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The Association of Pain Sensitization and Conditioned Pain Modulation to Pain Patterns in Knee Osteoarthritis

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Abstract

Objectives—To examine the cross-sectional association of ascending pain mechanisms (APM), implicated in pain sensitization (PS), and descending pain modulation with pain patterns and unpredictability of pain.

Methods—The Multicenter Osteoarthritis (OA) Study is a longitudinal cohort of older adults with or at risk of knee OA. Peripheral and central APM were assessed using quantitative sensory tests (QST); pressure pain thresholds (PPTs) using a handheld pressure algometer (knee/peripheral and wrist/central), temporal summation (TS) using weighted probes (wrist/central). Descending modulation was assessed by conditioned pain modulation (CPM) using PPTs and a forearm ischemia test. Pain patterns were characterized based on responses to the Intermittent and Constant OA Pain (ICOAP) questionnaire: 1) no intermittent or constant pain; 2) intermittent pain only; 3) constant pain only; and 4) combined constant and intermittent pain. A question regarding frequency assessed unpredictable pain. We assessed the association of QST measures to pain patterns using regression models with generalized estimating equations.

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Results—There were 2794 participants (mean age 63.9, BMI 29.5 kg/m^2, 57% female). Lower PS (by wrist PPT) OR = 0.80 (95% CI 0.68, 0.93) and adequate CPM, OR = 1.45 (1.10, 1.92) were associated with having constant +/− intermittent pain compared with intermittent pain only. Higher PS (by PPT and TS) was associated with higher likelihood of unpredictable pain.

Conclusions—Knee pain patterns appear to be related to peripheral +/− central facilitated APM, and descending modulatory mechanisms. These findings highlight the need for a broader approach to understanding pain mechanisms by symptomatic disease progression.

Keywords

ICOAP; intermittent and constant pain; pain sensitization; descending pain modulation

Introduction

The nature and causes of knee pain in osteoarthritis (OA) are complex and poorly understood. The contribution of facilitated ascending pain mechanisms causing pain sensitization to that complexity is becoming apparent, evidenced by its role in susceptibility to developing persistent pain (1) and association with joint inflammation (2). Altered nociceptive signalling that can impact the pain severity experienced is a complex process, comprising ascending facilitation of nociceptive signals and descending modulation that consists of facilitatory and inhibitory signals. Many questions about pain and its mechanisms in knee OA remain unanswered; for example, why is it that not everyone with knee OA progresses in severity or frequency of pain with worsening of disease? Qualitative work has suggested that with structural disease progression there is an evolution of pain whereby people experience intermittent activity-related pain in the earlier phases of the disease, constant pain as the disease progresses, and the late stage is demarcated by constant pain overlaid by more severe, often unpredictable, intermittent pain.(3) Sensitization in knee OA is known to be associated with intermittent pain that is higher in severity, particularly when evoked by movement or activity (4). However as yet, the relation of alterations in pain signalling (ascending and/or descending) to the evolution of pain becoming constant in nature is not known.

Using the Intermittent and Constant Osteoarthritis Pain scale (ICOAP), developed in response to the aforementioned qualitative work, we have recently shown that the patterns of intermittent, constant and constant +/− intermittent pain are associated with duration of disease, worsening pain severity and radiographic OA, thus supporting the qualitative work on which the scale is based.(5) In light of this evidence and our increasing understanding of altered pain signal processing, it is possible that different pain mechanisms may underlie these qualitative pain patterns and the transitions from one to another. For example, early intermittent pain may be due to peripherally-driven nociceptive input, while constant +/− intermittent pain may represent peripheral and/or central sensitization or poor descending inhibitory modulation of pain.

Pain sensitization is measured indirectly using quantitative sensory testing (QST) such as pressure pain thresholds (PPTs) or temporal summation (TS). Pressure pain thresholds when measured locally at the symptomatic knee for example, are thought to reflect primarily

peripheral sensitization. Central sensitization is commonly measured using PPTs measured at an anatomical site remote from a symptomatic joint or using temporal summation implicating the central nervous system. Conditioned pain modulation is another QST tool which measures the presence of endogenous descending pain inhibitory pathways using a "pain inhibits pain" premise(6). Therefore, the objectives of this study were to examine the association of pain sensitization (i.e., ascending facilitation) and descending pain modulation to ICOAP-defined pain patterns and the unpredictability of pain.

