Psychosocial factors partially mediate the relationship between mechanical hyperalgesia and self-reported pain

DOI:

[10.1515/sjpain-2017-0109](https://doi.org/10.1515/sjpain-2017-0109)

Document Version

Accepted author manuscript

[Link to publication record in Manchester Research Explorer](#)

Citation for published version (APA):

Mason, K., O'Neill, T., Lunt, M., Jones, A., & Mcbeth, J. (2018). Psychosocial factors partially mediate the relationship between mechanical hyperalgesia and self-reported pain. *Scandinavian Journal of Pain*, 18(1), 59-69. <https://doi.org/10.1515/sjpain-2017-0109>

Published in:

Scandinavian Journal of Pain

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Scandinavian Journal of Pain

Psychosocial factors partially mediate the relationship between mechanical hyperalgesia and self-reported pain

--Manuscript Draft--

Manuscript Number:	SJPAIN-D-17-00109R2
Article Type:	Observational studies
Keywords:	knee pain; quantitative sensory testing; sensitisation; psychosocial factors; altered central processing
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Order of Authors:	Kayleigh J Mason, PhD Terence W O'Neill Mark Lunt Anthony K Jones John McBeth
Abstract:	<p>Background and aim: Amplification of sensory signalling within the nervous system along with psychosocial factors contributes to the variation and severity of knee pain. Quantitative Sensory Testing (QST) is a non-invasive test battery that assesses sensory perception of thermal, pressure, mechanical and vibration stimuli used in the assessment of pain. Psychosocial factors also have an important role in explaining the occurrence of pain. The aim was to determine whether QST measures were associated with self-reported pain, and whether those associations were mediated by psychosocial factors.</p> <p>Methods: Participants with knee pain identified from a population-based cohort completed a tender point count and a reduced QST battery of thermal, mechanical and pressure pain thresholds, temporal summation, mechanical pain sensitivity, dynamic mechanical allodynia and vibration detection threshold performed following the protocol by the German Research Network on Neuropathic Pain. QST assessments were performed at the most painful knee and opposite forearm (if pain-free). Participants were asked to score for their global and knee pain intensities within the past month (range 0 to 10), and complete questionnaire items investigating anxiety, depression, illness perceptions, pain catastrophizing, and physical functioning. QST measures (independent variable) significantly correlated (Spearman's rho) with self-reported pain intensity (dependent variable) were included in structural equation models with psychosocial factors (latent mediators).</p> <p>Results: 72 participants were recruited with 61 participants (36 women; median age 64 years) with complete data included in subsequent analyses. Tender point count was significantly correlated with global pain intensity. Dynamic mechanical allodynia at the knee and mechanical pain sensitivity at the most painful knee and opposite pain-free forearm were significantly correlated with both global pain and knee pain intensities. Psychosocial factors including pain catastrophising sub-scales (rumination and helplessness) and illness perceptions (consequences and concern) were significant partial mediators of the association with global pain intensity when loaded on to a latent mediator for: tender point count (75% total effect; 95% confidence interval 22%, 100%); mechanical pain sensitivity at the knee (49%; 12%, 86%); and dynamic mechanical allodynia at the knee (63%; 5%, 100%). Latent psychosocial factors were also significant partial mediators of the association between pain intensity at the tested knee with mechanical pain sensitivity at the knee (30%; 2%, 58%), but not for dynamic mechanical allodynia at the knee.</p> <p>Conclusions: Measures of mechanical hyperalgesia at the most painful knee and pain-free opposite forearm were associated with increased knee and global pain indicative of altered central processing. Psychosocial factors were significant partial mediators, highlighting the importance of the central integration of emotional processing in pain</p>

perception.

Implications: Associations between mechanical hyperalgesia at the forearm and knee, psychosocial factors, and increased levels of clinical global and knee pain intensity provide evidence of altered central processing as a key mechanism in knee pain, with psychological factors playing a key role in the expression of clinical pain.

Ms. Ref. No.: SJPAIN-D-17-00109

Title: Psychosocial factors partially mediate the relationship between mechanical hyperalgesia and self-reported pain Scandinavian Journal of Pain

Dear Dr. Kayleigh J Mason,

I have received the reviewers' comments (included below) on the manuscript "Psychosocial factors partially mediate the relationship between mechanical hyperalgesia and self-reported pain" and as you will see some modifications have been requested. One expert reviewer has a few further comments. I hope you can respond to these comments as soon as possible.

Due to our ongoing transition to a new Publisher, the editorial handling has taken a bit more time than normal. I hope you can accept this inconvenience.

I invite you to submit a new version taking into account all the issues raised. Please include an outline of each change made, with a point-by-point response to the referees and the reason for any rebuttal.

The deadline for re-submission is Dec 02, 2017.

We look forward to receiving your revised manuscript.

Yours sincerely,

Harald Breivik, MD, DMedSci
Editor in Chief
Scandinavian Journal of Pain

Reviewers' comments: SJPAIN-D-17-00109

Reviewer #1: The authors have to a large degree adequately revised the manuscript. However, there are still open critical issues.

Re comment 1: The authors should clarify that classical radiological assessments (x-ray) is either not associated or very limited associated with pain in OA. Contrasting to this, MRI findings such as BMLs, synovitis or subchondral bone edemas seem to be associated with pain reports from patients (e.g. Barr et al.).

Response: We thank the reviewer for identifying this and have amended the third sentence of paragraph 1 to:

“Only moderate correlations exist between knee pain and the structural pathology of osteoarthritis (OA) **such as bone marrow lesions, synovitis and subchondral bone oedema**, suggesting that altered central processing may be responsible for certain components of chronic pain [3,4].”

Re comment 3: The authors could be more specific and use terms such as "hyperalgesia", "allodynia" or "facilitated temporal summation" instead of "central sensitization".

Response: We have amended sentence 4, paragraph 1 of the Introduction to include the following.

“In those with chronic pain, ~~central sensitisation due to~~ altered central processing through amplifications of somatosensory inputs **either via hyperalgesia (hypersensitivity to painful stimuli near a painful site) or allodynia (hypersensitivity to non-painful stimuli near a painful site)**, and the integration of emotional processing can contribute to the experience of pain in the absence of peripheral damage [5,6].”

Re comment 12: A reliability analysis regarding QST on 8-9 subjects is not very useful. A specific study on reliability should be conducted otherwise it is better removing this analysis from the manuscript.

Response: We have removed the section “2.7. Intra-rater reliability” from the methods.

Re comment 14: conducting 90 correlations without adjusting for multiple correlations is not advised and adjustment are needed. Alternatively, the authors should aim for a limited correlation analysis only including few parameters.

Response: We have included an asterisk next to each significant correlation in Table 3 and Table 4 where adjustment for the Bonferroni correction was satisfied. However, we have specified in section 2.8. “significant correlations (**p<0.05**)” were used to identify variables for our mediation analyses.

Table 3 caption: * **p<0.0029 (0.05/17; Bonferroni Correction).**

Table 4 caption: * **p<0.0036 (0.05/14; Bonferroni Correction).**

Re comment 18: It should be clarified in the manuscript that subjects who did not reach the CPT were classified as OC, since this can have major implications for comparisons between studies.

Response: We have added the following sentence to the end of section 2.6, paragraph 1.

“Participants who did not achieve a painful sensation during cold or heat pain thresholds were categorised as 0°C and 50°C, respectively.”

Reviewer #2: It appears to me that the Authors have responded well to the comments and questions of the reviewers. I have no further comments.

Highlights

In people with higher levels of self-reported knee pain, we identified:

- Widespread mechanical hyperalgesia was correlated with greater pain intensity
- Catastrophising and illness perceptions were correlated with greater pain intensity
- Psychosocial factors mediate the relationship between pain and hyperalgesia
- Altered central processing is likely to be a key mechanism in knee pain

Title: Psychosocial factors partially mediate the relationship between mechanical hyperalgesia and self-reported pain

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Abstract

Background and aim: Amplification of sensory signalling within the nervous system along with psychosocial factors contributes to the variation and severity of knee pain. Quantitative Sensory Testing (QST) is a non-invasive test battery that assesses sensory perception of thermal, pressure, mechanical and vibration stimuli used in the assessment of pain. Psychosocial factors also have an important role in explaining the occurrence of pain. The aim was to determine whether QST measures were associated with self-reported pain, and whether those associations were mediated by psychosocial factors.

Methods: Participants with knee pain identified from a population-based cohort completed a tender point count and a reduced QST battery of thermal, mechanical and pressure pain thresholds, temporal summation, mechanical pain sensitivity, dynamic mechanical allodynia and vibration detection threshold performed following the protocol by the German Research Network on Neuropathic Pain. QST assessments were performed at the most painful knee and opposite forearm (if pain-free). Participants were asked to score for their global and knee pain intensities within the past month (range 0 to 10), and complete questionnaire items investigating anxiety, depression, illness perceptions, pain catastrophizing, and physical functioning. QST measures (independent variable) significantly correlated (Spearman's rho) with self-reported pain intensity (dependent variable) were included in structural equation models with psychosocial factors (latent mediators).

Results: 72 participants were recruited with 61 participants (36 women; median age 64 years) with complete data included in subsequent analyses. Tender point count was significantly correlated with global pain intensity. Dynamic mechanical allodynia at the knee and mechanical pain sensitivity at the most painful knee and opposite pain-free forearm were significantly correlated with both global pain and knee pain intensities. Psychosocial factors including pain catastrophising sub-scales (rumination and helplessness) and illness perceptions (consequences and concern) were significant partial mediators of the association with global pain intensity when loaded on to a latent mediator for: tender point count (75% total effect; 95% confidence interval 22%, 100%); mechanical pain sensitivity at the knee (49%; 12%, 86%); and dynamic mechanical allodynia at the knee (63%; 5%, 100%). Latent psychosocial factors were also significant partial mediators of the association between pain intensity at the tested knee with mechanical pain sensitivity at the knee (30%; 2%, 58%), but not for dynamic mechanical allodynia at the knee.

Conclusions: Measures of mechanical hyperalgesia at the most painful knee and pain-free opposite forearm were associated with increased knee and global pain indicative of altered central processing.

Psychosocial factors were significant partial mediators, highlighting the importance of the central integration of emotional processing in pain perception.

Implications: Associations between mechanical hyperalgesia at the forearm and knee, psychosocial factors, and increased levels of clinical global and knee pain intensity provide evidence of altered central processing as a key mechanism in knee pain, with psychological factors playing a key role in the expression of clinical pain.

