Research Report

Expanded Distribution of Pain as a Sign of Central Sensitization in Individuals With Symptomatic Knee Osteoarthritis

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Background. Expanded distribution of pain is considered a sign of central sensitization (CS). The relationship between recording of symptoms and CS in people with knee osteoarthritis (OA) has been poorly investigated.

Objective. The aim of this study was to examine whether the area of pain assessed using pain drawings relates to CS and clinical symptoms in people with knee OA.

Design. This was a cross-sectional study.

Methods. Fifty-three people with knee OA scheduled to undergo primary total knee arthroplasty were studied. All participants completed pain drawings using a novel digital device, completed self-administration questionnaires, and were assessed by quantitative sensory testing. Pain frequency maps were generated separately for women and men. Spearman correlation coefficients were computed to reveal possible correlations between the area of pain and quantitative sensory testing and clinical symptoms.

Results. Pain frequency maps revealed enlarged areas of pain, especially in women. Enlarged areas of pain were associated with higher knee pain severity (r_s=.325, P<.05) and stiffness (r_s=.341, P<.05), lower pressure pain thresholds at the knee (r_s=−.306, P<.05) and epicondyle (r_s=−.308, P<.05), and higher scores with the Central Sensitization Inventory (r_s=.456, P<.01). No significant associations were observed between the area of pain and the remaining clinical symptoms and measures of CS.

Limitations. Firm conclusions about the predictive role of pain drawings cannot be drawn. Further evaluation of the reliability and validity of pain area extracted from pain drawings in people with knee OA is needed.

Conclusion. Expanded distribution of pain was correlated with some measures of CS in individuals with knee OA. Pain drawings may constitute an easy way for the early identification of CS in people with knee OA, but further research is needed.

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There is compelling evidence that central sensitization (CS) is present in a subgroup of people with knee osteoarthritis (OA) pain, especially in those with more advanced knee OA, and may be associated with knee OA symptom severity.[1,2] According to Woolf, CS is "operationally defined as an amplification of neural signaling within the central nervous system that elicits pain hypersensitivity."[3(p S4)] Central sensitization is a broad concept encompassing numerous and complex pathophysiological mechanisms, such as spinal cord sensitization, impaired functioning of brain-orchestrated descending antinociceptive (inhibitory) mechanisms, overactivation of descending pain facilitatory pathways, increased temporal summation (TS), or wind-up and alteration of sensory processing in the brain.[3]

If present in people with knee OA pain, CS may mediate treatment responses. For instance, the presence of preoperative CS (eg, widespread pain sensitization, enhanced TS of pain) was associated with poor outcomes after total knee replacement.[4,5] Therefore, it may be important for clinicians to identify CS in people with knee OA pain. In such patients, a broader therapeutic approach aiming to desensitize the central nervous system seems warranted.[6]

Several methods for assessing CS in people with knee OA pain are available. However, they are typically performed within laboratory conditions, including brain imaging techniques,[7,8] psychophysical testing with various stimuli (eg, quantitative sensory testing [QST][9,10]), and cerebral metabolism studies.[11] Currently, there is a lack of established criteria for the clinical diagnosis of CS in knee OA.[12] Laboratory-based measures such as the nociceptive flexor reflex[13] or laser-evoked potentials provide more objective evidence for hyperexcitability of central nervous system neurons, but no single measure can be regarded as the "gold standard" for establishing CS in knee OA. The lack of a gold standard may be due to the complexity and diversity of the underlying mechanisms.

Recently, a set of criteria to assist clinicians on the classification of CS pain has been published,[14] but the suitability of this classification algorithm to the OA knee pain population is unknown. One criterion included for the classification of CS pain is diffuse pain distribution (ie, large pain areas with a neuroanatomically illogical distribution) as identified from the clinical history and/or a body chart.[14] Expanded distribution of pain is a well-recognized sign of CS,[12,15,16] and, in this regard, pain drawings might be useful to identify extended areas of pain distribution in people with knee OA.

Pain drawings have been used to obtain a graphic representation of pain location and distribution in people with knee OA pain.[17–23] In pain drawings, the patient or clinician indicates the location of pain by shading the painful area.[24] Several methods and instruments have been described to record the pain location and classify the pattern of knee OA pain, and the most common method is asking people to draw where they feel pain on a body chart.[17,19,20] Based on studies investigating pain drawings in individuals with knee OA pain, the medial knee region appears to be the most frequently reported pain location among people with knee OA pain,[19,20,25,26] although generalized or diffuse knee pain also is commonly reported.[17,19] However, the location of pain is heterogeneous, with no single pattern of pain location being pathognomonic for knee OA,[19] which might be due to the multiple sources of pain (eg, stretched ligaments, subchondral bone damage, bone marrow lesions) in knee OA.[20]

Recently, the presence of widespread pain as recorded on pain drawings was most frequently reported by a subgroup of individuals with high levels of knee OA pain (particularly bilateral pain) and low levels of structural damage on radiography (eg, grades I and II on the Kellgren-Lawrence grading system for OA).[27] Enlarged areas of pain in this subgroup were attributed to a variety of etiological factors, including abnormal central pain processing mechanisms. Wood and colleagues[19] found that people with knee OA reporting enlarged areas of pain had more persistent and severe pain and higher anxiety levels, which also was interpreted as reflecting altered central

pain processing mechanisms. However, it must be emphasized that, in the abovementioned studies, CS was only hypothesized as the explanation of the study findings, and no attempts were made to directly measure CS.

