Title

Does weight-bearing versus non-weight-bearing pain reflect different pain mechanisms in knee osteoarthritis?: the Multicenter Osteoarthritis Study (MOST)

Journal

Osteoarthritis and Cartilage, 30(4)

ISSN

1063-4584

Authors

Aoyagi, K
Liew, JW
Farrar, JT
et al.

Publication Date

2022-04-01

DOI

10.1016/j.joca.2021.10.014

Peer reviewed

HHS Public Access

Author manuscript

Osteoarthritis Cartilage. Author manuscript; available in PMC 2023 April 01.

Published in final edited form as:

Osteoarthritis Cartilage. 2022 April ; 30(4): 545–550. doi:10.1016/j.joca.2021.10.014.

Does Weight-bearing Versus Non-weight-bearing Pain Reflect Different Pain Mechanisms in Knee Osteoarthritis?: The Multicenter Osteoarthritis Study (MOST)

K. Aoyagi[†], **J.W. Liew**[†], **J.T. Farrar**[^], **N. Wang**[‡], **L. Carlesso**[‖], **D. Kumar**[†], **L. Frey Law**[§], **C.E. Lewis**[#], **M. Nevitt**[¶], **T. Neogi**[†]

[†]Boston University School of Medicine, Boston, MA, USA

[^]University of Pennsylvania School of Medicine, Philadelphia, PA, USA

[‡]Boston University School of Public Health, Boston, MA, USA

[‖]McMaster University, ON, Canada

[§]University of Iowa, Iowa City, IA, USA

[#]University of Alabama, Birmingham, AL, USA

[¶]University of California San Francisco, San Francisco, CA, USA

Abstract

Objective—Knee osteoarthritis (OA) is predominantly characterized by pain with weight-bearing activities. Pain at rest also occurs but the mechanisms for this are not clear. We evaluated the relations of nociceptive signal alterations to weight-bearing and non-weight-bearing pain in knee OA.

Design—We used data from a NIH–funded longitudinal cohort of older adults with or at risk of knee OA. We evaluated quantitative sensory testing (QST) measures (pressure pain threshold (PPT) at patellae and the wrist; mechanical temporal summation (TS); conditioned pain modulation (CPM)). Each WOMAC pain question was dichotomized as having at least moderate pain, and we further categorized them as weight-bearing pain and non-weight-bearing pain. We

Corresponding author: Tuhina Neogi, MD, PhD, Professor of Medicine and of Epidemiology, Chief of Rheumatology, Boston University School of Medicine/Boston Medical Center, Boston University School of Public Health, 650 Albany Street, Suite X200, Boston, MA, 02118, T: 617-358-9650, F: 617-358-9653, tneogi@bu.edu.

Author contributions

TN, JF, JL, KA were involved in conception and design of the study. TN, CEL, MN, LFL were involved in acquisition of data. TN, JL, NW were involved in data analyses. All authors were fully involved in interpretation of the data. KA drafted the article. All authors were fully involved in critical revision of the article for important intellectual content and final approval of the article.

Conflict of interest

None.

Ethical Approval

The study protocol was approved by the institutional review boards at the University of Iowa, University of Alabama, Birmingham, University of California, San Francisco and Boston University Medical Campus, and written informed consent was obtained from all participants before enrollment.

evaluated the relation of QST measures to each pain outcome using logistic regression, adjusting for potential confounders.

Results—2749 participants (5479 knees) were included (mean age 64±11, 57% female). Each SD unit decrease in patellar PPT was associated with greater odds of both weight-bearing pain (OR 1.51 (95% CI 1.27, 1.79)) and non-weight-bearing pain (OR 1.46 (1.20–1.77)), while wrist PPT was associated with greater odds of weight-bearing pain (OR 1.27 (1.15, 1.39)) but only with pain during sitting/lying (OR 1.20 (1.01, 1.43)). TS was significantly associated with greater odds of pain with walking and stairs (OR 1.11 (1.01, 1.23), 1.11 (1.03, 1.20), respectively). CPM was not associated with any pain outcomes.

Conclusions—Our findings challenge the hypothesis that non-weight-bearing pain may reflect greater pain sensitization and/or inefficient CPM than weight-bearing pain in knee OA, suggesting other mechanisms are likely responsible.