Highlights

In people with higher levels of self-reported knee pain, we identified:

- Widespread mechanical hyperalgesia was correlated with greater pain intensity
- Catastrophising and illness perceptions were correlated with greater pain intensity
- Psychosocial factors mediate the relationship between pain and hyperalgesia
- Altered central processing is likely to be a key mechanism in knee pain

Key words

knee pain; quantitative sensory testing; sensitisation; psychosocial factors; altered central processing

Abbreviations

BMI	Body Mass Index
CI	Confidence Interval
DMA	Dynamic Mechanical Allodynia
EPIFUND	Epidemiology of Functional Disorders
HAD	Hospital Anxiety and Depression scale
ICC	Intraclass Correlation Coefficient
IPQ-brief	Brief Illness Perception Questionnaire
IQR	Interquartile Range
MPS	Mechanical Pain Sensitivity
OA	Osteoarthritis
PCS	Pain Catastrophising Scale
QST	Quantitative Sensory Testing
RAPA	Rapid Assessment of Physical Activity
SMD	Standardised Mean Difference

1. Introduction

Knee pain is a common complaint in the ageing population with an annual prevalence of 25% in those over 55 ^[1]. Knee pain may arise through local pathology stimulating the release of inflammatory mediators triggering nociceptive transmission ^[2]. Only moderate correlations exist between knee pain and the structural pathology of osteoarthritis (OA) such as bone marrow lesions, synovitis and subchondral bone oedema, suggesting that altered central processing may be responsible for certain components of chronic pain ^[3,4]. In those with chronic pain, ~~central sensitisation due to~~ altered central processing through amplifications of somatosensory inputs either via hyperalgesia (hypersensitivity to painful stimuli near a painful site) or allodynia (hypersensitivity to non-painful stimuli near a painful site), and the integration of emotional processing can contribute to the experience of pain in the absence of peripheral damage ^[5,6]; altered central processing is an important mechanism for understanding the discordance between pathological features of OA and knee pain intensity. Higher reported pain knee intensity is associated with increased sensitivity to temporal summation (repeated noxious stimulation lowering the threshold for nociceptive transmission) in patients with knee OA indicating altered central processing ^[7,8].

Quantitative sensory testing (QST) is a non-invasive technique used to assess somatosensory functioning ^[9]. There is preliminary evidence to suggest knee OA patients have diminished vibration detection ^[10] and thermal pain thresholds ^[11,12] compared with healthy volunteers; however, previous studies have not investigated whether these measures are associated with higher levels of self-reported knee pain intensity. Two recent systematic reviews investigated somatosensory functioning in OA samples. Lluch et al. ^[13] reported that despite diverse methodologies, increased levels of local hyperalgesia (at the knee, indicating peripheral sensitisation) and widespread hyperalgesia (indicating central sensitisation) were observed for knee OA participants compared with pain-free controls. A meta-analysis by Fingleton et al. ^[14] demonstrated pressure pain thresholds were significantly lower in patients with knee OA compared with pain-free controls (standardised mean difference [SMD] -0.85; 95% confidence interval [CI] -1.1, -0.6), and for knee OA groups with high symptom severity compared with those with low symptom severity (SMD -0.51; 95% CI -0.73, -0.30). The authors also identified temporal summation as present in knee OA patients compared with healthy controls, and for knee OA groups with high symptom severity compared with low symptom severity ^[14]. These findings suggest altered central processing is present within a sub-sample of individuals with knee OA and chronic pain.

Recent studies investigating QST in knee OA samples have included measures of psychosocial distress. Cruz-Almeida et al. ^[15] determined four distinct profiles from psychological and somatosensory measures for

194 individuals with knee OA using hierarchical cluster analysis with the two most severe clusters reporting the highest levels of pain, anger, depression and mechanical hyperalgesia ^[15]. Findings from Williams *et al.* ^[12] and Finan *et al.* ^[8] demonstrated higher levels of anxiety and depression in participants with lower grade radiographic disease and moderate to severe knee pain, which were associated with higher levels of disability and widespread hyperalgesia. These results indicate psychosocial factors are associated with altered central processing with low grades of underlying pathology. However, the role of illness perceptions, which have been demonstrated as possible targets for intervention in people with lower back pain ^[16], have not been addressed in people with knee pain.

The impact of psychosocial factors on the association between self-reported pain intensity and somatosensory functioning has yet to be investigated in a population-based sample of individuals with knee pain. The aim of the present study was to determine whether (i) higher levels of self-reported pain intensity were associated with greater sensitivity to QST measures; (ii) any association between QST measures and pain intensity was mediated by psychosocial factors.

2. Methods

2.1. Participants

565 participants with knee pain were identified from a prospective population-based cohort investigating chronic pain (the epidemiology of functional disorders [EPIFUND] cohort) ^[17]. Participants were eligible for this study if they responded to a postal survey, had knee pain, and consented to further contact. It was not possible to robustly identify whether participants in the EPIFUND cohort identified as having knee pain also had underlying OA.

2.2. Recruitment

A two-phase telephone recruitment strategy was used: eligible participants were first contacted to verify the presence of knee pain on at least one day in the past month and to consent to the mailing of the participant information sheet about the QST study for their consideration. The second phone call occurred at least 7 days following the first-call to ensure adequate time for delivery and consideration of the information sheet. A more detailed description of the study was provided during the second phone call and if they were interested, participants were invited to attend a 90 minute appointment at a local primary care or research centre. A letter containing details of the study appointment, including the time, date and location, was mailed to each

participant who agreed to take part. The present study received approval from the National Research Ethics Service Committee North West – Cheshire (12/NW/0556) in order to contact the cohort and complete the study assessments. All participants provided consent at the study visit prior to any assessments.

2.3. *Study Assessments*

All assessments during the study visit were performed by one rater (KJM).

2.4. *Self-reported pain intensity and body mass index (BMI)*

All participants were asked whether they had experienced pain that lasted one day or longer in the past 30 days and to indicate that pain on a blank-body manikin. Participants with knee pain were those who shaded one or both knee regions. Global and knee pain intensities were assessed using 0 to 10 (best to worst) numeric rating scales for the average pain severity experienced within the past 30 days. BMI was calculated from measured weight (kilograms) and height (metres²).

2.5. *Psychosocial Factors*

Participants were provided with a questionnaire, including items addressing anxiety, depression, illness perceptions, pain catastrophising and physical functioning, with a stamped and addressed envelope to mail back to the study team after the assessments were complete. The Hospital Anxiety and Depression (HAD) scale ^[18] comprises 7 anxiety and 7 depression items (items scored 0, no symptoms to 3, strong indication of symptoms; anxiety and depression scales score range 0-21; 0 to 7 classified as normal; 8 to 10 as borderline cases; and ≥ 11 as cases). The Pain Catastrophizing Scale (PCS) and Brief Illness Perception Questionnaire (IPQ-brief) measured cognitions about pain ^[19]. The PCS comprises 13 items scored 0 (not at all) to 4 (all of the time) forming three sub-scales: helplessness (6 items, range 0-24), rumination (4 items, range 0-16) and magnification (3 items, range 0-12). The IPQ-brief comprises 8 items scored using a 10-point numeric rating scale ^[20]; five items (consequences, timeline, personal control, treatment control and identity) address thoughts about the illness, two items (concern and emotion) address the emotional impact and the final item (coherence) relates to the understanding of the illness (pain in the present study). Physical functioning was addressed using the Rapid Assessment of Physical Activity (RAPA) scale. The RAPA includes 9 items (range 0-10) scored “yes” or “no” with 7 items for levels of physical activity (0 classified as

sedentary; 1 to 2 as underactive, 3 to 4 regular underactive, and ≥ 5 as regular active (>5), one item for strength (scored 0 or 1) and one item for flexibility (scored 0 or 2) ^[21].

2.6. Quantitative Sensory Testing

The QST assessments were performed following the protocol by the German Research Network on Neuropathic Pain ^[22]. A reduced QST protocol was used; there is limited evidence for the presence of abnormal mechanical or thermal detection thresholds, or paradoxical heat sensations, in knee OA patients. All other assessments were included as these are considered to be altered in those with knee pain (pressure pain; temporal summation) or the literature is conflicting (thermal and mechanical pain, and vibration detection thresholds). QST assessments, except for vibration detection, were performed at the tibial tuberosity of the most painful knee and two centimetres distal to the lateral epicondyle on the opposite forearm (if pain-free): vibration detection was performed on the nearest bony prominences to the test sites in accordance with the QST protocol (at the patella of the most painful knee and the opposite elbow).

Participants who did not achieve a painful sensation during cold or heat pain thresholds were categorised as 0°C and 50°C, respectively.

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 ^[23]. Participants were provided with standardised descriptions of the QST measures and ratings required; a summary of the test battery is provided in Appendix A.

2.7. ~~Intra-rater reliability~~

~~A convenience sample of 9 volunteers (5 males; median age 25 years; range 22-45 years) free from musculoskeletal pain completed two reliability sessions 7 days apart to determine intra-rater reliability (assessor KM). One male volunteer could not attend the second session and was not included in the analysis. A tender point examination was completed followed by a reduced QST battery (heat pain; mechanical pain; temporal summation; vibration detection; pressure pain) performed at one knee. Participants were randomised as to which knee was tested for both sessions. Intraclass correlation coefficients (ICC) calculated intra-rater reliability (session 1 compared with session2). ICC could not be determined for tender point counts or cold pain threshold due to 17 and 18 instances, respectively, of 0 scores recorded over the three sessions. ICC were interpreted as none or little correlation (0.00-0.24), low~~

(0.25-0.49), moderate (0.50-0.69), high (0.70-0.89) and very high (0.90-1.00) [24]. ICC for QST measures were moderate (mechanical 0.637; temporal summation 0.672; vibration 0.690) or high (heat 0.710; pressure 0.861) in correlation suggesting the assessor performed these assessments reliably.

2.7. Sample Size

In the EPIFUND study [25], the standard deviation of tender point count was 4.5 and of global pain intensity was 2.25, and the regression of global pain intensity on tender point count gave a regression coefficient of 0.16. Entering these values in the G*Power 3.1.2 software suggest that a sample size of 71 participants would be sufficient to give 80% power to detect this association at a significance level of 0.05.

2.8. Analysis

The characteristics of study participants, QST measures and psychosocial factors are presented as medians with the interquartile range (IQR) for continuous measures and proportions for categorical variables.

Spearman's correlation was used to determine associations between QST measures and psychosocial factors, and QST measures with both self-reported pain intensities. The QST measures (independent variables) with significant correlations ($p < 0.05$) with one or both measures of self-reported pain intensity (dependent variables) were selected for the mediation model (path c, Figure 1). Psychosocial factors which were significantly correlated ($p < 0.05$) with the QST measures selected as independent variables were selected as mediating variables for the mediation model (path a, Figure 1). Structural equation models with all psychosocial factors associated with each QST measure loading on to a latent mediator were also constructed (Figure 2). Only participants with complete observations for all measures of interest were included in the analyses. All analyses were performed using Stata 13.1 software (Stata, USA).

