Published in final edited form as:

Osteoarthritis Cartilage. 2022 January ; 30(1): 17–31. doi:10.1016/j.joca.2021.09.011.

Quantitative Sensory Testing: Identifying Pain Characteristics in Patients with Osteoarthritis

Kaetlyn R. Arant, BA[1], **Jeffrey N. Katz, MD, MSc**[1,2,3,4], **Tuhina Neogi, MD, PhD**[5]

[1.]The Orthopaedic and Arthritis Center for Outcomes Research, Brigham and Women's Hospital, Boston, MA, USA.

[2.]Harvard Medical School and Chan Harvard School of Public Health, Boston, MA, USA.

[3.]Department of Orthopedic Surgery, Brigham and Women's Hospital, Boston, MA, USA.

[4.]Section of Clinical Sciences, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, USA.

[5.]Section of Rheumatology, Boston University School of Medicine and Boston Medical Center, Boston, MA, USA

Abstract

Objective: This review outlines the most commonly used quantitative sensory tests to identify pain sensitization. We examine cross-sectional associations between quantitative sensory testing (QST) measures and OA symptoms and severity, along with longitudinal associations between QST findings and response to surgical and non-surgical treatments for OA.

Design: We conducted a search in PubMed for English language papers including 'osteoarthritis' and 'quantitative sensory testing' as search terms. Papers that did not pertain specifically to OA or QST were excluded.

Results: Pain Pressure Threshold (PPT), Conditioned Pain Modulation (CPM), and Temporal Summation (TS) are the QST measures used most frequently to identify pain sensitization. Findings indicate that persons with knee OA often exhibit lower PPT thresholds, inefficient CPM, and facilitated TS as compared with controls who do not have OA, supporting the discriminant validity of QST. Pre-treatment QST has shown some success in identifying persons who experience less pain relief from surgical and non-surgical treatments for knee OA. Post-treatment QST has shown that sometimes PPT and CPM can normalize (PPT thresholds increase, and CPM becomes efficient) in patients for whom joint replacement is successful. Recent studies

Corresponding author: Jeffrey N. Katz, MD, MSc, Orthopaedic and Arthritis Center for Outcomes Research, Brigham and Women's Hospital, 75 Francis Street, Building for Transformative Medicine, Suite 5016, Boston, MA 02115, jnkatz@bwh.harvard.edu, Phone: 617-732-5338, Fax: 627-525-7900.
Co-authors: Kaetlyn R. Arant, BA, Tuhina Neogi, MD

Author contributions: JK and KA conceived the study; KA drafted the manuscript and JK and TN provided scientific insights and critical editorial comments. All authors approved the final manuscript.

Conflicts of interest: Though not directly related to this publication, TN declares conflicts of interest with Pfizer/Lilly and Regeneron.

indicate that QST measures are more closely associated with pain severity than OA radiographic severity, suggesting that sensitization may be a trait rather than a state.

Conclusions: QST may have a role in identifying persons who are susceptible to chronic pain and may offer an opportunity for personalized, more effective treatment of OA.

Keywords

Osteoarthritis; Quantitative Sensory Testing; Sensitization

I. Introduction

Burden of chronic pain and role of central sensitization

Chronic pain affects over 100 million American adults.[1] Osteoarthritis (OA) affects ~ 54 million individuals in the US and over 240 million worldwide, making it among the most common sources of chronic pain.[2–5] As none of the currently available OA treatments reverse or delay the progression of joint damage, OA treatment often focuses on pain management and functional restoration. Recommended treatments include weight loss, exercise, physical therapy, NSAIDs, corticosteroid and other injections, adjunctive medications, and—for end-stage OA—total joint replacement.[6, 7]

Radiographic severity and pain levels are often discrepant in patients with OA, suggesting that processes other than joint damage play a role in the development and persistence of chronic pain; one such process is pain sensitization.[8] The International Association for the Study of Pain defines sensitization as an "increased responsiveness of nociceptive neurons to their normal input, and/or recruitment of a response to normally subthreshold inputs. [This] can include a drop in threshold and an increase in suprathreshold response."[9] Accumulating evidence suggests pain sensitization is a key contributor to chronic pain in OA.[10–15]

A better understanding of the contribution of pain sensitization to the chronic pain experience in OA could lead to more personalized treatment. Identifying pain mechanisms (e.g., relative contributions of tissue damage and pain sensitization) would help identify individuals likely to respond to therapies targeted at the joint, or, alternatively, towards the peripheral and/or central nervous system.[16]

Objectives of this review

This review focuses on associations between measures of pain sensitization and key patient-centered manifestations of OA including joint pain and stiffness. We begin by outlining the most frequently used techniques for assessing pain sensitization. We then review cross-sectional associations between these sensitization measures and OA case status and between these measures and the severity of OA symptoms and joint damage. Finally we review evidence of longitudinal associations between measures of pain sensitization and response to OA therapy.

We assembled evidence for these cross-sectional and longitudinal associations by searching PubMed along with bibliographies of papers identified in the search. We sought English language papers with search terms suggesting they addressed both OA and quantitative

sensory testing (QST). We reviewed titles and abstracts of all identified papers. Papers were excluded if they did not pertain specifically to OA or if there was no mention of QST.

Assessment of central sensitization

QST refers to a series of psychophysical techniques that quantify somatosensory function in experimental settings.[1] Unlike other techniques that assess nerve dysfunction, such as electromyography, QST targets the small sensory fibers that comprise much of the peripheral nervous system, along with pathways that transmit pain information to and from the central nervous system.[17] QST also allows for the detection and quantification of both heightened and diminished sensations.[1, 17] QST is an umbrella term that comprises a number of tests, each of which examines a different putative mechanism. Different stimuli can be used for sensory testing, including thermal, mechanical, electrical, and vibratory sensory thresholds.[18] We describe these tests below.

Static Tests

QST consists of static and dynamic tests, with static tests determining pain thresholds by comparing the objective intensity of a stimulus to the pain experienced by the participant when exposed to the stimulus. Pressure Pain Threshold (PPT) uses a mechanical stimulus to identify the point at which a stimulus-induced sensation of pressure first transitions to one of pain. Often, this test is performed by applying pressure using an algometer to sites both near to and distant from the site where subjects experience pain. PPT can be measured reliably with an algometer in people with knee OA, and is sensitive enough to detect changes in response to physical therapy intervention.[19–22] Several studies suggest PPT to be the most reliable QST measure.[10, 19, 21, 23] When testing the reproducibility of many sites around the knee 5–10 days apart, Wessel reported intraclass correlation coefficients (ICCs) ranging from 0.58 to 0.91.[21] Dua and Neogi found similar results, with Dua reporting ICCs between 0.70 and 0.96 between initial and repeat testing[23] and Neogi reporting a fourteen-day test-retest ICC between 0.85 and 0.90.[24]

Other static quantitative sensory tests include vibration perception threshold (VPT), which is a function of the posterior columns. Clinically, loss of vibration sense—in addition to loss of sensitivity to cold or light touch—can be used to assess for presence of peripheral neuropathy. Higher VPT, meaning a higher vibration frequency is necessary for detection, reflects poorer vibratory sensation.[25] While VPT is commonly used in persons with Type 1 diabetes, this test has also been used to examine subjects with hip and knee OA.[26, 27] Shakoor et al. reported that individuals with symptomatic, radiographic knee OA displayed increased VPTs at five different sites on the lower extremity.[26] In a similar study, persons with symptomatic, radiographic hip OA exhibited decreased levels of sensation at sites on lower and upper extremities.[27] Conversely, Dua et al. found *increased* sensitivity to vibratory stimuli (i.e., lower VPT) to be associated with greater levels of sensitization (lower PPT values) and the presence of allodynia.[23] While further research is necessary, these studies suggest that high VPT may signal sensory loss and low VPT may be associated with sensitization in persons with OA.

