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Experimental pain sensitivity differs as a function of clinical pain severity in symptomatic knee osteoarthritis

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Abstract

Objective—Pain in knee osteoarthritis (OA) has historically been attributed to peripheral pathophysiology; however, the poor correspondence between objective measures of disease severity and clinical symptoms suggests that non-local factors, such as altered central processing of painful stimuli, also contribute to clinical pain in knee OA. Consistent with this notion, recent evidence demonstrates that patients with knee OA exhibit increased sensitivity to painful stimuli at body sites unaffected by clinical pain.

Design—In order to further investigate the contribution of altered pain processing to knee OA pain, the current study tested the hypothesis that symptomatic knee OA is associated with enhanced sensitivity to experimental pain stimuli at the knee and at remote body sites unaffected by clinical pain. We further anticipated that pain sensitivity would differ as a function of the OA symptom severity. Older adults with and without symptomatic knee OA completed a series of experimental pain assessments. A median split of the Western Ontario and McMaster Universities Index of Osteoarthritis (WOMAC) was used to stratify participants into low vs. high OA symptom severity.

Results—Compared to controls and the low symptom group, individuals in the high symptom group were more sensitive to suprathreshold heat stimuli, blunt pressure, punctuate mechanical, and cold stimuli. Individuals in the low symptomatic OA group subgroup exhibited experimental pain responses similar to the pain-free group on most measures. No group differences in endogenous pain inhibition emerged.

Conclusions—These findings suggest that altered central processing of pain is particularly characteristic of individuals with moderate to severe symptomatic knee OA.

Keywords

WOMAC; knee osteoarthritis; experimental pain; severity

1. Introduction

Knee osteoarthritis (OA) is one of the most common causes of physical impairment and pain in the United States [1–3]. While objective structural changes in the joint characterize radiographic OA [4], subjective symptoms such as pain and physical functioning often are not strongly associated with measures of primary damage to knee tissues. For example, radiographic OA can be observed in individuals without pain (i.e., asymptomatic) and severity of radiographic OA is not highly associated with OA-related pain and disability [4–7]. While radiographic changes are important in knee OA, it is evident other biological and psychological factors contribute to OA-related pain.

One factor that may contribute to symptomatic OA is individual differences in transmission and modulation of nociceptive information by the peripheral and central nervous system. OA has been historically considered a peripheral disease (i.e., nociceptive damage at the knee [8]); however, central mechanisms that modulate pain contribute importantly to OA symptomatology [9]. The influence of these central mechanisms can be observed by assessing perceptual responses to quantifiable noxious stimuli at the knee (local hyperalgesia) and in areas remote to the knee (generalized hyperalgesia). Recent studies have highlighted the clinical relevance of altered central pain processing in OA, finding that individuals reporting more severe clinical pain in the past twenty-four [10] or forty-eight [11] hours showed greater sensitivity to experimental stimulation.

The current study investigated whether altered central pain processing was associated with the presence and symptomatic severity of knee OA. We sought to extend the findings of previous studies [10, 11] by including a larger and more diverse community-based sample and a more comprehensive assessment of clinical symptoms. Thus, we conducted a comprehensive battery of experimental pain procedures, including a measure of conditioned pain modulation, in a large cohort of middle-aged and older adults with and without symptomatic knee OA. Individuals with symptomatic OA were classified as high versus low symptom severity based on responses to the WOMAC, a standardized questionnaire measure of knee symptoms. We hypothesized that greater experimental pain sensitivity would be observed in individuals with more severe OA symptoms relative to those with lower OA symptom severity. The latter group also would exhibit greater sensitivity than persons without knee pain.

2. Methods

Participants

A community-based sample (n=316) was recruited for an ongoing project at the University of Florida (UF) and the University of Alabama at Birmingham (UAB) between January 2010 and August 2012. The major aim of the project was to elucidate racial/ethnic differences in pain and limitations among individuals with osteoarthritic disease (Understanding Pain and Limitations in Osteoarthritic Disease). All procedures were reviewed and approved by the UF and UAB Institutional Review Boards.

Inclusion Criteria—All participants were between the ages of 45 and 85 years of age and self identified as either African American or non-Hispanic whites. For the OA group (n=209), participants presented with unilateral or bilateral symptomatic knee OA based upon American College of Rheumatology clinical criteria [12] including self-reported unilateral or bilateral knee pain. Controls (n=107) reported no knee pain, though they could have pain unrelated to arthritis at other body sites. Additional exclusion criteria (see Supplementary Materials) were used during the screening process to eliminate the influence of confounding variables such as uncontrolled hypertension (>150/95), peripheral neuropathy, or daily opioid use.

Study overview

Participants attended two separate visits for a health assessment session (i.e., general health and demographic information) and a quantitative sensory testing session (see Supplementary Materials, Supplementary Table 1).

