Research Paper

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# Experimental pain phenotyping in community-dwelling individuals with knee osteoarthritis

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**Abstract**

Pain among individuals with knee osteoarthritis (OA) is associated with significant disability in older adults, and recent evidence demonstrates enhanced experimental pain sensitivity. Although previous research showed considerable heterogeneity in the OA clinical pain presentation, less is known regarding the variability in responses to experimental pain. The present study included individuals with knee OA (n = 292) who participated in the Understanding Pain and Limitations in Osteoarthritic Disease study and completed demographic and psychological questionnaires followed by a multimodal quantitative sensory testing (QST) session. Quantitative sensory testing measures were subjected to variable reduction procedures to derive pain sensitivity index scores, which in turn were entered into a cluster analysis. Five clusters were significantly different across all pain sensitivity index variables ($P < 0.001$) and were characterized by: (1) low pain sensitivity to pressure pain (N = 39); (2) average pain sensitivity across most modalities (N = 88); (3) high temporal summation of punctate pain (N = 38); (4) high cold pain sensitivity (N = 80); and (5) high sensitivity to heat pain and temporal summation of heat pain (N = 41). Clusters differed significantly by race, gender, somatic reactivity, and catastrophizing ($P < 0.05$). Our findings support the notion that there are distinct subgroups or phenotypes based on experimental pain sensitivity in community-dwelling older adults with knee OA, expanding previous findings of similar cluster characterizations in healthy adults. Future research is needed to further understand the pathophysiological mechanisms underlying pain within these subgroups, which may be of added value in tailoring effective treatments for people with OA.

**Keywords:** Pain phenotypes, QST, Principal component analysis, Hierarchical clustering, Experimental pain phenotypes

## 1. Introduction

Pain is the clinical hallmark of knee osteoarthritis (OA) and represents a significant source of disability in older adults. Knee OA has been viewed historically as a disease localized to the knee joint, but peripheral markers of disease severity measured using x-rays and/or magnetic resonance imaging account for only a limited proportion of OA-related clinical pain and associated disability. Given the complex array of factors known to contribute to the experience of pain, assessment of responses to well-controlled, experimental pain stimuli, or quantitative sensory testing (QST) can provide valuable insights into the pain experience and possible underlying mechanisms.[14] The QST methods include administration of multiple stimulus modalities (eg, thermal, mechanical) and assessment of various perceptual endpoints (eg, threshold, tolerance, and suprathreshold scaling). In addition, methods for assessing pain modulatory function, including both inhibition and facilitation, are increasingly used.[8] In general, a multimodal QST protocol is recommended to more fully characterize pain processing in clinical populations.

Recent QST studies in individuals with OA have revealed distinct subgroups consistent with significant central nervous system alterations to pain processing and even to predict treatment outcomes.[2,3,22,28,30,33,51] Whereas most previous investigators have examined QST measures as individual variables, a more sophisticated approach would consider patterns of responses across multiple QST measures. Although QST phenotypic heterogeneity has been reported in healthy individuals,[16,25,49] less is known in knee OA. Recent investigations have used pressure pain thresholds, temporal summation (TS) of pressure pain, and conditioned pain modulation (CPM) as a mechanism-based pain sensitivity index (PSI) to characterize knee OA with different disease stages and pain levels[2] and their associations with postoperative outcomes.[46] Accounting for interindividual variability in experimental pain may lead to improved translation of results from the laboratory to the clinic. Therefore, an integrated, multivariable assessment including multiple QST measures may be particularly relevant for elucidating the importance of altered somatosensory function among individuals with knee OA. This multifactorial approach may also

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lead to development of evidence-based treatments that are tailored to the individuals' QST profiles.

Previous research has demonstrated considerable heterogeneity in the OA clinical pain presentation including mixed neuropathic and nociceptive pain characteristics.[3,22,26,28,30,33] However, less is known regarding the variability in responses to experimental pain in this population that may provide significant insights into the clinical pain experienced by these individuals.[34] The present study aims to: (1) identify the somatosensory phenotype profiles within a sample of community-dwelling middle-aged and older adults with mild to moderate knee OA pain; (2) determine the psychosocial and demographic characteristics across these subgroups; and (3) determine the relationship between these experimental phenotype profiles and self-reported measures of clinical pain and physical function. Based on previous work,[16,25,41] we tested the hypothesis that modality-specific phenotypes could be reproduced in a sample of community-dwelling middle-aged and older adults with symptomatic knee OA. Last, we hypothesized that clusters would differ significantly across demographic, psychosocial, clinical pain, and physical function measures.

## 2. Methods

### 2.1. Study participants

The current investigation is a secondary data analysis from 292 community-dwelling individuals with knee OA who participated in the Understanding Pain and Limitations in OsteoArthritic Disease study at the University of Florida and the University of Alabama at Birmingham. The primary objective of the study was to elucidate the mechanisms underlying ethnic differences in pain and functional limitations in persons with knee OA. The sample included individuals between 45 and 85 years of age, who identified themselves as either African American or non-Hispanic whites. Based on the American College of Rheumatology clinical criteria for knee OA[1] participants had bilateral or unilateral symptomatic knee OA. Poster anterior and lateral radiographs of the knee were taken from participants for the purpose of determining radiographic severity of OA based on the Kellgren and Lawrence[29] system (score range, 0-4) during their first study session. Participants were excluded if they: (1) had cognitive impairment; (2) used opioids on a daily basis; (3) were hospitalized for a psychiatric illness in the preceding year; (4) had uncontrolled hypertension (blood pressure >150/95 mm Hg), a history of acute myocardial infarction or heart failure; (5) had a prosthetic knee replacement or other clinically significant surgery to the affected knee; (6) had peripheral neuropathy; (7) had systemic diseases including rheumatoid arthritis, systemic lupus erythematosus, or fibromyalgia. Participants were allowed to have other pain conditions given that their knee pain was their most significant pain problem as measured by their clinical pain ratings.

### 2.2. Study overview

Study procedures and details about the design have been previously reported elsewhere.[17,30] In summary, after obtaining informed consent, participants attended a general health assessment session and a QST session no more than 4 weeks apart. During the health assessment session, participants completed demographic, clinical, and psychosocial questionnaires (detailed below) and a physician or nurse practitioner conducted a health history and physical examination. During the QST session (detailed below), participants underwent thermal (cold and heat), mechanical (pressure and punctate), and TS of pain (to heat and punctate stimuli). The QST sessions started either with heat or mechanical pain procedures and the order was counterbalanced across participants. Both the University of Florida and University of Alabama at Birmingham Institutional Review Boards approved the study.