Keywords

Pain sensitization; weight-bearing pain; non-weight-bearing pain; knee OA

Introduction

Osteoarthritis (OA) affects about 500 million people worldwide and over 34 million people in the United States[1,2]. The knee is a common site affected by OA, typically manifesting with pain during weight-bearing activities. This weight-bearing pain is thought to be reflective of nociceptive pain[3,4]. Pain at rest, i.e., non-weight bearing pain, is also present in 23% to 81% of individuals with knee OA[5–8]. Given that joint loading during sitting or lying, while not absent, is substantially less than during weight-bearing activities like walking or stair-climbing, pain at rest may not reflect mechanical nociception.

Understanding mechanisms that distinguish between weight-bearing and non-weight-bearing pain can help advance rational pain management strategies. However, few studies to date have investigated mechanisms underlying the differences in these types of pain. Diffuse pain around the knee, greater constant or intermittent pain, and psychological symptoms have been associated with pain at rest; however, weight-bearing pain was not evaluated[9]. In studies that evaluated both types of pain, neuropathic-like symptoms, pain catastrophizing, depression, bone marrow lesions and joint effusions were associated with both types of pain, but the associations were of larger magnitudes for weight-bearing pain (i.e., pain with walking, standing, stairs)[8,10].

An important and potentially targetable mechanism that may contribute to the experience of non-weight bearing pain is an alteration of nociceptive signaling. In animal models, persistent painful inputs can induce neuroplastic changes in the peripheral nervous system (i.e., peripheral sensitization), and similar changes can occur in the central nervous system (i.e., central sensitization)[11,12]. Pain sensitization has been associated with pain presence and severity in knee OA[13,14], but its association with non-weight bearing pain has not been well-studied to date. Two prior small studies found that increased pain sensitivity measured by quantitative sensory testing (QST) at the knee or the hand was associated

with non-weight-bearing pain but not with weight-bearing pain in knee OA[15] or post-total knee replacement[16]. These studies suggest that pain sensitization (i.e., ascending facilitatory pathways) may contribute to non-weight-bearing pain to a greater degree than to weight-bearing pain. However, descending endogenous inhibitory signaling, also known as conditioned pain modulation (CPM), is another important nociceptive mechanism contributing to pain perception[17], but has not yet been studied in this regard.

We therefore sought to determine the relation of pain sensitization and CPM to non-weight-bearing and weight-bearing pain in knee OA. We hypothesized that pain sensitization and inefficient CPM are associated with non-weight-bearing pain (i.e., pain at rest) more so than with weight-bearing pain.

Methods

Study Sample

The Multicenter Osteoarthritis Study (MOST) is a National Institutes of Health–funded longitudinal cohort of older adults with or at risk of knee OA. At baseline, 3,026 subjects, aged 50–79 years, were recruited from Birmingham, Alabama, and Iowa City, Iowa. Details of the cohort have been published elsewhere[18,19]. The study protocol was approved by the institutional review boards at the University of Iowa, the University of Alabama at Birmingham, the University of California San Francisco, and Boston University Medical Center. In this cross-sectional study, we used data from the 144-month visit, which was the first visit at which conditioned pain modulation (CPM) was measured. Participants at the 144-month study visit comprised 2 cohorts: participants from the original cohort who were recruited between 2003 and 2005, had or were at risk of knee OA and were aged between 50–79 years at baseline (Original Cohort); and new participants recruited between 2016 and 2018, who were aged 45–69 years, with either no or only minimal knee pain and radiographic Kellgren-Lawrence grade ≤ 2 (New Cohort)[18,19]. For these analyses, participants who had a history of knee replacement and peripheral neuropathy were excluded from this study.