Experimental pain tests

The current study included four commonly used sensory testing procedures: heat, mechanical, cold, and conditioned pain modulation (CPM). Using the American College of

Rheumatology clinical criteria [12] for symptomatic knee osteoarthritis, the participants' most symptomatic/painful knee was designated as the index knee for future research considerations including the testing site. Thermal pain sensitivity was probed with several methods to detect the first sensations of warmth (i.e., warmth threshold, WTh) and pain (i.e., heat pain threshold, HPTh), pain tolerance (i.e., tolerance, HPTo), and temporal summation of heat pain. Testing sites included the medial portion of the index knee (medial joint line, patella, and tibial tuberosity distal to the joint) and the ipsilateral forearm (between the ventral wrist and below the antecubital space). For all of the thermal procedures, contact heat stimuli were delivered using a computer-controlled Medoc Pathway (Pain & Sensory Evaluation System, Ramat Yishai, Israel). The position of the thermode was moved between trials to avoid sensitization or habituation of cutaneous receptors. Mechanical pain sensitivity was probed with two methods: pressure pain (PPTh) and cutaneous mechanical stimulation. Pressure pain testing was performed on the index knee and several non-knee sites ipsilateral to the index knee, and cutaneous mechanical testing was conducted on the index knee and ipsliateral hand. The order of testing was counterbalanced between the two procedures. Following the thermal and mechanical procedures, cold sensitivity was assessed with a modified cold pressor test (CPT). The procedure consisted of three one-minute hand immersions in a cold-water bath (Thermo Scientific Refrigerated Bath), which was set at 16, 12, and 8°C. The last sensory test included a measure conditioned pain modulation, a marker of endogenous pain inhibition. CPM was evaluated by determining the ability of a cold-water immersion (right hand immersion) for 1 minute to diminish ratings of heat pain at the left forearm, as performed for the temporal summation of heat pain test.

Self-reported clinical assessments

Knee Pain and Function—After enrollment into the study, knee pain and function were assessed with several validated measures including the Graded Chronic Pain Scale (GCPS), which measures the severity of knee pain (i.e., current, worst, and average intensity) and disability over the past 6 months [13], and the 4-point scale version of the WOMAC (score range: 0–96), which is a commonly used instrument for assessing pain, stiffness, and physical limitations related to knee OA in the past 48 hours [14, 15]. To stratify individuals with symptomatic OA into low (n = 113, WOMAC score < 33) and high (n = 96, WOMAC score ≥ 34) symptom severity, a median split of the total WOMAC score was used.

Widespread pain (WPS)—WPS was determined [16] by determining presence of pain in four body quadrants (i.e., pain in right and left lower body and the right and left upper body) and the presence of axial skeletal pain (see Supplementary Materials for more details).

Data analysis

Data analysis was performed using SPSS (v20, IBM). Group differences on continuous variables were adjusted for standard covariates (i.e., Race, Study Site, Age, and Gender), and assessed using analysis of covariance (ANCOVA). Additional covariates were used in a subset of analyses including testing site, temperature, and sequence. For cutaneous mechanical stimuli, the pain intensity following a single contact (i.e., 1st trial) and a series of 10 contacts (i.e., 10th trial) was assessed using repeated measure analysis of covariance (RM-ANOVA) with a Greenhouse-Geisser correction as appropriate. Pairwise comparisions among the different groups were conducted with Bonferroni corrections. 95% confidence intervals (lower limit, upper limit) are reported with adjusted means. Partial eta squared (η_p^2) are presented as measures of effect size ($\eta_p^2 = 0.01$ is considered a small effect, $\eta_p^2 = 0.06$ a mediumsized effect and partial $\eta_p^2 = 0.14$ a large effect [17]).

3. Results

Demographic Characteristics

The demographic characteristics of the sample are presented in Table 1. No group differences emerged in age, gender or marital status (p's > .05). The high symptom severity OA group, compared to the other two groups, had a higher proportion of African Americans, a higher body mass index, and reported less education compared to the other two groups.

Clinical Pain and Disability

As expected, after controlling for covariates, the high symptom severity OA group reported greater pain severity, stiffness, and disability related to knee OA in the past 48 hours on the WOMAC and greater pain severity and disability over the past 6 months on the GCPS, compared to the other two groups (Table 1). In addition, participants in the low symptomatic knee OA group reported more pain and disability than the pain-free control group ($p < .001$) on these measures. Finally, differences were observed for the presence of widespread pain (WPS), the number of body sites with pain, and months with pain experienced on most days (p's < .001) in which participants in the high symptomatic knee OA group were more likely to have widespread pain, reported a greater number of sites with pain, and experienced knee pain for a longer period of time compared to the other groups (p's < .01).

Heat Pain

Table 2 shows the mean temperature and pain intensity ratings for WTh, HPTh, and HPTo in control and symptomatic knee OA groups. No differences were observed for warmth threshold at the forearm and the knee ($p's$ > .05) after controlling for covariates. However, the high symptomatic OA group reported greater pain at HPTh and HPTo at the forearm compared to the control and low symptomatic OA group (p's < .05), after controlling for the temperature at HPTh and HPTo. Similar differences were observed at the knee for HPTh but not HPTo.

Table 3 displays the responses of all groups to repeated suprathreshold heat stimuli (i.e., temporal summation) at the forearm and knee. After controlling for covariates, group differences in the pain ratings at the first trial were observed at 44, 46, and 48°C at the forearm and knee (p's < .02). Based on pair-wise comparisons, participants in the control and low symptomatic knee OA groups reported less pain than participants in the high symptomatic knee OA group at 46 and 48°C (p's < .01) at each site. No differences were observed between control and low symptomatic knee OA groups. Table 3 also shows that no group differences in temporal summation (i.e., change scores from first rating to the highest rating during the 5 thermal pulses) at either site (p's > .05).

