS, allodynia, wind-up ratio and vibration detection, indicate higher sensitivity at the post-injection visit compared to baseline. †= Wilcoxon matched-pairs signed-rank, p<0.05 in bold and 0.05≤p<0.1 if in italics; KOOS = Knee Osteoarthritis Outcome and Injury Score; MDT = mechanical detection threshold; MPT = mechanical pain threshold; MPS = mechanical pain sensitivity; mN = milli-Newton; NRS = numeric rating scale.

A marginal increase in sensitivity at the post-injection visit was observed for pressure pain, mechanical detection and mechanical pain thresholds at both knees and allostynia at the injected knee. A marginal decrease in sensitivity at the post-injection visit was also observed for mechanical pain sensitivity, wind-up ratio and vibration detection at both knees, allostynia at the contralateral knee, and tender point count. However, the mean changes were small. There were no significant
within-person differences in any of the QST measures, although mechanical pain sensitivity at the injected knee was approached significance (p=0.0888; Table 7.2).

Marginally higher sensitivity to pressure pain thresholds and wind-up ratio, though non-significant, were observed at the injected knee compared with the control knee following intra-articular steroid therapy. Marginally higher sensitivity was also observed for allodynia and mechanical detection and pain thresholds, though non-significant, at the control knee compared with the injected knee at both visits (Table 7.3). Other differences observed between knees were small and again not significantly different, including increased sensitivity to mechanical pain sensitivity and vibration detection at the injected knee at baseline and the control knee at the post-injection visit. Only mechanical pain sensitivity was approaching significance (p=0.0529) for within-person differences at the knees at baseline with the injected knee more sensitive than the control knee.

Table 7.3  Mean difference in QST between knees for each visit; one sample T-test

<table>
<thead>
<tr>
<th>Difference between knees †</th>
<th>Baseline (±SD)</th>
<th>p-value *</th>
<th>Week One (±SD)</th>
<th>p-value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical detection threshold</td>
<td>-20.2 (±73.8)</td>
<td>0.1446</td>
<td>-15.5 (±52.2)</td>
<td>0.1147</td>
</tr>
<tr>
<td>Mechanical pain threshold</td>
<td>-10.8 (±78.1)</td>
<td>0.4565</td>
<td>-1.92 (±77.8)</td>
<td>0.8932</td>
</tr>
<tr>
<td>Mechanical pain sensitivity</td>
<td>-1.88 (±5.1)</td>
<td>0.0529</td>
<td>0.08 (±3.5)</td>
<td>0.9000</td>
</tr>
<tr>
<td>Allodynia</td>
<td>0.75 (±2.8)</td>
<td>0.1674</td>
<td>0.18 (±2.4)</td>
<td>0.6800</td>
</tr>
<tr>
<td>Wind-up ratio</td>
<td>-0.16 (±1.5)</td>
<td>0.5607</td>
<td>-0.44 (±1.7)</td>
<td>0.1852</td>
</tr>
<tr>
<td>Vibration detection threshold</td>
<td>-0.23 (±1.5)</td>
<td>0.4226</td>
<td>0.14 (±17)</td>
<td>0.6471</td>
</tr>
<tr>
<td>Pressure pain threshold</td>
<td>0.01 (±1.4)</td>
<td>0.9583</td>
<td>0.13 (±1.1)</td>
<td>0.5245</td>
</tr>
</tbody>
</table>

† Contralateral knee minus injected knee; * 0.05≤p<0.1 if in italics; SD = standard deviation.

7.6.4. QST measures and change in pain

Baseline tender point count and measures of QST at the injected and contralateral knees were investigated as predictors of change in pain using the KOOS pain subscale. Tender point count and QST measures at baseline were not found to be significant predictors of change in pain at the 5% level (Table 7.4). The association between baseline pressure pain threshold at the injected knee and change in pain was identified as heteroscedastic (significant Chi² value for Cook-Weisberg test), with the Chi² value for the association between baseline wind-up ratio at the injected knee and change in pain approaching significance (p=0.0801) also indicating heteroscedasticity. Wind-up ratio at the contralateral knee was approaching significance for predicting pain scores following the injection (β 3.4859; 95% CI -0.037, 7.008) indicating that greater wind-up at the control knee at baseline predicts improvements in pain following treatment. Baseline pain was also regressed against baseline QST measures to determine if any of the associations occurred cross-sectionally; pressure pain at the injected knee was significantly associated with baseline pain (β 3.362; 95% CI 0.340, 6.384) with wind-up ratio at the injected knee (β -3.057; 95% CI -6.623, 0.510), wind-up ratio at the contralateral knee (β -2.633; 95% CI -5.285, 0.019) and pressure pain at the contralateral knee (β 3.333; 95% CI -0.008, 6.673)
approaching significance. No other associations were observed. Baseline pain was also included in the regression between baseline QST measures with change in pain as baseline pain may predict pain at follow-up; the results of this analysis are presented in Table VIII-1, Appendix VIII.

Table 7.4  Linear regression of change in pain against baseline QST measures

<table>
<thead>
<tr>
<th></th>
<th>β-coefficient</th>
<th>95% CI *</th>
<th>Cook-Weisberg *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tender point count</td>
<td>1.1843</td>
<td>-4.311, 6.680</td>
<td>0.15</td>
</tr>
<tr>
<td>Injected knee</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDT</td>
<td>0.0841</td>
<td>-0.026, 0.194</td>
<td>0.35</td>
</tr>
<tr>
<td>MPT</td>
<td>-0.0666</td>
<td>-0.154, 0.020</td>
<td>0.86</td>
</tr>
<tr>
<td>MPS</td>
<td>0.7559</td>
<td>-0.179, 1.691</td>
<td>0.02</td>
</tr>
<tr>
<td>Allodynia</td>
<td>-5.3949</td>
<td>-11.857, 1.067</td>
<td>0.01</td>
</tr>
<tr>
<td>Wind-up</td>
<td>3.7099</td>
<td>-1.117, 8.537</td>
<td>3.06</td>
</tr>
<tr>
<td>Vibration detection</td>
<td>-0.2901</td>
<td>-4.904, 4.324</td>
<td>0.22</td>
</tr>
<tr>
<td>Pressure pain</td>
<td>-0.8964</td>
<td>-5.190, 3.400</td>
<td><strong>3.98</strong></td>
</tr>
<tr>
<td>Contralateral knee</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDT</td>
<td>0.1962</td>
<td>-0.061, 0.453</td>
<td>0.89</td>
</tr>
<tr>
<td>MPT</td>
<td>-0.0747</td>
<td>-0.200, 0.051</td>
<td>0.00</td>
</tr>
<tr>
<td>MPS</td>
<td>0.9109</td>
<td>-0.360, 2.182</td>
<td>0.33</td>
</tr>
<tr>
<td>Allodynia</td>
<td>1.3005</td>
<td>-1.680, 4.281</td>
<td>0.51</td>
</tr>
<tr>
<td>Wind-up</td>
<td>3.4859</td>
<td>-0.037, 7.008</td>
<td>0.22</td>
</tr>
<tr>
<td>Vibration detection</td>
<td>-1.0079</td>
<td>-5.153, 3.138</td>
<td>0.64</td>
</tr>
<tr>
<td>Pressure pain</td>
<td>2.6543</td>
<td>-1.205, 6.514</td>
<td>1.18</td>
</tr>
</tbody>
</table>

CI = confidence interval; * p<0.05 if bold and 0.05≤p<0.1 if in italics; MDT = mechanical detection threshold; MPT = mechanical pain threshold; MPS = mechanical pain sensitivity.

A scatter plot of these variables illustrated observations that might be influential on the regression coefficient (circled in red; Figure 7.2). Cook’s distance was used to investigate these observations further; predicted values exceeding a threshold of 4/n (n=32 in this case) were identified as outliers (Table 7.5). Three outliers were identified and subsequently removed from the regression (Table 7.6), but the trend persisted with greater wind-up ratio at the control knee at baseline predicting improved pain after the injection (β 4.7352; 95% CI -0.063, 9.533).
Figure 7.2 Scatter plot illustrating the association between change in KOOS pain score and baseline wind-up ratio at the control knee with (A) and without (B) influential observations

Graph B depicts the impact that removal of three influential observations identified by red circles in graph A have on the association between wind-up ratio at the control knee at baseline with change in pain assessed using the Knee Osteoarthritis Outcome and Injury Score (KOOS).

Table 7.5 Change in pain against baseline wind-up ratio at the control knee: influential observations identified using Cook’s distance >4/32

<table>
<thead>
<tr>
<th>Subject Number</th>
<th>Change in KOOS</th>
<th>Baseline Wind-up (control knee)</th>
<th>Cook’s Distance</th>
</tr>
</thead>
<tbody>
<tr>
<td>128</td>
<td>65.63</td>
<td>12.0</td>
<td>0.255</td>
</tr>
<tr>
<td>130</td>
<td>-37.5</td>
<td>1.81</td>
<td>0.176</td>
</tr>
<tr>
<td>144</td>
<td>-3.13</td>
<td>7.65</td>
<td>0.453</td>
</tr>
</tbody>
</table>

Table 7.6 Linear regression of change in pain against baseline wind-up ratio at the control knee: outliers included and removed

<table>
<thead>
<tr>
<th>Control Knee WUR</th>
<th>β-coefficient</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outliers included</td>
<td>3.4859</td>
<td>-0.037, 7.008</td>
</tr>
<tr>
<td>Outliers removed</td>
<td>4.7352</td>
<td>-0.063, 9.533</td>
</tr>
</tbody>
</table>

WUR = wind-up ratio; 95% CI = 95% confidence interval.

7.6.5. QST measures and responder status

Twenty one subjects (65.6%) were classified as treatment responders using the OARSI-OMERACT criteria (see Section 4.3.4.2), with women more likely to respond to treatment than men (16 females and 5 males). The association between baseline tender point count and QST measures at the injected and contralateral knees were investigated as predictors of response to treatment (Table 7.7). Mechanical pain threshold at the injected knee was identified as a baseline predictor of
response to treatment, with responders more sensitive to this measure than non-responders. Baseline mechanical pain threshold, mechanical pain sensitivity, and allodynia at the contralateral knee were also approaching significance (p=0.0554, p=0.0946 and p=0.0954 respectively), again with responders more sensitive than non-responders.

Although baseline mechanical pain threshold at the injected knee differed significantly by responder status, the same measure was not a significant predictor of change in pain (Table 7.4). However, the association between baseline mechanical pain threshold and change in pain remained significant after adjusting for baseline pain (β -0.079; 95% CI -0.152, -0.006). A scatter plot of change in pain against baseline mechanical pain threshold at the injected knee and responder status against baseline mechanical pain threshold at the injected knee demonstrated that although there is a negative trend there are both responders and non-responders at all levels of mechanical pain threshold (Figure 7.3). The Lowess plot (smoothed prevalence of responder status against baseline mechanical pain threshold at the injected knee) showed a non-linear fit with a steeper curve which was significant.

Table 7.7  Median values for baseline QST measures by treatment responder status

<table>
<thead>
<tr>
<th>Variable (possible range)</th>
<th>Responder (IQR)</th>
<th>Non-responder (IQR)</th>
<th>p-value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tender point count (0-18)</td>
<td>1 (0-2)</td>
<td>0 (0-3)</td>
<td>0.9830</td>
</tr>
<tr>
<td>Injected knee MDT (0-512 mN)</td>
<td>9.9 (1.5-22.6)</td>
<td>3.7 (1.3-8.6)</td>
<td>0.2838</td>
</tr>
<tr>
<td>Injected knee MPT (0-512 mN)</td>
<td>59.7 (34.9-78.8)</td>
<td>97.0 (59.7-207.9)</td>
<td><strong>0.0224</strong></td>
</tr>
<tr>
<td>Injected knee MPS (0-100 NRS)</td>
<td>5.4 (1.3-14.4)</td>
<td>2.9 (0.5-7.2)</td>
<td>0.1649</td>
</tr>
<tr>
<td>Injected knee Allodynia (0-100 NRS)</td>
<td>0 (0-0.4)</td>
<td>0 (0-0.9)</td>
<td>0.9594</td>
</tr>
<tr>
<td>Injected knee Wind-up ratio (≥1)</td>
<td>2.8 (2.2-4.4)</td>
<td>2.3 (1.2-3.9)</td>
<td>0.2312</td>
</tr>
<tr>
<td>Injected knee Vibration detection (0-8)</td>
<td>3.3 (2.7-4.3)</td>
<td>3.0 (2-6.3)</td>
<td>0.7807</td>
</tr>
<tr>
<td>Injected knee Pressure pain (0-10 kg/cm²)</td>
<td>4.3 (3.0-6.1)</td>
<td>5.0 (3.2-7.0)</td>
<td>0.4999</td>
</tr>
<tr>
<td>Contralateral knee MDT (0-512 mN)</td>
<td>3.6 (1.0-13.5)</td>
<td>6.5 (1.4-9.9)</td>
<td>0.9649</td>
</tr>
<tr>
<td>Contralateral knee MPT (0-512 mN)</td>
<td>66.3 (22.6-142.1)</td>
<td>124.1 (59.7-168.9)</td>
<td><strong>0.0554</strong></td>
</tr>
<tr>
<td>Contralateral knee MPS (0-100 NRS)</td>
<td>3.1 (1.6-8.6)</td>
<td>2.0 (0.3-4.0)</td>
<td><strong>0.0946</strong></td>
</tr>
<tr>
<td>Contralateral knee Allodynia (0-100 NRS)</td>
<td>0 (0-1.2)</td>
<td>0 (0-0)</td>
<td><strong>0.0954</strong></td>
</tr>
<tr>
<td>Contralateral knee Wind-up ratio (≥1)</td>
<td>2.5 (1.7-5)</td>
<td>2.0 (1.4-3.2)</td>
<td>0.2513</td>
</tr>
<tr>
<td>Contralateral knee Vibration detection (0-8)</td>
<td>3.7 (1.5-4.8)</td>
<td>3.0 (1.7-4.0)</td>
<td>0.7230</td>
</tr>
<tr>
<td>Contralateral knee Pressure pain (0-10 kg/cm²)</td>
<td>5.0 (3.6-6.7)</td>
<td>3.8 (2.9-5.1)</td>
<td>0.2348</td>
</tr>
</tbody>
</table>

IQR = interquartile range; * Wilcoxon rank-sum test; p<0.05 in bold and 0.05≤p<0.1 if in italics. MDT = mechanical detection threshold; MPT = mechanical pain threshold; MPS = mechanical pain sensitivity.
7.6.6.  Psychosocial Factors and Change in Pain

The associations between change in pain (assessed using the KOOS pain subscale) and screening psychosocial factors were investigated using linear regression with psychosocial factors as predictors and change in pain as the outcome. The personal control, treatment control and coherence items of the IPQ-Brief are significantly associated with changes in pain scores following the injection (Table 7.8). Lower scores for each of these items indicate that subjects with stronger beliefs of control over their pain (personal control), treatment being beneficial (treatment control), and a greater understanding of their pain (coherence) were more likely to report improvements in pain. No other screening scores for psychosocial factors were associated with change in pain.

Screening psychosocial factors were also investigated as predictors of change in QST (see Table IX-1, Table IX-2, and Table IX-3 of Appendix IX). Three significant associations were identified; lower screening scores for anxiety (β=0.1815; 95% CI 0.026, 0.338) and depression (β=0.1721; 95% CI 0.007, 0.337) were both significant predictors of diminished sensitivity to allodynia at the contralateral knee following the injection (Table IX-1, Appendix IX), with lower screening scores for the personal control item of the IPQ-Brief indicating more control over pain significantly associated with lower sensitivity to wind-up ratio at the contralateral knee following the injection (β=0.2979; 95% CI 0.003, 0.593; Table IX-3, Appendix IX).
Table 7.8  Linear regression of change in pain against psychosocial factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>β-coefficient</th>
<th>95% CI *</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAD Anxiety</td>
<td>-0.4890</td>
<td>-2.879, 1.901</td>
</tr>
<tr>
<td>HAD Depression</td>
<td>-0.2051</td>
<td>-2.713, 2.303</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IPQ-Brief</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Consequences</td>
<td>0.4379</td>
<td>-3.094, 3.970</td>
</tr>
<tr>
<td>Timeline</td>
<td>-3.6074</td>
<td>-7.338, 0.123</td>
</tr>
<tr>
<td>Personal Control</td>
<td>-3.2663</td>
<td>-6.059, -0.473</td>
</tr>
<tr>
<td>Treatment Control</td>
<td>-5.9211</td>
<td>-9.537, -2.306</td>
</tr>
<tr>
<td>Identity</td>
<td>2.2299</td>
<td>-1.313, 5.773</td>
</tr>
<tr>
<td>Concern</td>
<td>0.1699</td>
<td>-3.717, 4.057</td>
</tr>
<tr>
<td>Coherence</td>
<td>-6.4934</td>
<td>-9.885, -3.102</td>
</tr>
<tr>
<td>Emotion</td>
<td>-1.0355</td>
<td>-3.943, 1.872</td>
</tr>
</tbody>
</table>

* p<0.05 if bold and 0.05≤p<0.1 if in italics. HAD = Hospital Anxiety and Depression Scale; IPQ-Brief = Illness Perception Questionnaire Brief.

Four associations between change in QST and screening items of the IPQ-Brief with p-values of less than 0.1 were also identified. Lower screening scores for personal control were associated with increased sensitivity to allodynia at the injected knee at the post-injection visit (β=0.2729; 95% CI: 0.552, 0.007; Table IX-2, Appendix IX) while higher screening scores for treatment control were related to diminished sensitivity for mechanical detection at the injected knee at the post-injection visit (β=12.401; 95% CI: 25.541, Table IX-2, Appendix IX). Higher screening scores for the identity item of the IPQ-Brief (greater number of pain-related symptoms experienced) were associated with lower pain ratings for mechanical pain sensitivity at the injected knee at the post-injection visit (β=-0.9339; 95% CI: -1.919, 0.051; Table IX-2, Appendix IX). Finally, greater scores for concern were related to diminished sensitivity to pressure pain threshold at the injected knee at the post-injection visit (β=0.2251; 95% CI: 0.461, Table IX-2, Appendix IX). However, these associations were no longer significant after calculating the Cook's distance (>4/32) and removing the outliers. The anxiety subscale was approaching significance (β=0.0786; 95% CI: 0.165; Table IX-1, Appendix IX), but all other associations were influenced by outliers and were not significant at the 10% level.

7.7. Discussion

In the analyses presented in this chapter, there were no significant within-person changes in QST between the baseline and post-injection visits or differences between knees in the present study. There were also no significant associations between baseline QST measures and change in pain following the injection, although treatment responders were significantly more sensitive to mechanical pain threshold at the injected knee at baseline and also more sensitive to allodynia and
mechanical pain threshold and sensitivity at the control knee at baseline (p<0.1) compared with treatment non-responders. Higher levels of perceived personal control, treatment control and coherence at screening were identified as significant predictors of improvements in pain scores following the injection.

