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Cold Pain Threshold Identifies a Subgroup of Individuals With Knee Osteoarthritis That Present With Multimodality Hyperalgesia and Elevated Pain Levels

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Objectives: Cold hyperalgesia has been established as an important marker of pain severity in a number of conditions. This study aimed to establish the extent to which patients with knee osteoarthritis (OA) demonstrate widespread cold, heat, and pressure hyperalgesia. OA participants with widespread cold hyperalgesia were compared with the remaining OA cohort to determine whether they could be distinguished in terms of hyperalgesia, pain report, pain quality, and physical function.

Methods: A total of 80 participants with knee OA and 40 matched healthy, pain-free controls participated. OA participants completed a washout of their usual medication. Quantitative sensory testing was completed at 3 sites using standard methods. Cold pain threshold (CPT) and heat pain thresholds (HPT) were tested using a Peltier thermode and pressure pain thresholds (PPT) using a digital algometer. All participants completed the short-form health survey questionnaire and OA participants completed the PainDETECT, Western Ontario and McMaster Universities Osteoarthritis Index of the Knee (WOMAC), and pain quality assessment scale questionnaires.

Results: OA participants demonstrated widespread cold hyperalgesia ($P < 0.0001$), had lower PPT at the index knee ($P < 0.0001$) compared with controls and reported decreased physical health on the SF-36 ($P = 0.01$). The OA subcohort with high global CPT (≥ 12.25°C) exhibited multimodality sensitization compared with the remaining OA cohort (PPT $P < 0.0001$; CPT $P < 0.0001$; HPT $P = 0.021$ index knee). This group also reported increased pain, decreased function, and more features of neuropathic pain.

Discussion: This study identified a specific subgroup of patients with knee OA who exhibited widespread, multimodality hyperalgesia, more pain, more features of neuropathic pain, and greater functional impairment. Identification of patients with this pain phenotype may permit more targeted and effective pain management.

Key Words: cold hyperalgesia, neuropathic pain, knee osteoarthritis, multimodality hyperalgesia, central sensitization

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Osteoarthritis (OA) is a common arthritic disorder[1,2] often associated with pain and local tenderness or pressure hyperalgesia around the affected joint(s).[3,4] Although knee OA has been considered the archetypal model of noninflammatory or nociceptive pain[5] it is now recognized that some patients with knee OA also exhibit features of neuropathic pain,[6] which may be associated with sensory deficits and widespread multimodality hyperalgesia.[7]

Local and widespread pressure hyperalgesia is well established in patients with knee OA, including evidence of pressure hyperalgesia at the contralateral knee or at sites in the upper or lower limb.[4,5,7–10] Research evaluating thermal hyperalgesia in this patient cohort is more limited. Cold and heat hyperalgesia has been demonstrated in hip OA[3] and we have recently demonstrated widespread cold and pressure hyperalgesia in a pilot study in patients with knee OA[9] but no difference between OA and control participants in cold or heat pain thresholds (HPT) across 3 test sites was reported in one study evaluating knee OA.[5] Wylde et al[7] reported no difference in HPT but did not analyze cold pain threshold (CPT) data due to technical issues with their thermode measurement. Therefore, while there is considerable evidence that local and widespread pressure hyperalgesia is a common feature in people with painful knee OA, the potential importance of heat and cold hyperalgesia has yet to be fully established.

Studies evaluating quantitative sensory testing (QST) data in other chronic musculoskeletal disorders suggest that pressure and cold hyperalgesia may copresent, for example, in tennis elbow,[11–13] spinal pain,[14,15] fibromyalgia,[16] temporomandibular joint disorder,[17] and whiplash-associated disorder (WAD).[18] An association between pain severity and chronicity and the presence of cold hyperalgesia has been suggested in WAD[19] and tennis elbow.[20] On the basis of the findings of systematic reviews, the presence of cold hyperalgesia has been proposed as a major prognostic factor in the development of increased central sensitization[21] and long-term pain and disability in WAD.[22,23] The presence of cold-evoked pain is also recognized as an important feature in neuropathic pain states[24,25] and has been linked to the presence of neuropathic pain following whiplash injury.[26] In combination, these findings indicate the value of identifying whether cold hyperalgesia is present alongside pressure hyperalgesia and heat hyperalgesia as these features may be linked to increased pain severity, greater functional impairment, and also potentially to the development of neuropathic pain.

The current study investigated the extent to which widespread cold, pressure, and heat hyperalgesia is experienced by participants with knee OA, compared with pain-free controls (PFC). The study also tested sensory detection thresholds to determine whether any sensory deficits were present. *Z*-score

analysis was used to identify a subcohort of knee OA participants who exhibited widespread cold hyperalgesia. This subcohort was compared with the remaining OA participants to determine differences in QST measures, levels of pain, pain characteristics, and perceived function.

METHODS

Participants

A total of 80 participants with painful knee OA and 40 PFC participants were recruited from the Perth community. Volunteers with painful knee OA (visual analog scale [VAS] score ≥ 3 of 10) were recruited and assessed for suitability by a Rheumatologist, using the American College of Rheumatology classification system.[27] Exclusion criteria included: history of systemic inflammatory conditions; neurological disorders affecting sensory or motor function; recent (< 6 mo) lower limb injury or surgery; or history of other chronic pain disorders (eg, fibromyalgia). PFC volunteers were included if aged 50 years or above, in good general health and with no current pain or history of OA.

All participants provided written informed consent before participating in the study. Ethical approval was provided by Royal Perth Hospital Medical Research Ethics Committee (Approval EC2009/100) and by Curtin University Human Research Ethics Committee (Approval HR26/2010).

Study Design

The study used a cross-sectional design, with participants attending the laboratory at Royal Perth Hospital for 1 test session. Participants with OA underwent a washout period equal to 5 half lives of their analgesic or non-steroidal anti-inflammatory drug medication before testing. They were able to use paracetamol for analgesia if required but were asked to refrain from its use for 12 hours before testing. All participants completed the Short-Form Health Survey (SF-36) quality of life questionnaire.[28] Participants with knee OA also completed the Western Ontario and McMaster Universities Osteoarthritis Index for the Knee (WOMAC),[29] the PainDETECT questionnaire,[30] and the pain quality assessment scale (PQAS).[31] All participants then completed QST measures. Order of testing was randomized between QST modalities, although for heat and cold stimuli, detection threshold was always tested before pain threshold.

QST

All QST were applied in triplicate using standardized instructions at standardized sites: at the OA knee and the contralateral knee (medial joint line) and at the ipsilateral elbow over the extensor carpi radialis brevis (ECRB) muscle.[32]

Pressure pain threshold (PPT) was assessed using an electronic digital pressure algometer (Somedic AB, Sweden), a device that has consistently shown good reliability.[33] A 1 cm^2 algometer probe was applied at 90 degrees to the skin at a rate of 40 kPa/s. Participants were instructed to depress the hand-held switch as soon as the sensation of pressure became one of painful pressure.[34] Lower PPT values indicated increased sensitivity.