<Figure 1; Figure 2>

3. Results

3.1. Participants

565 of 1530 responders (37%; median age 60 years; 62% female) of the EPIFUND cohort reported knee pain; 213 (38%) of those identified with knee pain were contacted during the first telephone recruitment phase (Figure 3). 133 people (24%) received a study information sheet and 80 people (14%) either could not

be contacted, reported no knee pain within the past month, or declined participation. 92 people (16%) agreed to participate in the study. However, 11 people (2%) did not attend study appointments and 8 people (1%) were withdrawn during the study visit. 72 participants (13%) completed the study. 61 participants (11%; median age 64 years; 59% women; Table 1) had complete data for QST measures, psychosocial factors, and self-reported pain intensities, and were included in the analyses. The proportion of female EPIFUND responders with knee pain was comparable to the proportion in this study (62% and 59%, respectively), although participants in this study were older than the EPIFUND responders (median age 64 years and 60 years, respectively).

<Figure 3>

3.2. Participant characteristics

The median BMI of the 61 participants was 27.7 (IQR 26 to 30.7; Table 1). The medians for self-reported global pain intensity and pain intensity at the tested knee were 5 (IQR 3-7 for both pain intensities). The median for tender point count was 0 (IQR 0 to 2) with no participants meeting the 11 tender point threshold outlined in the 1990 ACR Fibromyalgia criteria [23]. The median ratios for temporal summation at the knee and forearm exceeded 1 (2 and 1.9, respectively) indicating greater pain was reported in response to the train of mechanical stimuli compared with the single stimulus. Apart from the median scores for DMA (which were identical at both test sites), the median thresholds for cold pain, MPS and vibration detection were higher at the forearm than the knee. The median thresholds for heat and pressure pain were lower at the forearm than the knee.

The median scores for the HAD anxiety (3; IQR 1 to 6) and depression (5; IQR 2 to 8) sub-scales were below the score for borderline cases (0-7 normal; 8-10 borderline case; 11-21 case). In the present study, 12 borderline and 7 cases of anxiety, and 8 borderline and 3 cases of depression were identified using the HAD sub-scale cut-offs (Table 2) [18]. Median scores of 3 (IQR 1 to 2), 1 (IQR 1 to 3) and 3 (IQR 2 to 5) were reported for the rumination, magnification and helplessness sub-scales of the PCS, respectively. The median scores for items of the IPQ-Brief were: consequences (3; IQR 2 to 5); timeline (8; IQR 4 to 10; inversely scored); personal control (5; IQR 3 to 7; inversely scored); treatment control (5; IQR 2 to 7; inversely scored); identity (2; IQR 1 to 4); concern (4; IQR 2 to 7); coherence (2; IQR 1 to 5); emotion (3; IQR 1 to 4). A median score of 4 (regular underactive; IQR 4 to 5) was observed for the RAPA.

<Table 1; Table 2>

3.3. *Correlations between QST measures and self-reported pain intensity*

There were significant positive correlations ($p < 0.05$; Table 3) between global pain intensity and number of tender points, knee and forearm MPS, and DMA at the knee. Knee and forearm MPS, and DMA at the knee were also significantly positively correlated with higher pain intensity at the tested knee.

<Table 3>

3.4. *Correlations between QST measures and psychosocial factors*

In total, 10 psychosocial factors were significantly correlated ($p < 0.05$; Table 4) with tender point count; seven factors were significantly correlated with knee MPS; nine factors were significantly correlated with DMA at the knee; and 5 factors were significantly correlated with MPS at the forearm. Impact of illness on life, increased illness duration and higher levels of concern (illness perceptions) and magnification (pain catastrophizing) were all significantly positively correlated with tender point count, mechanical pain sensitivity at the knee and forearm, and dynamic mechanical allodynia at the knee.

<Table 4>

3.5. *Mediation Analysis*

Nine significant partial mediators of the associations between QST measures and the self-reported global and knee pain intensity measures were identified (Table 5). The total effect of tender point count on global pain intensity was 0.467 (β -coefficient; 95% CI 0.184, 0.749; Table 5). Within the mediation model, the direct effect (path c; Figure 1) between tender point count and global pain intensity was non-significant (β 0.467; 95% CI -0.086, 0.462). The indirect effect (path a x path b; Figure 1; β 0.279; 95% CI 0.093, 0.465) between tender point count and concern item of the IPQ-brief (path a), and between concern and global pain intensity (path b) was significant. The proportion of the total mediated effect was determined by dividing the β -coefficient for the indirect effect by the β -coefficient for the total effect ($0.279/0.467 = 60\%$).

The association between increased number of tender points and increased global pain intensity was also significantly partially mediated by the consequences item of the IPQ-brief, and the helplessness and rumination sub-scales of the PCS explaining 57%, 56% and 34% of the total effect, respectively.

Increased knee MPS and increased global pain intensity was partially mediated by concern, consequences and helplessness explaining 45%, 40% and 40% of the total effect respectively, and increased knee MPS and increased pain intensity at the tested knee were partially mediated by consequences and concern, explaining 30% and 29% of the total effect respectively.

<Table 5>

The inclusion of psychosocial factors loaded on to a latent mediator rather than individual items (Figure 2) accounted for 75%, 52%, 63% and 35% of the total effect of tender point, knee MPS and knee DMA on global pain intensity, and knee MPS on knee pain intensity, respectively (Table 6). However, the latent psychosocial mediator was not a partial mediator of the association between knee DMA on knee pain intensity (30% total effect mediated; Table 6).

<Table 6>

4. Discussion

The present study identified significant associations between greater levels of self-reported pain intensity (globally and at the knee) with measures of mechanical hyperalgesia (greater number of tender points, and increased MPS and DMA). The identification of widespread mechanical hyperalgesia (global pain intensity significantly associated with tender point count and forearm MPS) suggests that generalised alterations in central pain processing (an aspect of central sensitisation) contributes to mechanisms of knee pain. The associations between self-reported pain intensity and mechanical hyperalgesia were also explained in part by psychosocial factors, namely illness perceptions, suggests central integration of these phenomena and altered somatosensory processing in those with knee pain.

The present study demonstrated mechanical hyperalgesia (tender points, mechanical pain sensitivity and dynamic mechanical allodynia) at the knee and forearm were associated with greater levels of self-reported pain intensity, but that pain thresholds (heat, cold, mechanical and pressure) and temporal summation at the same sites were not. Previous studies have identified associations between the presence of temporal summation in knee OA samples compared with healthy controls, and between knee OA groups with high symptom severity compared with low symptom severity [7,26]. Within-person associations between increased pain severity and measures of pressure pain and temporal summation have been identified in one study [27]; however, the sample size was much larger (n=2126) and the temporal summation methodology applied for a longer time period (30 seconds), which may account for the lack of association in the present study.

While previous studies have shown somatosensory disturbances in samples with knee pain compared to pain-free controls, a recent population-based study of individuals with knee OA classified according to the median number of disease-related symptoms and a group of pain-free controls demonstrated no differences across the groups for the warm detection, heat pain, or heat pain tolerance thresholds at the knee or forearm, or for cold pain and cold pain tolerance thresholds at the right hand suggesting that peripheral somatosensory disturbances were not present in the knee OA groups [26]. However, significantly higher levels of pain intensity were reported for all QST assessments and at all test sites for the high and (to a lesser extent) low symptom count knee OA groups compared with controls [26]. These findings suggest the presence of amplification of somatosensory inputs within the central nervous system in those with knee pain.

A study by Neogi et al. posits that sensitisation is a trait already present with patients with knee OA and is not a consequence of joint pathology [27]: the authors did not observe associations between the duration, presence or severity of radiographic knee OA with increased sensitivity to pressure pain and mechanical temporal summation suggesting the presence of central sensitisation in their sample. The present study supports this finding as mechanical hyperalgesia at the forearm, a pain-free site opposite to the most painful knee, and a greater number of tender points were significantly associated with higher levels of global pain intensity suggesting the presence of altered central processing.

Only one previous study reported pain catastrophizing as a significant partial mediator of the association between female sex and higher levels of self-reported pain intensity, disability and pain behaviour modelled as a latent pain-related outcome measure in 168 subjects with knee OA; these findings indicate women are more likely to report pain, and catastrophizing explains a proportion of that association [28]. However, the study did not perform QST assessments [28]. The present study identified measures of catastrophizing along with illness perceptions as partial mediators of the association between QST measures and self-reported pain intensity demonstrating the role of central emotional processing in mediating increasing central pain processing.

Previous studies have demonstrated differences in sensory perception thresholds between participants with knee OA and pain-free controls [29,7,30]. However, pain-free controls may not be an appropriate comparator for people with chronic pain. Psychosocial factors such as depression, anxiety, pain catastrophizing and lowered physical functioning that influence pain perception occur less frequently in pain-free controls. Other studies have stratified knee OA patients by disease [12], symptom [26], or pain severity [8,7], or have used patients with inflammatory arthritis as a comparator group [31,32]. A meta-analysis demonstrated significantly lower pressure pain thresholds in those with knee OA compared with pain-free controls and for knee OA

groups with high symptom severity compared with those with low symptom severity ^[14]. The present study used a pain-free test site on the opposite side of the body to the most painful knee to eliminate person-level confounding as all control assessments were performed within-person; consequently, within-person mechanical hyperalgesia along with measures of pain catastrophising and illness perceptions were identified as indicators of greater self-reported pain intensity, suggesting that altered central pain processing contributes to mechanisms of knee pain.

A limitation of the present study is the cross-sectional study design. While insights into the associations between QST measures, pain and psychosocial factors have been provided, it is unknown whether mechanical hyperalgesia or illness perceptions are causal or a consequence of having pain. Another limitation is that the present study was underpowered to fully explore the role of age and sex as moderators of the associations between QST measures and self-reported pain intensity; Bartley et al. ^[33] demonstrated increased sensitivity to QST measures (cold pressor; mechanical pain; pressure pain) in 183 females compared with 105 males with symptomatic knee OA, despite similar mean values recorded for the WOMAC (34.5±20.5 for females; 34.1±20.7 for males). The authors did observe significantly wider distributions of pain sites in females (6.0±4.7 vs 4.3±3.2), which may suggest altered central processing contributing to increased sensitivity in females ^[33].

A further limitation is the numeric rating scale used to determine global and knee pain intensity levels in the past month in participants; pain intensity in the past month was not associated with current somatosensory thresholds. Previous studies have demonstrated significant associations between pain thresholds and pain in the previous 24 hours ^[7,34] and current pain ^[26,35]. The inclusion of multiple measures of current and recent knee and/or global pain intensities in future studies exploring current somatosensory functioning should be considered.

5. Conclusions

The present study emphasises the contributions of altered central processing and integration of psychosocial factors in the experience of knee pain. Few existing treatments are effective in reducing pain intensity in those with chronic pain in the long term ^[36]; improving our understanding of the mechanisms driving chronic pain provides new or alternative targets for intervention. The findings of the present study may help to explain inter-individual differences in pain reporting and underscores the role of psychosocial factors in pain research, particularly when investigating variations in the effectiveness of interventions for chronic pain.

6. Implications

Associations between mechanical hyperalgesia at the forearm and knee, psychosocial factors, and increased levels of clinical global and knee pain intensity provide evidence of altered central processing as a key mechanism in knee pain with psychological factors playing a key role in the expression of self-reported pain.