To our knowledge, only the abovementioned studies[19,27] related central pain mechanisms to individuals' recording of symptom location and distribution in people with knee OA pain. If CS was the dominant pain mechanism in an individual with knee OA pain, this finding should be reflected in more extended areas of pain mapped in pain drawings compared with people with a lesser degree of pain sensitization.[22]

Therefore, the primary aim of this study was to examine whether the area of pain assessed using pain drawings relates to direct (QST) and indirect (self-report questionnaires, neuropathic pain) measures of CS in people with different degrees of chronic knee OA pain. As opposed to quantitative pain assessment tools, which provide direct evidence of CS in chronic joint pain,[9,10,12] indirect measures of CS (eg, self-report questionnaires designed to determine presence of neuropathic pain) offer only indirect evidence of hypersensitivity of the central nervous system in people with knee OA pain.[1,14,28] As a secondary aim, the association between the area of pain and clinical symptoms (including the level of knee pain, disability, and psychosocial variables) also was investigated. Psychosocial factors (eg, cognitions and beliefs about pain) may explain some of the variation in pain reporting among individuals with knee OA.[29] For instance, catastrophic thinking and poor coping strategies in people with knee OA pain can predict the presence of more pain after total knee replacement surgery.[4]

Method

Participants

A convenience sample of 53 people with chronic knee OA pain of more than 3 months' duration who were scheduled to undergo primary total knee arthroplasty participated in the study. People with knee OA affecting the tibiofemoral and patellofemoral compartments were included. These individuals participated in a randomized controlled trial investigating the effects of pain neuroscience education on pain and function in people with chronic knee OA pain (ClinicalTrials.gov identifier NCT02246088). Baseline data from the entire cohort were used for this study. All participants were recruited from the Orthopedic Surgery Service of the Hospital Universitario de La Ribera (Alzira, Spain) between January 2014 and February 2015.

All participants underwent weight-bearing, fixed flexion posteroanterior and lateral radiographs of their affected knee. Radiographic disease severity of both the tibiofemoral (Kellgren-Lawrence 0–4 grading scale[30]) and patellofemoral (Ahlbäck 0–5 grading scale[31]) compartments was evaluated for each participant. Knee OA was diagnosed by a surgeon according to the American College of Rheumatology classification,[32] including the regular experience of knee pain, plus either osteophytes on radiography or a combination of morning stiffness, crepitus, and age 50 years or above. These criteria were found to be 89% sensitive and 88% specific for diagnosing knee OA.[32]

Individuals were excluded from study participation if they had previously undergone knee joint replacement surgery of the affected joint or any other lower limb surgery within the previous 6 months; had coexisting inflammatory, metabolic, neurological, or severe medical conditions hindering the ability to participate in the study; or had cognitive disturbances that could influence completion of the pain drawings. Before study participation, all individuals carefully read an information leaflet and signed informed consent forms.

Procedure

Demographic information, including age, sex, body mass index, and pain duration, were collected by self-report. Participants additionally completed an 11-point numeric rating scale to quantify their current pain intensity and were asked to complete a pain drawing to illustrate their area of pain.

Participants then completed the following self-administration questionnaires in a standardized order: the Western Ontario and McMaster Universities Arthritis Index (WOMAC), Pain Catastrophizing Scale (PCS), Central Sensitization Inventory (CSI), PainDETECT questionnaire (PD-Q), 11-item version of the Tampa Scale for Kinesiophobia (TSK-11), Pain Vigilance and Awareness Questionnaire (PVAQ), and Chronic Pain Acceptance Questionnaire (CPAQ).

Afterward, a standardized physical examination including physical performance tests was performed on each participant. Finally, all participants were assessed with QST to examine pressure pain thresholds (PPTs), TS, and conditioned pain modulation (CPM). All QST was carried out by the same researcher in one individual session in the laboratories of the Hospital Universitario de La Ribera. The participants were requested not to take analgesic medication 24 hours before the experiment. At the time of examination, the assessor was blinded to the questionnaire data, including analysis of the scores obtained with pain drawings. Statistical analysis of the pain drawing data was performed by a researcher who was blinded to the QST data.

Measurements of Area of Pain

A novel method for obtaining and quantifying the area of pain with a digital tablet was used.[33] Test-retest reliability of this method for acquisition of pain drawings was recently demonstrated in people with chronic neck and low back pain.[33] Pain drawings were completed on a digital tablet (iPad 2, Apple Inc, Cupertino, California) using a stylus pen for digital tablets (CS100B, Wacom Technology Corp, Vancouver, Washington) and commercially available sketching software (SketchBook Pro, Autodesk Inc, San Rafael, California). Depending on the participant's sex, a male or female body chart with different views of the knee region (frontal, dorsal) was chosen and opened in the sketching software (Fig. 1A). The type, size, and color of the pen stroke were standardized across all participants.

