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Research Report

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

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Abstract

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. To examine whether the area of pain assessed using pain drawings relates to CS and clinical symptoms in people with knee OA.

Design. Cross-sectional study.

Methods. Fifty-three subjects with knee OA scheduled to undergo primary total knee arthroplasty were studied. All participants completed pain drawings using a novel digital device, self-administration questionnaires and were assessed by quantitative sensory testing. Pain frequency maps were generated separately for women and men. Spearman's 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 < 0.05) and stiffness (r_s=.341, P < 0.05), lower pressure pain thresholds at the knee (r_s=-.306, P < 0.05) and epicondyle (r_s=-.308, P < 0.05) and higher scores with the Central Sensitization Inventory (r_s=.456, P < 0.01). 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 required.

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 required.

Introduction

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] CS is a broad concept encompassing numerous and complex pathophysiological mechanisms such as spinal cord sensitization, impaired functioning of brain-orchestrated descending anti-nociceptive (inhibitory) mechanisms, (over)activation 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 pre-operative CS [e.g. 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 [e.g. 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 like the nociceptive flexor reflex[13] or laser-evoked potentials provide more objective evidence for hyperexcitability of central nervous system neurons, but no single measurement can be regarded as gold standard for establishing CS in knee OA.

The lack of 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 have 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 (i.e. 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 distribution and location 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 seems to be the most frequently reported pain location amongst people with knee OA pain,[19,20,25,26] though generalized or diffuse knee pain is also commonly reported.[17,19] However, the location of pain is heterogeneous with no single pattern of pain location being pathognomonic for knee OA.[19] This might be due to the multiple sources of pain (e.g. ligaments stretch, 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 (in particular bilateral) knee OA pain and low level of structural damage on radiography (e.g. grade I

and II on the Kellgren-Lawrence grading system for OA).[27] Enlarged areas of pain in this subgroup was attributed to a variety of etiological factors, including abnormal central pain processing mechanisms. Wood and colleagues found that subjects with knee OA reporting enlarged areas of pain had more persistent and severe pain and higher anxiety levels, which was also interpreted as reflecting altered central pain processing mechanisms.[19] However, it must be emphasized that in the above mentioned 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 two above mentioned 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 should be reflected in more extended areas of pain mapped in pain drawings as compared to 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-reported 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 (e.g. self-report questionnaires designed to determine presence of neuropathic pain) only offer 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) was also investigated. Psychosocial factors (e.g. 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

Subjects

A convenience sample of fifty-three subjects with chronic knee OA pain of more than 3 months duration who were scheduled to undergo primary total knee arthroplasty participated in the study. Subjects with knee OA affecting the tibiofemoral and patellofemoral compartments were included. These subjects participated in a randomized controlled trial investigating the effects of pain neuroscience education on pain and function in subjects with chronic knee OA pain (ClinicalTrials.gov database 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 X-rays 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]

Subjects 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 past six months, had co-existing inflammatory, metabolic, neurological or severe medical conditions hindering the ability of the patient to participate in the study or cognitive disturbances that could influence completion of the pain drawings. Before study participation, all the subjects 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 a 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.

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

Afterwards, a standardized physical examination including physical performance tests was performed on each participant. Finally, all subjects were assessed by QST to examine pressure pain thresholds (PPT), 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 (Alzira, Spain). The participants were requested not to take analgesic medication 24h 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 drawings data was performed by a researcher who was blinded from the QST data.

Measurements

Area of pain

A novel method for obtaining and quantifying the area of pain using 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 Computer, Cupertino, CA, USA) using a stylus pen for digital tablets (CS100B, Wacom, Vancouver, WA, USA) and a commercially available sketching software (SketchBook Pro). Depending on the gender of the subject, a male or female body chart with different views of the knee region (frontal, dorsal) was chosen and opened in the sketching software (Figure 1**A**). The type, size and colour of the pen stroke were standardized across all participants.

An operator, who trained with the device in clinical practice one month prior to the start of the study, gave each subject a standardized verbal explanation on what the pain drawing was 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 subjects 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 colour 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 if 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 software was used to compute the total area of pain for each subject, and to generate two pain frequency maps (i.e. frontal and dorsal body chart) separately for men and women.[33] The area of pain was expressed as the total number of pixels coloured 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 subjects to illustrate the most frequently reported location of pain across the entire sample. This was done for women and men separately. A colour grid was used to indicate the percentage of individuals that reported pain in that specific area.