7.7.1. **Subject Characteristics**

Thirty-two subjects completed the study with 21 subjects classified as treatment responders according to the OARSI-OMERACT criteria. This finding is supported by a meta-analysis performed to determine the efficacy of intra-articular steroid injections against placebo in subjects with knee OA; six studies (160 subjects treated with steroids, 157 treated with placebo) reported a greater proportion of responders at two weeks post-injection in the treatment group (119; 74.4%) than in the control group (70; 44.6%) with a relative risk ratio of 1.66 (95% CI 1.37, 2.01) (Bruce et al. 2004). However, only one of these studies used the same steroid therapy as the present study although at a higher dose (120 mg methylprednisolone) and reported a similar proportion of responders in the steroid treatment group two weeks post-injection (25 of 38 subjects; 65.8%) (Smith et al. 2003). The median age for subjects in the present study was 61.5 years (IQR 54.5-72.5) with a higher proportion of women participating (21; 65.6%). These results are consistent with those of other studies included in a systematic review investigating predictors of response to intra-articular steroid injections (Maricar et al. 2013). Four studies (177 subjects treated with steroids, 14 treated with placebo) using the same steroid therapy in subjects with knee OA reported a range of mean ages from 62.2 years to 70.6 years and higher proportions of female subjects (range 67%-87%) (Maricar et al. 2013).

The subject characteristics for the present study were comparable to five other studies investigating altered somatosensory functioning in subjects with knee OA receiving an intervention; four of the five studies included a higher proportion of women (Moss et al. 2007; Martinez et al. 2007; Wylde et al. 2013; Burrows et al. 2014) with the fifth study recruiting an equal number of men and women (Takeda et al. 1994) (see Table 2.3). Three of these studies (Takeda et al. 1994; Moss et al. 2007; Burrows et al. 2014) also recruited subjects with a similar mean age as the sample in the present study. The other two studies had a higher mean age due to recruiting subjects awaiting total knee replacement who tend to be older with more severe disease progression (Takeda et al. 1994; Wylde et al. 2013). This indicates that the sample used in the present study was comparable with other studies in the current literature.

7.7.2. **Changes in QST measures following intervention**

The present study did not find any changes in somatosensory function, particularly pressure pain thresholds. Previous studies investigating differences in QST measures pre- and post-treatment in people with knee OA have suggested change in some measures including pressure pain thresholds (Takeda et al. 1994; Moss et al. 2007; Burrows et al. 2014). One study investigating the
impact of joint mobilisation performed by physiotherapists found that 38 subjects with knee OA had significantly higher pressure pain thresholds following joint mobilisation than those receiving no contact or those receiving contact without mobilisation (Moss et al. 2007). However, clinical pain ratings assessed by WOMAC did not improve (Moss et al. 2007). Another study investigating changes in pressure pain at upper and lower body sites in a group of 11 knee OA subjects following upper and lower body resistance exercise found significantly diminished sensitivity to pressure pain thresholds in the upper and lower test sites following upper body exercise compared with baseline (Burrows et al. 2014). Again, however, no significant differences in pain were observed following the exercise interventions (Burrows et al. 2014).

Takeda and Wessel (1994) investigated the effect of acupuncture in 40 knee OA subjects randomised to receive the real or sham conditions. Pressure pain thresholds were recorded before, during and after treatment at four sites on the index knee (medial and lateral joint line, and vastus medialis and vastus lateralis muscles) (Takeda et al. 1994). Sensitivity to pressure pain was significantly lower during treatment at each test site for both treatment groups compared with the thresholds before treatment (Takeda et al. 1994). Significant differences were also observed between test sites with lower sensitivity at both joint line sites compared to both muscle sites, but there were no significant differences in pressure pain thresholds or knee pain intensity ratings between the sham and real acupuncture groups, or for the pre- and post-treatment assessments (Takeda et al. 1994).

The findings of these studies suggest that changes in QST were detectable immediately after the intervention following a relatively short time interval, but that the interventions were not effective in relieving pain in the short term (Takeda et al. 1994; Moss et al. 2007; Burrows et al. 2014). The studies described previously also indicate that QST measures at the index knee were not associated with pain levels pre- or post-intervention (Takeda et al. 1994; Moss et al. 2007; Burrows et al. 2014). This suggests QST measures may not be good proxies for pain intensity in subjects with knee OA as changes in somatosensory function do not appear to be related to changes in pain. However, some caution is needed in interpretation of these data. There were substantive differences in the timing between assessments in the different studies. All three of the previous studies performed QST assessments following the intervention on the same day, which may explain the changes observed for pressure pain thresholds (Takeda et al. 1994; Moss et al. 2007; Burrows et al. 2014). Two alternative explanations for no observable changes in pain following the interventions in the previous studies could be that the analgesic effects were not captured during the study time frame, or that these treatments were not effective in reducing pain at least in the short term (Takeda et al. 1994; Moss et al. 2007; Burrows et al. 2014).

The findings of the present study contradict the previous findings with a significant reduction in pain observed for treatment responders although there were no observable changes in QST measures. Possible explanations for the discrepant findings include:

(i) because of the longer time interval between the baseline and post-injection assessments (10.0±3.7 days) changes in QST may have been missed if the changes occur rapidly following an intervention but are not long-lasting;
the sample of subjects in the steroid intervention study were centrally sensitised. Steroid injections target inflammation localised to the injection site and do not directly affect central pain processing pathways (Baddour et al. 1999). This may account for the lack of change observed for all QST measures despite a significant reduction in pain (Woolf 2010);

steroid injections are effective in providing pain relief in the short term for some people with knee OA (Bellamy et al. 2006), and may be more efficacious than acupuncture, knee mobilisation, or resistance exercise.

Although these studies used different QST protocols, diminished sensitivity to pressure pain at the knee was observed following treatment in three studies (Takeda et al. 1994; Moss et al. 2007; Burrows et al. 2014). However, these studies only used pressure pain thresholds to assess somatosensory function within knee OA subjects. The findings of the present study suggest the inclusion of assessments of mechanical pain.

7.7.3. Predictors of change in pain

Baseline QST predictors

In the analysis presented in this chapter, treatment responders were significantly more sensitive to baseline mechanical pain threshold at the injected knee (p=0.0224). Two studies have investigated QST measures as predictors of post-operative pain following total knee replacement surgery. Wylde et al. (2013) demonstrated that pressure pain thresholds at the forearm at baseline were predictive of postoperative WOMAC pain scores one year after total knee replacement in 51 knee OA subjects (rho = 0.37; p=0.008). The second study demonstrated that increased sensitivity to heat pain threshold prior to surgery was predictive of post-operative morphine consumption in 20 knee OA subjects, though QST measures were not associated with pre- or post-operative pain levels (Martinez et al. 2007). Repeat QST assessments were performed at one and four days following surgery while the patients were experiencing severe surgical pain and significant increased sensitivity to mechanical pain was observed at the operative knee during day one and day four (3.6±0.1 for both days one and four compared with 3.9±0.0 at baseline; p<0.01), and increased sensitivity to cold pain during day one only (23.5±2.5 compared with 16.9±2.6 at baseline; p<0.01) (Martinez et al. 2007). This was the only previous study to establish an association between mechanical hyperalgesia and pain in subjects with knee OA. However, the QST assessments performed post-operatively (day 1 and day 4) may have been affected by the use of post-operative morphine consumption (Martinez et al. 2007). As such, the role of mechanical hyperalgesia in subjects with knee OA requires further investigation.

Comparison of these studies with the results reported in this chapter is further limited because the time frames for QST assessments were different. One of the two studies using subjects who underwent total knee replacement found that forearm pressure pain threshold predicted chronic pain one year after surgery (Wylde et al. 2013) while the other study demonstrated diminished sensitivity to heat pain threshold one day after surgery (likely to be influenced by morphine). No
difference in QST measures were observed between baseline and assessment at 3 months post-surgery (Martinez et al. 2007). The other three non-surgical intervention studies described earlier showed immediate diminished sensitivity to QST at the knee following therapy, but did not demonstrate any changes in pain (Takeda et al. 1994; Moss et al. 2007; Burrows et al. 2014). Although the majority of subjects (65.6%) described in this chapter reported diminished pain at the post-injection visit, changes in QST were not observed. This suggests a longer follow-up period may be required to determine the effects of the intervention on pain and to determine whether diminished sensitivity is longer lasting.

The scope of the 5 interventional studies described so far in relation to QST assessments is limited. Only Martinez et al. (2007) and Wylde et al. (2013) included more than pressure pain thresholds in their QST batteries. There were also differences in QST protocols used and calculation of thresholds which makes comparisons of the results difficult. For example, Martinez et al. (2007) performed logarithmic transformations of the mean mechanical pain thresholds, while Wylde et al. (2011; 2012) calculated mechanical detection thresholds using a different scale (grams per millimetre squared) and provided median pressure pain thresholds. Future studies should consider the use of standardised testing protocols that have undergone rigorous testing in different patient populations (Rolke et al. 2006a; Rolke et al. 2006b; Maier et al. 2010; Geber et al. 2011).

**Screening psychosocial predictors**

In the current study, personal control, treatment control and coherence items of the IPQ-Brief at screening were identified as significant predictors of improvements in pain scores following the injection (Table 7.8). There are currently no studies which have investigated the role of illness perceptions and pain in knee OA subjects, but there is evidence for the role of illness perceptions in response to treatment in subjects with chronic lower back pain (Glattacker et al. 2012). Two hundred and four subjects with lower back pain were allocated to either receive information regarding their illness and current treatments through three 20 minute sessions (n=96) or receive standard care (n=105) using a sequential group design (Glattacker et al. 2012). The intervention group demonstrated significantly improved perceptions of personal control and satisfaction regarding their healthcare compared with the control group suggesting that patient education is a viable target for future intervention studies (Glattacker et al. 2012). It is difficult to discern though whether just by providing an intervention illness perceptions are altered, or if altered illness perceptions drive response to the intervention (Macfarlane 2008).

Recent guidelines for the treatment of knee OA have highlighted the need for greater patient education to improve self-management of the disease (Larmer et al. 2014; McAlindon et al. 2014; National Institute for Health and Care Excellence 2014). These guidelines do not address the role of psychological distress, but there is evidence to suggest that providing education about pain perception can reduce pain reporting. A study of 62 subjects with knee OA demonstrated diminished pain ratings and reduced sensitivity to the nociceptive flexion reflex following a 45 minute coping skills training session (Emery et al. 2006), though the longevity and maintenance of changes provided by an education program requires further investigation.
7.7.4.  **Strengths and limitations of the present study**

This is the first study to investigate changes in somatosensory functioning in relation to a pharmacological intervention in subjects with knee OA. As previously mentioned, there are few consistent predictors of response to treatment with intra-articular steroid injections with knee aspiration, effusion and disease severity identified as the strongest predictors to date (Maricar et al. 2013). Although the present study was small, it provides a foundation for future studies investigating QST and psychosocial predictors of response to treatment in subjects with knee OA.

The present study also provides support to the findings of the study described in Chapter 6 where mechanical hyperalgesia and illness perceptions were associated with higher levels of pain intensity. The present study demonstrated that baseline measures of mechanical pain threshold and illness perceptions were associated with response to treatment and changes in pain, respectively. However, these findings need to be replicated in a larger study with a control arm to determine whether these were true predictors of response to treatment or an artefact of the placebo effect.

There are though a number of limitations which need to be considered in interpreting the findings. Firstly, the number of subjects studied was relatively small and it is possible that because of this some biological associations were missed, though the magnitude of the observed differences in QST between visits was relatively small. Secondly, because a significant number of people (43%) had pain at the control site (contralateral knee) the identification of altered pain processing via central sensitisation was limited. Increased sensitivity at a control site is indicative of generalised alterations in pain processing which is also linked to central sensitisation (Wylde et al. 2013; Finan et al. 2013b). Another site (such as the contralateral forearm) would have provided a better indication of generalised changes in sensitivity (i.e. pain outside of the knee).

Thirdly, no assessment of descending pain modulation was performed to determine whether alterations in DNIC were present within the The majority of subjects in the present study did exhibit increased sensitivity to wind-up with 26 subjects (81.3%) reporting higher pain following the train of stimuli compared to the single application for both knees and at both visits. This represents the amplification of repeated mechanical sensations due to lowered transduction thresholds within the spinal cord, which is a mechanism of central sensitisation (Gracely et al. 2003). However, there is currently no consensus as to what constitutes a statistically or clinically significant wind-up ratio to aid in the identification of people with central sensitisation. Lastly, the lack of control arm means it is not possible to determine the presence of a placebo or contextual effect in explaining some of the findings particularly in relation to the psychosocial variables.

7.8.  **Conclusion**

In summary, increased sensitivity to mechanical pain threshold at the injected knee was identified as a baseline predictor of response to treatment. None of the QST measures changed significantly between baseline and follow up. Higher perceived levels of personal control, treatment control and
coherence at screening were significant predictors of change in pain following the injection. 
Measures of mechanical hyperalgesia warrant further investigation as putative predictors of 
response in studies of subjects with knee OA. QST measures are unlikely though to have a role as 
outcome measures in trials of knee OA.
CHAPTER 8. DISCUSSION

8.1. Overview

This chapter summarises the main findings of the thesis, implications of findings in relation to utility of QST in the assessment of knee pain, and outlines future research directions.

8.2. Main Findings

The studies presented in Chapter 6 and Chapter 7 were the first studies to demonstrate significant associations between mechanical hyperalgesia, illness perceptions and pain intensity in subjects with knee pain. The identification of mechanical hyperalgesia and illness perceptions as predictors of response to treatment and self-reported pain intensity were novel and provide insights for future research.

In a population based study of people with knee pain (Chapter 6), the consequences item of the IPQ-Brief and mechanical pain sensitivity at the knee were the best predictors of global pain intensity. The same two variables (the consequences item of the IPQ-Brief and mechanical pain sensitivity at the knee), mechanical pain threshold at the knee and the rumination subscale of the PCS were identified as the best predictors of knee pain intensity. The results of the mediation analyses demonstrated that psychosocial factors (when loaded on to a latent variable) were significant partial mediators of the associations between predictors (tender point count, mechanical pain sensitivity at the knee and allodynia at the knee) with global pain intensity. Conversely, the direct effect for associations between predictors (mechanical pain sensitivity and allodynia at the knee) with self-reported pain intensity at the tested knee was stronger than the indirect effect including psychosocial factors loaded on to a latent variable. This suggests there was significant and widespread mechanical hyperalgesia (including sensitivity at pain-free test sites) in those reporting higher levels of both global and knee pain intensity, with psychosocial factors (including measures of illness perceptions, catastrophising and disability) significantly contributing to the association between predictors and outcomes in this sample. The findings of this study provide a possible mechanism by which mechanical hyperalgesia and psychosocial factors interact and contribute to the pain experience in people with both global and knee pain intensity.

In the intervention study (Chapter 7) higher sensitivity to mechanical pain threshold at the injected knee predicted response to treatment. Stronger positive beliefs about personal control, treatment control and coherence measured using the IPQ-Brief specifically predicted improvements in pain. However, the study did not find any changes in QST measures over time. This suggests that while the steroid injection may be reducing peripheral input, the mechanisms driving sensitisation within the nervous system are likely to be unaffected. However, this is only one possible explanation of the results in a study that did not have a control arm.
8.3. Implications of Findings

The studies presented in Chapter 6 and Chapter 7 are the first to demonstrate the combined effect of mechanical hyperalgesia and psychosocial factors on pain intensity and in predicting response to treatment in subjects with knee pain. QST is a psychophysical technique designed to quantify losses or gains in somatosensory functioning. Previous studies have identified its utility in distinguishing between subjects with painful knee OA and comparator groups with reduced or no pain at the knee, particularly deep tissue hyperalgesia assessed by pressure pain thresholds (Wessel 1995; Imamura et al. 2008; Arendt-Nielsen et al. 2010; Lee et al. 2011; Wylde et al. 2012; Wylde et al. 2013), and for temporal summation and mechanical pain thresholds (Hendiani et al. 2003; Arendt-Nielsen et al. 2010). The present studies have indicated that assessments of mechanical hyperalgesia identified subjects with higher levels of self-reported pain intensity and in predicting response to treatment following an intra-articular steroid injection. The association between mechanical hyperalgesia at the knee and at a pain-free control site with self-reported pain intensities globally and at the knee suggests more generalised changes in pain processing, such as central sensitisation.

QST can be used to assess somatosensory abnormalities, such as small and large fibre peripheral neuropathies where subjects are insensitive to thermal pain, or display abnormal thermal and/or vibration detection thresholds, respectively (Shy et al. 2003). Studies of QST in knee OA have identified increased sensitivity compared with pain-free control groups, but there is no clear evidence of a threshold at which somatosensory functioning is defined as abnormal in subjects with knee OA. As such, QST measures cannot currently be used clinically to distinguish somatosensory abnormalities within samples of knee OA patients. The findings of the studies in this thesis provide a possible mechanism by which knee OA patients could be identified as potential treatment responders, though the use of mechanical assessments and psychosocial factors in distinguishing those reporting more widespread and higher levels of pain requires further investigation. It may be possible to refine the use of QST measures to be used in clinical practice to stratify patients with knee OA according to markers of peripheral and/or central sensitisation. This may inform decisions regarding which treatments may be beneficial for patients at an individual level.

Research into the role of QST measures and psychosocial factors in subjects with knee OA is expanding, although the available data are inconsistent. There is evidence to suggest that deep tissue hyperalgesia, assessed by pressure pain thresholds (Arendt-Nielsen et al. 2010; Lee et al. 2011; Wylde et al. 2012; Wylde et al. 2013), and psychosocial factors, such as depression, anxiety and pain catastrophizing (Williams et al. 2004; Finan et al. 2013b; Wideman et al. 2014), can be used to distinguish between subjects with painful knee OA and comparator groups (typically pain-free controls or subjects with knee OA reporting lower levels of pain). Research using QST measures other than pressure pain thresholds (Hendiani et al. 2003; Martinez et al. 2007; Emerson Kavchak et al. 2012) or studies using larger QST batteries (Wylde et al. 2012; King et al. 2013; Skou et al. 2013b) in subjects with knee OA is limited with conflicting findings that require further investigation. One of the major methodological problems with studies using QST is sample size with the required expertise of assessors and costs being two of the major limiting factors. The studies investigating the associations between QST measures and pain were typically small with
only one large population-based cohort study (Neogi et al. 2013) and four case-control studies using samples of 50 or more subjects per group (Wyde et al. 2011; Wyde et al. 2012; Wyde et al. 2013; King et al. 2013). Despite only 5 of 31 studies investigating QST measures in subjects with knee OA performing a sample size calculation, 28 studies (92.7%) did report significant associations between QST measures and the outcome variables of interest. A sample size calculation by Suokas et al. (2012) recommended 45 subjects per group to ensure 90% power for detecting differences in QST measures for subjects with OA and healthy controls.

Although the present studies did not appear to identify mechanisms of peripheral sensitisation, the KOPS study and previous studies of intra-articular steroid therapy have demonstrated that treatments targeting the site of pain can be effective in providing pain relief in the short term for some subjects with knee OA (Bellamy et al. 2006). Previous studies of total knee replacement have also demonstrated that pain can resolve following surgery suggesting a peripheral component to the knee pain experienced in some people with OA (Beswick et al. 2012). Conversely, knee pain can remain unchanged or worsen following total knee replacements possibly indicating the presence of central sensitisation (Beswick et al. 2012). A major challenge in developing appropriate targeted management strategies for patients with knee pain is to identify those whose pain is likely to have peripheral drivers and to target treatment appropriately.

Pain is multifaceted and requires a holistic approach to treatment including physical therapy, patient education and self-management programs, and psychological interventions alongside or in place of pharmacological analgesia with the aim of providing personalised and long term analgesia for those who need it (Tracy et al. 2013; Abdulla et al. 2013). There is also emerging evidence that interventions targeting psychosocial factors associated with greater pain intensity are effective in reducing pain, at least in the short term. Recent studies have demonstrated improvements in pain in subjects with chronic musculoskeletal pain conditions following interventions that target mindfulness (Brown et al. 2013), coping skills (Keefe et al. 1990; Emery et al. 2006; Riddle et al. 2011), and illness perceptions (Glattacker et al. 2012; Lochting et al. 2013a). However, any changes in pain observed following these interventions should be monitored to determine the longevity and maintenance of any positive changes.

