Observational study

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

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Abstract

Background and aims: 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 (MPS), dynamic mechanical allodynia (DMA) 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 0–10), and complete questionnaire items investigating anxiety, depression, illness perceptions, pain catastrophising, 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: Seventy-two 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. DMA at the knee and MPS 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 (CI) 22%, 100%]; MPS at the knee (49%; 12%, 86%); and DMA 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 MPS at the knee (30%; 2%, 58%), but not for DMA 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

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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.

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

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

Five hundred and sixty-five 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 1 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 min 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

All participants were asked whether they had experienced pain that lasted 1 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 0–10 (best to worst) numeric rating scales for the average pain severity experienced within the past 30 days. Body mass index (BMI) was calculated from measured weight (kilograms) and height (metres^2).

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 seven anxiety and seven depression items (items scored 0, no symptoms to 3, strong indication of symptoms; anxiety and depression scales score range 0–21; 0–7 classified as normal; 8–10 as borderline cases and ≥11 as cases). The pain catastrophising 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 subscales: helplessness (six items, range 0–24), rumination (four items, range 0–16) and magnification (three items, range 0–12). The IPQ-brief comprises eight 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 nine items (range 0–10) scored "yes" or "no" with seven items for levels of physical activity (0 classified as sedentary; 1–2 as underactive, 3–4 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 2 cm 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 in the Supplementary Material.

2.7 Sample size

In the EPIFUND study [24], 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, Fig. 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, Fig. 1). Structural equation models with all psychosocial factors associated with each QST measure loading on to a latent mediator were also constructed (Fig. 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).

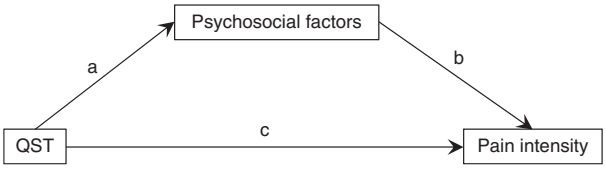

Fig. 1: Mediation model. The direct effect is represented by path c between the independent and dependent variables. The indirect path is represented by path a between the independent and mediator variables, and path b between the mediator and dependent variables.

3 Results

3.1 Participants

Five hundred and sixty-five 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 (Fig. 3). One hundred and thirty-three 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. Ninety-two people (16%) agreed to participate in the study. However, 11 people (2%) did not attend study appointments and eight people (1%) were withdrawn during the study visit. Seventy-two participants (13%) completed the study. Sixty-one 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).

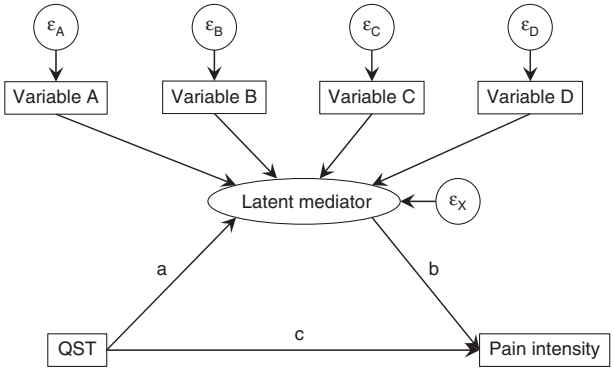

Fig. 2: Mediation model including latent psychosocial mediating variable. Path c represents the direct effect between the independent and dependent variables. Paths a and b represent the indirect path between the independent and mediator variables (path a), and between the mediator and dependent variables (path b). ε = error term; QST = quantitative sensory testing.

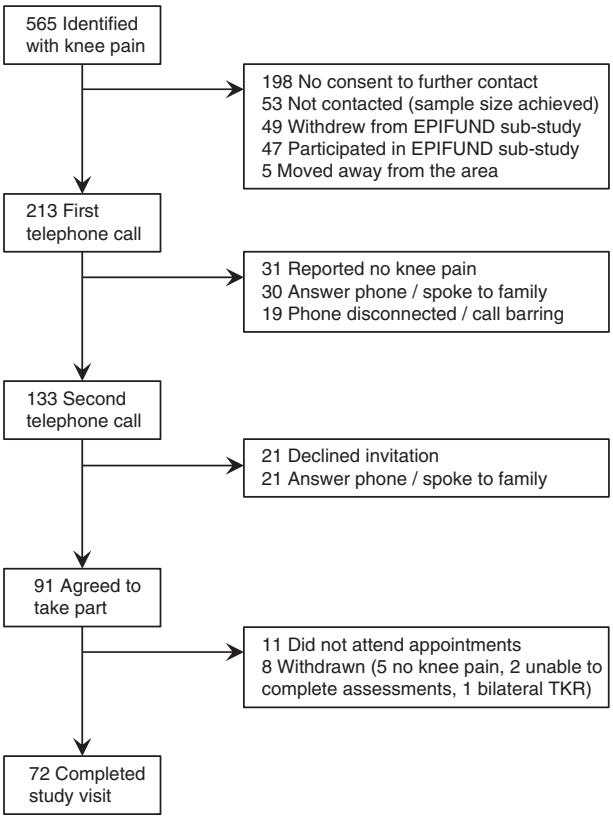

Fig. 3: Recruitment flowchart.