Direct measures of CS

Pressure pain threshold (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 edge of patella, respectively) and one control distant site on the ipsilateral extensor carpi radialis longus (5 cm distal to lateral epicondyle of humerus) were selected for PPT measurement.[21] The PPT was measured using an analogue Fisher algometer (Force Dial model FDK 40 Push Pull Force Gage, Wagner Instruments, P.O.B. 1217, Greenwich CT 06836) with a surface area at the round tip of $1cm^2$. The algometer probe tip was applied perpendicular to the skin at a rate of $1kg/cm^2/s$ until the first onset of pain. PPT

was measured three times on each site with a 30 s interstimulus interval between each measurement. The mean of the three measurements was used in the statistical analysis.

Temporal summation of pain and Conditioned pain modulation (CPM)

For measuring excitability of nociceptive pathways and efficacy of endogenous pain inhibition, the TS and CPM paradigms were used. TS 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 as described above. Second, TS was provoked by means of 10 consecutive pulses at previously determined PPT at each location. TS started 2 min 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 s before being released (1 s interstimulus interval). Pain intensity of the first, fifth, and tenth pulse was rated on a numerical rating scale (0: no pain to 10: worst possible pain). Afterwards, a rest period of 5 min was given.

Third, CPM was induced by combining the TS procedure namely the test stimulus and an inflated occlusion cuff around the subject'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 s. Afterwards, 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. TS 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

Central Sensitization Inventory (CSI)

The Central Sensitization Inventory is a self-report screening instrument to help identify people with central sensitivity syndromes for which CS may be a common etiology.[38] The part A of the CSI assesses symptoms common to CS and comprises of 25 items each ranged on a 5-point scale with the end points (0) "never" and (4) "always" (range: 0-100). It 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 non-patient 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 PainDETECT questionnaire (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 may also 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 comprised of 9 items: seven evaluating pain quality, one pain pattern and one pain radiation, which all 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 cut-off score of 19 were 85%, 80%, and 83%, respectively.[42] The relationship between PD-Q scores

and signs of central sensitization in people with hip OA has been previously demonstrated.[43]

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-reported 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 osteoarthritis.[44]

Physical performance tests

Range of motion measurement for both active knee flexion and extension and the Timed Up and Go test were performed in each participant. These objective measures were selected on the basis of their ability to reflect functional mobility impairments.

High intra- and intertester reliability and criterion validity of goniometry to measure range of motion has been documented for knee flexion and extension in subjects with knee restrictions of different etiologies.[45] The Timed Up and 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.[46,47] Intra-rater and inter-rater reliability of the Timed Up and Go test were 0.97 (95% confidence interval [CI], 0.95 - 0.98) and 0.96 (95% confidence interval [CI], 0.94 - 0.97), respectively. Its minimum detectable change, based on measurements performed by a single rater and between raters, was 1.10 and 1.14 seconds, respectively.[47]

Western Ontario and McMaster Universities (WOMAC) knee osteoarthritis index

The Spanish version of the self-administered Western Ontario and McMaster Universities (WOMAC) knee osteoarthritis was used.[48] The WOMAC comprises of five items for pain (score range 0–20), two for stiffness (score range 0–8), and 17 for functional limitation (score range 0–68). Total WOMAC score and scores from the pain, stiffness and functional subscales were considered. Higher scores on the WOMAC indicate worse pain, stiffness, and functional limitations. The test-retest reliability (intraclass correlation coefficients range: 0.66 to 0.81), internal consistency (Cronbach's alpha range: 0.81 to 0.93), convergent validity (Pearson's coefficients range: -0.52 to -0.63) and responsiveness (standardized response mean range: 0.8 to 1.5) of the Spanish version of the WOMAC has been demonstrated in people with hip and knee OA.[48]

Pain Catastrophizing Scale (PCS)

The Pain Catastrophizing Scale (PCS) is a valid and reliable instrument to measure pain catastrophizing in older adults with knee OA.[49,50] It comprises of 13 items each ranged 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’s alpha=0.79), test-retest reliability (intraclass correlation coefficient=0.84) and sensitivity to change (effect size<or=2) in patients with fibromyalgia.[51]