Dynamic Tests

Dynamic QSTs are used to investigate central processing of painful sensations by assessing an individual's response to multiple stimuli provided either concomitantly or in series.[28] One of the two most commonly performed dynamic QSTs is temporal summation (TS), which is used to evaluate central pain sensitization and is interpreted as reflecting ascending facilitation of nociceptive signaling.[28] TS is analogous to windup phenomenon in animals, characterized by a heightened sensitivity to pain even in areas unrelated to the original site of repeated painful stimulus.[29] To test for TS, the examiner applies a non-noxious stimulus of uniform intensity serially over time (e.g., tapping an anatomic site with a minimally painful stimulus ten times consecutively). If the subject perceives increasing levels of pain from the first to the tenth stimulus, they are said to exhibit TS.[30] Among people with knee OA, those with greater pain intensity and a longer duration of symptoms exhibit greater TS as compared to individuals with less pain and shorter duration of symptoms.[30]

A second dynamic QST is conditioned pain modulation (CPM), which evaluates endogenous descending inhibitory modulation. CPM assesses whether the perception of pain at an index site is diminished by a painful stimulus at a distant site, reflecting the concept of "pain inhibiting pain". To assess CPM, a test stimulus is first assessed. A noxious conditioning stimulus is then applied at a distant, contralateral site, and the initial test stimulus is reassessed. When CPM functions adequately, the second test stimulus results in a higher pain threshold (i.e., less pain sensitivity) than the first test stimulus.[1] When CPM is inefficient, the individual does not demonstrate a higher pain threshold despite the presence of a distant painful stimulus. For example, PPT may be assessed at the wrist or other non-involved site (e.g., trapezius) before and after a painful stimulus (e.g., ischemic pain or cold immersion) is applied to the contralateral upper extremity. Normally the pain threshold observed after stimulation at an index site (e.g., wrist) is increased (less pain sensitivity) in the presence of a painful stimulus at a distant site. This process is often impaired in people with chronic pain,[30] including persons with OA.[12] CPM has a relatively high level of accuracy. In a systematic review of 10 studies reporting test-retest reliability of CPM, 9 investigated intrasession reliability, with 78% of intrasession comparisons reporting intraclass correlation coefficients (ICCs) > 0.6. Eight studies included in this review also assessed the reliability of CPM between sessions; 4 out of 8 studies reported good (ICC>0.6) or excellent (ICC>0.75) values.[31] Direct comparison of these studies is difficult, as CPM protocols differ between studies.

Several studies of various pain conditions and among healthy adults have identified differences between males and females in response to QST. In general, women exhibit greater sensitivity to experimental noxious stimuli than men, including lower pain tolerance and threshold (heat and mechanical). They also demonstrate greater temporal summation and higher rated after-sensations after repeated mechanical stimuli.[32–36] Though much of this research does not pertain specifically to osteoarthritis, one study in particular investigated sex differences in central sensitization among participants (n=288) with symptomatic knee OA. Bartley et al. reported significantly lower PPTs for women compared to men, along with lower heat and cold pain tolerance thresholds and higher levels of TS.[36]

These differences in response to experimental pain stimuli suggest potential differences in how males and females process pain, similar to that noted in several other pain conditions.

II. Cross-Sectional associations between QST and severity of symptoms and structural damage

QST may identify individuals who experience pain due in part to sensitization. It is reasonable to hypothesize that persons with chronic pain conditions, like OA, have more abnormalities on QST than persons without chronic pain conditions. This section summarizes prior research on differences in QST findings among persons with and without OA. These studies, summarized in Table 1, show that—as hypothesized—individuals with OA have more QST abnormalities than controls, supporting the discriminant validity of QST.

Pain Pressure Threshold (PPT)

Persons with knee OA often display widespread reductions in PPT, indicating this test may be used to distinguish persons with symptomatic OA from controls, people without OA and without pain.[8, 10, 16, 37–41] Multiple studies have reported that subjects diagnosed with knee OA exhibited significantly lower PPT values at sites of OA involvement and uninvolved sites compared to control subjects, suggesting hyperalgesia among subjects with OA.[16, 37] A meta-analysis of PPT values (both at the knee and sites distant from the knee) of 1,003 participants with and without knee OA reported a 0.86-standard mean difference (SMD, difference in means divided by standard deviation) in PPT between persons with OA and controls.[42] SMDs >0.8 are considered to be large.[42] However, a limitation to interpretation of these studies is that the differences between those with OA versus healthy controls could be related to presence of OA or chronic pain or both.

While most studies of PPT in persons with OA have focused on the knee, several other studies have demonstrated these same principles in persons with hip and hand OA.[43–46] Studies by Kosek and O'Driscoll report an SMD in PPT around 0.75 between persons with hip OA and healthy controls.[10] Individuals with hand OA displayed significantly lower PPTs than controls at affected joints within the hand and distally at the wrist.[43, 44, 47] Among persons with hand OA, individuals who reported higher pain severity (measured on the Numeric Rating Scale) displayed significantly lower PPTs at symptomatic (fingers and wrist) and distal (trapezius and tibialis anterior muscle) sites.[14]

Several recent papers have suggested that QST measures are more closely associated with pain severity than OA severity.[8, 24, 48] Finan et al., for example, categorized participants into one of 4 subgroups based on pain level and knee OA radiographic (KL) grade: high pain/high OA grade, low pain/high OA grade, low pain/low OA grade, and high pain/low OA grade.[8] They observed that persons in the "high pain/low OA grade" group (indicative of symptom-structure discordance) had significantly heightened pain sensitivity across numerous QST measures, including lower average PPT values at the trapezius as compared to individuals in the low pain/high OA group (i.e., less pain sensitivity).[8, 30, 42, 49–51] Persons

with high pain and low OA grade also displayed significantly higher pain catastrophizing scores than all other groups.[8]

Similarly, Neogi et al. found no association between duration and severity of radiographic and symptomatic OA and PPT.[24] They reported, however, that individuals in the lowest PPT tertile (most sensitization) had greater odds of knee pain compared to persons in the top PPT tertile (OR=2.0 at the patella (proximal site) and 1.7 at the wrist (distal site)).[24] Among individuals with knee OA, PPT values both at the knee and at distant sites have also proven to be moderately, negatively correlated with the Visual Analog Pain Scale (VAS) (r= −0.55), the Western Ontario and McMaster Universities Arthritis (WOMAC) pain scale (r= −0.589), as well as SF-36 bodily pain scores, suggesting greater pain sensitivity (lower PPT) in those reporting more severe pain.[8, 16, 52]

Taken together, these findings suggest that sensitization is associated with severity of self-reported pain rather than radiographic severity. Using QST as a tool to identify persons with OA who may be susceptible to chronic pain could allow for more targeted treatment, as individuals who display signs of sensitization might benefit from treatments targeting central and neuropathic pathways.[8, 30, 42, 49–51]

QST measures may also vary with the presence of synovitis. Neogi et al. suggest that PPT values may be associated with synovitis and/or effusion in the knee. When controlling for age, sex, radiographic severity, among other factors, persons with MRI-detected synovitis or effusion displayed significantly lower PPT values at baseline. Further, individuals with synovitis at baseline exhibited worsening PPT values over time at the patella.[53] These data suggest that individuals with effusion or synovitis may display signs of increasing pain sensitization over time and support the association between inflammation—as reflected in synovitis and effusion—and pain sensitization.

Conditioned Pain Modulation (CPM)

As noted above, most persons experience a reduction in pain at the initial test site when they are subject to a noxious stimulus at a different anatomic site; this is the essence of CPM. Inefficient CPM is sometimes present among individuals with OA and in people with chronic pain, suggesting that impaired descending inhibition may contribute to centralized pain.[1, 11, 30, 54] In a study conducted by Arendt-Nielsen et al., subjects with knee OA had inefficient CPM in the peripatellar region, whereas controls displayed efficient CPM in this region. However, individuals with knee OA *did* exhibit efficient CPM at the tibialis anterior, a control site.[11] More recently, Carlesso et al. found the presence of CPM to be associated with higher scores on the Intermittent and Constant Osteoarthritis Pain scale, indicating a greater likelihood of constant +/− intermittent pain as opposed to only intermittent pain.[55] These findings may suggest that CPM is activated in the presence of pain, and could provide new insights into the distinction between intermittent and constant pain.

Temporal Summation (TS)

TS has also been shown to distinguish OA patients from persons without OA. TS is most frequently measured by gauging an individual’s pain during the repeated application of a mechanical (often a weighted punctate probe) or thermal (often heat pulses) stimulus. An

increase in pain from the first to last stimulus indicates TS. Arendt-Nielsen reported weak to modest positive correlations between TS and 1) the severity and area of saline evoked pain (r=0.28), 2) severity of pain after walking (r=0.33), 3) duration of pain (r=0.26), and 4) peak pain levels in the past 24 hours (r=0.27).[11] These findings indicate that TS may have potential to identify individuals with hypersensitivity to pain. Furthermore, several studies have reported that subjects with more pronounced TS had more painful responses to physical activity, measured by changes in pain during activity among knee OA patients.[38, 56] Specifically, individuals who exhibited greater levels of TS before completing a 6-minute walking test reported greater discomfort over the course of their walk.[38, 56] These investigators also found more painful response to physical activity to be associated with greater OA pain, functional limitation, and pain catastrophizing.[38]

Similar to their studies of PPT, Finan and Neogi found an association between pain severity and the presence of TS, but did not observe an association between duration and severity of radiographic OA and TS.[8, 24] Individuals with TS at the patella and the wrist were more likely to experience greater knee pain (OR=1.6 (patella), OR=1.3 (wrist)) than individuals without TS.[24]

Carlesso et al. recently examined whether PPT, CPM, and TS are associated with the pattern of OA pain. They showed that lower PPTs—locally and remotely—and the presence of CPM were both associated with a greater likelihood of constant +/− intermittent pain as opposed to only intermittent pain. Similarly, lower PPTs and the presence of greater TS were associated with higher odds of unpredictable pain.[55]

III. Longitudinal associations between QST and symptomatic and structural progression and response to therapy

This section examines studies of associations between QST findings and progression of OA (radiographically, symptomatically). We also examine associations between QST results and response to therapy. Studies addressing these questions are summarized in Table 2.