Exposures

Quantitative Sensory Testing measures: Quantitative sensory testing (QST) refers to a series of standardized psychophysical measures that are used to assess functioning of nociceptive signaling, enabling evaluation of pain sensitization and descending inhibitory pathways[20,21]. We used the following measures:

Pressure pain threshold (PPT).: PPT is a reliable measure of sensitivity to nociception evoked by mechanical stimulation using a pressure algometer[22,23]. We measured PPT at the right distal radioulnar joint (the wrist) and patellae. PPT at a local site (e.g., knee) is thought to reflect peripheral sensitization with or without central sensitization, while PPT at a distant non-diseased body site (e.g., wrist) is thought to reflect central sensitization[23,24]. PPT was assessed using a handheld pressure algometer (1 cm^2 rubber tip; Wagner FDIX25) applied at a constant rate of 0.5 kg/second on the testing body site. PPT was defined as the point at which the participant verbally indicated that the pressure first changed to slight pain. The

PPT at each anatomic site was calculated by averaging 3 trials. Lower PPT values indicate more pain sensitivity.

Mechanical Temporal Summation (TS).: TS, an amplified response to repetitive stimulation, is a sensitive measure of central augmented pain processing in chronic pain conditions including knee OA[20,23,24]. We assessed TS using a standard set of weighted probes from 64–512 mN. Participants rated the pain experienced by each successive weighted probe being touched on the skin of the right distal radioulnar joint (the wrist) until a pain rating of ≥ 4/10 was achieved. If a pain rating of ≥ 4/10 was not achieved by the highest weighted probe (512 mN), then the examiner proceeded with that highest weighted probe[25]. The selected probe was then applied at a frequency of 1 Hz for 10 seconds. Participants provided a pain rating at the completion of the train of 10 stimulations and 15 seconds post-stimulation. TS was defined as the difference between the highest post-stimulation pain rating and the initial pain rating. A post-stimulation pain rating greater than the initial pain rating was considered to be reflective of facilitated TS[23,24].

Conditioned Pain Modulation (CPM).: CPM evaluates the adequacy of the descending pain modulatory pathways[17,20]. We assessed CPM using PPT as the test stimulus (PPT1) at the wrist as described above, with forearm ischemia using a blood pressure cuff as the conditioning stimulus[25]. Briefly, the blood pressure cuff applied to the contralateral arm was inflated to 10mm Hg above systolic pressure. The participant was then instructed to perform hand grip squeezes until pain of at least 4/10 occurred in the forearm. PPT was then reassessed at the wrist 3 times and averaged (PPT2). CPM is considered to be inefficient when the post-conditioning stimulus PPT is the same or lower than the initial (pre-conditioning stimulus) PPT. Percent efficiency of CPM (%CPM) was computed as PPT2/PPT1, multiplied by 100; %CPM ≤ 100 indicates inefficient CPM[26,27].

Fourteen-day test–retest reliability for PPT was 0.85–0.90 (intraclass coefficients) and for temporal summation was 0.61 (kappa statistic)[13,28]. We did not assess test-retest reliability of CPM in this study.

Outcomes

The Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) pain subscale (0–20 score) was used to assess knee-specific pain severity over the past 30 days[29]. The pain subscale consists of 5 questions, 3 of which are related to weight-bearing pain (pain with walking, standing, and going up or down stairs), and 2 of which are related to non-weight-bearing pain (pain with sitting or lying, and with sleeping at night), each assessed on a 0–4 Likert scale (none (0), mild (1), moderate (2), severe (3), and extreme (4)). We dichotomized each of the individual WOMAC pain questions as having at least moderate pain (≥2)[10]. Additionally, we combined the 3 weight-bearing questions and the 2 non-weight-bearing questions as follows. We averaged the scores for the weight-bearing questions and for the non-weight-bearing questions (separately), and then dichotomized these average scores at a value of at least 2 as per our primary approach to denote having at least moderate pain overall for each pain category (weight-bearing, non-weight-bearing). In addition, we categorized people as having both types of pain if they met that threshold for both averages.

Statistical Analysis

We performed knee-specific analyses to separately evaluate the relation of each QST measure to presence of having at least moderate pain on each activity and combined activities for weight-bearing (i.e., walking, standing, stairs) and for non-weight-bearing (i.e., sitting/lying, sleeping at night) in separate models using logistic regression with generalized estimating equation (GEE) to account for correlations between two knees within an individual. We analyzed the QST exposures (all continuous) in the direction that would indicate more pain sensitivity, per standard deviation (SD) units to allow for comparisons across the exposures. As such, we analyzed PPT and %CPM per SD unit decrease while TS was analyzed per SD unit increase. Thus, for each of these analyses, a higher risk ratio represents a higher likelihood of the pain outcome.