Cold detection thresholds (CDT) and CPT were measured using a Peltier thermode (Medoc, Israel) and standard method of limits.[35] The probe was attached to the test site with a Velcro strap. The temperature reduced at a rate of 1°C/s from a baseline temperature of 32°C to a minimum of 0°C. CDT was always measured first. Participants were instructed to depress the hand-held switch as soon as they perceived any cooling change from baseline. For CPT, participants were instructed to press the switch as soon as the cooling sensation changed to one of painful cold. Some participants failed to indicate cold pain before the thermode reached the minimum temperature of 0°C. These participants were assigned a CPT of 0°C. Elevated CPT values indicated increased sensitivity.

Warm detection threshold (WDT) and HPT were measured with the Medoc Peltier thermode using similar methodology to cold testing (baseline 32°C, 1°C/s ascending ramp), with maximum temperature set at 50°C. WDT was defined as the temperature (°C) at which participants first perceived an increase in warmth from baseline, whereas HPT was defined as the temperature (°C) at which participants perceived that the heating sensation had become one of painful heat. Some participants failed to indicate heat pain before the thermode reached the maximum temperature of 50°C. These participants were assigned a HPT of 50°C. Lower HPT values indicated increased sensitivity.

Self-Report Questionnaires

SF-36 quality of life was evaluated with the SF-36v2, which has demonstrated good validity and reliability for a range of conditions and for healthy participants.[28] The tool measures the self-perceived impact of health status on quality of life via 8 domains, using Likert-type response categories. The current study calculated the physical and mental health subscales for analysis.

WOMAC was used to evaluate subjective pain, stiffness, and functional limitation for OA participants. This OA-specific self-report scale has been widely used to measure pain and disability from knee OA, demonstrating good internal validity and test-retest reliability.[29]

PainDETECT is a validated self-report tool that has been used to identify neuropathic pain features in a range of conditions.[30] The questionnaire uses a combination of VAS scale, body diagram, and Likert-type questions to ask about everyday frequency of symptoms such as "electric shocks" or painful light touch. A total score is calculated, with participants scoring < 13/35 classified as "negative neuropathic" and 19 + as "positive neuropathic."

PQAS was also used to provide data regarding the type of spontaneous pain experienced by OA participants.[31] The questionnaire includes 17 questions about the type of pain plus additional numerical rating scales for unpleasantness and surface versus deep pain. Three specific pain subscores are then calculated[31]: paroxysmal, surface, and deep. It has been suggested that differences between the deep and surface or paroxysmal subscales may differentiate nociceptive-type and neuropathic-type pain.[31]

Statistical Analysis

Data were analyzed using SPSS version 20 (IBM Corp.) with α set at $P < 0.05$. The data were analyzed in 2 stages. Initial comparisons were carried out between the OA and PFC groups. Shapiro-Wilk tests determined that the QST and PQAS data were not normally distributed and so nonparametric tests (Mann-Witney U test, Kruskal-Wallis test) were applied. WOMAC, PainDETECT, and SF-36 data met the assumption of normality based on the Shapiro-Wilk test and so were analyzed using parametric tests (t test, 1-way analysis of variance [ANOVA]).