QST Findings as Predictors of Treatment Response

As the preceding sections of this review have indicated, numerous studies have documented cross-sectional relationships between various quantitative sensory tests—such as PPT, CPM, and TS—and OA case status and pain severity. In contrast, few studies have examined associations between QST measures and subsequent, long-term outcomes in OA patients. In this section we ask: Can QST predict how individuals will respond to treatment over time or how their pain experience will change over time?

Carlesso et al. addressed this question by examining how QST measures (PPT, CPM, TS) may foretell the evolution of pain patterns in persons with OA. Using data from the Multicenter Osteoarthritis (MOST) Study, they identified 852 individuals who were free of persistent knee pain at baseline. These subjects were placed into one of four pain susceptibility **phenotypes** based on their demonstrated level of pain pressure sensitivity and/or facilitated temporal summation.[50] Individuals who exhibited high levels of pain pressure sensitivity *and* high temporal summation had twice the odds (OR 1.98) of

developing persistent knee pain over two years compared to individuals with normal pain pressure sensitivity and no temporal summation.[50]

Surgical Treatments

Several studies reported that individuals with QST findings indicating pain sensitization experience worse outcomes after total knee replacement. This suggests these subjects' pain may be due in part to sources other than the knee itself.[13, 15]

TS has shown some success in identifying persons who may experience less pain relief from total knee replacement surgery.[54, 57–60] Petersen et al. reported greater preoperative TS to be positively but weakly associated with greater pain intensity 12-months following TKR (Pearson Correlation r=0.2).[60] Another study by Petersen et al. reported similar findings.[58] Patients with high pain (VAS ≥ 3 at 12-months post-op) had greater facilitated TS scores pre-op compared to individuals with mild to no post-operative pain (VAS < 3 at 12-months post-op), suggesting that preoperative TS may serve as a predictor of postoperative pain. The univariate correlation coefficient was small (Spearman r = 0.240).[58] Abrecht et al. noted similar results, and additionally found preoperative TS to be associated with daily opioid use in the early post-op period.[59]

Preoperative CPM and PPT do not appear to be strong predictors of chronic pain after joint replacement surgery. One study by Wylde et al. found lower PPT values on the forearm (pre-surgery) to be strongly associated with a higher pain severity 12 months post-THR, but not with change in pain from baseline to 12 months post-THR. Further, preoperative PPTs were not associated with 12-month pain nor with change in pain severity from pre-op to 12-months post-op in TKR recipients.[61] Another study by Wylde et al. reported that individuals with higher pre-operative PPT values on the forearm (indicating less widespread hyperalgesia) experienced less severe pain post-TKR.[62] However, this relationship was weak, and other studies have not found meaningful correlations between pre-op PPTs and post-op pain severity.[46, 59] Other studies suggest neither TS nor CPM alone can predict post-operative pain relief, but when the combination of abnormal CPM and TS results are considered together, they may identify persons who are less likely to experience pain relief post-TKR.[54] More research is necessary to determine whether PPT and CPM can offer insight into surgical outcomes.

Response of QST Measures to Surgical Treatment

Several studies have found that in patients for whom joint replacement surgery is successful, CPM and PPT may normalize after surgery.[57, 58, 63, 64] Kosek et al. found that while hip OA patients exhibited lower PPTs and impaired CPM pre-surgery, post-THR PPT values were comparable to those of controls and CPM demonstrated 'normalization' (i.e., were now efficient). However, all patients had substantial improvements in pain after surgery.[57] Graven-Nielsen et al. found similar results in knee OA patients who underwent TKR.[65]

In addition to their small sample size, a limitation of these studies is that all participants reported improvements in pain post-surgery, so it is unclear whether CPM remains inefficient for patients who do not have pain relief post-TKR. Petersen et al. address this by comparing pre-operative QST measures and post-operative pain relief. Compared to pre-

operative values, persons with a maximum pain intensity <3 on the VAS scale post-surgery showed significantly higher PPTs at proximal and distal sites in *both* knees 12 months post-TKR. This indicates that pain PPTs may normalize in persons who experience pain relief post-TKR. These individuals also had efficient CPM both pre- and post-operatively.[58] Interestingly, the high-pain cohort, defined as persons with a peak VAS score ≥3 at 12 months post-surgery, demonstrated neither normalization of PPT nor CPM after TKR.[58] Given the small size of these studies, there is insufficient evidence to determine whether the normalization of QST measures is associated with pain improvement, or, similarly, whether lack of normalization is related to persistent pain.

Non-surgical Treatments

QST testing may serve to identify individuals who respond to non-surgical OA treatments such as physiotherapy and NSAID use. O'Leary et al. reported that greater pain sensitization pre-treatment is associated with nonresponse after physiotherapy.[22] In this study, participants—each of whom had been diagnosed with moderate to severe symptomatic, radiographic OA—underwent a baseline QST evaluation involving PPT, TS, CPM, VPT, and thermal hyperalgesia before completing a physiotherapy regimen.[22] Upon completion of the regimen, and again at 6 months follow-up, participants were classified either as "responders" or "nonresponders" according to OMERACT-OARSI responder criteria. O'Leary et al. found higher pre-treatment TS values and lower PPT values to be significant risk factors for nonresponse.[22]

Finally, some evidence suggests that QST testing may identify patients for whom NSAIDs may not be effective. Petersen et al. studied 132 participants with painful knee OA treated with ibuprofen, paracetamol, and pantoprazole for three weeks.[66] Nonresponders (individuals who did *not* achieve 50% pain relief from treatment), showed significantly higher levels of pain and facilitated TS before treatment as compared to responders (those with ≥ 50% pain relief). These data suggest that pre-treatment TS may serve as a predictor of response to analgesic agents.[66] A second study by Arendt-Nielsen et al. found that persons receiving etoricoxib (a COX-2 inhibitor) had, on average, greater improvement than placebo-treated groups in WOMAC pain, function, and stiffness scores.[67] Further, the investigators documented significantly greater increase in PPT and reduction in TS in the etoricoxib group than in the placebo group. The study design does not permit analysis of whether the effect of etoricoxib on normalizing QST measures is mediated by pain relief or whether it may be a direct effect of the medication.

IV. Summary and role of QST moving forward

In summary, studies to date confirm that QST can distinguish OA patients from controls. Specifically, persons with OA may exhibit lower PPT values and less efficient CPM. More importantly, recent studies suggest abnormalities in PPT and TS among persons with symptomatic OA are likely driven by pain rather than radiographic severity. Facilitated TS may help to identify individuals who are more prone to chronic pain, and who are less likely to respond to a range of medical and surgical therapies. The finding that individuals without knee pain who demonstrated low PPT and moderate TS were twice as likely to develop

persistent pain in the future[50] indicates that sensitization may be an inherent trait rather than a state induced by OA, as these individuals displayed signs of sensitization before they had developed persistent knee pain. These observations suggest that QST could potentially be used to offer a personalized and more effective treatment strategy to reduce pain associated with OA.

Funding sources:

This work was supported by NIH grants-P30AR072577, R21AR076156, K24 AR070892, R01AG066010. The funding sources played no role in the publication of this work.

