Osteoarthritis and Cartilage 28 (2020) 173–181

Osteoarthritis and Cartilage

Baseline self-report 'central mechanisms' trait predicts persistent knee pain in the Knee Pain in the Community (KPIC) cohort

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ARTICLE INFO

Article history:
Received 5 April 2019
Accepted 18 November 2019

Keywords:
Knee pain
Central pain mechanisms
Outcome measures
Quantitative sensory testing
Phenotypes

SUMMARY

Objectives: We investigated whether baseline scores for a self-report trait linked to central mechanisms predict 1 year pain outcomes in the Knee Pain in the Community cohort.
METHOD: 1471 participants reported knee pain at baseline and responded to a 1-year follow-up questionnaire, of whom 204 underwent pressure pain detection thresholds (PPTs) and radiographic assessment at baseline. Logistic and linear regression models estimated the relative risks (RRs) and associations (β) between self-report traits, PPTs and pain outcomes. Discriminative performance for each predictor was compared using receiver-operator characteristics (ROC) curves.
Results: Baseline Central Mechanisms trait scores predicted pain persistence (Relative Risk, RR = 2.10, $P = 0.001$) and persistent pain severity ($\beta = 0.47$, $P < 0.001$), even after adjustment for age, sex, BMI, radiographic scores and symptom duration. Baseline joint-line PPTs also associated with pain persistence (RR range = 0.65 to 0.68, $P < 0.02$), but only in univariate models. Lower baseline medial joint-line PPT was associated with persistent pain severity ($\beta = -0.29$, $P = 0.013$) in a fully adjusted model. The Central Mechanisms trait model showed good discrimination of pain persistence cases from resolved pain cases (Area Under the Curve, AUC = 0.70). The discrimination power of other predictors (PPTs (AUC range = 0.51 to 0.59), radiographic OA (AUC = 0.62), age, sex and BMI (AUC range = 0.51 to 0.64), improved significantly ($P < 0.05$) when the central mechanisms trait was included in each logistic regression model (AUC range = 0.69 to 0.74).
Conclusion: A simple summary self-report Central Mechanisms trait score may indicate a contribution of central mechanisms to poor knee pain prognosis.

Introduction

One quarter of individuals aged over 55 have chronic knee pain, often due to osteoarthritis (OA)[1]. Knee pain might be due to structural changes or inflammation linked to OA within the affected knee (peripheral mechanisms). However, previous experimental and therapeutic studies have demonstrated that knee pain is often intensified by processing of afferent signals by the central nervous system (central mechanisms)[2–5]. Identification of underlying pain mechanisms is important for optimal management of chronic knee pain, and for predicting responses to existing therapies[6].

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https://doi.org/10.1016/j.joca.2019.11.004

Quantitative Sensory Testing (QST) modalities such as pressure pain detection thresholds (PPT), and imaging- (e.g., functional magnetic resonance imaging, fMRI) provide methods for assessing central mechanisms of knee pain[2]. Low PPT scores distal to the affected joint in people with OA have been associated with central sensitization[2]. However, employing PPT or brain imaging would be resource-intensive during normal clinical encounters. Thus, there is need for a clinically feasible screening tool that identifies contributions to knee pain from the central nervous system. Such a screening tool might inform mechanism-based treatment for individuals with knee pain[6]. Self-report traits of anxiety[7,8], depression[7,8], catastrophizing[7,9], neuropathic-like pain[7,10], fatigue[7,11], sleep disturbance[7,9], pain distribution[7], and cognitive impact[7] each is associated with pain intensity and clinical and experimental markers for central pain mechanisms in individuals reporting knee pain. In a previous study, we demonstrated that 8 self-report items, each measuring one of these characteristics, contribute to a single latent 'Central Mechanisms' trait[7]. This Central Mechanisms trait was associated with pressure pain detection thresholds (PPTs) at a distal site in individuals with knee pain, an index of central sensitization[7].

Knee pain might either resolve or persist over time. Knee pain persistence after therapeutic intervention is weakly predicted by structural factors within the knee, including radiographic OA and ultrasound effusion[12]. Other characteristics have also been found to predict worse pain at follow up, particularly after surgical intervention. These include high Body Mass Index (BMI)[13], longer duration of pain[14], PPT, and self-report traits[3,4,15]. However, possible associations of central mechanisms with knee pain prognosis in non-surgical contexts have been less thoroughly explored[14]. In comparison to these different demographic and disease specific predictors, self-report measures of central mechanisms might more accurately predict how knee pain might change over time across individuals. Their measurement might help to improve knee pain prognosis by identifying individuals who might benefit from interventions aiming to reduce central sensitisation.

We hypothesized that: (i) baseline scores for a self-report Central Mechanisms trait predict worse pain outcomes (pain persistence or persistent pain severity) at 1-year follow-up in people with knee pain more strongly than any single component characteristic, and; (ii) the prognostic performance of the Central Mechanisms trait is superior to predictors of unfavourable pain prognosis such as radiographic evidence of OA pathology[3,4,13–15].

Methods

Study population

This study is a secondary analysis of the Nottinghamshire community-based Knee Pain and related health In the Community (KPIC) cohort study[26].

Participants aged 40 years or older provided baseline and year 1 follow-up data within, as shown in Fig. 1.

Out of 2512 participants reporting current knee pain at baseline, 1471 responded to the Knee Pain In the Community (KPIC) survey at 1-year follow-up. A subset of participants reporting knee pain for $\leq$3 years ($n = 219$) or >3 years ($n = 103$) at baseline underwent PPT and radiographic assessments[26]. According to our power analyses, to achieve 90% power with 5% type 1 error, 203 participants were required for logistic regression analyses between pain persistence and two covariates in the model, assuming a multiple correlation coefficient of 0.3 between covariates[26].

The KPIC study protocol (clinicaltrials.gov portal: NCT02098070) was approved by the Nottingham Research Ethics Committee 1 (NREC Ref: 14/EM/0015) and all participants provided informed written consent.