Mechanical Pain

Table 4 presents group differences in PPTh. After controlling for covariates, group differences were observed at each testing site, including at the index knee (p's < .001) and non-knee sites (p's ≤ .002). Pair-wise comparisons revealed that participants in the high symptomatic knee OA group required less pressure to produce pain than the control group at both sites of the knee, quadriceps, trapezius, and forearm (p's < .01). However, participants in the low and high symptomatic knee OA groups only differed at the knee sites (p's < .01). In Table 5, differences among the control and symptomatic OA groups in pain intensity ratings following a single and a series of ten punctate stimuli are reported for the hand and knee. Controlling for covariates, the main effects of both trial (i.e., 1^{st} vs. 10^{th} trial) and group as well as their interaction were significant ($p's \leq 0.01$) for the knee. For the hand, only the main effect of group and its interaction with trial were significant ($p's \leq 0.001$). Pair-wise comparisons revealed higher ratings at the knee in the high symptomatic knee OA

group compared to the control and low symptomatic knee OA groups at the 1st ($p < .01$) and 10th ($p < .01$) trials. For the hand, pain ratings were higher at the 10th trial ($p < .01$) in the high symptomatic group compared to the other groups (p's < 0.01). Additionally, significant differences in mechanical temporal summation were observed at the hand and knee (p's < 0.01), with participants in the high symptomatic knee OA group exhibiting a greater increase in pain ratings from the 1st trial to the 10th trial compared to participants in the control and low symptomatic knee OA groups (p's < 0.01).

Cold Pain

Table 6 shows responses to the immersion of the right hand into the cold-water bath at 16, 12, and 8°C. Overall, the threshold to report cold pain (CPTh) and the time to tolerance (CPTo) did not differ among the three groups (p's > 0.05). Evaluation of cold pain intensity ratings across the three temperatures revealed significant group differences at 12°C and 8°C (p's £ 0.02). Further inspection revealed that participants in the control group reported less cold pain compared to the high symptomatic knee OA group at 8°C ($p < 0.01$). For ratings of cold pain unpleasantness, ratings differed among the groups only at 12°C, with participants in the control (p's < 0.01) group reporting lower unpleasantness compared to the high symptomatic knee OA group.

Conditioned Pain Modulation

As reported in the Table 7, evaluation of CPM was based on change scores (i.e., pain ratings of the first thermal pulse before and after hand immersion). CPM is a commonly used model to evaluate endogenous pain modulation, which commonly involves inhibition of a heat pain stimulus during exposure to a second noxious conditioning stimulus (i.e., cold water). The main effect for group ($p < .01$) was significant, indicating that the high symptomatic OA group reported greater heat pain compared to controls. However, neither the main effect of time nor the interaction between group and time reached significance ($p's > .05$). Overall, the procedure did not detect significant pain inhibition.

4. Discussion

In the current study, experimental pain sensitivity and modulation were assessed in a sample of middle-aged and older adults with and without symptomatic knee OA. OA participants were divided into high and low symptom severity groups. Group differences emerged between the healthy controls, the low symptomatic OA group, and the high symptomatic OA group for a number of clinical and experimental outcomes. Results supported our hypothesis that individuals with higher symptomatic OA would exhibit greater sensitivity to experimental pain measures compared to individuals without knee pain and those with lower symptomatic OA. However, no differences between the groups in pain inhibition were observed. Overall, among individuals presenting with symptomatic knee OA, generalized sensitivity to painful stimuli varies as a function of symptom severity, which has implications for mechanisms underlying OA and treatment.

Subgrouping of symptomatic OA

Using QST methods to phenotype individuals with symptomatic OA offers another tool to examine potential mechanisms contributing to their clinical symptoms. Recent studies have highlighted differences in pain sensitivity depending on the severity of clinical pain, which has been characterized in OA [10, 11] and other conditions [18, 19]. Based on clinical pain in the past 24 hours, two cohorts of participants with symptomatic OA exhibited differences in experimental pain outcomes with the "severe knee pain group" experiencing more pain compared to the "mild to moderate knee pain group" [10]. Finan et al. [11] split a sample of persons with knee OA into four groups based on clinical pain severity (i.e. WOMAC) and

radiographic OA severity and observed no group differences in experimental pain measures at the affected knee. However, these authors reported greater sensitivity outside the knee in OA patients with high pain and low radiographic severity compared to those with low pain and high radiographic severity. The current study corroborates and extends prior findings [10, 11] by showing that greater OA symptoms are associated with greater pain sensitivity at both affected and unaffected sites including the forearm (pressure, heat), shoulder (pressure), and hand (cold, mechanical punctate).

QST Measures

The current study found differences in a majority of experimental pain procedures as a function of symptomatic OA severity. For HPTh and HPTo, no group differences emerged for any test site; however, the lack of differences in HPTh and HPTo should be interpreted in light of the pain ratings provided for each of these measures. That is, while similar temperatures were required to reach threshold and tolerance, these temperatures evoked greater pain in the high symptom severity group. Moreover, pain ratings in response to the series of heat pulses were greater in the high symptom severity group at both sites tested. Taken together, these findings suggest a generalized enhancement of heat pain sensitivity in the high symptom severity group, consistent with central sensitization.

Pressure pain has been shown to be effective in differentiating controls and individuals with OA at the affected knee and remote sites [20] and demonstrates greater reliability within the OA population compared to other QST methods [21]. In the current study, robust differences in pressure pain were observed in which controls were less sensitive at the knee and other sites compared to individuals with highly symptomatic OA. Furthermore, the high versus low symptomatic OA groups only differed at the knee. One of the unique findings of the study is that pressure pain thresholds did not differ between the low symptomatic and control groups at any site. Similar findings have been reported previously. For example, Arendt-Nielsen et al. [10] assessed pressure pain thresholds at 8 sites around the symptomatic knee and one site at the forearm, with results suggesting that the high severity OA group exhibited lower pressure thresholds at all sites compared to controls. No reference was made to the OA group with low pain, but inspection of the means suggests responses similar to the present study.

