Traits associated with central pain augmentation in the Knee Pain in the Community (KPIC) cohort

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ABSTRACT

This study aimed to identify self-report correlates of central pain augmentation in individuals with knee pain. A subset of participants (n=420) in the Knee Pain and related health In the Community (KPIC) baseline survey undertook pressure pain threshold (PPT) assessments. Items measuring specific traits related to central pain mechanisms were selected from the survey based on expert consensus, face validity, item association to underlying constructs measured by originating host questionnaires, adequate targeting and PPT correlations. Pain distribution was reported on a body manikin. A `central pain mechanisms' factor was sought by factor analysis. Associations of items, the derived factor and originating questionnaires with PPTs were compared. Eight self-report items measuring traits of anxiety, depression, catastrophizing, neuropathic- like pain, fatigue, sleep disturbance, pain distribution and cognitive impact, were identified as likely indices of central pain mechanisms. PPTs were associated with items representing each trait and with their originating scales. Pain distribution classified as "pain below the waist additional to knee pain" was more strongly associated with low PPT than were alternative classifications of pain distribution. A single factor, interpreted as "central pain mechanisms", was identified across the 8 selected items and explained variation in PPT (R^2 = 0.17) better than did any originating scale (R^2 = 0.10 to 0.13). In conclusion, including representative items within a composite self-report tool might help identify people with centrally augmented knee pain.

Keywords: Knee Pain, Phenotypes, central mechanisms, Quantitative Sensory Testing

INTRODUCTION

Knee pain is a major source of disability, and in people aged over 50 years is most commonly attributed to osteoarthritis (OA).[60] OA pain is perceived as originating from the joint, often associated with structural changes or inflammation, and exacerbated by joint loading and movement. However, OA pain is often troublesome even in the absence of severe radiographic change,[24] and might persist after removal of the peripheral nociceptive drive, with persistent pain being reported by 10-20% of people following total knee replacement for knee OA.[4, 79, 80] Evidence from mechanistic (i.e., experimental pain testing and functional neuroimaging studies)[25, 30, 33, 59, 60, 69] and therapeutic trials,[11, 29] indicate that the central nervous system (CNS) might amplify neural signalling and influence OA knee pain sensitivity, leading to central pain augmentation.[42, 78] Optimal management of OA knee pain therefore requires that underlying pain mechanisms be identified in each individual.[3]

Quantitative Sensory Testing (QST) can indicate changes in pain sensitivity. Pressure pain detection thresholds (PPT) might be reduced at a site of clinical pain, suggesting neuronal sensitization of the affected area. More widespread increased sensitivity at pain-free control sites is suggestive of altered pain processing in the central nervous system.[16, 31] In animal models of OA, pain sensitivity (reduced withdrawal thresholds to punctate stimulation) at a site distal to the affected knee (hindpaw) is characterized by spinal hyperexcitability of neurons innervating sites distal to the affected joint.[23, 56, 63, 64] Furthermore, pain sensitivity distal to the affected joint in people with OA has been associated with changes to descending pain control mechanisms,[33] as has more widespread pain in people with fibromyalgia.[5]

Individual differences in distinct observable traits (phenotypes), measured by questionnaires addressing depression, anxiety, catastrophizing, neuropathic- like pain, or

widespread pain (WSP), have been associated with knee pain severity.[10, 16, 35, 39, 62, 67, 68] Each of these traits might also be associated with markers of central pain mechanisms.[6, 7, 36, 45, 46, 49, 51, 62, 71] High scores on these questionnaires, and low PPTs, have each predicted poor outcome following treatment directed to the painful joint,[2, 59, 60, 79, 80] raising the possibility that treatments directed to central pain mechanisms might be useful for those patients. Using a full battery of existing questionnaires plus PPT measurement would be resource-intensive during normal clinical encounters. A concise composite self-report tool is needed to help identify people with centrally augmented knee pain.

We hypothesise that each of these traits might reflect aspects of central pain mechanisms. By combining evidence from expert opinion and statistical analysis of questionnaire data from a community-based study in people with knee pain, we aimed to identify a concise, yet psychometrically reliable and valid set of self-report questions that measure a phenotypic trait associated with central pain augmentation, as indicated by reduced PPT at the proximal tibia, a site distal to the painful knee.

METHODS

Study Population

Participants, aged ≥40 years provided baseline data within the Nottinghamshire community-based Knee Pain and Related Health in the Community study (KPIC) cohort study.[22] Questionnaires factor structure was confirmed using data from 2,512 participants who reported current knee pain (61 ± 10 years, 57% female). A purposive subset of KPIC participants (n=420) underwent further clinical, PPT and radiographic assessments.[22] This subset comprised people with no knee pain (n=98), or pain for <3 years (n=219) or >3 years (n=103). 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-report questionnaires

Presence of current knee pain was determined by response to the question: "Have you had knee pain for most days of the past one month?"[61, 74]

Participants reporting knee pain indicated the affected knee if unilateral, or the worst affected knee if bilateral.

The KPIC baseline survey included established self-report questionnaires for neuropathic-like pain (painDETECT modified for use in people with knee OA),[39] intermittent and constant osteoarthritis knee pain (ICOAP),[37] catastrophic thinking (Pain Catastrophizing Scale, PCS),[72] and anxiety and depression (Hospital Anxiety and Depression Scale, HADS).[81] Traits of fatigue, cognitive impact,[65] and pain distribution,[40] were each measured by single items. Rasch-transformed questionnaire scores were used when previously validated in knee pain cases (painDETECT, ICOAP),[37, 39] otherwise non-transformed scores were used (HADS, PCS). Items were coded so that higher scores represented greater pain or distress.

Pain distribution was captured using areas shaded by the participant on a body manikin. The manikin was coded according to shading in 7-and 25- topographical areas.[15, 77] Pain distribution was also categorized using American College of Rheumatology Widespread Pain (ACR's WSP) criteria,[77] and based on the presence or absence of pain (i) contralateral to the index knee, (ii) above the waist, (iii) below the waist, or (iv) axial.

Pressure pain detection thresholds

PPT was measured using a hand-held pressure algometer with a circular (1cm^2) padded-tipped probe connected to a computer (HP ProBook 4520s), with outputs computer

analysed by dedicated software (Somedic AB, Sweden). Pressure was applied with a standardised 30kPa/s ramp until the participant indicated by pressing a button, a change from pressure to pain sensation. Participants were familiarised prior to testing by twice PPT testing on a fingernail of the dominant hand. Each PPT testing cycle was conducted at the sternum (3cm caudal to the sternal notch), the medial and lateral tibiofemoral joint lines adjacent to the patellar ligament of each knee, and the proximal tibia (5 cm distal to the tibial tuberosity of each leg). The PPT cycle was repeated three times with a 2 minute rest period between each cycle. PPT values (kPA) for each site were averaged across the 3 cycles. PPT assessments for each participant was undertaken using a standardized protocol by one of two trained researchers, blinded to participant characteristics including pain status.[22]

Raw PPT values were not normally distributed, thus PPTs were logarithmically transformed before statistical analysis to achieve normality of the data, and normality confirmed using the Shapiro-Wilk test.

PPT values served as a reference test during Receiver Operating Curve (ROC) analysis to identify the number of painful sites other than the knee, reported on the body pain manikin that is indicative of central pain mechanisms. Preliminary analysis demonstrated no significant differences in PPT between participants with or without knee pain, and therefore, standardized z-scores were computed from log PPT data for all 420 participants. PPT values below the 10^{th} percentile ($z > 1.28$) were classified as abnormally increased sensitivity (gain-of-function) at the measured site.[14] Number of painful sites were selected that maximized sensitivity while maintaining a minimum specificity of 0.75 for predicting PPT gain-of-function.[54]

Unless otherwise stated, results are reported in the main text for primary analyses using PPTs (following log-transformation) at the proximal tibia distal to the participant's worst affected knee, taken to be an index for centrally augmented pain.[73] Results for secondary analyses using PPT measured at other sites are reported within the supplementary tables.