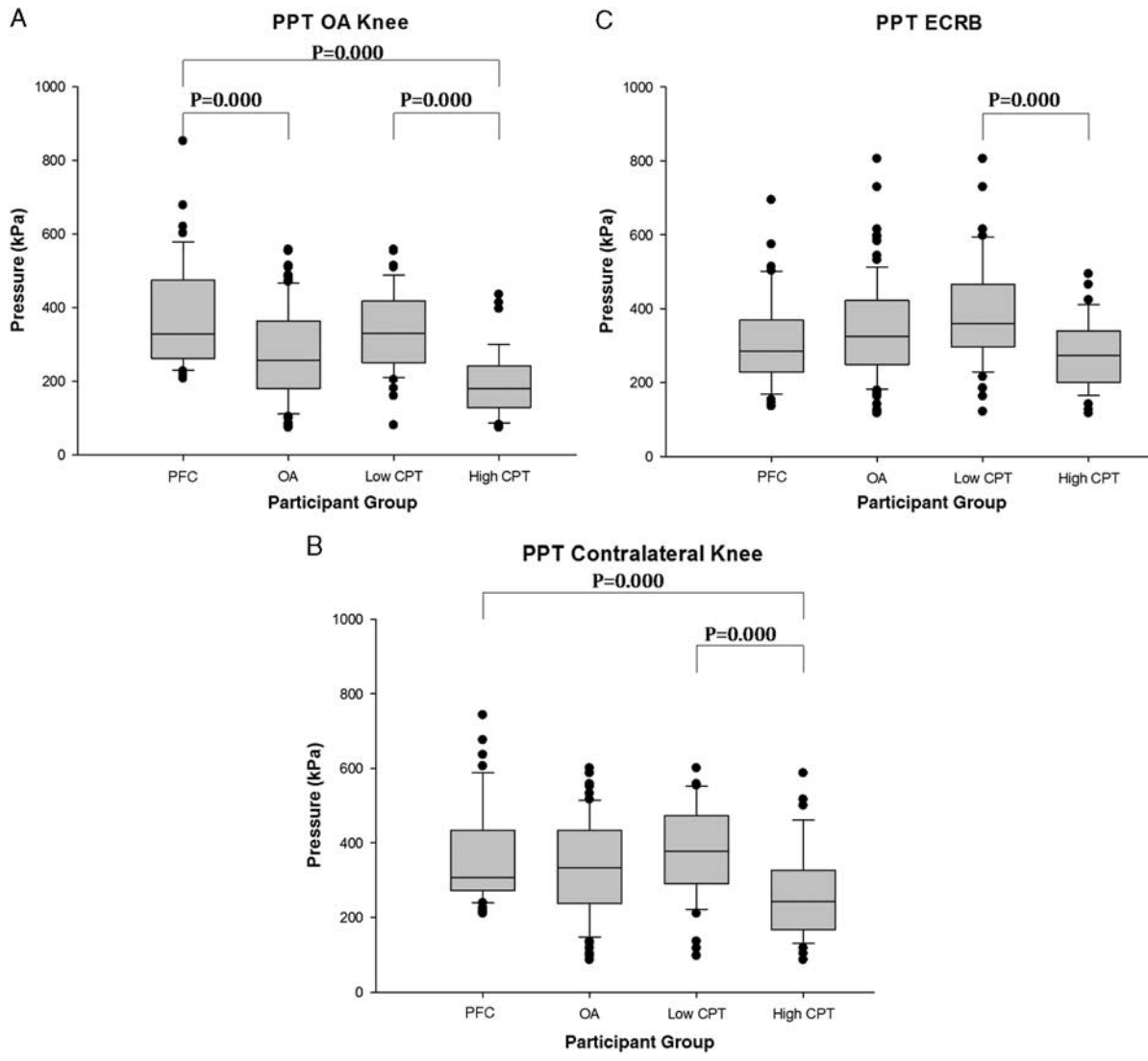

FIGURE 1. PPT at each of the 3 test sites. There was a significant difference in PPT between the OA and control groups at the index knee (A). There was a significant difference in PPT between the low CPT and high CPT groups at all sites (A–C) and there was a significant difference between the high CPT and PFC PPT measures at the index knee and the contralateral knee (A, B). CPT indicates cold pain thresholds; ECRB, extensor carpi radialis brevis; OA, osteoarthritis; PPT, pressure pain thresholds; PFC, pain-free control group.

On the basis of a previous study it was predicted that 20% to 30% participants would present with elevated CPT, potentially associated with more severe pain.[9] With an estimated sample size of n = 20 for the elevated CPT group, it was calculated that the study would have 80% power to detect a between-groups mean difference of 38 kPa (SD, 57 kPa) in PPT, a 5.4°C (SD, 2.3°C) difference in CPT, and a 7.8 mm (SD, 16 mm) difference in total WOMAC score.[9] These values equate to a 15% to 20% between group difference.[9] On the basis of the elevated CPT group constituting 25% of the overall cohort a sample of 80 participants with knee OA was recruited for the study.

Following initial comparisons and using the approach suggested by the German Research Network on Neuropathic Pain (DFNS),[36] *Z*-scores for all measures were calculated for individual participants with knee OA using the mean and SD data from the group. Data for cold and heat measures were converted to difference values from the baseline temperature of 32°C. All data were log transformed and the *Z*-score calculated using the following formula:

$$Z\text{score} = \frac{(X\,\text{subject} - \text{mean painfree controls})}{\text{SD painfree controls}}.$$

OA participants with *Z*-scores outside the 95% confidence interval of the mean of the group (*Z*-score < -1.96 or > 1.96) were identified and classified as abnormal. The percentage of abnormal participants in the OA group for each measure at each site was calculated.[7]

A global CPT value (mean of all sites) was calculated and *Z*-scores determined. This identified that 35 of 80 participants with OA exhibited a global CPT value that was at least 1 *Z*-score higher than the control group mean. This indicates greater cold pain sensitivity. This high CPT (increased cold pain sensitivity) OA group was then compared with the remaining OA cohort and the PFC group

using parametric and nonparametric tests as appropriate. Correlations between global CPT and other key variables were also evaluated.

RESULTS

Participant Demographics

The OA cohort comprised 80 participants (36 male: 44 female) with a mean age of 64 years (range, 50 to 86 y). Mean body mass index was in the overweight category, with 38% participants categorized as obese. They reported moderate pain (WOMAC pain, 18.5/50) and functional disability (WOMAC function, 53.4/250). Two thirds of the OA participants reported regular use of at least 1 analgesic medication: slow release high dose paracetamol ("Panadol Osteo") (40%) or non-steroidal anti-inflammatory drugs (36%). Two participants reported opioid use. The participants self-reported their most painful knee which was defined as the index knee.

The pain-free cohort of 40 participants (16 male: 24 female) had a similar mean age of 64 years (range, 50 to 81 y) and mean body mass index in the overweight category but only 10% classified as obese.

Comparisons Between the OA and Pain-free Groups

PPT (OA vs. PFC)

OA participants had lower mean PPT than the PFCs at the index knee ($P < 0.0001$) (Fig. 1) but there was no significant difference in mean PPT values at the contralateral knee or the ECRB sites. *Z*-score analysis showed that 22.50% of OA participants exhibited pressure hyperalgesia at the index knee, 16.25% at the contralateral knee, and 3.75% at the ECRB site (Fig. 2).

CDT and CPT (OA vs. PFC)

OA participants had significantly reduced CDT at the index knee ($P = 0.008$) and contralateral knee ($P = 0.027$) but not at the ECRB site ($P = 0.132$) (Fig. 3). CPT were significantly higher at all sites ($P < 0.0001$) in the OA group compared with the PFC group (Fig. 4). *Z*-score analysis: 11.25% of OA participants had cold hypoesthesia at the index knee, 17.50% at the contralateral knee, and 17.50% at the ECRB site. Cold hyperalgesia was present in a large percentage of OA participants with 47.5% of participants exhibiting abnormal CPT at the index knee, 37.5% at the contralateral knee, and 43.75% at the ECRB sites (Fig. 2).

WDT and HPT (OA vs. PFC)

WDT were significantly elevated at the index knee ($P = 0.01$), contralateral knee ($P = 0.022$), and ECRB sites ($P = 0.033$) (Fig. 5). However, there was no significant difference in HPT (Fig. 6) at any site (index knee $P = 0.956$; contralateral knee $P = 0.824$; ECRB $P = 0.486$). In total, 8.75% of OA participants had heat hypoesthesia at the index knee, 11.25% at the unaffected knee, and 7.50% at the ECRB sites (*Z*-score analysis). 10% of participants in the OA group exhibited heat hyperalgesia at the index knee with 15% and 13.75% at the unaffected knee and ECRB site, respectively (Fig. 2).

SF-36 (OA vs. PFC)

Participants with knee OA exhibited reduced scores on the physical health subscale of the SF-36 ($P = 0.01$) but were not significantly different on the mental health subscale ($P = 0.513$) compared with pain-free controls.

