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Pain hypervigilance is associated with greater clinical pain severity and enhanced experimental pain sensitivity among adults with symptomatic knee osteoarthritis

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Abstract

Background—Pain hypervigilance is an important aspect of the fear-avoidance model of pain that may help explain individual differences in pain sensitivity among persons with knee osteoarthritis (OA).

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Declaration of Overlapping Reports: The following publications have used data from the same study (Understanding Pain and Limitations in Osteoarthritic Disease, UPLoad) as was used in this manuscript.

Goodin BR, Glover TL, Sotolongo A, et al. The association of greater dispositional optimism with less endogenous pain facilitation is indirectly transmitted through lower levels of pain catastrophizing. *J pain* 2013; **14**: 126–135.

Glover TL, Goodin BR, Horgas AL, et al. Vitamin D, race, and experimental pain sensitivity in older adults with knee osteoarthritis. *Arthritis Rheum* 2012; **64**: 3926–3935.

Sibille KT, Witek-Janusek L, Mathews HL, Fillingim RB. Telomeres and epigenetics: potential relevance to chronic pain. *Pain* 2012; **153**: 1789–1793.

Purpose—The purpose of this study was to examine the contribution of pain hypervigilance to clinical pain severity and experimental pain sensitivity in persons with symptomatic knee OA.

Methods—We analyzed cross-sectional data from 168 adults with symptomatic knee OA. Quantitative sensory testing was used to measure sensitivity to heat pain, pressure pain, and cold pain, as well as temporal summation of heat pain, a marker of central sensitization.

Results—Pain hypervigilance was associated with greater clinical pain severity, as well as greater pressure pain. Pain hypervigilance was also a significant predictor of temporal summation of heat pain.

Conclusions—Pain hypervigilance may be an important contributor to pain reports and experimental pain sensitivity among persons with knee OA.

Introduction

The most prominent and disabling symptom of knee osteoarthritis (OA) is pain. The well-documented discordance between radiographic and symptomatic knee OA (1,2) suggests the experience of pain in individuals with knee OA cannot be fully explained by peripheral pathophysiology alone. Indeed, psychosocial factors, such as anxiety, depression, and coping style have been implicated in OA-related pain and disability (3,4,5).

The fear-avoidance model of pain provides a suitable heuristic for conceptualizing the contributions of psychosocial factors to the experience of OA-related pain (6). This model posits that a cycle of pain chronicity and disability may be initiated when the appraisal of pain is influenced by negative psychosocial factors. The resultant maladaptive appraisal gives rise to pain-related fear and anxiety, as well as associated safety seeking behaviors such as avoidance/escape, which can be adaptive in the acute pain stage, but paradoxically exacerbate persistent pain. The long-term consequences, such as enhanced disability or depression, in turn may lower the threshold at which subsequent pain is detected and/or enhance the intensity of the pain experience.

Hypervigilance represents an important aspect of the fear-avoidance model that may contribute to OA-related pain. Rollman (7) defined hypervigilance as an enhanced state of sensory sensitivity accompanied by an exaggerated scan or search for threatening information. It has been proposed that some individuals who live with chronic or recurrent pain may develop a pain-specific ‘hypervigilance’ as a result of continual effort to detect painful sensations and other pain-related information, which may in turn exacerbate the pain experience (8). Generalized hypervigilance (i.e., heightened vigilance for internal and external signals in addition to pain) and pain-specific hypervigilance have been studied in several samples of adults with disorders characterized by recurrent or persistent pain. For example, pain hypervigilance was positively associated with greater pain intensity, emotional distress, psychosocial disability and pain-related health care utilization in patients with chronic back pain (9). McDermid (10) showed that patients with fibromyalgia and rheumatoid arthritis reported greater generalized hypervigilance and displayed greater sensitivity to experimental pain compared to controls.

The association of pain hypervigilance with increased clinical and experimental pain may be related to central sensitization, a phenomenon in which nociceptive pathways in the central nervous system become sensitized by repeated or sustained nociceptive input (11). Evidence of central sensitization has been demonstrated in a number of disorders characterized by chronic or recurrent pain (12,13), including knee OA (14). Theorists have posited that some OA patients may have a greater propensity to develop central sensitization, which may underlie the discordance between symptomatic and radiographic OA (15). Although the impact of psychosocial factors on central sensitization has yet to be well characterized, pain hypervigilance has been postulated to play a role in central sensitization via descending pain modulatory pathways (16).