Acknowledgements

The authors express their gratitude to all study participants, Bollington Health and Leisure and NIHR Wellcome Trust Manchester Clinical Research Facility, and to members of the Pain Across the Adult Lifespan study team (James Anderson; Claire Bennett; Dr Deborah Brown; Rosie Duncan; Dr Matthew Mulvey; Dr Amir Rashid).

Funding

Arthritis Research UK programme grant 17552. This report includes independent research supported by (or funded by) the National Institute for Health Research Biomedical Research Unit Funding Scheme. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

Disclosures

KJM received honoraria for developing and delivering an educational presentation for Janssen-Cilag Ltd and Eli Lilly Ltd. AKPJ is National PI on a drug trial supported by Daichi-Sankyo. The other authors (ML; TON; JM) have no conflicts of interest, including relevant financial interests, activities, relationships, and affiliations.

Ethical Issues

The present study received approval from the National Research Ethics Service Committee North West – Cheshire (12/NW/0556) in order to contact the cohort and complete the study assessments. All participants

provided consent at the study visit prior to any assessments. Participants were anonymised to maintain their privacy.

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Figure 1 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.

Figure 2 Mediation model including latent psychosocial mediating variable

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.

Figure 3 Recruitment flowchart

Table 1 Participant characteristics: self-reported pain and QST measures

Variable (observed range)	N=61
Females (%)	36 (59.0%)
Age (years; median (IQR))	64 (56 to 69)
BMI (kg/m ² ; median (IQR))	27.7 (26 to 30.7)
Outcome Measures	
Global pain intensity (0 to 10 NRS)	5 (3 to 7)
Tested knee pain intensity (0 to 10 NRS)	5 (3 to 7)
Central QST	
Tender point (0 to 18)	0 (0 to 2)
Knee temporal summation (≥ 1)	1 (0.8 to 1.48)
Forearm temporal summation (≥ 1)	2 (1.42 to 2.67)
Knee QST	
Cold pain (0 to 32.0°C)	0 (0 to 0.8)
Heat pain (32.0 to 50°C)	48.33 (45.3 to 50)
Mechanical pain (0 to 512 mN)	90.51 (42.22 to 174.18)
MPS (0 to 100 NRS)	2.49 (0.86 to 5.97)
DMA (0 to 100 NRS)	0 (0 to 1)
Vibration (0 to 8)	4.33 (3.33 to 5.33)
Pressure pain (0 to 10 kg/cm ²)	5.6 (3.4 to 7.3)
Forearm QST	
Cold pain (0 to 32.0°C)	1.3 (0 to 14.3)
Heat pain (32.0 to 50°C)	47.03 (45.1 to 48.57)
Mechanical pain (0 to 512 mN)	45.25 (21.11 to 105)
MPS (0 to 100 NRS)	2.97 (0.94 to 7.17)
DMA (0 to 100 NRS)	0 (0 to 0.2)
Vibration (0 to 8)	6 (5.33 to 6.67)
Pressure pain (0 to 10 kg/cm ²)	3.67 (2.57 to 5.13)

IQR = interquartile range; NRS = numeric rating scale; CPT = cold pain threshold; HPT = heat pain threshold; MPT = mechanical pain threshold; mN = milli-Newton; MPS = mechanical pain sensitivity; DMA = dynamic mechanical allodynia; VDT = vibration detection threshold; PPT = pressure pain threshold.

Table 2 Participant characteristics: psychosocial factors

Variable (observed range)	Median (IQR)
HAD (0 to 21 sub-scale)	
Anxiety	5 (2 to 8)
Depression	3 (1 to 6)
PCS	
Rumination (4 items; 0 to 16)	3 (1 to 5)
Magnification (3 items; 0 to 12)	1 (1 to 3)
Helplessness (6 items; 0 to 24)	3 (2 to 5)
IPQ-brief (0 to 10 NRS per item)	
Consequences	3 (2 to 5)
Timeline	8 (4 to 10)
Personal Control	5 (3 to 7)
Treatment Control	5 (2 to 7)
Identity	2 (1 to 4)
Concern	4 (2 to 7)
Coherence	2 (1 to 5)
Emotion	3 (1 to 4)
Physical Functioning	
RAPA (7 items; 0 to 7)	4 (4 to 5)

HAD = Hospital Anxiety and Depression Scale; PCS = Pain Catastrophizing Scale; IPQ-brief = Illness Perception Questionnaire Brief;
RAPA = Rapid Assessment of Physical Activity.

Table 3 Association between self-reported pain intensity and QST measures

	Pain Intensity (NRS)	
	Global	Tested knee
Central QST		
Tender point	0.3364	0.1811
Knee TS	-0.0608	-0.1034
Forearm TS	0.0970	0.1433
Knee QST		
CPT	0.1948	0.2430
HPT	-0.0731	0.0153
MPT	0.0844	0.1146
MPS	0.3366	0.3350
DMA	0.3336	0.4358*
VDT	0.0169	-0.0929
PPT	-0.2211	-0.1443
Forearm QST		
CPT	-0.0760	-0.0396
HPT	-0.1429	-0.0385
MPT	-0.0364	-0.0379
MPS	0.3319	0.3333
DMA	0.2413	0.1949
VDT	-0.0049	-0.1158
PPT	-0.1852	-0.1183

p<0.05 for values in bold; *[p<0.0029 \(0.05/17; Bonferroni Correction\)](#).

NRS = numeric rating scale; TS = temporal summation; CPT = cold pain threshold; HPT = heat pain threshold; MPT = mechanical pain threshold; MPS = mechanical pain sensitivity; DMA = dynamic mechanical allodynia; VDT = vibration detection threshold; PPT = pressure pain threshold.

Table 4 Association between QST measures and psychosocial factors

	TPC	Knee MPS	Knee DMA	Forearm MPS
HAD				
Anxiety	0.117	0.1251	0.2332	0.0498
Depression	0.178	0.1539	0.2994	0.0275
PCS				
Rumination	0.265	0.2117	0.3120	0.1165
Magnification	0.401*	0.3374	0.3550	0.2850
Helplessness	0.330	0.3946*	0.3548	0.2259
IPQ-brief				
Consequences	0.452*	0.3833*	0.3237	0.2839
Timeline	0.323	0.3820*	0.2778	0.2700
Personal control	-0.125	0.0885	0.1257	0.0255
Treatment control	-0.230	-0.1237	0.0348	-0.3002
Identity	0.433*	0.2777	0.1980	0.2361
Concern	0.445*	0.3676*	0.2801	0.2911
Coherence	-0.196	0.0029	-0.1074	0.0577
Emotion	0.406*	0.3185	0.3391	0.1652
Physical Functioning				
RAPA	-0.311	-0.1339	-0.0600	-0.0839

p<0.05 for values in bold; * [p<0.0036 \(0.05/14; Bonferroni Correction\)](#).

TPC = tender point count; MPS = mechanical pain sensitivity; DMA = dynamic mechanical allodynia; HAD = Hospital Anxiety and Depression Scale; PCS = Pain Catastrophizing Scale; IPQ-brief = Illness Perception Questionnaire Brief; RAPA = Rapid Assessment of Physical Activity.

Table 5 Effect of psychosocial factors on the association between pain intensity and QST measures

		β (95% CI)*	SE	Z	Proportion of Total Effect Mediated (95% CI)
Tender point count --> global pain intensity					
Concern	Total Effect	0.47 (0.18, 0.75)	0.144	3.24	----
	Path a	0.63 (0.31, 0.95)	0.163	3.88	60% (17%, 100%)
	Path b	0.44 (0.25, 0.63)	0.098	4.48	
	Direct Effect (Path c)	0.19 (-0.09, 0.46)	0.140	1.35	
	Indirect Effect (Path a x b)	0.28 (0.09, 0.47)	0.095	2.93	
Consequences	Path a	0.49 (0.23, 0.75)	0.134	3.64	57% (17%, 98%)
	Path b	0.55 (0.32, 0.78)	0.119	4.64	
	Direct Effect (Path c)	0.20 (-0.07, 0.47)	0.137	1.45	
	Indirect Effect (Path a x b)	0.27 (0.09, 0.45)	0.094	2.86	
Helplessness	Path a	0.72 (0.39, 1.05)	0.168	4.30	56% (12%, 100%)
	Path b	0.36 (0.17, 0.56)	0.099	3.66	
	Direct Effect (Path c)	0.20 (-0.09, 0.50)	0.150	1.37	
	Indirect Effect (Path a x b)	0.26 (0.08, 0.45)	0.094	2.79	
Rumination	Path a	0.58 (0.23, 0.93)	0.178	3.28	34% (0.5%, 68%)
	Path b	0.27 (0.08, 0.46)	0.098	2.80	
	Direct Effect (Path c)	0.31 (0.02, 0.60)	0.147	2.09	
	Indirect Effect (Path a x b)	0.16 (0.01, 0.31)	0.075	2.13	
Knee MPS --> global pain intensity					
Concern	Total Effect	0.12 (0.05, 0.20)	0.038	3.26	----
	Path a	0.13 (0.04, 0.22)	0.045	2.79	45% (11%, 79%)
	Path b	0.44 (0.26, 0.62)	0.092	4.76	
	Direct Effect (Path c)	0.07 (0.00, 0.14)	0.035	1.99	
	Indirect Effect (Path a x b)	0.06 (0.01, 0.10)	0.023	2.41	
Consequences	Path a	0.09 (0.02, 0.17)	0.037	2.44	40% (8%, 73%)
	Path b	0.55 (0.33, 0.77)	0.110	4.99	
	Direct Effect (Path c)	0.07 (0.01, 0.14)	0.034	2.2	
	Indirect Effect (Path a x b)	0.05 (0.01, 0.10)	0.023	2.19	
Helplessness	Path a	0.13 (0.04, 0.23)	0.048	2.81	40% (6%, 73%)
	Path b	0.37 (0.19, 0.54)	0.091	4.03	
	Direct Effect (Path c)	0.08 (0.01, 0.15)	0.036	2.09	
	Indirect Effect (Path a x b)	0.05 (0.01, 0.09)	0.021	2.30	
Knee MPS --> tested knee pain intensity					
Consequences	Total Effect	0.13 (0.06, 0.20)	0.034	3.79	----
	Path a	0.09 (0.02, 0.17)	0.037	2.44	30% (4%, 57%)
	Path b	0.43 (0.23, 0.63)	0.103	4.19	
	Direct Effect (Path c)	0.09 (0.03, 0.15)	0.031	2.86	
	Indirect Effect (Path a x b)	0.04 (0.00, 0.08)	0.019	2.11	
Concern	Path a	0.13 (0.04, 0.22)	0.045	2.79	29% (3%, 56%)
	Path b	0.30 (0.13, 0.47)	0.088	3.41	
	Direct Effect (Path c)	0.09 (0.03, 0.16)	0.033	2.75	
	Indirect Effect (Path a x b)	0.04 (0.00, 0.07)	0.018	2.16	

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

Table 6 Mediation analysis for QST measures and self-reported pain intensity including a latent psychosocial mediating variable