Item selection

We used a sequential strategy to select items representing traits reflecting central pain mechanisms (Figure 1):

(1) Items not relevant to the study hypothesis were excluded, following initial screening by the research team.

(2) Where items originated from established questionnaires (PCS, HADS, painDETECT, and ICOAP), the 2 items were selected with highest loading to each questionnaire's latent constructs. Item loading was determined by exploratory Structural Equation Modelling (ESEM)[18] across each questionnaire, using data from KPIC participants who reported current knee pain (n=2152).

(3) Items were excluded if there was below moderate expert agreement (k^*<0.60) on their relevance to central mechanisms of knee pain.[12, 27] Invited experts comprised experienced clinical and research experts (n = 25) across various pain research disciplines (orthopaedics, rheumatology, sports and exercise medicine, psychology, neuroscience, physiotherapy, pharmacy, genetics and musculoskeletal epidemiology) within the Arthritis Research UK (ARUK) Pain Centre. Experts indicated relevance for each item using a four-point Likert scale (0 "not relevant" to 3 "highly relevant").

(4) The percentage of respondents selecting each response category for an item was examined in order to ensure adequate targeting (a balanced frequency (%) of selection for

each response category provided for an item across a study population). Items were excluded if any single response category was selected by ≥80% of participants.[8, 47]

(5) Items were excluded if associations with PPT at the proximal tibia were not statistically significant. PPT at the proximal tibia (an unaffected site, distal to the affected knee) was taken to be indicative of central pain mechanisms.[73] Lack of a relationship between a self-report item and PPT was taken to indicate that the item might itself, not be indicative of central pain mechanisms.

----------*Insert Figure 1 (Flow chart)* ----------

Data Analysis

PPT homogeneity was assessed using concordance correlation coefficient (CCC) to establish intra- and inter-rater agreement for the 2 PPT assessors.[43]

Associations between PPT and questionnaire data in participants with knee pain (n=322) are presented as Spearman's correlation coefficients (r) or standardized regression coefficients (β) from linear regression models. Adjusted p values were obtained using Bonferroni correction. All analyses utilised complete case data due to low levels of missing data.

Validation of selected items

For factor analysis of the selected items, participants with knee pain who had undergone PPT assessment (n=322) were randomly allocated into two equal groups using Stata, version 14.2,[70] in order to avoid spurious or chance effects.[28] Exploratory Structural Equation Modelling (ESEM) was used with one group and the resulting model was tested in the other group using confirmatory factor analysis (CFA). PPT variance explained by the identified factor(s) in fully adjusted models (Adjusted for age, sex and BMI), were compared with the

variance explained by the host scales. To explore equivalence of the identified factor(s) and selected items with respect to age, sex and BMI, Multiple-Indicator Multiple-Causal (MIMIC) models were employed. MIMIC models are a type of CFA model where the latent factors and the items are simultaneously regressed on to demographics and other relevant covariates.[57]

We further sought to determine whether traits represented by the host scale explained the associations between PPT and items selected from that scale. Derived scale scores for each host scale were calculated by subtracting 'the score for each selected item' from 'the summary score for the respective host scale'. Each model testing the association between PPT and a selected item, or between PPT and any identified factor(s), was adjusted for derived scale scores.

Analyses were performed using Stata, version 14.2,[70] except that ESEM and CFA used MPlus, version 7.4.[52] Except where stated, all analyses were conducted within the participant group that reported knee pain and who had undergone PPT assessment (n=322). Demographics are presented as mean (SD) or median (Interquartile Range). Between-group comparisons used Student's t test and, where appropriate, 95% Confidence Intervals (CIs) are presented.

RESULTS

Study Population

The 322 participants with knee pain were on average 59 (SD 10) years of age, had an average BMI of 29 (SD 7), and most were female (61%). Participants without knee pain (n=98, 60% female, age 60±10 y) displayed geometric mean PPT at the proximal tibia of 383 (95% CI 169 to 780) kPA, similar to those with knee pain (358 (95% CI 134 to 871) kPa, p=0.27).

Demographic and clinical characteristics for the knee pain group are presented in Table 1.

----------*Insert Table 1*----------

Pressure pain detection thresholds

PPTs at the proximal tibia displayed moderate inter-rater reliability (CCC = 0.51) and intra-rater reliability (CCC = 0.60) (Supplementary Table 1). Lower PPTs were associated with female sex (females; 314 (287 to 343) kPa, males; 428 (391 to 473) kPa, p<0.0001) and higher BMI (*r* = -0.19, *P* = 0.002), but not with age (*r* = -0.01, *P* = 0.83). For those with knee pain, PPT was not associated with radiographic x-ray scores (*r* = -0.041, p = 0.491), but was associated with a painDETECT measure of knee pain severity ("How would you rate your most painful knee pain on a 0-10 scale at the present time, that is right now") (r=-0.18, p=0.002). Pain severity showed a weak but significant relationship with radiographic scores (*r* = 0.15, p = 0.007).

Pain distribution

The number of other sites reported as painful in addition to knee pain was negatively correlated with PPT distal to the index knee (23 other sites: r =-0.16, p=0.008; 7 other sites: r =-0.16, p=0.007). Cut off points of ≥5/7 or ≥6/23 painful sites additional to knee, optimally predicted low PPT (specificity >0.75, accuracy 73.4%). `Knee pain plus other pain below the waist' showed significant association with PPT (β=-0.14; p<0.02), but other pain distribution categories did not (Table 2). ACR widespread pain classification did not significantly predict PPT, whether including (β = -0.03, p=0.55) or excluding (β= -0.05; p=0.37) knees as painful sites. The presence of "knee pain plus other pain below the waist" was selected for further analyses over `number of sites' criteria due to ease of application.

----------*Insert Table 2*----------

Item Selection

Twenty-five items potentially reflecting central mechanisms were selected for expert review. ESEM confirmed 11 latent factors from 4 questionnaires, representing anxiety or depression (HADS), magnification or rumination (PCS), pain intensity, evoked or spontaneous neuropathic-like pain (painDETECT), psychological or somatic effects of pain (both in each of the ICOAP Constant and Intermittent ICOAP subscales)(Supplementary Tables 2 to 6). Two items were selected with highest loading to each of these factors. Additional items measured traits of fatigue, cognitive impact, and pain distribution (pain manikin). Sixteen (64%) experts responded to the consensus task, and displayed moderate to excellent agreement (k>0.6) for relevance of 19 of the 25 items to central pain mechanisms (Table 3).

Supplementary Table 7 gives item response distributions in people with knee pain. Each scale was positively associated with scores on other scales (r=0.23 to 0.63, p<0.05, Supplementary Table 8). The 19 items selected after expert review also all displayed significant positive associations with each other (r=0.07 to 0.87, Supplementary Table 9). Items from the intermittent ICOAP subscale showed strong correlations (r>0.8, p <0.05) with corresponding constant ICOAP items.

Association between PPT and self-report scales or items

Each scale was negatively associated at a univariate level with PPT (β= -0.09 to -0.21, each p<0.05 except intermittent-ICOAP, p=0.13). A significant proportion of variation in PPT was explained by each scale alone (R^2 values = 0.10 to 0.13, p<0.05). Individual items displayed negative associations with PPT (Table 3). After excluding intermittent pain (to avoid item redundancy), a single item was selected to represent each of 8 remaining traits; fatigue,

cognitive impact, pain distribution, anxiety, depression, catastrophic thinking, neuropathic-like, and constant pain (Table 3).