Self-reported questionnaires

Presence of knee pain at baseline was determined by response to the question: "Have you had knee pain for most days of the past month?"[16]. Persistence or resolution of knee pain over the past year was determined by response to the question: "In the past 12 months, have you had any pain in or around a knee on most days for at least a month?"[17]. Knee pain severity, reported by individuals with pain at each time point, was determined by response to the 11- point numerical rating scale (NRS) question: "In the past month, how intense was your 'worst knee pain' rated on a 0–10 scale, where 0 is 'no pain' and 10 is 'pain as bad as could be'?[18] Participants reporting knee pain indicated the affected knee if unilateral, or the worst affected knee if bilateral. Individuals reporting knee pain at baseline, but no knee pain at follow-up, were classified as a 'resolved pain' group, and those reporting knee pain at follow-up were classified as a 'pain persistence' group.

The KPIC survey at both baseline and follow-up included established self-report questionnaires for neuropathic-like pain (painDETECT modified for use in people with knee OA)[18], intermittent and constant OA knee pain (ICOAP)[19], catastrophic thinking (Pain Catastrophizing Scale [PCS])[20], and anxiety and depression (Hospital Anxiety and Depression Scale [HADS])[21]. Fatigue, cognitive impact[22], and pain distribution[23] were each measured by single items. Rasch transformed questionnaire scores were used when previously validated in knee pain cases (painDETECT and ICOAP)[24,25], otherwise original published protocols for scales were followed.

Central mechanisms trait score

The Central Mechanisms trait score was derived from 8 items (Supplementary Table 1) representative of the individual component self-report traits measuring anxiety, catastrophizing, cognitive impact, depression, fatigue, neuropathic-like pain, pain distribution and sleep[7]. Reverse worded items were coded so that higher scores represented greater pain or distress. Previous work established that these 8 items contributed significantly to one factor, interpreted as "central pain mechanisms". Together these items showed good internal consistency. Raw scores were linearly transformed to achieve a possible score range for each item of 0–3. Pain distribution classified as "pain below the waist additional to knee pain" was captured using areas shaded by the participant on a body manikin[7]. For each participant, a summary score for the Central Mechanisms trait (out of 24) was derived by summating transformed scores from each of the 8 self-report items.

Pressure pain detection threshold (PPT) and radiographic assessment

PPT and radiographic assessment were measured as described within the KPIC study protocol[26]. Intra-rater and inter-rater agreements for PPT scores used in this study have previously been published[7], and concordance correlation coefficients (CCC) were moderate (Intra-rater CCC range = 0.51 to 0.86; Inter-rater CCC range = 0.39 to 0.90). Raw PPT values were logarithmically transformed before statistical analysis to achieve normality of the data, and normality confirmed using the Shapiro–Wilk test.

In this study, established radiographic OA (KL score $\geq$3), defined as "definite osteophytes and definite narrowing of joint space" within the tibiofemoral joint[27], was used for the main analysis. The Nottingham Derived Line Atlas (NDLA) approach, which classifies

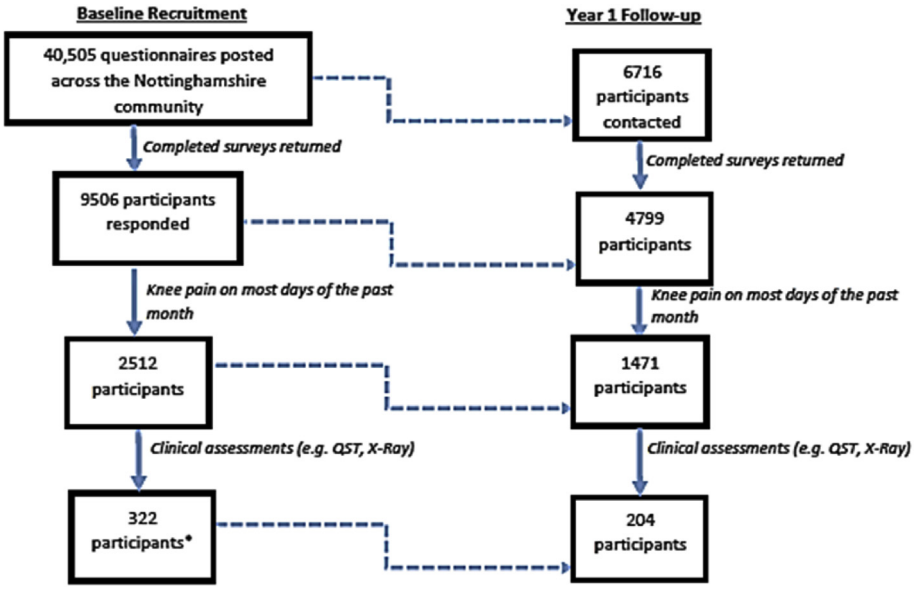

Fig. 1. Kpic baseline and 1-year follow-up recruitment flowchart. Survey and clinical assessment data from participants reporting knee pain on most days of the past month either at (i) baseline or (ii) at baseline and year 1 follow up, were assessed in this study. *At baseline, 322 participants with knee pain underwent PPT and radiographic assessment (these included (i) 219 participants with early knee pain for ≤3 years who were selected at random from the respondents consenting to further contact; and (ii)103 participants with established knee pain for >3 years who were age- and gender- matched to the early knee pain group). Of these, 204 (134 participoants with early knee pain at baseline, and 70 participants with established knee pain at baseline) responded to the year-1 questionnaire.

knee OA as definite JSN and definite osteophyte in any compartment[28], was used in secondary analyses. Intra- and inter-rater agreements for classification of radiographic OA and radiographic scoring were substantial (Supplementary Table 2).

Data analysis

Analyses were performed using Stata, version 14.2[29]. Between-group comparisons used Student t test and, where appropriate, 95% confidence intervals (CIs) are presented. All analyses used complete case data because of low levels of missing data (<5%).