### 2.3. Quantitative sensory testing

#### 2.3.1. Heat pain procedure

Heat thermal stimuli were delivered using a computer-controlled Medoc PATHWAY Pain & Sensory Evaluation System. The position of the thermode was moved between trials to avoid sensitization and/or habituation of cutaneous nociceptors. Heat pain threshold and tolerance were assessed on both the index knee (ie, the most painful knee) and ipsilateral ventral forearm. Specifically, 3 sites were assessed across 3 trials around the joint line of the index knee (ie, where the femur and tibia meet). The sites were: (1) the medial joint line, which was located immediately medial to the patella, (2) the area above the patella, which was medially and above the joint line, and (3) the area below the patella, which was medially and below the joint line. We used the ascending method of limits with a 16 × 16 mm Advanced Thermal Stimulator (Medoc, Ramat Yishai, Israel). Heat pain threshold was assessed first. For each trial, the thermode would start at a baseline temperature of 32°C and increase at a rate of 0.5°C/s until the participant responded by pressing a button as soon as the sensation "first became painful." Subsequently, heat pain tolerance was assessed. Participants were instructed to press the button when they "no longer felt able to tolerate the pain." For both the heat pain threshold and tolerance procedures, each test was repeated 3 times and the mean temperature was used for analysis.

#### 2.3.2. Temporal summation of heat pain

Five minutes after the assessment of heat pain threshold and tolerance, participants went through a second thermal procedure to assess TS of heat pain. Participants were instructed to verbally rate the intensity of peak pain evoked by each of 5 brief, repetitive, suprathreshold heat pulses on a visual analogue scale of 0 to 100, where 0 = no pain sensation and 100 = the most intense pain sensation imaginable. Target temperatures were delivered by a Contact Heat-Evoked Potential Stimulator (Medoc) thermode. Stimuli were applied on the dorsal forearm and the index knee for 750 milliseconds duration, with a 2.5-second interstimulus interval (ie, ~0.4 Hz). During the TS trials, 2 different temperatures were used (46°C and 48°C). The procedure was terminated if the participant rated the thermal pain at 100. The average rating over the 5 stimuli per TS trial was used for each temperature as an index of overall sensitivity to suprathreshold heat pain. A measure of TS was also calculated by subtracting the fifth trial pain rating from the first trial pain rating provided at each temperature.

#### 2.3.3. Pressure pain procedure

Pressure pain threshold was evaluated at multiple sites, including 2 sites on the index knee or the most affected knee and on ipsilateral sites including the quadriceps, trapezius, and extensor carpi radialis longus. Specifically, the site along the knee medial joint line was determined by palpating the medial aspect of the joint line (ie, the joint line is where the femur and tibia meet). We applied pressure to the medial femoral condyle while supporting

the opposite side of the knee with an open hand. The second knee site was along the lateral joint line of the knee, which was determined by palpating the lateral aspect of the joint line. We applied pressure to the lateral femoral condyle while supporting the opposite side of the knee with an open hand. The order of testing was counterbalanced and randomized. For each site, a handheld digital pressure algometer (AlgoMed; Medoc) was applied at a constant rate of 30 kPa/s using a rubber tip probe of 10 mm diameter. The participant was instructed to press a button when the sensation "first became painful." The amount of pressure (kPa) that first produced a painful sensation was recorded. The pressure pain threshold procedure was repeated 3 times for each testing site to create an average pressure pain threshold for the site. The maximum pressure for the 2 knee sites was 600 kPa, whereas the other sites were set at 1000 kPa due to safety and ethical concerns for our participants with knee pain. If participants did not report pain at the maximum pressure level, the procedure was terminated and a score of 600 or 1000 was assigned for that trial.

#### 2.3.4. Temporal summation of punctate pain

After pressure pain, participants underwent a second procedure to assess sensitivity to punctate mechanical stimuli with a calibrated nylon monofilament delivering a target force of 300 g. Testing sites included the patella of the index knee and the back of the ipsilateral hand, in a randomized order. To assess TS of mechanical pain at each site, participants were instructed to provide a verbal 0 to 100 rating of pain after a single contact of the monofilament. Then, participants were instructed to provide another 0 to 100 rating of their greatest pain intensity experienced after a series of 10 contacts, which were provided at a rate of 1 contact per second. This procedure was repeated twice at each anatomical location. Pain ratings performed at each anatomical location were averaged across the 2 trials. A measure of TS was determined for each participant by subtracting the first trial rating from the last rating provided at each site.

#### 2.3.5. Cold pain procedure

The participants immersed the right hand up to the wrist during 3 separate trials with 16˚C, 12˚C, and 8˚C water temperature. The water temperature was maintained (+0.1˚C) by a refrigeration unit (Neslab, Portsmouth, NH), and the water was constantly recirculated to prevent local warming around the submerged hand. The time to first feeling of pain was recorded as the cold pain threshold separately for 16˚C, 12˚C, and 8˚C water temperatures. A cold pain threshold measure obtained from each of the cold-pressor test temperatures (16˚C, 12˚C, and 8˚C) was used for the analysis. Cold pain threshold was recorded in seconds. Each water immersion was separated by a 10-minute break, in which time a heating pad was applied to rewarm the hand.

#### 2.3.6. Conditioned pain modulation

After a 20-minute rest period, participants began CPM, a marker of endogenous pain inhibition. The conditioning stimulus was the cold-pressor task applied to the right hand, the temperature of which was based on the results of cold-pressor testing from the first cold-pressor procedure. The temperature was tailored to the individual participant to achieve a stimulus that produced moderate pain (ie, a rating of 40-60 on the 0-100 scale) and could be tolerated for a 60-second period. The test stimulus was "TS of heat pain" applied to the left ventral forearm, at a predetermined stimulus intensity, which produced moderate but tolerable pain based on the results of the first heat TS procedure. For the analysis, CPM was calculated by the difference between the TS of heat pain before and after a cold-water immersion at the individualized temperature. The CPM measure was subsequently used to compare between the clusters.

### 2.4. Clinical and psychosocial assessments

The following psychological instruments were administered.

#### 2.4.1. Coping Strategies Questionnaire—Revised

The Coping Strategies Questionnaire (CSQ) assesses passive and active coping techniques related to pain in general.[7,53] Participants rated the frequency with which they engage in various coping techniques using a 7-point scale.

#### 2.4.2. In Vivo Coping Questionnaire

The In Vivo Coping Questionnaire (IVC) is a 10-item questionnaire rated on a 5-point scale that measures the degree to which participants used various strategies to deal with experimental pain. The IVC was administered on the second study session following the sensory testing procedures.