8.4. Future Research

The studies presented in this thesis highlighted the inclusion of mechanical QST assessments, a need for standardised methodologies for QST measures, and the inclusion of psychosocial factors when investigating QST measures in subjects with knee pain. This would provide robust answers as to the role of QST measures in distinguishing between central and peripheral mechanisms of sensitisation or predicting response to treatment in people with knee pain. One study that could be conducted to determine possible markers of sensitisation in people with knee pain would be to perform a randomised control trial investigating a psychosocial intervention (such as altering illness perceptions) in a clinical setting with subjects assigned to the intervention with standard care, or standard care alone. A reduced battery of QST measures, including assessments of mechanical pain, and responses to a survey (including measures of knee pain and psychosocial state, such as
the KOOS and measures of illness perceptions, anxiety, depression, disability, and others) obtained at baseline could be used to determine predictors of change in pain, improvements in illness perception scores and to investigate the impact on other psychosocial factors.

Most studies to date have included small numbers of subjects; further studies, such as validation in a larger observational cohort of people with knee pain, are needed to confirm the findings in this thesis and whether QST measures, particularly mechanical assessments, can identify responders to targeted interventions.

8.5. Summary

The studies presented in this thesis demonstrated the importance of mechanical hyperalgesia and psychosocial factors, particularly illness perceptions, in people who were experiencing higher levels of pain intensity, and were more likely to respond to intra-articular steroid therapy. These findings provide a potential explanation for differences in the pain experience among people with knee pain and may inform future studies seeking to assess the effectiveness of identifying inter-individual differences in pain to target interventions.
REFERENCES


APPENDIX I. Systematic Review Methodology

The search strategy used to identify the studies presented in Table 2.3 is shown in Table I-1. The search strategy was originally designed to investigate mechanical, pressure and thermal QST methodologies in people with Fibromyalgia, lower back pain and knee OA. The search strategy was last run in July 2012 with 641 titles identified. The titles and abstracts were reviewed for relevance with a total of 25 studies including people with knee pain identified and 21 studies included in Table 2.3.

Table I-1 Search strategy used to identify studies presented in Table 2.3

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<table>
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<tr>
<td>Thesis review</td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>exp fibromyalgia/</td>
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<tr>
<td>2.</td>
<td>exp back pain/</td>
</tr>
<tr>
<td>3.</td>
<td>exp knee osteoarthritis/</td>
</tr>
<tr>
<td>4.</td>
<td>exp knee pain/</td>
</tr>
<tr>
<td>5.</td>
<td>(chronic widespread pain or CWP or fibromyalgia or fibrositis or fibromyositis or FM or FMS or central sens$ syndrome or CSS).mp.</td>
</tr>
<tr>
<td>6.</td>
<td>((back pain or lower back pain or LBP or knee pain or knee osteoarthritis or knee osteoarth$ or knee gonarth$ or knee coxarth$) adj6 chronic).mp.</td>
</tr>
<tr>
<td>7.</td>
<td>(quantitative sens$ test$ or QST or “quantitative sensory testing” or sensory threshold or perception threshold or pain threshold or detection threshold or psychophysical test$ or $physical$ test$).mp.</td>
</tr>
<tr>
<td>8.</td>
<td>(heterotopic noxious condition$ stimul$ or HNCS).mp.</td>
</tr>
<tr>
<td>9.</td>
<td>(diffuse noxious inhib$ control$ or DNIC).mp.</td>
</tr>
<tr>
<td>10.</td>
<td>(temporal summation or wind up or wind up ratio or WUR).mp.</td>
</tr>
<tr>
<td>11.</td>
<td>hyperalges$.mp.</td>
</tr>
<tr>
<td>12.</td>
<td>allodyn$.mp.</td>
</tr>
<tr>
<td>13.</td>
<td>1 or 2 or 3 or 4 or 5 or 6</td>
</tr>
<tr>
<td>14.</td>
<td>7 or 8 or 9 or 10 or 11 or 12</td>
</tr>
<tr>
<td>15.</td>
<td>13 and 14</td>
</tr>
<tr>
<td>16.</td>
<td>limit 15 to “review articles”</td>
</tr>
<tr>
<td>17.</td>
<td>15 not 16</td>
</tr>
<tr>
<td>18.</td>
<td>Limit 17 to (cats or cattle or chick embryo or dogs or goat or guinea pigs or hamsters or mice or rabbits or rats or sheep or swine)</td>
</tr>
<tr>
<td>19.</td>
<td>17 not 18</td>
</tr>
<tr>
<td>20.</td>
<td>Limit 19 to humans</td>
</tr>
<tr>
<td>21.</td>
<td>Limit 20 to yr=“1806 - 2012”</td>
</tr>
</tbody>
</table>

# 641*
† 25

# = number of titles identified through database searches; * = search ran in July 2012.  
† = number of studies identified fulfilling inclusion and exclusion criteria.
A systematic review published by Suokas et al. (2012) investigating chemical, electrical, mechanical, pressure and thermal QST methodologies in people with hand, hip and knee OA identified 23 studies (19 of which are included in Table 2.3) fulfilling the criteria outlined above. Four studies were identified by both search strategies, but were excluded from Table 2.3. The reasons for exclusion are summarised below:

- Buffington et al. (2005); although the study used a heat stimulus, a standard temperature was applied and a pain and/or detection and/or tolerance threshold was not determined.

- Creamer et al. (1999b); acupuncture used as mechanical pain methodology and intervention.

- Krause et al. (1995) and Schmidt et al. (2010); translation from German not obtained.

Two studies (Shakoor et al. 2012; Tena et al. 2012) were also identified and included in Table 2.3 that were not present in the Suokas et al. (2012) review as the former strategy included studies published up to 2012, whereas the search for Suokas et al. (2012) was completed in May 2011. An additional 10 studies were identified through non-systematic searches conducted up to December 2013.
APPENDIX II. KEEPS Study Documentation

Figure II-1
KEEPS Participant Information Sheet
KEEPS Appointment Letter

Dear

I am sending you confirmation of your appointment to attend the Wellcome Trust Clinical Research Facility following our recent telephone conversation. We look forward to seeing you on [DATE] at [LOCATION]. I have enclosed in the envelope a map, directions to the centre and details about car parking. Please keep hold of your travel receipts on the day of the visit so we can refund your travel costs.

On the day please remember:
- To wear loose fitting clothing

When we arrive you will have the chance to ask any questions you might have, and the researcher will take you through the information and consent form before you sign to take part. If you have any queries in the mean time please contact me on 0161 275 1604 or 0161 275 5596 or [REDACTED] (out of office hours).

Thank you for your help.

Yours sincerely,

Kayleigh Mason
PhD Student
The Knee Pain Sensitivity Study (KEEPS)

PARTICIPANT CONSENT

Name of researcher: Dr John McBeth
Contact details: Pain Research Group, Arthritis Research UK EU University of Manchester Oxford Road, Manchester, M13 9PT Tel: 0161 275 5788

1. I have read and understand the information sheet on the above project dated 29/08/2012 and have been given a copy to keep. I have had the opportunity to consider the information and ask questions and have these answered satisfactorily. I understand why the research is being done and any risks involved.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving a reason, without my medical care or legal rights being affected.

3. I understand that all information collected from me for this study will be held in confidence and that my personal details will not appear on any publication of results.

4. I understand that if I decide to withdraw from the study, identifiable data already collected would be retained and used in the study.

5. I agree that any data collected may be passed to other researchers from the University of Manchester.

6. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the University of Manchester, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.

7. I know how to contact the research team if I need to, and how to get information about the results of the research.

8. I agree to take part in this study.

---------------------------------------
Name of participant Date Signature
---------------------------------------
Name of person taking consent (if different from researcher) Date Signature
---------------------------------------
Researcher Date Signature
Figure II-4

KEEPS Study Questionnaire (continued over page)
<table>
<thead>
<tr>
<th>Q. 86</th>
<th>Are you able to open a new file?</th>
</tr>
</thead>
<tbody>
<tr>
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<td>No</td>
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<td>2</td>
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<table>
<thead>
<tr>
<th>Q. 87</th>
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</tr>
</thead>
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<td>2</td>
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<table>
<thead>
<tr>
<th>Q. 88</th>
<th>Are you able to close a file you are working on?</th>
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</thead>
<tbody>
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<td>No</td>
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<td>2</td>
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<table>
<thead>
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<th>Are you able to print a document?</th>
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<td>2</td>
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<table>
<thead>
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<th>Are you able to save a document?</th>
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<tr>
<td>2</td>
<td>Yes</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Q. 91</th>
<th>Are you able to save a document to a network drive?</th>
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<td>1</td>
<td>No</td>
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<td>2</td>
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<table>
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<td>2</td>
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<tr>
<td>2</td>
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<tr>
<td>2</td>
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<table>
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<tr>
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<tr>
<td>2</td>
<td>Yes</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Q. 96</th>
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</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Figure II-5

Standardised QST Instructions
APPENDIX III.
KOPS Study Documentation

Figure III-1
Knee Osteoarthritis Outcome and Injury Score (KOOS) (Roos et al., 1998)
Figure III-2
KOPS Participant Information Sheet

The University of Manchester

KOPS Participant Information Sheet

The research is being conducted under the ethical framework of the NIHR
Clinical Research Facility (CRF). This framework is approved by the
National Research Ethics Service (NRES). The study is being conducted
in accordance with the principles of Good Clinical Practice (GCP) and
the requirements of the Medicines for Human Use (Clinical Trials) Act

The study is being conducted in accordance with the principles of Good Clinical Practice (GCP) and
the requirements of the Medicines for Human Use (Clinical Trials) Act 2001, as amended by the
Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2004.
Figure III-3  KOPS Consent Form

Salford Royal  NHS
NHS Foundation Trust

Study Code________________

Subject Number________________

INFORMED CONSENT FORM

KOPS: Knee Osteoarthritis Pain Sensitivity Study

(A sub-study of TASK: Targeting Synovitis in Knee Osteoarthritis)

Principal Investigator: Dr Terence O’Neill

1. I confirm that I have read and understand the information sheet (Version 1.0 dated 22/09/11) for the above sub-study and have had the opportunity to ask questions and have these answered satisfactorily.

2. I agree to have one or both knees assessed for pain sensitivity (depending on time available) before the steroid injection to my knee and one week later.

3. I understand that relevant sections of my medical notes and data collected during this study may be looked at by responsible individuals involved in the running of the study or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.

4. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

5. I agree to my General Practitioner/Health Care Professional being notified of my participation in this study and when the study ends.

6. I agree to take part in the above study.

________________________  ______________________  ______________________
Name of Patient              Date                      Signature

________________________  ______________________  ______________________
Name of person taking consent if not PI  Date                      Signature

________________________  ______________________  ______________________
PI/Researcher               Date                      Signature

Combining the strengths of UMIST and The Victoria University of Manchester

PAGE KOPS 1CP
Version: 1.0 22.09.11

Arthritis Research UK
Providing answers today and tomorrow
APPENDIX IV. Randomisation for Reliability Assessments

Figure IV-1 KEEPS Rater Observation Checklist (continued over page)
Figure IV-2  Random number generator

Random Integer Generator

Here are your random numbers:

9235

Timestamp: 2013-03-17 20:22:13 UTC

Figure IV-3  Randomisation plan

A Randomization Plan from http://www.randomization.com

1. * Right
   * Left
2. * Left
   * Right
3. * Right
   * Left
4. * Left
   * Right
5. * Left
   * Right
6. * Left
   * Right
7. * Right
   * Left
8. * Right
   * Left
9. * Left
   * Right

9 subjects randomized into 1 block
To reproduce this plan, use the seed 9235
Randomization plan created on 17/3/2013 20:29:50
APPENDIX V. The effect of age and sex on all outcome measures

Table V-1 The effect of age on QST, psychosocial factors and pain intensity

<table>
<thead>
<tr>
<th>Variable</th>
<th>Chi²</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain Intensity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global pain</td>
<td>1.721</td>
<td>0.6323</td>
</tr>
<tr>
<td>Knee pain</td>
<td>1.295</td>
<td>0.7304</td>
</tr>
<tr>
<td>Central QST</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tender point</td>
<td>5.514</td>
<td>0.1378</td>
</tr>
<tr>
<td>Knee wind-up</td>
<td>3.707</td>
<td>0.2949</td>
</tr>
<tr>
<td>Forearm wind-up</td>
<td>4.924</td>
<td>0.1775</td>
</tr>
<tr>
<td>DNIC</td>
<td>0.875</td>
<td>0.8315</td>
</tr>
<tr>
<td>Knee QST</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cold pain</td>
<td>0.764</td>
<td>0.8580</td>
</tr>
<tr>
<td>Heat pain</td>
<td>3.217</td>
<td>0.3594</td>
</tr>
<tr>
<td>Mechanical pain</td>
<td>2.229</td>
<td>0.5263</td>
</tr>
<tr>
<td>Vibration</td>
<td>1.903</td>
<td>0.5927</td>
</tr>
<tr>
<td>Pressure pain</td>
<td>1.240</td>
<td>0.7434</td>
</tr>
<tr>
<td>Forearm QST</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cold pain</td>
<td>2.840</td>
<td>0.4169</td>
</tr>
<tr>
<td>Heat pain</td>
<td>4.068</td>
<td>0.2542</td>
</tr>
<tr>
<td>MPS</td>
<td>1.804</td>
<td>0.6141</td>
</tr>
<tr>
<td>Allodynia</td>
<td>4.983</td>
<td>0.1730</td>
</tr>
<tr>
<td>Vibration</td>
<td>2.839</td>
<td>0.4233</td>
</tr>
<tr>
<td>Pressure pain</td>
<td>3.865</td>
<td>0.2764</td>
</tr>
<tr>
<td>Hospital Anxiety and Depression Scale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>3.367</td>
<td>0.3384</td>
</tr>
<tr>
<td>Depression</td>
<td>1.242</td>
<td>0.7430</td>
</tr>
<tr>
<td>Pain Catastrophising Scale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rumination</td>
<td>2.011</td>
<td>0.5702</td>
</tr>
<tr>
<td>Magnification</td>
<td>2.086</td>
<td>0.5547</td>
</tr>
<tr>
<td>Helplessness</td>
<td>3.519</td>
<td>0.3183</td>
</tr>
<tr>
<td>Illness Perception Questionnaire Brief</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consequences</td>
<td>3.717</td>
<td>0.2937</td>
</tr>
<tr>
<td>Timeline</td>
<td>0.144</td>
<td>0.9861</td>
</tr>
<tr>
<td>Personal Control</td>
<td>4.623</td>
<td>0.2016</td>
</tr>
<tr>
<td>Treatment Control</td>
<td>1.439</td>
<td>0.6964</td>
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<tr>
<td>Identity</td>
<td>3.127</td>
<td>0.3725</td>
</tr>
<tr>
<td>Concern</td>
<td>0.442</td>
<td>0.9314</td>
</tr>
<tr>
<td>Emotion</td>
<td>3.244</td>
<td>0.3555</td>
</tr>
<tr>
<td>RAPA</td>
<td>1.891</td>
<td>0.5954</td>
</tr>
<tr>
<td>HAQ-DI</td>
<td>6.028</td>
<td>0.1102</td>
</tr>
</tbody>
</table>

QST = quantitative sensory testing; DNIC = diffuse noxious inhibitory controls; MPS = mechanical pain sensitivity; RAPA = Rapid Assessment of Physical Activity; HAQ-DI = Health Assessment Questionnaire Disability Index.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Chi²</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain Intensity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global pain</td>
<td>0.444</td>
<td>0.6574</td>
</tr>
<tr>
<td>Knee pain</td>
<td>-1.147</td>
<td>0.2515</td>
</tr>
<tr>
<td>Central QST</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee wind-up</td>
<td>-1.086</td>
<td>0.2777</td>
</tr>
<tr>
<td>Forearm wind-up</td>
<td>-0.051</td>
<td>0.9590</td>
</tr>
<tr>
<td>DNIC</td>
<td>-0.435</td>
<td>0.6638</td>
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<tr>
<td>Knee QST</td>
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<tr>
<td>Cold pain</td>
<td>1.411</td>
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<tr>
<td>Mechanical pain</td>
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<tr>
<td>Allodynia</td>
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<tr>
<td>Vibration</td>
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<td>0.5558</td>
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<td>Pressure pain</td>
<td>-3.109</td>
<td>0.0019</td>
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<tr>
<td>Forearm QST</td>
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<tr>
<td>Cold pain</td>
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<td>0.3500</td>
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<td>Heat pain</td>
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<td>0.1485</td>
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<td>Vibration</td>
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<td>0.4000</td>
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<td>Hospital Anxiety and Depression Scale</td>
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<tr>
<td>Anxiety</td>
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<td>0.4138</td>
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<tr>
<td>Depression</td>
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<td></td>
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<td>Rumination</td>
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<td>0.6789</td>
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<td>Illness Perception Questionnaire Brief</td>
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<td></td>
</tr>
<tr>
<td>Consequences</td>
<td>-0.015</td>
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<td>-0.164</td>
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<td>RAPA</td>
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<tr>
<td>HAQ-DI</td>
<td>0.901</td>
<td>0.3674</td>
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</tbody>
</table>

QST = quantitative sensory testing; DNIC = diffuse noxious inhibitory controls; MPS = mechanical pain sensitivity; RAPA = Rapid Assessment of Physical Activity; HAQ-DI = Health Assessment Questionnaire Disability Index.
## APPENDIX VI. Mediation Analysis

Table VI-1 Mediation analysis for tender point count and global pain intensity

<table>
<thead>
<tr>
<th></th>
<th>Coefficient</th>
<th>95% CI *</th>
<th>SE</th>
<th>Z</th>
<th>Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Effect</strong></td>
<td>0.4666</td>
<td><strong>0.1841 to 0.7492</strong></td>
<td>0.1442</td>
<td>3.24</td>
<td>---</td>
</tr>
<tr>
<td><strong>HAQ-DI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct Effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Path a</td>
<td>0.1932</td>
<td><strong>0.1181 to 0.2684</strong></td>
<td>0.0383</td>
<td>5.04</td>
<td>25.65%</td>
</tr>
<tr>
<td>Path b</td>
<td>0.6195</td>
<td>-0.3112 to 1.5501</td>
<td>0.4748</td>
<td>1.30</td>
<td></td>
</tr>
<tr>
<td>Path c</td>
<td>0.3469</td>
<td><strong>0.0153 to 0.6786</strong></td>
<td>0.1692</td>
<td>2.05</td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.1197</td>
<td>-0.0661 to 0.3054</td>
<td>0.0948</td>
<td>1.26</td>
<td></td>
</tr>
<tr>
<td><strong>IPQ-Brief Emotion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Direct Effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Path a</td>
<td>0.5069</td>
<td><strong>0.2255 to 0.7883</strong></td>
<td>0.1436</td>
<td>3.53</td>
<td>21.09%</td>
</tr>
<tr>
<td>Path b</td>
<td>0.1941</td>
<td>-0.0532 to 0.4413</td>
<td>0.1261</td>
<td>1.54</td>
<td></td>
</tr>
<tr>
<td>Path c</td>
<td>0.3683</td>
<td><strong>0.0640 to 0.6725</strong></td>
<td>0.1552</td>
<td>2.37</td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0984</td>
<td>-0.0383 to 0.2351</td>
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<td>-0.2102 to 0.0006</td>
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CI = confidence interval; * p<0.05 if bold. SE = standard error; Z = Z-score; HAQ-DI = Health Assessment Questionnaire – Disability Index; IPQ-Brief = Illness Perception Questionnaire Brief; PCS = Pain Catastrophizing Scale; RAPA = Rapid Assessment of Physical Activity.
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CI = confidence interval; * p<0.05 if bold; SE = standard error; Z = Z-score; IPQ-Brief = Illness Perception Questionnaire Brief; PCS = Pain Catastrophizing Scale.
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<th>Z</th>
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### PCS Helplessness