Central mechanisms trait at baseline as a predictor of pain outcomes at 1 year follow-up

Presence/absence of pain persistence (pain present at baseline and year 1) served as the primary pain outcome. In those reporting pain persistence, persistent pain severity (residualized pain severity change scores) served as the secondary pain outcome. Residualized change score (RCS) adjusts the portion of change in pain between baseline and 1 year follow-up that could have been predicted linearly from the baseline scores[30,31]. RCS was derived from the following formula: RCS = (Y-MY) - b(X-MX), where Y = Pain score for individual at follow-up; MY = Mean score for knee pain group at follow-up; X = Pain score for individual at baseline; MX = Mean score for knee pain group at baseline; b = Regression coefficient for regressing Y onto X.

Pain outcomes were entered into regression models as the dependent variable, with baseline scores serving as the independent variable. Univariate logistic regression models were employed to assess and compare relationships between baseline scores and persistence of knee pain. To ease interpretation, we used the Stata "oddsrisk" command to convert odds ratios to risk ratios (RR) with associated CIs[32]. For participants reporting persistent knee pain, associations between RCS for knee pain severity serving as the dependent variable, and baseline scores serving as the independent variable, were tested using linear regression models. Associations for linear regression models are presented as standardized regression coefficients (β). Estimates are presented from crude models, and from fully adjusted models which accounted for other predictors shown here or in previous studies to be associated with knee pain persistence (including age, sex, BMI, radiographic OA, and symptom duration)[3,4,12]. Spearman (r) and eta (η) CCC for univariate associations are also presented.

Where both knees were measured during clinical assessment (radiographic and PPT assessment), scores from the index knee were employed.

Prognostic characteristics of the central mechanisms trait

The performance of the latent Central Mechanisms trait and other baseline predictors in discriminating between pain persistence cases and resolved pain cases was assessed using Receiver-operator-characteristic (ROC) curves. Univariate logistic regression models were used to estimate and compare the area under the receiver-operator characteristics (ROC) curve (AUC) for the self-report Central Mechanisms trait, as well as for other predictors[33]. Further ROC analyses sought to establish incremental validity by assessing whether the Central Mechanisms trait contributed significantly to univariate models for other predictors of pain persistence[34]. To test for incremental validity, the Central Mechanisms trait score was entered sequentially into logistic regression models for each predictor.

Results

Participant characteristics

The study population comprised KPIC participants with knee pain at baseline who responded to 1-year follow-up (n = 1471, mean (SD) age = 62 (10) years, BMI = 28.9 (6.0) kg/m^2, 60% female). As expected because of their selection criteria, participants who underwent radiographic and PPT assessment (n = 204) were slightly younger and reported having had knee pain for a shorter duration, but otherwise did not significantly differ from the total study population (Table I).

Across all participants with knee pain at baseline ($n = 1471$), higher baseline Central Mechanisms trait scores were associated with longer symptom duration ($r = 0.14$, $P < 0.0001$, older age ($r = -0.12$, $P < 0.0001$), female sex ($\eta = 0.30$, $P < 0.001$) and higher BMI ($r = 0.27$, $P < 0.0001$). In those who underwent radiographic and PPT assessment ($n = 204$), higher baseline Central Mechanisms trait scores were associated with lower PPT at each anatomical site (range $r = -0.21$ to -0.37, $P < 0.05$) and with radiographic OA ($\eta = 0.37$, $P = 0.034$)(Supplementary Table 3).

Prediction of knee pain persistence

Knee pain persistence at 1 year was reported by 976 (66%) participants, of whom 133 had radiographic and PPT assessments at baseline. Compared to participants reporting pain resolution at 1-year follow-up ($n = 476$), those with pain persistence ($n = 976$) had significantly higher baseline self-report Central Mechanisms trait score, longer symptom duration and higher BMI (Table II). Associations between Central Mechanisms trait and pain persistence were also demonstrated in the subgroup of participants who underwent radiographic and PPT assessment ($n = 204$, RR = 2.14, 95%C.I. 1.49,3.08, $P = 0.001$). In this subgroup ($n = 204$), pain persistence was also associated with lower baseline PPT at the medial joint line (RR = −0.65, 95%C.I. 0.47, 0.89, $P = 0.009$) and lateral joint line (RR = −0.68, 95%C.I. 0.49, 0.93, $P = 0.017$) of the index knee, and with the presence of radiographic OA (RR = 1.69, 95%C.I. 1.40, 1.85 $P = 0.001$)(Table II).

Prediction of pain persistence by Central Mechanisms trait score remained significant after adjustment for age, sex, BMI, radiographic OA, and symptom duration (RR = 2.10, 95%C.I. 1.36, 3.25, $P = 0.001$, Table III). Self-report traits of neuropathic-like symptoms, catastrophizing, anxiety, depression, cognitive impact and pain distribution also significantly predicted knee pain persistence in models adjusted for demographic variables, radiographic OA and symptom duration (range RR = 1.58 to 2.17, $P < 0.02$, Table III). Baseline PPTs did not significantly predict pain persistence after adjustment for demographic variables, radiographic OA and symptom duration (range RR = 0.78 to 0.99, $P > 0.25$, Table III). OA classification using KL score ≥2 or using the NDLA produced similar findings to those obtained using KL score ≥3 (Supplementary Table 4).

Prediction of persistent pain severity

Individuals with knee pain persistence ($n = 976$) rated their persistent knee pain severity in the past month at 1 year follow up as median 6 (IQR 4 to 8, possible range 0–10). Higher baseline Central Mechanisms trait scores were associated with higher RCSs for increasing pain severity in people with persistent knee pain ($n = 1471$, $\beta = 0.47$, 95%C.I. 0.42,0.53, $P < 0.001$, Table II). Associations between baseline Central Mechanisms trait and increasing pain severity in people with persistent knee pain were also demonstrated in the subgroup of participants who underwent radiographic and PPT assessment ($n = 133$, $\beta = 0.58$, 95%C.I. 0.39,0.76, $P < 0.001$). In this subgroup, RCS for increasing persistent knee pain severity also was positively associated with lower baseline PPT at the medial joint line (β = -0.27, 95%C.I. −0.46, −0.07, $P = 0.009$) and lateral joint line (β = -0.27, 95%C.I. −0.50, −0.08, $P = 0.003$) of the index knee, although association with the presence of radiographic OA did not reach statistical significance ($\beta = 0.18$, 95%C.I. −0.03, 0.36 $P = 0.054$) (Table II).