Tampa Scale of Kinesiophobia (TSK)

The Spanish version of the TSK-11 was used.[52] The TSK-11 is an 11-item questionnaire assessing fear of movement or fear of (re)injury during movement and

eliminates psychometrically poor items from the original version of the TSK,[53] thus creating a shorter questionnaire with comparable internal consistency. It is comprised of 11 items each ranged 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: activity avoidance and harm, and has demonstrated acceptable internal consistency and validity (convergent and predictive) in both subjects with acute (Cronbach's alpha= 0.79) and chronic musculoskeletal pain (Cronbach's alpha= 0.79).[52] Higher scores indicate more fear-avoidance behavior.

Pain Vigilance and Awareness Questionnaire (PVAQ)

The Spanish version of the Pain Vigilance and Awareness Questionnaire (PVAQ) was used to evaluate participants' preoccupation with or attention to pain associated with pain-related fear and perceived pain severity.[54] The PVAQ comprises of nine 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[54] and fibromyalgia[55,56] showing good internal consistency,[55,56] reliability[54,55] and validity.[54,55] A cutoff score of 24.5 out of 45 was able to identify fibromyalgia women with worse daily functioning with a sensitivity of .71 and a specificity of .75.[55]

Chronic Pain Acceptance Questionnaire (CPAQ)

The Chronic Pain Acceptance Questionnaire (CPAQ) is the questionnaire most often used to measure pain acceptance in chronic pain populations.[57] It comprises of 20 items each rated on a scale from 0 (never true) to 6 (always true) (range: 0-120) and it has a two-factor structure: activities engagement and pain willingness. The total score

results from the sum of these two factors with higher scores indicating a higher degree of chronic pain acceptance. The Spanish version of the CPAQ, which is reliable (intraclass correlation coefficient=0.83) and has valid construct validity (Cronbach's alpha: 0.83) for people with fibromyalgia, was used in this study.[57]

Statistical 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 if there were differences in baseline clinical variables between males and females. Pain frequency maps were generated by superimposing the scores obtained with pain drawings considering men and women separately. TS was calculated as the difference percentage between the 10^{th} and the 1^{st} pain rating score before occlusion using the formula: ((TS10th-TS1st)/TS1st)*100.[58] The outcome measure for CPM was calculated as the difference between the 10th pain rating score before occlusion and the 10th during occlusion.[37] Spearman's correlation coefficients were computed to reveal possible correlations: (1) between the area of pain and direct measures of CS (i.e. PPT knee, PPT epicondyle, knee TS, epicondyle TS, knee CPM, epicondyle CPM), (2) between the area of pain and indirect measures of CS (i.e. CSI and PD-Q) and (3) between the area of pain and clinical symptoms (i.e. VAS, WOMAC, WOMAC pain subscale, WOMAC stiffness subscale, WOMAC functional limitation scale, PCS, TSK, PVAQ, CPAQ). Statistical analyses were performed using SPSS 22 (SPSS INc, Chicago, IL, USA). The significance level was set at $P < 0.05$.

Results

Fifty-three individuals with knee OA (34 woman and 19 men) were enrolled in the study. Subjects' demographic data are reported in Table 1 and ~~including~~ clinical characteristics and measurements of CS are detailed in Table 2~~1~~. Mean and median scores for the area of pain, ROM for active knee flexion, Timed Up and 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 males and females ($p<0.05$). Seven out of the fifty-three subjects (13.2%) had scores that correspond to likely neuropathic pain (≥19 on the PD-Q).

The area of pain was 12766 ± 13494 pixels across the entire group of subjects whereas it was 15012 ± 14327 and 8747 ± 11096 pixels 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, $P < 0.05$) and epicondyle (r_s= -.308, $P < 0.05$) signifying lower PPT at both sites in individuals with larger pain areas. Figure 2 visualizes 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 knee, -.087 epicondyle) or the area of pain and CPM (r_s= -.066 knee, -.040 epicondyle). A significant correlation was identified between the area of pain and the CSI score (r_s=.456, $P < 0.01$); subjects with higher scores on the CSI showed larger areas of pain.