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<td>0.1884</td>
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<td>4.65%</td>
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**Indirect Effect**: 0.0154 -0.0087 to 0.3165 | 0.0829 | 1.86 |

### HAD Depression

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<th>SE</th>
<th>Z</th>
<th>p value</th>
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<tr>
<td>c</td>
<td>0.3243</td>
<td><strong>0.0291 to 0.6195</strong></td>
<td>0.1506</td>
<td>2.15</td>
<td></td>
</tr>
</tbody>
</table>

**Indirect Effect**: 0.0067 -0.0419 to 0.0553 | 0.0248 | 0.27 |

CI = confidence interval; * p<0.05 if bold. SE = standard error; Z = Z-score; IPQ-Brief = Illness Perception Questionnaire Brief; PCS = Pain Catastrophizing Scale; HAQ-DI = Health Assessment Questionnaire – Disability Index; HAD = Hospital Anxiety and Depression Scale.
### Table VI-4  
Mediation analysis for mechanical pain sensitivity at the forearm and global pain intensity

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>95% CI *</th>
<th>SE</th>
<th>Z</th>
<th>Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Effect</strong></td>
<td>0.0721</td>
<td>0.0058 to 0.1383</td>
<td>0.0338</td>
<td>2.13</td>
</tr>
<tr>
<td><strong>IPQ-Brief Concern</strong></td>
<td></td>
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<tr>
<td><strong>Direct Effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Path a</td>
<td>0.0697</td>
<td>-0.0084 to 0.1478</td>
<td>0.0398</td>
<td>1.75</td>
</tr>
<tr>
<td>Path b</td>
<td>0.4725</td>
<td><strong>0.2958 to 0.6492</strong></td>
<td>0.0902</td>
<td>5.24</td>
</tr>
<tr>
<td>Path c</td>
<td>0.0391</td>
<td>-0.0172 to 0.0955</td>
<td>0.0288</td>
<td>1.36</td>
</tr>
<tr>
<td><strong>Indirect Effect</strong></td>
<td>0.0329</td>
<td>-0.0060 to 0.0718</td>
<td>0.0199</td>
<td>1.66</td>
</tr>
<tr>
<td><strong>IPQ-Brief Consequences</strong></td>
<td></td>
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<tr>
<td><strong>Direct Effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Path a</td>
<td>0.0452</td>
<td>-0.0188 to 0.1092</td>
<td>0.0327</td>
<td>1.39</td>
</tr>
<tr>
<td>Path b</td>
<td>0.5916</td>
<td><strong>0.3786 to 0.8046</strong></td>
<td>0.1087</td>
<td>5.44</td>
</tr>
<tr>
<td>Path c</td>
<td>0.0453</td>
<td>-0.0099 to 0.1005</td>
<td>0.0282</td>
<td>1.61</td>
</tr>
<tr>
<td><strong>Indirect Effect</strong></td>
<td>0.0268</td>
<td>-0.0123 to 0.0658</td>
<td>0.0199</td>
<td>1.34</td>
</tr>
<tr>
<td><strong>PCS Magnification</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Direct Effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Path a</td>
<td>0.0639</td>
<td><strong>0.0132 to 0.1146</strong></td>
<td>0.0259</td>
<td>2.47</td>
</tr>
<tr>
<td>Path b</td>
<td>0.3232</td>
<td><strong>0.0055 to 0.6408</strong></td>
<td>0.1621</td>
<td>1.99</td>
</tr>
<tr>
<td>Path c</td>
<td>0.0514</td>
<td>-0.0159 to 0.1187</td>
<td>0.0343</td>
<td>1.50</td>
</tr>
<tr>
<td><strong>Indirect Effect</strong></td>
<td>0.0206</td>
<td>-0.0054 to 0.0467</td>
<td>0.0133</td>
<td>1.55</td>
</tr>
<tr>
<td><strong>IPQ-Brief Timeline</strong></td>
<td></td>
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<tr>
<td><strong>Direct Effects</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Path a</td>
<td>0.0643</td>
<td>-0.0181 to 0.1466</td>
<td>0.0420</td>
<td>1.53</td>
</tr>
<tr>
<td>Path b</td>
<td>0.2538</td>
<td><strong>0.0623 to 0.4453</strong></td>
<td>0.0977</td>
<td>2.60</td>
</tr>
<tr>
<td>Path c</td>
<td>0.0558</td>
<td>-0.0083 to 0.1198</td>
<td>0.0327</td>
<td>1.71</td>
</tr>
<tr>
<td><strong>Indirect Effect</strong></td>
<td>0.0163</td>
<td>-0.0079 to 0.0406</td>
<td>0.0124</td>
<td>1.32</td>
</tr>
<tr>
<td><strong>IPQ-Brief Treatment Control</strong></td>
<td></td>
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<tr>
<td><strong>Direct Effects</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Path a</td>
<td>-0.0520</td>
<td>-0.1331 to 0.0273</td>
<td>0.0404</td>
<td>-1.29</td>
</tr>
<tr>
<td>Path b</td>
<td>-0.2299</td>
<td><strong>-0.4316 to -0.0281</strong></td>
<td>0.1029</td>
<td>-2.23</td>
</tr>
<tr>
<td>Path c</td>
<td>0.0601</td>
<td>-0.0044 to 0.1246</td>
<td>0.0329</td>
<td>1.83</td>
</tr>
<tr>
<td><strong>Indirect Effect</strong></td>
<td>0.0119</td>
<td>-0.0091 to 0.0329</td>
<td>0.0107</td>
<td>1.11</td>
</tr>
</tbody>
</table>

CI = confidence interval; * p<0.05 if bold. SE = standard error; Z = Z-score; IPQ-Brief = Illness Perception Questionnaire Brief; PCS = Pain Catastrophizing Scale.
Table VI-5  
Mediation analysis for mechanical pain sensitivity at the knee and pain intensity at the tested knee

<table>
<thead>
<tr>
<th></th>
<th>Coefficient</th>
<th>95% CI *</th>
<th>SE</th>
<th>Z</th>
<th>Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Effect</td>
<td>0.1290</td>
<td>0.0623 to 0.1956</td>
<td>0.0340</td>
<td>3.79</td>
<td>----</td>
</tr>
<tr>
<td><strong>IPQ-Brief Timeline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Direct Effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Path a</td>
<td>0.1184</td>
<td>0.0239 to 0.2128</td>
<td>0.0482</td>
<td>2.46</td>
<td>18.53%</td>
</tr>
<tr>
<td>Path b</td>
<td>0.2017</td>
<td>0.0319 to 0.3714</td>
<td>0.0866</td>
<td>2.33</td>
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</tr>
<tr>
<td>Path c</td>
<td>0.1051</td>
<td>0.0381 to 0.1721</td>
<td>0.0342</td>
<td>3.08</td>
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</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0239</td>
<td>-0.0038 to 0.0516</td>
<td>0.0141</td>
<td>1.69</td>
<td></td>
</tr>
<tr>
<td><strong>PCS Helplessness</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Direct Effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Path a</td>
<td>0.1343</td>
<td>0.0405 to 0.2281</td>
<td>0.0479</td>
<td>2.81</td>
<td>15.19%</td>
</tr>
<tr>
<td>Path b</td>
<td>0.1460</td>
<td>-0.0286 to 0.3205</td>
<td>0.0891</td>
<td>1.64</td>
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<tr>
<td>Path c</td>
<td>0.1094</td>
<td>0.0401 to 0.1787</td>
<td>0.0354</td>
<td>3.09</td>
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</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0196</td>
<td>-0.0075 to 0.0467</td>
<td>0.0139</td>
<td>1.42</td>
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</tr>
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<td><strong>IPQ-Brief Identity</strong></td>
<td></td>
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<td>Direct Effects</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Path a</td>
<td>0.0864</td>
<td>0.0105 to 0.1623</td>
<td>0.0387</td>
<td>2.23</td>
<td>14.34%</td>
</tr>
<tr>
<td>Path b</td>
<td>0.2136</td>
<td>-0.0001 to 0.4273</td>
<td>0.1090</td>
<td>1.96</td>
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</tr>
<tr>
<td>Path c</td>
<td>0.1105</td>
<td>0.0433 to 0.1778</td>
<td>0.0343</td>
<td>3.22</td>
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</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0185</td>
<td>-0.0061 to 0.0430</td>
<td>0.0125</td>
<td>1.47</td>
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</tr>
<tr>
<td><strong>IPQ-Brief Emotion</strong></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Direct Effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Path a</td>
<td>0.0567</td>
<td>-0.0238 to 0.1373</td>
<td>0.0411</td>
<td>1.38</td>
<td>8.60%</td>
</tr>
<tr>
<td>Path b</td>
<td>0.1960</td>
<td>-0.0058 to 0.3978</td>
<td>0.1029</td>
<td>1.90</td>
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</tr>
<tr>
<td>Path c</td>
<td>0.1179</td>
<td>0.0521 to 0.1836</td>
<td>0.0336</td>
<td>3.51</td>
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</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0111</td>
<td>-0.0084 to 0.0306</td>
<td>0.0100</td>
<td>1.12</td>
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</tr>
<tr>
<td><strong>PCS Magnification</strong></td>
<td></td>
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<td>Direct Effects</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Path a</td>
<td>0.0696</td>
<td>0.0093 to 0.1298</td>
<td>0.0308</td>
<td>2.26</td>
<td>6.59%</td>
</tr>
<tr>
<td>Path b</td>
<td>0.1218</td>
<td>-0.1541 to 0.3976</td>
<td>0.1407</td>
<td>0.87</td>
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</tr>
<tr>
<td>Path c</td>
<td>0.1205</td>
<td>0.0515 to 0.1895</td>
<td>0.0352</td>
<td>3.42</td>
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</tr>
<tr>
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<td>0.0085</td>
<td>-0.0121 to 0.0290</td>
<td>0.0105</td>
<td>0.81</td>
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</tr>
</tbody>
</table>

CI = confidence interval; * p<0.05 if bold. SE = standard error; Z = Z-score; IPQ-Brief = Illness Perception Questionnaire-Brief; PCS = Pain Catastrophizing Scale.
Table VI-6  Mediation analysis for allodynia at the knee and pain intensity at the tested knee (continued over page)

<table>
<thead>
<tr>
<th></th>
<th>Coefficient</th>
<th>95% CI *</th>
<th>SE</th>
<th>Z</th>
<th>Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Effect</strong></td>
<td>0.4341</td>
<td>0.1722 to 0.6960</td>
<td>0.1336</td>
<td>3.25</td>
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</tr>
<tr>
<td><strong>IPQ-Brief Consequences</strong></td>
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<tr>
<td>Direct Effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Path a</td>
<td>0.3020</td>
<td>0.0183 to 0.5858</td>
<td>0.1448</td>
<td>2.09</td>
<td>31.49%</td>
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<td>Path b</td>
<td>0.4526</td>
<td>0.2507 to 0.6545</td>
<td>0.1030</td>
<td>4.39</td>
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</tr>
<tr>
<td>Path c</td>
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<td>0.0611 to 0.5337</td>
<td>0.1206</td>
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<tr>
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<td>-0.0055 to 0.2789</td>
<td>0.0725</td>
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<td><strong>IPQ-Brief Concern</strong></td>
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<td>Direct Effects</td>
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<tr>
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<td>0.3735</td>
<td>0.0243 to 0.7227</td>
<td>0.1782</td>
<td>2.10</td>
<td>27.94%</td>
</tr>
<tr>
<td>Path b</td>
<td>0.3247</td>
<td>0.1551 to 0.4944</td>
<td>0.0866</td>
<td>3.75</td>
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<tr>
<td>Path c</td>
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<td>0.0683 to 0.5572</td>
<td>0.1247</td>
<td>2.51</td>
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</tr>
<tr>
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<td>0.0663</td>
<td>1.83</td>
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<tr>
<td><strong>IPQ-Brief Timeline</strong></td>
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<td>Direct Effects</td>
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</tr>
<tr>
<td>Path a</td>
<td>0.3604</td>
<td>-0.0077 to 0.7285</td>
<td>0.1878</td>
<td>1.92</td>
<td>18.75%</td>
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<tr>
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<td>0.2258</td>
<td>0.0565 to 0.3952</td>
<td>0.0864</td>
<td>2.61</td>
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<tr>
<td>Path c</td>
<td>0.3527</td>
<td>0.0969 to 0.6085</td>
<td>0.1305</td>
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<td>Indirect Effect</td>
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<td><strong>HAQ-DI</strong></td>
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<td>Direct Effects</td>
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<tr>
<td>Path a</td>
<td>0.0839</td>
<td>-0.0043 to 0.1721</td>
<td>0.0450</td>
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<tr>
<td>Path b</td>
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<td>0.1677 to 1.5911</td>
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<tr>
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<td>0.3603</td>
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<td>-0.0241 to 0.1717</td>
<td>0.0499</td>
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<td><strong>PCS Helplessness</strong></td>
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<td></td>
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</tr>
<tr>
<td>Direct Effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Path a</td>
<td>0.3847</td>
<td>0.0155 to 0.7539</td>
<td>0.1884</td>
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<td>15.80%</td>
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<tr>
<td>Path b</td>
<td>0.1782</td>
<td>0.0059 to 0.3506</td>
<td>0.0879</td>
<td>2.03</td>
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</tr>
<tr>
<td>Path c</td>
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<td>0.1035 to 0.6276</td>
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<tr>
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<td>-0.0248 to 0.1620</td>
<td>0.0477</td>
<td>1.44</td>
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</tr>
<tr>
<td><strong>IPQ-Brief Emotion</strong></td>
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<td></td>
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<tr>
<td>Direct Effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Path a</td>
<td>0.2083</td>
<td>-0.1005 to 0.5171</td>
<td>0.1575</td>
<td>1.32</td>
<td>9.91%</td>
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<tr>
<td>Path b</td>
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<td>0.0001 to 0.4131</td>
<td>0.1053</td>
<td>1.96</td>
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<td>0.3910</td>
<td>0.1334 to 0.6487</td>
<td>0.1315</td>
<td>2.97</td>
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</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0430</td>
<td>-0.0339 to 0.1200</td>
<td>0.0393</td>
<td>1.10</td>
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</tr>
<tr>
<td><strong>PCS Magnification</strong></td>
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<td></td>
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</tr>
<tr>
<td>Direct Effects</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Path a</td>
<td>0.2302</td>
<td>-0.0030 to 0.4634</td>
<td>0.1190</td>
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<td>8.27%</td>
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<td>-0.1234 to 0.435</td>
<td>0.1424</td>
<td>1.09</td>
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<tr>
<td>Path c</td>
<td>0.3982</td>
<td>0.1310 to 0.6654</td>
<td>0.1364</td>
<td>2.92</td>
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<tr>
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<td>-0.0380 to 0.1097</td>
<td>0.0377</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td><strong>HAD Depression</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Direct Effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Path a</td>
<td>0.0557</td>
<td>-0.3397 to 0.4511</td>
<td>0.2017</td>
<td>0.28</td>
<td>1.52%</td>
</tr>
<tr>
<td>Path b</td>
<td>0.1180</td>
<td>-0.0456 to 0.2816</td>
<td>0.0835</td>
<td>1.41</td>
<td></td>
</tr>
<tr>
<td>Path c</td>
<td>0.4275</td>
<td>0.1696 to 0.6854</td>
<td>0.1316</td>
<td>3.25</td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0066</td>
<td>-0.0410 to 0.0541</td>
<td>0.0243</td>
<td>0.27</td>
<td></td>
</tr>
</tbody>
</table>
### Table VI-7  Mediation analysis for mechanical pain sensitivity at the forearm and pain intensity at the tested knee

<table>
<thead>
<tr>
<th></th>
<th>Coefficient</th>
<th>95% CI</th>
<th>SE</th>
<th>Z</th>
<th>Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Effect</strong></td>
<td>0.0767</td>
<td><strong>0.0169 to 0.1364</strong></td>
<td>0.0305</td>
<td>2.51</td>
<td>----</td>
</tr>
<tr>
<td><strong>IPQ-Brief Concern</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Direct Effects Path a</td>
<td>0.0697</td>
<td>-0.0084 to 0.1478</td>
<td>0.0398</td>
<td>1.75</td>
<td>31.42%</td>
</tr>
<tr>
<td>Path b</td>
<td>0.3449</td>
<td><strong>0.1735 to 0.5134</strong></td>
<td>0.0875</td>
<td>3.94</td>
<td></td>
</tr>
<tr>
<td>Path c</td>
<td>0.0526</td>
<td><strong>-0.0021 to 0.1073</strong></td>
<td>0.0279</td>
<td>1.89</td>
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<tr>
<td>Indirect Effect</td>
<td>0.0241</td>
<td>-0.0054 to 0.0535</td>
<td>0.0150</td>
<td>1.60</td>
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<tr>
<td><strong>IPQ-Brief Consequences</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Direct Effects Path a</td>
<td>0.0452</td>
<td>-0.0188 to 0.1092</td>
<td>0.0327</td>
<td>1.39</td>
<td>28.42%</td>
</tr>
<tr>
<td>Path b</td>
<td>0.4812</td>
<td><strong>0.2803 to 0.6820</strong></td>
<td>0.1025</td>
<td>4.70</td>
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<tr>
<td>Path c</td>
<td>0.0549</td>
<td><strong>0.0029 to 0.1069</strong></td>
<td>0.0265</td>
<td>2.07</td>
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<tr>
<td>Indirect Effect</td>
<td>0.0218</td>
<td>-0.0103 to 0.0539</td>
<td>0.0164</td>
<td>1.33</td>
<td></td>
</tr>
<tr>
<td><strong>IPQ-Brief Timeline</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Direct Effects Path a</td>
<td>0.0643</td>
<td>-0.0181 to 0.1466</td>
<td>0.0420</td>
<td>1.53</td>
<td>20.60%</td>
</tr>
<tr>
<td>Path b</td>
<td>0.2466</td>
<td><strong>0.0752 to 0.4179</strong></td>
<td>0.0874</td>
<td>2.82</td>
<td></td>
</tr>
<tr>
<td>Path c</td>
<td>0.0608</td>
<td><strong>0.0036 to 0.1181</strong></td>
<td>0.0292</td>
<td>2.08</td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0158</td>
<td>-0.0073 to 0.0389</td>
<td>0.0118</td>
<td>1.34</td>
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<tr>
<td><strong>IPQ-Brief Treatment Control</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct Effects Path a</td>
<td>-0.0520</td>
<td>-0.1331 to 0.0273</td>
<td>0.0404</td>
<td>-1.29</td>
<td>15.78%</td>
</tr>
<tr>
<td>Path b</td>
<td>-0.2326</td>
<td><strong>-0.4128 to -0.0525</strong></td>
<td>0.0919</td>
<td>-2.53</td>
<td></td>
</tr>
<tr>
<td>Path c</td>
<td>0.0646</td>
<td><strong>0.0070 to 0.1222</strong></td>
<td>0.0294</td>
<td>2.20</td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0121</td>
<td>-0.0086 to 0.0328</td>
<td>0.0105</td>
<td>1.15</td>
<td></td>
</tr>
<tr>
<td><strong>PCS Magnification</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct Effects Path a</td>
<td>0.0639</td>
<td><strong>0.0132 to 0.1146</strong></td>
<td>0.0259</td>
<td>2.47</td>
<td>13.43%</td>
</tr>
<tr>
<td>Path b</td>
<td>0.1614</td>
<td>-0.1317 to 0.4545</td>
<td>0.1495</td>
<td>1.08</td>
<td></td>
</tr>
<tr>
<td>Path c</td>
<td>0.0664</td>
<td><strong>0.0043 to 0.1285</strong></td>
<td>0.0317</td>
<td>2.09</td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0103</td>
<td>-0.0101 to 0.0307</td>
<td>0.0104</td>
<td>0.99</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; * p<0.05 if bold. SE = standard error; Z = Z-score; IPQ-Brief = Illness Perception Questionnaire Brief; HAQ-DI = Health Assessment Questionnaire – Disability Index; PCS = Pain Catastrophizing Scale; HAD = Hospital Anxiety and Depression Scale.
APPENDIX VII. Mediation Analysis II

Mediation analyses were performed using the model depicted in Figure 6.1, with psychosocial factors used as the independent variables and QST measures as mediators. Psychosocial factors which significantly correlated with global pain intensity or pain intensity at the tested knee were used as the independent variables in this model with eleven correlations identified; HAD depression subscale, and the rumination and magnification subscales of the PCS with global pain intensity, and the helplessness subscale of the PCS, the consequences, timeline, treatment control, identity, concern and emotion items of the IPQ-Brief, and HAQ-DI with both pain intensity measures (Table 6.6). QST measures which significantly correlated with the aforementioned psychosocial factors were identified as variables which would be entered into each model as the mediating variable (VII-1 Correlati). A total of 111 mediation models were constructed with 1 mediating variable identified for the model for HAD depression and global pain intensity (Table VII-2), 4 mediating variables identified for PCS rumination and global pain intensity (Table VII-3), and 8 mediating variables identified for PCS magnification and global pain intensity (Table VII-4). Seven mediating variables were identified for PCS helplessness (Table VII-5 & Table VII-6), 9 mediators for IPQ-Brief consequences (Table VII-7 & Table VII-8), 10 mediators for IPQ-Brief timeline (Table VII-9 & Table VII-10), 2 mediators for IPQ-Brief treatment control (Table VII-11 & Table VII-12), 4 mediators for IPQ-Brief identity (Table VII-13 & Table VII-14), 6 mediators for IPQ-Brief concern (Table VII-15 & Table VII-16), 6 mediators for IPQ-Brief emotion (Table VII-17 & Table VII-18), and 5 mediators for HAQ-DI (Table VII-19 & Table VII-20) with both pain intensity measures.