Differences in cold pain sensitivity are not commonly assessed in OA. Finan and colleagues [11] observed higher cold pain ratings in their high pain/low radiographic severity group compared to individuals with low pain/high radiographic severity. The authors suggested that greater hypersensitivity in the unaffected site can be used as a marker of central sensitization [11]. Similarly, in the current study, ratings of pain intensity and unpleasantness at certain temperatures were greater or trended toward greatein the high symptomatic OA group after controlling for covariates, providing further evidence of generalized pain hypersensitivity in this group.

A method commonly used to assess temporal summation involves the repeated application of a thermal or mechanical stimulus [22]. Temporal summation (i.e., greater pain during the course of repeated stimulus presentation) is thought to reflect transient central sensitization and is often greater in chronic pain cohorts. Our temporal summation results varied depending on the modality. For example, while general heat hyperalgesia was observed at the forearm and the knee in the high symptomatic OA group, no differences emerged in temporal summation of heat pain at either site. However, greater temporal summation of mechanical pain at the hand and knee was observed in the high symptomatic OA group. While both represent measures of pain facilitation, different mechanisms appear to underlie mechanical and thermal temporal summation. Indeed, similar measures of thermal and mechanical temporal summation were recently shown to load on different factors, and

patients with temporomandibular disorder differed from controls only in their mechanical temporal summation [23]. Thus, the mechanisms reflected by mechanical temporal summation may be more relevant for musculoskeletal pain.

Finally, lack of any modulatory effect following cold water immersion is atypical for studies related to CPM, which have reported reduced endogenous pain inhibition in various chronic pain cohorts compared to age- and/or gender-matched controls [24]. However, one study reported no differences in CPM in OA patients [11]. In addition to methodological factors, several explanations could account for these results. First, the magnitude of CPM is affected by a number of psychological [25, 26] and cognitive [27] factors. Even though the current study did not evaluate relationships among psychological functioning and CPM, it is possible that these factors influenced CPM responses. In addition, demographic factors such as older age [28], gender (i.e., lower CPM in females [29]), and race/ethnicity (i.e., lower CPM in African-Americans [30]) are known to influence CPM. Thus, it is possible that the lack of CPM was driven by our sample, comprised predominantly of female and older participants.

Presumed mechanisms

The current study supports the possibility that the neurological processes involved in the transmission and modulation of nociceptive information differ as a function of OA symptom severity, such that more severe OA pain is associated with augmented processing (i.e., greater sensitivity to pressure pain and suprathreshold heat and mechanical pain, cold pain). That these differences in experimental pain sensitivity emerged across all stimulus modalities and at both affected and unaffected body sites argues for a central nervous system role. While historically considered a peripheral disease (i.e., nociceptive damage at the knee), increasing evidence, including the current findings, implicate central mechanisms in the clinical symptomatology of OA. Whether these differences in central pain processing represent a consequence or a cause of symptomatic knee OA cannot be ascertained by the current study, but both possibilities are plausible. Regarding the former, pathophysiological changes at the knee may include local changes to inflammatory and anti-inflammatory markers [31, 32], which can activate and sensitize peripheral nociceptors in joint tissues leading to neuroplastic changes in the peripheral [33] and central nervous system (i.e., dorsal horn neurons, changes in receptive fields) [33–35]. Consequently, central processing of painful information from the knee will be augmented due to both peripheral and central segmental sensitization [8, 36]. This can be manifested by several outcomes including increased sensitivity to painful (i.e., hyperalgesia) stimuli applied to the affected site. However, once these central changes transpire, nociceptive processing is enhanced in the area of localized pain but also in secondary areas distant to affected site, which is commonly observed as widespread sensitivity.

Another possibility is that heightened pain sensitivity predates the onset of symptomatic OA and represents a premorbid risk factor for development of more severe symptoms as OA-related pathophysiological changes occur. Indeed, previous studies have reported that QST measures of pain sensitivity can predict future development of clinical pain. For example, a global index of pain sensitivity across multiple stimulus modalities predicted future development of temporomandibular disorder [37]. Also, increased sensitivity to cold and pressure pain shortly after a motor vehicle accident predicted chronic whiplash symptoms one year following the accident [38]. Finally, inadequate CPM measured before surgery predicted development of chronic pain after surgery among patients undergoing thoracotomy [39]. Thus, it seems plausible that heightened pain sensitivity and poorer pain inhibitory function may confer increased risk for developing more severe OA-related symptoms.

Treatment implications

Individual differences in severity of symptomatic OA may have treatment implications. In the current study, participants were categorized into low and high symptomatic OA groups based on their clinical report of knee pain, stiffness, and disability on the total WOMAC score, and these groups differed substantially in both local and generalized pain sensitivity. Widespread central sensitization may account for these individual differences in hypersensitivity to experimental stimuli [10, 36, 40] and may contribute to the severity of symptomatic knee OA [9], which could have implications for tailoring treatment interventions to address central mechanisms [41]. Thus, individuals with severe OA and widespread pain hypersensitivity may require more centrally acting pharmacological treatments. For example, duloxetine relieve OA pain due to its central actions [42, 43]. A recent study of neuropathic pain demonstrated that patients with poorer pre-treatment pain inhibitory function, assessed with CPM, showed better clinical response to duloxetine [44]. However, clinical trials of duloxetine for OA have not included experimental methods to determine the association of central mechanisms with efficacy. Finally, it is possible that the heightened experimental sensitivity observed in individuals with high symptomatic OA could be used to predict poor responses to surgeries including total knee replacement (TKR) surgery. Based on a recent prospective study in England, a strong predictor of poor TKR outcomes was greater pre-operative pain [45]. Thus, using experimental methods to identify at-risk patients could assist in determining the use of more central acting medications that would manage pain prior to surgery and in turn would lead to better surgical outcomes.