As a sensitivity analysis, we evaluated the relation of each QST measure to a multi-level pain outcome defined as no pain, non-weight-bearing pain only, weight-bearing pain only, or both, using multinomial regression, with weight-bearing pain only as the referent group.

All analyses were adjusted for potential confounders including age, sex, BMI, race, depressive symptoms (defined as ≥16 on Center for Epidemiologic Studies Depression Scale[30]), pain catastrophizing (one item from the Coping Strategies Questionnaire[31]), sleep quality (poor sleep was defined very bad or fairly bad sleep in the last 7 days from a Likert scale sleep question), and widespread pain using a body homunculus defined as pain being present above and below the waist, on the right and left sides of the body, and axial pain.[32] Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, North Carolina, USA).

Results

There were 2749 participants (5479 knees) eligible for this study (Supplementary Figure 1). The mean age was 64 years, and more than half of the participants were female (57%) and Caucasian (53%) (Table 1). Depressive symptoms, pain catastrophizing, poor sleep and widespread pain were present in 12%, 41%, 16%, and 34% of the participants, respectively. Overall mean values of PPT at the patellae and wrist, TS (i.e., different in pain rating pre- to post-train of stimuli), %CPM efficiency were 5.6kgf, 3.9kgf, 1.41 (0–10 pain scale), and 109%, respectively.

Of 5479 knees, 8.5%, 8.1% and 23.5% had at least moderate pain during walking, standing and stairs, respectively while 5.6% and 6.6% had at least moderate pain during sitting/lying and sleeping at night. Further, 6.3% and 4.3% had at least moderate pain for overall weight-bearing pain and non-weight-bearing pain, respectively.

Each SD unit decrease in patellar PPT (signifying more sensitization) was associated with 1.32 to 1.52 times significantly greater odds of having at least moderate pain on each of the individual WOMAC pain questions as well as for overall weight-bearing and overall non-weight-bearing pain (Figure 1A). The numerical effect estimates are presented in Supplementary Table 1.

Similarly, each SD unit decrease in wrist PPT was associated with 1.27 to 1.36 times significantly greater odds of pain with weight-bearing activities (i.e., walking, standing, stairs, and overall weight-bearing activities).(Figure 1B) and 1.2 times significantly greater odds of having at least moderate pain during sitting/lying. However, wrist PPT was not significantly associated with pain during sleeping at night or overall non-weight bearing pain (aOR 1.13, 95%CI 0.97–1.31 and aOR 1.11, 95% CI 0.92–1.34, respectively).

Each SD unit increase in TS was associated with 1.11 times greater odds of having at least moderate pain with walking and stairs (aOR 1.11, 95% CI 1.01–1.23 and aOR 1.11, 95% CI: 1.03–1.20) (Figure 1C). TS was not significantly associated with pain during standing (OR 1.09, 95% CI 0.98,1.22), although this effect estimate was similar to that for pain with walking. Further, TS was not associated with pain during non-weight-bearing activities, with effect estimates being close to the null.

CPM was not associated with any of the five pain outcomes, with all aORs being close to the null (Figure 1D).

In sensitivity analyses, PPT at the patella and wrist had similar lower odds of having non-weight-bearing pain only compared with weight-bearing pain only (OR 0.77, 95% CI 0.58–1.02 and 0.61–0.98, respectively) (Supplementary Table 2). PPT at the patella was significantly associated with greater likelihood of having both types of pain (OR 1.20, 95% CI 1.02–1.42). There were no significant associations of TS or %CPM with non-weight-bearing pain compared with weight-bearing pain.

Discussion

We found that greater pain sensitization measured by patellar PPT was associated with both weight-bearing and non-weight-bearing pain. Wrist PPT and TS, both measures of central pain sensitization, were associated with weight-bearing pain; wrist PPT was also associated with non-weight-bearing pain. CPM, reflecting descending pain modulation, was not associated with any of the pain outcomes. These results were contrary to our hypothesis that pain sensitization and/or inefficient CPM contribute to non-weight-bearing pain. Our results therefore suggest that other mechanisms are likely important for understanding non-weight-bearing pain in knee OA, and that perhaps there is not a simple dichotomy between peripheral or central pain mechanisms to explain pain presence with different types of weight-bearing versus non-weight-bearing activities.