Complete mediation was not observed for any of the 111 models and only 2 models demonstrated significant partial mediation with Z-scores of 2.08 and 1.96 for the indirect effect (PCS helplessness and knee mechanical pain sensitivity with knee pain intensity, Table VII-6; IPQ-Brief concern and knee mechanical pain sensitivity with knee pain intensity, Table VII-16).

However, there are other factors thought to influence psychosocial factors and pain intensity, such as deprivation status, which are not included in the present models. As such, the proportion of the total mediated effect provides only an estimate of the strength of the indirect effect in the models tested. The total proportion of mediated effect explained by the psychosocial factors added to each model totals more than 100% in Table VII-4, Table VII-9, Table VII-10 and Table VII-17. This finding suggests there may be a latent variable that correlates with each of the QST measures. New models were constructed to include all QST measures significantly correlated with each psychosocial factor (as identified in VII-1 Correlati) loading on to a single latent mediator (depicted in Figure VII-1). The variance of the latent mediator is undefined in the model; therefore the regression coefficient for path b is uninterpretable and is constrained to 1.0 (not included in Table VII-21 or Table VII-22).
This figure depicts the mediation model constructed to include the individual QST measures identified in Table VII-1 loading on to a latent mediator. Path c represents the direct effect between the independent and dependent variables. Paths a and b represent the indirect path between the independent and mediator variables (path a), and between the mediator and dependent variables (path b). Ψ = psychosocial; ε = error term.

The inclusion of a latent variable in the mediation models instead of individual QST measures accounted for between 12.2% and 82.4% of the total effect of the psychosocial factors in VII-1 Correlati on global pain intensity (Table VII-21). Significant partial mediation was only observed for the identity item of the IPQ-Brief with the inclusion of a latent sensitisation mediator; for all other models, the direct effect between each psychosocial factor and global pain intensity was significant (Table VII-21). These findings suggest that individual psychosocial factors could be markers of increased global pain intensity rather than a latent sensitisation mediator, with the exception of the identity item of the IPQ-Brief.

The inclusion of a latent variable in the mediation models instead of individual QST measures accounted for between 1.4% and 64.9% of the total effect of the helplessness subscale of the PCS, the consequences, timeline, treatment control, identity, concern and emotion items of the IPQ-Brief, and HAQ-DI on pain intensity at the tested knee (Table VII-22). The latent sensitisation variables for the timeline item of the IPQ-Brief and the helplessness subscale of the PCS were significant partial mediators of pain intensity at the tested knee, and accounted for 46.8% and 44.8% of the total effect respectively (see Table VII-22); however, the latent variable included in the mediation model for the identity item of the IPQ-Brief was not a significant partial mediator of the association with pain intensity at the tested knee despite accounting for 64.9% of the total mediated effect. No other significant partial mediators were identified in Table VII-22. These findings also suggest individual psychosocial factors could be markers of increased pain intensity at the tested knee rather than a latent sensitisation mediator, with the exception of the timeline item of the IPQ-Brief and helplessness subscale of the PCS.
Table VII - Correlations between psychosocial factors that are significantly correlated with pain intensity and QST measures (n=61)

| HAD | HAQ-DI | Pain Catastrophizing Scale | Illness Perception Questionnaire Brief | Depression | Rumination | Magnification | Helplessness | Consequences | TimeLine | Treatment control | Identity | Concern | Emotion | MALE | ALL | PPT | NDI | fPPT |
|-----|--------|---------------------------|----------------------------------------|-----------|------------|--------------|-------------|--------------|----------|----------------|----------|---------|---------|-------|-----|-----|-----|-----|-----|
| 0.2919 | 0.1802 | 0.3395 | 0.3462 | 0.3303 | 0.3927 | 0.3267 | 0.2759 | 0.3207 | 0.3339 | 0.3064 | 0.2975 | 0.2700 | 0.3239 | 0.2599 | 0.3159 | 0.2233 | 0.2772 | 0.3676 | 0.2626 | 0.1977 |
| 0.2661 | 0.1916 | 0.3120 | 0.3180 | 0.3030 | 0.3627 | 0.2967 | 0.2459 | 0.2907 | 0.3039 | 0.2764 | 0.2495 | 0.2320 | 0.2869 | 0.2229 | 0.2799 | 0.1853 | 0.2342 | 0.3392 | 0.2362 | 0.1652 |
| 0.3085 | 0.2333 | 0.2800 | 0.2860 | 0.2710 | 0.3307 | 0.2647 | 0.2159 | 0.2607 | 0.2739 | 0.2464 | 0.2195 | 0.1820 | 0.2379 | 0.1839 | 0.2389 | 0.1563 | 0.2066 | 0.3133 | 0.2103 | 0.1452 |
| 0.2804 | 0.1728 | 0.2272 | 0.2332 | 0.2182 | 0.2777 | 0.2117 | 0.1627 | 0.2077 | 0.2209 | 0.1934 | 0.1665 | 0.1395 | 0.2049 | 0.1559 | 0.2069 | 0.1283 | 0.1886 | 0.2752 | 0.1822 | 0.1171 |
| 0.2906 | 0.2255 | 0.2721 | 0.2781 | 0.2631 | 0.3130 | 0.2470 | 0.1981 | 0.2430 | 0.2561 | 0.2286 | 0.2016 | 0.1746 | 0.2300 | 0.1810 | 0.2320 | 0.1544 | 0.2147 | 0.3037 | 0.2087 | 0.1436 |
| 0.3096 | 0.2461 | 0.2930 | 0.2990 | 0.2840 | 0.3330 | 0.2670 | 0.2181 | 0.2630 | 0.2762 | 0.2487 | 0.2217 | 0.1947 | 0.2480 | 0.1990 | 0.2490 | 0.1714 | 0.2317 | 0.3187 | 0.2237 | 0.1566 |
| 0.2804 | 0.2255 | 0.2721 | 0.2781 | 0.2631 | 0.3130 | 0.2470 | 0.1981 | 0.2430 | 0.2561 | 0.2286 | 0.2016 | 0.1746 | 0.2300 | 0.1810 | 0.2320 | 0.1544 | 0.2147 | 0.3037 | 0.2087 | 0.1436 |
| 0.2906 | 0.2255 | 0.2721 | 0.2781 | 0.2631 | 0.3130 | 0.2470 | 0.1981 | 0.2430 | 0.2561 | 0.2286 | 0.2016 | 0.1746 | 0.2300 | 0.1810 | 0.2320 | 0.1544 | 0.2147 | 0.3037 | 0.2087 | 0.1436 |

P-values: *p<0.05; **p<0.01. HAD = Hospital Anxiety and Depression Scale; HAD-DI = Health Assessment Questionnaire Disability Index; k denotes assessments performed at the knee; DNIC = Diffuse Noxious Inhibitory Control; CPT = Cold Pain Threshold; HPT = Heat Pain Threshold; ALL = Allodynia; PPT = Pressure Pain Threshold; f denotes assessments performed at the forearm; WUR = Wind-Up Ratio; MPS = Mechanical Pain Sensitivity; WC = Wind-Up Control.
### Table VII-2  Mediation analysis for HAD depression and global pain intensity

<table>
<thead>
<tr>
<th></th>
<th>β-coefficient</th>
<th>95% CI *</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Effect</strong></td>
<td>0.1273</td>
<td>-0.0668, 0.3215</td>
<td>0.0990</td>
<td>1.29</td>
<td>----</td>
</tr>
<tr>
<td><strong>Knee Allodynia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0073</td>
<td>-0.0448, 0.0593</td>
<td>0.0265</td>
<td>0.27</td>
<td>5.7%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.1201</td>
<td><strong>-0.0672, 0.3073</strong></td>
<td>0.1506</td>
<td>1.26</td>
<td></td>
</tr>
</tbody>
</table>

HAD = Hospital Anxiety and Depression Scale; CI = confidence interval; * p<0.05 if bold. SE = standard error; Z = Z-score.

### Table VII-3  Mediation analysis for PCS Rumination and global pain intensity

<table>
<thead>
<tr>
<th></th>
<th>β-coefficient</th>
<th>95% CI *</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Effect</strong></td>
<td>0.3517</td>
<td><strong>0.1691, 0.5342</strong></td>
<td>0.0931</td>
<td>3.78</td>
<td>----</td>
</tr>
<tr>
<td><strong>Tender Point Count</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0788</td>
<td>-0.0089, 0.1666</td>
<td>0.0448</td>
<td>1.76</td>
<td>22.4%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.2728</td>
<td><strong>0.0816, 0.4641</strong></td>
<td>0.0976</td>
<td>2.80</td>
<td></td>
</tr>
<tr>
<td><strong>Knee Allodynia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0278</td>
<td>-0.0228, 0.0783</td>
<td>0.0258</td>
<td>1.08</td>
<td>7.9%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.3239</td>
<td><strong>0.1430, 0.5048</strong></td>
<td>0.0923</td>
<td>3.51</td>
<td></td>
</tr>
<tr>
<td><strong>Forearm Alloodynia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0124</td>
<td>-0.0414, 0.0662</td>
<td>0.0274</td>
<td>0.45</td>
<td>3.5%</td>
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<tr>
<td>Direct Effect</td>
<td>0.3393</td>
<td><strong>0.1642, 0.5143</strong></td>
<td>0.0893</td>
<td>3.80</td>
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<tr>
<td><strong>Forearm Wind-up Ratio</strong></td>
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</tr>
<tr>
<td>Indirect Effect</td>
<td>-0.0102</td>
<td>-0.0409, 0.0206</td>
<td>0.0157</td>
<td>-0.65</td>
<td>2.9%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.3618</td>
<td><strong>0.1788, 0.5449</strong></td>
<td>0.0934</td>
<td>3.87</td>
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</tr>
</tbody>
</table>

PCS = Pain Catastrophising Scale; CI = confidence interval; * p<0.05 if bold. SE = standard error; Z = Z-score.
<table>
<thead>
<tr>
<th></th>
<th>β-coefficient</th>
<th>95% CI *</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Effect</strong></td>
<td>0.3963</td>
<td><strong>0.0880, 0.7047</strong></td>
<td>0.1573</td>
<td>2.52</td>
<td>----</td>
</tr>
<tr>
<td><strong>Tender Point Count</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.1391</td>
<td>-0.0044, 0.2825</td>
<td>0.0732</td>
<td>1.90</td>
<td>35.1%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.2573</td>
<td>-0.0547, 0.5692</td>
<td>0.1592</td>
<td>1.62</td>
<td></td>
</tr>
<tr>
<td><strong>Knee Mechanical Pain Sensitivity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.1166</td>
<td>-0.0150, 0.2482</td>
<td>0.0672</td>
<td>1.74</td>
<td>29.4%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.2797</td>
<td>-0.0236, 0.5831</td>
<td>0.1548</td>
<td>1.81</td>
<td></td>
</tr>
<tr>
<td><strong>Forearm Mechanical Pain Sensitivity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0732</td>
<td>-0.0388, 0.1852</td>
<td>0.0571</td>
<td>1.28</td>
<td>18.5%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.3232</td>
<td><strong>0.0055, 0.6408</strong></td>
<td>0.1621</td>
<td>1.99</td>
<td></td>
</tr>
<tr>
<td><strong>Knee Allodynia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0639</td>
<td>-0.0349, 0.1628</td>
<td>0.0504</td>
<td>1.27</td>
<td>16.1%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.3324</td>
<td><strong>0.0218, 0.6430</strong></td>
<td>0.1585</td>
<td>2.10</td>
<td></td>
</tr>
<tr>
<td><strong>Knee Cold Pain Threshold</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0402</td>
<td>-0.0398, 0.1202</td>
<td>0.0408</td>
<td>0.99</td>
<td>10.2%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.3561</td>
<td><strong>0.0449, 0.6673</strong></td>
<td>0.1588</td>
<td>2.24</td>
<td></td>
</tr>
<tr>
<td><strong>Knee Pressure Pain Threshold</strong></td>
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<tr>
<td>Indirect Effect</td>
<td>0.0359</td>
<td>-0.0385, 0.1104</td>
<td>0.0380</td>
<td>0.95</td>
<td>9.1%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.3604</td>
<td><strong>0.0508, 0.6700</strong></td>
<td>0.1580</td>
<td>2.28</td>
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</tr>
<tr>
<td><strong>Diffuse Noxious Inhibitory Controls</strong></td>
<td></td>
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</tr>
<tr>
<td>Indirect Effect</td>
<td>-0.0126</td>
<td>-0.0598, 0.0345</td>
<td>0.0241</td>
<td>-0.53</td>
<td>3.4%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.4090</td>
<td><strong>0.0989, 0.7191</strong></td>
<td>0.1582</td>
<td>2.58</td>
<td></td>
</tr>
<tr>
<td><strong>Forearm Wind-up Ratio</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>-0.0075</td>
<td>-0.0421, 0.0271</td>
<td>0.0176</td>
<td>-0.43</td>
<td>1.9%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.4038</td>
<td><strong>0.0950, 0.7127</strong></td>
<td>0.1576</td>
<td>2.56</td>
<td></td>
</tr>
</tbody>
</table>

PCS = Pain Catastrophising Scale; CI = confidence interval; * p<0.05 if bold. SE = standard error; Z = Z-score.
Table VII-5  Mediation analysis for PCS Helplessness and global pain intensity

<table>
<thead>
<tr>
<th></th>
<th>β-coefficient</th>
<th>95% CI *</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Effect</strong></td>
<td>0.4295</td>
<td>0.2563, 0.6027</td>
<td>0.0884</td>
<td>4.86</td>
<td>----</td>
</tr>
<tr>
<td><strong>Tender Point Count</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0654</td>
<td>-0.0331, 0.1639</td>
<td>0.0503</td>
<td>1.30</td>
<td>15.2%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.3641</td>
<td>0.1694, 0.5588</td>
<td>0.0994</td>
<td>3.66</td>
<td></td>
</tr>
<tr>
<td><strong>Knee Mechanical Pain Sensitivity</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0640</td>
<td>-0.0109, 0.1389</td>
<td>0.0382</td>
<td>1.67</td>
<td>14.9%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.3655</td>
<td>0.1878, 0.5433</td>
<td>0.0907</td>
<td>4.03</td>
<td></td>
</tr>
<tr>
<td><strong>Knee Allodynia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0295</td>
<td>-0.0234, 0.0823</td>
<td>0.0270</td>
<td>1.09</td>
<td>6.9%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.4000</td>
<td>0.2234, 0.5766</td>
<td>0.0901</td>
<td>4.44</td>
<td></td>
</tr>
<tr>
<td><strong>Forearm Wind-up Ratio</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>-0.0193</td>
<td>-0.0602, 0.0216</td>
<td>0.0209</td>
<td>-0.93</td>
<td>4.5%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.4488</td>
<td>0.2751, 0.6226</td>
<td>0.0887</td>
<td>5.06</td>
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<tr>
<td><strong>Knee Cold Pain Threshold</strong></td>
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</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0142</td>
<td>-0.0394, 0.0678</td>
<td>0.0273</td>
<td>0.52</td>
<td>3.3%</td>
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<tr>
<td>Direct Effect</td>
<td>0.4153</td>
<td>0.2348, 0.5958</td>
<td>0.0921</td>
<td>4.51</td>
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<tr>
<td><strong>Knee Pressure Pain Threshold</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0096</td>
<td>-0.0503, 0.0695</td>
<td>0.0306</td>
<td>0.31</td>
<td>2.2%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.4199</td>
<td>0.2370, 0.6029</td>
<td>0.0934</td>
<td>4.50</td>
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<tr>
<td><strong>Knee Heat Pain Threshold</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>-0.0063</td>
<td>-0.0318, 0.0192</td>
<td>0.0130</td>
<td>-0.48</td>
<td>1.5%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.4359</td>
<td>0.2637, 0.6079</td>
<td>0.0878</td>
<td>4.96</td>
<td></td>
</tr>
</tbody>
</table>

PCS = Pain Catastrophising Scale; CI = confidence interval; * p<0.05 if bold. SE = standard error; Z = Z-score.
Table VII-6  Mediation analysis for PCS Helplessness and pain intensity at the tested knee