#### 2.4.3. Kohn Reactivity Scale

The Kohn Reactivity Scale (KRS) is commonly used to measure aspects of hypervigilance and general reactivity and arousability[31] to common experiences across 24 items using a 5-point scale. Higher reactivity scores indicate increased sensitivity to low-level stimulation and increased distractibility.

#### 2.4.4. Pain Vigilance and Awareness Questionnaire

The Pain Vigilance and Awareness Questionnaire (PVAQ) assesses attention and vigilance to pain[38] as well as a participant's preoccupation with or attention to pain, which was found to be related to fear of pain and perceived pain severity. This instrument consists of 16 items and participants indicated how frequently they engaged in various behaviors over the past few weeks using a 6-point scale.

### 2.5. Self-report measures of clinical pain and function

The following pain measures were included to characterize cluster participants using a comprehensive pain and functional assessment battery.

#### 2.5.1. Graded Chronic Pain Scale

The Graded Chronic Pain Scale (GCPS) evaluates global pain severity and pain-related interference over the past 6 months and consists of 7 items related to pain intensity and pain interference (ie, loss of work days due to pain, interference in daily activities).[57] With a 0 to 10 numerical rating scale, participants rated the intensity of their current knee pain and the worst and average pain during the past 6 months. These 3 items were averaged and multiplied by 10 to generate a characteristic pain intensity score. Using the same scale, participants rated the degree to which their knee pain

interfered with daily activities (3 items) during the past 6 months, which was averaged and multiplied by 10 to generate a disability score.

#### 2.5.2. Western Ontario and McMaster Universities Osteoarthritis Index

The Western Ontario and McMaster Universities Osteoarthritis Index assesses symptoms of knee OA in the past 48 hours.[4,12,54] For this study, the 4-point Likert scale version was used. The Index yields 3 subscales, including pain during activities (5 items), stiffness during the day (2 items), and impairments in physical function (17 items), with higher scores indicating worse pain, stiffness, and impairments in physical function.

#### 2.5.3. Widespread pain condition

Participants were asked to check-off on a table, body areas where they experienced pain, in addition to the knee. The areas included were the head, neck, hands, arms, chest, shoulders, stomach, upper and lower back, legs, and feet. These areas were used to determine if participants had a widespread pain condition according to the American College of Rheumatology criteria[60] operationalized as pain that was present in upper and lower quadrants and on both sides of the body.

### 2.6. Statistical methods

#### 2.6.1. Variable reduction of experimental pain measures

The following 18 variables were entered into a principal component analysis (PCA):

(1) Pressure Pain Threshold at the medial joint line of the index knee (mean of 3 trials)
(2) Pressure Pain Threshold at the lateral joint line of the index knee (mean of 3 trials)
(3) Pressure Pain Threshold at the quadriceps muscle (mean of 3 trials)
(4) Pressure Pain Threshold at the trapezius muscle (mean of 3 trials)
(5) Pressure Pain Threshold at the extensor carpi radialis muscle (mean of 3 trials)
(6) Heat Pain Threshold at the medial joint line of the index knee (mean of 3 trials)
(7) Heat Pain Threshold at the ventral forearm (mean of 3 trials)
(8) Heat Pain Tolerance at the medial joint line of the index knee (mean of 3 trials)
(9) Heat Pain Tolerance at the ventral forearm (mean of 3 trials)
(10) TS of Punctate Pain at the patella of the index knee (mean of 2 trials)
(11) TS of Punctate Pain at the back of the hand (mean of 2 trials)
(12) TS of Heat Pain at the medial joint line of the index knee at 46°C (only 1 trial)
(13) TS of Heat Pain at the dorsal forearm at 46°C (only 1 trial)
(14) TS of Heat Pain at the medial joint line of the index knee at 48°C (only 1 trial)
(15) TS of Heat Pain at the dorsal forearm at 48°C (only 1 trial)
(16) Cold Pain Threshold at 8°C (only 1 trial)
(17) Cold Pain Threshold at 12°C (only 1 trial)
(18) Cold Pain Threshold at 16°C (only 1 trial)

Principal components were identified using both orthogonal and oblique rotations in a PCA to compare item loadings and to be certain that we had identified the most consistent latent structure within our sample. The results were examined to ascertain the concordance of primary loadings for individual experimental measures. Components with eigenvalues greater than 1 were retained for further analysis and the scree plot was inspected to confirm that the proper number of factors had been selected. Additionally, web-based parallel analysis (PA) using O'Connor's[43] SAS-based code for PA was also used as a method to determine the proper number of components.[44,45] The eigenvalues from the PCA were compared with the eigenvalues in the 95th percentile of 1000 randomly generated correlation matrices that had the same number of variables and observations as the real data. Components from the real data were then retained wherever the i-th eigenvalue from the real data set was larger than the i-th eigenvalue from the random correlation matrices. Last, PSI scores were calculated for each factor by averaging the z-scores of the raw variables that corresponded with the primary loadings. All z-scores were computed such that positive PSI scores indicated greater pain sensitivity, whereas negative PSI scores indicated less pain sensitivity.

#### 2.6.2. Cluster analysis of component scores

Following the PCA, hierarchical clustering analysis using Ward's clustering method with squared Euclidean distances was used to assess similarities in PSI scores and to identify homogenous clusters of observations. The optimal number of clusters was determined by examining the agglomeration coefficients of hierarchical clusters and analysis of the dendogram. Differences in sensitivity to various pain modalities were probed with analysis of covariance to assess the appropriateness and internal validity of the cluster solution.

#### 2.6.3. Differences between and within clusters on demographic, psychosocial, and general health measures

Differences between cluster demographic composition or psychosocial characteristics and physical function were assessed using $\chi^2$ analysis for categorical variables and analysis of variance for continuous variables. Differences in binomial variables such as gender and race within clusters were examined with binomial tests. Analysis of covariance with Bonferroni post hoc adjustments was also used to account for age, sex, race, body mass index, level of education, income, and study site. Descriptive statistics are reported as mean and standard deviation wherever applicable. Pearson correlations were used to examine associations between the pain index scores. Statistical significance was set to 0.05. All analysis was conducted using the SAS 9.4 software for Windows (SAS Institute Inc, Cary, NC).

## 3. Results

### 3.1. Study participants

The present study sample consisted mainly of female (63.5%) and African-American (56.9%) participants, with an average age of 57 years. Most of the participants included in the study were tested at the University of Florida (68%). Overall, 47% of the participants had a KL grade score of 0, 15% had a KL grade score of 1, 12% had a KL grade score of 2, 16% had a KL grade score of 3, and 9% had a KL grade score of 4.