References

1. Edwards RR, Dworkin RH, Turk DC, Angst MS, Dionne R, Freeman R, et al. Patient phenotyping in clinical trials of chronic pain treatments: IMMPACT recommendations. Pain 2016; 157: 1851–1871. doi: 10.1097/j.pain.0000000000000602. [PubMed: 27152687]
2. Hawker G Osteoarthritis: a serious disease Osteoarthris Research Society International 2016.
3. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015; 386: 743–800. doi: 10.1016/s0140-6736(15)60692-4. [PubMed: 26063472]
4. Barbour KE, Helmick CG, Boring M, Brady TJ. Vital Signs: Prevalence of Doctor-Diagnosed Arthritis and Arthritis-Attributable Activity Limitation - United States, 2013–2015. MMWR Morb Mortal Wkly Rep 2017; 66: 246–253. doi: 10.15585/mmwr.mm6609e1. [PubMed: 28278145]
5. Disease GBD, Injury I, Prevalence C. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet (London, England) 2018; 392: 1789–1858. doi: 10.1016/S0140-6736(18)32279-7.
6. Bannuru RR, Osani MC, Vaysbrot EE, Arden NK, Bennell K, Bierma-Zeinstra SMA, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis Cartilage 2019; 27: 1578–1589. doi: 10.1016/j.joca.2019.06.011. [PubMed: 31278997]
7. Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Care Res (Hoboken) 2020; 72: 149–162. doi: 10.1002/acr.24131. [PubMed: 31908149]
8. Finan PH, Buenaver LF, Bounds SC, Hussain S, Park RJ, Haque UJ, et al. Discordance between pain and radiographic severity in knee osteoarthritis: findings from quantitative sensory testing of central sensitization. Arthritis Rheum 2013; 65: 363–372. doi: 10.1002/art.34646. [PubMed: 22961435]
9. Pain IAftSo. IASP Terminology In: Bogduk HMaN Ed.
10. Suokas AK, Walsh DA, McWilliams DF, Condon L, Moreton B, Wylde V, et al. Quantitative sensory testing in painful osteoarthritis: a systematic review and meta-analysis. Osteoarthritis Cartilage 2012; 20: 1075–1085. doi: 10.1016/j.joca.2012.06.009. [PubMed: 22796624]
11. Arendt-Nielsen L, Nie H, Laursen MB, Laursen BS, Madeleine P, Simonsen OH, et al. Sensitization in patients with painful knee osteoarthritis. Pain 2010; 149: 573–581. doi: S0304–3959(10)00209–5 [pii] 10.1016/j.pain.2010.04.003. [PubMed: 20418016]
12. Arendt-Nielsen L, Fernández-de-Las-Peñas C, Graven-Nielsen T. Basic aspects of musculoskeletal pain: from acute to chronic pain. J Man Manip Ther 2011; 19: 186–193. doi: 10.1179/106698111×13129729551903. [PubMed: 23115471]
13. Soni A, Wanigasekera V, Mezue M, Cooper C, Javaid MK, Price AJ, et al. Central Sensitization in Knee Osteoarthritis: Relating Presurgical Brainstem Neuroimaging and PainDETECT-Based

Patient Stratification to Arthroplasty Outcome. Arthritis Rheumatol 2019; 71: 550–560. doi: 10.1002/art.40749. [PubMed: 30295432]

14. Steen Pettersen P, Neogi T, Magnusson K, Berner Hammer H, Uhlig T, Kvien TK, et al. Peripheral and Central Sensitization of Pain in Individuals With Hand Osteoarthritis and Associations With Self-Reported Pain Severity. Arthritis & Rheumatology 2019; 71: 1070–1077. doi: 10.1002/art.40850. [PubMed: 30741501]
15. Kim MS, Koh IJ, Sohn S, Kang BM, Kwak DH, In Y. Central Sensitization Is a Risk Factor for Persistent Postoperative Pain and Dissatisfaction in Patients Undergoing Revision Total Knee Arthroplasty. J Arthroplasty 2019; 34: 1740–1748. doi: 10.1016/j.arth.2019.03.042. [PubMed: 30992238]
16. Kavchak AJ, Fernández-de-Las-Peñas C, Rubin LH, Arendt-Nielsen L, Chmell SJ, Durr RK, et al. Association between altered somatosensation, pain, and knee stability in patients with severe knee osteoarthrosis. Clin J Pain 2012; 28: 589–594. doi: 10.1097/AJP.0b013e31823ae18f. [PubMed: 22146110]
17. Uddin Z, MacDermid JC. Quantitative Sensory Testing in Chronic Musculoskeletal Pain. Pain Med 2016; 17: 1694–1703. doi: 10.1093/pm/pnv105. [PubMed: 26893116]
18. Gruener G, Dyck PJ. Quantitative sensory testing: methodology, applications, and future directions. J Clin Neurophysiol 1994; 11: 568–583. doi: [PubMed: 7860720]
19. Wylde V, Palmer S, Learmonth ID, Dieppe P. Test-retest reliability of Quantitative Sensory Testing in knee osteoarthritis and healthy participants. Osteoarthritis Cartilage 2011; 19: 655–658. doi: 10.1016/j.joca.2011.02.009. [PubMed: 21329759]
20. Mutlu EK, Ozdincler AR. Reliability and responsiveness of algometry for measuring pressure pain threshold in patients with knee osteoarthritis. J Phys Ther Sci 2015; 27: 1961–1965. doi: 10.1589/jpts.27.1961. [PubMed: 26180358]
21. Wessel J The reliability and validity of pain threshold measurements in osteoarthritis of the knee. Scand J Rheumatol 1995; 24: 238–242. doi: [PubMed: 7481589]
22. O'Leary H, Smart KM, Moloney NA, Blake C, Doody CM. Pain sensitization associated with nonresponse after physiotherapy in people with knee osteoarthritis. Pain 2018; 159: 1877–1886. doi: 10.1097/j.pain.0000000000001288. [PubMed: 29794610]
23. Dua AB, Neogi T, Mikolaitis RA, Block JA, Shakoor N. Somatosensation in OA: exploring the relationships of pain sensitization, vibratory perception and spontaneous pain. BMC musculoskeletal disorders 2018; 19: 307–307. doi: 10.1186/s12891-018-2206-4. [PubMed: 30144797]
24. Neogi T, Frey-Law L, Scholz J, Niu J, Arendt-Nielsen L, Woolf C, et al. Sensitivity and sensitisation in relation to pain severity in knee osteoarthritis: trait or state? Annals of the Rheumatic Diseases 2015; 74: 682. doi: 10.1136/annrheumdis-2013-204191. [PubMed: 24351516]
25. Martin CL, Waberski BH, Pop-Busui R, Cleary PA, Catton S, Albers JW, et al. Vibration perception threshold as a measure of distal symmetrical peripheral neuropathy in type 1 diabetes: results from the DCCT/EDIC study. Diabetes Care 2010; 33: 2635–2641. doi: 10.2337/dc10-0616. [PubMed: 20833868]
26. Shakoor N, Agrawal A, Block JA. Reduced lower extremity vibratory perception in osteoarthritis of the knee. Arthritis and rheumatism 2008; 59: 117–121. doi: 10.1002/art.23241. [PubMed: 18163397]
27. Shakoor N, Lee KJ, Fogg LF, Block JA. Generalized vibratory deficits in osteoarthritis of the hip. Arthritis and rheumatism 2008; 59: 1237–1240. doi: 10.1002/art.24004. [PubMed: 18759259]
28. Mackey IG, Dixon EA, Johnson K, Kong JT. Dynamic Quantitative Sensory Testing to Characterize Central Pain Processing. J Vis Exp 2017. doi: 10.3791/54452.
29. Staud R, Robinson ME, Price DD. Temporal summation of second pain and its maintenance are useful for characterizing widespread central sensitization of fibromyalgia patients. The journal of pain 2007; 8: 893–901. doi: 10.1016/j.jpain.2007.06.006. [PubMed: 17681887]
30. Skou ST, Graven-Nielsen T, Rasmussen S, Simonsen OH, Laursen MB, Arendt-Nielsen L. Widespread sensitization in patients with chronic pain after revision total knee arthroplasty. Pain 2013; 154: 1588–1594. doi: 10.1016/j.pain.2013.04.033. [PubMed: 23707268]