An operator, who trained with the device in clinical practice 1 month prior

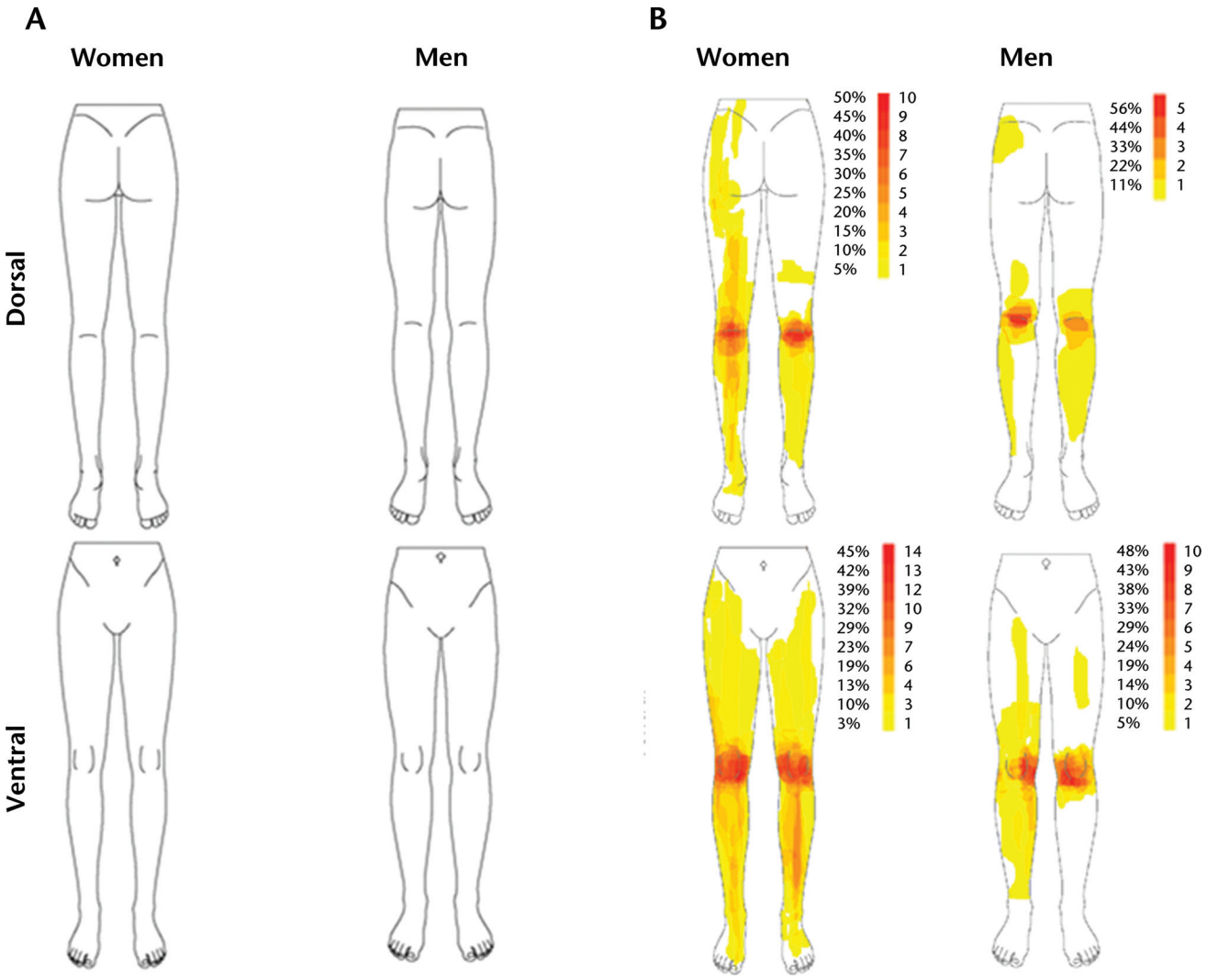

Figure 1.
(A) Example of the available templates. (B) Pain frequency maps generated separately for men and women by superimposing the pain drawings of all individuals with knee osteoarthritis pain. The color grid indicates both the number and the percentage of individuals who reported pain in that specific area. Dark red represents the most frequently reported area of pain.

to the start of the study, gave each participant a standardized verbal explanation of what the pain drawing is and how to complete it using the digital tablet. The pain drawing was presented to participants as a tool where they should illustrate precisely where they had felt pain during the previous week. The assessor highlighted the importance of fully illustrating all pain sites. After a demonstration and brief training to familiarize the participants with the device, they were asked to complete their pain drawings. Participants were instructed as follows: "Please shade the areas where you felt your usual pain during the last week on this body chart, and try to be as precise as possible." They were instructed to color every part of the body where they perceived pain in the previous week, independently from the type and the severity of pain. Before saving and storing the pain drawing, participants were asked whether the pain drawing corresponded to their real pain distribution. If not, they were given the possibility to correct the drawing using the "eraser" tool.

A custom-designed software program was used to compute the total area of pain for each participant and to generate 2 pain frequency maps (ie, frontal and dorsal body chart) separately for men and women.[33] The area of pain was expressed as the total number of pixels colored inside the frontal and dorsal body chart perimeter. Thus, the area of pain extracted from the dorsal view and frontal view were combined to generate a single value of area of pain. Pain frequency maps were obtained by superimposing the pain drawings from all participants to illustrate the most frequently reported location of pain across the entire sample. This was done for women and men separately. A color grid was

used to indicate the percentage of individuals who reported pain in that specific area.

Direct Measures of CS

PPT. A standardized protocol for evaluating PPT was used.[34] Two test sites in the peripatellar region (3 cm medial and lateral to the midpoint of the medial and lateral edges of the patella, respectively) and one control distant site on the ipsilateral extensor carpi radialis longus muscle (5 cm distal to lateral epicondyle of humerus) were selected for PPT measurement.[21] The PPT was measured using an analog Fisher algometer (Force Dial model FDK 40 Push-Pull Force Gage, Wagner Instruments, Greenwich, Connecticut) with a surface area at the round tip of 1 cm^2. The algometer probe tip was applied perpendicular to the skin at a rate of 1 kg/cm^2/s until the first onset of pain. Pain pressure threshold was measured 3 times on each site, with a 30-second interstimulus interval between measurements. The mean of the 3 measurements was used in the statistical analysis.