The relationship between pain hypervigilance and central sensitization has not been examined among persons with knee OA. Therefore, in the present study, temporal summation of heat pain, a widely used quantitative sensory testing method that invokes neural mechanisms related to central sensitization (17), was specifically examined in relation to pain hypervigilance. We also sought to determine whether pain hypervigilance is related to reports of clinical OA pain and disability. In addition, to determine the relationship between pain hypervigilance and pain modality, three major types of stimuli used in laboratory pain research (i.e., heat pain, pressure pain, cold pain) were assessed. The following hypotheses were tested: 1) pain hypervigilance will predict greater severity of clinical pain and disability; 2) pain hypervigilance will predict greater sensitivity to experimental pain stimuli beyond what can be explained by clinical pain and; 3) pain hypervigilance will predict greater temporal summation of heat pain after adjusting for confounding variables, including clinical pain. Demographic variables (age, ethnicity, gender, and education) and depressive symptoms were statistically controlled for in all analyses. In addition, clinical pain intensity and situational passive coping were added as additional covariates for analyses examining experimental pain sensitivity.

Methods

Participants

The current study is part of a larger ongoing project that aims to enhance the understanding of biopsychosocial factors contributing to pain and functional limitations among individuals with knee osteoarthritis (Understanding Pain and Limitations in Osteoarthritic Disease, UPLOAD). The UPLOAD study is a multi-site investigation that recruits participants at the University of Alabama at Birmingham and the University of Florida. The individuals described in the current study were recruited at both study sites between January, 2010 and May, 2012. The measures and procedures described below are limited to those involved in the current study.

Participants consisted of 168 community-dwelling adults with symptomatic knee OA recruited via posted fliers, radio and print media advertisements, orthopedic clinic recruitment, and word-of-mouth referral. Criteria for inclusion into the study were as follows: 1) between 45 and 85 years of age; 2) unilateral or bilateral symptomatic knee osteoarthritis based upon American College of Rheumatology clinical criteria (18); and, 3) availability to complete the two-session protocol. Individuals were excluded from

participation if they met any of the following criteria: 1) prosthetic knee replacement or other clinically significant surgery to the affected knee; 2) uncontrolled hypertension, heart failure, or history of acute myocardial infarction; 3) peripheral neuropathy; 4) systemic rheumatic disorders including rheumatoid arthritis, systemic lupus erythematosus, and fibromyalgia; 5) daily opioid use; 6) cognitive impairment (Mini Mental Status Exam (MMSE) score ≥ 22); 7) excessive anxiety regarding protocol procedures (e.g., blood draws and controlled noxious stimulation procedures); and 8) hospitalization within the preceding year for psychiatric illness.

On the day of testing, individuals were instructed to refrain from using opioid analgesic medications taken on an “as needed” (i.e., PRN) basis. All procedures were reviewed and approved by the University of Alabama at Birmingham and the University of Florida Institutional Review Boards. Participants provided informed consent and were compensated for their participation.

After screening, all participants completed the health assessment session. The following demographic and health data were obtained: self-reported sex, age, ethnicity, years of school completed, as well as health history that included information pertaining to whether individuals had any mental or physical health conditions that required hospitalization in the past year. Next, an index of cognitive capacity, the MMSE, was administered to determine if cognitive or attentional deficits were present that would rule out participation in a study of pain responses. Additionally, all individuals underwent a bilateral knee joint evaluation by an experienced examiner (i.e., the study rheumatologist or study nurse practitioner). As part of the health assessment session, participants completed a battery of psychosocial and clinical pain measures. Between one and four weeks following the health assessment session, participants completed a session of quantitative sensory testing for the assessment of experimental pain sensitivity. Prior to commencing the quantitative sensory session, participants were provided with audio recorded instructions regarding how to rate the intensity of the pain produced by the experimental pain stimuli on a “0–100” numeric rating scale, such that 0 = no pain and 100 = the most intense pain imaginable.

Psychosocial Questionnaires

Pain Vigilance and Awareness Questionnaire (PVAQ)—The PVAQ was developed as a measure of attention to pain (9). The PVAQ consists of 16 items that asks respondents to indicate on a six point scale (0 = ‘never’ to 5 = ‘always’) the degree to which each description of pain behavior corresponds with their behavior. The PVAQ has satisfactory internal consistency (Cronbach’s $\alpha = 0.86$), test-retest reliability ($r = 0.80$), and convergent validity (9,19,20).

Center for Epidemiologic Studies Depression Scale (CES-D)—The CES-D is a 20-item self-report tool that measures symptoms of depression including depressed mood, guilt/worthlessness, helplessness/hopelessness, psychomotor retardation, loss of appetite and sleep disturbance (21). The total score of the CES-D (range 0 – 60) was used in the current study as an estimate of the degree of participants’ depressive symptomatology. The validity

and internal consistency of the CES-D in the general population and persons with chronic pain have been reported to be acceptable (22,23).

Situational Passive Coping (SPC)—The SPC scale consists of 4-items that are answered on a 1 – 5 Likert scale. This questionnaire was administered directly after quantitative sensory testing to determine the degree that passive coping strategies were utilized during the procedures (e.g., “I felt that if the pain got any worse, I wouldn’t be able to tolerate it.”). The 4 items on this scale were subsequently averaged together (range 1 – 5), such that higher mean scores were representative of greater use of passive cognitive coping strategies. Items on the SPC have previously been shown to correlate with pain responses during quantitative sensory testing (24). In addition, the internal consistency of this scale was adequate (Cronbach’s $\alpha = 0.76$).