	β (95% CI)*	SE	Z	Proportion of Total Effect Mediated (95% CI)
Global Pain Intensity				
Exogenous: Tender Point				
Total Effect	0.47 (0.18, 0.75)	0.144	3.24	----
Indirect Effect (path $a \times b$)	0.35 (0.13, 0.57)	0.112	3.15	75% (22%, 100%)
Direct Effect (path c)	0.12 (-0.18, 0.41)	0.149	0.77	
Exogenous: Knee MPS				
Total Effect	0.12 (0.05, 0.20)	0.038	3.26	----
Indirect Effect (path $a \times b$)	0.07 (0.02, 0.12)	0.026	2.54	49% (12%, 86%)
Direct Effect (path c)	0.06 (-0.01, 0.13)	0.035	1.69	
Exogenous: Knee DMA				
Total Effect	0.33 (0.03, 0.63)	0.153	2.17	----
Indirect Effect (path $a \times b$)	0.21 (0.01, 0.41)	0.010	2.10	63% (5%, 100%)
Direct Effect (path c)	0.12 (-0.14, 0.38)	0.134	0.90	
Knee Pain intensity				
Exogenous: Knee MPS				
Total Effect	0.13 (0.06, 0.20)	0.034	3.79	----
Indirect Effect (path $a \times b$)	0.04 (0.00, 0.07)	0.020	2.09	30% (2%, 58%)
Direct Effect (path c)	0.08 (0.02, 0.15)	0.034	2.50	
Exogenous: Knee DMA				
Total Effect	0.43 (0.17, 0.70)	0.134	3.25	----
Indirect Effect (path $a \times b$)	0.13 (-0.01, 0.27)	0.070	1.90	31% (0%, 61%)
Direct Effect (path c)	0.30 (0.05, 0.56)	0.129	2.34	

β = β -coefficient; CI = confidence interval; * $p < 0.05$ if bold. SE = standard error; Z = Z-score; MPS = mechanical pain sensitivity; DMA = dynamic mechanical allodynia.

Appendix A

Quantitative sensory testing battery

Tender point count

An 18 point tender point count was performed following the ACR protocol for classifying Fibromyalgia ^[23].

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). 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.

Thermal pain thresholds

Heat and cold pain thresholds were assessed using the TSA 2001-II Thermode (MEDOC, Israel) at the knee and forearm (0 to 50°C; MEDOC, Israel). The thermode was set to a baseline temperature of 32° and increased (heat pain) or decreased (cold pain) in temperature at a rate of 1°C per second until the participant indicated pain or until the safety cut-off points at 50°C or 0°C were reached. Thresholds were determined by taking the average of three readings for each threshold.

Mechanical pain threshold

Mechanical pain thresholds were assessed using 7 punctate probes (8 – 512 milli-Newton (mN); MRC Systems GmbH, Germany); the probes were applied in ascending order until a participant reported the probe to feel “sharp”. Once a “sharp” response was obtained, the probes were applied in descending order until a “blunt” response was achieved. Mechanical pain threshold was determined by taking the geometric mean of the weight of the probes for 5 “sharp” and 5 “blunt” responses.

Mechanical pain sensitivity

The 7 punctate probes were also used to assess MPS as well as two cotton buds of differing size and a brush to determine DMA as part of the stimulus response function at the knee and forearm. The 10 stimuli

were applied in a random order and five times each in total with participants asked to provide a rating of pain scored from 0 (no pain) to 100 (worst pain imaginable) for each stimulus. The 35 scores for the punctate probes were averaged to provide a score for MPS with the mean of the 15 responses to the cotton buds and brush forming the score for DMA.

Temporal summation

Central measures of QST included wind-up ratio at the knee and forearm. A single application of the 256 mN punctate probe and series of 10 applications of the same probe at a rate of one per second was applied to the knee and forearm; participants were asked to rate the single and series of applications using the 0 to 100 NRS described above. Wind-up ratio was calculated from the mean rating of 5 series of applications divided by the mean rating for 5 single applications of the probe.

Vibration detection threshold

Vibration detection was assessed using a 64 Hz Rydel Seiffer tuning fork (US Neurologicals, USA); the tuning fork was placed upon the patella or at the elbow while vibrating with participants asked to report whether they felt vibration, and to indicate when the vibration stopped. A scale of 0 to 8 on the tuning fork was used to identify the point of cessation. Thresholds were calculated by taking the mean of three assessments.

Pressure pain threshold

Pressure pain thresholds were assessed using a hand-held algometer (0 to 10 kg / cm²; Pain Diagnostics and Thermography, USA) with pressure applied at a rate of 1 kg per second at the knee and forearm until 10 kg was reached or the participant indicated pain. Thresholds were calculated as the mean of three assessments.

Psychosocial factors partially mediate the relationship between mechanical hyperalgesia and self-reported pain

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Abstract

Background and aim: Amplification of sensory signalling within the nervous system along with psychosocial factors contributes to the variation and severity of knee pain. Quantitative Sensory Testing (QST) is a non-invasive test battery that assesses sensory perception of thermal, pressure, mechanical and vibration stimuli used in the assessment of pain. Psychosocial factors also have an important role in explaining the occurrence of pain. The aim was to determine whether QST measures were associated with self-reported pain, and whether those associations were mediated by psychosocial factors.

Methods: Participants with knee pain identified from a population-based cohort completed a tender point count and a reduced QST battery of thermal, mechanical and pressure pain thresholds, temporal summation, mechanical pain sensitivity, dynamic mechanical allodynia and vibration detection threshold performed following the protocol by the German Research Network on Neuropathic Pain. QST assessments were performed at the most painful knee and opposite forearm (if pain-free). Participants were asked to score for their global and knee pain intensities within the past month (range 0 to 10), and complete questionnaire items investigating anxiety, depression, illness perceptions, pain catastrophizing, and physical functioning. QST measures (independent variable) significantly correlated (Spearman's rho) with self-reported pain intensity (dependent variable) were included in structural equation models with psychosocial factors (latent mediators).

Results: 72 participants were recruited with 61 participants (36 women; median age 64 years) with complete data included in subsequent analyses. Tender point count was significantly correlated with global pain intensity. Dynamic mechanical allodynia at the knee and mechanical pain sensitivity at the most painful knee and opposite pain-free forearm were significantly correlated with both global pain and knee pain intensities. Psychosocial factors including pain catastrophising sub-scales (rumination and helplessness) and illness perceptions (consequences and concern) were significant partial mediators of the association with global pain intensity when loaded on to a latent mediator for: tender point count (75% total effect; 95% confidence interval 22%, 100%); mechanical pain sensitivity at the knee (49%; 12%, 86%); and dynamic mechanical allodynia at the knee (63%; 5%, 100%). Latent psychosocial factors were also significant partial mediators of the association between pain intensity at the tested knee with mechanical pain sensitivity at the knee (30%; 2%, 58%), but not for dynamic mechanical allodynia at the knee.

Conclusions: Measures of mechanical hyperalgesia at the most painful knee and pain-free opposite forearm were associated with increased knee and global pain indicative of altered central processing.

Psychosocial factors were significant partial mediators, highlighting the importance of the central integration of emotional processing in pain perception.

Implications: Associations between mechanical hyperalgesia at the forearm and knee, psychosocial factors, and increased levels of clinical global and knee pain intensity provide evidence of altered central processing as a key mechanism in knee pain, with psychological factors playing a key role in the expression of clinical pain.

Key words

knee pain; quantitative sensory testing; sensitisation; psychosocial factors; altered central processing

Abbreviations

BMI	Body Mass Index
CI	Confidence Interval
DMA	Dynamic Mechanical Allodynia
EPIFUND	Epidemiology of Functional Disorders
HAD	Hospital Anxiety and Depression scale
ICC	Intraclass Correlation Coefficient
IPQ-brief	Brief Illness Perception Questionnaire
IQR	Interquartile Range
MPS	Mechanical Pain Sensitivity
OA	Osteoarthritis
PCS	Pain Catastrophising Scale
QST	Quantitative Sensory Testing
RAPA	Rapid Assessment of Physical Activity
SMD	Standardised Mean Difference

1. Introduction

Knee pain is a common complaint in the ageing population with an annual prevalence of 25% in those over 55^[1]. Knee pain may arise through local pathology stimulating the release of inflammatory mediators triggering nociceptive transmission^[2]. Only moderate correlations exist between knee pain and the structural pathology of osteoarthritis (OA) such as bone marrow lesions, synovitis and subchondral bone oedema, suggesting that altered central processing may be responsible for certain components of chronic pain^[3,4]. In those with chronic pain, altered central processing through amplifications of somatosensory inputs either via hyperalgesia (hypersensitivity to painful stimuli near a painful site) or allodynia (hypersensitivity to non-painful stimuli near a painful site), and the integration of emotional processing can contribute to the experience of pain in the absence of peripheral damage^[5,6]; altered central processing is an important mechanism for understanding the discordance between pathological features of OA and knee pain intensity. Higher reported pain knee intensity is associated with increased sensitivity to temporal summation (repeated noxious stimulation lowering the threshold for nociceptive transmission) in patients with knee OA indicating altered central processing^[7,8].

Quantitative sensory testing (QST) is a non-invasive technique used to assess somatosensory functioning^[9]. There is preliminary evidence to suggest knee OA patients have diminished vibration detection^[10] and thermal pain thresholds^[11,12] compared with healthy volunteers; however, previous studies have not investigated whether these measures are associated with higher levels of self-reported knee pain intensity. Two recent systematic reviews investigated somatosensory functioning in OA samples. Lluch et al.^[13] reported that despite diverse methodologies, increased levels of local hyperalgesia (at the knee, indicating peripheral sensitisation) and widespread hyperalgesia (indicating central sensitisation) were observed for knee OA participants compared with pain-free controls. A meta-analysis by Fingleton et al.^[14] demonstrated pressure pain thresholds were significantly lower in patients with knee OA compared with pain-free controls (standardised mean difference [SMD] -0.85; 95% confidence interval [CI] -1.1, -0.6), and for knee OA groups with high symptom severity compared with those with low symptom severity (SMD -0.51; 95% CI -0.73, -0.30). The authors also identified temporal summation as present in knee OA patients compared with healthy controls, and for knee OA groups with high symptom severity compared with low symptom severity^[14]. These findings suggest altered central processing is present within a sub-sample of individuals with knee OA and chronic pain.

Recent studies investigating QST in knee OA samples have included measures of psychosocial distress. Cruz-Almeida et al.^[15] determined four distinct profiles from psychological and somatosensory measures for

194 individuals with knee OA using hierarchical cluster analysis with the two most severe clusters reporting the highest levels of pain, anger, depression and mechanical hyperalgesia ^[15]. Findings from Williams *et al.* ^[12] and Finan *et al.* ^[8] demonstrated higher levels of anxiety and depression in participants with lower grade radiographic disease and moderate to severe knee pain, which were associated with higher levels of disability and widespread hyperalgesia. These results indicate psychosocial factors are associated with altered central processing with low grades of underlying pathology. However, the role of illness perceptions, which have been demonstrated as possible targets for intervention in people with lower back pain ^[16], have not been addressed in people with knee pain.