----------*Insert Table 3*----------

Validation of selected items

The 8 selected items displayed a Cronbach's alpha (α) of 0.80, and predicted proximal tibia PPT in a multiple regression model (R^2 = 0.18, $p<0.05$) more than did any trait specific scale or item. Competing 2- and 3- factor models for these items were not identified in the exploratory group and a specified 2-factor CFA models did not significantly alter the one-factor model, supporting the one-factor model. The one-factor model also showing the best fit to data from the Confirmatory group (RMSEA = 0.07; WRMR = 0.5; X^2(df) = 43(20)). Each item was significantly associated with the single latent construct, interpreted as representing central mechanisms of knee pain (Table 4).

----------*Insert Table 4*----------

The latent construct was associated with PPT (β=-0.27; SE = 0.07; $p<0.001$), independent of each scale from which items were derived (Table 5). Associations between each selected item and PPT were reduced and lacked significance after adjusting for derived host scale scores (Supplementary Table 10), except for the neuropathic item on cold or heat on the area causing pain (β= -0.21, SE = 0.08, $p<0.05$) and the anxiety item "I get sudden feelings of panic" (β= -0.19, SE = 0.09, $p<0.05$), where the relationship remained significant after adjusting for derived host scale scores.

The latent construct explained a higher proportion of PPT variance at the proximal tibia (R^2 = 0.17, SE = 0.05, $p<0.001$), compared to that explained by any multi-item, trait-specific questionnaire (R^2 values = 0.10 to 0.13, $p<0.05$). The latent construct also explained a high

proportion of PPT variance at the sternum (R^2 = 0.20, SE = 0.05, p<0.001), medial- (R^2 = 0.34, SE = 0.05, p<0.001) and lateral- (R^2 = 0.24, SE = 0.05; p<0.001) joint line. The latent construct was also associated with knee pain severity (β =0.66; S.E. = 0.05, p<0.001), but not radiographic scores (β=0.10; SE=0.07; p=0.160). The relationship between the latent construct and PPT remained significant even when radiographic scores, or pain severity, were accounted for within the model (β=-0.267; SE=0.07; p<0.001, and β=-0.213; SE=0.06; p<0.001, respectively).

----------*Insert Table 5*----------

The final best fitting MIMIC model was a good fit to the data (CFI = 0.943, TLI = 0.924; RMSEA = 0.050; WRMR = 0.761; x2(df) = 53.696 (33)). An effect of BMI on the latent construct (β=0.310, SE=0.064, p<0.001), but not gender (β=0.073, SE=0.070, p=0.295) nor age (β=-0.064, SE=0.069, p=0.357), was observed. Item specific effects for age (anxiety item: β =-0.114, SE=0.055, p=0.038) and BMI (depression item: β =0.135, SE=0.056, p=0.015) were observed, but not for gender.

All secondary analyses using PPT at the index knee joint line or sternum produced similar results to those using proximal tibia PPT (Supplementary Tables 11 and 12).

DISCUSSION

In the current study, we identified 8 key traits, represented by 8 self-report items which together load onto a single construct interpreted as reflecting central pain mechanisms in people with knee pain. The 8 key traits were anxiety, depression, catastrophizing, neuropathic-like pain, fatigue, sleep disturbance, pain distribution and cognitive impact.

Items representative of these traits displayed high face validity based on expert opinion and external validity by association with high pain sensitivity (low PPT) at a site distal to the index knee, indicative of central sensitization.[31] These items might identify people whose knee pain could benefit from treatments directed towards central mechanisms.

Consistent with prior studies, we show that in individuals with knee pain, associations exist between reduced PPTs and increased scores on each of the eight traits.[7, 30, 45] Scores for each trait were significantly correlated with the other traits, consistent with a single latent construct, but a combination of the 8 traits explained more variation in PPTs compared to any originating questionnaire alone. We conclude that a combination of items from across these 8 traits might indicate the extent of central pain augmentation in people with knee pain. Consistent with previous reports where between 5% - 20% of PPT variance was explained by demographic, psychological and/or genetic variables,[19, 76] the latent construct explains a significant proportion of PPT variance. This provides evidence of validity as a model of central sensitisation, but further research would be required to determine whether the identified construct explains a greater proportion of variation in other indices of central sensitisation, or variation in pain relief in response to interventions that target central sensitisation in people with knee pain.[66]

Augmented central pain processing is well recognised in people with chronic widespread pain (WSP), but can be more difficult to identify when pain is focussed on a specific anatomical site such as the knee. Further research might define whether the traits identified in the current study of people with knee pain, might also reflect augmented central pain processing in people with pain at another site. Several items identified in this study represent the emotional component of pain, and shared mechanisms within the central nervous system might underpin associations with central pain augmentation.[48, 71] Cognitive

difficulties or `brain fog' are frequent complaints of people with musculoskeletal pain,[50] and experimental pain impairs performance in cognitive tasks.[20, 75] Neuropathic-like pain is also prevalent in people reporting knee OA pain and has been associated with reduced PPTs.[39, 49] Sleep disruption can lead to augmented central pain processing,[34] and fatigue is strongly associated with musculoskeletal pain severity.[67] Association between WSP and central mechanisms has been described previously.[10] We extend these findings to show that higher numbers of painful sites, and pain below the waist other than knee pain, were each associated with reduced PPT. A minority of participants in our study satisfied ACR criteria for WSP and we might have lacked sufficient power to detect associations of WSP with PPT. However, our data indicate that central mechanisms might still contribute to pain in people with multisite pain who do not satisfy classification criteria for WSP.

Strength of association between each selected item and PPT was reduced following adjustment for originating questionnaire derived score, suggesting at least partial mediation by the host construct. However, associations between PPT and items addressing neuropathic-like pain in response to cold or heat, or addressing feelings of panic remained statistically significant even after adjustment for the derived painDETECT and HADS-anxiety scores. These items might have specific associations with central mechanisms over and above representing neuropathic-like pain or anxiety respectively.

The 'central mechanisms' construct identified here explains slightly more PPT variance than that explained by any of the individual traits. Association between PPTs and the 'central mechanisms' construct was found to be not explained by originating questionnaire derived scores, disease- or pain- severity. Together, these findings support use of a composite tool to identify the extent of central pain augmentation in people with knee pain rather than individual assessment of each trait on a case-by-case basis in clinical practice. Identification

of these central pain mechanisms might well have prognostic relevance, and further work should assess whether central pain mechanisms might at least in part, explain the predictive values of other prognostic tools such as the Orebro Musculoskeletal Pain Screening Questionnaire,[44] or StartBACK.[38] Items reflecting psychological distress, similar to those included in the current study, are included within these scales. However, the Orebro and StartBACK questionnaires do not assess other key traits that we have identified in the current study, such as somatic traits of neuropathic-like symptoms and pain distribution.

Associations between the 'central mechanisms' construct and increased BMI during MIMIC analysis supports previous work in other chronic pain conditions which demonstrate significant associations between BMI and other markers of central pain mechanisms.[26, 58] Addressing central pain mechanisms using non-pharmacological and/or pharmacological approaches is likely to improve pain treatment response, physical function, and other important outcomes for the individual.[32] Further research should explore whether the core construct discovered here can predict pain outcome or response to treatment or help improve healthcare efficiency by directing targeted treatments. Randomized Control Trials (RCTs) might explore responsiveness of individuals with knee pain to novel or repurposed pharmacological and non-pharmacological therapies targeted to traits of psychological distress, neuropathic-like pain and somatic disturbances identified in the current work.[21] Longitudinal research might explore whether traits, or the central construct identified in the current study might predict better treatment response to such centrally targeted treatments. Conversely, traits identified in this study might indicate a central knee pain component which might not necessarily respond to a treatment that targets peripheral nociceptive drive.[48] High catastrophizing predicted worse pain improvement after total knee arthroplasty (TKA) in a previous study.[62]

This study is not without its limitations. Participant selection within KPIC for PPT assessments was weighted towards an early knee pain sample (pain for < 3 years), and a high proportion had radiographic KL scores <2. Previous studies have demonstrated a lack of association between PPTs and symptom duration in individuals with OA knee pain,[55] but further research should determine whether our findings can be generalised to people with longer symptom duration or more severe OA structural change. The traits analysed were limited to those included within the KPIC baseline survey, and initial screening by the researchers may have allowed subjective bias during the initial stage of item selection. All experts involved within the current study originated from a single centre in the UK. Their breadth of expertise reflected multiple disciplines involved in the treatment and research of knee pain, but it is possible that additional traits might further contribute to the identification of pain mechanisms in people with knee pain. The current work is also limited due to the cross sectional approach employed, and longitudinal studies might help disentangle the nature of the relationship between pain severity, peripheral pathology, PPTs, and traits identified in the current study.