31. Kennedy DL, Kemp HI, Ridout D, Yarnitsky D, Rice AS. Reliability of conditioned pain modulation: a systematic review. Pain 2016; 157: 2410–2419. doi: 10.1097/j.pain.0000000000000689. [PubMed: 27559835]
32. Costa YM, de Araújo-Júnior ENS, Fiedler LS, de Souza PRJ, Silva L, Ferreira D, et al. Reproducibility of quantitative sensory testing applied to musculoskeletal orofacial region: Site and sex differences. Eur J Pain 2019; 23: 81–90. doi: 10.1002/ejp.1287. [PubMed: 29989267]
33. Meints SM, Wang V, Edwards RR. Sex and Race Differences in Pain Sensitization among Patients with Chronic Low Back Pain. J Pain 2018; 19: 1461–1470. doi: 10.1016/j.jpain.2018.07.001. [PubMed: 30025944]
34. Fillingim RB, Maixner W, Kincaid S, Silva S. Sex differences in temporal summation but not sensory-discriminative processing of thermal pain. Pain 1998; 75: 121–127. doi: 10.1016/s0304-3959(97)00214-5. [PubMed: 9539681]
35. Sarlani E, Grace EG, Reynolds MA, Greenspan JD. Sex differences in temporal summation of pain and aftersensations following repetitive noxious mechanical stimulation. Pain 2004; 109: 115–123. doi: 10.1016/j.pain.2004.01.019. [PubMed: 15082133]
36. Bartley EJ, King CD, Sibille KT, Cruz-Almeida Y, Riley JL 3rd, Glover TL, et al. Enhanced Pain Sensitivity Among Individuals With Symptomatic Knee Osteoarthritis: Potential Sex Differences in Central Sensitization. Arthritis Care Res (Hoboken) 2016; 68: 472–480. doi: 10.1002/acr.22712. [PubMed: 26434740]
37. Lee YC, Lu B, Bathon JM, Haythornthwaite JA, Smith MT, Page GG, et al. Pain sensitivity and pain reactivity in osteoarthritis. Arthritis Care Res (Hoboken) 2011; 63: 320–327. doi: 10.1002/acr.20373. [PubMed: 20957660]
38. Wideman TH, Finan PH, Edwards RR, Quartana PJ, Buenaver LF, Haythornthwaite JA, et al. Increased sensitivity to physical activity among individuals with knee osteoarthritis: relation to pain outcomes, psychological factors, and responses to quantitative sensory testing. Pain 2014; 155: 703–711. doi: 10.1016/j.pain.2013.12.028. [PubMed: 24378879]
39. Jaber K, O'Leary S, Pedler A, Sterling M, McAuliffe M. Evidence of Generalised Mechanical Hyperalgesia in Patients with Advanced Knee Osteoarthritis Undergoing Total Knee Arthroplasty The Knee 2018; 25: 459–465. doi: 10.1016/j.knee.2018.03.002. [PubMed: 29685500]
40. Wright A, Benson HAE, Will R, Moss P. Cold Pain Threshold Identifies a Subgroup of Individuals With Knee Osteoarthritis That Present With Multimodality Hyperalgesia and Elevated Pain Levels. Clin J Pain 2017; 33: 793–803. doi: 10.1097/ajp.0000000000000458. [PubMed: 27898461]
41. Rakel B, Vance C, Zimmerman MB, Petsas-Blodgett N, Amendola A, Sluka K. Mechanical Hyperalgesia and Reduced Quality of Life Occur in People With Mild Knee Osteoarthritis Pain. The Clinical journal of pain 2014; 31. doi: 10.1097/AJP.0000000000000116.
42. Fingleton C, Smart K, Moloney N, Fullen BM, Doody C. Pain sensitization in people with knee osteoarthritis: a systematic review and meta-analysis. Osteoarthritis and Cartilage 2015; 23: 1043–1056. doi: 10.1016/j.joca.2015.02.163. [PubMed: 25749012]
43. Wajed J, Ejindu V, Heron C, Hermansson M, Kiely P, Sofat N. Quantitative sensory testing in painful hand osteoarthritis demonstrates features of peripheral sensitisation. International journal of rheumatology 2012; 2012: 703138–703138. doi: 10.1155/2012/703138. [PubMed: 23209475]
44. Chiarotto A, Fernandez-de-Las-Peñas C, Castaldo M, Villafañe JH. Bilateral pressure pain hypersensitivity over the hand as potential sign of sensitization mechanisms in individuals with thumb carpometacarpal osteoarthritis. Pain Med 2013; 14: 1585–1592. doi: 10.1111/pme.12179. [PubMed: 23802919]
45. Kuni B, Wang H, Rickert M, Ewerbeck V, Schiltenwolf M. Pain threshold correlates with functional scores in osteoarthritis patients. Acta orthopaedica 2015; 86: 215–219. doi: 10.3109/17453674.2014.973343. [PubMed: 25323797]
46. Izumi M, Petersen K, Laursen M, Arendt-Nielsen L, Graven-Nielsen T. Facilitated temporal summation of pain correlates with clinical pain intensity after hip arthroplasty. PAIN 2016; 158: 1. doi: 10.1097/j.pain.0000000000000764.
47. Steen Pettersen P, Neogi T, Magnusson K, Berner Hammer H, Uhlig T, Kvien TK, et al. Peripheral and Central Sensitization of Pain in Individuals With Hand Osteoarthritis and Associations With

Self-Reported Pain Severity. Arthritis Rheumatol 2019; 71: 1070–1077. doi: 10.1002/art.40850. [PubMed: 30741501]

48. Arendt-Nielsen L, Egsgaard LL, Petersen KK, Eskehave TN, Graven-Nielsen T, Hoeck HC, et al. A mechanism-based pain sensitivity index to characterize knee osteoarthritis patients with different disease stages and pain levels. Eur J Pain 2015; 19: 1406–1417. doi: 10.1002/ejp.651. [PubMed: 25545011]
49. Moss P, Benson HAE, Will R, Wright A. Patients With Knee Osteoarthritis Who Score Highly on the PainDETECT Questionnaire Present With Multimodality Hyperalgesia, Increased Pain, and Impaired Physical Function. Clin J Pain 2018; 34: 15–21. doi: 10.1097/ajp.0000000000000504. [PubMed: 28379872]
50. Carlesso LC, Segal NA, Frey-Law L, Zhang Y, Na L, Nevitt M, et al. Pain Susceptibility Phenotypes in Those Free of Knee Pain With or at Risk of Knee Osteoarthritis: The Multicenter Osteoarthritis Study. Arthritis & Rheumatology 2019; 71: 542–549. doi: 10.1002/art.40752. [PubMed: 30307131]
51. Arendt-Nielsen L, Eskehave TN, Egsgaard LL, Petersen KK, Graven-Nielsen T, Hoeck HC, et al. Association between experimental pain biomarkers and serologic markers in patients with different degrees of painful knee osteoarthritis. Arthritis Rheumatol 2014; 66: 3317–3326. doi: 10.1002/art.38856. [PubMed: 25168637]
52. Imamura M, Imamura ST, Kaziyama HH, Targino RA, Hsing WT, de Souza LP, et al. Impact of nervous system hyperalgesia on pain, disability, and quality of life in patients with knee osteoarthritis: a controlled analysis. Arthritis Rheum 2008; 59: 1424–1431. doi: 10.1002/art.24120. [PubMed: 18821657]
53. Neogi T, Guermazi A, Roemer F, Nevitt MC, Scholz J, Arendt-Nielsen L, et al. Association of Joint Inflammation With Pain Sensitization in Knee Osteoarthritis: The Multicenter Osteoarthritis Study. Arthritis Rheumatol 2016; 68: 654–661. doi: 10.1002/art.39488. [PubMed: 26554395]
54. Petersen KK, Graven-Nielsen T, Simonsen O, Laursen MB, Arendt-Nielsen L. Preoperative pain mechanisms assessed by cuff algometry are associated with chronic postoperative pain relief after total knee replacement. Pain 2016; 157: 1400–1406. doi: 10.1097/j.pain.0000000000000531. [PubMed: 27331347]
55. Carlesso LC, Hawker GA, Torner J, Lewis CE, Nevitt M, Neogi T, et al. Association of intermittent and constant knee pain patterns with knee pain severity, radiographic knee osteoarthritis duration and severity. Arthritis Care Res (Hoboken) 2020. doi: 10.1002/acr.24194.
56. Miller L, Ohlman T, Naugle KM. Sensitivity to Physical Activity Predicts Daily Activity Among Pain-Free Older Adults. Pain Med 2018; 19: 1683–1692. doi: 10.1093/pm/pnx251. [PubMed: 29036332]
57. Kosek E, Ordeberg G. Lack of pressure pain modulation by heterotopic noxious conditioning stimulation in patients with painful osteoarthritis before, but not following, surgical pain relief. PAIN 2000; 88. doi:
58. Petersen KK, Arendt-Nielsen L, Simonsen O, Wilder-Smith O, Laursen MB. Presurgical assessment of temporal summation of pain predicts the development of chronic postoperative pain 12 months after total knee replacement. Pain 2015; 156: 55–61. doi: 10.1016/j.pain.0000000000000022. [PubMed: 25599301]
59. Abrecht CR, Cornelius M, Wu A, Jamison RN, Janfaza D, Urman RD, et al. Prediction of Pain and Opioid Utilization in the Perioperative Period in Patients Undergoing Primary Knee Arthroplasty: Psychophysical and Psychosocial Factors. Pain Med 2019; 20: 161–171. doi: 10.1093/pm/pny020. [PubMed: 29522115]
60. Petersen KK, Simonsen O, Laursen MB, Arendt-Nielsen L. The Role of Preoperative Radiologic Severity, Sensory Testing, and Temporal Summation on Chronic Postoperative Pain Following Total Knee Arthroplasty. The Clinical Journal of Pain 2018; 34. doi:
61. Wylde V, Sayers A, Lenguerrand E, Gooberman-Hill R, Pyke M, Beswick AD, et al. Preoperative widespread pain sensitization and chronic pain after hip and knee replacement: a cohort analysis. Pain 2015; 156: 47–54. doi: 10.1016/j.pain.0000000000000002. [PubMed: 25599300]
62. Wylde V, Palmer S, Learmonth ID, Dieppe P. The association between pre-operative pain sensitisation and chronic pain after knee replacement: an exploratory study. Osteoarthritis Cartilage 2013; 21: 1253–1256. doi: 10.1016/j.joca.2013.05.008. [PubMed: 23973138]