3.2 Participant characteristics

The median BMI of the 61 participants was 27.7 (IQR 26–30.7; 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 0–2) 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 dynamic mechanical allodynia (DMA) (which were identical at both test sites), the median thresholds for cold pain, mechanical pain sensitivity (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 1–6) and depression (5; IQR 2–8) 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 seven cases of anxiety, and eight borderline and three cases of depression were identified using the HAD sub-scale cut-offs (Table 2) [18]. Median scores of 3 (IQR 1–2), 1 (IQR 1–3) and 3 (IQR 2–5) 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 2–5); timeline (8; IQR 4–10; inversely scored); personal control (5; IQR 3–7; inversely scored); treatment control (5; IQR 2–7; inversely scored); identity (2; IQR 1–4); concern (4; IQR 2–7); coherence (2; IQR 1–5); emotion (3; IQR 1–4). A median score of 4 (regular underactive; IQR 4–5) was observed for the RAPA.

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

Variable (observed range)	*n* = 61
Females (%)	36 (59.0%)
Age (years; median [IQR])	64 (56–69)
BMI (kg/m²; median [IQR])	27.7 (26–30.7)
Outcome measures	
Global pain intensity (0–10 NRS)	5 (3–7)
Tested knee pain intensity (0–10 NRS)	5 (3–7)
Central QST	
Tender point (0–18)	0 (0–2)
Knee temporal summation (≥1)	1 (0.8–1.48)
Forearm temporal summation (≥1)	2 (1.42–2.67)
Knee QST	
Cold pain (0–32.0 °C)	0 (0–0.8)
Heat pain (32.0–50 °C)	48.33 (45.3–50)
Mechanical pain (0–512 mN)	90.51 (42.22–174.18)
MPS (0–100 NRS)	2.49 (0.86–5.97)
DMA (0–100 NRS)	0 (0–1)
Vibration (0–8)	4.33 (3.33–5.33)
Pressure pain (0–10 kg/cm²)	5.6 (3.4–7.3)
Forearm QST	
Cold pain (0–32.0 °C)	1.3 (0–14.3)
Heat pain (32.0–50 °C)	47.03 (45.1–48.57)
Mechanical pain (0–512 mN)	45.25 (21.11–105)
MPS (0–100 NRS)	2.97 (0.94–7.17)
DMA (0–100 NRS)	0 (0–0.2)
Vibration (0–8)	6 (5.33–6.67)
Pressure pain (0–10 kg/cm²)	3.67 (2.57–5.13)

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.

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

Table 2: Participant characteristics: psychosocial factors.

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

HAD = hospital anxiety and depression scale; PCS = pain catastrophising 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**[a]
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; [a]$p < 0.0029$ (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.

knee. Knee and forearm MPS, and DMA at the knee were also significantly positively correlated with higher pain intensity at the tested knee.

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 five 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 catastrophising) were all significantly positively correlated with tender point count, MPS at the knee and forearm and DMA at the knee.

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).

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**[a]	**0.3374**	**0.3550**	**0.2850**
Helplessness	**0.330**	**0.3946**[a]	**0.3548**	0.2259
IPQ-brief				
Consequences	**0.452**[a]	**0.3833**[a]	**0.3237**	**0.2839**
Timeline	**0.323**	**0.3820**[a]	**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**[a]	**0.2777**	0.1980	0.2361
Concern	**0.445**[a]	**0.3676**[a]	**0.2801**	**0.2911**
Coherence	−0.196	0.0029	−0.1074	0.0577
Emotion	**0.406**[a]	**0.3185**	**0.3391**	0.1652
Physical functioning				
RAPA	**−0.311**	−0.1339	−0.0600	−0.0839

$p < 0.05$ for values in bold; [a]$p < 0.0036$ (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 catastrophising 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)[a]	SE	Z	Proportion of total effect mediated (95% CI)
Tender point count → global pain intensity				
Total effect	**0.47 (0.18, 0.75)**	0.144	3.24	–
Concern				
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 × 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 × 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 × 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 × b)	**0.16 (0.01, 0.31)**	0.075	2.13	
Knee MPS → global pain intensity				
Total effect	**0.12 (0.05, 0.20)**	0.038	3.26	–
Concern				
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 × 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 × 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 × 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	–
Consequences				
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 × 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 × b)	**0.04 (0.00, 0.07)**	0.018	2.16	

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

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; Fig. 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 × path b; Fig. 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 subscales 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.

The inclusion of psychosocial factors loaded on to a latent mediator rather than individual items (Fig. 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).

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, MPS and DMA) at the knee and forearm were associated with greater levels of self-reported

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

	β (95% CI)[a]	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 × 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 × 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 × 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 × 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 × 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; SE = standard error; Z = Z-score; MPS = mechanical pain sensitivity; DMA = dynamic mechanical allodynia. [a]$p < 0.05$ if bold.

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, 25]. Within-person associations between increased pain severity and measures of pressure pain and temporal summation have been identified in one study [26]; however, the sample size was much larger ($n = 2126$) and the temporal summation methodology applied for a longer time period (30 s), which may account for the lack of association in 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 [25]. 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 [25]. 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. [26] posits that sensitisation is a trait already present with patients with knee OA and is not a consequence of joint pathology: 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 catastrophising 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 catastrophising explains a proportion of that association [27]. However, the study did not perform QST assessments [27]. The present study identified measures of catastrophising 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 [7, 28, 29]. However, pain-free controls may not be an appropriate comparator for people with chronic pain. Psychosocial factors such as depression, anxiety, pain catastrophising 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 [25], or pain severity [7, 8], or have used patients with inflammatory arthritis as a comparator group [30, 31]. 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. [32] 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 [32].

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 h [7, 33] and current pain [25, 34]. 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 [35]; 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.

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