Temporal summation of pain and CPM. For measuring excitability of nociceptive pathways and efficacy of endogenous pain inhibition, the TS and CPM paradigms were used. Temporal summation and CPM are established ways of measuring excitability of nociceptive pathways and pain inhibition, respectively.[35,36]

First, PPTs were measured at the peripatellar region and the ipsilateral extensor carpi radialis longus muscle as described above. Second, TS was provoked by means of 10 consecutive pulses at a previously determined PPT at each location. Temporal summation started 2 minutes after PPT measurement. For each pulse, pressure was gradually increased at a rate of 2 kg/s to the determined PPT and maintained for 1 second before being released (1-second interstimulus interval). Pain intensity of the 1st, 5th, and 10th pulses was rated on a numerical rating scale (0="no pain" to 10="worst possible pain"). Afterward, a rest period of 5 minutes was given.

Third, CPM was induced by combining the TS procedure (namely, the test stimulus) and an inflated occlusion cuff around the participant's arm, contralateral to the side of the affected knee, to a painful intensity (conditioning stimulus). The occlusion cuff was inflated at a rate of 20 mm Hg/s until "the first sensation of pain" and maintained for 30 seconds. Afterward, pain intensity, as a result of cuff inflation, was rated on a numerical rating scale. Next, cuff inflation was increased or decreased until the pain intensity was rated as 3/10. The length of time to reach 3/10 pain was recorded. Temporal summation assessment was then repeated during maintenance of the cuff inflation.[37] The details and data supporting the test-retest reliability and validity of the protocol for examining TS and CPM are described elsewhere.[37]

Indirect Measures of CS

CSI. The CSI is a self-report screening instrument to help identify people with central sensitivity syndromes for which CS may be a common etiology.[38] Part A of the CSI assesses symptoms common to CS and comprises 25 items, each rated on a 5-point scale with the end points 0 ("never") and 4 ("always") (range=0–100). The CSI has high reliability and validity,[38] and a cutoff score of 40 out of 100 was able to distinguish between individuals diagnosed with central sensitivity syndromes and a nonpatient comparison sample (sensitivity=81%, specificity=75%).[39] The Spanish version of the CSI was used in this study.

Neuropathic pain. The Spanish version of the PD-Q was used to facilitate the identification of neuropathic pain related to knee OA.[40] Although developed as a screening questionnaire for neuropathic pain, the PD-Q also may function as a measure of characteristics that indicate augmented central pain processing in people with knee OA pain.[41]

The PD-Q is a self-administered questionnaire comprising 9 items (7 evaluating pain quality, 1 evaluating pain pattern, and 1 evaluating pain radiation), all of which contribute to an aggregate score (range=−1 to 38). Sensitivity, specificity, and positive predictive values for neuropathic pain symptoms in people with back pain using the cutoff score of 19 were 85%, 80%, and 83%, respectively.[42] The relationship between PD-Q scores and signs of CS in people with hip OA has been demonstrated previously.[8]

Clinical Symptoms

Self-reported knee pain. Participants were asked to indicate the intensity of their pain in the last week on a numeric rating pain scale ranging from 0 ("no pain") to 10 ("worst pain imaginable"). The patient-report numeric rating scale has demonstrated good construct validity and moderate-to-large responsiveness (standardized response mean and effect size ranging from 0.6 [hip OA] to 0.9 [knee OA]) for evaluating functional disability in people with hip and knee OA.[43]

Physical performance tests. Range of motion for both active knee flexion and extension was measured for each participant, and each participant performed the Timed "Up & Go" Test. These objective measures were selected on the basis of their ability to reflect functional mobility impairments.

High intratester and intertester reliability and criterion validity of goniometry to measure range of motion has been documented for knee flexion and extension in people with knee restrictions of different etiologies.[44] The Timed "Up & Go" Test is a reliable test with adequate minimum detectable change for clinical use in individuals with doubtful-to-moderate (grade 1–3) knee OA.[45,46] Intrarater and interrater reliability of the Timed "Up & Go" Test were .97 (95% confidence interval [CI]=.95, .98) and .96 (95% CI=.94, .97), respectively. Its minimum detectable change, based on measurements performed by a single rater and between raters, was 1.10 and 1.14 seconds, respectively.[46]

WOMAC. The Spanish version of the self-administered WOMAC for individuals with knee and hip OA was used.[47] The WOMAC comprises 5 items for pain (score range=0–20), 2 items for stiffness (score range=0–8), and 17 items for functional limitation (score range=0–68). Total WOMAC score and scores from the pain, stiffness, and functional limitation subscales were considered.

Higher scores on the WOMAC indicate worse pain, stiffness, and functional limitation. The test-retest reliability (intraclass correlation coefficients range=.66–.81), internal consistency (Cronbach alpha range=.81–.93), convergent validity (Pearson coefficient range=−.52 to −.63), and responsiveness (standardized response mean range=0.8–1.5) of the Spanish version of the WOMAC have been demonstrated in people with hip and knee OA.[47]

PCS. The PCS is a valid and reliable instrument to measure pain catastrophizing in older adults with knee OA.[48,49] It comprises 13 items, each rated on a 5-point scale with the end points 0 ("not at all") and 4 ("all the time") (range=0–52). Higher scores indicate a higher degree of pain catastrophizing. The Spanish version of the PCS showed appropriate internal consistency (Cronbach alpha=.79), test-retest reliability (intraclass correlation coefficient=.84) and sensitivity to change (effect size ≤2) in patients with fibromyalgia.[50]

TSK-11. The Spanish version of the TSK-11 was used.[51] The TSK-11 is an 11-item questionnaire assessing fear of movement or fear of injury or reinjury during movement and eliminates psychometrically poor items from the original 17-item version of the TSK,[52] thus creating a shorter questionnaire with comparable internal consistency. It comprises 11 items, each rated on a 4-point scale with the end points 1 ("totally agree") and 4 ("totally disagree") (range=11–44). The TSK-11 has a 2-factor structure (ie, activity avoidance and harm) and has demonstrated acceptable internal consistency and validity (convergent and predictive) in both people with acute musculoskeletal pain (Cronbach alpha=.79) and those with chronic musculoskeletal pain (Cronbach alpha=.79).[51] Higher scores indicate more fear-avoidance behavior.