The impact of psychosocial factors on the association between self-reported pain intensity and somatosensory functioning has yet to be investigated in a population-based sample of individuals with knee pain. The aim of the present study was to determine whether (i) higher levels of self-reported pain intensity were associated with greater sensitivity to QST measures; (ii) any association between QST measures and pain intensity was mediated by psychosocial factors.

2. Methods

2.1. Participants

565 participants with knee pain were identified from a prospective population-based cohort investigating chronic pain (the epidemiology of functional disorders [EPIFUND] cohort) ^[17]. Participants were eligible for this study if they responded to a postal survey, had knee pain, and consented to further contact. It was not possible to robustly identify whether participants in the EPIFUND cohort identified as having knee pain also had underlying OA.

2.2. Recruitment

A two-phase telephone recruitment strategy was used: eligible participants were first contacted to verify the presence of knee pain on at least one day in the past month and to consent to the mailing of the participant information sheet about the QST study for their consideration. The second phone call occurred at least 7 days following the first-call to ensure adequate time for delivery and consideration of the information sheet. A more detailed description of the study was provided during the second phone call and if they were interested, participants were invited to attend a 90 minute appointment at a local primary care or research centre. A letter containing details of the study appointment, including the time, date and location, was mailed to each

participant who agreed to take part. The present study received approval from the National Research Ethics Service Committee North West – Cheshire (12/NW/0556) in order to contact the cohort and complete the study assessments. All participants provided consent at the study visit prior to any assessments.

2.3. *Study Assessments*

All assessments during the study visit were performed by one rater (KJM).

2.4. *Self-reported pain intensity and body mass index (BMI)*

All participants were asked whether they had experienced pain that lasted one day or longer in the past 30 days and to indicate that pain on a blank-body manikin. Participants with knee pain were those who shaded one or both knee regions. Global and knee pain intensities were assessed using 0 to 10 (best to worst) numeric rating scales for the average pain severity experienced within the past 30 days. BMI was calculated from measured weight (kilograms) and height (metres²).

2.5. *Psychosocial Factors*

Participants were provided with a questionnaire, including items addressing anxiety, depression, illness perceptions, pain catastrophising and physical functioning, with a stamped and addressed envelope to mail back to the study team after the assessments were complete. The Hospital Anxiety and Depression (HAD) scale ^[18] comprises 7 anxiety and 7 depression items (items scored 0, no symptoms to 3, strong indication of symptoms; anxiety and depression scales score range 0-21; 0 to 7 classified as normal; 8 to 10 as borderline cases; and ≥ 11 as cases). The Pain Catastrophizing Scale (PCS) and Brief Illness Perception Questionnaire (IPQ-brief) measured cognitions about pain ^[19]. The PCS comprises 13 items scored 0 (not at all) to 4 (all of the time) forming three sub-scales: helplessness (6 items, range 0-24), rumination (4 items, range 0-16) and magnification (3 items, range 0-12). The IPQ-brief comprises 8 items scored using a 10-point numeric rating scale ^[20]; five items (consequences, timeline, personal control, treatment control and identity) address thoughts about the illness, two items (concern and emotion) address the emotional impact and the final item (coherence) relates to the understanding of the illness (pain in the present study). Physical functioning was addressed using the Rapid Assessment of Physical Activity (RAPA) scale. The RAPA includes 9 items (range 0-10) scored “yes” or “no” with 7 items for levels of physical activity (0 classified as

sedentary; 1 to 2 as underactive, 3 to 4 regular underactive, and ≥ 5 as regular active (>5), one item for strength (scored 0 or 1) and one item for flexibility (scored 0 or 2) [21].

2.6. Quantitative Sensory Testing

The QST assessments were performed following the protocol by the German Research Network on Neuropathic Pain [22]. A reduced QST protocol was used; there is limited evidence for the presence of abnormal mechanical or thermal detection thresholds, or paradoxical heat sensations, in knee OA patients. All other assessments were included as these are considered to be altered in those with knee pain (pressure pain; temporal summation) or the literature is conflicting (thermal and mechanical pain, and vibration detection thresholds). QST assessments, except for vibration detection, were performed at the tibial tuberosity of the most painful knee and two centimetres distal to the lateral epicondyle on the opposite forearm (if pain-free): vibration detection was performed on the nearest bony prominences to the test sites in accordance with the QST protocol (at the patella of the most painful knee and the opposite elbow). Participants who did not achieve a painful sensation during cold or heat pain thresholds were categorised as 0°C and 50°C, respectively.

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 [23]. Participants were provided with standardised descriptions of the QST measures and ratings required; a summary of the test battery is provided in Appendix A.

2.7. Sample Size

In the EPIFUND study [25], the standard deviation of tender point count was 4.5 and of global pain intensity was 2.25, and the regression of global pain intensity on tender point count gave a regression coefficient of 0.16. Entering these values in the G*Power 3.1.2 software suggest that a sample size of 71 participants would be sufficient to give 80% power to detect this association at a significance level of 0.05.

2.8. Analysis

The characteristics of study participants, QST measures and psychosocial factors are presented as medians with the interquartile range (IQR) for continuous measures and proportions for categorical variables.

Spearman's correlation was used to determine associations between QST measures and psychosocial factors, and QST measures with both self-reported pain intensities. The QST measures (independent variables) with significant correlations ($p < 0.05$) with one or both measures of self-reported pain intensity (dependent variables) were selected for the mediation model (path c, Figure 1). Psychosocial factors which were significantly correlated ($p < 0.05$) with the QST measures selected as independent variables were selected as mediating variables for the mediation model (path a, Figure 1). Structural equation models with all psychosocial factors associated with each QST measure loading on to a latent mediator were also constructed (Figure 2). Only participants with complete observations for all measures of interest were included in the analyses. All analyses were performed using Stata 13.1 software (Stata, USA).

<Figure 1; Figure 2>

3. Results

3.1. Participants

565 of 1530 responders (37%; median age 60 years; 62% female) of the EPIFUND cohort reported knee pain; 213 (38%) of those identified with knee pain were contacted during the first telephone recruitment phase (Figure 3). 133 people (24%) received a study information sheet and 80 people (14%) either could not be contacted, reported no knee pain within the past month, or declined participation. 92 people (16%) agreed to participate in the study. However, 11 people (2%) did not attend study appointments and 8 people (1%) were withdrawn during the study visit. 72 participants (13%) completed the study. 61 participants (11%; median age 64 years; 59% women; Table 1) had complete data for QST measures, psychosocial factors, and self-reported pain intensities, and were included in the analyses. The proportion of female EPIFUND responders with knee pain was comparable to the proportion in this study (62% and 59%, respectively), although participants in this study were older than the EPIFUND responders (median age 64 years and 60 years, respectively).

<Figure 3>

3.2. Participant characteristics

The median BMI of the 61 participants was 27.7 (IQR 26 to 30.7; Table 1). The medians for self-reported global pain intensity and pain intensity at the tested knee were 5 (IQR 3-7 for both pain intensities). The

median for tender point count was 0 (IQR 0 to 2) with no participants meeting the 11 tender point threshold outlined in the 1990 ACR Fibromyalgia criteria [23]. The median ratios for temporal summation at the knee and forearm exceeded 1 (2 and 1.9, respectively) indicating greater pain was reported in response to the train of mechanical stimuli compared with the single stimulus. Apart from the median scores for DMA (which were identical at both test sites), the median thresholds for cold pain, MPS and vibration detection were higher at the forearm than the knee. The median thresholds for heat and pressure pain were lower at the forearm than the knee.

The median scores for the HAD anxiety (3; IQR 1 to 6) and depression (5; IQR 2 to 8) sub-scales were below the score for borderline cases (0-7 normal; 8-10 borderline case; 11-21 case). In the present study, 12 borderline and 7 cases of anxiety, and 8 borderline and 3 cases of depression were identified using the HAD sub-scale cut-offs (Table 2) [18]. Median scores of 3 (IQR 1 to 2), 1 (IQR 1 to 3) and 3 (IQR 2 to 5) were reported for the rumination, magnification and helplessness sub-scales of the PCS, respectively. The median scores for items of the IPQ-Brief were: consequences (3; IQR 2 to 5); timeline (8; IQR 4 to 10; inversely scored); personal control (5; IQR 3 to 7; inversely scored); treatment control (5; IQR 2 to 7; inversely scored); identity (2; IQR 1 to 4); concern (4; IQR 2 to 7); coherence (2; IQR 1 to 5); emotion (3; IQR 1 to 4). A median score of 4 (regular underactive; IQR 4 to 5) was observed for the RAPA.

<Table 1; Table 2>

3.3. Correlations between QST measures and self-reported pain intensity

There were significant positive correlations ($p < 0.05$; Table 3) between global pain intensity and number of tender points, knee and forearm MPS, and DMA at the knee. Knee and forearm MPS, and DMA at the knee were also significantly positively correlated with higher pain intensity at the tested knee.

<Table 3>

3.4. Correlations between QST measures and psychosocial factors

In total, 10 psychosocial factors were significantly correlated ($p < 0.05$; Table 4) with tender point count; seven factors were significantly correlated with knee MPS; nine factors were significantly correlated with DMA at the knee; and 5 factors were significantly correlated with MPS at the forearm. Impact of illness on life, increased illness duration and higher levels of concern (illness perceptions) and magnification (pain

catastrophizing) were all significantly positively correlated with tender point count, mechanical pain sensitivity at the knee and forearm, and dynamic mechanical allodynia at the knee.

<Table 4>

3.5. Mediation Analysis

Nine significant partial mediators of the associations between QST measures and the self-reported global and knee pain intensity measures were identified (Table 5). The total effect of tender point count on global pain intensity was 0.467 (β -coefficient; 95% CI 0.184, 0.749; Table 5). Within the mediation model, the direct effect (path c; Figure 1) between tender point count and global pain intensity was non-significant (β 0.467; 95% CI -0.086, 0.462). The indirect effect (path a x path b; Figure 1; β 0.279; 95% CI 0.093, 0.465) between tender point count and concern item of the IPQ-brief (path a), and between concern and global pain intensity (path b) was significant. The proportion of the total mediated effect was determined by dividing the β -coefficient for the indirect effect by the β -coefficient for the total effect ($0.279/0.467 = 60\%$).

The association between increased number of tender points and increased global pain intensity was also significantly partially mediated by the consequences item of the IPQ-brief, and the helplessness and rumination sub-scales of the PCS explaining 57%, 56% and 34% of the total effect, respectively.

Increased knee MPS and increased global pain intensity was partially mediated by concern, consequences and helplessness explaining 45%, 40% and 40% of the total effect respectively, and increased knee MPS and increased pain intensity at the tested knee were partially mediated by consequences and concern, explaining 30% and 29% of the total effect respectively.