We employed only one modality of QST assessment - PPT - which was both employed for item selection and other validation analysis. PPT has consistently been associated with knee pain in previous studies and displays good measurement properties in people with knee pain.[53] Our study design selected proximal tibia PPT, distal to the index knee, as a primary outcome index of central sensitisation. Index knee joint-line PPT displayed higher reliability than proximal tibia PPT, but is likely to be dependent on peripheral as well as central sensitization.[55] PPTs at remote sites displayed lower reliability than other sites, and are less strongly associated with OA pain when compared to PPTs from sites distal to the affected

joint.[55, 73] Further work is needed to confirm the specific central pathways that drive distal and remote pain sensitivity in knee OA.

Previous work has demonstrated associations between other modalities for accessing central pain mechanisms (e.g. temporal summation or brain imaging), and self-report questionnaires about pain distribution, neuropathic-like symptoms, catastrophizing, sleep disturbance, fatigue, depression and anxiety.[1, 9, 13, 17, 45] These other modalities for assessing central mechanisms, especially those with higher reliability than PPTs, might produce more confident estimates of associations with the construct identified here.[41]

Further research should determine whether the central construct identified in the current study might also predict these other indices of central pain mechanisms. Central mechanisms and their self-report correlates present across a spectrum, rather than dichotomous presence or absence, and further research should define clinical thresholds that might predict or represent important response to treatment.

In conclusion, we show that 8 individual phenotypic traits, as well as a single overall construct (interpreted as 'central pain mechanisms') represented by 8 items, are correlates of a PPT index for centrally augmented pain in individuals with knee pain. These items might be combined to identify the extent of central pain augmentation in people with knee pain. Future research should determine whether a `central pain mechanisms' questionnaire can predict prognosis or treatment responses in people who present in a clinical setting with a local pain problem such as knee pain.

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Conflicts of interest Statement:

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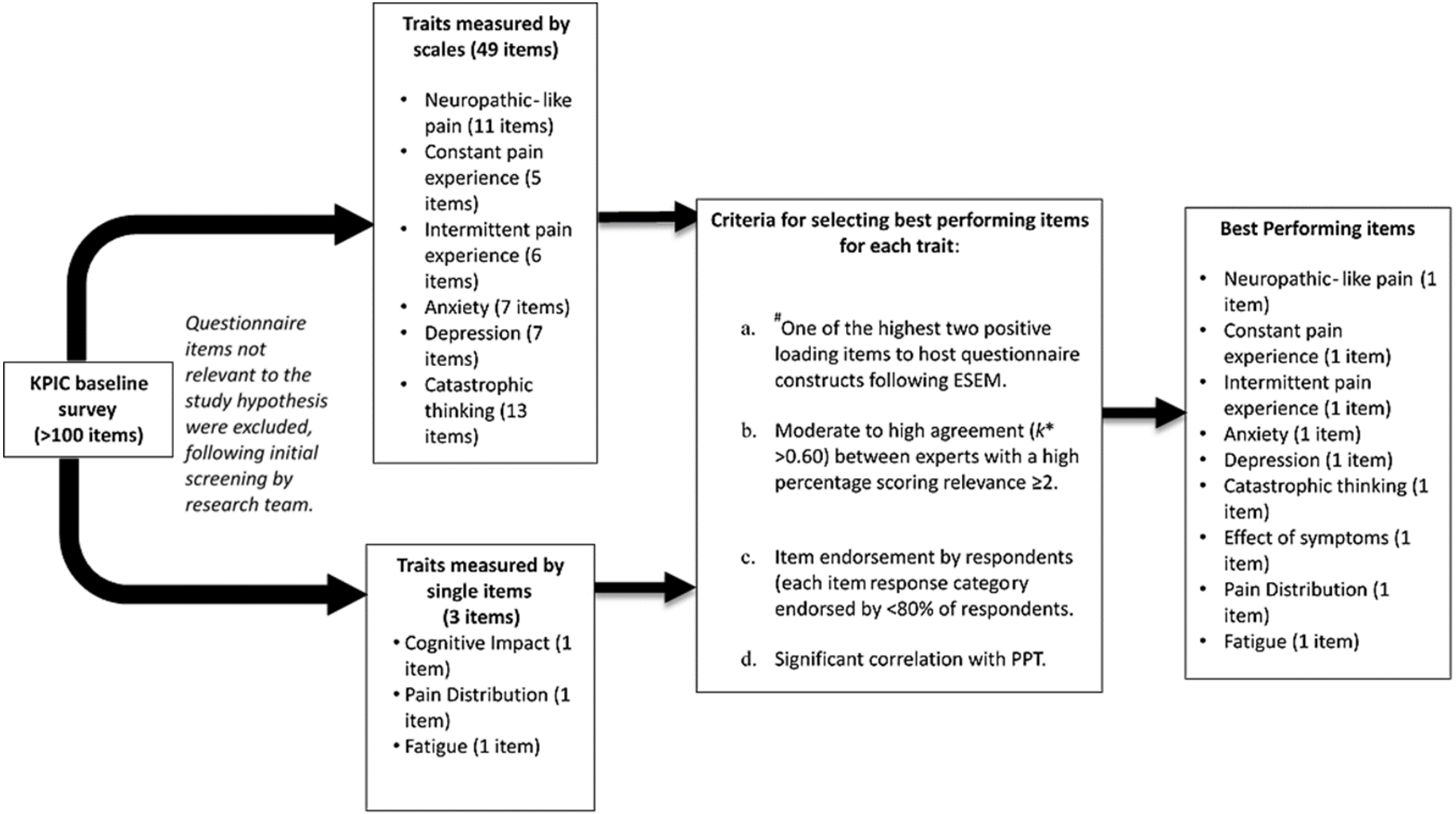
FIGURE

Figure 1. Flow chart showing the item selection process across traits.



ESEM = Exploratory Structural Equation Modelling. # Only relevant for items originating from established questionnaires measuring specific traits.