PVAQ. The Spanish version of the PVAQ was used to evaluate participants' preoccupation with or attention to pain associated with pain-related fear and perceived pain severity.[53] The PVAQ comprises 9 items, each rated on a scale from 0 ("never") to 5 ("always") (range=0–45). Higher scores indicate a higher degree of pain vigilance and awareness. Psychometric properties of the PVAQ were previously reported in people with chronic back pain[53] and fibromyalgia,[54,55] showing good internal consistency,[54,55] reliability,[53,54] and validity.[53,54] A cutoff score of 24.5 out of 45 was able to identify women with fibromyalgia who had worse daily functioning (sensitivity=.71, specificity=.75).[54]

CPAQ. The CPAQ is the questionnaire most often used to measure pain acceptance in chronic pain populations.[56] The CPAQ comprises 20 items, each rated on a scale from 0 ("never true") to 6 ("always true") (range=0–120), and it has a 2-factor structure: activities engagement and pain willingness. The total score results from the sum of these 2 factors, with higher scores indicating a higher degree of chronic pain acceptance. The Spanish version of the CPAQ, which is reliable (intraclass correlation coefficient=.83) and has valid construct validity (Cronbach alpha=.83) for people with fibromyalgia, was used in this study.[56]

Data Analysis

Distribution of the data was tested with the Shapiro-Wilk test, and non-normally distributed data were identified. Descriptive statistics were used to describe the baseline characteristics of the individuals with knee OA pain. A Mann-Whitney *U* test was run to determine whether there were differences in baseline clinical variables between male and female participants. Pain frequency maps were generated by superimposing the scores obtained with pain drawings, considering men and women separately. Temporal summation was calculated as the difference percentage between the 1st and 10th pain rating scores before occlusion using the formula: ([TS 10th−TS 1st]/TS 1st) × 100.[57] The outcome measure for CPM was calculated as the difference between the 10th pain rating score before occlusion and the 10th pain rating score during occlusion.[37] Spearman correlation coefficients were computed to reveal possible correlations: (1) between the area of pain and direct measures of CS (ie, PPT knee, PPT epicondyle, knee TS, epicondyle TS, knee CPM, and epicondyle CPM), (2) between the area of pain and indirect measures of CS (ie, CSI and PD-Q), and (3) between the area of pain and clinical symptoms (ie, visual analog scale, WOMAC, WOMAC pain subscale, WOMAC stiffness subscale, WOMAC functional limitation scale, PCS, TSK, PVAQ, and CPAQ). Statistical analyses were performed using IBM SPSS version 22 (IBM Corp, Armonk, New York). The significance level was set at $P<.05$.

Results

Fifty-three individuals with knee OA (34 woman and 19 men) were enrolled in the study. Participants' demographic data are reported in Table 1, and clinical characteristics and measurements of CS are detailed in Table 2. Mean and median scores for the area of pain, range of motion for active knee flexion, Timed "Up & Go" Test, WOMAC and WOMAC pain and functional limitation subscale, PCS, CPAQ, TSK, CSI, PD-Q, and PPT at the knee were significantly different between male and female participants ($P<.05$). Seven out of the 53 participants (13.2%) had scores that correspond to likely neuropathic pain (≥19 on the PD-Q). The mean area of pain was 12,766 pixels (SD=13,494) across the entire sample, whereas it was 15,012 pixels (SD=14,327) and 8,747 pixels (SD=11,096) for women and men, respectively. Pain frequency maps for the individuals with knee OA are illustrated in Figure 1B, and correlations between the area of pain and measures of CS and clinical symptoms are reported in Table 3.

Area of Pain and Direct and Indirect Measures of CS

Significant correlations were identified between the area of pain and PPT at the knee ($r_s=-.306$, $P<.05$) and epicondyle ($r_s=-.308$, $P<.05$), signifying lower PPT at both sites in individuals with larger pain areas. Figure 2 illustrates the relationship between the area of pain and the PPT for both knee and epicondyle. No significant associations were observed between the area of pain and TS ($r_s=-.0183$ for knee, $r_s=-.087$ for epicondyle) or the area of pain and CPM ($r_s=-.066$ for knee, $r_s=-.040$ for epicondyle). A significant correlation was identified between the area of pain and

Table 1.
Participant Demographic Characteristics[a]

Baseline Demographic Characteristics of Patients With OA	All Participants (N=53) $\bar{X}$ (SD) Median (IQR)	Female Participants (n=34) $\bar{X}$ (SD) Median (IQR)	Male Participants (n=19) $\bar{X}$ (SD) Median (IQR)	*P*[b]
Age (y)	70.2 (7.4)	71.2 (7.8)	68.5 (6.3)	.130
	72 (11.5)	73 (11.2)	70 (7)	
BMI (kg/m^2)	29.9 (3.9)	30.4 (4.2)	28.9 (3.1)	.183
	30 (5.5)	30 (6.2)	28 (5)	
Area of pain (no. of pixels)	12,766 (13,494)	15,012 (14,327)	8,747 (11,096)	.017
	8,272 (12,190)	10,314 (12,382)	5,816 (7,083)	
Pain duration (y)	7.5 (6)	6.7 (5.7)	9.1 (6.3)	.127
	5 (10)	4 (10.3)	6 (11)	
Kellgren-Lawrence grade (tibiofemoral joint), n (%)				.115
0	0 (0)	0 (0)	0 (0)	
1	0 (0)	0 (0)	0 (0)	
2	15 (28.3)	7 (20.5)	8 (42.1)	
3	22 (41.5)	11 (32.3)	11 (57.8)	
4	16 (30.1)	8 (23.5)	8 (42.1)	
Ahlbäck grade (patellofemoral joint), n (%)				.231
1	3 (5.6)	2 (5.8)	1 (5.2)	
2	19 (35.8)	10 (29.4)	19 (47.3)	
3	30 (56.6)	15 (44.1)	15 (78.9)	
4	1 (1.8)	0 (0)	1 (5.2)	
5	0 (0)	0 (0)	0 (0)	

[a] OA=osteoarthritis, IQR=interquartile ratio, BMI=body mass index.
[b] *P* values refer to potential differences between male and female participants.

the CSI score (r_s=.456, P<.01); participants with higher scores on the CSI showed larger areas of pain.