<table>
<thead>
<tr>
<th></th>
<th>β-coefficient</th>
<th>95% CI *</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Effect</td>
<td>0.2390</td>
<td><strong>0.0624, 0.4157</strong></td>
<td>0.0901</td>
<td>2.65</td>
<td>----</td>
</tr>
<tr>
<td>Knee Mechanical Pain Sensitivity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0931</td>
<td><strong>0.0053, 0.1809</strong></td>
<td>0.0448</td>
<td>2.08</td>
<td>38.9%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.1460</td>
<td>-0.0286, 0.3205</td>
<td>0.0891</td>
<td>1.64</td>
<td></td>
</tr>
<tr>
<td>Knee Allodynia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0608</td>
<td>-0.0120, 0.1337</td>
<td>0.0372</td>
<td>1.64</td>
<td>25.5%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.1782</td>
<td><strong>0.0059, 0.3506</strong></td>
<td>0.0879</td>
<td>2.03</td>
<td></td>
</tr>
<tr>
<td>Knee Cold Pain Threshold</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0461</td>
<td>-0.0186, 0.1107</td>
<td>0.0330</td>
<td>1.40</td>
<td>19.3%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.1930</td>
<td><strong>0.0128, 0.3732</strong></td>
<td>0.0919</td>
<td>2.10</td>
<td></td>
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<tr>
<td>Tender Point Count</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0107</td>
<td>-0.0866, 0.1080</td>
<td>0.0497</td>
<td>0.22</td>
<td>4.5%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.2283</td>
<td><strong>0.0268, 0.4299</strong></td>
<td>0.1028</td>
<td>2.22</td>
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<tr>
<td>Forearm Wind-up Ratio</td>
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</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0097</td>
<td>-0.0246, 0.0440</td>
<td>0.0175</td>
<td>0.55</td>
<td>4.1%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.2293</td>
<td><strong>0.0504, 0.4082</strong></td>
<td>0.0913</td>
<td>2.51</td>
<td></td>
</tr>
<tr>
<td>Knee Pressure Pain Threshold</td>
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</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0064</td>
<td>-0.0545, 0.0673</td>
<td>0.0311</td>
<td>0.21</td>
<td>2.7%</td>
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<tr>
<td>Direct Effect</td>
<td>0.2326</td>
<td><strong>0.0459, 0.4194</strong></td>
<td>0.0953</td>
<td>2.44</td>
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</tr>
<tr>
<td>Knee Heat Pain Threshold</td>
<td></td>
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</tr>
<tr>
<td>Indirect Effect</td>
<td>-0.0036</td>
<td>-0.0216, 0.0143</td>
<td>0.0092</td>
<td>-0.40</td>
<td>1.5%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.2427</td>
<td><strong>0.0660, 0.4193</strong></td>
<td>0.0901</td>
<td>2.69</td>
<td></td>
</tr>
</tbody>
</table>

PCS = Pain Catastrophising Scale; CI = confidence interval; * p<0.05 if bold. SE = standard error; Z = Z-score.
### Table VII-7  
Mediation analysis for IPQ-Brief Consequences and global pain intensity

<table>
<thead>
<tr>
<th>Variable</th>
<th><strong>β-coefficient</strong></th>
<th>**95% CI ***</th>
<th><strong>SE</strong></th>
<th><strong>Z</strong></th>
<th><strong>Proportion of Total Effect Mediated</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Effect</strong></td>
<td>0.6222</td>
<td><strong>0.4080, 0.8363</strong></td>
<td>0.1093</td>
<td>5.69</td>
<td>----</td>
</tr>
<tr>
<td><strong>Tender Point Count</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0728</td>
<td>-0.0329, 0.1784</td>
<td>0.0539</td>
<td>1.35</td>
<td>11.7%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.5494</td>
<td><strong>0.3171, 0.7817</strong></td>
<td>0.1185</td>
<td>4.64</td>
<td></td>
</tr>
<tr>
<td><strong>Knee Mechanical Pain Sensitivity</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0723</td>
<td>-0.0144, 0.1591</td>
<td>0.0443</td>
<td>1.63</td>
<td>11.6%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.5498</td>
<td><strong>0.3339, 0.7658</strong></td>
<td>0.1102</td>
<td>4.99</td>
<td></td>
</tr>
<tr>
<td><strong>Knee Allodynia</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0338</td>
<td>-0.0311, 0.0987</td>
<td>0.0331</td>
<td>1.02</td>
<td>5.4%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.5884</td>
<td><strong>0.3692, 08075</strong></td>
<td>0.1118</td>
<td>5.26</td>
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</tr>
<tr>
<td><strong>Forearm Mechanical Pain Sensitivity</strong></td>
<td></td>
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</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0305</td>
<td>-0.0265, 0.0876</td>
<td>0.0291</td>
<td>1.05</td>
<td>4.9%</td>
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<tr>
<td>Direct Effect</td>
<td>0.5916</td>
<td><strong>0.3786, 0.8046</strong></td>
<td>0.1087</td>
<td>5.44</td>
<td></td>
</tr>
<tr>
<td><strong>Forearm Wind-up Ratio</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>-0.0299</td>
<td>-0.0861, 0.0263</td>
<td>0.0287</td>
<td>-1.04</td>
<td>4.8%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.6520</td>
<td><strong>0.4379, 0.8662</strong></td>
<td>0.1093</td>
<td>5.97</td>
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</tr>
<tr>
<td><strong>Knee Cold Pain Threshold</strong></td>
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<tr>
<td>Indirect Effect</td>
<td>0.0155</td>
<td>-0.0453, 0.0763</td>
<td>0.0310</td>
<td>0.50</td>
<td>2.5%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.6067</td>
<td><strong>0.3849, 0.8284</strong></td>
<td>0.1131</td>
<td>5.36</td>
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<tr>
<td><strong>Forearm Pressure Pain Threshold</strong></td>
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<tr>
<td>Indirect Effect</td>
<td>0.0136</td>
<td>-0.0499, 0.0771</td>
<td>0.0324</td>
<td>0.42</td>
<td>2.2%</td>
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<tr>
<td>Direct Effect</td>
<td>0.6086</td>
<td><strong>0.3858, 0.8313</strong></td>
<td>0.1137</td>
<td>5.35</td>
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</tr>
<tr>
<td><strong>Knee Heat Pain Threshold</strong></td>
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<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>-0.0032</td>
<td>-0.0285, 0.0222</td>
<td>0.0129</td>
<td>-0.25</td>
<td>0.5%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.6253</td>
<td><strong>0.4125, 0.8382</strong></td>
<td>0.1086</td>
<td>5.76</td>
<td></td>
</tr>
<tr>
<td><strong>Knee Pressure Pain Threshold</strong></td>
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</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0016</td>
<td>-0.0759, 0.0790</td>
<td>0.0395</td>
<td>0.04</td>
<td>0.3%</td>
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<tr>
<td>Direct Effect</td>
<td>0.6206</td>
<td><strong>0.3929, 0.8483</strong></td>
<td>0.1162</td>
<td>5.34</td>
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</tr>
</tbody>
</table>

IPQ-Brief = Illness Perception Questionnaire Brief; CI = confidence interval; * p<0.05 if bold. SE = standard error; Z = Z-score.
Table VII-8  Mediation analysis for IPQ-Brief Consequences and pain intensity at the tested knee

<table>
<thead>
<tr>
<th></th>
<th>β-coefficient</th>
<th>95% CI *</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Effect</strong></td>
<td>0.5182</td>
<td><strong>0.3136, 0.7227</strong></td>
<td>0.1044</td>
<td>4.97</td>
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</tr>
<tr>
<td><strong>Knee Mechanical Pain Sensitivity</strong></td>
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<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0875</td>
<td>-0.0049, 0.1800</td>
<td>0.0472</td>
<td>1.86</td>
<td>16.9%</td>
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<tr>
<td>Direct Effect</td>
<td>0.4307</td>
<td><strong>0.2294, 0.6319</strong></td>
<td>0.1027</td>
<td>4.19</td>
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<tr>
<td><strong>Knee Allodynia</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0656</td>
<td>-0.0151, 0.1463</td>
<td>0.0412</td>
<td>1.59</td>
<td>12.7%</td>
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<tr>
<td>Direct Effect</td>
<td>0.4526</td>
<td><strong>0.2507, 0.6545</strong></td>
<td>0.1030</td>
<td>4.39</td>
<td></td>
</tr>
<tr>
<td><strong>Knee Cold Pain Threshold</strong></td>
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</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0405</td>
<td>-0.0262, 0.1073</td>
<td>0.0341</td>
<td>1.19</td>
<td>7.8%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.4777</td>
<td><strong>0.2689, 0.6865</strong></td>
<td>0.1065</td>
<td>4.48</td>
<td></td>
</tr>
<tr>
<td><strong>Forearm Mechanical Pain Sensitivity</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0370</td>
<td>-0.0260, 0.1001</td>
<td>0.0322</td>
<td>1.15</td>
<td>7.2%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.4812</td>
<td><strong>0.2803, 0.6820</strong></td>
<td>0.1025</td>
<td>4.70</td>
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</tr>
<tr>
<td><strong>Tender Point Count</strong></td>
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<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>-0.0242</td>
<td>-0.1203, 0.0718</td>
<td>0.0490</td>
<td>-0.49</td>
<td>4.7%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.5424</td>
<td><strong>0.3172, 0.7676</strong></td>
<td>0.1149</td>
<td>4.72</td>
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</tr>
<tr>
<td><strong>Knee Pressure Pain Threshold</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>-0.0201</td>
<td>-0.0952, 0.0550</td>
<td>0.0383</td>
<td>-0.53</td>
<td>3.9%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.5383</td>
<td><strong>0.3213, 0.7553</strong></td>
<td>0.1107</td>
<td>4.86</td>
<td></td>
</tr>
<tr>
<td><strong>Forearm Pressure Pain Threshold</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>-0.0108</td>
<td>-0.0712, 0.0496</td>
<td>0.0308</td>
<td>-0.35</td>
<td>2.1%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.5290</td>
<td><strong>0.3162, 0.7419</strong></td>
<td>0.1086</td>
<td>4.87</td>
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</tr>
<tr>
<td><strong>Forearm Wind-up Ratio</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0054</td>
<td>-0.0339, 0.0446</td>
<td>0.0200</td>
<td>0.27</td>
<td>1.0%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.5128</td>
<td><strong>0.3048, 0.7208</strong></td>
<td>0.1061</td>
<td>4.83</td>
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</tr>
<tr>
<td><strong>Knee Heat Pain Threshold</strong></td>
<td></td>
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</tr>
<tr>
<td>Indirect Effect</td>
<td>-0.0020</td>
<td>-0.0190, 0.0149</td>
<td>0.0086</td>
<td>-0.23</td>
<td>0.4%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.5202</td>
<td><strong>0.3161, 0.7243</strong></td>
<td>0.1041</td>
<td>5.00</td>
<td></td>
</tr>
</tbody>
</table>

IPQ-Brief = Illness Perception Questionnaire Brief; CI = confidence interval; * p<0.05 if bold. SE = standard error; Z = Z-score.
<table>
<thead>
<tr>
<th></th>
<th>β-coefficient</th>
<th>95% CI *</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Effect</strong></td>
<td>0.2859</td>
<td><strong>0.0935, 0.4783</strong></td>
<td>0.0982</td>
<td>2.91</td>
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</tr>
<tr>
<td><strong>Tender Point Count</strong></td>
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<tr>
<td>Indirect Effect</td>
<td>0.0772</td>
<td>-0.0070, 0.1615</td>
<td>0.0430</td>
<td>1.80</td>
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<tr>
<td>Direct Effect</td>
<td>0.2086</td>
<td><strong>0.0160, 0.4012</strong></td>
<td>0.0983</td>
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</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0756</td>
<td>-0.0077, 0.1588</td>
<td>0.0425</td>
<td>1.78</td>
<td>26.4%</td>
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<tr>
<td>Direct Effect</td>
<td>0.2103</td>
<td><strong>0.0188, 0.4018</strong></td>
<td>0.0977</td>
<td>2.15</td>
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<tr>
<td><strong>Knee Alldynia</strong></td>
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</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0382</td>
<td>-0.0224, 0.0987</td>
<td>0.0309</td>
<td>1.24</td>
<td>13.4%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.2477</td>
<td><strong>0.0537, 0.4417</strong></td>
<td>0.0990</td>
<td>2.50</td>
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<tr>
<td><strong>Forearm Alldynia</strong></td>
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<tr>
<td>Indirect Effect</td>
<td>0.0384</td>
<td>-0.0218, 0.0985</td>
<td>0.0307</td>
<td>1.25</td>
<td>13.4%</td>
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<td>Direct Effect</td>
<td>0.2475</td>
<td><strong>0.0559, 0.4390</strong></td>
<td>0.0977</td>
<td>2.53</td>
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<tr>
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<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>-0.0335</td>
<td>-0.0916, 0.0247</td>
<td>0.0297</td>
<td>-1.13</td>
<td>11.7%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.3193</td>
<td><strong>0.1239, 0.5147</strong></td>
<td>0.0997</td>
<td>3.20</td>
<td></td>
</tr>
<tr>
<td><strong>Forearm Mechanical Pain Sensitivity</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0321</td>
<td>-0.0231, 0.0872</td>
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<td>11.2%</td>
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<tr>
<td>Direct Effect</td>
<td>0.2538</td>
<td><strong>0.0623, 0.4453</strong></td>
<td>0.0977</td>
<td>2.60</td>
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<td><strong>Knee Cold Pain Threshold</strong></td>
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<tr>
<td>Indirect Effect</td>
<td>0.0282</td>
<td>-0.0413, 0.0977</td>
<td>0.0355</td>
<td>0.80</td>
<td>9.9%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.2576</td>
<td><strong>0.0551, 0.4602</strong></td>
<td>0.1033</td>
<td>2.49</td>
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</tr>
<tr>
<td><strong>Knee Pressure Pain Threshold</strong></td>
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</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0263</td>
<td>-0.0522, 0.1047</td>
<td>0.0400</td>
<td>0.66</td>
<td>9.2%</td>
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<tr>
<td>Direct Effect</td>
<td>0.2596</td>
<td><strong>0.0531, 0.4661</strong></td>
<td>0.1054</td>
<td>2.46</td>
<td></td>
</tr>
<tr>
<td><strong>Forearm Wind-up Ratio</strong></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>-0.0170</td>
<td>-0.0602, 0.0262</td>
<td>0.0220</td>
<td>-0.77</td>
<td>6.0%</td>
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<tr>
<td>Direct Effect</td>
<td>0.3029</td>
<td><strong>0.1081, 0.4976</strong></td>
<td>0.0994</td>
<td>3.05</td>
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<tr>
<td><strong>Forearm Heat Pain Threshold</strong></td>
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</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0024</td>
<td>-0.0679, 0.0728</td>
<td>0.0359</td>
<td>0.07</td>
<td>0.9%</td>
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<td>Direct Effect</td>
<td>0.2834</td>
<td><strong>0.0786, 0.4882</strong></td>
<td>0.1045</td>
<td>2.71</td>
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</tr>
</tbody>
</table>

IPQ-Brief = Illness Perception Questionnaire Brief; CI = confidence interval; * p<0.05 if bold. SE = standard error; Z = Z-score.
Table VII-10  Mediation analysis for IPQ-Brief Timeline and pain intensity at the tested knee

<table>
<thead>
<tr>
<th></th>
<th>β-coefficient</th>
<th>95% CI *</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
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<tbody>
<tr>
<td><strong>Indirect Effect</strong></td>
<td></td>
<td></td>
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<tr>
<td>Total Effect</td>
<td>0.2816</td>
<td><strong>0.1075, 0.4556</strong></td>
<td>0.0888</td>
<td>3.17</td>
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</tr>
<tr>
<td>Tender Point Count</td>
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<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0157</td>
<td>-0.0423, 0.0738</td>
<td>0.0296</td>
<td>0.53</td>
<td>5.6%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.2658</td>
<td><strong>0.0832, 0.4485</strong></td>
<td>0.0932</td>
<td>2.85</td>
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<td>Knee Cold Pain Threshold</td>
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<tr>
<td>Indirect Effect</td>
<td>0.0456</td>
<td>-0.0223, 0.1135</td>
<td>0.0346</td>
<td>1.32</td>
<td>16.2%</td>
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<tr>
<td>Direct Effect</td>
<td>0.2360</td>
<td><strong>0.0551, 0.4168</strong></td>
<td>0.0905</td>
<td>2.56</td>
<td></td>
</tr>
<tr>
<td>Knee Heat Pain Threshold</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Indirect Effect</td>
<td>-0.0268</td>
<td>-0.0777, 0.0240</td>
<td>0.0259</td>
<td>-1.03</td>
<td>9.5%</td>
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<tr>
<td>Direct Effect</td>
<td>0.3084</td>
<td><strong>0.1311, 0.4857</strong></td>
<td>0.0905</td>
<td>3.41</td>
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<tr>
<td>Knee Mechanical Pain Sensitivity</td>
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<td></td>
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<tr>
<td>Indirect Effect</td>
<td>0.0799</td>
<td>-0.0017, 0.1615</td>
<td>0.0416</td>
<td>1.92</td>
<td>28.4%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.2016</td>
<td><strong>0.0319, 0.3714</strong></td>
<td>0.0866</td>
<td>2.33</td>
<td></td>
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<tr>
<td>Knee Allodynia</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0557</td>
<td>-0.0141,0.1255</td>
<td>0.0356</td>
<td>1.56</td>
<td>19.8%</td>
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<tr>
<td>Direct Effect</td>
<td>0.2258</td>
<td><strong>0.0565, 0.3952</strong></td>
<td>0.0864</td>
<td>2.61</td>
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<tr>
<td>Knee Pressure Pain Threshold</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>-0.0037</td>
<td>-0.0734, 0.0659</td>
<td>0.0356</td>
<td>-0.10</td>
<td>1.3%</td>
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<tr>
<td>Direct Effect</td>
<td>0.2853</td>
<td><strong>0.0979, 0.4727</strong></td>
<td>0.0956</td>
<td>2.98</td>
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<tr>
<td>Forearm Heat Pain Threshold</td>
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<tr>
<td>Indirect Effect</td>
<td>-0.0280</td>
<td>-0.0941, 0.0380</td>
<td>0.0337</td>
<td>-0.83</td>
<td>10.0%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.3096</td>
<td><strong>0.1254, 0.4937</strong></td>
<td>0.0939</td>
<td>3.30</td>
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<tr>
<td>Forearm Mechanical Pain Sensitivity</td>
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</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0350</td>
<td>-0.0206, 0.0906</td>
<td>0.0284</td>
<td>1.23</td>
<td>13.6%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.2466</td>
<td><strong>0.0752, 0.4179</strong></td>
<td>0.0874</td>
<td>2.82</td>
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<tr>
<td>Forearm Allodynia</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0283</td>
<td>-0.0212, 0.0777</td>
<td>0.0252</td>
<td>1.12</td>
<td>10.1%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.2533</td>
<td><strong>0.0784, 0.4281</strong></td>
<td>0.0892</td>
<td>2.84</td>
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</tr>
<tr>
<td>Forearm Wind-up Ratio</td>
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<tr>
<td>Indirect Effect</td>
<td>0.0084</td>
<td>-0.0271, 0.0439</td>
<td>0.0181</td>
<td>0.46</td>
<td>3.0%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.2732</td>
<td><strong>0.0962, 0.4501</strong></td>
<td>0.0903</td>
<td>3.03</td>
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</tr>
</tbody>
</table>

IPQ-Brief = Illness Perception Questionnaire Brief; CI = confidence interval; * p<0.05 if bold. SE = standard error; Z = Z-score.
### Table VII-11  Mediation analysis for IPQ-Brief Treatment Control and global pain intensity

<table>
<thead>
<tr>
<th></th>
<th>β-coefficient</th>
<th>95% CI *</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Effect</td>
<td>-0.2604</td>
<td>-0.4648, -0.0560</td>
<td>0.1043</td>
<td>-2.50</td>
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</tr>
<tr>
<td><strong>Forearm Mechanical Pain Sensitivity</strong></td>
<td></td>
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</tr>
<tr>
<td>Indirect Effect</td>
<td>-0.0305</td>
<td>-0.0875, 0.0264</td>
<td>0.0290</td>
<td>-1.05</td>
<td>11.7%</td>
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<tr>
<td>Direct Effect</td>
<td>-0.2299</td>
<td>-0.4316, -0.0281</td>
<td>0.1029</td>
<td>-2.23</td>
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</tr>
</tbody>
</table>

IPQ-Brief = Illness Perception Questionnaire Brief; CI = confidence interval; * p<0.05 if bold. SE = standard error; Z = Z-score.