TABLES

Table 1. Baseline demographics and clinical characteristics of participants with knee pain

	knee pain sample			p
	Overall (n = 322)	**Exploratory (n = 168)**	**Confirmatory (n = 154)**	
Gender; n (%) female	197 (61%)	99 (50%)	98 (50%)	0.38
Age; mean ± SD years	59.4 ± 9.5	59.9 ± 9.7	59.9 ± 9.8	0.98
BMI; mean ± SD kg/m^2	29.5 ± 6.1	29.3 ±5.6	30.0 ± 6.5	0.30
Proximal tibia PPT (kPA)	372 (265 – 528)	391 (268 – 523)	361 (249 – 528)	0.96
Tibiofemoral KL>=2; n (%)	96 (30%)	55 (33%)	41 (27%)	0.22
Questionnaire Scores				
Constant pain-ICOAP (possible range 0 – 24)	6 (3 – 11)	6 (3 – 11)	6 (3 – 12)	0.75
Intermittent pain-ICOAP (possible range 0 – 22)	8 (5 – 14)	8 (5 – 14)	9 (5 – 14)	0.94
Modified PainDETECT (possible range -1 – 38)	9 (5 – 14)	9 (5 – 14)	9 (5 – 14)	0.56
Pain Catastrophizing Scale (possible range 0 – 52)	8 (3 – 20)	8 (3 – 20)	8 (3 – 19)	0.83
Anxiety-HADS (possible range 0 – 14)	6 (4 – 10)	6 (4 – 9)	7 (4 – 10)	0.09
Depression-HADS (possible range 0 – 14)	5 (3 – 8)	4 (3 – 8)	5 (3 – 8)	0.78

Data are median (interquartile ranges, IQR) except where indicated. Gender, age, Body Mass Index (BMI) and geometric mean of log-transformed pressure pain detection thresholds (PPT) are given for all 322 cases. Questionnaire data are presented where complete data available (constant-Intermittent and Constant Osteoarthritis Pain scale (ICOAP) n=280; intermittent-ICOAP n=296; Anxiety-Hospital Anxiety and Depression scale (HADS) n=315; Depression-HADS n=314; Pain Catastrophizing Scale, PCS, n = 314; Modified PainDETECT Questionnaire n=282).

Table 2. Pressure pain detection thresholds (PPT) at the proximal tibia are predicted by ROC- and *a priori*- binary manikin classifications in individuals within the knee pain sample (n=322).

	n (%)	b (95% CI)	β	p
ROC-Derived Classifications				
≥5/7 other sites	**62 (19%)**	**-0.20 (-0.37 to -0.03)**	**-0.14**	**0.02**
≥6/23 other sites	**86 (27%)**	**-0.19 (-0.34 to -0.04)**	**-0.14**	**0.01**
A priori Classifications				
Above waist	189 (59%)	-0.08 (-0.22 to -0.06)	-0.07	0.26
Below waist	**169 (52%)**	**-0.17 (-0.30 to -0.03)**	**-0.14**	**0.02**
Contralateral to index knee	119 (37%)	-0.14 (-0.28 to 0.002)	-0.12	0.05
Axial pain	151 (47%)	-0.01 (-0.15 to 0.12)	-0.01	0.87
Widespread pain[a]	31 (10%)	-0.08 (-0.34 to 0.18)	-0.03	0.55

Classifications are based on number or distribution of painful sites in addition to knee pain reported by participants on a body manikin. ROC; receiver-operating curve.

[a]Widespread pain; classified according to American College of Rheumatology criteria[37], including knee pain.

Bold indicates statistically significant associations.

Proportion (n, %) of participants with knee pain reporting other pain according to classifications are presented.

Unstandardized (b) and standardized (β) regression coefficients are presented

Table 3. Item performance for each statistical criteria to select "best performing items" across traits

Shortlisted Items (items = 19)[#]	Traits	Scale - ESEM construct (loading score)	Expert rating (*k**)	Respondents endorsing scores >0 (%)	Correlation with log-PPTs (Spearman's rho)
1. "I look forward with enjoyment to things"	Depression	HADS - Depression (0.93)	0.71	54%	-0.12*
2. "I still enjoy the things I used to enjoy"	**Depression**	**HADS -Depression (0.82)**	**0.64**	**75%**	**-0.15***
3. "I can't seem it keep it out of my mind"	Catastrophic thinking	PCS - Rumination (0.92)	0.71	52%	-0.11
4. "I keep thinking about how much it hurts"	**Catastrophic thinking**	**PCS - Rumination (1.08)**	**0.83**	**59%**	**-0.13***
5. "I feel I can't go on"	Catastrophic thinking	PCS - Helplessness (0.99)	0.78	24%	-0.09
6. "I feel I can't stand it anymore"	Catastrophic thinking	PCS - Helplessness (0.93)	0.78	56%	-0.09
7. Is cold or heat (bath water) in this area occasionally painful?	**Neuropathic Symptoms**	**MPDQ - Evoked symptoms (0.85)**	**0.73**	**43%**	**-0.23***
8. Over the past month, in your most painful knee, is light touching (clothing, a blanket) in this area painful?	Neuropathic Symptoms	MPDQ - Evoked symptoms (0.56)	0.79	40%	-0.21*
9. Over the past month, do you have a tingling or prickling sensation in the area of your most painful knee 'pain' (like crawling ants or electrical tingling)?	Neuropathic Symptoms	MPDQ - Spontaneous symptoms (1.15)	0.66	50%	-0.09
10. In the past week, how much has your knee pain that comes and goes affected your sleep?	Intermittent pain experience	Intermittent ICOAP - Somatic symptoms (0.71)	0.64	56%	-0.17*
11. In the past week, how upset or worried have you been by your knee pain that comes and goes?	Intermittent pain experience	Intermittent ICOAP - Psychological symptoms (0.76)	0.69	71%	-0.14*
12. In the past week, how frustrated or annoyed have you been by your constant knee pain?	Constant pain experience	Intermittent ICOAP - Psychological symptoms (0.78)	0.60	76%	-0.17*
13. In the past week, how upset or worried have you been by your constant knee pain?	Constant pain experience	Constant ICOAP - Psychological symptoms (0.90)	0.78	69%	-0.16*
14. In the past week, how much has your constant knee pain affected your sleep?	**Constant pain experience**	**Constant ICOAP - Somatic symptoms (0.88)**	**0.78**	**68%**	**-0.21***
15. "I get a sort of frightened feeling as if something awful is about to happen"	Anxiety	HADS -Anxiety (0.83)	0.69	60%	-0.08
16. "I get sudden feelings of panic"	**Anxiety**	**HADS -Anxiety (0.82)**	**0.61**	**53%**	**-0.19***
17. Knee pain plus other pain below the waist	**Pain Distribution**	**-**	**0.81**	**52%**	**-0.14***
18. Does your pain or other bodily symptoms stop you from concentrating on what you are doing?	**Cognitive Impact**	**-**	**0.71**	**74%**	**-0.18***
19. In the past month, did you feel tired on most days?	**Fatigue**	**-**	**0.61**	**96%**	**-0.15***

Items in bold represent items selected as "best performing items". *p<0.05 (Bonferroni corrected).

[#]Items presented (items = 19) were rated by experts to show relevance to centrally augmented mechanisms following expert rating (*k**>0.60).

Items originating from established scales showed the highest significant (p<0.05) associations with each identified latent construct during ESEM analysis. Domains measured by singular items (item specific domains) not entered into ESEM.

Hospital Anxiety and Depression scale (HADS); Modified PainDETECT Questionnaire (MPDQ); Pain Catastrophizing Scale (PCS), Intermittent and Constant Osteoarthritis Pain (ICOAP) scale.

Fatigue, Pain Distribution and Cognitive Impact measured by singular items.

Table 4. Standardized item loadings for the 8 selected items in a single factor model in exploratory and confirmatory subgroups.