In our study, pain sensitization, as assessed by patellar PPT, was associated with both weight-bearing and non-weight-bearing pain whereas a recent small study found that patellar PPT was associated with pain at rest but not with weight-bearing[15], though their sample predominantly comprised those with moderate pain during walking so there may not have been a sufficient range in pain severity to evaluate this. Our results suggest factors at the joint level may contribute to pain under both weight-bearing and non-weight-bearing conditions. One such joint-level factor that could contribute to both pain and pain sensitization is inflammation. Joint effusion and synovitis have been associated with both weight-bearing and non-weight bearing pain in some[10,33], but not all[15,34], studies.

Nonetheless, it is recognized that inflammation can sensitize peripheral nociceptors leading to peripheral sensitization[35]. We have previously reported that synovitis and effusion were associated with patellar PPT[28]. There are also data to suggest that different inflammatory cytokines may have differential associations with pain at rest versus with weight-bearing; synovial fluid IL-6, IL-8, and TNFα have been associated with pain during gait or standing, while only TNFα was associated with night pain and pain with sitting or lying[33].

Central sensitization may also be associated with inflammation. Peripheral inflammatory mediators can lead to neuroplastic changes in the central nociceptive system, resulting in widespread hyperalgesia and ascending pain facilitation[12,35]. We found that both wrist PPT and TS were significantly associated with weight-bearing pain. Wrist PPT was also associated with pain during sitting/lying; however, the effect estimate was slightly smaller than that for weight-bearing outcomes. Central sensitization is an amplified responsiveness to stimuli in the central nervous system[36] and therefore greater stimuli (e.g., greater mechanical loading to the knee) could feasibly have an impact on nociceptive signaling in the central nervous system. Thus, weight-bearing activities may be expected to have greater effects on ascending nociceptive facilitated signaling than non-weight-bearing activities where there may be less nociceptive input.

CPM, which aims to evaluate the efficiency of descending pain modulatory pathways[17,20], was not associated with any of the pain outcomes in our study. With point estimates close to the null for each of the activities, our findings suggest that descending pain modulation is unlikely to play an important role in differentiating pain with versus without weight-bearing activities.

A strength of our study is its large size, and evaluation of both ascending and descending nociceptive pathways using QST. Our sample consisted of a community-based cohort that reflects a broad range of age and disease duration, contributing to generalizability. Limitations include our cross-sectional study design, which precludes conclusions regarding the direction of the associations. The study sample had a low prevalence of individuals with at least moderate pain with sitting or lying, although a similar low prevalence was noted for having at least moderate pain with walking and standing; thus, the lack of associations with non-weight-bearing pain is unlikely related to lack of sufficient precision. We cannot rule out potential for measurement error for our CPM assessment. The effect estimates were relatively small across many of our results; however, given that pain is multifactorial in nature, these results can provide insights regarding the potential contribution of pain sensitization to weight-bearing and/or non-weight-bearing pain. Although we controlled for several relevant potential confounders, residual confounding may remain. When we additionally adjusted for sleep quality and radiographic knee OA severity, the results did not materially change (Supplementary Table 3), which is consistent with prior findings[28]. We were unable to assess whether duration of pain may have impacted these associations, though we previously did not note an association between duration of knee OA and pain sensitization[13].

In conclusion, our findings challenge the hypothesis that non-weight-bearing pain may reflect greater pain sensitization and inefficient CPM than weight-bearing pain. Other

mechanisms, such as inflammation, may be responsible for non-weight-bearing pain in knee OA. Alternatively, the same mechanisms may underlie both weight-bearing and non-weight-bearing pain without distinction between the two.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors acknowledge the staff at the UCSF Coordinating Center and all MOST participants.

Role of the funding source

The Multicenter Osteoarthritis Study was funded by the NIH (U01-AG18820, U01-AG18832, U01-AG18947, U01-AG19069 and AR47785). TN was supported by NIH/NIAMS P30 AR072571, K24 AR070892, R01 AG066010 and DK was supported by NIH-NIAMS K01 AR069720. JTF was supported by NIH-NIDDK - U01 Grant (CoI), grants from NIH-NINDS - U24 Grant (PI) and grants from FDA-BAA Contract. Funding sources had no role in study design, data collection and analysis, data interpretation, or the decision to submit the manuscript for publication.