Clinical Pain

Western Ontario McMaster Universities Osteoarthritis Scale (WOMAC) pain subscale—The WOMAC pain subscale consists of 5 questions answered on a 0 – 4 likert scale. On this subscale, respondents report the degree of arthritis related knee pain during everyday activities (e.g., walking, sitting, standing) over the last 48 hours. The WOMAC pain subscale is a reliable and valid measure of clinical pain (25).

Clinical Disability

The *Knee Injury and Osteoarthritis Outcome Score-Physical Function Short-Form (KOOS-PS)* is a 7-item scale derived from the full-length KOOS that measures difficulties with physical activities (e.g., rising from bed, kneeling, squatting) due to knee pain (26). The internal consistency and test-retest reliability of the KOOS-PS is satisfactory in persons with knee OA (26).

Quantitative Sensory Testing

Thermal Heat—A series of controlled thermal stimulation procedures were used to assess heat pain sensitivity, particularly heat pain threshold and heat pain tolerance. Heat pain threshold refers to the temperature at which a person first perceives the heat stimulus to be painful. Heat pain tolerance refers to the maximum level of pain that a person is able to tolerate.

Heat pain threshold and tolerance were assessed using a Medoc Pathway Neurosensory Analyzer (Medoc, Ltd., Ramat Yishai, Israel) with a 16×16 mm thermode using an ascending method of limits procedure. From a baseline of 32°C , probe temperature increased at a rate of $0.5^{\circ}\text{C}/\text{sec}$ until participants responded by pressing a button to indicate when they first felt pain, and when they were no longer able to tolerate the pain. Heat pain threshold and tolerance were assessed on individuals’ index knee and ipsilateral ventral forearm. If a participant had bilateral knee pain, the knee with a greater amount of reported pain intensity was designated as the index knee. In cases where an equal amount of pain intensity was endorsed in both knees, the index knee was randomized.

Three trials of heat pain threshold and three trials of heat pain tolerance were completed separately on the index knee and ventral ipsilateral forearm for each individual (6 trials of heat pain threshold and heat pain tolerance per individual). The position of the thermode was altered slightly between trials (though it remained on the index knee and ventral forearm). For each measure at each anatomical site, the average of all three trials was computed for use in subsequent analyses.

Temporal Summation of Heat Pain—After assessment of heat pain threshold and heat pain tolerance, participants underwent a second thermal procedure with repeated trials of suprathreshold heat pulses applied to the index knee and ipsilateral ventral forearm. Participants were instructed to verbally rate the intensity of peak pain of 5 brief pulses on a scale of 0 (no pain) to 100 (the most intense pain imaginable). The procedure was terminated if the participant rated the thermal pain at 100. For each temperature and site, a change score was calculated by subtracting the first rating from the highest rating during the 5 repeated trials. This change score was used as an index of temporal summation (27). Target temperatures were delivered by a Contact Heat-Evoked Potential Stimulator (CHEPS, MEDOC, Ramat Yishai, Israel) thermode for less than 1 second, with an approximately 2.5-second inter-pulse interval during which the temperature of the contactor returned to a baseline of 32°C. During the temporal summation trials at the index knee and ipsilateral forearm, three different temperatures were used (44, 46, and 48°C) for a total of six trials (three at the knee, three at the forearm). Consistent with previous investigators (28,29), last-observation-carried-forward (LOCF) methods was used to handle missing data during the temporal summation procedures.

Mechanical Pressure—To determine mechanical pain sensitivity at the site of clinical pain, six total trials of pressure pain threshold were assessed at the medial (3 trials) and lateral (3 trials) joint lines of the index knee using a handheld Medoc digital pressure algometer (Ramat Yishai, Israel). Additionally, pressure pain thresholds were assessed at the ipsilateral quadriceps, trapezius and dorsal forearm. To assess pressure pain threshold, the examiner applied pressure at a rate of 30 kilopascals (kPa) per second and the participant was instructed to press a button when the stimulus “first becomes painful,” at which time the device recorded the pressure in kPa. The averages of the three trials for the medial knee and lateral knee, as well as the ipsilateral quadriceps, trapezius and forearm were calculated to create an overall pressure pain sensitivity score.

Cold Pressor—Each participant completed a series of hand immersions in a cold water bath (Neslab, RTE-111, Portsmouth, NH) at temperatures of 16°, 12°, and 8° C, with 5-minutes separating each exposure. Participants were first instructed regarding the differences between pain intensity and pain unpleasantness. Next, they were instructed to place their hand in the cold water bath up to their wrist for as long as possible up to 60 seconds. Participants were informed they could remove their hand from the cold water at any time if the pain became intolerable. Immediately after participants removed their hand, they rated the intensity and unpleasantness of any pain they were experiencing using 0 to 100 numeric rating scales. In addition to ratings of intensity and unpleasantness, a measure of cold pain

tolerance was captured. Specifically, cold pain tolerance was measured as the time at which participants removed their hand from the cold water.