Area of pain and clinical symptoms

Higher scores on the pain (r_s=.325, P < 0.05) and stiffness (r_s=.341, P < 0.05) subscale 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 two-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 (i.e. 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 a valid instrument for screening people with central sensitivity syndromes.[59] In addition, individuals with knee OA pain with preoperative high levels of comorbid centrally mediated symptoms

measured by the CSI showed severe pain, increased analgesic requirements and were at higher risk of persistent pain after total knee arthroplasty in the early postoperative period.[60]

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 non-organic pain drawings and higher scores with the Waddell's non-organic physical signs was found in people with chronic low back pain.[61] 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.[62] Nonorganic pain drawings were defined as those with poorly defined pain patterns, bizarre or non-anatomical pain areas.[61] In addition, nonorganic pain drawings were associated with maladaptive psychosocial factors (i.e. high levels of catastrophizing, anxiety and depression) in people with chronic neck-shoulder and lower-back/lower limb pain[63] and chronic low back pain.[64] However, maladaptive psychosocial factors including magnified symptom behavior as assessed with the Waddell's scale provide no direct evidence for CS. In fact, psychosocial factors were not included as essential criteria for classification of CS pain as they are also 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 by Valdes and colleagues[65], where 14.8% of people with knee OA pain had likely neuropathic pain, and superior to the percentage obtained by Ohtori et al.[66] (e.g. 5.4%). Some studies have inferred CS based on neuropathic-like descriptors of symptoms.[67,68] 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 be either due 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 (*m*PD-Q) recently recommended for the OA pain population.[67] Like the original PD-Q, the *m*PD-Q is comprised of nine 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 non-neuropathic 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.[69,70] The quantification of CS is in turn multidimensional by 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 could justify why the areas of pain as assessed with pain drawings were correlated with some (PPT) but no other pain biomarkers of CS such as TS and CPM.

Area of pain and clinical symptoms

A significant positive correlation between knee pain severity and stiffness and the area of pain reported by subjects 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 seen 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 can be seen in Figure **1B~~2~~**. 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 also showed significantly larger referred pain areas after intramuscular hypertonic saline infusion in subjects with knee OA, when compared with controls.[71] Referred pain is a phenomenon attributed to CS.[12,15] In addition, enlarged areas of pain were observed in individuals with knee OA pain, in particular 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 subjects with knee OA pain contained more women than men.[72,73] In addition, a recent study[74] looking at the moderator effect of sex in centrally-mediated changes in people with knee OA pain, found 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.[75] 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 didn't collect information on the reliability or stability of pain location over time in our sample. Reliability was assumed based on previous studies using this method for

pain drawings analysis in other chronic pain populations (e.g. chronic low back and neck pain).[33] Expanded distribution of pain (e.g. referred pain) may be more commonly observed in those populations as compared to individuals with knee OA pain, although no comparative data exist in that regard. Our assumption may thus have influenced the results of this study. Future research is therefore 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 could for instance explore the possible association between the scores obtained with pain drawings and outcome measures after treatment (i.e. surgery), to determine the real clinical utility of pain drawings for people with knee OA pain. In this regard, Skou and colleagues found that subjects with pain after re-total knee arthroplasty demonstrated significantly more pain sites using a region-divided body chart when compared to participants without pain.[22]

Screening for the presence of concurrent comorbidities (e.g. 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.

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 two (i.e. PPT and CSI) of the six 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 (i.e. 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 five minutes after the TS procedure following the protocol described by others.[37] TS is short-lasting; the effects last for no more than a couple of seconds-to-minutes after stimulus application.[3] Therefore, a 5 minute wash-out period in between procedures was deemed appropriate to preclude a carry-over 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 CS plays in a subgroup of people with knee OA pain and that CS can mediate treatment responses (i.e. after surgery[76,77]), classification of people with knee OA pain in terms of pain mechanisms is a research priority.[6,23,78] However, since costly and unattainable laboratory equipment 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 required before its use can be advocated in clinical practice.

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Table 1. Subjects demographic characteristics are reported. *P-values refer to potential differences between male and females.

Table 2. Baseline clinical measurements are reported. *P-values refer to potential differences between male and females.

Table 3. Spearman's correlation coefficients between the area of pain (total pain area extracted from the dorsal and ventral body views) computed using pain drawings, and measures of CS and clinical symptoms for the entire cohort of individuals with knee OA pain (n=53). *Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.001 level (2-tailed).