The relationship between baseline Central Mechanisms trait and persistent knee pain severity remained significant in models adjusted for age, sex, BMI, radiographic OA, and symptom duration ($\beta = 0.46$; $P < 0.001$, Table III). After adjustment for demographic variables, radiographic OA and symptom duration, persistent pain severity was also significantly predicted by self-report traits of

Table I
Participant characteristics at baseline

	Total knee pain sample ($n = 1471$)	Radiographic and PPT assessed subgroup ($n = 204$)	P
n (%) female	876 (60%)	124 (61%)	0.776
Age; mean ± SD years	**62 ± 10**	**61 ± 10**	**0.018**
BMI; mean ± SD kg/m^2	28.9 ± 6.0	29.5 ± 5.8	0.148
Self-report scores			
Central Mechanisms (possible range 0–24)	8 (5–11)	8 (5–11)	0.539
Modified painDETECT (possible range -1 – 38)	12 (9–14)	11 (9–15)	0.698
Pain Catastrophising Scale (possible range 0–52)	8 (3–19)	8 (3–21)	0.454
Anxiety-HADS (possible range 0–14)	7 (4–10)	6 (4–10)	0.279
Depression-HADS (possible range 0–14)	5 (3–8)	4 (3–7)	0.087
Cognitive Impact*(possible range 0–4)	2 (0–2)	2 (0–2)	0.429
Pain Distribution†,*n (%)	791 (54%)	109 (53%)	0.916
Fatigue*(possible range 0–4)	2 (2–3)	2 (2–3)	0.999
Sleep*(possible range 0–4)	1 (0–2)	1 (0–2)	0.624
Pain in the past month* (possible range 0–10)	4 (2–7)	4 (2–7)	0.891
Symptom duration; years	**10 (4–20)**	**2 (1–3)**	**<0.0001**
Radiography and pressure pain detection thresholds (PPT)			
Radiographic OA (KL scores≥3); n (%)	–	71 (35%)	–
Proximal tibia PPT (kPa)	–	528 (420–678)	–
Sternum PPT (KPa)	–	358 (268–450)	–
Medial Joint Line (KPa)	–	508 (327–692)	–
Lateral Joint Line (KPa)	–	1261 (1043–1451)	–

PPT = Pressure Pain Detection Thresholds.
Data are median (interquartile ranges [IQRs]) except where indicated. Geometric values for log-transformed PPTs are given for all 204 cases.
Questionnaire data are presented where complete data available for questionnaire (Constant-Intermittent and Constant Osteoarthritis Pain scale [ICOAP] $n = 1354$; intermittent-ICOAP $n = 1319$; Anxiety-Hospital Anxiety and Depression scale [HADS] $n = 1431$; Depression-HADS $n = 1439$; Pain Catastrophizing Scale [PCS], $n = 1409$; Modified PainDETECT Questionnaire $n = 1155$ and Central Mechanisms trait score $n = 1300$). For pain persistence outcome, models including self-report traits employ data from individuals reporting knee pain at baseline and responding at 1 year follow-up ($n = 1471$), while models for PPT and radiographic variables employ data from individuals reporting knee pain at baseline and responding at 1 year follow-up who also underwent clinical assessment at baseline ($n = 204$).
For persistent pain severity outcome, models including self-report traits employ data from individuals reporting knee pain both at baseline and at 1 year follow-up ($n = 976$), while models for PPT and radiographic variables employ data from individuals reporting knee pain both at baseline and at 1 year follow-up, who also underwent clinical assessment at baseline ($n = 133$). Rows in bold indicate significant differences between total sample and clinically assessed subgroup ($P < 0.05$).
* Measured by single items.
† Pain Distribution measured on the body pain manikin is coded as present when individual reports knee pain plus, other pain below the waist.

Table II
Participant baseline characteristics and pain persistence or persistent pain severity