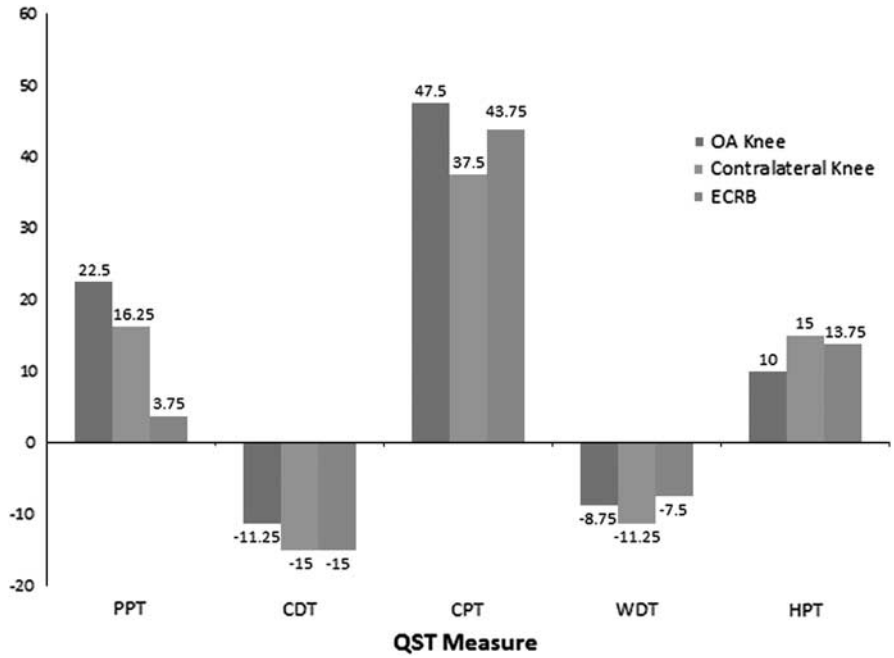

FIGURE 2. Percentages of OA participants with test values >1 *Z*-score higher or <95% confidence interval of the mean value for the control group. Values that indicate hyperalgesia are presented as positive scores. Values that indicate hypoesthesia are presented as negative scores. CDT indicates cold detection thresholds; CPT, cold pain threshold; ECRB, extensor carpi radialis brevis; HPT, heat pain thresholds; OA, osteoarthritis; QST, quantitative sensory testing; PPT, pressure pain thresholds; WDT, warm detection threshold.

Comparison Between the Cold Hyperalgesic and Nonhyperalgesic OA Subgroups

Following *Z*-score analysis of global CPT values 43.75% of the OA cohort were classified as cold hyperalgesic, equating to a CPT cut-off $\geq 12.25^{\circ}$C. This group had elevated CPT indicative of increased cold pain sensitivity. The OA cohort was therefore divided into a high CPT group (n = 35) and a low CPT group (n = 55). Comparisons were then made between these 2 OA subgroups and the control group across the range of measures.

PPT (High CPT vs. Low CPT vs. Control)

The Kruskal-Wallis test showed there was a significant difference in PPT at all sites ($P < 0.0001$). Between-group comparisons (Mann-Witney *U*) showed a significant difference in PPT between the high CPT and low CPT OA groups at all sites ($P < 0.0001$: Fig. 1) with the cold hyperalgesic OA group exhibiting greater pressure hyperalgesia. The cold hyperalgesic group also exhibited greater pressure hyperalgesia than the PFC group at the index knee ($P < 0.0001$) and contralateral knee ($P < 0.0001$) but no significant difference at the ECRB site ($P = 0.329$) (Fig. 1).

CDT and Pain Thresholds (High CPT vs. Low CPT vs. Control)

There was a significant difference between groups in CDT (Kruskal-Wallis) at all sites (OA knee $P < 0.0001$; contralateral knee $P = 0.001$; ECRB $P < 0.0001$). Between-group comparisons (Mann-Witney *U*) showed the low CPT OA group exhibited significantly reduced CDT, indicative of impaired cold perception at all sites (index knee $P = 0.001$; contralateral knee $P = 0.002$; ECRB $P = 0.0001$) (Fig. 3). However, there were no significant differences in CDT between the cold hyperalgesic OA group and the control group (index knee $P = 0.467$; contralateral knee $P = 0.853$; ECRB $P = 0.161$). The Kruskal-Wallis test was significant at all sites for CPT ($P < 0.0001$). Between-group comparisons showed differences in CPT ($P < 0.0001$) between the high CPT and low CPT OA groups at all sites (Fig. 4) and also