Item	Domain	Exploratory sample (n=166)	Confirmatory sample (n=154)
"I get sudden feelings of panic"	Anxiety	0.53*	0.49*
"I still enjoy the things I used to enjoy"	Depression	0.57*	0.52*
“Over the past month, in your most painful knee, is cold or heat (bath water) in this area occasionally painful?”	Neuropathic symptoms	0.52*	0.57*
“In the past month, did you feel tired on most days?”	Fatigue	0.62*	0.61*
“Does your pain or other bodily symptoms stop you from concentrating on what you are doing?”	Attention to pain	0.79*	0.81*
“Knee pain plus other pain below waist”	Pain distribution	0.44*	0.40*
"I keep thinking about how much it hurts"	Catastrophising	0.57*	0.58*
“In the past week, how much has your constant knee pain affected your sleep?”	Sleep	0.66*	0.69*

*$p<0.05$

Table 5. Prediction of proximal tibia PPT by identified factor independent of derived host scale scores (host scale score minus selected items score

Scales adjusted for	β	S.E	p
Unadjusted Model	**-0.27**	**0.07**	**<0.001**
Constant Pain - ICOAP	**-0.19**	**0.07**	**0.01**
Neuropathic Pain - PainDETECT	**-0.21**	**0.07**	**0.01**
Catastrophizing - PCS	**-0.28**	**0.08**	**<0.001**
Anxiety - HADS	**-0.24**	**0.07**	**0.001**
Depression - HADS	**-0.26**	**0.08**	**0.001**

The single latent construct identified through the 8 selected items, interpreted as `central mechanisms of knee pain', was associated with log transformed pressure pain detection thresholds (PPT) distal (Proximal tibia) from the index knee in an unadjusted model, and in models where total scores derived from each of the originating scales (scale summary score minus selected item) were adjusted for.
Standardized coefficients (β) presented.

SUPPLEMENTARY INFORMATION

Supplementary Table 1. Inter- and intra- observer agreement for pressure pain detection threshold (PPT) assessments

	Inter-observer agreement			Intra-observer agreement		
Anatomical site	Observers	n	CCC (95% C.I.)	Observers	n	CCC (95% C.I.)
Proximal tibia	NF-LM	8	0.51 (-0.01 to 1.02)	LM	8	0.60 (0.28 to 0.92)
Sternum	NF-LM	8	0.61 (0.17 to 1.05)	LM	9	0.39 (-0.13 to 0.91)
Medial Joint Line	NF-LM	8	0.75 (0.43 to 1.07)	LM	8	0.90 (0.76 to 1.05)
Lateral Joint Line	NF-LM	8	0.86 (0.68 to 1.03)	LM	8	0.61 (0.10 to 1.13)

List of assessors: Laura Marshall (LM), Nadia Frowd (NF).

Abbreviations: CCC – concordance correlation coefficient, CI – confidence interval, PPT – pain pressure thresholds, n=number of participants assessed

Supplementary Table 2: Standardized item loading for the Hospital Anxiety and Depression Scale (HADS) two factor model.

Items	Factor 1 (Depression)	Factor 2 (Anxiety)
1. I feel tense or wound up	0.245***	0.603***
2. I still enjoy the things I used to enjoy	**0.840*****	0.177**
3. I get a sort of frightened feeling as if something awful is about to happen	0.004	**0.836*****
4. I can laugh and see the funny side of things	0.759***	0.054
5. Worrying thoughts go through my mind	0.045	0.816***
6. I feel cheerful	0.739***	0.074
7. I can sit at ease and feel relaxed	0.629***	0.205***
8. I feel as if I am slowed down	0.129	0.226***
9. I get a sort of frightened feeling like 'butterflies' in the stomach	0.092	0.484***
10. I have lost interest in my appearance	0.592***	0.008
11. I feel restless as if I have to be on the move	0.112*	0.419***
12. I look forward with enjoyments to things	**0.943*****	-0.109
13. I get sudden feelings of panic	0.031	**0.868*****
14. I can enjoy a good book or radio or television programme	0.591***	0.028

Fit statistics for two factor model: CFI = 0.985; TLI=0.979; RMSEA = 0.073; WRMR = 3.127; X^2(df) = 220 (64).

Items in bold represents the two highest loading items within each identified factor.

* p<0.05 **p<0.01 *** p<0.001

Supplementary Table 3: Standardized item loading for the Pain Catastrophizing Scale (PCS) two factor model.

Items	Factor 1 (Helplessness)	Factor 2 (Rumination)
1. I worry all the time about whether the pain will end	0.470***	0.395***
2. I feel I can't go on	**1.000***	0.131*
3. It's terrible and I think it's never going to get any better	0.858***	0.074
4. It's awful and I feel that it overwhelms me	0.871***	0.101**
5. I feel I can't stand it anymore	**0.932***	0.001
6. I become afraid that the pain will get worse	0.495***	0.384***
7. I keep thinking of other painful events	0.460***	0.361***
8. I anxiously want the pain to go away	0.069	0.814***
9. I can't seem it keep it out of my mind	0.000	**0.921***
10. I keep thinking about how much it hurts	0.169***	**1.097***
11. I keep thinking about how badly I want the pain to stop	0.041	0.901***
12. There's nothing I can do to reduce the intensity of the pain	0.310***	0.542***
13. I wonder whether something serious may happen	0.240**	0.519***

Fit statistics for two factor model: CFI = 0.998; TLI=0.997; RMSEA = 0.043; WRMR = 1.183; X^2(df) = 253 (53)

Items in bold represents the two highest loading items within each identified factor.

* p<0.05 **p<0.01 *** p<0.001

Supplementary Table 4: Standardized item loading for the PainDETECT (PDQ) three factor model.

	Items	Factor 1 (Pain Intensity)	Factor 2 (Spontaneous Neuropathic-Like pain)	Factor 3 (Evoked Neuropathic-Like pain)
1.	Over the past month, does your pain run up and down your leg?	0.218***	0.424***	0.033
2.	How would you rate your most painful knee pain on a 0-10 scale at the present time, that is right now, where 0 is 'no pain' and 10 is 'pain as bad as could be'?	0.664***	0.063	0.109*
3.	**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'?**	**0.926*** **	0.006	0.005
4.	**In the past month, on average, how intense was the pain in your most painful knee rated on a 0-10 scale, where 0 is 'no pain' and 10 is 'pain as bad as could be'?**	**0.959*** **	0.005	0.023
5.	The next question is on the pattern of your pain in your most painful knee. Which of the 4 different options below is the one that best describes the pattern of your worst knee pain over the past month?	-0.283***	0.043	0.273
6.	**Do you suffer from a burning sensation (e.g., stinging nettles) in or around your most painful knee?**	0.100*	**0.710*** **	0.007***
7.	**Do you have a tingling or prickling sensation in the area of your most painful knee 'pain' (like crawling ants or electrical tingling)?**	0.001	**1.153*** **	0.226*
8.	**Is light touching (clothing, a blanket) in this area painful?**	0.149**	0.191***	**0.559*** **
9.	Do you have sudden pain attacks in the area of your pain, like electric shocks?	0.237***	0.240***	0.177**
10.	**Is cold or heat (bath water) in this area occasionally painful?**	0.001	0.002	**0.861*** **
11.	Do you suffer from a sensation of numbness in the areas that you marked?	0.102*	0.400***	0.361***
12.	Does slight pressure in this area, e.g., with a finger, trigger pain?	0.152	0.001	0.520***

Fit statistics for two factor model: CFI = 0.987; TLI=0.974; RMSEA = 0.038; WRMR = 0.54; X^2(df) = 65.41 (33)

Items in bold represents the two highest loading items within each identified factor.

* p<0.05 **p<0.01 *** p<0.001

Supplementary Table 5: Standardized item loading for the Constant pain ICOAP two factor model.

	Items	Factor 1 (Somatic effects of constant pain)	Factor 2 (Psychological effects of constant pain)
1.	**In the past week, how intense has your *constant knee pain* been?**	**0.797***	0.165
2.	**In the past week, how much has your *constant knee pain* affected your sleep?**	**0.888***	0.005
3.	In the past week, how much has your *constant knee pain* affected your overall quality of life?	0.417*	0.552*
4.	**In the past week, how frustrated or annoyed have you been by your *constant knee pain*?**	0.184	**0.780***
5.	**In the past week, how upset or worried have you been by your *constant knee pain*?**	0.006	**0.940***

Fit statistics for two factor model: CFI = 1.00; TLI=1.00; RMSEA = 0.014; WRMR = 0.106; X^2(df) = 1.15 (1)

Items in bold represents the two highest loading items within each identified factor.