	Baseline characteristics			Pain persistence at year 1		Persistent pain severity	
	Resolved pain	Pain persistence	*p*	Unadjusted RR (95% CI)	*p*	Unadjusted B (95% C.I.)	*p*
Female; *n* (%)	277 (58%)	591 (61%)	0.402	1.05 (0.94, 1.17)	0.402	**0.06 (0.001, 0.13)**	**0.048**
Age; mean ± SD years	62 ± 10	62 ± 10	0.643	1.03 (0.92, 1.14)	0.643	0.01 (−0.06, 0.07)	0.830
BMI; mean ± SD kg/m^2	**28.0 ± 5.3**	**29.4 (6.3)**	**0.0001**	**1.29 (1.14, 1.46)**	**<0.001**	**0.18 (0.11, 0.24)**	**<0.001**
Questionnaire Scores	(*n* = 476)	(*n* = 976)		(*n* = 1471)		(*n* = 976)	
Central mechanisms (possible range 0–24)	**6 (4–10)**	**9 (5–11)**	**<0.0001**	**1.73 (1.52, 1.98)**	**<0.001**	**0.47 (0.42, 0.53)**	**<0.001**
Modified painDETECT (possible range -1 – 38)	**4 (2–9)**	**10 (5–16)**	**<0.0001**	**2.32 (1.98, 2.72)**	**<0.001**	**0.35 (0.28, 0.42)**	**<0.001**
Pain Catastrophizing Scale (possible range 0–52)	**5 (2–13)**	**10 (4–22)**	**<0.0001**	**1.65 (1.44, 1.89)**	**<0.001**	**0.47 (0.41, 0.52)**	**<0.001**
Anxiety-HADS (possible range 0–14)	**6 (3–9)**	**7 (4–11)**	**<0.0001**	**1.30 (1.16, 1.46)**	**<0.001**	**0.26 (0.19, 0.32)**	**<0.001**
Depression-HADS (possible range 0–14)	**4 (2–7)**	**5 (3–8)**	**<0.0001**	**1.47 (1.30, 1.66)**	**<0.001**	**0.29 (0.24, 0.36)**	**<0.001**
Cognitive Impact* (possible range 0–4)	**1 (0–2)**	**2 (1–2)**	**<0.001**	**1.45 (1.29, 1.63)**	**<0.001**	**0.36 (0.30, 0.42)**	**<0.001**
Pain Distribution‡,**n* (%)	**0 (0–1)**	**1 (0–1)**	**<0.001**	**1.26 (1.13, 1.40)**	**<0.001**	**0.12 (0.05, 0.18)**	**<0.001**
Fatigue*(possible range 0–4)	**2 (2–3)**	**2(2–3)**	**<0.001**	**1.27 (1.13, 1.42)**	**<0.001**	**0.22 (0.16, 0.29)**	**<0.001**
Sleep*(possible range 0–4)	**0 (0–1)**	**1 (0–2)**	**<0.001**	**1.90 (1.66, 2.19)**	**<0.001**	**0.56 (0.51, 0.61)**	**<0.001**
Symptom duration*,†; years (possible range 0–79)	**7 (2–17)**	**11 (5–22)**	**0.013**	**1.17 (1.03, 1.32)**	**0.013**	0.06 (−0.01, 0.13)	0.102
PPT and radiographic OA	(*n* = 85)	(*n* = 118)		(*n* = 204)		(*n* = 133)	
Proximal tibia PPT (kPa)	561 (518–609)	513 (473–555)	0.123	0.79 (0.58, 1.07)	0.125	−0.18 (−0.39, 0.02)	0.083
Sternum PPT (KPa)	365 (337–399)	337 (308–369)	0.214	0.82 (0.61, 1.12)	0.214	−0.16 (−0.37, 0.04)	0.110
Medial Joint Line (KPa)	**523 (469–589)**	**407 (358–469)**	**0.008**	**0.65 (0.47, 0.89)**	**0.009**	**−0.27 (-0.46, -0.07)**	**0.008**
Lateral Joint Line (KPa)	**1299 (1236–1380)**	**1188 (1130–1249)**	**0.015**	**0.68 (0.49, 0.93)**	**0.017**	**−0.27 (-0.50, -0.08)**	**0.007**
Radiographic OA (KL scores≥3); *n* (%)	**6 (14%)**	**37 (86%)**	**<0.001**	**1.69 (1.40, 1.85)**	**0.001**	0.18 (−0.03, 0.36)	0.054

Rows in bold indicate significant associations ($P < 0.05$).
Baseline characteristics data are median (interquartile ranges [IQRs]) except where indicated, and standardised coefficients for Risk Ratio (RR) and beta (β) are reported. Geometric values of pressure pain detection thresholds (PPTs) are presented.
Questionnaire data are presented where complete data available for questionnaire (Constant-Intermittent and Constant Osteoarthritis Pain scale [ICOAP] $n = 1354$; intermittent-ICOAP $n = 1319$; Anxiety-Hospital Anxiety and Depression scale [HADS] $n = 1431$; Depression-HADS $n = 1439$; Pain Catastrophizing Scale [PCS], $n = 1409$; Modified PainDETECT Questionnaire $n = 1155$ and Central Mechanisms trait score $n = 1300$).
For pain persistence outcome, models including self-report traits employ data from individuals reporting knee pain at baseline and responding at 1 year follow-up ($n = 1471$), while models for PPT and radiographic variables employ data from individuals reporting knee pain at baseline and responding at 1 year follow-up who also underwent clinical assessment at baseline ($n = 204$).
For persistent pain severity outcome, models including self-report traits employ data from individuals reporting knee pain both at baseline and at 1 year follow-up ($n = 976$), while models for PPT and radiographic variables employ data from individuals reporting knee pain both at baseline and at 1 year follow-up, who also underwent clinical assessment at baseline ($n = 133$).
* Measured by single items.
† Risk ratio for pain persistence per annual increase in symptom duration.
‡ Pain Distribution measured on the body pain manikin was coded as present when individual reported knee pain plus other pain below the waist.

catastrophizing, anxiety, depression, and cognitive impact (range $\beta = 0.23$ to 0.63, $P < 0.035$), and by medial joint line PPTs ($\beta = -0.29$, $P = 0.013$)(Table III). OA classification using KL score≥2 or using the NDLA produced similar findings to those obtained using KL score≥3 (Supplementary Table 4).

Prognostic characteristics of the central mechanisms trait

ROC curves demonstrated good performance of baseline scores for the Central Mechanisms trait in distinguishing pain persistence cases from resolved pain cases in an unadjusted logistic regression model (AUC = 0.70; 95%C.I. = 0.60,0.77; $n = 1471$). The performance of the Central Mechanisms trait model was further improved when it was adjusted for age, sex, BMI, symptoms duration, and radiographic OA (AUC = 0.77; 95%C.I. = 0.71,0.85; $n = 204$, $P = 0.007$)(Fig. 2).

The performance of other predictors, including age, sex, BMI, PPTs and radiographic OA, in distinguishing pain persistence cases from resolved pain cases, was each improved significantly ($P < 0.05$) when the Central Mechanisms trait was included in each logistic regression model (AUC range = 0.69 to 0.74, Table IV).

Discussion

In this cohort of 1471 individuals with knee pain at baseline, 66% reported knee pain persistence at 1-year follow-up. Knee pain persistence and persistent knee pain severity were predicted by the self-report Central Mechanisms trait, derived from 8 component characteristics (anxiety, depression, catastrophizing, neuropathic-like pain, fatigue, sleep disturbance, pain distribution, and cognitive impact). The prognostic performance of the Central Mechanisms trait was superior to that of other demographic and clinical factors, including measures of any of the 8 component characteristics or radiographic evidence of OA pathology.