<Table 5>

The inclusion of psychosocial factors loaded on to a latent mediator rather than individual items (Figure 2) accounted for 75%, 52%, 63% and 35% of the total effect of tender point, knee MPS and knee DMA on global pain intensity, and knee MPS on knee pain intensity, respectively (Table 6). However, the latent psychosocial mediator was not a partial mediator of the association between knee DMA on knee pain intensity (30% total effect mediated; Table 6).

<Table 6>

4. Discussion

1 The present study identified significant associations between greater levels of self-reported pain intensity
2 (globally and at the knee) with measures of mechanical hyperalgesia (greater number of tender points, and
3 increased MPS and DMA). The identification of widespread mechanical hyperalgesia (global pain intensity
4 significantly associated with tender point count and forearm MPS) suggests that generalised alterations in
5 central pain processing (an aspect of central sensitisation) contributes to mechanisms of knee pain. The
6 associations between self-reported pain intensity and mechanical hyperalgesia were also explained in part
7 by psychosocial factors, namely illness perceptions, suggests central integration of these phenomena and
8 altered somatosensory processing in those with knee pain.
9

10 The present study demonstrated mechanical hyperalgesia (tender points, mechanical pain sensitivity and
11 dynamic mechanical allodynia) at the knee and forearm were associated with greater levels of self-reported
12 pain intensity, but that pain thresholds (heat, cold, mechanical and pressure) and temporal summation at the
13 same sites were not. Previous studies have identified associations between the presence of temporal
14 summation in knee OA samples compared with healthy controls, and between knee OA groups with high
15 symptom severity compared with low symptom severity [7,26]. Within-person associations between increased
16 pain severity and measures of pressure pain and temporal summation have been identified in one study [27];
17 however, the sample size was much larger (n=2126) and the temporal summation methodology applied for a
18 longer time period (30 seconds), which may account for the lack of association in in the present study.
19

20 While previous studies have shown somatosensory disturbances in samples with knee pain compared to
21 pain-free controls, a recent population-based study of individuals with knee OA classified according to the
22 median number of disease-related symptoms and a group of pain-free controls demonstrated no differences
23 across the groups for the warm detection, heat pain, or heat pain tolerance thresholds at the knee or
24 forearm, or for cold pain and cold pain tolerance thresholds at the right hand suggesting that peripheral
25 somatosensory disturbances were not present in the knee OA groups [26]. However, significantly higher levels
26 of pain intensity were reported for all QST assessments and at all test sites for the high and (to a lesser
27 extent) low symptom count knee OA groups compared with controls [26]. These findings suggest the
28 presence of amplification of somatosensory inputs within the central nervous system in those with knee pain.
29

30 A study by Neogi et al. posits that sensitisation is a trait already present with patients with knee OA and is
31 not a consequence of joint pathology [27]: the authors did not observe associations between the duration,
32 presence or severity of radiographic knee OA with increased sensitivity to pressure pain and mechanical
33 temporal summation suggesting the presence of central sensitisation in their sample. The present study
34 supports this finding as mechanical hyperalgesia at the forearm, a pain-free site opposite to the most painful
35

knee, and a greater number of tender points were significantly associated with higher levels of global pain intensity suggesting the presence of altered central processing.

Only one previous study reported pain catastrophizing as a significant partial mediator of the association between female sex and higher levels of self-reported pain intensity, disability and pain behaviour modelled as a latent pain-related outcome measure in 168 subjects with knee OA; these findings indicate women are more likely to report pain, and catastrophizing explains a proportion of that association [28]. However, the study did not perform QST assessments [28]. The present study identified measures of catastrophizing along with illness perceptions as partial mediators of the association between QST measures and self-reported pain intensity demonstrating the role of central emotional processing in mediating increasing central pain processing.

Previous studies have demonstrated differences in sensory perception thresholds between participants with knee OA and pain-free controls [29,7,30]. However, pain-free controls may not be an appropriate comparator for people with chronic pain. Psychosocial factors such as depression, anxiety, pain catastrophizing and lowered physical functioning that influence pain perception occur less frequently in pain-free controls. Other studies have stratified knee OA patients by disease [12], symptom [26], or pain severity [8,7], or have used patients with inflammatory arthritis as a comparator group [31,32]. A meta-analysis demonstrated significantly lower pressure pain thresholds in those with knee OA compared with pain-free controls and for knee OA groups with high symptom severity compared with those with low symptom severity [14]. The present study used a pain-free test site on the opposite side of the body to the most painful knee to eliminate person-level confounding as all control assessments were performed within-person; consequently, within-person mechanical hyperalgesia along with measures of pain catastrophising and illness perceptions were identified as indicators of greater self-reported pain intensity, suggesting that altered central pain processing contributes to mechanisms of knee pain.

A limitation of the present study is the cross-sectional study design. While insights into the associations between QST measures, pain and psychosocial factors have been provided, it is unknown whether mechanical hyperalgesia or illness perceptions are causal or a consequence of having pain. Another limitation is that the present study was underpowered to fully explore the role of age and sex as moderators of the associations between QST measures and self-reported pain intensity; Bartley et al. [33] demonstrated increased sensitivity to QST measures (cold pressor; mechanical pain; pressure pain) in 183 females compared with 105 males with symptomatic knee OA, despite similar mean values recorded for the WOMAC (34.5±20.5 for females; 34.1±20.7 for males). The authors did observe significantly wider distributions of pain

sites in females (6.0 ± 4.7 vs 4.3 ± 3.2), which may suggest altered central processing contributing to increased sensitivity in females [33].

A further limitation is the numeric rating scale used to determine global and knee pain intensity levels in the past month in participants; pain intensity in the past month was not associated with current somatosensory thresholds. Previous studies have demonstrated significant associations between pain thresholds and pain in the previous 24 hours [7,34] and current pain [26,35]. The inclusion of multiple measures of current and recent knee and/or global pain intensities in future studies exploring current somatosensory functioning should be considered.

5. Conclusions

The present study emphasises the contributions of altered central processing and integration of psychosocial factors in the experience of knee pain. Few existing treatments are effective in reducing pain intensity in those with chronic pain in the long term [36]; improving our understanding of the mechanisms driving chronic pain provides new or alternative targets for intervention. The findings of the present study may help to explain inter-individual differences in pain reporting and underscores the role of psychosocial factors in pain research, particularly when investigating variations in the effectiveness of interventions for chronic pain.

6. Implications

Associations between mechanical hyperalgesia at the forearm and knee, psychosocial factors, and increased levels of clinical global and knee pain intensity provide evidence of altered central processing as a key mechanism in knee pain with psychological factors playing a key role in the expression of self-reported pain.

Acknowledgements

The authors express their gratitude to all study participants, Bollington Health and Leisure and NIHR Wellcome Trust Manchester Clinical Research Facility, and to members of the Pain Across the Adult Lifespan study team (James Anderson; Claire Bennett; Dr Deborah Brown; Rosie Duncan; Dr Matthew Mulvey; Dr Amir Rashid).

Research Funding: Arthritis Research UK programme grant 17552. This report includes independent research supported by (or funded by) the National Institute for Health Research Biomedical Research Unit Funding Scheme. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

Conflict of interest: KJM received honoraria for developing and delivering an educational presentation for Janssen-Cilag Ltd and Eli Lilly Ltd. AKPJ is National PI on a drug trial supported by Daichi-Sankyo. The other authors (ML; TON; JM) have no conflicts of interest, including relevant financial interests, activities, relationships, and affiliations.

Informed Consent: All participants provided consent at the study visit prior to any assessments. Participants were anonymised to maintain their privacy.

Ethical approval: The present study received approval from the National Research Ethics Service Committee North West – Cheshire (12/NW/0556) in order to contact the cohort and complete the study assessments.

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Figure 1 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.

Figure 2 Mediation model including latent psychosocial mediating variable

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.

Figure 3 Recruitment flowchart

Table 1 Participant characteristics: self-reported pain and QST measures

Variable (observed range)	N=61
Females (%)	36 (59.0%)
Age (years; median (IQR))	64 (56 to 69)
BMI (kg/m ² ; median (IQR))	27.7 (26 to 30.7)
Outcome Measures	
Global pain intensity (0 to 10 NRS)	5 (3 to 7)
Tested knee pain intensity (0 to 10 NRS)	5 (3 to 7)
Central QST	
Tender point (0 to 18)	0 (0 to 2)
Knee temporal summation (≥ 1)	1 (0.8 to 1.48)
Forearm temporal summation (≥ 1)	2 (1.42 to 2.67)
Knee QST	
Cold pain (0 to 32.0°C)	0 (0 to 0.8)
Heat pain (32.0 to 50°C)	48.33 (45.3 to 50)
Mechanical pain (0 to 512 mN)	90.51 (42.22 to 174.18)
MPS (0 to 100 NRS)	2.49 (0.86 to 5.97)
DMA (0 to 100 NRS)	0 (0 to 1)
Vibration (0 to 8)	4.33 (3.33 to 5.33)
Pressure pain (0 to 10 kg/cm ²)	5.6 (3.4 to 7.3)
Forearm QST	
Cold pain (0 to 32.0°C)	1.3 (0 to 14.3)
Heat pain (32.0 to 50°C)	47.03 (45.1 to 48.57)
Mechanical pain (0 to 512 mN)	45.25 (21.11 to 105)
MPS (0 to 100 NRS)	2.97 (0.94 to 7.17)
DMA (0 to 100 NRS)	0 (0 to 0.2)
Vibration (0 to 8)	6 (5.33 to 6.67)
Pressure pain (0 to 10 kg/cm ²)	3.67 (2.57 to 5.13)

IQR = interquartile range; NRS = numeric rating scale; CPT = cold pain threshold; HPT = heat pain threshold; MPT = mechanical pain threshold; mN = milli-Newton; MPS = mechanical pain sensitivity; DMA = dynamic mechanical allodynia; VDT = vibration detection threshold; PPT = pressure pain threshold.

Table 2 Participant characteristics: psychosocial factors

Variable (observed range)	Median (IQR)
HAD (0 to 21 sub-scale)	
Anxiety	5 (2 to 8)
Depression	3 (1 to 6)
PCS	
Rumination (4 items; 0 to 16)	3 (1 to 5)
Magnification (3 items; 0 to 12)	1 (1 to 3)
Helplessness (6 items; 0 to 24)	3 (2 to 5)
IPQ-brief (0 to 10 NRS per item)	
Consequences	3 (2 to 5)
Timeline	8 (4 to 10)
Personal Control	5 (3 to 7)
Treatment Control	5 (2 to 7)
Identity	2 (1 to 4)
Concern	4 (2 to 7)
Coherence	2 (1 to 5)
Emotion	3 (1 to 4)
Physical Functioning	
RAPA (7 items; 0 to 7)	4 (4 to 5)

HAD = Hospital Anxiety and Depression Scale; PCS = Pain Catastrophizing Scale; IPQ-brief = Illness Perception Questionnaire Brief;
RAPA = Rapid Assessment of Physical Activity.