### Table VII-12  Mediation analysis for IPQ-Brief Treatment Control and pain intensity at the tested knee

<table>
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<tr>
<th></th>
<th>β-coefficient</th>
<th>95% CI *</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Effect</td>
<td>-0.2654</td>
<td>-0.4501, -0.0808</td>
<td>0.0942</td>
<td>-2.82</td>
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</tr>
<tr>
<td><strong>Forearm Mechanical Pain Sensitivity</strong></td>
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</tr>
<tr>
<td>Indirect Effect</td>
<td>-0.0328</td>
<td>-0.0907, 0.0251</td>
<td>0.0296</td>
<td>-1.11</td>
<td>12.4%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>-0.2326</td>
<td>-0.4128, -0.0525</td>
<td>0.0919</td>
<td>-2.53</td>
<td></td>
</tr>
</tbody>
</table>

IPQ-Brief = Illness Perception Questionnaire Brief; CI = confidence interval; * p<0.05 if bold. SE = standard error; Z = Z-score.

### Table VII-13  Mediation analysis for IPQ-Brief Identity and global pain intensity

<table>
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<th>β-coefficient</th>
<th>95% CI *</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Effect</td>
<td>0.3371</td>
<td>0.0939, 0.5803</td>
<td>0.1241</td>
<td>2.72</td>
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</tr>
<tr>
<td>Indirect Effect</td>
<td>0.1144</td>
<td>-0.0027, 0.2315</td>
<td>0.0597</td>
<td>1.92</td>
<td>33.9%</td>
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<tr>
<td>Direct Effect</td>
<td>0.2227</td>
<td>-0.0269, 0.4723</td>
<td>0.1274</td>
<td>1.75</td>
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**Knee Mechanical Pain Sensitivity**

<table>
<thead>
<tr>
<th></th>
<th>β-coefficient</th>
<th>95% CI *</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indirect Effect</td>
<td>0.0898</td>
<td>-0.0129, 0.1924</td>
<td>0.0524</td>
<td>1.71</td>
<td>26.6%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.2473</td>
<td>0.0081, 0.4865</td>
<td>0.1221</td>
<td>2.03</td>
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</table>

**Knee Allodynia**

<table>
<thead>
<tr>
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<th>β-coefficient</th>
<th>95% CI *</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indirect Effect</td>
<td>0.0467</td>
<td>-0.0280, 0.1214</td>
<td>0.0381</td>
<td>1.23</td>
<td>13.9%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.2904</td>
<td>0.0466, 0.5341</td>
<td>0.1244</td>
<td>2.33</td>
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</table>

**Knee Cold Pain Threshold**

<table>
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<th></th>
<th>β-coefficient</th>
<th>95% CI *</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indirect Effect</td>
<td>0.0372</td>
<td>-0.0446, 0.1190</td>
<td>0.0418</td>
<td>0.89</td>
<td>11.0%</td>
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<tr>
<td>Direct Effect</td>
<td>0.2999</td>
<td>0.0468, 0.5531</td>
<td>0.1292</td>
<td>2.32</td>
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**Knee Pressure Pain Threshold**

<table>
<thead>
<tr>
<th></th>
<th>β-coefficient</th>
<th>95% CI *</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indirect Effect</td>
<td>0.0334</td>
<td>-0.0367, 0.1034</td>
<td>0.0357</td>
<td>0.93</td>
<td>9.9%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.3037</td>
<td>0.0547, 0.5526</td>
<td>0.1270</td>
<td>2.39</td>
<td></td>
</tr>
</tbody>
</table>

IPQ-Brief = Illness Perception Questionnaire Brief; CI = confidence interval; * p<0.05 if bold. SE = standard error; Z = Z-score.
### Table VII-14  Mediation analysis for IPQ-Brief Identity and pain intensity at the tested knee

<table>
<thead>
<tr>
<th></th>
<th>β-coefficient</th>
<th>95% CI *</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Effect</strong></td>
<td>0.3100</td>
<td>0.0878, 0.5323</td>
<td>0.1134</td>
<td>2.73</td>
<td>----</td>
</tr>
<tr>
<td><strong>Knee Mechanical Pain Sensitivity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0964</td>
<td>-0.0067, 0.1995</td>
<td>0.0526</td>
<td>1.83</td>
<td>31.1%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.2136</td>
<td>-0.0001, 0.4273</td>
<td>0.1090</td>
<td>1.96</td>
<td></td>
</tr>
<tr>
<td><strong>Knee Allodynia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0811</td>
<td>-0.0208, 0.1570</td>
<td>0.0454</td>
<td>1.50</td>
<td>26.2%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.2419</td>
<td>0.0273, 0.4565</td>
<td>0.1095</td>
<td>2.21</td>
<td></td>
</tr>
<tr>
<td><strong>Knee Cold Pain Threshold</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0590</td>
<td>-0.0242, 0.1421</td>
<td>0.0424</td>
<td>1.39</td>
<td>19.0%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.2511</td>
<td>0.0232, 0.4789</td>
<td>0.1163</td>
<td>2.16</td>
<td></td>
</tr>
<tr>
<td><strong>Tender Point Count</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0225</td>
<td>-0.0664, 0.1115</td>
<td>0.0454</td>
<td>0.50</td>
<td>7.3%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.2875</td>
<td>0.0490, 0.5261</td>
<td>0.1217</td>
<td>2.36</td>
<td></td>
</tr>
<tr>
<td><strong>Knee Pressure Pain Threshold</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0114</td>
<td>-0.0468, 0.0696</td>
<td>0.0297</td>
<td>0.39</td>
<td>3.7%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.2986</td>
<td>0.0694, 0.5278</td>
<td>0.1170</td>
<td>2.55</td>
<td></td>
</tr>
</tbody>
</table>

IPQ-Brief = Illness Perception Questionnaire Brief; CI = confidence interval; * p<0.05 if bold. SE = standard error; Z = Z-score.

### Table VII-15  Mediation analysis for IPQ-Brief Concern and global pain intensity

<table>
<thead>
<tr>
<th></th>
<th>β-coefficient</th>
<th>95% CI *</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Effect</strong></td>
<td>0.4993</td>
<td>0.3243, 0.6743</td>
<td>0.0893</td>
<td>5.59</td>
<td>----</td>
</tr>
<tr>
<td><strong>Knee Mechanical Pain Sensitivity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0615</td>
<td>-0.0129, 0.1360</td>
<td>0.0380</td>
<td>1.62</td>
<td>12.3%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.4378</td>
<td>0.2576, 0.6179</td>
<td>0.0919</td>
<td>4.76</td>
<td></td>
</tr>
<tr>
<td><strong>Tender Point Count</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0589</td>
<td>-0.0319, 0.1497</td>
<td>0.0463</td>
<td>1.27</td>
<td>11.8%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.4404</td>
<td>0.2477, 0.6330</td>
<td>0.0983</td>
<td>4.48</td>
<td></td>
</tr>
<tr>
<td><strong>Forearm Wind-up Ratio</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>-0.0317</td>
<td>-0.0839, 0.0205</td>
<td>0.0267</td>
<td>-1.19</td>
<td>6.3%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.5310</td>
<td>0.3556, 0.7064</td>
<td>0.0895</td>
<td>5.93</td>
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</tr>
<tr>
<td><strong>Knee Alodynia</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0279</td>
<td>-0.0254, 0.0811</td>
<td>0.0272</td>
<td>1.03</td>
<td>5.6%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.4714</td>
<td>0.2922, 0.6506</td>
<td>0.0914</td>
<td>5.16</td>
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</tr>
<tr>
<td><strong>Forearm Mechanical Pain Sensitivity</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0268</td>
<td>-0.0221, 0.0758</td>
<td>0.0250</td>
<td>1.07</td>
<td>5.4%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.4725</td>
<td>0.2958, 0.6492</td>
<td>0.0902</td>
<td>5.24</td>
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<tr>
<td><strong>Knee Pressure Pain Threshold</strong></td>
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</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0124</td>
<td>-0.0366, 0.0614</td>
<td>0.0250</td>
<td>0.50</td>
<td>2.5%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.4869</td>
<td>0.3059, 0.6679</td>
<td>0.0924</td>
<td>5.27</td>
<td></td>
</tr>
</tbody>
</table>

IPQ-Brief = Illness Perception Questionnaire Brief; CI = confidence interval; * p<0.05 if bold. SE = standard error; Z = Z-score.
<table>
<thead>
<tr>
<th></th>
<th>β-coefficient</th>
<th>95% CI *</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Effect</strong></td>
<td>0.3810</td>
<td><strong>0.2089, 0.5531</strong></td>
<td>0.0878</td>
<td>4.34</td>
<td>----</td>
</tr>
<tr>
<td><strong>Knee Mechanical Pain Sensitivity</strong></td>
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</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0814</td>
<td><strong>-0.00003, 0.1629</strong></td>
<td>0.0416</td>
<td>1.96</td>
<td>21.4%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.2996</td>
<td><strong>0.1272, 0.4720</strong></td>
<td>0.0880</td>
<td>3.41</td>
<td></td>
</tr>
<tr>
<td><strong>Knee Allodynia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0563</td>
<td><strong>-0.0123, 0.1249</strong></td>
<td>0.0350</td>
<td>1.61</td>
<td>14.8%</td>
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<tr>
<td>Direct Effect</td>
<td>0.3247</td>
<td><strong>0.1551, 0.4944</strong></td>
<td>0.0866</td>
<td>3.75</td>
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<tr>
<td><strong>Forearm Mechanical Pain Sensitivity</strong></td>
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<tr>
<td>Indirect Effect</td>
<td>0.0361</td>
<td><strong>-0.0190, 0.0912</strong></td>
<td>0.0281</td>
<td>1.28</td>
<td>9.5%</td>
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<tr>
<td>Direct Effect</td>
<td>0.3449</td>
<td><strong>0.1735, 0.5164</strong></td>
<td>0.0875</td>
<td>3.94</td>
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<tr>
<td>Indirect Effect</td>
<td>-0.0167</td>
<td><strong>-0.1026, 0.0692</strong></td>
<td>0.0438</td>
<td>-0.38</td>
<td>4.4%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.3977</td>
<td><strong>0.2057, 0.5897</strong></td>
<td>0.0980</td>
<td>4.06</td>
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<tr>
<td><strong>Forearm Wind-up Ratio</strong></td>
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</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0042</td>
<td><strong>-0.0341, 0.0425</strong></td>
<td>0.0195</td>
<td>0.22</td>
<td>1.1%</td>
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<tr>
<td>Direct Effect</td>
<td>0.3768</td>
<td><strong>0.2006, 0.5530</strong></td>
<td>0.0900</td>
<td>4.19</td>
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<tr>
<td><strong>Knee Pressure Pain Threshold</strong></td>
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</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0001</td>
<td><strong>-0.0468, 0.0470</strong></td>
<td>0.0239</td>
<td>0.00</td>
<td>0.0%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.3809</td>
<td><strong>0.2025, 0.5593</strong></td>
<td>0.0910</td>
<td>4.19</td>
<td></td>
</tr>
</tbody>
</table>

IPQ-Brief = Illness Perception Questionnaire Brief; CI = confidence interval; * p<0.05 if bold. SE = standard error; Z = Z-score.
### Table VII-17  Mediation analysis for IPQ-Brief Emotion and global pain intensity

<table>
<thead>
<tr>
<th></th>
<th>β-coefficient</th>
<th>95% CI *</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Effect</strong></td>
<td>0.3173</td>
<td>0.0819, 0.5528</td>
<td>0.1201</td>
<td>2.64</td>
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</tr>
<tr>
<td><strong>Tender Point Count</strong></td>
<td></td>
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<tr>
<td>Indirect Effect</td>
<td>0.1233</td>
<td>0.0006, 0.2460</td>
<td>0.0626</td>
<td>1.97</td>
<td>38.9%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.1941</td>
<td>-0.0532, 0.4413</td>
<td>0.1261</td>
<td>1.54</td>
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</tr>
<tr>
<td><strong>Knee Mechanical Pain Sensitivity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0585</td>
<td>-0.0332, 0.1502</td>
<td>0.0468</td>
<td>1.25</td>
<td>18.4%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.2588</td>
<td>0.0351, 0.4826</td>
<td>0.1141</td>
<td>2.27</td>
<td></td>
</tr>
<tr>
<td><strong>Forearm Wind-up Ratio</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>-0.0380</td>
<td>-0.1131, 0.0371</td>
<td>0.0383</td>
<td>-0.99</td>
<td>12.0%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.3553</td>
<td>0.1126, 0.5981</td>
<td>0.1238</td>
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<tr>
<td><strong>Knee Allodynia</strong></td>
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</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0365</td>
<td>-0.0301, 0.1030</td>
<td>0.0339</td>
<td>1.07</td>
<td>11.5%</td>
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<tr>
<td>Direct Effect</td>
<td>0.2809</td>
<td>0.0485, 0.5133</td>
<td>0.1186</td>
<td>2.37</td>
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<tr>
<td><strong>Knee Pressure Pain Threshold</strong></td>
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</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0345</td>
<td>-0.0400, 0.1091</td>
<td>0.0380</td>
<td>0.91</td>
<td>10.9%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.2828</td>
<td>0.0394, 0.5262</td>
<td>0.1242</td>
<td>2.28</td>
<td></td>
</tr>
<tr>
<td><strong>Knee Cold Pain Threshold</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0309</td>
<td>-0.0310, 0.0927</td>
<td>0.0316</td>
<td>0.98</td>
<td>9.7%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.2865</td>
<td>0.0483, 0.5246</td>
<td>0.1215</td>
<td>2.36</td>
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</tr>
</tbody>
</table>

IPQ-Brief = Illness Perception Questionnaire Brief; CI = confidence interval; * p<0.05 if bold. SE = standard error; Z = Z-score.

---

247
<table>
<thead>
<tr>
<th></th>
<th>β-coefficient</th>
<th>95% CI *</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Effect</strong></td>
<td>0.2589</td>
<td><strong>0.0411, 0.4767</strong></td>
<td>0.1111</td>
<td>2.33</td>
<td>----</td>
</tr>
<tr>
<td><strong>Knee Mechanical Pain Sensitivity</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0629</td>
<td>-0.0331, 0.1589</td>
<td>0.0490</td>
<td>1.28</td>
<td>24.3%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.1960</td>
<td>-0.0058, 0.3978</td>
<td>0.1029</td>
<td>1.90</td>
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</tr>
<tr>
<td><strong>Knee Allodynia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0523</td>
<td>-0.0325, 0.1372</td>
<td>0.0433</td>
<td>1.21</td>
<td>20.2%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.2066</td>
<td><strong>0.0001, 0.4131</strong></td>
<td>0.1053</td>
<td>1.96</td>
<td></td>
</tr>
<tr>
<td><strong>Knee Cold Pain Threshold</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0460</td>
<td>-0.0242, 0.1161</td>
<td>0.0358</td>
<td>1.28</td>
<td>17.8%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.2130</td>
<td>-0.0032, 0.4291</td>
<td>0.1103</td>
<td>1.93</td>
<td></td>
</tr>
<tr>
<td><strong>Tender Point Count</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0271</td>
<td>-0.0723, 0.1264</td>
<td>0.0507</td>
<td>0.53</td>
<td>10.5%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.2319</td>
<td>-0.0066, 0.4703</td>
<td>0.1217</td>
<td>1.91</td>
<td></td>
</tr>
<tr>
<td><strong>Knee Pressure Pain Threshold</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0132</td>
<td>-0.0515, 0.0780</td>
<td>0.0330</td>
<td>0.40</td>
<td>5.1%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.2457</td>
<td><strong>0.0190, 0.4724</strong></td>
<td>0.1157</td>
<td>2.12</td>
<td></td>
</tr>
<tr>
<td><strong>Forearm Wind-up Ratio</strong></td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0134</td>
<td>-0.0507, 0.0775</td>
<td>0.0327</td>
<td>0.41</td>
<td>5.2%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.2455</td>
<td><strong>0.0191, 0.4720</strong></td>
<td>0.1156</td>
<td>2.12</td>
<td></td>
</tr>
</tbody>
</table>

IPQ-Brief = Illness Perception Questionnaire Brief; CI = confidence interval; * p<0.05 if bold. SE = standard error; Z = Z-score.
### Table VII-19  Mediation analysis for HAQ-DI and global pain intensity

<table>
<thead>
<tr>
<th></th>
<th>β-coefficient</th>
<th>95% CI *</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
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<tbody>
<tr>
<td><strong>Total Effect</strong></td>
<td>0.1434</td>
<td><strong>0.0424, 0.2445</strong></td>
<td>0.0516</td>
<td>2.78</td>
<td>----</td>
</tr>
<tr>
<td><strong>Tender Point Count</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0660</td>
<td>-0.0021, 0.1341</td>
<td>0.0347</td>
<td>1.90</td>
<td>46.0%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.0774</td>
<td><strong>-0.0389, 0.1938</strong></td>
<td>0.0594</td>
<td>1.30</td>
<td></td>
</tr>
<tr>
<td><strong>Knee Allodynia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0199</td>
<td>-0.0116, 0.0515</td>
<td>0.0161</td>
<td>1.24</td>
<td>13.9%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.1235</td>
<td><strong>0.0219, 0.2251</strong></td>
<td>0.0519</td>
<td>2.38</td>
<td></td>
</tr>
<tr>
<td><strong>Forearm Allodynia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0171</td>
<td>-0.0130, 0.0472</td>
<td>0.0153</td>
<td>1.12</td>
<td>11.9%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.1263</td>
<td><strong>0.0269, 0.2257</strong></td>
<td>0.0507</td>
<td>2.49</td>
<td></td>
</tr>
<tr>
<td><strong>Forearm Pressure Pain Threshold</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0146</td>
<td>-0.0167, 0.0460</td>
<td>0.0160</td>
<td>0.92</td>
<td>10.2%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.1288</td>
<td><strong>0.0246, 0.2330</strong></td>
<td>0.0532</td>
<td>2.42</td>
<td></td>
</tr>
<tr>
<td><strong>Knee Pressure Pain Threshold</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0139</td>
<td>-0.0328, 0.0606</td>
<td>0.0238</td>
<td>0.58</td>
<td>9.7%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.1295</td>
<td><strong>0.0187, 0.2403</strong></td>
<td>0.0565</td>
<td>2.29</td>
<td></td>
</tr>
</tbody>
</table>

HAQ-DI = Health Assessment Questionnaire Disability Index; CI = confidence interval; * p<0.05 if bold. SE = standard error; Z = Z-score.