### 3.2. Variable reduction of experimental pain measures

The PCA was carried out on the experimental pain variables using both orthogonal and oblique rotations to account for

**Table 1**

**Principal components analysis: loadings and eigenvalues of experimental pain measures.**

| Pain measures | Pressure pain | Heat pain | Temporal summation of heat pain | Cold pain | Temporal summation of punctate pain |
|---|---|---|---|---|---|
| PP threshold mJL | **0.850** | 0.229 | −0.006 | 0.126 | −0.150 |
| PP threshold lateral JL | **0.848** | 0.207 | −0.028 | 0.098 | −0.109 |
| PP threshold quadriceps | **0.860** | 0.209 | −0.037 | 0.147 | −0.016 |
| PP threshold trapezius | **0.787** | 0.185 | −0.126 | 0.262 | −0.060 |
| PP threshold epicondyle | **0.815** | 0.182 | −0.086 | 0.136 | −0.086 |
| HP tolerance knee | 0.205 | **0.855** | −0.131 | 0.014 | −0.144 |
| HP tolerance arm | 0.244 | **0.806** | −0.166 | −0.016 | −0.194 |
| HP threshold knee | 0.201 | **0.776** | −0.067 | 0.226 | −0.017 |
| HP threshold arm | 0.261 | **0.794** | −0.029 | 0.112 | −0.037 |
| TS arm at 46°C (Δ0-100) | −0.121 | −0.128 | **0.750** | −0.092 | −0.069 |
| TS arm at 48°C (Δ0-100) | −0.044 | −0.002 | **0.785** | 0.087 | 0.119 |
| TS knee at 46°C (Δ0-100) | −0.014 | −0.166 | **0.785** | −0.083 | 0.074 |
| TS knee at 48°C (Δ0-100) | −0.049 | −0.028 | **0.795** | −0.039 | 0.086 |
| CP threshold 8°C | 0.154 | 0.151 | −0.055 | **0.858** | −0.010 |
| CP threshold 12°C | 0.183 | 0.125 | −0.003 | **0.899** | −0.084 |
| CP threshold 16°C | 0.198 | 0.001 | −0.053 | **0.747** | −0.032 |
| Punctate patella (Δ0-100) | −0.172 | −0.113 | 0.093 | −0.117 | **0.870** |
| Punctate hand (Δ0-100) | −0.097 | −0.159 | 0.097 | −0.077 | **0.888** |
| % of variance | 34.4 | 13.4 | 10.2 | 8.6 | 7.6 |
| Cumulative % variance | 34.4 | 47.8 | 58.0 | 66.6 | 74.2 |

CP, cold pain; HP, heat pain; JL, joint line; mJL, medial joint line; PP, pressure pain; TS, temporal summation.

variable associations. Given that the variable loadings were almost identical between the orthogonal and oblique rotations, we chose to present the orthogonal rotation since they minimize cross loadings while the substantive interpretations are essentially the same. After agreement of the solution, the varimax rotation was reported. All variables had values greater than 0.70 on Kaiser–Meyer–Olkin measures of sampling adequacy, indicating satisfactory matrix factorability. The 5 components that arose from the PCA are presented in **Table 1**. Furthermore, PA yielded similar results, where only the first 5 eigenvalues in the real data set were greater than the corresponding eigenvalues from the 95th percentile of 1000 randomly generated correlation matrices. The eigenvalues of retained components spanned from 1.36 to 6.19, and they explained 74.1% of the total variance. The factor loadings on each of the 5 components revealed the following 5 factors: pressure pain, heat pain, TS of heat pain, cold pain, and TS of mechanical pain (**Table 1**). The experimental pain measures that comprised the pressure pain factor were pressure pain threshold on the medial and lateral knee joints, the quadriceps, the trapezius, and the epicondyle (factor loadings 0.79-0.86). Heat pain was the second factor, and it included heat pain threshold and tolerance tests on the arm and knee (factor loadings, 0.79-0.86). The heat TS factor comprised heat TS change scores for the knee and arm at 46°C and 48°C (factor loadings 0.75-0.80). The fourth factor contained cold pain threshold measures at 8, 12, and 16°C (factor loadings 0.75-0.90). Last, the fifth factor included the change scores from mechanical pain ratings for the patella and the hand (factor loadings, 0.87-0.89). Correlations between the PSI scores were generally small to moderate in magnitude (**Table 2**).

### *3.3. Cluster analysis of pain sensitivity index scores*

The PSI scores were subjected to hierarchical clustering procedure to determine subgroupings based on the patterns of pain sensitivity to the different pain modalities. A 5-cluster solution was selected based on agglomeration coefficients of hierarchical clusters and analysis of the dendogram. The following 5 clusters emerged: (1) participants with the lowest pain sensitivity across all pain modalities, but particularly to pressure pain (low pressure pain sensitivity, N = 39); (2) participants with average pain sensitivity across most modalities (average pain sensitivity, N = 88); (3) participants who displayed the greatest TS of punctate

**Table 2**

**Correlation coefficients between the pain sensitivity index scores used for hierarchical cluster analysis.**

| | Pressure pain | Heat pain | Temporal summation of heat pain | Cold pain | Temporal summation of punctate pain |
|---|---|---|---|---|---|
| Pressure pain | ** | | | | |
| Heat pain | 0.50 | ** | | | |
| Heat temporal summation | −0.15 | −0.21 | ** | | |
| Cold pain | 0.38 | 0.26 | −0.14 | ** | |
| Punctate temporal summation | −0.31 | −0.33 | 0.20 | −0.20 | ** |

** indicates that this correlation is irrelevant because it is perfectly correlated with itself.

pain (high TS of punctate pain, N = 38); (4) participants who showed the greatest cold pain sensitivity (high cold pain sensitivity, N = 80); and (5) participants with the greatest sensitivity to heat pain and with the greatest TS of heat pain (high heat pain sensitivity/high TS of heat pain, N = 41) (**Fig. 1**). The 5 clusters were also analyzed with respect to the non-transformed values to assess the internal validity of the cluster solution. In concordance with the previous analysis, the clusters differed significantly with respect to the original raw, untransformed variables ($P < 0.0001$, **Table 3**).

### *3.4. Differences across and within clusters on demographic, psychological, and health-related measures*

Clusters were similar in age; however, differences in sex and race emerged across clusters ($P < 0.0001$; **Table 4**). Specifically, women and African Americans comprised the most participants in the high heat pain sensitive cluster and in the high TS of punctate pain cluster. In contrast, the low pressure pain sensitive cluster was predominantly male (68.4%) and non-Hispanic white (67.6%). Higher income and education characterized the low pressure Pain sensitive cluster, whereas the high heat pain/high TS of heat pain and high TS of punctate pain cluster showed lower income and education. However, there were no differences in CPM responses across the clusters.