Limitations of the current study

Several limitations of our study should be considered when interpreting the findings. First, this study used median splits to form group with differing OA symptom severity. Therefore, the grouping, which is based on clinical pain severity, is data driven rather than driven by a validated clinical cut-off. Second, the current study did not explore other biopsychosocial factors contributing to OA symptom severity. For example, a greater number of participants in the high symptomatic OA group were African-American, and ethnic and racial differences have been reported for both clinical [46, 47] and laboratory-based assessments of pain (see review [48]). However, to account for these effects, race was a covariate in all analyses. In addition, psychosocial factors not reported in this study may also differ as a function of OA symptom severity. Based on the Biopsychosocial Model of Pain [49], multiple factors can explain individual differences in pain, and future studies should include additional variables in order to explicate these findings. Finally, while participants indicate the presence of pain over the past three months, we did not assess the duration of pain experienced in other areas of the body, which was used to determine widespread pain. It is possible that experience of pain in sites outside the knee may also indicate the presence of central sensitization.

Summary

In summary, the current study demonstrates that individuals whose OA symptoms are more severe show local and widespread increases in pain sensitivity compared to both controls and to individual with mildly symptomatic OA. This abnormal sensory processing may reflect different underlying peripheral and/or central mechanisms. Development of tools to differentiate subgroups of patients with symptomatic OA will enhance our understanding of this condition but also inform better preventative and treatment options to individuals suffering with this condition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Adjusted means (95% confidence interval) for demographic and clinical pain characteristics of healthy controls and individuals with low and high symptomatic knee OA.

		Symptomatic Knee OA		
	Controls (N = 107)	**Low (N = 113)**	**High (N = 96)**	**Analysis (Bold if significant)**
DEMOGRAPHIC CHARACTERISTICS				
Age (Years) †	56.8 (55.3, 58.4)	58.1 (56.7, 59.5)	56.4 (54.8, 58.1)	F = 1.42, *n.s.*, η_p^2 = .01
BMI (Weight/Height^2) †	28.7 (27.2, 30.2) *a*	29.3 (27.9, 30.6) *b*	33.5 (31.9, 35.1)	**F = 9.49, *p* < .001, η_p^2 = .06**
Education (% ≤ HH)	71.9%	66.4%	45.8%	**χ^2 = 16.08, *p* < .001**
Employment (% NoW)	50.5%	40.7%	60.4%	**χ^2 = 8.08, *p* < 0.05**
Gender (%F)	65.4%	72.6%	66.7%	χ^2 = 1.48, *n.s.*
Marital Status (% Married)	44.7%	45.1%	35.4%	χ^2 = 2.52, *n.s.*
Race (%NHW)	77.6%	59.3%	34.4%	**χ^2 =38.87, *p* < .001**
Widespread pain				
% Subjects with WPS	.9%	15.0%	36.5%	**χ^2 =46.1, *p* < .001**
Number of sites – Total Group	.98 (.4, 1.6)	3.58 (2.9, 4.2)	7.4 (6.6, 8.1)	**F = 9.49, *p* < .001, η_p^2 = .06**
CLINICAL OUTCOMES				
WOMAC				
Total score *(range 0–96)* †	3.5 (1.5, 5.4) *ac*	18.4 (16.7, 20.2) *b*	49.6 (47.5. 51.7)	**F = 450, *p* < .001, η_p^2 = .75**
Subscales				
Pain (range 0–20) †	.7 (.2, 1.2) *ac*	4.2 (3.8, 4.7) *b*	10.3 (9.7, 10.8)	**F = 310.01, *p* < .001, η_p^2 = .67**
Stiffness (range 0–8) †	.5 (.2, .7) *ac*	2.1 (1.9, 2.3) *b*	4.6 (4.3, 4.9)	**F = 184.2, *p* < .001, η_p^2 = .55**
Physical function (range 0–68) †	2.3 (.8, 3.7) *ac*	12.1 (10.8, 13.4) *b*	34.8 (33.2, 36.4)	**F = 392.91, *p* < .001, η_p^2 = .72**
GCPS				
Characteristic Pain Intensity *(range 0–100)* †	13.4 (9.8, 16.9) *ac*	37.4 (34.1, 40.6) *b*	59.4 (55.5, 63.2)	**F = 130.21, *p* < .001, η_p^2 = .46**
Disability Score *(range 0–100)* †	4.9 (1.4, 8.6) *ac*	24.93 (21.5, 28.3) *b*	57.2 (53.1, 61.2)	**F = 151.47, *p* < .001, η_p^2 = .51**
Grading Chronic Pain Grade				**χ^2 = 252.63, *p* < .001**
0 – Normal	59	3	0	
I - Low Pain Intensity	42	75	13	
II - High Pain Intensity	5	24	25	
III - Moderate Disability	0	6	29	
IV - High Disability	0	3	27	
Knee pain duration				
Pain on most days (months) †	.17 (−10.5, 19.5) *a*	24.7 (11.8, 37.5) *b*	57.8 (43.7, 71.8)	**F = 11.66, *p* < .001, η_p^2 = .10**

Group comparisons

a Significant group difference between the control and high symptomatic knee OA groups (p < .01, Bonferroni)

b Significant group difference compared between the low and high symptomatic knee OA groups (p < .01, Bonferroni)

[c] Significant group difference compared between the control and low symptomatic knee OA groups ($p < .01$, Bonferroni)

Covariates for adjusted analysis:

[†] Controlling for race (0 = NHW, 1 = AA), age, widespread pain (0 = No, 1 = Yes), gender (0 = Female, 1 = Male), and study site (0 = UF, 1 = UAB) as a covariates.