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 OA pain. The colour grid indicates both the number and the percentage of individuals that reported pain in that specific area. Dark red represents the most frequently reported area of pain.

Figure 2. The two scatter plots illustrating the relationship between the area of pain and the PPT for both knee and epicondyle.

Table 1

Baseline demographic characteristics of OA patients	**All subjects (n=53)** Mean (SD) Median (IQR)	**Female (n=34)** Mean (SD) Median (IQR)	**Male (n=19)** Mean (SD) Median (IQR)	**P- value***
Age (years)	70.2 (7.4) 72 (11.5)	71.2 (7.8) 73 (11.2)	68.5 (6.3) 70 (7)	.130
BMI (Kg/m^2)	29.9 (3.9) 30 (5.5)	30.4 (4.2) 30 (6.2)	28.9 (3.1) 28 (5)	.183
Area of pain (**number of** pixels)	12766 (13494) 8272 (12190)	15012 (14327) 10314 (12382)	8747 (11096) 5816 (7083)	**.017**
Pain duration (years)	7.5 (6) 5 (10)	6.7 (5.7) 4 (10.3)	9.1 (6.3) 6 (11)	.127
Kellgren–Lawrence grade (tibiofemoral joint) grade 0 n (%)	**0 (0)**	**0 (0)**	**0 (0)**	**.115**
Kellgren–Lawrence grade (tibiofemoral joint) grade 1 n (%)	**0 (0)**	**0 (0)**	**0 (0)**	
Kellgren–Lawrence grade (tibiofemoral joint) grade 2 n (%)	**15 (28.3)**	**7 (20.5)**	**8 (42.1)**	
Kellgren–Lawrence grade (tibiofemoral joint) grade 3 n (%)	**22 (41.5)**	**11 (32.3)**	**11 (57.8)**	
Kellgren–Lawrence grade (tibiofemoral joint) grade 4 n (%)	**16 (30.1)**	**8 (23.5)**	**8 (42.1)**	
Ahlbäck grade (patellofemoral joint) grade 1 n (%)	**3**	**2**	**1**	**.231**
Ahlbäck grade (patellofemoral joint) grade 2 n (%)	**19**	**10**	**19**	
Ahlbäck grade (patellofemoral joint) grade 3 n (%)	**30**	**15**	**15**	
Ahlbäck grade (patellofemoral joint) grade 4 n (%)	**1**	**0**	**1**	
Ahlbäck grade (patellofemoral joint) grade 5 n (%)	**0**	**0**	**0**	

BMI, Body Mass Index.