The catastrophizing score of the CSQ differed significantly across the clusters after adjusting for race, sex, site of the experiment, annual income, education, and BMI ($P = 0.0001$; **Table 5**). Bonferroni post hoc test revealed significant differences on average catastrophizing score between the low pressure pain cluster and the high heat pain cluster ($P < 0.0001$). In addition, the low pressure pain group and the high heat pain/high TS of heat pain group were significantly different in CSQ passive coping and IVC active coping scores ($P < 0.0001$ and $P = 0.0365$, respectively). The KRS and the PVAQ total scores were also significantly different across all clusters ($P = 0.006$ and $P = 0.005$, respectively). As shown by post hoc analysis, the low pressure pain sensitivity cluster had the lowest KRS and PVAQ scores (**Table 5**). In addition, GCPS pain intensity scores were significantly different between clusters ($P = 0.0385$; **Table 6**). Post hoc tests show that the high TS of punctate pain and the high heat pain/high TS of heat pain clusters had significantly higher clinical pain intensity scores compared with both the low pressure pain group and the average pain sensitive group.

## 5. Discussion

We sought to identify experimental pain phenotype profiles in a large cohort of non-Hispanic white and African-American community-dwelling middle-aged and older adults with symptomatic knee OA and to determine the relationship between these profiles with demographic and psychosocial variables. Our findings suggest that in individuals with mild to moderate knee OA pain, responses to experimental pain stimuli are distinct phenomena consistent with the organization of the somatosensory system. The factors that emerged generally followed stimulus modalities: pressure pain, heat pain, cold pain, with 2 additional factors of heat and punctate TS of pain. Consistent with our findings, neuroimaging has uncovered different patterns of activation across various stimulation modalities,[20] and Nielsen et al.[42] reported that the genetic and environmental factors that accounted for most cold and heat pain sensitivity were modality specific. Furthermore, others have reported that adaptation and facilitation in response to cold and pressure stimulation show weak correlations.[47] Taken together, the present study lends support for the utility of a multimodal pain assessment approach in persons with knee OA.

The ensuing cluster analysis resulted in 5 groups characterized by: (1) low pressure pain sensitivity; (2) average pain sensitivity; (3) high TS of punctate pain; (4) high cold pain sensitivity; and (5) high heat pain sensitivity/high TS of heat pain. These clusters replicate and extend those originally reported by our group in healthy individuals.[16,25] Specifically, we found a group of participants who were particularly sensitive to both painful heat and experienced high heat TS. Previous studies have reported that heat pain sensitivity may be an important predictor of chronic pain. Individuals who were sensitive to experimental heat pain

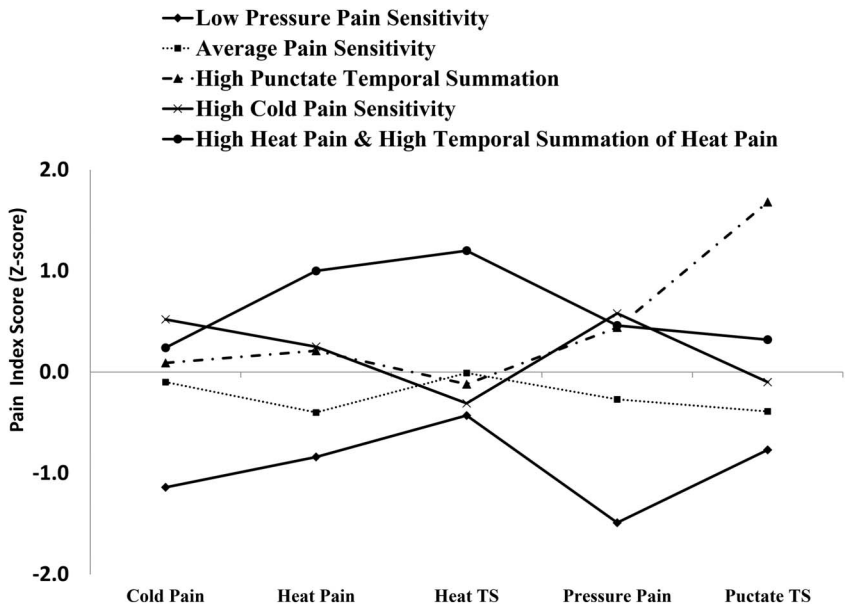


**Figure 1.** Pain index scores by cluster. CP, cold pain; HP, heat pain; HTS, heat temporal summation; PrP, pressure pain; PuP, punctate pain.