Abbreviations: High School (HH); Not working (NoW); Non-Hispanic White (NHW); African American (AA); Body Mass Index (BMI); Yes in past year (Y); University of Florida (UF); Western Ontario and McMaster Universities Index of Osteoarthritis (WOMAC), Knee Injury Osteoarthritis Outcome Score Physical Function (KOOS-PS), Graded Chronic Pain Scale (GCPS).

Table 2

Adjusted means (95% confidence interval) for warmth and heat pain thresholds, heat pain tolerance, and heat pain ratings at the forearm and knee in healthy controls and individuals with low and high symptomatic knee OA (± 95% CI).

		Symptomatic Knee OA		
	Controls (N = 107)	**Low (N = 113)**	**High (N = 96)**	**Analysis (Bold if significant)**
Heat Temperatures (°C) †				
Forearm				
WTh	36.1 (35.7, 36.6)	35.5 (35.1, 35.9)	35.3 (34.7, 35.8)	F = 2.81, *n.s.*, η_p^2 = .02
HPTh	42.7 (42.1, 43.3)	42.1 (41.5, 42.6)	41.4 (40.8, 72.1)	F = 3.19, *p* = 0.04, η_p^2 = .02
HPTo	46.7 (46.3, 47.1)	46.3 (45.9, 46.7)	45.8 (45.4, 46.3)	F = 3.21, *p* = 0.04, η_p^2 = .02
Knee				
WTh	36.9 (36.4, 37.5)	37.1 (36.5, 37.5)	37.6 (37.1, 38.2)	F = 1.46, *n.s.*, η_p^2 = .01
HPTh	42.2 (41.6, 42.8)	42.1 (41.6, 42.7)	41.6 (40.9, 42.3)	F = .71, *n.s.*, η_p^2 = .01
HPTo	46.4 (45.9, 46.8)	46.2 (45.8, 46.6)	45.7 (45.2, 46.2)	F = 2.23, *n.s.*, η_p^2 = .01
VAS Intensity Ratings‡*				
Forearm				
HPTh	19.6 (15.3, 23.9)[a]	17.9 (13.8. 22.1)[b]	27.6 (22.8, 32.5)	**F = 4.62, *p* = .011, η_p^2 = .04**
HPTo	52.5 (46.8, 58.2)	50.9 (45.4, 56.4)[b]	63.4 (56.9, 69.9)	**F = 4.31, *p* = .015, η_p^2 = .04**
Knee				
HPTh	19.5 (14.7, 23.0) [a]	18.9 (14.7, 23.0)[b]	28.6 (23.6, 33.5)	**F = 4.68, *p* = .01, η_p^2 = .04**
HPTo	56.7 (50.7, 62.7)	53.9 (48.1, 59.9)	64.9 (58.0, 71.8)	F = 2.8, *p* = .07, η_p^2 = .02

Group comparisons

[a]Significant group difference between the control and high symptomatic knee OA groups (p < .01, Bonferroni)

[b]Significant group difference compared between the low and high symptomatic knee OA groups (p < .01, Bonferroni)

Covariates for adjusted analysis

†Controlling for race (0 = NHW, 1 = AA), study site (0 = UF, 1 = UAB), age, widespread pain (0 = No, 1 = Yes), gender (0 = Female, 1 = Male), and testing sequence (0 = Thermal First, 1 = Pressure First) as a covariates

Abbreviations

Warmth Thresholds, WTh; Heat Pain Thresholds, HPTh; Heat Pain Tolerance, HPTo, Visual Analog Scale, VAS

Additional notes related to data analysis

*Analysis completed with 92 control, 81 low symptomatic OA, and 76 high symptomatic OA participants

Table 3

Adjusted means (95% confidence interval) for pain rating for the first trial and indexes of temporal summation (highest rating – rating at 1st pulse) at the forearm and knee in healthy controls and individuals with low and high symptomatic knee OA.

		Symptomatic Knee OA		
	Control (N = 107)	Low (N = 113)	High (N = 96)	Analysis (Bold if Significant)
Pain Intensity †				
Forearm				
44°C	24.3 (19.4, 29.2) *a*	27.7 (23.2, 32.2) *b*	38.9 (33.5, 44.4)	**F = 7.17, *p* = .001, η_p^2 = .05**
46°C	26.7 (24.4, 34.9) *a*	32.0 (27.3, 36.8) *b*	43.7 (37.9, 49.5)	**F = 6.10, *p* = .003, η_p^2 = .04**
48°C	33.8 (28.3, 39.4) *a*	38.6 (33.5, 43.7) *b*	50.8 (44.6, 56.9)	**F = 7.23, *p* = .001, η_p^2 = .05**
Knee				
44°C	22.3 (17.8, 26.8)	21.7 (17.6, 25.9)	30.6 (25.6, 35.6)	**F = 3.8, *p* = 02, η_p^2 = .03**
46°C	28.3 (23.3, 33.3) *a*	29.7 (25.2, 34.3) *b*	42.6 (36.9, 47.9)	**F = 7.30, *p* = .001, η_p^2 = .05**
48°C	32.3 (26.8, 37.8) *a*	35.1 (30.1, 40.1) *b*	48.6 (42.5, 54.6)	**F = 7.53, *p* = .001, η_p^2 = .05**
Temporal Summation †				
Forearm				
44°C	5.8 (3.5, 8.2)	6.1 (3.9, 8.2)	7.9 (1.3, 10.6)	F = .78, n.s., η_p^2 = .01
46°C	6.5 (3.9, 8.9)	7.4 (5.2, 9.8)	8.9 (6.2, 11.7)	F = .73, *n.s.*, η_p^2 = .01
48°C	11.6 (8.3, 14.9)	13.7 (10.6, 16.7)	12.7 (8.9, 16.3)	F = .42, *n.s.*, η_p^2 = .00
Knee				
44°C	3.5 (1.5, 5.5)	5.1 (3.2, 6.9)	5.6 (3.4, 7.9)	F = .38, *n.s.*, η_p^2 = .01
46°C	7.1 (4.1, 10.1)	10.5 (7.7, 13.2)	9.1 (5.7, 12.4)	F = 1.33, *n.s.*, η_p^2 = .01
48°C	10.3 (7.0, 13.5)	13.9 (10.9, 16.9)	12.7 (9.1, 16.3)	F = 1.34, *n.s.*, η_p^2 = .01