We have previously shown in a cross-sectional analysis of KPIC participants with knee pain that the 8 self-report items used here together defined a single latent trait, and were significantly associated with QST evidence of central sensitisation (reduced PPT at anatomical sites away from the affected joint)[1]. Previous interventional studies have also found that pain outcomes can be predicted by self-report measures of psychological distress[15,35], and experimental QST indices of central pain mechanisms[3,4]. Our findings indicate that pain outcome prediction by these characteristics might be explained, at least in part, by a shared Central Mechanisms trait. Additional characteristics of cognitive impact, catastrophizing, sleep disturbance, fatigue, neuropathic-like pain quality and pain distribution each might contribute to this predictive trait. A composite score from self-report items, each addressing one of these 8 characteristics, better predicted pain outcomes than did measures of any single characteristic alone.

Our composite measure of the Central Mechanisms trait predicted cases in whom pain persisted or resolved with an AUC of 0.70. This indicates acceptable discrimination[36], but also suggests that other factors might contribute to pain outcomes. Combining mechanistically discrete factors might further improve pain outcome prediction, as previously found by combining

Table III
Prediction of pain persistence and persistent pain severity at year 1 follow up by baseline self-report traits and PPT in adjusted models*

	Pain persistence at year 1		Persistent pain severity	
	RR (95% CI)	*P*	β (95% CI)	*p*
Traits	($n = 1471$)		($n = 976$)	
Central Mechanism	**2.10 (1.36, 3.25)**	**0.001**	**0.46 (0.25, 0.68)**	**<0.001**
Neuropathic-like symptoms	**2.17 (1.34, 3.49)**	**0.001**	0.23 (−0.01, 0.47)	0.057
Catastrophizing	**1.94 (1.29, 2.93)**	**0.001**	**0.49 (0.32, 0.65)**	**<0.001**
Anxiety	**1.61 (1.01, 2.32)**	**0.011**	**0.39 (0.20, 0.58)**	**<0.001**
Depression	**1.92 (1.22, 3.02)**	**0.005**	**0.23 (0.02, 0.44)**	**0.035**
Cognitive Impact†	**1.60 (1.08, 2.37)**	**0.018**	**0.39 (0.17, 0.62)**	**0.001**
Pain Distribution†,‡	**1.58 (1.14, 2.19)**	**0.006**	0.03 (−0.20, 0.21)	0.964
Fatigue†	1.36 (0.97, 1.92)	0.075	0.11 (−0.11, 0.33)	0.337
Sleep†	**1.98 (1.329, 3.05)**	**0.002**	**0.63 (0.46, 0.80)**	**<0.001**
PPT Scores	($n = 204$)		($n = 133$)	
Proximal tibia PPT (kPa)	0.98 (0.67, 1.43)	0.918	−0.05 (−0.28, 0.17)	0.647
Sternum PPT (KPa)	0.99 (0.67, 1.46)	0.954	−0.07 (−0.29, 0.14)	0.493
Medial Joint Line (KPa)	0.78 (0.51, 1.19)	0.257	**−0.29 (-0.52, -0.06)**	**0.013**
Lateral Joint Line (KPa)	0.79 (0.54, 1.18)	0.263	−0.21 (−0.45, 0.02)	0.067

Rows in bold indicate significant associations ($P < 0.05$).
Standardised coefficients for Risk Ratio (RR) and beta (β) reported.
Variables employ data from individuals reporting knee pain at baseline and responding at 1 year follow-up who also underwent clinical assessment at baseline ($n = 204$).
For pain persistence outcome, models including self-report traits employ data from individuals reporting knee pain at baseline and responding at 1 year follow-up ($n = 1471$), while models for PPT and radiographic.
For persistent pain severity outcome, models including self-report traits employ data from individuals reporting knee pain both at baseline and at 1 year follow-up ($n = 976$), while models for PPT and radiographic variables employ data from individuals reporting knee pain both at baseline and at 1 year follow-up, who also underwent clinical assessment at baseline ($n = 133$).

* Each model in this table displays the relationship between each outcome (presented per column) and each exposure (presented per row), after adjusting for demographic variables (age, sex and BMI), radiographic OA (KL scores≥3) and symptom duration.

† Measured by single items.

‡ Pain Distribution measured on the body pain manikin was coded as present when individual reported knee pain plus other pain below the waist.

demographic and psychological characteristics[13]. Radiographic OA present within the tibiofemoral (AUC = 0.62) or patellofemoral (AUC = 0.53) compartments significantly predicted knee pain persistence, and combining radiographic OA classification with scores for the Central Mechanism trait improved this prediction. Indeed, scores for the Central Mechanisms trait better predicted pain outcomes than did radiographic OA classification. Our findings extend previous evidence that central mechanisms might influence pain intensity over and above effects of radiographic joint damage [38] or disease duration[37].