### Table VII-20  Mediation analysis for HAQ-DI and pain intensity at the tested knee

<table>
<thead>
<tr>
<th></th>
<th>β-coefficient</th>
<th>95% CI *</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Effect</strong></td>
<td>0.1389</td>
<td><strong>0.0471, 0.2306</strong></td>
<td>0.0468</td>
<td>2.97</td>
<td>----</td>
</tr>
<tr>
<td><strong>Knee Allodynia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0289</td>
<td>-0.0078, 0.0657</td>
<td>0.0188</td>
<td>1.54</td>
<td>20.8%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.1099</td>
<td><strong>0.0210, 0.1989</strong></td>
<td>0.0454</td>
<td>2.42</td>
<td></td>
</tr>
<tr>
<td><strong>Forearm Allodynia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0130</td>
<td>-0.0114, 0.0374</td>
<td>0.0125</td>
<td>1.04</td>
<td>9.4%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.1259</td>
<td><strong>0.0348, 0.2169</strong></td>
<td>0.0465</td>
<td>2.71</td>
<td></td>
</tr>
<tr>
<td><strong>Tender Point Count</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>-0.0044</td>
<td>-0.0636, 0.0548</td>
<td>0.0302</td>
<td>-0.14</td>
<td>3.2%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.1432</td>
<td><strong>0.0341, 0.2524</strong></td>
<td>0.0557</td>
<td>2.57</td>
<td></td>
</tr>
<tr>
<td><strong>Knee Pressure Pain Threshold</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>-0.0038</td>
<td>-0.0458, 0.0382</td>
<td>0.0214</td>
<td>-0.18</td>
<td>2.8%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.1427</td>
<td><strong>0.0419, 0.2435</strong></td>
<td>0.0514</td>
<td>2.77</td>
<td></td>
</tr>
<tr>
<td><strong>Forearm Pressure Pain Threshold</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0019</td>
<td>-0.0243, 0.0281</td>
<td>0.0134</td>
<td>0.14</td>
<td>1.4%</td>
</tr>
<tr>
<td>Direct Effect</td>
<td>0.1370</td>
<td><strong>0.0416, 0.2323</strong></td>
<td>0.0487</td>
<td>2.82</td>
<td></td>
</tr>
</tbody>
</table>

HAQ-DI = Health Assessment Questionnaire Disability Index; CI = confidence interval; * p<0.05 if bold. SE = standard error; Z = Z-score.
Table VII-21  Mediation analysis for psychosocial factors and global pain intensity including a latent sensitisation mediating variable

<table>
<thead>
<tr>
<th>Exogenous: IPQ-Brief Identity</th>
<th>Coefficient</th>
<th>95% CI</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Effect</td>
<td>0.3371</td>
<td>0.0939, 0.5803</td>
<td>0.1241</td>
<td>2.72</td>
<td>----</td>
</tr>
<tr>
<td>Indirect Effect (path a x b)</td>
<td>0.2776</td>
<td>0.0115, 0.5437</td>
<td>0.1358</td>
<td>2.04</td>
<td>82.4%</td>
</tr>
<tr>
<td>Direct Effect (path c)</td>
<td>0.0595</td>
<td>-0.2663, 0.3853</td>
<td>0.1662</td>
<td>0.36</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exogenous: PCS Magnification</th>
<th>Coefficient</th>
<th>95% CI</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Effect</td>
<td>0.3963</td>
<td>0.0880, 0.7047</td>
<td>0.1573</td>
<td>2.52</td>
<td>----</td>
</tr>
<tr>
<td>Indirect Effect (path a x b)</td>
<td>0.1243</td>
<td>-0.0152, 0.2639</td>
<td>0.0712</td>
<td>1.75</td>
<td>31.4%</td>
</tr>
<tr>
<td>Direct Effect (path c)</td>
<td>0.2720</td>
<td>-0.0346, 0.5786</td>
<td>0.1564</td>
<td>1.74</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exogenous: IPQ-Brief Timeline</th>
<th>Coefficient</th>
<th>95% CI</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Effect</td>
<td>0.2859</td>
<td>0.0935, 0.4783</td>
<td>0.0982</td>
<td>2.91</td>
<td>----</td>
</tr>
<tr>
<td>Indirect Effect (path a x b)</td>
<td>0.0897</td>
<td>-0.0078, 0.1742</td>
<td>0.0464</td>
<td>1.79</td>
<td>29.1%</td>
</tr>
<tr>
<td>Direct Effect (path c)</td>
<td>0.2027</td>
<td>0.0082, 0.3971</td>
<td>0.0992</td>
<td>2.04</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exogenous: HAQ-DI</th>
<th>Coefficient</th>
<th>95% CI</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Effect</td>
<td>0.1434</td>
<td>0.0424, 0.2445</td>
<td>0.0516</td>
<td>2.78</td>
<td>----</td>
</tr>
<tr>
<td>Indirect Effect (path a x b)</td>
<td>0.0346</td>
<td>-0.0308, 0.1000</td>
<td>0.0334</td>
<td>1.04</td>
<td>24.1%</td>
</tr>
<tr>
<td>Direct Effect (path c)</td>
<td>0.1088</td>
<td>-0.0095, 0.2271</td>
<td>0.0603</td>
<td>1.80</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exogenous: IPQ-Brief Emotion</th>
<th>Coefficient</th>
<th>95% CI</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Effect</td>
<td>0.3173</td>
<td>0.0819, 0.5528</td>
<td>0.1201</td>
<td>2.64</td>
<td>----</td>
</tr>
<tr>
<td>Indirect Effect (path a x b)</td>
<td>0.0645</td>
<td>-0.0361, 0.1650</td>
<td>0.0513</td>
<td>1.26</td>
<td>20.3%</td>
</tr>
<tr>
<td>Direct Effect (path c)</td>
<td>0.2529</td>
<td>0.0262, 0.4795</td>
<td>0.1156</td>
<td>2.19</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exogenous: PCS Helplessness</th>
<th>Coefficient</th>
<th>95% CI</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Effect</td>
<td>0.4295</td>
<td>0.2563, 0.6027</td>
<td>0.0884</td>
<td>4.86</td>
<td>----</td>
</tr>
<tr>
<td>Indirect Effect (path a x b)</td>
<td>0.0676</td>
<td>-0.0131, 0.1483</td>
<td>0.0412</td>
<td>1.64</td>
<td>15.9%</td>
</tr>
<tr>
<td>Direct Effect (path c)</td>
<td>0.3620</td>
<td>0.1818, 0.5421</td>
<td>0.0919</td>
<td>3.94</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exogenous: IPQ-Brief Concern</th>
<th>Coefficient</th>
<th>95% CI</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Effect</td>
<td>0.4993</td>
<td>0.3243, 0.6743</td>
<td>0.0893</td>
<td>5.59</td>
<td>----</td>
</tr>
<tr>
<td>Indirect Effect (path a x b)</td>
<td>0.0699</td>
<td>-0.0157, 0.1551</td>
<td>0.0436</td>
<td>1.60</td>
<td>14.0%</td>
</tr>
<tr>
<td>Direct Effect (path c)</td>
<td>0.4294</td>
<td>0.2456, 0.6135</td>
<td>0.0939</td>
<td>4.58</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exogenous: PCS Rumination</th>
<th>Coefficient</th>
<th>95% CI</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Effect</td>
<td>0.3517</td>
<td>0.1691, 0.5342</td>
<td>0.0931</td>
<td>3.78</td>
<td>----</td>
</tr>
<tr>
<td>Indirect Effect (path a x b)</td>
<td>0.0473</td>
<td>-0.0362, 0.1308</td>
<td>0.0426</td>
<td>1.11</td>
<td>13.5%</td>
</tr>
<tr>
<td>Direct Effect (path c)</td>
<td>0.3044</td>
<td>0.1238, 0.4849</td>
<td>0.0921</td>
<td>3.30</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exogenous: IPQ-Brief Consequences</th>
<th>Coefficient</th>
<th>95% CI</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Effect</td>
<td>0.6222</td>
<td>0.4080, 0.8363</td>
<td>0.1093</td>
<td>5.69</td>
<td>----</td>
</tr>
<tr>
<td>Indirect Effect (path a x b)</td>
<td>0.0757</td>
<td>-0.0157, 0.1671</td>
<td>0.0466</td>
<td>1.62</td>
<td>12.2%</td>
</tr>
<tr>
<td>Direct Effect (path c)</td>
<td>0.5465</td>
<td>0.3285, 0.7644</td>
<td>0.1112</td>
<td>4.91</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; * p<0.05 if bold. SE = standard error; Z = Z-score; MPS = mechanical pain sensitivity.
Table VII-22  Mediation analysis for psychosocial factors and pain intensity at the tested knee including a latent sensitisation mediating variable

<table>
<thead>
<tr>
<th>Exogenous: IPQ-Brief Identity</th>
<th>Coefficient</th>
<th>95% CI</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Effect</td>
<td>0.3100</td>
<td>0.0878, 0.5323</td>
<td>0.1134</td>
<td>2.73</td>
<td>----</td>
</tr>
<tr>
<td>Indirect Effect (path a x b)</td>
<td>0.2012</td>
<td>-0.0481, 0.4504</td>
<td>0.1272</td>
<td>1.58</td>
<td>64.9%</td>
</tr>
<tr>
<td>Direct Effect (path c)</td>
<td>0.1089</td>
<td>-0.2066, 0.4243</td>
<td>0.1610</td>
<td>0.68</td>
<td></td>
</tr>
</tbody>
</table>

Exogenous: IPQ-Brief Timeline

<table>
<thead>
<tr>
<th>Exogenous: PCS Helplessness</th>
<th>Coefficient</th>
<th>95% CI</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Effect</td>
<td>0.2816</td>
<td>0.1075, 0.4556</td>
<td>0.0888</td>
<td>3.17</td>
<td>----</td>
</tr>
<tr>
<td>Indirect Effect (path a x b)</td>
<td>0.0897</td>
<td>0.0001, 0.1793</td>
<td>0.0457</td>
<td>1.96</td>
<td>46.8%</td>
</tr>
<tr>
<td>Direct Effect (path c)</td>
<td>0.1918</td>
<td>0.0198, 0.3639</td>
<td>0.0878</td>
<td>2.19</td>
<td></td>
</tr>
</tbody>
</table>

Exogenous: IPQ-Brief Emotion

<table>
<thead>
<tr>
<th>Exogenous: IPQ-Brief Concern</th>
<th>Coefficient</th>
<th>95% CI</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Effect</td>
<td>0.2589</td>
<td>0.0411, 0.4767</td>
<td>0.1111</td>
<td>2.33</td>
<td>----</td>
</tr>
<tr>
<td>Indirect Effect (path a x b)</td>
<td>0.0769</td>
<td>-0.0328, 0.1866</td>
<td>0.0560</td>
<td>1.37</td>
<td>29.7%</td>
</tr>
<tr>
<td>Direct Effect (path c)</td>
<td>0.1820</td>
<td>-0.0226, 0.3866</td>
<td>0.1044</td>
<td>1.74</td>
<td></td>
</tr>
</tbody>
</table>

Exogenous: HAQ-DI

<table>
<thead>
<tr>
<th>Exogenous: IPQ-Brief Concern</th>
<th>Coefficient</th>
<th>95% CI</th>
<th>SE</th>
<th>Z</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Effect</td>
<td>0.1389</td>
<td>0.0471, 0.2306</td>
<td>0.0468</td>
<td>2.97</td>
<td>----</td>
</tr>
<tr>
<td>Indirect Effect (path a x b)</td>
<td>0.0019</td>
<td>-0.0113, 0.0151</td>
<td>0.0067</td>
<td>0.28</td>
<td>1.4%</td>
</tr>
<tr>
<td>Direct Effect (path c)</td>
<td>0.1370</td>
<td>0.0443, 0.2296</td>
<td>0.0473</td>
<td>2.90</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; * p<0.05 if bold, 0.05≤p<0.1 if in italics. SE = standard error; Z = Z-score; MPS = mechanical pain sensitivity.
Table VIII-1  Linear regression of change in pain against baseline QST measures and baseline pain

<table>
<thead>
<tr>
<th></th>
<th>β-coefficient</th>
<th>95% CI *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tender point count</td>
<td>-0.8991</td>
<td>-4.595, 2.797</td>
</tr>
<tr>
<td>Injected knee</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDT</td>
<td>0.0822</td>
<td>-0.010, 0.174</td>
</tr>
<tr>
<td>MPT</td>
<td>-0.0790</td>
<td>-0.152, 0.006</td>
</tr>
<tr>
<td>MPS</td>
<td>0.6041</td>
<td>-0.232, 1.441</td>
</tr>
<tr>
<td>Allodynia</td>
<td>-3.6245</td>
<td>-9.554, 2.305</td>
</tr>
<tr>
<td>Wind-up</td>
<td>1.8562</td>
<td>-2.769, 6.482</td>
</tr>
<tr>
<td>Vibration detection</td>
<td>0.1445</td>
<td>-3.934, 4.223</td>
</tr>
<tr>
<td>Pressure pain</td>
<td>1.5468</td>
<td>-2.521, 5.614</td>
</tr>
<tr>
<td>Contralateral knee</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDT</td>
<td>0.0496</td>
<td>-0.147, 0.246</td>
</tr>
<tr>
<td>MPT</td>
<td>-0.1037</td>
<td>-0.213, 0.005</td>
</tr>
<tr>
<td>MPS</td>
<td>0.9352</td>
<td>-0.182, 2.052</td>
</tr>
<tr>
<td>Allodynia</td>
<td>1.8791</td>
<td>-0.709, 4.467</td>
</tr>
<tr>
<td>Wind-up</td>
<td>2.0821</td>
<td>-1.4558, 5.620</td>
</tr>
<tr>
<td>Vibration detection</td>
<td>-0.4738</td>
<td>-4.203, 3.256</td>
</tr>
<tr>
<td>Pressure pain</td>
<td>3.3326</td>
<td>-0.008, 6.673</td>
</tr>
</tbody>
</table>

CI = confidence interval; * p<0.05 if bold and 0.05≤p<0.1 if in italics; MDT = mechanical detection threshold; MPT = mechanical pain threshold; MPS = mechanical pain sensitivity.
APPENDIX IX. Psychosocial predictors of change in QST

Table IX-1 Screening measures of anxiety and depression as predictors of change in QST

<table>
<thead>
<tr>
<th>Change Score</th>
<th>Anxiety</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β (95% CI) *</td>
<td>β (95% CI) *</td>
</tr>
<tr>
<td>Tender point</td>
<td>-0.0788 (-0.340, 0.183)</td>
<td>0.0030 (-0.274, 0.279)</td>
</tr>
<tr>
<td>Injected Knee</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDT</td>
<td>0.1785 (-6.718, 7.075)</td>
<td>0.4879 (-7.698, 6.721)</td>
</tr>
<tr>
<td>MPT</td>
<td>-4.5885 (-11.061, 1.884)</td>
<td>-2.9397 (-9.904, 4.024)</td>
</tr>
<tr>
<td>MPS</td>
<td>0.2610 (-0.478, 1.000)</td>
<td>0.0765 (-0.704, 0.857)</td>
</tr>
<tr>
<td>Allodynia</td>
<td>-0.0160 (-0.273, 0.241)</td>
<td>0.1814 (-0.065, 0.428)</td>
</tr>
<tr>
<td>Wind-up ratio</td>
<td>-0.0172 (-0.183, 0.148)</td>
<td>0.0531 (-0.129, 0.235)</td>
</tr>
<tr>
<td>Vibration detection</td>
<td>-0.0480 (-0.233, 0.137)</td>
<td>-0.1007 (-0.291, 0.089)</td>
</tr>
<tr>
<td>Pressure pain</td>
<td>-0.0679 (-0.224, 0.109)</td>
<td>0.0144 (-0.162, 0.190)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contralateral Knee</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDT</td>
<td>2.5699 (-1.637, 6.777)</td>
<td>0.9756 (-3.520, 5.471)</td>
</tr>
<tr>
<td>MPT</td>
<td>-3.6545 (-10.207, 2.898)</td>
<td>-3.7182 (-10.505, 3.069)</td>
</tr>
<tr>
<td>MPS</td>
<td>0.3833 (-0.049, 0.815)</td>
<td>0.2867 (-0.177, 0.751)</td>
</tr>
<tr>
<td>Allodynia</td>
<td>0.1815 <strong>0.026, 0.338</strong></td>
<td>0.1721 <strong>0.007, 0.337</strong></td>
</tr>
<tr>
<td>Wind-up ratio</td>
<td>0.0976 (-0.131, 0.326)</td>
<td>0.0360 (-0.219, 0.291)</td>
</tr>
<tr>
<td>Vibration detection</td>
<td>-0.0043 (-0.200, 0.191)</td>
<td>0.0434 (-0.158, 0.245)</td>
</tr>
<tr>
<td>Pressure pain</td>
<td>0.0070 (-0.109, 0.123)</td>
<td>0.0135 (-0.106, 0.133)</td>
</tr>
</tbody>
</table>

CI = confidence interval; * p<0.05 if bold.
CI = confidence interval; *p<0.05 if bold. MDT = mechanical detection threshold; MPT = mechanical pain threshold; MPS = mechanical pain sensitivity.

<table>
<thead>
<tr>
<th>CI</th>
<th>β (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0948</td>
<td>1.7299</td>
</tr>
<tr>
<td>0.2851</td>
<td>1.2401</td>
</tr>
<tr>
<td>0.0979</td>
<td>1.8469</td>
</tr>
<tr>
<td>0.0076</td>
<td>0.7201</td>
</tr>
<tr>
<td>0.2277</td>
<td>0.3994</td>
</tr>
<tr>
<td>0.0630</td>
<td>1.9969</td>
</tr>
<tr>
<td>0.2373</td>
<td>0.1172</td>
</tr>
<tr>
<td>0.1380</td>
<td>0.3898</td>
</tr>
<tr>
<td>0.2590</td>
<td>0.1223</td>
</tr>
<tr>
<td>0.2865</td>
<td>0.1223</td>
</tr>
<tr>
<td>0.3290</td>
<td>0.3560</td>
</tr>
<tr>
<td>0.0314</td>
<td>0.0585</td>
</tr>
<tr>
<td>0.0314</td>
<td>0.0585</td>
</tr>
<tr>
<td>0.0314</td>
<td>0.0585</td>
</tr>
</tbody>
</table>

Table IX-2: Screening items for the PGP-B score predictors of change in tender point count and change in QST at the injected knee.
Table IX-3

Screening items of the IPQ-Brief as predictors of change in QST at the contralateral knee

<table>
<thead>
<tr>
<th>Consequences</th>
<th>Timeline</th>
<th>Personal</th>
<th>Treatment</th>
<th>Coherence</th>
<th>Emotion</th>
</tr>
</thead>
<tbody>
<tr>
<td>β (95% CI)</td>
<td>β (95% CI)</td>
<td>β (95% CI)</td>
<td>β (95% CI)</td>
<td>β (95% CI)</td>
<td>β (95% CI)</td>
</tr>
<tr>
<td>Pressure</td>
<td>Allodynia</td>
<td>Vibration</td>
<td>Wind-up Ratio</td>
<td>MDT</td>
<td>MPS</td>
</tr>
<tr>
<td>(0.114, 0.115)</td>
<td>(0.186, 0.197)</td>
<td>(0.214, 0.215)</td>
<td>(0.121, 0.214)</td>
<td>(0.392, 0.395)</td>
<td>(0.310, 0.311)</td>
</tr>
<tr>
<td>(0.219, 0.220)</td>
<td>(0.344, 0.345)</td>
<td>(0.221, 0.222)</td>
<td>(0.251, 0.252)</td>
<td>(0.504, 0.505)</td>
<td>(0.487, 0.488)</td>
</tr>
<tr>
<td>(0.330, 0.331)</td>
<td>(0.510, 0.511)</td>
<td>(0.302, 0.303)</td>
<td>(0.305, 0.306)</td>
<td>(0.673, 0.674)</td>
<td>(0.656, 0.657)</td>
</tr>
</tbody>
</table>

CI = confidence interval; *p < 0.05 if bold. MDT = mechanical detection threshold; MPT = mechanical pain threshold; MPS = mechanical pain sensitivity.