**Table 3**

**Means for each experimental pain measure across the 5 clusters.**

| Pain measures means (SD) | Low pressure pain sensitivity (n = 39) | Average pain sensitivity (n = 88) | High temporal summation of punctate pain (n = 38) | High cold pain sensitivity (n = 80) | High heat pain and temporal summation of heat pain (n = 41) | Probability | |
|---|---|---|---|---|---|---|---|
| | | | | | | Unadjusted | Adjusted[a] |
| PP threshold medial JL[b] | 528.5 (91.4) | 350.5 (132.5) | 193.3 (129.8) | 177.9 (78.3) | 210.3 (125.8) | <0.0001 | <0.0001 |
| PP threshold lateral JL[b] | 534.9 (113.9) | 360.5 (130.8) | 215.5 (162.8) | 205.9 (108.7) | 224.5 (138.8) | <0.0001 | <0.0001 |
| PP threshold quadriceps[b] | 732.7 (217.3) | 494.2 (175.5) | 340.3 (173.1) | 276.4 (120.6) | 334.1 (178.2) | <0.0001 | <0.0001 |
| PP threshold trapezius[b] | 550.6 (179.2) | 295.2 (114.5) | 201.5 (139.3) | 173.7 (80.4) | 185.5 (113.6) | <0.0001 | <0.0001 |
| PP threshold epicondyle[b] | 505.5 (205.0) | 268.0 (140.9) | 178.9 (99.5) | 165.2 (63.6) | 159.4 (74.1) | <0.0001 | <0.0001 |
| HP tolerance knee[b],c | 48.1 (1.4) | 46.9 (1.6) | 45.3 (2.3) | 45.0 (2.7) | 42.8 (3.5) | <0.0001 | <0.0001 |
| HP tolerance arm[b],c | 48.1 (1.5) | 47.0 (1.6) | 44.9 (2.1) | 45.4 (2.1) | 42.5 (3.6) | <0.0001 | <0.0001 |
| HP threshold knee[b],c | 44.7 (2.5) | 43.3 (2.7) | 41.5 (3.0) | 40.8 (2.8) | 39.3 (3.7) | <0.0001 | <0.0001 |
| HP threshold arm[b],c | 44.7 (1.9) | 42.9 (2.6) | 40.9 (3.2) | 40.9 (2.8) | 38.6 (3.7) | <0.0001 | <0.0001 |
| TS arm at 46°C (Δ0-100)[b] | −7.6 (35.7) | 2.4 (14.9) | −0.7 (23.8) | −1.4 (11.9) | 29.7 (21.2) | <0.0001 | <0.0001 |
| TS arm at 48°C (Δ0-100)[b] | 3.8 (12.2) | 12.5 (18.4) | 7.8 (12.8) | 3.6 (10.4) | 34.8 (21.5) | <0.0001 | <0.0001 |
| TS knee at 46°C (Δ0-100)[b] | −2.1 (9.1) | 2.9 (16.9) | 4.9 (17.1) | −0.9 (16.8) | 31.2 (21.7) | <0.0001 | <0.0001 |
| TS knee at 48°C (Δ0-100)[b] | 1.7 (17.2) | 11.6 (18.0) | 9.5 (21.9) | 5.0 (12.4) | 32.3 (23.6) | <0.0001 | <0.0001 |
| CP threshold 8°C[b] | 26.6 (18.0) | 12.6 (8.7) | 9.5 (6.4) | 7.6 (4.9) | 9.0 (7.3) | <0.0001 | <0.0001 |
| CP threshold 12°C[b] | 38.7 (18.1) | 21.0 (14.2) | 17.4 (11.4) | 11.7 (7.6) | 14.8 (11.9) | <0.0001 | <0.0001 |
| CP threshold 16°C[b] | 50.1 (14.0) | 36.4 (16.9) | 35.7 (19.5) | 22.7 (13.5) | 31.4 (17.6) | <0.0001 | <0.0001 |
| Punctate patella (Δ0-100)[d] | 3.8 (5.6) | 12.4 (12.9) | 51.9 (15.4) | 20.1 (15.2) | 25.3 (13.6) | <0.0001 | <0.0001 |
| Punctate hand (Δ0-100)[d] | 2.9 (8.7) | 9.0 (11.1) | 47.7 (20.4) | 12.7 (12.4) | 23.6 (18.1) | <0.0001 | <0.0001 |
| Conditioned pain modulation[e] | −0.9 (16.6) | 2.4 (15.5) | 4.3 (16.8) | 2.9 (13.8) | 3.9 (12.9) | 0.3865 | 0.7815 |

[a] Statistical analysis adjusted for age, sex, race, body mass index, level of education, income and study site.
[b] Significant group differences between the low pressure pain cluster and all other clusters ($P < 0.05$, Bonferroni).
[c] Significant group differences between the high heat pain and high TS of heat pain cluster and all other clusters ($P < 0.05$, Bonferroni).
[d] Significant group differences between the high punctate pain TS cluster and all other clusters ($P < 0.05$, Bonferroni).
[e] Conditioned pain modulation was calculated as postconditioning stimulus pain ratings minus the preconditioning stimulus pain ratings with negative values suggesting a pain inhibition and positive values suggesting pain facilitation.
CP, cold pain; HP, heat pain; JL, joint line; PP, pressure pain; TS, temporal summation.

preoperatively had a greater risk of developing postsurgical chronic pain.[58] Heat pain hyperalgesia has also been predictive of postsurgical morphine consumption.[37] Similarly, suprathreshold heat pain responses were a consistent predictor of activity-related pain in an exercise-induced injury model.[13] Recent findings of a novel association between genes along the angiotensin pathway with heat pain sensitivity[59] may provide a platform for future research to use similar experimental pain modality profiling to probe homogeneous subgroups with common underlying mechanisms.

The present study also revealed a cluster that showed high TS of punctate mechanical pain. Although OA-related pain is known to be exacerbated by mechanical forces applied to the joints,[32] the greater TS in this subgroup likely represents a centrally mediated form of sensitization,[48] especially since our measure of TS reflects the response to mechanical stimulation of the ipsilateral nonpainful hand in addition to the index knee. Previous reports in healthy adults identified a subgroup of individuals who show increased summation in response to heat pain, similar to another cluster in the present sample. In patients with knee OA, TS of pressure pain together with impaired CPM predicted pain relief after knee surgery.[46] However, no previous experimental study has reported this punctate summation phenotype and this subgroup may be particularly relevant to OA, as these individuals also reported the highest clinical pain severity of the sample. It is possible that this subgroup is unique to joint-related pain conditions such as knee OA and that the underlying mechanisms contributing to their pain are distinct from those contributing to the clinical presentation of the other TS cluster. Future studies are needed to replicate our findings and to further characterize the mechanisms contributing to the QST profile of this unique subgroup.

It is also interesting to note that there were no differences in pain inhibition between the clusters. It is possible that these various sensory phenotypes tap into different mechanisms as measured by CPM. Alternatively, it is possible that these individuals already had a deficient pain inhibitory system either due to chronic pain or older age. The latter 2 are supported by the fact that the present sample as a whole did not experience significant pain inhibition. Interestingly, a recent exploratory study in patients with knee OA reported that a combination of increased TS of pressure pain with impaired CPM predicted less pain relief after knee surgery.[46] More work is needed to determine how and if these QST phenotypes are related to pain inhibition and the endogenous pain modulatory systems.

Differences in psychosocial functioning were also observed across clusters including pain coping. Pain catastrophizing, a major component of passive coping, is a predictor of pain chronicity and poorer pain prognosis both in acute and chronic pain settings.[5,56] Moreover, individuals who use passive coping strategies after a whiplash injury are more likely to have a slowed recovery or develop disabling pain.[11,39] Similarly, the high heat