Methods

The Multicenter Osteoarthritis (MOST) Study is a NIH-funded longitudinal study of community dwelling adults. The study now comprises two cohorts. The original cohort was of adults between the ages of 50–79 years who had or were at risk of developing knee OA at baseline, and were recruited from Birmingham, Alabama and Iowa City, Iowa from 2003–2005. Details of the original cohort have been published elsewhere.(6) In 2016–17 a second cohort was added consisting of adults age 45–69 years at baseline from the same regions, having Kellgren Lawrence grade <=2, and either knee pain that is not reported as constant or severe, or having no knee pain. The study was approved by the institutional review boards at the University of Iowa, University of Alabama at Birmingham, University of California at San Francisco, and Boston University Medical Center (6). The current sample comprised participants who attended the 12^{th} year (original cohort) and baseline (second cohort) visits (baseline for this study) since it was the first time that conditioned pain modulation (CPM) (described below) was measured. The sample included the original cohort: n=1284 and the new cohort: n=1510.

Sensitization measures

Three commonly employed quantitative sensory tests were used to determine sensitivity of the peripheral and central nervous systems to nociceptive input. PPTs were assessed by applying an algometer (1 cm^2 rubber tip, FDIX25; Wagner) at a rate of 0.5 kg/second on the center of the patellae bilaterally and distal radioulnar joint (control site; right side unless contraindicated); PPT was defined as the point at which participants indicated the pressure first changed to slight pain(7). The PPT at each anatomic site was calculated by averaging 3 trials. Those demonstrating lower PPTs represent those with a higher degree of pressure pain sensitivity. Temporal summation (TS) is a measure of central nervous system sensitivity and was assessed using a standard set of 7 weighted probes from 8–512 Nm (University of North Carolina at Chapel Hill). Participants rated pain experienced by each probe being touched on the skin of the wrist until a pain rating of at least 4/10 was achieved. If that pain rating did not occur with any of the probes, then the highest weighted probe (#7) was used. The selected probe was applied at a rate of 1Hz for 10 seconds (i.e., 10 touches). TS was calculated as the difference in pain ratings between the end and beginning of the trial(8). Greater increases in pain ratings indicated greater TS. Conditioned pain modulation (CPM) is a means of assessing the descending pain modulatory pathways, in which a test stimulus (PPT) is assessed prior to and after a painful conditioning stimulus, a forearm ischemia test. CPM was calculated as ratio of final pain threshold and initial pain threshold (9). Presence of adequate CPM was defined as CPM ratio >1, i.e., the post-conditioning PPT was greater

than the initial PPT. PPTs were assessed at the index knee described above (mean of 3 trials). Then a blood pressure cuff was applied to the contralateral arm and the cuff 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 at the index knee was then repeated, after which the cuff was deflated.

ICOAP pain and pain patterns

The ICOAP is an 11-item measure consisting of items for two subscales, Intermittent and Constant Pain. Each respective subscale item assessed the pain severity ranging from 'none' to 'extremely' on a 5 point Likert scale, where higher scores are indicative of greater severity. The Constant pain subscale score ranges from 0–20, whereas the Intermittent pain subscale ranges from 0–24. Each are then transformed to a score out of 100. Initial psychometric testing of the scale demonstrated good validity and reliability(10). The ICOAP was obtained in a knee-specific manner, inquiring about symptom type and severity over the prior 7 days, following a previously validated method (5, 11) ICOAP pain patterns were defined as follows: 1) no intermittent or constant pain; 2) intermittent pain only (of at least 'mild' severity and with a frequency of at least 'sometimes'); 3) constant pain only (of at least 'mild' severity); and 4) a combination of constant and intermittent pain. We further qualified the occurrence of unpredictable pain using a question from the ICOAP that asks about pain that comes on without warning. Answers were dichotomized as unpredictable (i.e., 'sometimes' or 'often' responses) vs 'rarely' or 'never' responses.

Confounding variables

Potential confounders included age, sex, body mass index (BMI), depressive symptoms, pain catastrophizing, study site, and race at the 144-month visit. BMI was calculated from measurements for weight and height taken by a trained researched assistant. The Center for Epidemiologic Studies Depression Scale (CES-D) score of 16 or greater was utilized to define presence of depressive symptoms (12). Pain catastrophizing was measured using one item from the Coping Strategies Questionnaire, which has been shown to be valid and reliable (13). Race was categorized as Caucasian vs other. In a sensitivity analysis, we additionally adjusted for pain medication use, which included opioid use, though we recognize that pain medication use may be an intermediate in the causal pathway and not necessarily a true confounder.