Group comparisons

a Significant group difference between the control and high symptomatic knee OA groups (p < .01, Bonferroni)

b Significant group difference compared between the low and high symptomatic knee OA groups (p < .01, Bonferroni)

Covariates for adjusted analysis

† Controlling for race (0 = NHW, 1 = AA), study site (0 = UF, 1 = UAB), age, widespread pain (0 = No, 1 = Yes), gender (0 = Female, 1 = Male), and testing sequence (0 = Thermal First, 1 = Pressure First) as a covariates

Table 4

Adjusted means (95% confidence interval) for pressure pain thresholds at the knee and sites proximal and distal to the knee in healthy controls and individuals with low and high symptomatic knee OA.

		Symptomatic Knee OA		
	Controls (N = 107)	**Low (N = 113)**	**High (N = 96)**	**Analysis (Bold if significant)**
Knee (kPa) †				
Medial Joint Line (MJL)	368.6 (337.6, 399.6) *a*	334.9 (306.7, 363.2) *b*	253.1 (219.4, 286.9)	**$F = 11.05$, $p < .001$, $\eta_p^2 = .07$**
Lateral Joint Line (LJL)	392.3 (360.4, 424.2) *a*	350.2 (321.1, 379.3) *b*	273.4 (238.6, 308.2)	**$F = 10.73$, $p < .001$, $\eta_p^2 = .07$**
Leg (kPa) †				
Quadriceps (Q)	545.2 (499.2, 591.1) *ac*	450.8 (408.8, 492.7)	367.5 (317.3, 417.6)	**$F = 11.55$, $p < .001$, $\eta_p^2 = .07$**
Upper Body (kPa) †				
Forearm (FA)	310.7 (278.0, 343.3) *a*	255.3 (225.3, 285.2)	218.6 (182.9, 254.3)	**$F = 6.34$, $p = .002$, $\eta_p^2 = .04$**
Trapezius (TP)	353.6 (203.5, 279.2) *ac*	282.1 (250.5, 313.8)	241.3 (203.5, 279.2)	**$F = 8.57$, $p < .001$, $\eta_p^2 = .06$**

Group comparisons

a Significant group difference between the control and high symptomatic knee OA groups ($p < .01$, Bonferroni)

b Significant group difference compared between the low and high symptomatic knee OA groups ($p < .01$, Bonferroni)

c Significant group difference compared between the control and low symptomatic knee OA groups (p < .01, Bonferroni)

Covariates for adjusted analysis

† Controlling for race (0 = NHW, 1 = AA), study site (0 = UF, 1 = UAB), age, widespread pain (0 = No, 1 = Yes), gender (0 = Female, 1 = Male), and testing sequence (0 = Heat First, 1 = Pressure First), and study site (1 = Medial Joint Line First, 2 = Lateral Joint Line First, 3= Quadriceps, 4 = Forearm, 5 = Trapezius) as a covariates

Abbreviations: kilopascal, kPa

Table 5

Adjusted means (95% confidence interval) for pain ratings and indexes of temporal summation (rating at 10th trial – rating at 1st trial) following a single and repeated stimulation with a punctate probe at the hand and knee (patella) in healthy controls and individuals with low and high symptomatic knee OA.

		Symptomatic Knee OA		Analysis (Bold if significant)		
	Control (N = 107)	Low (N = 113)	High (N = 96)	Group (G)	Trial (T)	T × G
Hand Pain Ratings						
Hand						
1st Trial	6.5 (3.9, 9.2) *a*	7.0 (4.6, 9.4) *b*	11.4 (8.5, 14.4)	**F = 8.23, *p* < 0.001, η_p^2 = .05**	F = 4.33, *p* = 0.038, η_p^2 = .02	**F = 8.6, *p* <, 0.001, η_p^2 = .06**
10th Trial	16.5 (12.2, 20.8) *a*	17.4 (13.5, 21.3) *b*	30.6 (25.8, 35.4)			
Knee						
1st Trial	11.4 (8.1, 14.6) *a*	9.8 (6.9, 12.7) *b*	16.9 (13.4, 20.5)	**F = 10.85, *p* = .005, η_p^2 = .07**	**F = 8.07, *p* = .005, η_p^2 = .03**	**F = 13.82, *p* < 0.001, h_p^2 = .09**
10th Trial	24.3 (19.3, 29.3) *a*	25.9 (21.4, 30.4) *b*	43.6 (38.1, 49.2)			
Temporal Summation						
Hand	9.9 (6.9, 13.1) *a*	10.5 (7.6, 13.3) *b*	19.2 (15.7, 22.6)	**F = 8.58, *p* < .001, η_p^2 = .06**		
Knee	12.9 (9.6, 16.3) *a*	16.2 (13.2, 19.2) *b*	26.7 (22.9, 30.3)	**F = 13.8, *p* < .001, η_p^2 = .09**		