*p < 0.001

Supplementary Table 6: Standardized item loading for the Intermittent pain ICOAP two factor model.

Items	Factor 1 (Somatic effects of constant pain)	Factor 2 (Psychological effects of constant pain)
1. In the past week, how intense has your knee pain that comes and goes been?	**0.967****	0.003
2. In the past week, how much has your knee pain that comes and goes affected your sleep?	**0.709****	0.246*
3. In the past week, how much has your knee pain that comes and goes affected your overall quality of life?	0.485**	0.380**
4. In the past week, how frustrated or annoyed have you been by your knee pain that comes and goes?	0.379**	0.601**
5. In the past week, how upset or worried have you been by your knee pain that comes and goes?	0.215*	**0.758****
6. In the past week, how frequently has this knee pain that comes and goes occurred?	0.006	**0.964****

Fit statistics for two factor model: CFI = 1.00; TLI=0.99; RMSEA = 0.06; WRMR = 0.353; X^2(df) = 15.8 (4)

Items in bold represents the two highest loading items within each identified factor.

* p<0.05** p < 0.001

Supplementary Table 7. Responses from participants with knee pain to items selected as relevant to central pain mechanisms

Domains	Items	knee pain sample			p
		Overall (n = 322)	Exploratory (n = 168)	Confirmatory (n = 154)	
Anxiety	I get sudden feelings of panic (possible range 0 to 3)	1 (0 to 1)	1 (0 to 1)	1 (0 to 1)	0.204
	I get a sort of frightened feeling as if something awful is about to happen (possible range 0 to 3)	1 (0 to 2)	1 (0 to 2)	1 (0 to 2)	0.199
Depression	I still enjoy the things I used to enjoy (possible range 0 to 3)	1 (0 to 1)	1 (0 to 1)	1 (1 to 1)	0.887
	I look forward with enjoyments to things (possible range 0 to 3)	1 (0 to 1)	1 (0 to 1)	1 (0 to 1)	0.746
Neuropathic-like pain	Do you have a tingling or prickling sensation in the area of your most painful knee 'pain' (like crawling ants or electrical tingling)? (possible range 0 to 5)	1 (0 to 2)	0 (0 to 2)	1 (0 to 2)	0.991
	Is light touching (clothing, a blanket) in this area painful? (possible range 0 to 5)	0 (0 to 1)	0 (0 to 1)	0 (0 to 2)	0.832
	Is cold or heat (bath water) in this area occasionally painful? (possible range 0 to 5)	0 (0 to 1)	0 (0 to 1)	0 (0 to 1)	0.984
Fatigue	In the past month, did you feel tired on most days? (possible range 0 to 5)	2 (2 to 3)	2 (2 to 3)	2 (2 to 3)	0.352
Cognitive Impact	Does your pain or other bodily symptoms stop you from concentrating on what you are doing? (possible range 0 to 4)	1 (0 to 2)	2 (1 to 2)	1 (0 to 2)	0.481
Pain Distribution	Other pain below waist (possible range 0 to 1)	1 (0 to 1)	1 (0 to 1)	1 (0 to 1)	0.793
Pain Catastrophizing	I feel I can't stand it anymore (possible range 0 to 4)	0 (0 to 1)	0 (0 to 1)	0 (0 to 1)	0.359
	I feel I can't go on (possible range 0 to 4)	0 (0 to 0)	0 (0 to 1)	0 (0 to 0)	0.415
	I can't seem it keep it out of my mind (possible range 0 to 4)	1 (0 to 2)	1 (0 to 2)	1 (0 to 1)	0.423
	I keep thinking about how much it hurts (possible range 0 to 4)	1 (0 to 2)	1 (0 to 2)	1 (0 to 2)	0.788
Constant pain experience	In the past week, how much has your *constant knee pain* affected your sleep? (possible range 0 to 4)	1 (0 to 2)	1 (0 to 2)	1 (0 to 2)	0.504
	In the past week, how frustrated or annoyed have you been by your *constant knee pain*? (possible range 0 to 4)	1 (1 to 3)	1 (1 to 3)	2 (0 to 3)	0.792
	In the past week, how upset or worried have you been by your *constant knee pain*? (possible range 0 to 4)	1 (0 to 2)	1 (0 to 2)	1 (0 to 2)	0.651
Intermittent pain experience	In the past week, how much has your knee pain that comes and goes affected your sleep? (possible range 0 to 4)	1 (0 to 2)	1 (0 to 2)	1 (0 to 2)	0.915
	In the past week, how upset or worried have you been by your knee pain that comes and goes? (possible range 0 to 4)	1 (0 to 2)	1 (0 to 2)	1 (0 to 2)	0.229

Data are median (interquartile ranges, IQR).

Supplementary Table 8. Associations between self-report measures.

	Neuropathic-like pain – painDETECT	Constant Pain - ICOAP	Intermittent pain - ICOAP	Depression -HADS	Anxiety - HADS
Constant Pain – ICOAP	0.63*	-	-	-	-
Intermittent pain – ICOAP	0.62*	0.62*	-	-	-
Depression – HADS	0.39*	0.43*	0.32*	-	-
Anxiety- HADS	0.33*	0.30*	0.23*	0.57*	-
Pain Catastrophizing - PCS	0.50*	0.57*	0.47*	0.57*	0.58*

ICOAP (Intermittent and Constant Osteoarthritis Pain), HADS (Hospital Anxiety and Depression scale), PCS (Pain Catastrophizing Scale). Data from participants with knee pain (n=322). Data are Spearman correlation coefficients using untransformed total scale scores. *P<0.05

Supplementary Table 9. Inter-item correlation matrix for 19 items putatively reflecting central mechanisms in people with knee pain.

Domains		Anxiety		Depression		Neuropathic- like pain			Fatigue	Cognitive Impact	Pain Distribution	Pain Catastrophizing				Constant pain experience			Intermittent pain experience
	Items	Fright	Panic	Still enjoy	Look forward	Tingling	Light touch	Cold heat	Tired	Concentrate on pain	Other pain below waist	Can't stand it	Can't go on	Out of mind	Keep thinking	Sleep	Frustrate	Upset	Sleep
Anxiety	Panic	0.66*	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Depression	Still enjoy	0.19*	0.20*	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Look forward	0.32*	0.28*	0.56*	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Neuropathic-like pain	Tingling	0.24*	0.20*	0.27*	0.20*	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-
	Light touch	0.22*	0.29*	0.26*	0.23*	0.51*	1.00	-	-	-	-	-	-	-	-	-	-	-	-
	Cold/heat	0.21*	0.20*	0.25*	0.26*	0.47*	0.65*	1.00	-	-	-	-	-	-	-	-	-	-	-
Fatigue	Tired	0.41*	0.39*	0.33*	0.37*	0.23*	0.31*	0.33*	1.00	-	-	-	-	-	-	-	-	-	-
Cognitive Impact	Concentrate on pain	0.35*	0.33*	0.41*	0.38*	0.38*	0.41*	0.37*	0.44*	1.00	-	-	-	-	-	-	-	-	-
Pain Distribution	Other pain below waist	0.11	0.07	0.21*	0.24*	0.07	0.19*	0.13*	0.18*	0.29*	1.00	-	-	-	-	-	-	-	-
Pain Catastrophizing	Can't stand it	0.41*	0.34*	0.35*	0.43*	0.42*	0.29*	0.33*	0.36*	0.49*	0.11	1.00		-	-	-	-	-	-
	Can't go on	0.40*	0.32*	0.37*	0.44*	0.36*	0.31*	0.33*	0.32*	0.42*	0.11	0.67*	1.00	-	-	-	-	-	-
	Out of mind	0.46*	0.40*	0.28*	0.44*	0.39*	0.33*	0.35*	0.38*	0.44*	0.17*	0.69*	0.53*	1.00	-	-	-	-	-
	Keep thinking	0.44*	0.39*	0.22*	0.41*	0.35*	0.38*	0.34*	0.33*	0.42*	0.19*	0.71*	0.51*	0.78*	1.00	-	-	-	-
Constant pain experience	Sleep	0.17*	0.19*	0.27*	0.29*	0.45*	0.53*	0.51*	0.35*	0.48*	0.26*	0.44*	0.32*	0.41*	0.43*	1.00	-	-	-
	Frustrate	0.22*	0.18*	0.36*	0.32*	0.49*	0.42*	0.45*	0.35*	0.47*	0.24*	0.52*	0.36*	0.50*	0.48*	0.67*	1.00	-	-
	Upset	0.26*	0.26*	0.31*	0.32*	0.49*	0.41*	0.41*	0.32*	0.45*	0.20*	0.47*	0.37*	0.51*	0.49*	0.60*	0.87*	1.00	-
Intermittent pain experience	Sleep	0.24*	0.26*	0.26*	0.30*	0.48*	0.53*	0.48*	0.33*	0.46*	0.26*	0.46*	0.33*	0.42*	0.44*	0.85*	0.63*	0.59*	1.00
	Upset	0.26*	0.26*	0.29*	0.33*	0.49*	0.37*	0.42*	0.31*	0.45*	0.21*	0.48*	0.39*	0.53*	0.51*	0.50*	0.78*	0.87*	0.54*