We found that of the sites investigated by PPT in the current study, only joint line PPT significantly predicted knee pain persistence or severity. Furthermore, PPT predicted pain persistence less strongly (medial joint line PPT AUC = 0.59) than did the Central Mechanisms trait, and prediction of pain persistence by PPT was not statistically significant after adjustment for demographic variables, radiographic OA and symptom duration. Baseline joint line PPTs might also not predict post-arthroplasty pain[40], although another study found that PPT both at sites local to, and remote from the affected knee predicted pain severity[39]. Joint line PPTs may be influenced both by peripheral and by central sensitisation, whereas PPT at sites away from the affected joint is more likely to reflect central than peripheral sensitisation[5]. That peripheral sensitisation may contribute to poor pain prognosis is also suggested by pain prediction by radiographic OA classification, and by ultrasound evidence of synovitis[41]. Future studies should explore whether treatments to reduce peripheral sensitisation (e.g., by inhibiting inflammation or blocking nerve growth factor) can reduce knee

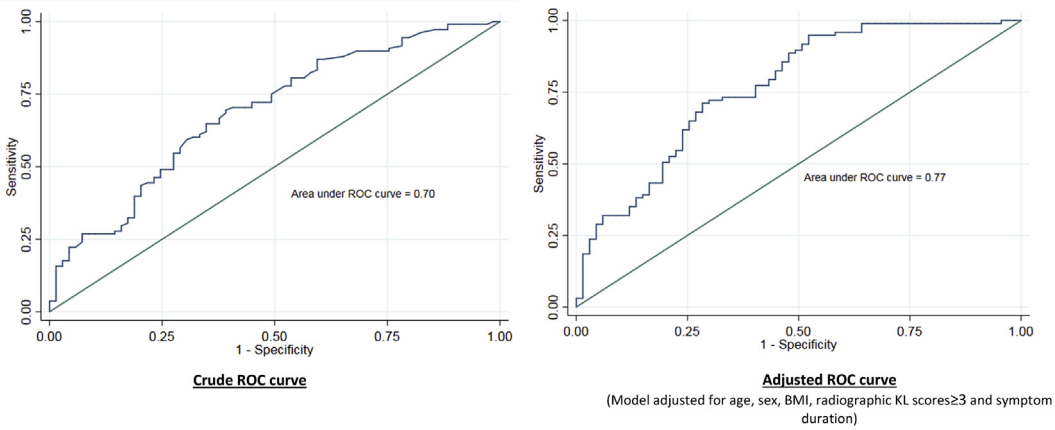

Fig. 2. Receiver operating characteristic (roc) curve for prediction of pain persistence by central mechanisms trait scores in unadjusted and adjusted models. Area Under the Curve (AUC) for crude (unadjusted) model, and for a model adjusted for study covariates (age, sex, BMI, radiographic KL ≥3 and symptom duration) presented. Analyses performed across individuals who underwent radiographic and QST assessment at baseline (n=204).

Table IV
Central Mechanisms trait score improves performance of clinical predictors for pain persistence at 1 year-follow up

Predictors	AUC (95% CI)		
	Predictor only AUC (95% CI)	Predictor + Central Mechanisms trait score AUC (95% CI)	*P* value
Age	**0.53 (0.44, 0.62)**	**0.71 (0.63, 0.79)**	**0.001**
Sex	**0.51 (0.44, 0.59)**	**0.70 (0.61; 0.77)**	**0.001**
BMI	**0.64 (0.56, 0.72)**	**0.72 (0.64, 0.80)**	**0.038**
Symptom duration	0.62 (0.54, 0.71)	0.70 (0.62, 0.78)	0.108
Radiographic OA	**0.62 (0.57, 0.68)**	**0.73 (0.65, 0.80)**	**0.001**
Proximal Tibia PPT	**0.55 (0.44, 0.66)**	**0.70 (0.59, 0.79)**	**0.025**
Sternum PPT	**0.51 (0.40, 0.62)**	**0.62 (0.58, 0.79)**	**0.014**
Medial Joint Line PPT	**0.58 (0.48, 0.69)**	**0.70 (0.59, 0.79)**	**0.046**
Lateral Joint Line PPT	**0.54 (0.43, 0.65)**	**0.69 (0.59, 0.79)**	**0.022**

AUC – Area Under the Curve.
Analyses performed across individuals who underwent radiographic and QST assessment at baseline ($n = 204$). Rows in bold indicate significant improvement in model following inclusion of Central Mechanisms trait ($P < 0.05$).

pain persistence, as well as relieving current pain[42]. Prediction of pain outcomes by the Central Mechanisms trait in the current study remained significant after adjustment for PPT scores, suggesting that central mechanisms additional to those indicated by PPT contribute to pain outcomes. Such mechanisms might include dysregulated descending pain modulation[43].

This study has several limitations. We employed only one QST modality (PPT) and dynamic modalities such as temporal summation[37], might have greater potential to predict knee pain outcomes. PPT assessments displayed limited reliability[44,45] and wide CIs, suggesting uncertainty of the PPT point estimates[7]. PPT may be influenced by factors other than central sensitisation, such as participant reporting styles, attention, participant–researcher interactions, and also peripheral sensitisation. Further work is needed to confirm the nature of the relationship between reliable estimates of sensitization and the Central Mechanisms trait discussed in this study. However, we show that self-report items have potential to identify in clinical practice people whose pain is augmented by central mechanisms, where special skills or equipment required for reliable estimation of sensitization might not be available.

Our findings help achieve the aim of the KPIC project to identify knee pain phenotypes and risk factors for knee pain progression[26]. However, only a subpopulation of the KPIC cohort underwent radiography and PPT. Participant selection was weighted towards an early knee pain sample (younger and shorter symptom duration), although other measured characteristics did not differ significantly from the overall study population. We adjusted all models for age and symptom duration, but it remains possible that pain prognosis would be predicted differently in later stages of knee pain and OA. Our measure of Central Mechanisms trait requires validation in an external study population, and across different clinical and community settings. We used several different radiographic classification thresholds, including the NDLA which addresses patellofemoral changes. However, other radiographic or imaging criteria might better predict knee pain outcomes. Our Central Mechanisms trait score was derived as a summary score across 8 items embedded within validated questionnaires administered as a questionnaire booklet[7]. Future work should determine whether these 8 items alone, when standardised within a simple composite tool, will also predict pain outcomes, either in cohort studies or in response to treatment. Future work should also determine whether other factors not investigated in this study, such as socioeconomic factors, can predict worse pain outcomes in people with knee pain, over and beyond the performance of the Central Mechanisms trait.