**Table 4**

**Demographic characteristics of the 5 clusters.**

| | Low pressure pain sensitivity (n = 39) | Average pain sensitivity (n = 88) | High TS of punctate pain (n = 38) | High cold pain sensitivity (n = 80) | High heat pain and TS of heat pain (n = 41) | *P* |
|---|---|---|---|---|---|---|
| Age, mean ± SD, y | 55.8 ± 7.1 | 57.1 ± 8.0 | 55.2 ± 7.0 | 57.7 ± 7.9 | 56.1 ± 6.6 | 0.427 |
| BMI, mean ± SD, kg/m$^2$[a] | 29.8 ± 5.6 | 29.7 ± 6.3 | 34.2 ± 9.3 | 32.2 ± 8.2 | 32.8 ± 7.0 | 0.005 |
| KL score of index knee (%), $\chi^2$ | | | | | | 0.586 |
| KL score of 0 | 15 (41.67) | 36 (45.57) | 12 (34.29) | 42 (58.33) | 16 (45.71) | |
| KL score of 1 | 8 (22.22) | 12 (15.19) | 6 (17.14) | 9 (12.50) | 4 (11.43) | |
| KL score of 2 | 2 (5.56) | 13 (16.46) | 5 (14.29) | 5 (6.94) | 6 (17.14) | |
| KL score of 3 | 7 (19.44) | 13 (16.46) | 9 (25.71) | 9 (12.50) | 5 (14.29) | |
| KL score of 4 | 4 (11.11) | 5 (6.33) | 3 (8.57) | 7 (9.72) | 4 (11.43) | |
| Race, n (%), $\chi^2$ | | | | | | |
| African Americans | 12 (32.4) | 39 (44.3) | 31 (81.6) | 45 (57.0) | 34 (85.0) | <0.0001 |
| Non-Hispanic whites | 25 (67.6) | 49 (55.7) | 7 (18.4) | 34 (43.0) | 6 (15.0) | |
| Sex, n (%), $\chi^2$ | | | | | | |
| Female | 12 (31.6) | 48 (55.2) | 27 (71.1) | 64 (80.0) | 31 (75.6) | <0.0001 |
| Male | 26 (68.4) | 39 (44.8) | 11 (28.9) | 16 (20.0) | 10 (24.4) | |
| Annual income, no. (%), $\chi^2$ | | | | | | |
| <$20,000 | 7 (18.9) | 30 (34.9) | 15 (40.5) | 26 (32.5) | 21 (52.5) | 0.009 |
| $20,000-29,999 | 7 (18.9) | 18 (20.9) | 5 (13.5) | 13 (16.3) | 6 (15.0) | |
| $30,000-49,999 | 6 (16.2) | 10 (11.6) | 10 (27.0) | 18 (22.5) | 9 (22.5) | |
| >$49,999 | 17 (46.0) | 28 (32.6) | 7 (18.9) | 23 (28.7) | 4 (10.0) | |
| Education, no. (%), $\chi^2$ | | | | | | 0.011 |
| High school | 14 (36.8) | 36 (40.9) | 21 (55.3) | 34 (42.5) | 29 (70.7) | |
| 2-y college degree | 9 (23.7) | 24 (27.3) | 5 (13.2) | 20 (25.0) | 5 (12.2) | |
| 4-y college degree | 7 (18.4) | 16 (18.2) | 9 (23.7) | 12 (15.0) | 7 (17.1) | |
| Graduate degree | 8 (21.1) | 12 (13.6) | 3 (7.9) | 14 (17.5) | 0 | |
| Test, site n (%), $\chi^2$ | | | | | | 0.001 |
| University of Florida | 30 (81.1) | 60 (72.3) | 17 (46.0) | 52 (70.3) | 24 (61.5) | |
| University of Alabama at Birmingham | 7 (18.9) | 23 (27.7) | 20 (54.0) | 22 (29.7) | 15 (38.5) | |

[a] Significant group differences between the High TS of punctate pain cluster and all other clusters ($P < 0.05$, Bonferroni).
BMI, body mass index; KL, Kellgren-Lawrence.

pain/high heat TS cluster and the high mechanical TS of pain cluster showed significantly higher somatic reactivity (as measured by the KRS) and pain vigilance (as measured by the PVAQ) compared with the low pain sensitive cluster consistent with a more maladaptive set of psychological behaviors.[15,16,19,25,40] Finally, similar to past work by our group and others,[23,30] clinical pain severity was significantly higher for the heat pain sensitive and the high punctate TS clusters compared with both the pressure pain insensitive and the average pain sensitivity clusters.

Interestingly, the high heat pain/high TS of heat pain cluster also reported greater levels of active coping compared with the least pain sensitive cluster as measured by the IVC. While

**Table 5**

**Means (SD) for the psychosocial variables measured across the 5 clusters.**

| Measures means (SD) | Low pressure pain sensitivity (n = 39) | Average pain sensitivity (n = 88) | High TS of punctate pain (n = 38) | High cold pain sensitivity (n = 80) | High heat pain and TS of heat Pain (n = 41) | Probability | |
|---|---|---|---|---|---|---|---|
| | | | | | | Unadjusted | Adjusted[a] |
| CSQ | | | | | | | |
| Catastrophizing[b] | 1.0 (0.9) | 1.3 (1.0) | 1.9 (1.2) | 1.8 (1.2) | 2.4 (1.3) | <0.0001 | 0.0001 |
| Active coping | 3.0 (0.9) | 2.9 (1.1) | 3.0 (1.0) | 2.7 (0.8) | 3.1 (1.0) | 0.1159 | 0.1603 |
| Passive coping[c] | 1.9 (1.2) | 2.5 (1.3) | 3.3 (1.0) | 3.1 (1.1) | 3.5 (1.1) | <0.0001 | <0.0001 |
| IVC | | | | | | | |
| Active coping[b] | 2.3 (0.7) | 2.6 (0.8) | 2.7 (0.9) | 2.6 (0.8) | 2.9 (1.0) | 0.0076 | 0.0365 |
| Passive coping | 2.2 (1.1) | 2.5 (1.2) | 2.8 (1.2) | 2.7 (1.2) | 3.3 (1.4) | 0.0023 | 0.1358 |
| KRS—total score[c] | 68.8 (12.9) | 76.7 (11.0) | 80.1 (10.2) | 79.8 (11.6) | 83.4 (12.8) | <0.0001 | 0.0060 |
| PVAQ—total score[c] | 36.2 (14.3) | 45.2 (13.7) | 48.8 (15.5) | 45.4 (14.5) | 53.1 (13.1) | <0.0001 | 0.0055 |
| EOD—total score | 8.9 (13.2) | 5.3 (7.3) | 9.6 (9.9) | 5.4 (8.5) | 7.4 (8.7) | 0.0319 | 0.0830 |

[a] Statistical analysis adjusted for age, sex, race, body mass index, level of education, income, and study site.
[b] Significant group differences between the low pressure pain cluster and the high heat and heat temporal cluster ($P < 0.05$, Bonferroni).
[c] Significant group differences between the low pressure pain cluster and all other clusters ($P < 0.05$, Bonferroni).
CSQ, Coping Strategies Questionnaire; EOD, Experiences of Discrimination questionnaire; IVC, In Vivo Coping Questionnaire; KRS, Kohn Reactivity Scale; PVAQ, Pain Vigilance and Awareness Questionnaire.