Table 2

Baseline measurements of OA patients	**All subjects (n=53)** Mean (SD) Median (IQR)	**Female (n=34)** Mean (SD) Median (IQR)	**Male (n=19)** Mean (SD) Median (IQR)	**P- value***
NRPS (0-10)	5.92 (17) 5.9 (22.5)	6.19 (17.2) 6.05 (27.3)	5.44 (15.8) 5.8 (20)	.217
ROM active knee flexion (degree)	115.5 (11.4) 115.5 (10)	113.9 (9.8) 115 (8.7)	118.3 (13.5) 118.5 (9.2)	**.047**
ROM active knee extension (degree)	-2.41 (6.3) -2 (7.9)	-3.2 (6.7) -2.6 (7.96)	-0.9 (5.4) -1.6 (5.3)	.30
Timed Up and Go test (seconds)	11.4 (5.7) 9.8 (5)	13.4 (6.2) 11.8 (5.5)	7.9 (1.6) 7.7 (2.6)	**.000**
WOMAC (0-**9668**)	49.4 (16.5) 49 (25)	54.1 (16.1) 56 (24.5)	40.9 (13.9) 38 (20)	**.006**
WOMAC pain subscale **(0-20)**	9.53 (3.31) 10 (5)	10.6 (3.1) 10 (4)	7.6 (2.9) 7 (3)	.001
WOMAC stiffness subscale **(0-8)**	3.79 (2.11) 3 (3)	4.1 (2.3) 4 (3.8)	3.2 (1.7) 3 (2)	.119
WOMAC functional limitation scale **(0-68)**	36.09 (12.66) 36 (19)	39.4 (12.5) 42.5 (19.8)	30.1 (10.7) 29 (17)	**.010**
PCS **(0-52)**	23.77 (12.51) 25 (17)	27.2(11.7) 26 (15.5)	17.7 (11.8) 20 (19)	**.012**
PVAQ **(0-45)**	28.66 (6.95) 28 (9)	28.6 (7.5) 28 (10.8)	28.8 (6) 29 (6.5)	.773
CPAQ **(0-120)**	52.83 (18.26) 52 (28)	48.5 (17.2) 47.5 (27.8)	60.6 (18) 64 (23)	**.022**
TSK **(11-44)**	33.68 (5.98) 34 (9)	35.1 (5.6) 35 (7.8)	31.2 (5.9) 32 (8)	**.029**
CSI **(0-100)**	36.21 (15.62) 37 (23)	40.1 (16.6) 42 (22.5)	29.2 (10.8) 30 (19.5)	**.014**
PD-Q **(-1-38)**	12.25 (6.3) 11 (8)	13.6 (6.6) 12 (9)	9.8 (5.1) 10 (8.5)	**.041**
PPT knee (Kg/cm^2)	4.82 (2.62) 4 (3.15)	4 (1.6) 3.8 (2.5)	6.2 (3.4) 6.1 (4.9)	**.018**
PPT epicondyle (Kg/cm^2)	4.03 (1.72) 3.7 (2)	3.7 (1.5) 3.6 (1.3)	4.6 (2) 4.4 (2.4)	0.55
Knee TS (%)	40.44 (23.11) 43.75 (23.08)	40.53 (24.16) 42.46 (21.32)	40.28 (21.76) 44.44 (25.71)	.853
Epicondyle TS (%)	43.39 (21.46) 50 (32.14)	3 (1.7) 3 (2)	43.19 (17.79) 50 (29.56)	.978
Knee CPM (Kg/cm^2)	-0.44 (1.66) 0 (2)	-0.6 (1.6) -1 (1.5)	-0.1 (1.8) 0.50 (1.5)	.054
Epicondyle CPM (Kg/cm^2)	-0.43 (1.76) 0 (3)	-0.7 (1.7) -1 (2)	0 (1.8) 0 (2)	.200

CPAQ, Chronic Pain Acceptance Questionnaire; CPM, Conditioned pain Modulation; CSI, Central Sensitization Inventory; NRPS, Numeric Rating Pain 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 knee osteoarthritis index.

		Correlation with pain area r_s
Direct measures of CS	PPT knee (Kg/cm^2)	**-.306***
	PPT epicondyle (Kg/cm^2)	**-.308***
	Knee TS (%)	**-.0183**
	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	**NRPS (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

CPAQ, Chronic Pain Acceptance Questionnaire; CPM, Conditioned pain Modulation; CSI, Central Sensitization Inventory; NRPS, Numeric Rating Pain Scale; PCS, Pain Catastrophizing Scale; PD-Q, PainDETECT Questionnaire; PPT, Pressure Pain Threshold; PVAQ, Pain Vigilance and Awareness Questionnaire; TS, Temporal Summation; TSK, Tampa Scale of Kinesiophobia; WOMAC, Western Ontario and McMaster Universities knee osteoarthritis index.