63. Kurien T, Arendt-Nielsen L, Petersen KK, Graven-Nielsen T, Scammell BE. Preoperative Neuropathic Pain-like Symptoms and Central Pain Mechanisms in Knee Osteoarthritis Predicts Poor Outcome 6 Months After Total Knee Replacement Surgery. J Pain 2018; 19: 1329–1341. doi: 10.1016/j.jpain.2018.05.011. [PubMed: 29920331]

64. Lluch E, Dueñas L, Falla D, Baert I, Meeus M, Sánchez-Frutos J, et al. Preoperative Pain Neuroscience Education Combined With Knee Joint Mobilization for Knee Osteoarthritis: A Randomized Controlled Trial. Clin J Pain 2018; 34: 44–52. doi: 10.1097/ajp.0000000000000511. [PubMed: 28514231]

65. Graven-Nielsen T, Wodehouse T, Langford RM, Arendt-Nielsen L, Kidd BL. Normalization of widespread hyperesthesia and facilitated spatial summation of deep-tissue pain in knee osteoarthritis patients after knee replacement. Arthritis & Rheumatism 2012; 64: 2907–2916. doi: 10.1002/art.34466. [PubMed: 22421811]

66. Petersen KK, Olesen AE, Simonsen O, Arendt-Nielsen L. Mechanistic pain profiling as a tool to predict the efficacy of 3-week nonsteroidal anti-inflammatory drugs plus paracetamol in patients with painful knee osteoarthritis. Pain 2019; 160: 486–492. doi: 10.1097/j.pain.0000000000001427. [PubMed: 30371559]

67. Arendt-Nielsen L, Egsgaard LL, Petersen KK. Evidence for a central mode of action for etoricoxib (COX-2 inhibitor) in patients with painful knee osteoarthritis. Pain 2016; 157: 1634–1644. doi: 10.1097/j.pain.0000000000000562. [PubMed: 27007068]

Table 1:

Literature summaries of manuscripts addressing cross sectional associations between QST and OA

CROSS SECTIONAL			
OA patients v. healthy controls			
Source	**Test Used**	**Sample**	**Findings**
Arendt-Nielsen; 2010	PPT, CPM, TS	48 subjects with knee OA who were divided into 2 age-and sex-matched groups according to peak pain intensity (VAS ≥ 6 versus VAS <6) and 24 age- and sex-matched controls with no knee pain in the past year	• Lower mean PPT (pooled from 8 sites around the knee) was correlated with higher VAS pain ratings (r=0.24^) • Significant correlation between PPT at distal sites and VAS scores – Tibialis anterior: r = −0.36 – Extensor carpi radialis longus: r= −0.32 • More pain as demonstrated by lower PPTs indicates more localized and diffuse hyperalgesia • All groups showed effective CPM at tibialis anterior control site; control site showed significantly higher PPT values during cuff stimulation versus baseline (~ 100 kPa increase in PPT) • High pain OA group and control group showed efficient CPM at forearm control site, but the low pain OA group did not • Positive correlation between TS and saline evoked pain (r=0.28^), pain after walking (r=0.33^, pain duration (r=0.26^), and peak pain in the past 24h (r=0.27^) ** ^ indicates significant result
Dua, 2018	VPT, PPT, allodynia	42 persons with moderate to severe OA and 12 controls without OA	• Mechanical allodynia was significantly more common in persons with OA versus controls (54.8% versus 16.6% at index knee, 42.9% v. 0% at contralateral knee) • Persons with increased sensitivity to vibration had lower PPTs and presence of allodynia – Correlation between VPT at several sites and PPT on medial index joint line: ♦ VPT (index knee, medial) Spearman r= .389, p =.01 ♦ VPT (index knee, lateral) Spearman r=.405, p=.008 – VPT (ipsilateral ankle, medial) Spearman r=.476, p=.001
Fingleton, 2015	PPT, CPM, TS	Meta-analysis of 8 studies that compared PPT in healthy individuals to controls (n=1003). **Included from this table:** Arendt-Nielsen 2010, Lee 2011, Kavchak 2012, Skou 2013, Wylde 2013 (Table 2), Neogi 2015	• Point estimates for SMD in PPT – Using average of one local and one remote testing site: −0.86; – Using only local sites: −0.97 – Using only remote sites: −0.74 * Negative values indicate greater sensitivity in OA group, 0.8-point estimate is considered large, 0.5 = medium • Dysfunctional CPM at local sites in knee OA v. controls – Greater TS facilitation at knee (local) and forearm (remote) between OA and controls
Imamura, 2008	PPT	62 female patients with symptomatic, radiographic knee OA and 22 age-matched controls	Individuals underwent PPT testing on the lower extremities and the spine • Lower PPT values were moderately correlated with: – Higher pain intensity (WOMAC pain); r =−0.589, (PPT done at patellar tendon)

CROSS SECTIONAL			
OA patients v. healthy controls			
Source	**Test Used**	**Sample**	**Findings**
			– Higher functional limitation scores (WOMAC physical activity); r= −0.571, (PPT done at peroneus longus) – Poorer QoL values (SF-36 bodily pain); r= 0.569 (PPT done at adductor longus)
Jaber, 2018	CPT, PPT	30 patients with KOA about to undergo TKR and 30 healthy controls	• Mean PPT values were significantly reduced in knee OA group versus controls; no significant differences between index and contralateral knee in knee OA patients – Mean PPT (SD) for OA patients and controls: ♦ Operative knee medial: 314.19 kPa (181.75) ♦ Non-operative knee medial: 366.51 (204.02) ♦ Left knee medial control: 590.4 (226.26) ♦ Right knee medial control: 613.46 (247.50) No significant differences in CPT between groups
Kavchak; 2012	PPT, VPT MDT	16 patients diagnosed with OA KL ≥2 and 16 age-matched controls	Individuals underwent QST testing before performing a step-up-and-over task • PPTs were significantly lower at the medial joint line in OA patients v. controls (p=0.03) – PPT knee OA: 17.21 kPa (16.12)*; – PPT controls: 31.53 kPa (16.12) • VPT^{+} significantly increased at medial knee in OA group – VPT knee OA: 30.18$^{\wedge}$ (8.54) – VPT controls: 19.18$^{\wedge}$ (7.00) * mean values are followed by SD in parentheses $^{\wedge}$ in biothesiometer units
Kuni, 2015	PPT	50 patients with knee OA and 49 patients with hip OA, scheduled for joint replacement + 15 controls	• Median PPT values lower in knee OA patients v. controls (4.0 versus 7.8 on a scale of 0–10 for the affected knee) Median PPT values lower in hip OA patients v. controls (4.5 v. 6.8 on a scale of 0–10 for the affected hip)
Lee; 2011	PPT; heat pain ratings	26 patients with clinically diagnosed OA and 33 age- and sex-matched controls	• OA patients had lower PPT values** at all distal and proximal sites as compared to controls – PPT knee OA leg: 511.5 (221.1) – PPT control leg: 732.2 (307.3); p=0.003 – PPT knee OA trapezius: 342.3 (132.6) – PPT control trapezius: 501.7 (220.5);p=0.001 **all measurements in kPa • Lower PPT values were associated with higher log CRP levels (F value for association between baseline leg PPT and log CRP = 8.13, p=.009) • Inflammation may be a key source of pain in OA patients; PPT may indicate greater levels of inflammation
Rakel, 2015	PPT, punctate pain intensity (PPI), heat pain	75 persons with knee OA and 25 age- and sex-matched controls	• Persons with OA had significantly lower PPT values in index knee (248 ± 12.9 kPa) versus control (322±22.5) but not in contralateral knee • PPI significantly higher (indicating greater sensitivity) in persons with knee OA (7.45 ± 1.07 at index knee; 6.17±0.91 at anterior tibialis)