Data analysis

Hypothesis 1—Two separate linear regression models were used to determine the predictive value of pain hypervigilance on WOMAC pain and KOOS-PS scores. The following *a priori* covariates were added to the regression model: age, ethnicity (0 = non-Hispanic White, 1 = African American), gender (0 = female, 1 = male), education (0 = high school or less, 1 = some college or more), and depressive symptoms as measured by the CES-D.

Hypothesis 2—Linear regression was similarly used to assess the relationship between pain hypervigilance and experimental pain responses, with the exception of cold pain tolerance, which was assessed by binary logistic regression. The latter procedure was used because the majority of participants completed the full duration of cold water exposure (maximum 60 seconds) at each measured temperature. Therefore, to avoid statistical problems associated with abnormal distributions, cold pain tolerance was dichotomized. Specifically, participants were classified as ‘tolerant’ if they did not remove their hand for the full 60 seconds immersion and classified as ‘intolerant’ if they removed their hand before the full 60 seconds. In addition to controlling for demographic characteristics as described above, the WOMAC pain subscale and SPC scale were included as additional covariates to determine if pain hypervigilance explained variance in quantitative sensory testing beyond ratings of clinical pain and situation specific coping, respectively. Lastly, cold pain tolerance was added as a covariate for pain intensity and pain unpleasantness analyses for each respective temperature to determine if pain hypervigilance differentiated pain ratings beyond what cold water exposure could explain.

Hypothesis 3—Before assessing temporal summation of heat pain, paired t-tests analyzing the difference between the first and highest pain ratings were inspected to verify significant temporal summation prior to determining its relationship with pain hypervigilance. Linear regression was used to determine the relationship between pain hypervigilance and temporal summation of heat pain while controlling for age, ethnicity, gender, education, depression, WOMAC pain, and SPC.

Due to the large number of statistical analyses performed, corrections for multiple testing were employed. To accomplish this, we first categorized our dependent variables into separate “families” based on stimulus type. These are 1) clinical outcomes (WOMAC pain, KOOS-PS); 2) thermal heat (heat pain thresholds and tolerances at the forearm and knee); 3) mechanical pressure (pressure pain thresholds at the lateral knee, medial knee, forearm, quadriceps, and trapezius); 4) cold pressor (pain intensity/unpleasantness ratings and cold pain tolerance); and 5) temporal summation of heat pain. We then performed a Holm-Bonferroni procedure to obtain corrected p-values (30). Briefly, for each “family,” obtained p-values were ordered from lowest to highest. The lowest p-value was then compared to the p-value obtained using a standard Bonferroni correction (i.e., $0.05/C$ [where C is the number of tests performed within a given “family”]). If the p-value was lower than this adjusted p-

value, the next lowest p-value was compared to an alpha correction of $0.05/C - 1$. This procedure is continued until the first non-significant test is obtained.

For all analyses, Cohen's f^2 effect sizes are presented where appropriate. Per Cohen's guidelines, $f^2 = 0.02$ is considered a small effect, $f^2 = 0.15$ a medium-sized effect, and $f^2 = 0.35$ a large effect (31). All variables had complete data except temporal summation of heat pain. Because only a small number of data were missing for temporal summation of heat pain (n ranged from 162 to 166), missing cases were deleted listwise. All analyses were carried out using SPSS, version 19.

Results

Demographic variables (age, ethnicity, gender and education), clinical characteristics (CES-D), and mean PVAQ scores of research participants are presented in Table 1. Participants were primarily female (73.8%) with a mean age of $56.9 (\pm 7.66)$. The first order intercorrelations among the PVAQ and control variables are presented in Table 2. Greater scores on the PVAQ were associated with being younger in age ($P < 0.05$), African-American ($P < 0.001$), and having high school education or less ($P < 0.001$). Table 3 shows the first order intercorrelations of the PVAQ and control variables with the outcome variables. Table 4 shows the characteristics of all outcome variables.

Hypothesis 1

Pain hypervigilance was significantly related to clinical pain intensity and disability. Specifically, pain hypervigilance was positively associated with greater WOMAC pain ($P < 0.01$; $f^2 = 0.08$) and KOOS-PS scores ($P < 0.01$; $f^2 = 0.06$) after adjusting for age, ethnicity, gender, education, and depression (see Table 5). Both WOMAC pain and KOOS-PS remained significant after applying Holm-Bonferroni corrections for multiple testing.

Hypothesis 2

Pain hypervigilance was not a significant predictor of heat pain threshold or heat pain tolerance at the index knee or ipsilateral ventral forearm.