**Table 6**

**Means (SD) for clinical pain and function measured across the 5 clusters.**

| Measures, means (SD) | Low pressure pain sensitivity (n = 39) | Average pain sensitivity (n = 88) | High TS of punctate pain (n = 38) | High cold pain sensitivity (n = 80) | High heat pain and TS of heat pain (n = 41) | Probability | |
|---|---|---|---|---|---|---|---|
| | | | | | | Unadjusted | Adjusted[a] |
| SPPB—total score[b] | 10.3 (1.7) | 10.1 (1.6) | 9.8 (1.9) | 9.6 (2.1) | 9.3 (2.1) | 0.0960 | 0.6707 |
| GCPS | | | | | | | |
| Pain intensity score[c],d,e | 41.7 (20.3) | 44.8 (23.0) | 60.6 (19.4) | 52.8 (20.7) | 57.6 (23.5) | <0.0001 | 0.0948 |
| Disability score | 35.1 (26.8) | 38.2 (28.5) | 52.4 (28.3) | 46.5 (29.9) | 48.6 (26.0) | 0.0166 | 0.2120 |
| KOOS-PS—total score[c] | 10.0 (6.3) | 11.4 (6.6) | 14.6 (6.4) | 13.7 (6.2) | 12.4 (7.0) | 0.0152 | 0.2846 |
| WOMAC | | | | | | | |
| Pain score[c],d,e | 5.0 (3.9) | 6.6 (4.2) | 9.4 (4.9) | 7.7 (4.0) | 7.9 (4.2) | <0.0001 | 0.0097 |
| Stiffness score | 2.8 (1.9) | 3.3 (1.9) | 4.2 (2.3) | 3.5 (2.1) | 3.5 (1.9) | 0.0867 | 0.5770 |
| Physical function score[c],d | 16.8 (14.3) | 20.6 (14.0) | 29.6 (15.2) | 25.8 (14.3) | 25.6 (15.1) | 0.0005 | 0.1114 |
| Number of pain sites | 3.8 (2.7) | 5.7 (4.6) | 5.2 (3.4) | 5.8 (4.5) | 6.1 (4.8) | 0.1001 | 0.4349 |
| Widespread pain condition, (%), $\chi^2$ | 13.0 (25.0) | 23.0 (24.5) | 12.0 (24.0) | 13.0 (24.5) | 8.0 (22.2) | 0.3964 | — |

[a] Statistical analysis adjusted for age, sex, race, body mass index, level of education, income and study site.
[b] Significant group differences between the low pressure pain cluster and the high heat/TS of heat cluster ($P < 0.05$, Bonferroni).
[c] Significant group differences between the low pressure pain cluster and the high TS of punctate pain cluster ($P < 0.05$, Bonferroni).
[d] Significant cluster differences between the average pain cluster and the high TS of punctate pain cluster ($P < 0.05$, Bonferroni).
[e] Significant cluster differences between the average pain cluster and the high heat/TS of heat cluster ($P < 0.05$, Bonferroni).
GCPS, Graded Chronic Pain Scale; KOOS-PS, Knee Injury and Osteoarthritis Outcome Score Physical Function Short Form; SPPB, Short Physical Performance Battery; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

previous literature has found active coping to be associated with less pain, less depression, and less functional impairment,[7,35,55] such studies used measures that assess clinical pain and "dispositional" measures of coping such as the CSQ, whereas the IVC is a "situational" measure of coping assessing experimental pain at that moment. It seems plausible that the most sensitive cluster engaged in a wide range of coping strategies in an effort to manage their experience of experimental pain, which they found to be more painful. In contrast, the least pain sensitive cluster showed lower levels of both passive and active coping, ostensibly because they did not experience significant amounts of either experimental or clinical pain to cope with. Studies are needed to examine these associations in experimental settings.

The present study included an approximately equal number of non-Hispanic white and African Americans of both sexes. The high heat pain cluster was comprised mostly of African-American women, whereas the low cold and pressure pain sensitivity group consisted mostly of non-Hispanic white men. This is consistent with our previous findings in healthy adults with a large number of minority individuals.[16] Previous research both in clinical and healthy samples has reported that non-Hispanic white men have lower pain sensitivity compared with minority persons.[10,16,21,52] Multiple biopsychosocial mechanisms have been proposed to explain sex and ethnic differences in experimental pain responses.[21,50] Similar mechanisms may also be contributing to the consistent disparities in ethnic composition of our clusters and others previously reported, but this needs to be further investigated.

Several limitations of the present analysis are worth noting. First, our sample comprised community-dwelling middle-aged and older adults with mild to moderate levels of knee pain; thus, results may not generalize to participants who have severe pain or in clinical environments. Second, we did not incorporate genetic and other relevant biomarkers including neuroimaging into this analysis, which may be associated with the reported pain sensitivity profiles and provide further insight into the meaning of these subgroupings. Third, it is not possible using our study design to determine the directionality of the relationships between experimental pain phenotypes, demographic, clinical pain, and psychological variables. Future studies using a priori defined phenotypes such as those reported in our sample could be used to better explore these associations.

## 6. Conclusions

Similar to previous studies, we found major differences between the most pain insensitive cluster relative to the other clusters. In addition, we also found a subset of individuals who experienced high TS of punctate pain and these individuals also reported the highest clinical pain severity. These results, along with the psychosocial and demographic differences support a multimodal QST protocol as a way of identifying subgroups of community-dwelling middle-aged and older individuals with symptomatic knee OA. These QST profiles likely reflect the influence of different central and peripheral mechanisms, opening the possibility that each subgroup's clinical symptoms are likewise driven by distinct mechanisms. Experimental pain in persons with knee OA appears to be processed within the same brain regions as their clinical pain[34] further justifying the use of experimental pain in humans as a tool for investigating potential mechanisms of pain perception. Indeed, recent studies of neuropathic pain suggest that QST profiles can predict responses to pharmacotherapy,[18,36] supporting the notion that QST may provide mechanism-based phenotyping that can be useful in treatment selection. Whether such findings will extend to patients with OA and other forms of musculoskeletal pain remains to be determined. Given the potential clinical utility of multimodal QST and the stability of these subgroups in the literature, future clinical trials should be cognizant of these pain phenotypes in assessing treatment responses as well as probing underlying mechanisms.[6,9,24,27,46,58]

## Conflict of interest statement

R. B. Fillingim is a stockholder in Algynomics. The remaining authors have no conflicts of interest to declare.

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