Area of Pain and Clinical Symptoms

Higher scores on the pain subscale (r_s=.325, P<.05) and stiffness subscale (r_s=.341, P<.05) of the WOMAC were significantly associated with larger pain areas.

Discussion

Several methods for illustrating the area of pain in people with chronic knee OA pain have been used. We explored, for the first time, the utility of a novel digital device using 2-dimensional body charts for acquisition and analysis of the scores obtained with pain drawings[33] in a sample of individuals with chronic knee OA pain. Through a digital tablet using a user-friendly digital device, participants reported their pattern of pain on a body chart. Other systems, such as the photographic knee pain map, have shown good validity and reliability for people with regional knee pain to identify its location.[20]

Area of Pain and Direct and Indirect Measures of CS

The results of this study showed a significant positive correlation between the area of pain and some direct and indirect measures of CS. On the one hand, a more expanded distribution of pain was correlated with a lower PPT at a remote site from the knee (ie, epicondyle). Increased pain sensitivity distantly from the knee may reflect widespread hyperalgesia, thus providing evidence of CS in people with knee OA.[9,10,12] On the other hand, we found that a greater expansion of symptoms was associated with a higher degree of subjective CS pain descriptors as assessed with the CSI questionnaire. The CSI was recently shown to be a useful and valid instrument for screening people with central sensitivity syndromes.[58] In addition, individuals with knee OA pain who had preoperative high levels of comorbid centrally mediated symptoms measured by the CSI showed severe pain and increased analgesic requirements and were at higher risk of persistent pain after total knee arthroplasty in the early postoperative period.[59]

Previous studies have established associations between the scores obtained with pain drawings and central pain mechanisms, although in non-OA populations. For instance, a significant correlation between nonorganic pain drawings and higher scores with the Waddell's nonorganic physical signs was found in people with chronic low back pain.[60] Waddell's signs include physical signs or symptoms that are inconsistent with pathology and are suggestive of the presence of symptom magnification or pain behavior.[61] Nonorganic pain drawings were defined as those with poorly defined pain patterns and bizarre or nonanatomical pain areas.[60] In addition, nonorganic pain drawings were associated with maladaptive psychosocial factors (ie, high levels of catastrophizing, anxiety, and depression) in people with chronic neck/shoulder and lower back/lower limb pain[62] and those with chronic low back pain.[63] However, maladaptive psychosocial factors, including magnified symptom behavior as assessed with Waddell's scale, provide no direct evidence for CS. Psychosocial factors were not included as essential criteria for classification of CS pain, as they also are prevalent in nociceptive and neuropathic pain.[14]

Based on results of the PD-Q, 13.2% of our sample had scores that correspond to likely neuropathic pain (≥19). These results are comparable to those reported

Table 2.
Baseline Clinical Measurements[a]

Baseline Measurements of Patients With OA	All Participants (N=53) $\bar{X}$ (SD) Median (IQR)	Female Participants (n=34) $\bar{X}$ (SD) Median (IQR)	Male Participants (n=19) $\bar{X}$ (SD) Median (IQR)	*P*[b]
NPRS (0–10)	5.92 (17)	6.19 (17.2)	5.44 (15.8)	.217
	5.9 (22.5)	6.05 (27.3)	5.8 (20)	
ROM active knee flexion (°)	115.5 (11.4)	113.9 (9.8)	118.3 (13.5)	.047
	115.5 (10)	115 (8.7)	118.5 (9.2)	
ROM active knee extension (°)	−2.41 (6.3)	−3.2 (6.7)	−0.9 (5.4)	.30
	−2 (7.9)	−2.6 (7.96)	−1.6 (5.3)	
Timed "Up & Go" Test (s)	11.4 (5.7)	13.4 (6.2)	7.9 (1.6)	.000
	9.8 (5)	11.8 (5.5)	7.7 (2.6)	
WOMAC (0–96)	49.4 (16.5)	54.1 (16.1)	40.9 (13.9)	.006
	49 (25)	56 (24.5)	38 (20)	
WOMAC pain subscale (0–20)	9.53 (3.31)	10.6 (3.1)	7.6 (2.9)	.001
	10 (5)	10 (4)	7 (3)	
WOMAC stiffness subscale (0–8)	3.79 (2.11)	4.1 (2.3)	3.2 (1.7)	.119
	3 (3)	4 (3.8)	3 (2)	
WOMAC functional limitation scale (0–68)	36.09 (12.66)	39.4 (12.5)	30.1 (10.7)	.010
	36 (19)	42.5 (19.8)	29 (17)	
PCS (0–52)	23.77 (12.51)	27.2 (11.7)	17.7 (11.8)	.012
	25 (17)	26 (15.5)	20 (19)	
PVAQ (0–45)	28.66 (6.95)	28.6 (7.5)	28.8 (6)	.773
	28 (9)	28 (10.8)	29 (6.5)	
CPAQ (0–120)	52.83 (18.26)	48.5 (17.2)	60.6 (18)	.022
	52 (28)	47.5 (27.8)	64 (23)	
TSK-11 (11–44)	33.68 (5.98)	35.1 (5.6)	31.2 (5.9)	.029
	34 (9)	35 (7.8)	32 (8)	
CSI (0–100)	36.21 (15.62)	40.1 (16.6)	29.2 (10.8)	.014
	37 (23)	42 (22.5)	30 (19.5)	
PD-Q (−1 to 38)	12.25 (6.3)	13.6 (6.6)	9.8 (5.1)	.041
	11 (8)	12 (9)	10 (8.5)	
PPT knee (kg/cm^2)	4.82 (2.62)	4 (1.6)	6.2 (3.4)	.018
	4 (3.15)	3.8 (2.5)	6.1 (4.9)	
PPT epicondyle (kg/cm^2)	4.03 (1.72)	3.7 (1.5)	4.6 (2)	.55
	3.7 (2)	3.6 (1.3)	4.4 (2.4)	
Knee TS (%)	40.44 (23.11)	40.53 (24.16)	40.28 (21.76)	.853
	43.75 (23.08)	42.46 (21.32)	44.44 (25.71)	
Epicondyle TS (%)	43.39 (21.46)	3 (1.7)	43.19 (17.79)	.978
	50 (32.14)	3 (2)	50 (29.56)	
Knee CPM (kg/cm^2)	−0.44 (1.66)	−0.6 (1.6)	−0.1 (1.8)	.054
	0 (2)	1 (1.5)	0.50 (1.5)	
Epicondyle CPM (kg/cm^2)	−0.43 (1.76)	−0.7 (1.7)	0 (1.8)	.200
	0 (3)	1 (2)	0 (2)	