In conclusion, we show that a single overall Central Mechanisms trait represented by items addressing 8 individual phenotypic traits, predicts pain persistence and persistent pain severity in people with knee pain. Future research should determine whether a central mechanisms questionnaire can predict treatment responses in people with knee pain, and in other chronic pain conditions where central mechanisms are at play[46]. Such a questionnaire might help identify those destined to experience a poor pain prognosis in the absence of specific intervention, and might indicate central mechanisms that could benefit from non-pharmacological (e.g., cognitive behavioural therapy) or centrally acting pharmacological treatment.

Author contributions

Study conception and design: KAA, DMcW, EF and DAW. KPIC cohort study design: DAW, MD, AV and GSF. KPIC clinical data collection: NF, LM and JS. Radiograph grading: GSF and AS. Statistical analysis: KAA. Data interpretation: KAA, DMcW, EF and DAW. All authors critically reviewed and edited the manuscript and approved the final version.

Role of the funding source

Versus Arthritis UK (Centre initiative grant number = 20777), and University of Nottingham as sponsor and host institution. Study sponsors had no role in the design and conduct of the study; collection, management, analysis and interpretation of data; and preparation, review or approval of manuscript.

Competing interests

Kehinde Akin-Akinyosoye: None declared.
Aliya Sarmanova: None declared.
Gwen Sascha Fernandes: None declared.
Nadia Frowd: None declared.
Laura Marshall: None declared.
Joanne Stocks: None declared.
Ana Valdes: None declared.
Daniel McWilliams: None declared.
Michael Doherty: None declared.
Weiya Zhang: Consultation fees: AstraZeneca (Lesinurad) and Gruenthal (Lesinurad);
Speaker fees: Husin (Chinese Society of Rheumatology Annual Congress 2016) and Bioberica (EULAR 2016 symposium) in the past 3 years;
Eamonn Ferguson: Royalties: GL assessment for the Paediatric Index of Emotional Distress (PI-ED);
Research grants: Co-investigator on the US Defense Medical Research and Development Program (Study to examine psychological processes in suicidal ideation and behaviour), the ESRC (Individual Differences in the Impact of Socio- Economic Events on

Health and Well-being), the ESRC (Integrating Prospect theory (Framing Effects) and the Common Sense Model of illness to improve medication compliance in glaucoma patients), Chief Scientists Office – Scotland (A randomised controlled trial to test if a simple anticipated regret manipulation leads to a significant increase in organ donor registrations), DEFRA (Overcoming barriers to uptake of best welfare practice by sheep farmers), Pfizer (Pain phenotypes in rheumatoid arthritis: a patient-centred, stratified approach to optimising disease modifying and analgesic treatments), Arthritis UK Research (Pain Centre) that funds the current work, ESRC PhD studentships on reluctant altruism and Schizophrenia and Empathy;

Paid Journal Editorships: Deputy Editor British Journal of Psychology and Associate Editor for Annals of Behavioral Medicine;

Honorariums and expenses paid: Speaker at ISBT, Workshops include (i) Right Patient, Right Place, Right Time: When and How to Use the Emergency Department: Health Literacy, Decision-Making and Communication. Unversita Cattolic del Sacro Cuore. Milan, Italy, April 11th-12th, (ii) Taxometrics, Psychometrics and Clinometrics: Stratified Medicine and Assessing Phenotypes. ESRC Advanced Quantitative Methods National Conference, White Rose DTC, Sheffield University, Sheffield, 24th to 25th July 2014, (iii) Personality: Myths, Misconceptions and Misunderstandings – Implications for Current and Future Medical Education, Selection and Training. INReSH London, 10- 11th November, (iv) ABC (America's Blood Centres) 55th Annual Meeting in Washington (24th to 28th March 2017). Motivation and Innovations in Donor Recruitment, Australian Red Cross Transfusion Update Meeting Sydney 2017 (27th to 28th April). (v) What really motivates people to donate and what can we do with what we find out? Australian Red Cross Transfusion Sydney 2017 (26th April). (vi) What really motivates people to donate and what can we do with what we find out. Address to Sydney Office Staff, Australian Red Cross Transfusion Melburne 2017 (1st May). (vii) What really motivates people to donate and what can we do with what we find out. Address to Melbourne Office Staff;

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Presidential roles (unpaid): co-founding president of the British Society for the Psychology of Individual Differences (BSPID).

David Walsh: Employment: University of Nottingham as Professor of Rheumatology, Director of Arthritis Research UK Pain Centre and Musculoskeletal Theme lead in the NIHR Nottingham Biomedical Research Centre, with honorary consultant appointments with Sherwood Forest Hospitals NHS Foundation Trust and Nottingham University Hospitals NHS Trust. Paid employments include the management of patients with arthritis pain, and developing and delivering on a programme of research aiming to better understand the mechanisms of arthritis pain in order to improve its treatment;

Research grants: Nottingham Hospital Charity N of 1 trial for topical ibuprofen gel and capsaicin cream, NIHR Clinical Research Facility of £2.4 across 5 research themes in Nottingham, NIHR Biomedical Research Centre (musculoskeletal theme) of £23.6 m total award to Nottingham, ERAN Database support, Arthritis Research Campaign Centre Initiative grant Centre of Excellence in Mechanisms of Pain in Arthritis, NIHR Programme: Chronic pain after total knee replacement: better post-operative prevention and management NIHR HTA Sub-Cutaneous Injection of Adalimumab Trial compared with Control (SCIATiC), NIHR HTA Facet Feasibility (FF). Chief Investigator Prof Martin Underwood, University of Warwick, Assessing surgical outcomes for osteoarthritis of the knee following short-term psychological therapy: A single blind feasibility randomised controlled trial;

Funds for staff or department: Consultancy for Pfizer Ltd 2017 undertaken through Nottingham University Consultancy Ltd, providing approximately £3,000 to facilitate staff development within the Arthritis Research UK Pain Centre;

Non-financial interests: Trustee of the Early Rheumatoid Arthritis Network, UK Registered Charity.

Acknowledgements

The authors will like to thank the study participants for the time and effort they contributed towards the study.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.joca.2019.11.004.

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