Pain hypervigilance was significantly related to lower pressure pain thresholds at the lateral knee ($P < 0.05$; $f^2 = 0.04$), quadriceps ($P < 0.05$; $f^2 = 0.03$), and trapezius ($P < 0.01$; $f^2 = 0.07$), but not at the medial knee or forearm (see Table 5). After applying a Holm-Bonferroni correction for multiple testing, only the pressure pain threshold at the lateral knee and trapezius remained significant.

Prior to applying Holm-Bonferroni corrections, pain hypervigilance was significantly related to pain intensity and pain unpleasantness at 12°C , as well as cold pain tolerance at 8°C cold water immersions. However, there were no significant relationships after correcting for multiple testing.

Hypothesis 3

Paired t-tests analyzing the difference between the first and highest pain ratings during temporal summation of heat pain were significant for all measured temperatures at both

anatomical sites ($P < 0.05$). Significant positive associations between pain hypervigilance and greater temporal summation of heat pain were found at all measured temperatures at the index knee and forearm with f^2 values ranging from 0.04 to 0.07 (see Table 6). All analyses remained significant after applying Holm-Bonferroni corrections for multiple testing.

Discussion

The aim of the present study was to determine the association of pain hypervigilance with clinical pain ratings, clinical disability, and experimental pain sensitivity in individuals with symptomatic knee OA. As predicted, pain hypervigilance was significantly related to greater reports of clinical knee pain and disability, as well as greater sensitivity to pressure. In addition, pain hypervigilance was a significant predictor of temporal summation of heat pain, a marker of central sensitization, at both the knee and forearm at all measured temperatures. Importantly, the associations among pain hypervigilance and experimental pain sensitivity were found after ratings of clinical pain severity were statistically controlled, suggesting pain hypervigilance is related to greater experimental pain sensitivity independently of clinical pain severity.

Hypervigilance leads to an increased ability to detect potentially harmful stimuli (32). In regard to pain, hypervigilance results in heightened attention to pain and pain-related information (33). Although adaptive in the acute stage of pain, hypervigilance in chronic or recurrent pain states may decrease pain detection thresholds and increase pain-related interference (6). In the present study, pain hypervigilance was associated with greater knee OA related pain intensity (WOMAC pain), as well as greater pain-related disability (KOOS-PS).

This is the first study to investigate the relationship between pain hypervigilance and experimental pain sensitivity in persons with symptomatic knee OA. The finding that experimental pain was predicted by pain hypervigilance beyond what could be explained by clinical pain intensity may point to a cognitive/affective exacerbation of pain in individuals who exhibit a high degree of pain hypervigilance. For example, Crombez et al. (33) showed that in addition to pain intensity, fearful apprehension about pain was a unique predictor of attention to pain in persons with conditions associated with chronic pain (e.g., back pain, generalized widespread pain). Therefore, among knee OA patients with high levels of pain hypervigilance, it may be possible to reduce pain severity and pain disability using cognitive-behavioral modification or similar interventions. Keefe and colleagues (34,35) have demonstrated the effectiveness of cognitive-behavioral interventions in improving pain coping skills and reducing pain, physical disability, and psychological disability in persons with knee OA. However, no studies have assessed the efficacy of cognitive-behavioral interventions in reducing pain hypervigilance among persons with knee OA. In patients with chronic low back pain, de Jong et al. (36) showed that a 6-week cognitive-behavioral *in vivo* graded exposure intervention led to reductions in pain hypervigilance, pain intensity, pain catastrophizing, and fear of pain, as well as improvements in daily functioning. This intervention is unique in that it was developed according to the fear-avoidance model of pain and is aimed at reducing pain-related fear, of which pain hypervigilance is believed to be a

component (37). It will be important in the future to determine the efficacy of *in vivo* graded exposure in patients with knee OA.

It has been postulated that recurrent or chronic pain in knee OA may be influenced by central sensitization (38,39), especially in those with little radiographic evidence of joint pathology (40). Central sensitization has been operationalized as a hypersensitivity to prolonged or repeated suprathreshold pain stimuli (i.e., temporal summation) or by enhanced pain sensitivity at anatomic sites distal to the affected site (15,40). In the present study, pain hypervigilance was significantly related to temporal summation of heat pain and pressure pain threshold at the trapezius, suggesting pain hypervigilance may be associated with central sensitization in knee OA.