Table 3 Association between self-reported pain intensity and QST measures

	Pain Intensity (NRS)	
	Global	Tested knee
Central QST		
Tender point	0.3364	0.1811
Knee TS	-0.0608	-0.1034
Forearm TS	0.0970	0.1433
Knee QST		
CPT	0.1948	0.2430
HPT	-0.0731	0.0153
MPT	0.0844	0.1146
MPS	0.3366	0.3350
DMA	0.3336	0.4358*
VDT	0.0169	-0.0929
PPT	-0.2211	-0.1443
Forearm QST		
CPT	-0.0760	-0.0396
HPT	-0.1429	-0.0385
MPT	-0.0364	-0.0379
MPS	0.3319	0.3333
DMA	0.2413	0.1949
VDT	-0.0049	-0.1158
PPT	-0.1852	-0.1183

p<0.05 for values in bold; * p<0.0029 (0.05/17; Bonferroni Correction).

NRS = numeric rating scale; TS = temporal summation; CPT = cold pain threshold; HPT = heat pain threshold; MPT = mechanical pain threshold; MPS = mechanical pain sensitivity; DMA = dynamic mechanical allodynia; VDT = vibration detection threshold; PPT = pressure pain threshold.

Table 4 Association between QST measures and psychosocial factors

	TPC	Knee MPS	Knee DMA	Forearm MPS
HAD				
Anxiety	0.117	0.1251	0.2332	0.0498
Depression	0.178	0.1539	0.2994	0.0275
PCS				
Rumination	0.265	0.2117	0.3120	0.1165
Magnification	0.401*	0.3374	0.3550	0.2850
Helplessness	0.330	0.3946*	0.3548	0.2259
IPQ-brief				
Consequences	0.452*	0.3833*	0.3237	0.2839
Timeline	0.323	0.3820*	0.2778	0.2700
Personal control	-0.125	0.0885	0.1257	0.0255
Treatment control	-0.230	-0.1237	0.0348	-0.3002
Identity	0.433*	0.2777	0.1980	0.2361
Concern	0.445*	0.3676*	0.2801	0.2911
Coherence	-0.196	0.0029	-0.1074	0.0577
Emotion	0.406*	0.3185	0.3391	0.1652
Physical Functioning				
RAPA	-0.311	-0.1339	-0.0600	-0.0839

p<0.05 for values in bold; * p<0.0036 (0.05/14; Bonferroni Correction).

TPC = tender point count; MPS = mechanical pain sensitivity; DMA = dynamic mechanical allodynia; HAD = Hospital Anxiety and Depression Scale; PCS = Pain Catastrophizing Scale; IPQ-brief = Illness Perception Questionnaire Brief; RAPA = Rapid Assessment of Physical Activity.

Table 5 Effect of psychosocial factors on the association between pain intensity and QST measures

		β (95% CI)*	SE	Z	Proportion of Total Effect Mediated (95% CI)
Concern	Tender point count --> global pain intensity				
	Total Effect	0.47 (0.18, 0.75)	0.144	3.24	----
	Path a	0.63 (0.31, 0.95)	0.163	3.88	60% (17%, 100%)
	Path b	0.44 (0.25, 0.63)	0.098	4.48	
	Direct Effect (Path c)	0.19 (-0.09, 0.46)	0.140	1.35	
	Indirect Effect (Path a x b)	0.28 (0.09, 0.47)	0.095	2.93	
	Path a	0.49 (0.23, 0.75)	0.134	3.64	57% (17%, 98%)
	Path b	0.55 (0.32, 0.78)	0.119	4.64	
	Direct Effect (Path c)	0.20 (-0.07, 0.47)	0.137	1.45	
	Indirect Effect (Path a x b)	0.27 (0.09, 0.45)	0.094	2.86	
	Path a	0.72 (0.39, 1.05)	0.168	4.30	56% (12%, 100%)
	Path b	0.36 (0.17, 0.56)	0.099	3.66	
	Direct Effect (Path c)	0.20 (-0.09, 0.50)	0.150	1.37	
	Indirect Effect (Path a x b)	0.26 (0.08, 0.45)	0.094	2.79	
	Path a	0.58 (0.23, 0.93)	0.178	3.28	34% (0.5%, 68%)
	Path b	0.27 (0.08, 0.46)	0.098	2.80	
Consequences	Knee MPS --> global pain intensity				
	Total Effect	0.12 (0.05, 0.20)	0.038	3.26	----
	Path a	0.13 (0.04, 0.22)	0.045	2.79	45% (11%, 79%)
	Path b	0.44 (0.26, 0.62)	0.092	4.76	
	Direct Effect (Path c)	0.07 (0.00, 0.14)	0.035	1.99	
	Indirect Effect (Path a x b)	0.06 (0.01, 0.10)	0.023	2.41	
	Path a	0.09 (0.02, 0.17)	0.037	2.44	40% (8%, 73%)
	Path b	0.55 (0.33, 0.77)	0.110	4.99	
	Direct Effect (Path c)	0.07 (0.01, 0.14)	0.034	2.2	
	Indirect Effect (Path a x b)	0.05 (0.01, 0.10)	0.023	2.19	
	Path a	0.13 (0.04, 0.23)	0.048	2.81	40% (6%, 73%)
	Path b	0.37 (0.19, 0.54)	0.091	4.03	
	Direct Effect (Path c)	0.08 (0.01, 0.15)	0.036	2.09	
	Indirect Effect (Path a x b)	0.05 (0.01, 0.09)	0.021	2.30	
	Knee MPS --> tested knee pain intensity				
	Total Effect	0.13 (0.06, 0.20)	0.034	3.79	----
Helplessness	Path a	0.09 (0.02, 0.17)	0.037	2.44	30% (4%, 57%)
	Path b	0.43 (0.23, 0.63)	0.103	4.19	
	Direct Effect (Path c)	0.09 (0.03, 0.15)	0.031	2.86	
	Indirect Effect (Path a x b)	0.04 (0.00, 0.08)	0.019	2.11	
	Path a	0.13 (0.04, 0.22)	0.045	2.79	29% (3%, 56%)
	Path b	0.30 (0.13, 0.47)	0.088	3.41	
	Direct Effect (Path c)	0.09 (0.03, 0.16)	0.033	2.75	
	Indirect Effect (Path a x b)	0.04 (0.00, 0.07)	0.018	2.16	

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

Table 6 Mediation analysis for QST measures and self-reported pain intensity including a latent psychosocial mediating variable

	β (95% CI)*	SE	Z	Proportion of Total Effect Mediated (95% CI)
Global Pain Intensity				
Exogenous: Tender Point				
Total Effect	0.47 (0.18, 0.75)	0.144	3.24	----
Indirect Effect (path $a \times b$)	0.35 (0.13, 0.57)	0.112	3.15	75% (22%, 100%)
Direct Effect (path c)	0.12 (-0.18, 0.41)	0.149	0.77	
Exogenous: Knee MPS				
Total Effect	0.12 (0.05, 0.20)	0.038	3.26	----
Indirect Effect (path $a \times b$)	0.07 (0.02, 0.12)	0.026	2.54	49% (12%, 86%)
Direct Effect (path c)	0.06 (-0.01, 0.13)	0.035	1.69	
Exogenous: Knee DMA				
Total Effect	0.33 (0.03, 0.63)	0.153	2.17	----
Indirect Effect (path $a \times b$)	0.21 (0.01, 0.41)	0.010	2.10	63% (5%, 100%)
Direct Effect (path c)	0.12 (-0.14, 0.38)	0.134	0.90	
Knee Pain intensity				
Exogenous: Knee MPS				
Total Effect	0.13 (0.06, 0.20)	0.034	3.79	----
Indirect Effect (path $a \times b$)	0.04 (0.00, 0.07)	0.020	2.09	30% (2%, 58%)
Direct Effect (path c)	0.08 (0.02, 0.15)	0.034	2.50	
Exogenous: Knee DMA				
Total Effect	0.43 (0.17, 0.70)	0.134	3.25	----
Indirect Effect (path $a \times b$)	0.13 (-0.01, 0.27)	0.070	1.90	31% (0%, 61%)
Direct Effect (path c)	0.30 (0.05, 0.56)	0.129	2.34	

β = β -coefficient; CI = confidence interval; * $p < 0.05$ if bold. SE = standard error; Z = Z-score; MPS = mechanical pain sensitivity; DMA = dynamic mechanical allodynia.

Appendix A

Quantitative sensory testing battery

Tender point count

An 18 point tender point count was performed following the ACR protocol for classifying Fibromyalgia ^[23].

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). 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.

Thermal pain thresholds

Heat and cold pain thresholds were assessed using the TSA 2001-II Thermode (MEDOC, Israel) at the knee and forearm (0 to 50°C; MEDOC, Israel). The thermode was set to a baseline temperature of 32° and increased (heat pain) or decreased (cold pain) in temperature at a rate of 1°C per second until the participant indicated pain or until the safety cut-off points at 50°C or 0°C were reached. Thresholds were determined by taking the average of three readings for each threshold.

Mechanical pain threshold

Mechanical pain thresholds were assessed using 7 punctate probes (8 – 512 milli-Newton (mN); MRC Systems GmbH, Germany); the probes were applied in ascending order until a participant reported the probe to feel “sharp”. Once a “sharp” response was obtained, the probes were applied in descending order until a “blunt” response was achieved. Mechanical pain threshold was determined by taking the geometric mean of the weight of the probes for 5 “sharp” and 5 “blunt” responses.

Mechanical pain sensitivity

The 7 punctate probes were also used to assess MPS as well as two cotton buds of differing size and a brush to determine DMA as part of the stimulus response function at the knee and forearm. The 10 stimuli

were applied in a random order and five times each in total with participants asked to provide a rating of pain scored from 0 (no pain) to 100 (worst pain imaginable) for each stimulus. The 35 scores for the punctate probes were averaged to provide a score for MPS with the mean of the 15 responses to the cotton buds and brush forming the score for DMA.

Temporal summation

Central measures of QST included wind-up ratio at the knee and forearm. A single application of the 256 mN punctate probe and series of 10 applications of the same probe at a rate of one per second was applied to the knee and forearm; participants were asked to rate the single and series of applications using the 0 to 100 NRS described above. Wind-up ratio was calculated from the mean rating of 5 series of applications divided by the mean rating for 5 single applications of the probe.

Vibration detection threshold

Vibration detection was assessed using a 64 Hz Rydel Seiffer tuning fork (US Neurologicals, USA); the tuning fork was placed upon the patella or at the elbow while vibrating with participants asked to report whether they felt vibration, and to indicate when the vibration stopped. A scale of 0 to 8 on the tuning fork was used to identify the point of cessation. Thresholds were calculated by taking the mean of three assessments.

Pressure pain threshold

Pressure pain thresholds were assessed using a hand-held algometer (0 to 10 kg / cm²; Pain Diagnostics and Thermography, USA) with pressure applied at a rate of 1 kg per second at the knee and forearm until 10 kg was reached or the participant indicated pain. Thresholds were calculated as the mean of three assessments.