[a] OA=osteoarthritis, IQR=interquartile range, CPAQ=Chronic Pain Acceptance Questionnaire, CPM=conditioned pain modulation, CSI=Central Sensitization Inventory, NPRS=numeric pain rating scale, PCS=Pain Catastrophizing Scale, PD-Q=PainDETECT questionnaire, PPT=pressure pain threshold, PVAQ=Pain Vigilance and Awareness Questionnaire, ROM=range of motion, TS=temporal summation, TSK=Tampa Scale of Kinesiophobia, WOMAC=Western Ontario and McMaster Universities Arthritis Index.
[b] *P* values refer to potential differences between male and female participants.

Table 3.
Spearman Correlation Coefficients Between Area of Pain (Total Pain Area Extracted From Dorsal and Ventral Body Views) Computed Using Pain Drawings and Measures of Central Sensitization and Clinical Symptoms for Entire Cohort of Individuals With Knee Osteoarthritis Pain (N=53)[a]

Measure/Clinical Symptoms	Correlation With Pain Area (r_s)
Direct measures of CS	
PPT knee (kg/cm^2)	−.306*
PPT epicondyle (kg/cm^2)	−.308*
Knee TS (%)	−.018
Epicondyle TS (%)	−.087
Knee CPM (kg/cm^2)	−.066
Epicondyle CPM (kg/cm^2)	−.040
Indirect measures of CS	
CSI	.456**
PD-Q	.266
Clinical symptoms	
NPRS (0-10)	.221
WOMAC	.259
WOMAC pain subscale	.325*
WOMAC stiffness subscale	.341*
WOMAC functional limitation scale	.183
PCS	.145
PVAQ	.100
CPAQ	−.195
TSK	−.195

[a] CPAQ=Chronic Pain Acceptance Questionnaire, CPM=conditioned pain modulation, CSI=Central Sensitization Inventory, NPRS=numeric pain rating scale, PCS=Pain Catastrophizing Scale, PD-Q=PainDETECT questionnaire, PPT=pressure pain threshold, PVAQ=Pain Vigilance and Awareness Questionnaire, TS=temporal summation, TSK-11=11-item Tampa Scale of Kinesiophobia, WOMAC=Western Ontario and McMaster Universities Arthritis Index.
* Correlation is significant at the .05 level (2-tailed). ** Correlation is significant at the .001 level (2-tailed).

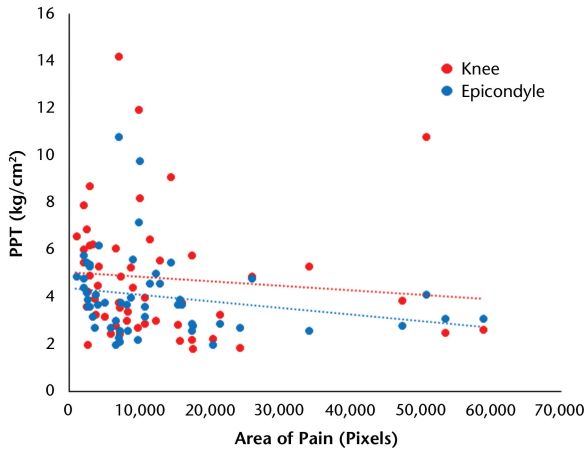

Figure 2.
Scatter plots illustrating the relationship between the area of pain and the pressure pain threshold (PPT) for both knee and epicondyle.

by Valdes and colleagues,[64] where 14.8% of people with knee OA pain had likely neuropathic pain, and superior to the percentage obtained by Ohtori et al[65] (ie, 5.4%). Some studies have inferred CS based on neuropathic-like descriptors of symptoms.[66,67] Contrary to what may have been expected, we did not find an association between the presence of a more expanded distribution of pain and self-reported neuropathic pain scores. This lack of association may have been due either to the small number of participants with likely neuropathic pain or to the fact that we used the PD-Q and not the modified version of this questionnaire recently recommended for the OA pain population.[66] Like the original PD-Q, the modified PD-Q comprises 9 items but with some modifications adapted to people with OA, such as framing of questions to ask about symptoms "in or around" the worst knee, over a specific time frame. Also, the presence of more extended areas of pain in people with knee OA may reflect nonneuropathic CS rather than neuropathic pain, making the lack of association between the scores obtained from the pain drawings and the PD-Q plausible.