Contrary to predictions, pain hypervigilance was not significantly related to heat pain threshold, heat pain tolerance, or cold water pain (see Table 5). It may be that the other experimental procedures used in the present study are more relevant to pain hypervigilance in this clinical population. For example, pressure pain mechanically stimulates deep tissue nociceptors, unlike the heat pain procedures, which stimulate superficial cutaneous nociceptors. Thus, the relationship between pain hypervigilance and experimental pain may be more pronounced when deep tissue is stimulated, especially among individuals with clinical pain arising from deep structures. It is also important to note that although heat pain threshold, heat pain tolerance, and temporal summation of heat pain use the same stimulus modality, temporal summation of heat pain is believed to be a proxy for central sensitization where repeated heat pulses of the same intensity are perceived to increase in their painfulness. This progressive enhancement of unmyelinated afferent responses or “wind up” is reflected in the change score (highest pain rating minus the first pain rating) which was used as the dependent measure. It is likely that pain hypervigilance is more highly associated with this dynamic pain facilitatory process (i.e., “wind up”), as opposed to single, discrete heat pain stimuli. This point is further strengthened because pain hypervigilance was not a significant predictor of the first pain rating during temporal summation of heat pain (data not shown).

Although pain hypervigilance is often conceptualized as a ‘psychosocial’ construct, it is likely that the development of pain hypervigilance is associated with alterations in underlying neural function. In the present study, the relationship between pain hypervigilance and markers of central sensitization may have emerged in part because both constructs share common neural pathways. For example, in the anxiety literature, hypervigilance is related to increased activity in the anterior cingulate cortex, a dense interconnected brain center involved in attention selection (41). Activity in the anterior cingulate cortex is positively associated with clinical and experimental-induced pain in knee OA (42). Furthermore, the functional connectivity between the anterior cingulate cortex and other brain areas known to be involved in the perception of pain, such as the periaqueductal gray, has been demonstrated using functional magnetic resonance imaging (fMRI) and implicated in the development and maintenance of chronic pain states (43). This is important because recent fMRI studies have shown that central sensitization in hip OA is associated with increased activation in the periaqueductal gray (14). Although speculative, pain hypervigilance may result in the strengthening of facilitatory connections between the

anterior cingulate cortex and periaqueductal gray that may contribute to the maintenance of central sensitization and/or exacerbate the pain related to central sensitization.

A number of covariates were significantly correlated with outcomes in the present investigation (see Table 3). Consistent with previous findings (3), depressive symptoms were correlated with reports of clinical pain and disability. In addition, African Americans tended to report greater clinical pain and disability, and tended to be more pain sensitive than non-Hispanic Whites across a number of experimental pain stimuli, which is also consistent with existing literature (44,45). African Americans were also more likely to report greater pain hypervigilance than non-Hispanic whites (see Table 2). Although beyond the scope of the present study, it may be important for future research to investigate the mediating role of pain hypervigilance in the relationship between ethnicity and pain sensitivity.

The findings of the present study should be interpreted in light of its limitations. First, due to the cross-sectional design of the study, it is unknown if the development of pain hypervigilance precedes knee pain, or occurs as a result of knee pain in certain individuals. We also did not control for the use of non-opioid analgesics in the present investigation. Although this likely did not influence experimental pain sensitivity (46), it is possible the use of non-opioid analgesics may have affected reports of clinical pain and disability. In addition, although we screened for a number of comorbid conditions (see Methods section), we also acknowledge that other comorbidities were not systematically assessed and may have contributed to our findings. Further, the associations between pain hypervigilance and pain measures were generally small in magnitude and the clinical implications remain unknown. Lastly, it will be important for future studies investigating pain hypervigilance to incorporate radiographic results in their findings, as this may shed further light on the discordance between joint pathology and pain severity.

In the present study, we show that pain hypervigilance is associated with greater ratings of clinical pain and clinical disability, as well as enhanced pressure pain sensitivity. In addition, we show that pain hypervigilance is a significant predictor of temporal summation of heat pain, a marker for central sensitization. These findings provide support for the role of pain hypervigilance in the experience of pain among individuals with symptomatic knee OA. It will be important in the future to determine if pain hypervigilance can be reduced by psychosocial or other interventions.

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Table 1

Characteristics of participants

N	168
Mean age (SD)	56.9 (7.66)
Female gender	124 (73.8%)
Ethnicity	
Non-Hispanic white	87 (51.8%)
African-American	81 (48.2%)
Education	
High school or less	70 (41.7%)
Some college or more	98 (58.3%)
CES-D (SD)	16.14 (5.81)
PVAQ	44.26 (15.53)

Note: Data presented as means (SD) or count (%); CES-D = Center for Epidemiologic Studies Depression Scale, possible range = 0 – 60; PVAQ = Pain Vigilance and Awareness Questionnaire, possible range = 0 – 80

Table 2

First order intercorrelations among pain hypervigilance and covariates

	Age	Ethnicity	Gender	Education	CES-D	SPC
PVAQ	−0.15*	0.39**	0.07	−0.24**	−0.00	0.13
Age		−0.26**	−0.05	0.12	−0.19*	−0.10
Ethnicity			0.02	−0.22**	−0.01	0.16*
Gender				−0.12	−0.04	−0.16*
Education					−0.02	−0.06
CES-D						0.13