Effort developed by investigators at four core sites and funded by NIH/NIA grants: U01 AG18820 (David Felson, Boston University); U01 AG18947 (Cora E. Lewis, University of Alabama at Birmingham); U01 AG18832 (James Torner, University of Iowa); U01 AG19069 (Michael Nevitt, University of California, San Francisco).

References:

1. Safiri S, Kolahi AA, Smith E, et al. Global, regional and national burden of osteoarthritis 1990–2017: a systematic analysis of the Global Burden of Disease Study 2017. Annals of the rheumatic diseases. 2020;79(6):819–828. [PubMed: 32398285]
2. Hunter DJ, March L, Chew M. Osteoarthritis in 2020 and beyond: a Lancet Commission. The Lancet. 2020;396(10264):1711–1712.
3. Neogi T The epidemiology and impact of pain in osteoarthritis. Osteoarthritis and cartilage. 2013;21(9):1145–1153. [PubMed: 23973124]
4. Segal NA, Anderson DD, Iyer KS, et al. Baseline articular contact stress levels predict incident symptomatic knee osteoarthritis development in the MOST cohort. Journal of orthopaedic research. 2009;27(12):1562–1568. [PubMed: 19533741]
5. Woolhead G, Gooberman-Hill R, Dieppe P, Hawker G. Night pain in hip and knee osteoarthritis: a focus group study. Arthritis care & research. 2010;62(7):944–949. [PubMed: 20191575]
6. Frey-Law LA, Bohr NL, Sluka KA, et al. Pain sensitivity profiles in patients with advanced knee osteoarthritis. Pain. 2016;157(9):1988–1999. [PubMed: 27152688]
7. Hawker G, Stewart L, French M, et al. Understanding the pain experience in hip and knee osteoarthritis–an OARSI/OMERACT initiative. Osteoarthritis and cartilage. 2008;16(4):415–422. [PubMed: 18296075]
8. Power JD, Perruccio AV, Gandhi R, et al. Neuropathic pain in end-stage hip and knee osteoarthritis: differential associations with patient-reported pain at rest and pain on activity. Osteoarthritis and cartilage. 2018;26(3):363–369. [PubMed: 29326061]
9. Nian X, He Y, Ji Y, Huang Y, Sun E, Li L. Associations Between Pain Patterns and Self-Reported Clinical Outcomes in Patients with Knee Osteoarthritis. Pain medicine (Malden, Mass). 2019;20(4):818–825.
10. Lo GH, McAlindon TE, Niu J, et al. Bone marrow lesions and joint effusion are strongly and independently associated with weight-bearing pain in knee osteoarthritis: data from the osteoarthritis initiative. Osteoarthritis and cartilage. 2009;17(12):1562–1569. [PubMed: 19583959]
11. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. J Pain. 2009;10(9):895–926. [PubMed: 19712899]

12. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain. 2011;152(3 Suppl):S2–15. [PubMed: 20961685]
13. Neogi T, Frey-Law L, Scholz J, et al. Sensitivity and sensitisation in relation to pain severity in knee osteoarthritis: trait or state? Annals of the rheumatic diseases. 2015;74(4):682–688. [PubMed: 24351516]
14. Finan PH, Buenaver LF, Bounds SC, et al. Discordance between pain and radiographic severity in knee osteoarthritis: findings from quantitative sensory testing of central sensitization. Arthritis and rheumatism. 2013;65(2):363–372. [PubMed: 22961435]
15. Satake YIM, Aso K, Igarashi Y, Sasaki N, Ikeuchi M. Comparison of Predisposing Factors Between Pain on Walking and Pain at Rest in Patients with Knee Osteoarthritis. J Pain Res 2021;14:1113–1118. 2021. [PubMed: 33907458]
16. Lundblad H, Kreicbergs A, Jansson KA. Prediction of persistent pain after total knee replacement for osteoarthritis. J Bone Joint Surg Br. 2008;90(2):166–171. [PubMed: 18256082]
17. Lewis GN, Rice DA, McNair PJ. Conditioned pain modulation in populations with chronic pain: a systematic review and meta-analysis. The journal of pain : official journal of the American Pain Society. 2012;13(10):936–944.
18. Englund M, Felson DT, Guermazi A, et al. Risk factors for medial meniscal pathology on knee MRI in older US adults: a multicentre prospective cohort study. Annals of the rheumatic diseases. 2011;70(10):1733–1739. [PubMed: 21646417]
19. Segal NA, Nevitt MC, Gross KD, et al. The Multicenter Osteoarthritis Study: opportunities for rehabilitation research. PM & R : the journal of injury, function, and rehabilitation. 2013;5(8):647–654.
20. Arendt-Nielsen L, Nie H, Laursen MB, et al. Sensitization in patients with painful knee osteoarthritis. Pain. 2010;149(3):573–581. [PubMed: 20418016]
21. Uddin Z, MacDermid JC. Quantitative sensory testing in chronic musculoskeletal pain. Pain Medicine. 2016;17(9):1694–1703. [PubMed: 26893116]
22. Wessel J The reliability and vatidity of pain threshold measurements in osteoarthritis of the knee. Scandinavian journal of rheumatology. 1995;24(4):238–242. [PubMed: 7481589]
23. Neogi T, Frey-Law L, Scholz J, et al. Sensitivity and sensitisation in relation to pain severity in knee osteoarthritis: trait or state? Annals of the rheumatic diseases. 2015;74(4):682–688. [PubMed: 24351516]
24. Neogi T, Guermazi A, Roemer F, et al. Association of Joint Inflammation With Pain Sensitization in Knee Osteoarthritis: The Multicenter Osteoarthritis Study. Arthritis & rheumatology (Hoboken, NJ). 2016;68(3):654–661.
25. Carlesso LC, Frey Law L, Wang N, Nevitt M, Lewis CE, Neogi T. The Association of Pain Sensitization and Conditioned Pain Modulation to Pain Patterns in Knee Osteoarthritis. Arthritis Care Res (Hoboken). 2020.
26. Edwards RR, Dolman AJ, Martel MO, et al. Variability in conditioned pain modulation predicts response to NSAID treatment in patients with knee osteoarthritis. BMC musculoskeletal disorders. 2016;17(1):1–9. [PubMed: 26728594]
27. Yarnitsky D, Arendt-Nielsen L, Bouhassira D, et al. Recommendations on terminology and practice of psychophysical DNIC testing. European journal of pain. 2010;14(4):339–339. [PubMed: 20227310]
28. Neogi T, Guermazi A, Roemer F, et al. Association of joint inflammation with pain sensitization in knee osteoarthritis: the Multicenter Osteoarthritis Study. Arthritis & rheumatology. 2016;68(3):654–661. [PubMed: 26554395]
29. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. The Journal of rheumatology. 1988;15(12):1833–1840. [PubMed: 3068365]
30. Radloff LS. The CES-D scale: A self-report depression scale for research in the general population. Applied psychological measurement. 1977;1(3):385–401.
31. Jensen MP, Keefe FJ, Lefebvre JC, Romano JM, Turner JA. One-and two-item measures of pain beliefs and coping strategies. Pain. 2003;104(3):453–469. [PubMed: 12927618]

32. Leveille SG, Ling S, Hochberg MC, et al. Widespread musculoskeletal pain and the progression of disability in older disabled women. Annals of internal medicine. 2001;135(12):1038–1046. [PubMed: 11747382]

33. Leung YY, Huebner JL, Haaland B, Wong SBS, Kraus VB. Synovial fluid pro-inflammatory profile differs according to the characteristics of knee pain. Osteoarthritis and cartilage. 2017;25(9):1420–1427. [PubMed: 28433814]

34. Sarmanova A, Hall M, Moses J, Doherty M, Zhang W. Synovial changes detected by ultrasound in people with knee osteoarthritis–a meta-analysis of observational studies. Osteoarthritis and cartilage. 2016;24(8):1376–1383. [PubMed: 26973325]

35. Schaible HG. Mechanisms of chronic pain in osteoarthritis. Current rheumatology reports. 2012;14(6):549–556. [PubMed: 22798062]

36. Nijs J, George SZ, Clauw DJ, et al. Central sensitisation in chronic pain conditions: latest discoveries and their potential for precision medicine. The Lancet Rheumatology. 2021.