Full item texts were the same as given in Supplementary Table 7. Data are Spearman correlation coefficients from participants with knee pain (n=322). *p<0.05.

Supplementary Table 10. Associations between selected items and proximal tibia pressure pain detection threshold (PPT) are dependent on constructs measured by their host questionnaires.

	Unadjusted model			Adjusted model		
Domains	b (95% CI)	β	p	b (95% CI)	β	p
Constant Pain Experience “In the past week, how much has your constant knee pain affected your sleep?”	**-0.11 (-0.17 to -0.04)**	**-0.21**	**0.001**	-0.08 (-0.17 to 0.02)	-0.15	0.119
Neuropathic- like pain “Over the past month, in your most painful knee, is cold or heat (bath water) in this area occasionally painful?”	**-0.10 (-0.17 to -0.05)**	**-0.23**	**<0.001**	**-0.10 (-0.17 to -0.03)**	**-0.21**	**0.008**
Catastrophizing "I keep thinking about how much it hurts"	**-0.06 (-0.12 to -0.01)**	**-0.13**	**0.03**	0.004 (-0.12 to 0.12)	0.007	0.953
Anxiety "I get sudden feelings of panic"	**-0.13 (-0.21 to -0.05)**	**-0.19**	**0.001**	**-0.12 (-0.24 to -0.01)**	**-0.19**	**0.032**
Depression "I still enjoy the things I used to enjoy"	**-0.10 (-0.18 to -0.02)**	**-0.15**	**0.01**	-0.06 (-0.16 to 0.04)	-0.09	0.252

In order to explore whether observed univariate associations between each selected item and proximal tibia log-PPTs might be explained by the construct measured by the host scale from the host scale from which it originated, we adjusted each univariate association for the derived host scale score (scale summary score minus selected item). Data are from participants with knee pain sample (n=322). Bold indicates significant associations after adjustment. Unstandardized (b) and standardized coefficients (β) are presented.

Supplementary Table 11: PPTs at sites other than the proximal tibia are predicted by ROC- derived and *a priori*- binary manikin classifications in individuals within the knee pain sample (n=322)

	Sternum			**Med JL**			**Lat JL**		
	b (95% CI)	β	p	b (95% CI)	β	p	b (95% CI)	β	p
Roc-Derived Classifications									
≥5/7 other sites	**-0.20 (-0.37 to -0.03)**	**-0.18**	**0.002**	**-0.24 (-0.39 to -0.09)**	**-0.15**	**0.011**	**-0.29 (-0.47 to -0.12)**	**-0.19**	**0.001**
≥6/23 other sites	**-0.19 (-0.34 to -0.04)**	**-0.14**	**0.019**	**-0.16 (-0.30 to -0.03)**	**-0.14**	**0.018**	**-0.21 (-0.36 to -0.05)**	**-0.15**	**0.010**
A priori Classifications									
Above waist	-0.08 (-0.22 to -0.06)	-0.05	0.430	-0.05 (-0.17 to 0.07)	-0.08	0.205	-0.08 (-0.22 to 0.06)	-0.07	0.266
Below waist	**-0.17 (-0.30 to -0.03)**	**-0.16**	**0.007**	**-0.27 (-0.42 to -0.12)**	**-0.21**	**0.001**	**-0.22 (-0.36 to -0.08)**	**-0.18**	**0.002**
Contralateral to index knee	-0.14 (-0.28 to 0.002)	-0.08	0.165	-0.18 (-0.34 to 0.03)	**-0.14**	**0.021**	-0.12 (-0.27 to 0.02)	-0.09	0.100
Axial pain	-0.01 (-0.15 to 0.12)	-0.05	0.441	-0.08 (-0.23 to 0.07)	-0.06	0.318	-0.07 (-0.21 to 0.07)	-0.06	0.309
ACR's Widespread pain[a]	-0.10 (-0.34 to 0.14)	-0.05	0.407	-0.09 (-0.39 to 0.20)	-0.04	0.533	0.01 (-0.22 to 0.25)	0.007	0.910

Classifications are based on number or distribution of painful sites in addition to knee pain reported by participants on a body manikin. [a]Widespread pain; classified according to American College of Rheumatology criteria[37], including knee pain. Bold indicates statistically significant associations. ROC; receiver-operating curve. Log-transformed pressure pain detection thresholds (PPT) at (medial or lateral tibiofemoral joint line (JL), or remote (sternum) from the index knee reported here. Data utilized from knee pain sample (n=322). Unstandardized (b) and standardized (β) regression coefficients are presented.

Supplementary Table 12. Associations between latent construct `Central mechanisms' and PPTs for sites other than proximal tibia within the knee pain sample (n=322)

Scales adjusted for	Sternum			Medial JL			Lateral JL		
	β	S.E	P	β	S.E	P	β	S.E	P
Unadjusted Model	**-0.25**	**0.06**	**<0.001**	**-0.41**	**0.06**	**<0.001**	**-0.39**	**0.06**	**<0.001**
Constant Pain experience - ICOAP	**-0.22**	**0.07**	**0.001**	**-0.32**	**0.06**	**<0.001**	**-0.29**	**0.07**	**<0.001**
Neuropathic- like pain - PainDETECT	**-0.22**	**0.06**	**0.001**	**-0.31**	**0.07**	**<0.001**	**-0.30**	**0.07**	**<0.001**
Catastrophizing - PCS	**-0.21**	**0.07**	**0.003**	**-0.38**	**0.07**	**<0.001**	**-0.34**	**0.07**	**<0.001**
Anxiety - HADS	**-0.20**	**0.07**	**0.003**	**-0.37**	**0.06**	**<0.001**	**-0.35**	**0.06**	**<0.001**
Depression - HADS	**-0.19**	**0.07**	**0.008**	**-0.42**	**0.07**	**<0.001**	**-0.37**	**0.07**	**<0.001**

The single latent construct identified through the 8 selected items, interpreted as `central mechanisms of knee pain', was associated with log-transformed pressure pain detection thresholds (PPT) at (medial or lateral tibiofemoral joint line (JL), or remote (sternum) from the index knee in an unadjusted model, and in models where total scores derived from each of the originating scales (scale summary score minus selected item) were adjusted for.
Standardized regression coefficients (β) presented.