Group comparisons

a Significant group difference between the control and high symptomatic knee OA groups (p < .01, Bonferroni)

b Significant group difference compared between the low and high symptomatic knee OA groups (p < .01, Bonferroni)

Covariates for adjusted analysis

† Controlling for race (0 = NHW, 1 = AA), study site (0 = UF, 1 = UAB), age, widespread pain (0 = No, 1 = Yes), gender (0 = Female, 1 = Male), and testing sequence (0 = Thermal First, 1 = Pressure First), and testing site (0 = Hand First, 1 = Patella First) as a covariates

Table 6

Adjusted means (95% confidence interval) for threshold, tolerance, and pain ratings during cold immersions at 16, 12, and 8°C in healthy controls and individuals with low and high symptomatic knee OA.

		Symptomatic Knee OA Group		
	Controls (N = 107)	Low (N = 113)	High (N = 96)	Analysis
Cold Pain Outcomes (Seconds)				
Threshold (CPTh) †				
16°C	31.9 (28.2, 35.6)	33.1 (29.7, 36.5)	31.4 (27.3, 35.5)	F = .23, *n.s.*, η_p^2 = 0.00
12°C	18.5 (15.5, 21.4)	18.6 (15.9, 21.3)	18.7 (15.5, 31.9)	F = .01, *n.s.*, η^2 = 0.00
8°C	12.1 (9.9, 14.3)	12.8 (10.8, 14.8)	11.4 (8.9. 13.9)	F = .39, *n.s.*, η_p^2 = 0.00
Tolerance (CPTo) †				
16°C	59.8 (58.8, 60.8)	58.8 (57.9, 59.7)	59.2 (58.2, 60.3)	F = 1.23, *n.s.*, η_p^2 = 0.01
12°C	53.6 (50.9, 56.3)	54.7 (52.2, 57.1)	51.7 (48.7, 54.6)	F = 1.13, *n.s.*, η^2 = 0.01
8°C	46.8 (43.1, 50.4)	48.6 (45.2, 51.9)	43.6 (39.5, 47.6)	F = 1.72 *n.s.*, η_p^2 = 0.01
Cold Pain Ratings (0–100)				
Intensity †				
16°C	29.5 (23.7, 35.3)	28.9 (23.7, 35.3)	38.5 (32.2, 44.8)	F = 2.80, *n.s.*, η_p^2 = 0.02
12°C	54.6 (48.2, 60.9)	55.9 (49.7, 61.3)	67.4 (60.4, 74.4)	**F = 3.94, *p* = 0.02, η_p^2 = 0.03**
8°C	65.9 (60.1, 71.8) [a]	70.3 (65.1, 75.5)	80.0 (73.7, 86.3)	**F = 4.69, *p* = 0.01, η_p^2 = 0.03**
Unpleasantness †				
16°C	34.8 (28.8, 40.9)	30.9 (25.4, 36.5)	10.8 (35.2, 48.4)	F = 3.00, *p* = 0.05, η_p^2 = 0.02
12°C	58.7 (52.4, 64.9) [a]	57.7 (52.1, 63.4)	70.7 (63.9, 77.6)	**F = 4.40, *p* = 0.013, η_p^2 = 0.03**
8°C	69.9 (64.1, 75.7)	72.4 (67.1, 77.6)	81.4 (75.1, 87.7)	F = 3.39, *p* = 0.03, η_p^2 = 0.02

Group comparisons

[a] Significant group difference between the control and high symptomatic knee OA groups (p < .01 Bonferroni)

[b] Significant group difference compared between the low and high symptomatic knee OA groups (p < .01, Bonferroni)

Covariates for adjusted analysis

† Controlling for race (0 = NHW, 1 = AA), study site (0 = UF, 1 = UAB), age, widespread pain (0 = No, 1 = Yes), and gender (0 = Female, 1 = Male) as a covariates

Table 7

Adjusted means (95% confidence interval) for changes to heat pain ratings before and following hand immersion in healthy controls individuals with low and high symptomatic knee OA.

		Symptomatic Knee OA		Analysis		
	Control (N = 107)	**Low (N = 113)**	**High (N = 96)**	**Group (G)**	**Time (T)**	**T × G**
Highest Pain Rating[†]						
Pre-Immersion	35.5 (30.2, 40.9)	40.8 (36.0, 45.6)	45.9 (40.1, 51.9)	**F = 6.06 *p* = .003, η_p^2 = .04**	F = .17, *n.s.*, η_p^2 = .00	F = 0.41, *n.s.*, η_p^2 = .00
Post-Immersion	37.8 (32.7, 42.9)	43.6 (38.9, 48.2)	47.8 (42.3, 53.4)			
Change Score[†]	1.95 (−1.5, 5.4)	2.3 (−.7, 5.4)	1.4 (−2.4, 5.2)	F = .75, *n.s.*, η_p^2 = 0.01		

Covariates for adjusted analysis

[†] *Controlling for race (0 = NHW, 1 = AA), study site (0 = UF, 1 = UAB),* widespread pain (0 = No, 1 = Yes), *and gender (0 = Female, 1 = Male) as a covariates*