CROSS SECTIONAL			
OA patients v. healthy controls			
Source	**Test Used**	**Sample**	**Findings**
	tolerance, heat pain threshold		versus controls (2.88 ± 0.81 at index knee, 2.22 ±0.67 at anterior tibialis) *measured on a VAS scale 0–10 cm
Skou; 2013	PPT, CPM, TS	40 individuals who had undergone TKA followed by revision TKA (20 with pain in revised knee (chronic pain), 20 without)	• PPTs significantly lower in group with pain after revision TKA v. group without pain after revision TKA (10 kPa v. 15 kPa) • Impaired CPM in chronic pain group; CPM functioned properly in individuals without pain after revision TKA
Suokas; 2012	PPT	Meta-analysis; 2281 participants; 41 studies included. **Included from this table:** Arendt-Nielsen 2010, Imamura 2008, Kosek 2000, & Lee 2011.	• PPT can differentiate between OA patients and controls, with OA patients having lower PPTs – Standard mean differences (SMD) for PPT between OA patients and controls: ♦ Affected joint: −1.24 (−1.54, −0.93) ♦ Distal site: −1.22 (−2.69, 0.26) ♦ Remote site: −0.88 (−1.11, −0.65) **Distal indicates below affected joint; remote indicates site above/contralateral to affected joint; negative sign indicates lower PPT in OA
Wright, 2017	PPT, cold pain threshold (CPT), heat pain threshold, warm detection threshold	80 patients with knee OA and 40 healthy controls underwent QST	• Persons with OA had lower mean PPT than controls at index knee; no significant results at the contralateral knee or elbow • PPT was significantly lower in OA and control groups at index knee: – OA group: 240 kPa v. normal group: 320 kPa • CPT significantly higher in OA group v. control at all sites (higher CPT indicates increased sensitivity) – At index knee: OA group had CPT of 14°C versus 2°C for controls – At contralateral knee: OA group had CPT of 5°C versus 1°C for controls – At ipsilateral elbow over extensor carpi radialis brevis muscle: OA group had CPT of 7°C versus 1°C for controls
Distinguishing Among Individuals with OA			
Arendt-Nielsen; 2010	PPT, CPM, TS	48 subjects with knee OA who were divided into 2 age-and sex-matched groups according to peak pain intensity (VAS ≥ 6 versus VAS <6) and 24 age- and sex-matched controls with no knee pain in the past year	• Neither OA group (high and low pain) demonstrated efficient CPM in peripatellar region, whereas controls showed functioning CPM – Difference between PPT values at baseline and during cuff stimulation (kPa) ♦ High pain group: ~ 30 kPa ♦ Low pain group: ~10 kPa ♦ Control group: ~100 kPa
Arendt-Nielsen, 2015	PPT, TS, CPM	217 OA patients, 64 controls, persons with OA categorized into groups: low pain/low KL grade, high pain/low KL grade, high pain/high KL grade, high pain/low KL grade, where low pain was defined as 0–51 on VAS 0–100 scale and low KL grade is	• Controls had significantly higher PPT values versus OA groups • TS facilitation was higher in high pain OA groups v. low pain OA groups – Controls with VAS pain 0–9 (0–100 scale): 18.3 ± 14.2 – Knee patients with VAS 70–100: 40.2 ± 20.5 • CPM was significantly more efficient in control groups as compared with high pain OA groups

CROSS SECTIONAL			
OA patients v. healthy controls			
Source	**Test Used**	**Sample**	**Findings**
		defined as KL 0, 1, and 2	– CPM ratio* for controls with VAS pain 0–9 (0–100 scale): 576.4 ± 170.4 kPa – Knee patients with VAS 70–100: 366.8 ± 181.0 kPa) • Pain intensity was significantly correlated with PPT (r= −0.342) and CPM (r= −0.345) – *CPM ratio is the mean ratio between PPT during cuff stimulation (in kPa) and PPT at baseline
Carlesso, 2020	PPT, CPM, TS	2794 participants from the MOST study	• Higher PPTs (proximally and distally) were associated with lower odds of having constant +/− intermittent pain as compared with intermittent pain only – Proximal (patella): OR (per SD) = 0.80 (0.68, 0.93) – Distal (wrist): OR (per SD) =0.80 (0.66, 0.93) • Greater TS was associated with higher likelihood of unpredictable pain; OR= 0.96, (0.84, 1.09) • Presence of CPM was associated with greater likelihood of constant +/− intermittent pain versus intermittent pain only; OR= 1.45 (1.10, 1.92)
Finan, 2013	PPT, cold pressor test, mechanical and heat TS	113 persons with knee OA were divided into subgroups according to pain level and KL-grade; individuals had low pain if WOMAC knee pain score ≤ 4.22 (median pain score), high pain if >4.22. KL scores were split between KL grade 1–2, versus 3–4	• PPT at the quadriceps significantly correlated with anxiety and depression symptoms • TS at the finger significantly associated with pain catastrophizing and depression • High pain/low KL displayed significantly higher pain catastrophizing than all other groups; significantly greater sleep disturbance than both low pain groups; and significantly higher anxiety and depression symptoms as compared to Low pain/high KL group • High pain/low KL showed significantly higher response to mechanical TS (scale of 0–100): – High pain/low KL: 44.59 ± 33.33 – Low pain/high KL: 22.32 ± 19.90 – High pain/high KL: 37.47 ± 29.84 – Low pain/low KL: 30.54 + 30.64 • High pain/low KL group showed significantly lower PPT values at trapezius (321.07 ± 120.44 kPa) versus low pain/high KL (434.58 ± 144.76) and higher pain ratings during cold pressor test (75.68 ± 22.51; scale of 0–100) as compared to low pain/high KL group (68.8 ± 16.90)
Fingleton, 2015	PPT	Meta-analysis where 3 studies compared high and low symptom severity among knee OA patients (n=316). **Included from this table:** Lee 2011, Kavchak 2012, Skou 2013 Wylde 2013 (Table 2), Neogi 2015	• Point estimates for differences in PPT for patients with high v. low symptom severity – Using one local and one remote testing site: −0.51 (−0.73, −0.30)* – Using only local sites: −0.57 (−0.80, −0.34) – Using only remote sites: −0.48 (−0.91, −0.06) * Negative values indicate greater sensitivity in OA group, 0.8 point estimate is considered large, 0.5= medium • Greater facilitation of TS in OA patients with high symptom severity as compared to those with low symptom severity
Kavchak; 2012	PPT, VPT MDT	16 patients diagnosed with OA KL ≥2 and 16	Individuals underwent QST testing before performing a step-up-and-over task*

CROSS SECTIONAL			
OA patients v. healthy controls			
Source	**Test Used**	**Sample**	**Findings**
		age- and sex-matched controls	• PPT were significantly decreased at medial joint line (17.21 N v. 31.53 N) and distal site (14.62 N v. 27.23 N) in individuals with knee OA versus controls • Significant differences in PPT values at the medial joint line, but not at distal sites when comparing individuals with severe (KL ≥ 3) v. moderate (KL 2) radiographic changes *For the step-up-and-over task, participants were asked to step onto and over a 4- or 8-in step depending on patient stability.
Moss, 2017	PPT, cold pain threshold	130 individuals with KOA, characterized as positive or negative neuropathic based on PainDETECT score (≥19 out of 30 considered positive)	• Significantly lower PPT values for "positive neuropathic" compared to "negative neuropathic" group at the index knee (240 v. 350 kPa), contralateral knee (255 v. 390 kPa), and extensor carpi radialis brevis (ECRB) elbow (250 v. 370 kPa) • Cold Pain Thresholds were significantly higher (indicating hyper-sensitivity) for "positive neuropathic" group versus "negative neuropathic" group at the index knee (22 v. 8°C), contralateral knee (18 v. 4°C), and ECRB (19.5 v. 7°C) • Both of these QST measures indicate sensitization in "positive neuropathic" group
Neogi, 2015	PPT and TS	PPT and TS were assessed in 2126 subjects (4226 knees) from the MOST study	• PPT and TS at the patella (local) and wrist (distal) were *not* associated with radiographic OA • Persons with PPT in the lowest tertile were more likely (OR=2.0 for patella and OR=1.7 for wrist) to have greater knee pain severity compared to those in the top tertile • Persons with TS were more likely (OR=1.6 for patella, OR=1.3 for wrist) to have greater knee pain severity than those without temporal summation
Skou, 2013	PPT, CPM, TS	40 participants who had all undergone primary TKA and revision TKA due to pain post TKA. 20 participants had pain in the revised knee, 20 did not.	• Among patients with chronic knee OA, those with higher pain intensity and longer pain duration showed more temporal summation than those with less pain and a shorter duration of symptoms – "Pain" group: ♦ Mean normalized VAS score of ~3 cm by 10th stimulation – "No Pain" group: ♦ Mean normalized VAS score of ~ 1 cm by 10th stimulation ♦ CPM inhibited in "pain" group versus "no pain" group – Δ PPT from before to during CPM ♦ Pain group: −20 kPa ♦ No pain group: 100 kPa
Steen Pettersen, 2019	PPT, TS	282 participants with confirmed hand OA, underwent QST testing and NRS and AUSCAN pain scales	• Participants displayed lower PPTs at wrist and finger joints as compared to more distant locations • Individuals with lower PPTs at distant body sites (lowest PPT tertiles) reported between 0.9 and 1.6-points higher pain on NRS scale (statistically significant) • Those with facilitated TS reported an average of 1.0 points higher on NRS scale and 1.1 points higher on AUSCAN pain scale • **NRS pain scale is 0–10, AUSCAN pain scale is 0–20