No significant associations were observed between the area of pain and TS or the area of pain and CPM. Pain associated with knee OA is recognized as a complex phenomenon encompassing several mechanisms such as CS.[68,69] The quantification of CS, in turn, is multidimensional, including several objective QST techniques such as pain and tolerance thresholds, spatial summation, TS, or CPM.[9,10,12] These QST techniques assess the same underlying biological concept (CS), but in its different manifestations related to the different aspects of sensitization. This factor could justify why the areas of pain as assessed with pain drawings were correlated with some pain biomarkers (eg, PPT) but not with other pain biomarkers of CS (eg, TS, CPM).

Area of Pain and Clinical Symptoms

A significant positive correlation between knee pain severity and stiffness and the area of pain reported by participants was observed. Although the area of pain, pain intensity, and stiffness are variables assessing different constructs, it could be expected that people with knee OA with more diffuse or more extended areas of pain would report higher pain intensity and stiffness scores. As shown in the pain frequency maps, the most common pattern of pain reported by our sample was anterior knee pain, in particular medial knee and peripatellar pain, which is in accordance with previous research.[19,20,25,26] Interestingly, besides local knee symptoms, many participants also perceived enlarged and distant pain areas, as shown in Figure 1B. This expansion of pain to larger areas may reflect the presence of CS in these individuals.[12]

Although using an experimental pain design, Bajaj and colleagues[70] also showed significantly larger referred pain areas after intramuscular hypertonic saline infusion in individuals with knee OA compared with controls. Referred pain is a phenomenon attributed to CS.[12,15] In addition, enlarged areas of pain were observed in individuals with knee OA pain, particularly in those with more persistent and severe symptoms.[19]

In our study, enlarged areas of pain were especially noticeable in women. This finding is consistent with previous research where the most sensitized groups of participants with knee OA pain contained more women than men.[71,72] In addition, a recent study[73] looking at the moderator effect of sex in centrally mediated changes in people with knee OA pain showed a greater number of pain sites reported by women relative to men (P=.001).

Psychosocial variables were unrelated to the area of pain in our study. This lack of correlation is in accordance with previous research done in non-OA pain populations, where no correlation between the area of pain and the individual psychological state was demonstrated.[74] Indeed, a systematic review on pain drawings did not support the assumption that unusual or extensive pain drawings indicate disturbed psychological state.[24]

In this study, there are some methodological issues that should be considered. We did not collect information on the reliability or stability of pain location over time in our sample. Reliability was assumed based on a previous study using this method for pain drawings analysis in other chronic pain populations (eg chronic low back and neck pain).[33] Expanded distribution of pain (eg, referred pain) may be more commonly observed in those populations compared with individuals with knee OA pain, although no comparative data exist in that regard. Thus, our assumption may have influenced the results of this study. Future research, therefore, is warranted to evaluate the clinimetric properties of pain drawings in people with knee OA pain.

In addition, as positive and negative predictive values of pain drawings were not calculated and the study design was cross-sectional, firm conclusions about the predictive role of pain drawings on knee OA pain cannot be drawn. Future studies, for instance, could explore the possible association between the scores obtained with pain drawings and outcome measures after treatment (ie, surgery) in order to determine the real clinical utility of pain drawings for people with knee OA pain. In this regard, Skou and colleagues[22] found that individuals with pain after total knee arthroplasty demonstrated significantly more pain sites using a region-divided body chart compared with those without pain.

Screening for the presence of concurrent comorbidities (eg, hip joint or lumbar spine pathology, fibromyalgia) was not performed in this study. However, these comorbid conditions could have influenced the patterns of pain described by participants. For instance, referred pain from the lumbar spine may have contributed to the posterior areas of symptoms, especially noted in female participants.

Despite the associations between direct and indirect measures of CS and the area of pain, it must be noted that most associations were not statistically significant. Only 2 (ie, PPT and CSI) of the 6 measures of CS were significantly associated with an expanded distribution of pain. In addition, even though positive associations were observed, the strength of those associations was low, as reflected by the small amount of the variance of CS (ie, 9%) explained by the areas of pain.

Examining TS directly before measurement of CPM is a challenge, as the TS measurement could potentially have an effect on the results of CPM testing. However, we performed the measurement of CPM 5 minutes after the TS procedure, following the protocol described by others.[37] Temporal summation is short-lasting; the effects last for no more than a couple of seconds to minutes after stimulus application.[3] Therefore, a 5-minute washout period between procedures was deemed appropriate to preclude a carryover effect.

In conclusion, this study has shown that the area of pain reported by individuals with knee OA pain is associated with some measures of CS. Given the significant role that CS plays in a subgroup of people with knee OA pain and that CS can mediate treatment responses (ie, after surgery[75,76]), classification of people with knee OA pain in terms of pain mechanisms is a research priority.[6,23,77] However, as laboratory equipment that is costly and not widely available is usually necessary for diagnosis, identification of CS is clinically challenging. In this regard, pain drawings may constitute an easy and cheap way for the early identification of CS in people with knee OA pain. Clinicians should be attentive for individuals showing extended areas of pain, as this may be an indicator of CS. However, further evaluation of the reliability and validity of pain area reported on pain drawings in this population is needed before its use can be advocated in clinical practice.

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This study was approved by the Ethics Committee of the Hospital Universitario de La Ribera (Alzira, Spain) and conducted in accordance with the Declaration of Helsinki.

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