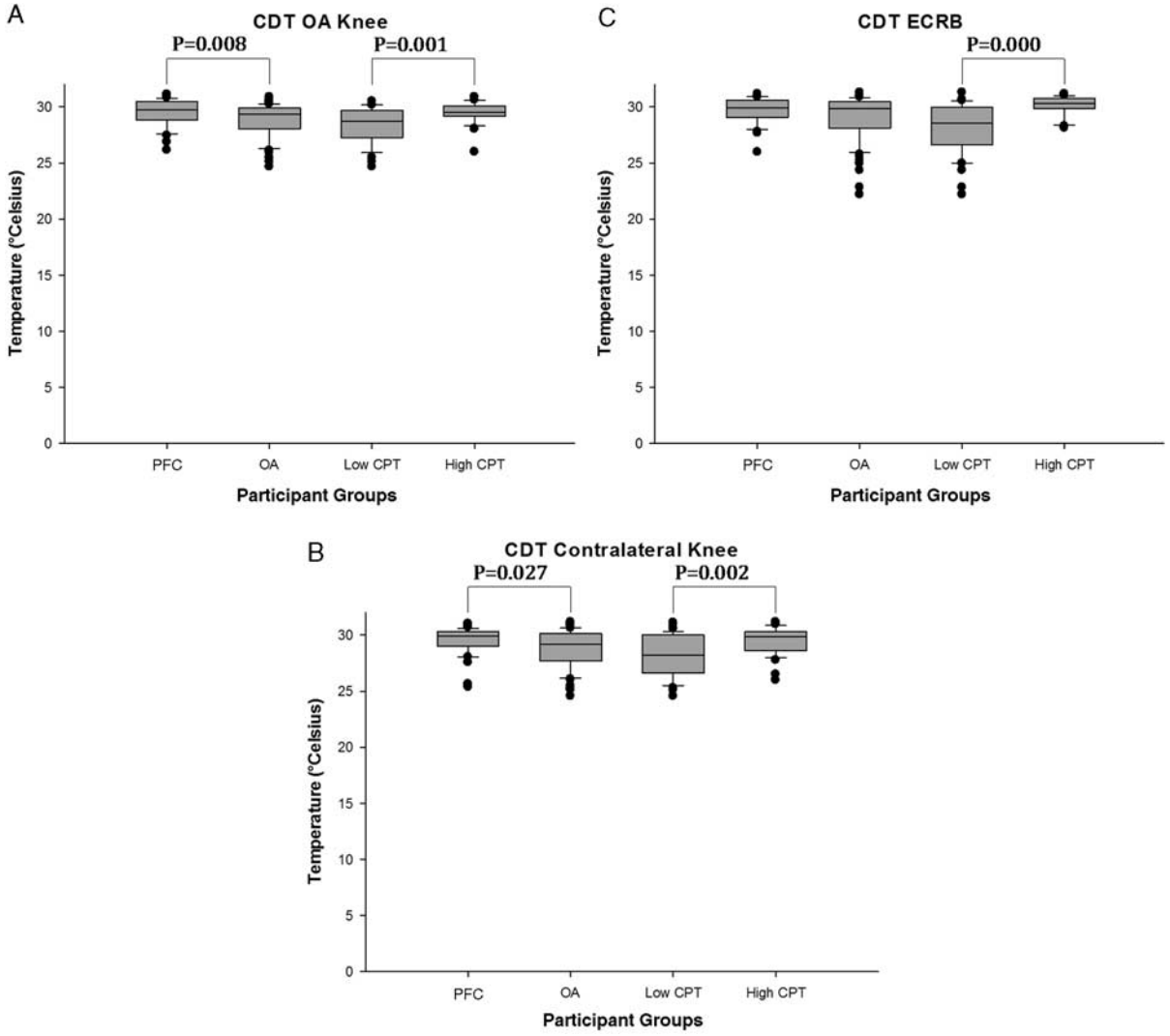

FIGURE 3. CDT at each of the 3 test sites. There was a significant difference in CDT between the OA and groups at the index knee and the contralateral knee (A, B). There was also a significant difference in CDT between the high and low CPT groups at all sites (A–C). CDT indicates cold detection thresholds; CPT, cold pain thresholds; ECRB, extensor carpi radialis brevis; OA, osteoarthritis; PFC, pain-free control.

between the cold hyperalgesic group and the PFC group ($P < 0.0001$) at all sites. No significant difference was seen between the low CPT group and the PFC group.

WDT and HPT (High CPT vs. Low CPT vs. Control)

There was a significant group difference in WDT at the index knee ($P = 0.015$) and ECRB sites ($P = 0.022$) but not at the contralateral knee ($P = 0.073$). Between-groups comparison showed no significant differences in WDT between the 2 OA subgroups (index knee $P = 0.168$; contralateral knee $P = 0.961$; ECRB $P = 0.082$). A significant difference in WDT existed between the cold hyperalgesic OA group and the PFC group at the contralateral knee ($P = 0.046$) but not at the other sites (index knee $P = 0.137$; ECRB $P = 0.410$) (Fig. 5). HPT was significantly different between groups at all sites (index knee $P = 0.021$; contralateral knee $P = 0.037$; ECRB $P = 0.01$). Between-groups comparison showed that the cold hyperalgesic OA group exhibited greater heat hyperalgesia at all sites (index knee $P = 0.007$; contralateral knee $P = 0.017$; ECRB $P = 0.005$) (Fig. 6) compared with the remaining OA participants although HPT did not differ between the cold hyperalgesic group and the control group at any site (index knee $P = 0.098$; contralateral knee $P = 0.08$; ECRB $P = 0.216$).

SF-36 (High CPT vs. Low CPT vs. Control)

There was a significant difference between groups for the SF-36 physical health subscale ($F_{2,117} = 4.649$, $P = 0.011$). Cold hyperalgesic OA participants had significantly reduced scores on the SF-36 physical health subscale compared with the PFC group ($P = 0.006$), although not compared with the remaining OA participants ($P = 0.093$). There was no difference in mental health

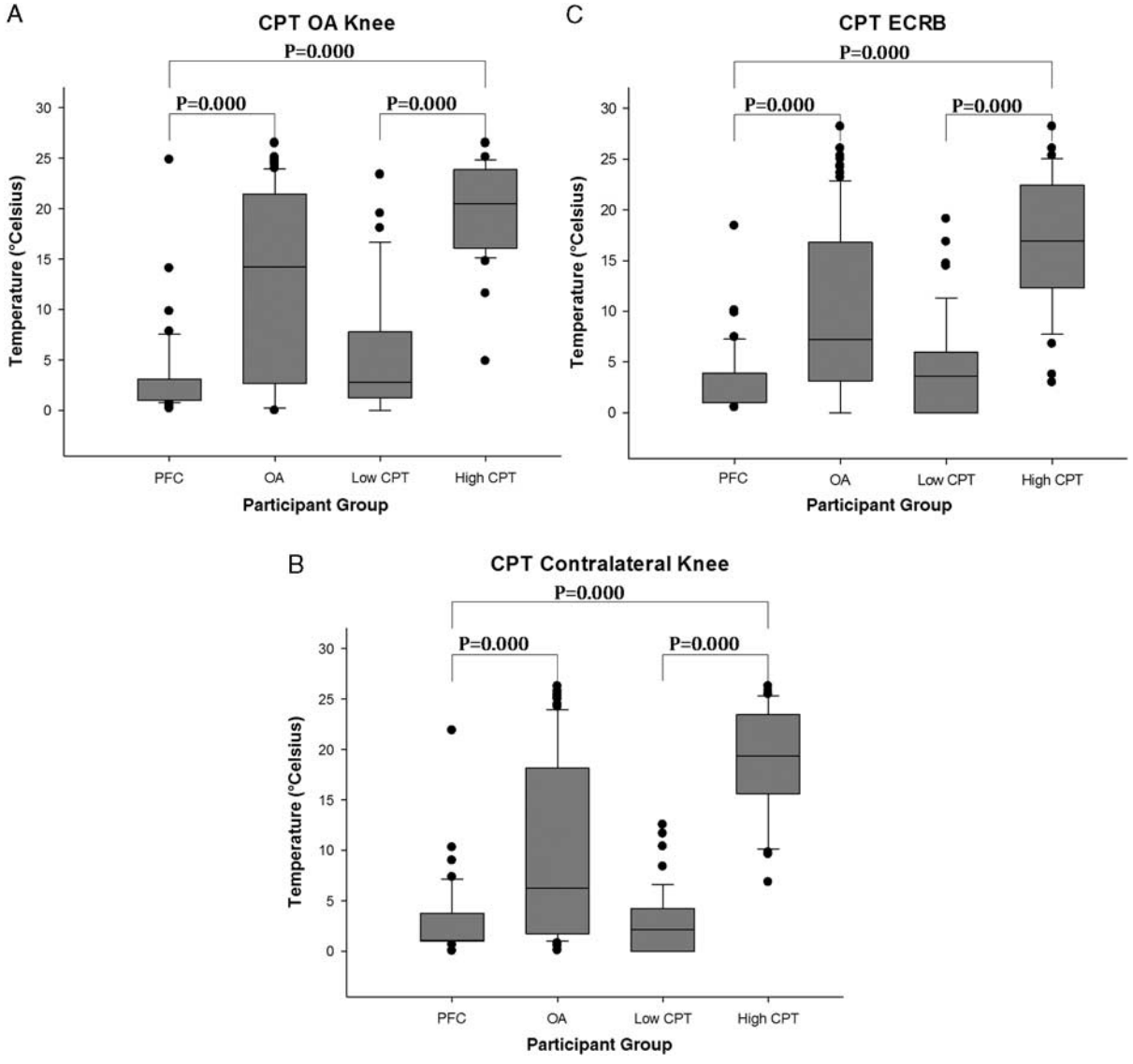

FIGURE 4. CPT at each of the 3 test sites. There was a significant difference in CPT between the OA and control groups at all sites (A–C). There was also a significant difference in CPT between the low CPT and high CPT groups at all sites (A–C) and there was a significant difference between the high CPT and control group CPT measures at all sites (A–C). CPT indicates cold pain thresholds; ECRB, extensor carpi radialis brevis; OA, osteoarthritis; PFC, pain-free control.