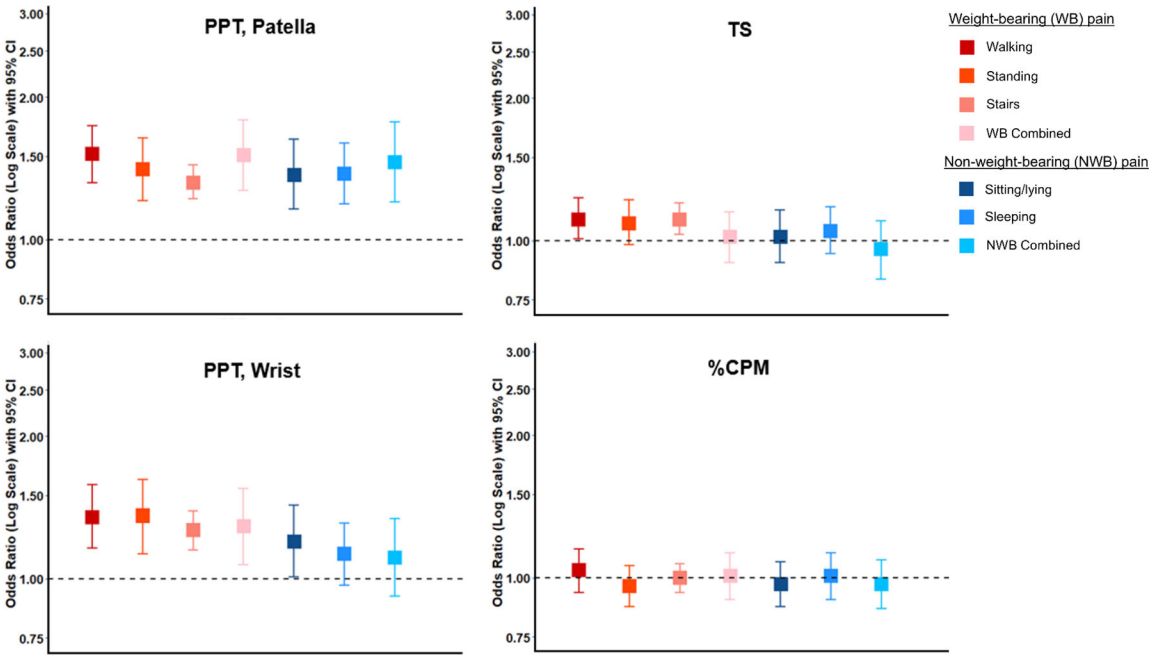

Figure 1:

Relations of patellar PPT, wrist PPT, TS and CPM to individual and combined WOMAC pain

Outcomes: At least having moderate pain on individual WOMAC questions or at least moderate pain on the average of combined WB (or NWB) pain questions. Pressure pain threshold (PPT) and % conditioned pain modulation (CPM) are presented as standardized effect estimates per standard deviation unit decrease whereas temporal summation (TS) is presented as standardized effect estimates per standard deviation unit increase.

Table 1:

Participant Characteristics

Descriptive Statistics	N = 2749 participants (5479 knees)
Age, mean ± SD (years)	63.9 ± 10.6
Women, n (%)	1563 (57)
Caucasian, n (%)	1456 (53)
BMI, mean ± SD (kg/m^2)	29.5 ± 5.72
Depressive Symptom, n (%)	325 (12)
Pain Catastrophizing, n (%)	1134 (41)
Poor Sleep, n (%)	446 (16)
Widespread Pain, n (%)	936 (34)
PPT patellae (kgf) mean ± SD	5.60 ± 2.51
PPT wrist (kgf), mean ± SD	3.90 ± 2.0
TS * (0–10 pain scale), mean ± SD	1.41 ± 1.7
%CPM †, mean ± SD	109.1 ± 30.1

* TS: temporal summation was calculated by post-stimulation pain rating (0–10) minus th initial pain rating

† %CPM: % efficiency of conditioned pain modulation was computed as PPT2/PPT1, multiplied by 100

Abbreviations: BMI: body mass index; PPT: pressure pain threshold; TS: temporal summation; CPM: conditioned pain modulation