Figure 1

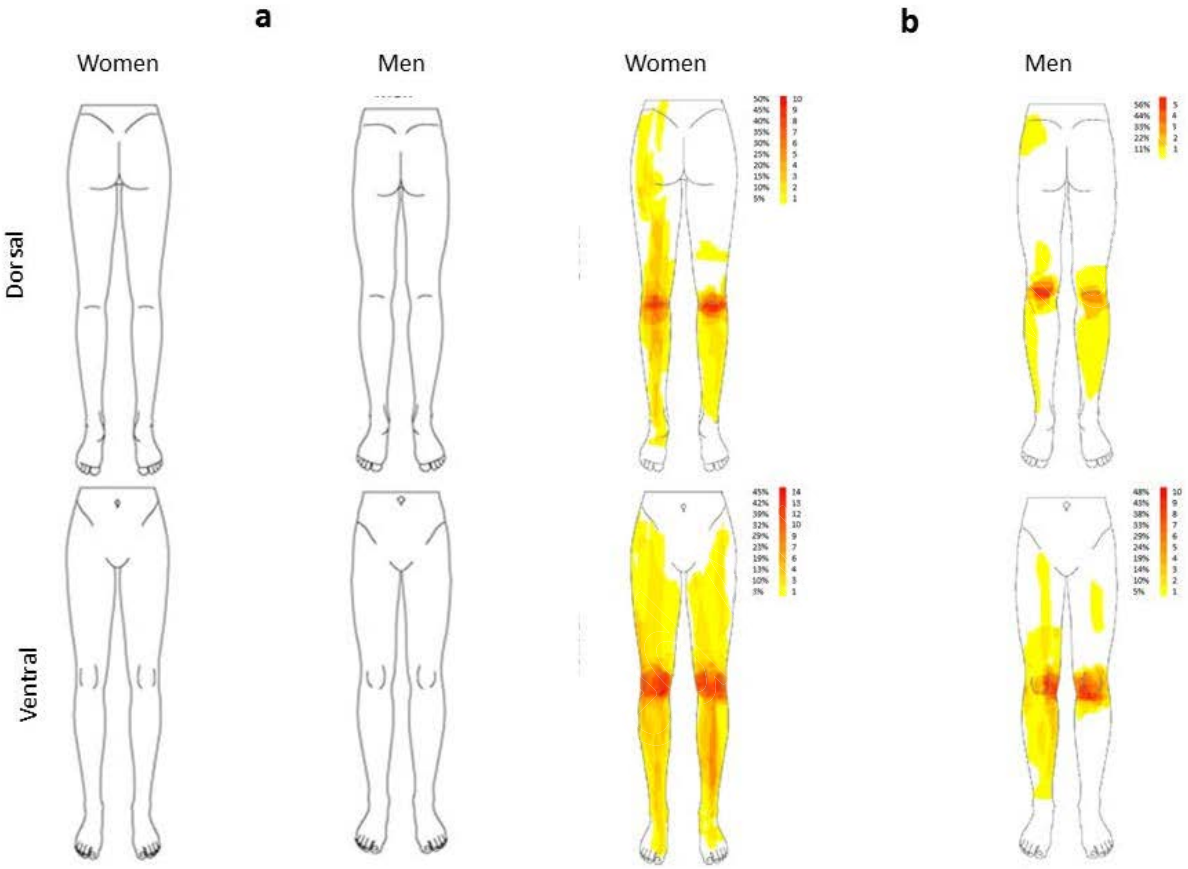
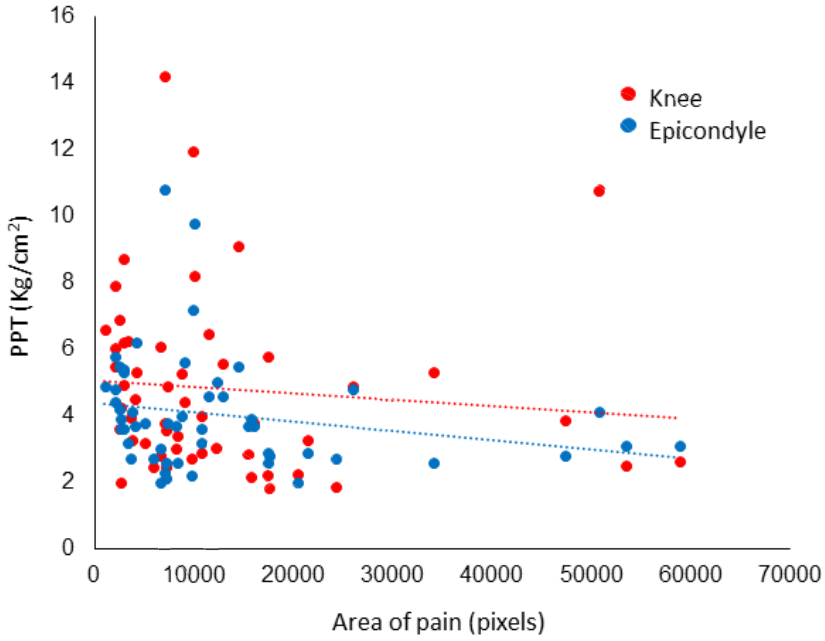


Figure 2


16
14
12
10
8
6
4
2
0
PPT (Kg/cm²)
0
10000
20000
30000
40000
50000
60000
70000
Area of pain (pixels)
Knee
Epicondyle