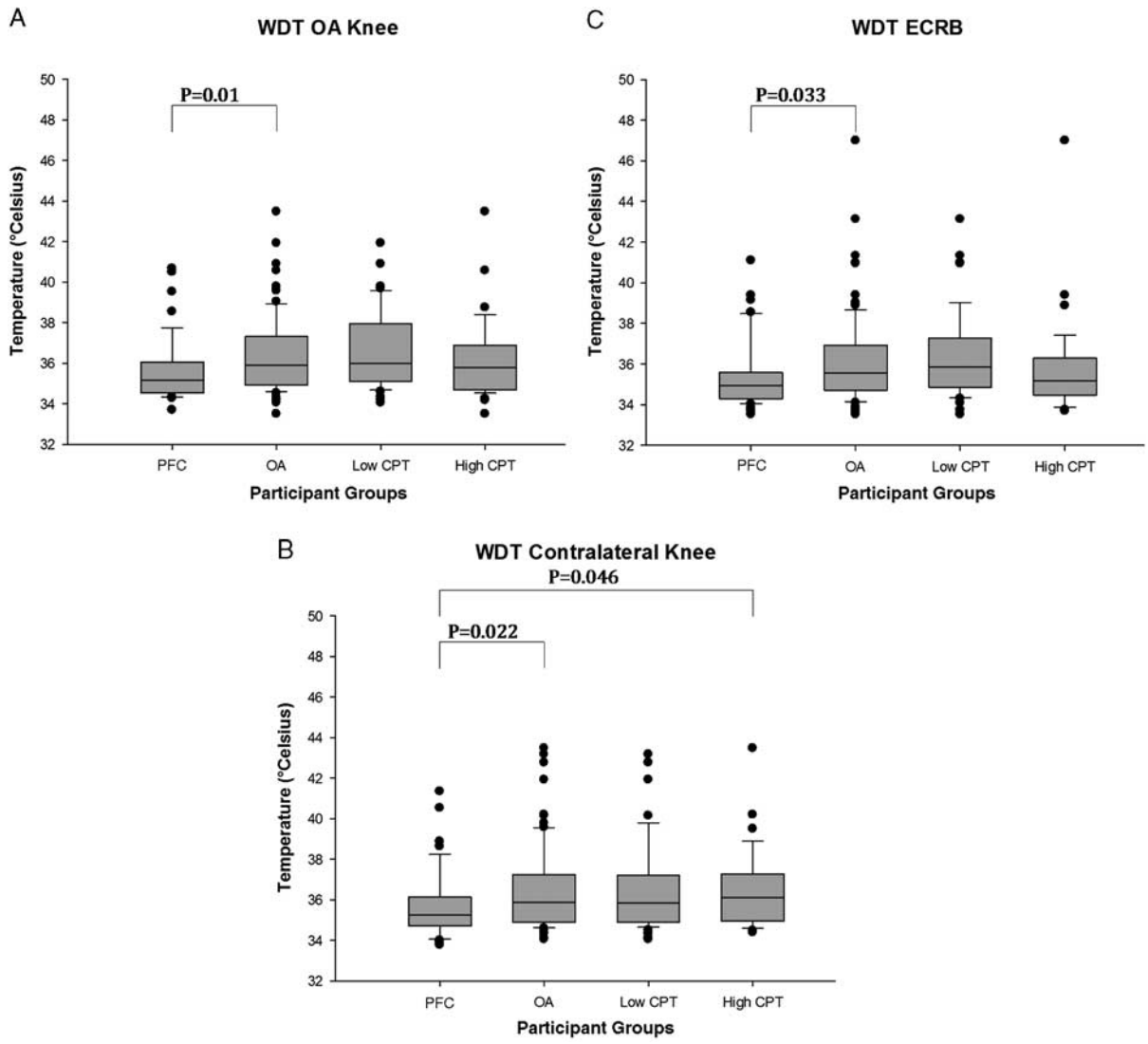

FIGURE 5. WDT at each of the 3 test sites. There was a significant difference in WDT between the high CPT group and the control group at the contralateral knee (B). There was also a significant difference in WDT between the OA and control groups at all sites (A–C). CPT indicates cold pain thresholds; ECRB, extensor carpi radialis brevis; OA, osteoarthritis; WDT, warm detection thresholds; PFC, pain-free control.

subscale score ($F_{2,117} = 0.140$; $P = 0.87$) between the 3 groups.

WOMAC (High CPT vs. Low CPT)

OA participants with elevated CPT also reported significantly greater pain and more impaired function than the remaining cohort: WOMAC pain ($P = 0.014$); WOMAC function ($P = 0.032$); however there was no difference in WOMAC stiffness score ($P = 0.46$) (Fig. 7).

PainDETECT and PQAS (High CPT vs. Low CPT)

The high CPT OA subgroup exhibited more features of neuropathic pain, reporting significantly higher PainDETECT scores ($P < 0.0001$) (Fig. 7) and higher scores for PQAS surface ($P = 0.017$) and paradoxical ($P = 0.045$) pain subscores but no difference in the PQAS deep pain subscore ($P = 0.297$) compared with the low CPT OA group (Fig. 7).

Correlations Between Global CPT and Other Key Variables

The global mean CPT measure showed significant correlations with PPT ($r = -0.533$, $P = 0.0001$), CPT ($r = 0.893$, $P = 0.0001$), and HPT ($r = -0.398$, $P = 0.0002$) at the index knee as well as well as PainDETECT score 0.566, $P = 0.0001$), WOMAC Pain ($r = 0.323$, $P = 0.003$), and function ($r = 0.240$, $P = 0.032$) scores and SF-35 physical health subscore ($r = -0.273$, $P = 0.014$). Global mean CPT was not correlated with WOMAC stiffness ($r = 0.117$, $P = 0.30$), and SF-36 mental health subscore ($r = -0.086$, $P = 0.449$).