* = P < 0.05,
** = P < 0.001

Note: PVAQ = Pain Vigilance and Awareness Questionnaire, possible range = 0 – 80; Age, observed range = 45 – 85; Ethnicity: 0 = non-Hispanic White, 1 = African American; Gender: 0 = female, 1 = male; Education: 0 = high school or less, 1 = some college; CES-D = Center for Epidemiologic Studies Depression Scale, possible range = 0 – 60; SPC = Situational Passive Coping, possible range = 1 – 5

Table 3

First order intercorrelations of pain hypervigilance and covariates with outcome variables

	WOMAC pain	KOOS-PS	HPTb Forearm	HPTb Knee	HPTb Forearm	HPTb Knee	RPTb Medial	RPTb Lateral	RPTb Forearm	RPTb Quadriceps	RPTb Trapezius	Intensity 16°C	Unpleasantness 16°C	Intensity 12°C	Unpleasantness 12°C	Intensity 8°C	Unpleasantness 8°C	CPTo 16°C	CPTo 12°C	CPTo 8°C	TS Forearm 44°C	TS Forearm 46°C	TS Forearm 48°C	TS Knee 44°C	TS Knee 46°C	TS Knee 48°C
PVAQ	.35**	.30**	-.13	-.13	-.17*	-.22*	-.26*	-.15	-.19*	-.14	-.28**	.21*	.19*	.26*	.26*	.22*	.21*	-.16*	-.24*	-.30**	.30**	.34*	.31**	.28**	.25*	.21*
Age	-.11	-.11	-.08	.02	-.02	.03	.06	-.13	-.14	-.07		.14	.08	.06	.03	.00	-.01	-.06	-.02	.01	-.00	-.07	-.04	-.04	-.01	-.04
Gender	-.08	-.03	.15	.07	.27**	.34**	.36**	.35**	.23*	.23*	.27	-.07	-.08	-.13	-.13	-.11	-.04	-.10	.13	.18*	-.10	-.07	-.10	-.08	-.13	-.10
Ethnicity	.27**	.22*	-.27*	-.23*	-.40**	-.21*	-.20*	-.06	-.06	-.06	-.08	.10	.13	.17*	.18*	.11	.10	-.09	-.30**	-.28**	.25*	.30**	.31**	.26*	.24*	.20*
Education	-.27**	-.17*	.02	.08	.11	.05	.07	-.00	.03	.09	.09	.00	.05	-.05	-.06	-.15*	-.12	.12	.09	.24*	-.13	-.17*	-.12	-.08	-.07	-.02
CES-D	.28**	.22*	.08	.02	.03	-.06	-.09	-.03	-.05	-.07	-.07	.09	.08	.12	.11	.11	.16*	-.10	-.03	-.14	.01	-.02	.09	-.05	.05	.10
SPC	.21*	.16*	-.17*	-.10	-.16*	-.25*	-.19*	-.14	-.17*	-.18*	-.18*	.13	.15	.16*	.20*	.15	.16*	.05	-.18*	-.23*	.10	.17*	.14	.10	.19*	.21*

* = P < 0.05,
** = P < 0.001

Note: PVAQ = Pain Vigilance and Awareness Questionnaire, possible range = 0–80; Age, observed range = 45 – 85; Ethnicity: 0 = non-Hispanic White, 1 = African American; Gender: 0 = female, 1 = male; Education: 0 = high school or less, 1 = some college; CES-D = Center for Epidemiologic Studies Depression Scale, possible range = 0–60; SPC = Situational Passive Coping, possible range = 1–5; WOMAC = Western Ontario McMaster Universities Osteoarthritis Scale, possible range = 0–20; KOOS-PS = Knee Injury and Osteoarthritis Outcome Score-Physical Function Short-Form, possible range = 0–28; HPTb = Heat pain threshold; HPTTh = Heat pain tolerance; PPTh = Pressure pain threshold; C = Celsius; CPTo = Cold pain tolerance; TS = Temporal summation

Table 4

Characteristics of clinical pain, clinical disability, and quantitative sensory testing variables

WOMAC pain	7.32 (4.45)
KOOS-PS	12.38 (6.80)
HPT _h forearm temp (C)	41.74 (3.11)
HPT _o forearm temp (C)	46.01 (2.40)
HPT _h knee temp (C)	41.82 (3.21)
HPT _o knee temp (C)	45.82 (2.77)
PPT _h medial knee (kPa)	302.76 (155.80)
PPT _h lateral knee (kPa)	311.12 (171.62)
PPT _h forearm (kPa)	247.10 (150.21)
PPT _h quadriceps (kPa)	414.98 (215.82)
PPT _h trapezius (kPa)	270.46 (156.90)
Intensity ratings at 16° C	31.60 (28.47)
Unpleasantness ratings at 16° C	34.30 (30.73)
Intensity ratings at 12° C	59.03 (31.24)
Unpleasantness ratings at 12° C	62.67 (32.02)
Intensity ratings at 8° C	73.28 (27.99)
Unpleasantness ratings at 8° C	75.32 (28.49)
CPT _o 16° C (Count reaching full tolerance [60 seconds])	159 (94.6%)
CPT _o 12° C (Count reaching full tolerance [60 seconds])	121 (72.0%)
CPT _o 8° C (Count reaching full tolerance [60 seconds])	93 (55.5%)
TS forearm 44° C (Max rating minus first rating)	7.23 (12.35)
TS forearm 46° C (Max rating minus first rating)	8.83 (13.51)
TS forearm 48° C (Max rating minus first rating)	12.96 (16.29)
TS knee 44° C (Max rating minus first rating)	5.72 (11.44)
TS knee 46° C (Max rating minus first rating)	9.84 (15.51)
TS knee 48° C (Max rating minus first rating)	13.17 (16.59)