CROSS SECTIONAL			
OA patients v. healthy controls			
Source	**Test Used**	**Sample**	**Findings**
Wideman; 2014	PPT, TS	107 patients over the age of 50 with chronic knee OA, with or without insomnia	Individuals underwent QST and completed self-report measures of pain and function before performing 6-minute walking test, during which patients rated pain levels • OA is associated with widespread reductions in knee PPTs (correlation between knee PPT and WOMAC pain: r = −0.191) • PPT at knee is *not* significantly related to SPA[$] (r= −0.076), but TS at knee *is* significantly correlated with SPA (r=0.305) • Performance on the 6-minute walk test was weakly correlated with PPT at the knee (r=0.226) and shoulder (r=0.204) • SPA moderately correlated to WOMAC pain (r=0.426) and WOMAC function (r =0.418)

[+]VPT = vibration detection threshold

[$]SPA= sensitivity to physical activity

[^]SMD= standard mean difference

Table 2:

Literature summaries of manuscripts addressing longitudinal associations between QST and OA

LONGITUDINAL			
OA Patients v. Healthy Controls			
Source	**Test Used**	**Sample**	**Findings**
Carlesso, 2019	TS, PPT	852 participants from the MOST study who did *not* have persistent knee pain (PKP) at baseline Categorized participants into 4 Pain Susceptibility Phenotypes (PSPs) based on TS, PPT, sleep, and psychological factors.	• Persons with a high sensitivity to PPT and moderate facilitation of TS was nearly twice as likely (OR 1.98) to develop incident PKP over two years compared to individuals with low-to no PPT sensitivity or facilitated TS.
Izumi, 2017	PPT, CPM, TS, thermal detection threshold, thermal pain threshold	40 persons with hip OA about to undergo THA and 40 asymptomatic controls; all subjects underwent QST at baseline, persons with hip OA underwent QST a second time ~6 weeks post THA	• PPTs increased after THA in patients with hip OA – PPTs increased ~ 75 kPa at each hip site on affected side between pre- and post-op – PPTs increased between 50 and 75 kPa at arm and tibialis anterior • Preoperative rest pain intensity (on VAS scale) significantly, negatively correlated with preoperative PPTs around index hip (r= −.42). • TS facilitated in hip OA patients pre-THA as compared with controls; – VAS sum of persons with OA, index hip: 22.4 cm (19.9, 24.9) – VAS sum of control subjects: 8.6 (6.5, 10.7) • TS normalized in hip OA patients who were pain-free post-THA, but not in patients who experienced pain post-THA – VAS sum of pain-free persons with OA, index hip: 11.6 (8.8, 14.4) • VAS sum of persons with OA in pain: 22.4 (17.1, 27.7)
Kurien, 2018	PPT, CPM, TS	50 patients with knee OA undergoing TKR and 22 controls; individuals with OA characterized into high and low pain groups using painDETECT survey (High pain ≥19)	• Pre-TKR: – Both high and low pain groups showed lower PPT values than controls at sites proximal to the index knee ♦ High pain group: ~ 260 kPa ♦ Low pain group ~ 420 kPa ♦ Controls: ~ 640 kPa – High pain knee OA group showed lower PPTs as compared to controls and low pain knee OA group at sites distal to index knee (tibialis anterior) ♦ High pain group: ~ 250 kPa ♦ Low pain group: ~ 425 kPa ♦ Controls: ~580 kPa – No differences in CPM observed between OA groups and controls – Persons with OA demonstrated facilitated TS as compared to controls ♦ High pain group: 2.5 cm (VAS Score, 0–10)

LONGITUDINAL			
OA Patients v. Healthy Controls			
Source	**Test Used**	**Sample**	**Findings**
			♦ Low pain group: 2 cm ♦ Controls: 1 cm • 6 months post-TKR: – PPT values at 6 mo were significantly increased from pre-TKR values for both the high and low pain OA groups at the index knee and tibialis anterior (TA). Difference between baseline and 6-month shown below: ♦ High pain, index knee: ~30 kPa increase ♦ Low pain, index knee: ~70 kPa increase ♦ High pain, TA: ~ 50 kPa ♦ Low pain, TA: ~50 kPa – Normalization of widespread hyperalgesia post-TKR in OA patients with preop nociceptive pain – No significant differences observed between persons with OA and controls when comparing TS ♦ High pain group: 1.7 cm ♦ Low pain group: 1 cm ♦ Controls: 1 cm
Distinguishing Among Individuals with OA			
QST as a Predictor to Treatment Response			
Abrecht, 2019	PPT, CPM, TS	126 patients undergoing TKR underwent preoperative QST testing; monitored for perioperative pain scores and opioid consumption	• TS is an independent predictor of perioperative pain scores (Pearson r =.342, p<.001) and daily opioid use (r=.322, p<.001) • **Here, r is based on average pain scores and opioid consumption from postoperative days 0–2
Arendt-Nielsen et al., 2016	PPT, TS, CPM	37 subjects were randomized to one of 1 treatment sequences: 60 mg/d of etoricoxib for 4 weeks followed by 4 weeks of placebo, or 4 weeks of placebo followed by 4 weeks receiving 60 mg/d of etoricoxib. Both sequences had at least a 6-day washout between treatments. QST was completed at the start of each treatment period.	• WOMAC total score and sub scores (Pain, Stiffness, Physical Function) were significantly superior for etoricoxib versus placebo • PPT assessed at the index knee and tibialis anterior increased significantly more in the etoricoxib group than in the placebo group • TS significantly decreased at the index knee and tibialis anterior for etoricoxib compared to placebo • CPM did not differ significantly between the placebo and etoricoxib groups, though descending pain inhibition did increase at the index knee, lower leg, and arm with etoricoxib but not for placebo treatment
Petersen; Graven Nielsen, 2016	PPT, PDT, CPM, TS	135 patients scheduled for TKR underwent QST testing before surgery, follow-up at 12-months post TKR Individuals were categorized into 4 groups: facilitated TS and impaired CPM, facilitated TS and normal CPM, normal TS and impaired CPM, normal TS and CPM	• Neither PPT, CPM, nor TS alone could predict postoperative pain relief • Low pressure pain detection threshold (PDT) preoperatively (indicative of greater sensitivity) was significantly associated with less postop pain relief) Pearson r= −0.216 p=0.021)

LONGITUDINAL			
OA Patients v. Healthy Controls			
Source	**Test Used**	**Sample**	**Findings**
Petersen, 2018	PPT, TS, cold detection threshold, warm detection threshold	130 participants undergoing TKR were characterized as having chronic pain or not based on pain outcomes 1-year post TKR; individuals with <30% pain reduction of pre-op pain score were deemed as having chronic pain	• 19% of patients were categorized into chronic pain group • Facilitated pre-operative TS was greater in chronic pain group (4.19 points on VAS** scale) versus normal group (3.13 points on VAS scale) • No differences in thermal thresholds between chronic and normal groups • Preoperative TS was an independent factor of pain intensity ratings 1-year post TKR **VAS scale is 0–10 points
Petersen, 2019	Pain detection (PDT), pain tolerance (PTT), and TS	132 patients with symptomatic knee OA underwent QST testing before NSAID treatment regimen (400 mg ibuprofen 3x per day, paracetamol 3x per day, pantoprazole 1x per day for 3 weeks) and were included in the final analysis; “non responders” characterized as individuals who did not report ≥ 50% pain relief after treatment	• Nonresponders showed significantly greater values of TS as compared to responders before treatment (TS of 3 points on VAS scale for nonresponders v. ~2 points for responders) • No differences were observed between groups for PDT or PTT
Wylde, 2013	**PPT, Hot pain thresholds (HPT)**	**51 patients about to undergo TKR participated in a pre-op QST session and completed a WOMAC Pain score questionnaire 1-year post-op**	• No correlation between pre-op HPTs or PPT tested at the knee and post-op WOMAC • There was a small, but significant correlation between pre-op PPT at the forearm and post-op WOMAC; patients with lower PPTs at their forearm expressed greater pain severity 1-year after surgery
Wylde, 2015	**PPT**	**322 patients undergoing THR and 316 undergoing TKR underwent PPT testing preoperatively; WOMAC was evaluated both preoperatively and 12-months post-op**	• Preoperative PPT was strongly associated with preoperative and 12-month postoperative pain in THR participants • Preoperative PPT was weakly associated with preoperative pain and not associated with postoperative pain in TKR participants
Effect of Treatment Response on QST Measures			
Neogi, 2016	PPT, TS	1,111 subjects from the Multicenter Osteoarthritis Study (MOST) underwent QST at baseline and 2 years later	• Individuals with Hoffa synovitis on MRI at baseline had significantly lower PPT values at baseline and a significant decrease in PPT values at the patella at 2 years follow-up • Effusion was significantly associated with baseline PPT and a decreased PPT at the wrist at 2 years follow-up • These data suggest that inflammation is associated with worsening in pain sensitization