DISCUSSION

Findings

Compared with PFCs, a cohort of 80 individuals with knee OA exhibited signs of widespread cold hyperalgesia, pressure hyperalgesia at the index knee, and no evidence of heat hyperalgesia. When individuals with OA were divided

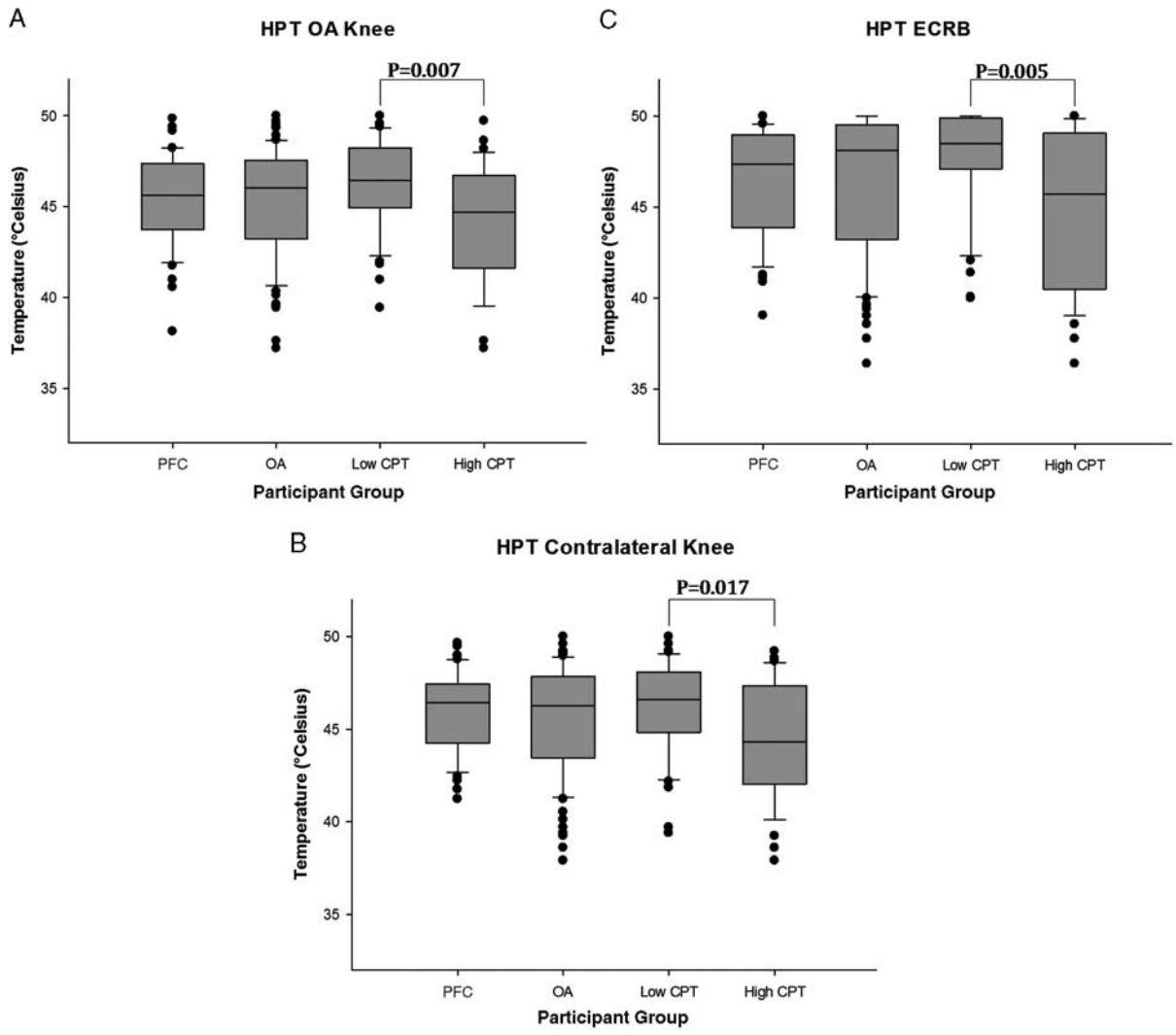

FIGURE 6. HPT at each of the 3 test sites. There was a significant difference in HPT between the low CPT and high CPT groups at all sites (A–C). CPT indicates cold pain thresholds; ECRB, extensor carpi radialis brevis; HPT, heat pain thresholds; OA, osteoarthritis; PFC, pain-free control.

into high and low CPT groups according to normalized *Z*-scores, there was clear differentiation, with the high CPT (cold hyperalgesic) subgroup showing widespread hyperalgesia to pressure and to thermal modalities compared with the remaining OA cohort. Importantly, the cold hyperalgesic group also reported higher pain levels, more reduced function, and increased features of neuropathic-type pain, as compared with the low CPT group whose pain appeared to be more limited and nociceptive in quality. Interestingly, there was no difference in the scores for the mental health subscale of the SF-36 between any of the groups, suggesting that while the high CPT group experienced more pain and functional limitation they did not appear to experience significantly elevated psychological distress. A single measure of global CPT clearly differentiated 2 OA subgroups: one with modest pain and modest self-reported functional impairment and another with more widespread multimodality hyperalgesia, much greater levels of pain and dysfunction and more evidence of neuropathic-type pain. Further research is clearly warranted to determine if the presence of an elevated CPT is a useful prognostic indicator in patients with knee OA, as has been found with WAD and tennis elbow.[20,22]

Our study confirmed previous research by demonstrating the presence of pressure hyperalgesia around the index knee in patients with OA. Although the cold hyperalgesic subgroup showed some evidence of pressure hyperalgesia in the contralateral knee, evidence of widespread pressure hyperalgesia across the whole OA cohort was not seen, with no indication of any difference at the upper limb ECRB site. This contrasts with our previous findings[9] and the findings of Wylde et al[7] and Harden et al[5] who demonstrated the presence of pressure hyperalgesia at upper limb test sites. Further research is required to determine the extent to which widespread pressure hyperalgesia might vary in the total OA cohort.

There were, however, clear differences in CPT at all sites, indicating widespread cold hyperalgesia in the OA cohort. Our finding that a substantial proportion of OA participants (between 37.5% and 47.5%) exhibited cold