Note: Data presented as means (SD) or count (%); WOMAC = Western Ontario McMaster Universities Osteoarthritis Scale; KOOS-PS = Knee Injury and Osteoarthritis Outcome Score-Physical Function Short-Form; HPT_h = Heat pain threshold; C = Celsius; HPT_o = Heat pain tolerance; PPT_h = Pressure pain threshold; kPa = kilopascals; CPT_o = Cold pain tolerance; TS = Temporal summation

Table 5

Multiple regression predicting pain outcomes as a function of pain hypervigilance

	B	SEB	95% CI	β	f^2
Pain Outcome Variables					
<i>a</i> WOMAC pain	0.08	0.02	0.03, 0.12	0.26*	0.08
<i>a</i> KOOS-PS	0.11	0.04	0.04, 0.17	0.24*	0.06
<i>b</i> HPTh forearm	-0.01	0.02	-0.05, 0.02	-0.06	0.00
<i>b</i> HPTo forearm	-0.01	0.01	-0.03, 0.02	-0.03	0.00
<i>b</i> HPTh knee	-0.01	0.02	-0.05, 0.03	-0.05	0.00
<i>b</i> HPTo knee	-0.01	0.01	-0.04, 0.02	-0.04	0.00
<i>b</i> PPTh lateral knee	-2.05	0.85	-3.72, -0.38	-0.19*	0.04
<i>b</i> PPTh medial knee	-1.13	0.78	-2.70, 0.43	-0.11	0.01
<i>b</i> PPTh forearm	-1.44	0.79	-3.00, 0.13	-0.15	0.02
<i>b</i> PPTh quadriceps	-2.33	1.14	-4.58, -0.08	-0.17	0.03
<i>b</i> PPTh trapezius	-2.77	0.82	-4.38, -1.15	-0.27*	0.07
<i>c</i> Intensity 16° C	0.29	0.15	-0.01, 0.59	0.16	0.02
<i>c</i> Unpleasantsness 16° C	0.24	0.17	-0.10, 0.57	0.12	0.01
<i>c</i> Intensity 12° C	0.37	0.16	0.06, 0.69	0.19	0.04
<i>c</i> Unpleasantsness 12° C	0.41	0.17	0.08, 0.74	0.20	0.04
<i>c</i> Intensity 8° C	0.23	0.15	-0.07, 0.52	0.13	0.02
<i>c</i> Unpleasantsness 8° C	0.26	0.16	-0.05, 0.57	0.14	0.02

* Significant after applying a Holm-Bonferroni adjustment for multiple testing

a = Adjusted for age, ethnicity, gender, education, and CES-D

b = Adjusted for age, ethnicity, gender, education, CES-D, WOMAC pain, and SPC

c = Adjusted for age, ethnicity, gender, education, CES-D, WOMAC pain, SPC, and CPTo

Note: WOMAC = Western Ontario McMaster Universities Osteoarthritis Scale; KOOS-PS = Knee Injury and Osteoarthritis Outcome Score-Physical Function Short-Form; HPTh = Heat pain threshold; HPTo = Heat pain tolerance; PPTh = Pressure pain threshold

Table 6

Multiple regression predicting temporal summation of heat pain as a function of pain hypervigilance

	B	SEB	95% CI	β	f^2
TS of Heat Pain Variables					
TS forearm 44° C	0.20	0.07	0.06, 0.33	0.25*	0.05
TS forearm 46° C	0.24	0.07	0.10, 0.39	0.28*	0.07
TS forearm 48° C	0.29	0.09	0.12, 0.46	0.28*	0.07
TS knee 44° C	0.17	0.06	0.04, 0.29	0.23*	0.04
TS knee 46° C	0.22	0.09	0.05, 0.39	0.22*	0.04
TS knee 48° C	0.22	0.91	0.05, 0.41	0.21*	0.04

* Significant after applying a Holm-Bonferroni adjustment for multiple testing

Note: All analyses adjusted for age, ethnicity, gender, education, CES-D, WOMAC pain, and SPC; TS = temporal summation