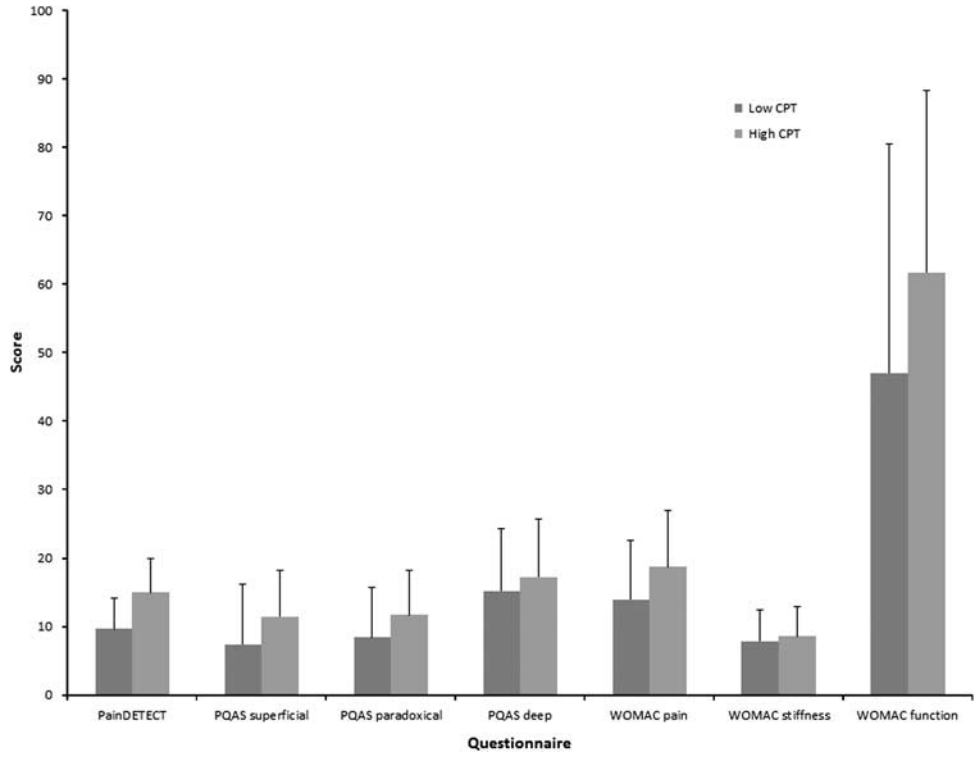

FIGURE 7. Comparison between low and high CPT groups for scores obtained for the WOMAC, PainDETECT, and PQAS (mean ± SD) questionnaires. CPT indicates cold pain thresholds; PQAS, pain quality assessment scale; WOMAC, Western Ontario and McMaster Universities questionnaires.

hyperalgesia based on *Z*-scores has not previously been reported. Given the importance of elevated CPT as an indicator of pain severity and chronicity in other conditions[19,20,22] this is a very important finding that has potential clinical implications for prognosis and warrants further investigation in OA.

There were no significant differences in HPT between the knee OA and PFC groups, reflecting previous studies in OA[5,7] and tennis elbow.[11,37] However, the study found significantly increased HPT in the cold hyperalgesic subgroup compared with both the remaining OA cohort and the PFC group, suggesting there is a substantial subgroup of people with knee OA who experience widespread heat hyperalgesia. This is also reflected in the 10% and 15% of participants who had HPTs >1 *Z*-score less than the PFC group mean. Our study is the first to identify a subgroup of individuals with OA with widespread, multimodality hyperalgesia to heat, cold, and pressure. This may be an important marker of central sensitization in this cohort.

Consistent differences in cold and WDT existed between the OA and PFC groups at each test site. Participants with knee OA exhibited elevated WDTs and reduced CDTs, reflecting impaired detection of both heat and cold. These findings were present at all test sites, perhaps suggestive of widespread sensory impairment. The impaired warmth detection seemed to be a feature of the entire OA cohort as there were no differences between the high and low CPT groups. In contrast, the difference in CDT seems to be predominantly driven by the low CPT (noncold hyperalgesic) group who demonstrated impaired cold detection compared with the cold hyperalgesic group. It might be thought that the cold hyperalgesic OA group was simply hypersensitive to all cold sensation; however their mean CDT were not significantly different to the control group. This therefore suggests that the OA participants with the greatest sensory impairment were not those exhibiting the greatest sensitization. It should be acknowledged that multiple comparisons increase the risk of type 1 error for some of these measures. The presence of sensory impairments in patients with OA has been identified and requires further investigation.

Implications for Research and Clinical Practice

The OA subgroup with cold hyperalgesia demonstrated widespread pressure hyperalgesia, similar to previous studies[5,7,9] but also widespread thermal hyperalgesia. This widespread multimodality hyperalgesia (pressure, heat, cold) may be indicative of increased central sensitization.[21,38] The cold hyperalgesic subgroup also had elevated pain and dysfunction scores on the WOMAC questionnaire although no difference in stiffness scores. This would suggest that they were experiencing greater pain severity and more functional limitation than the remaining OA cohort. This subgroup also had significantly elevated scores on PainDETECT and on the surface and paradoxical components of PQAS, although not on the deep component, suggesting that they also exhibited more features of neuropathic pain than the remaining OA cohort. It must be noted that mean PainDETECT score for the cold hyperalgesic subgroup was 14.97, which is in the unclear category (13 to 18) rather than the positive neuropathic category (19 +), meaning that this group would not meet established criteria for a neuropathic pain classification.[39] A number of previous studies have identified a subcohort of

people with knee OA who have elevated scores on the PainDETECT questionnaire, placing them in the positive neuropathic category.[6,40–42] It remains an open question as to whether people with knee OA can be classified as having probable or definite neuropathic pain.[39] It has been suggested that elevated PainDETECT scores may be more reflective of centrally augmented pain rather than the presence of identifiable neuropathic pain.[42]

Overall therefore, there were differences between the OA CPT subgroups in multimodality hyperalgesia, pain report, neuropathic pain features, and perceived physical function, suggesting that the presence of cold hyperalgesia identifies a group with a more severe pain presentation. The suggestion that these people may be experiencing some degree of neuropathic pain has to be tempered by the fact that they exhibit only minor evidence of sensory deficit in WDT. The additional pain sensitivity they exhibit may be reflective of more extensive sensitization within the nervous system and significant central augmentation of pain. It is apparent from this study that many of the differences in pain sensitivity between OA and PFC cohorts are driven by a subgroup of $< 50\%$ of participants, with the remaining OA participants exhibiting pain thresholds very similar to normal, pain-free individuals. Future studies would therefore benefit from including CPT measures and determining the percentage of participants with multimodality hyperalgesia in any OA cohort. A recent study[43] demonstrated that patients with ongoing pain 1 year after total knee arthroplasty exhibit many similar features to the cold hyperalgesic cohort in this study including the presence of cold hyperalgesia, suggesting that this might be a potential indicator of poor outcomes following surgery. Evaluation of CPT and identification of this subgroup in future intervention studies could provide valuable prognostic information that could help to determine if they have an increased likelihood of poor treatment outcomes following pharmacological, physical, or surgical treatments. Elevated CPT has been identified as an important prognostic indicator for WAD and tennis elbow and this measure may be of similar value in OA.

CONCLUSIONS

This study identified a substantial subgroup of patients with knee OA who exhibited marked cold hyperalgesia. These individuals demonstrated widespread, multimodality hyperalgesia for cold, heat, and pressure stimuli suggesting significant sensitization of their nociceptive systems. They reported more pain, more features of neuropathic pain and greater functional impairment than the remaining OA group.

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