Analyses

We first evaluated the association of PPT, TS and CPM (exposures) to the total ICOAP scale and the two subscale totals (Constant and Intermittent pain) (outcomes) using multivariable linear regression with generalized estimating equations (GEE) to account for two knees within an individual. We then assessed the association of the measures of sensitization (exposures) to the pre-specified ICOAP pain patterns (e.g. Constant +/− intermittent pain vs. intermittent pain only) and presence of unpredictable pain (outcomes) using logistic regression with GEE. We hypothesized that evidence of pain sensitization would be associated with pain patterns indicative of later stages of the pain experience in OA, specifically constant pain with, or without, intermittent pain compared to intermittent pain only. To facilitate interpretation of comparative metrics, the effect estimates were computed

per one standard deviation unit of change for PPT and TS. All models were adjusted for age, sex, BMI, depressive symptoms, pain catastrophizing, clinic site and race. As our main model was based on a minimum of 'mild' severity of either intermittent or constant pain, we conducted a sensitivity analysis to assess the impact of having more severe pain. We therefore employed a model using at least 'moderately' as the indicator of intermittent and constant pain intensity to assess the association of the measures of sensitization (exposures) to the pre-specified ICOAP pain patterns (e.g. Constant +/− intermittent pain vs. intermittent pain only) and presence of unpredictable pain (outcomes) using logistic regression with GEE. Lastly we conducted a second sensitivity analysis that added pain medications as a potential confounder to the original model. All analyses were performed using SAS 9.4 (SAS Institute, Gary, North Carolina, USA).

Results

For the sample of n=2794 at 144 months (i.e., the baseline for this study), the mean (SD) age was 63.9 yrs (10.6), 57% were female and mean BMI was 29.5 (5.7) kg/m^2. Mean ICOAP scores were 10.3, 2.2 and 6.6 for the intermittent and constant subscales, and the total scale respectively. The majority of knees (67%) had neither intermittent nor constant pain, 26% had intermittent pain only, and 7% had constant pain (3% with constant pain only, and 4% constant and intermittent). Unpredictable pain was experienced by 18%. (Table 1)

Quantitative sensory tests by ICOAP totals

Greater pain sensitization (i.e., more pain sensitivity) as assessed by greater TS was associated with higher ICOAP Intermittent subscale scores. Higher PPT values, indicative of less pain sensitization, at both the knee and the wrist were associated with lower Intermittent, Constant and Total ICOAP scores, with the largest coefficient seen with Intermittent pain. Those with CPM (ratio >1) were more likely to have higher Constant ICOAP scores compared to those without CPM. (Table 2)

Quantitative sensory tests by pre-specified ICOAP pain patterns derived from qualitative data

Higher PPTs locally and remotely (less pain sensitivity) were associated with lower odds of having constant +/−intermittent compared with intermittent pain only. Similarly, higher PPTs were associated with lower likelihood of having unpredictable pain occurring at least sometimes or very often compared with rarely or never. The association of greater TS with having unpredictable pain was borderline significant. Greater TS (i.e., more pain sensitivity) was also associated with higher likelihood of having unpredictable pain. The presence of adequate CPM, however, was associated with greater likelihood of having constant +/−intermittent compared with intermittent pain only (Table 3).

Sensitivity analysis—The sensitivity analysis, using a model where intermittent and constant pain severity was set at a minimum as 'moderately', demonstrated a small increase in the association of the presence of adequate CPM, OR 1.53 (95% CI 1.07, 2.19), with having constant +/−intermittent compared with intermittent pain, whereas PPT at the wrist was no longer significant OR 0.83 (0.67, 1.03), thought the effect estimate remained similar,

likely reflecting loss of precision with fewer participants meeting this definition. All other values were unchanged. (see supplementary table)

The addition of pain medications as a confounder to our original model did not change the results in any meaningful way with the exception of the association of TS with intermittent pain, OR 0.43 (−0.08, 0.93) and with unpredictable pain OR 1.07 (0.99, 1.16), both of which became non-significant.

Discussion

In light of the body of literature substantiating the role of sensitization in this population (4) and recent work validating ICOAP identified pain patterns with disease duration, pain and radiographic severity,(5) we sought to evaluate whether these ICOAP identified pain patterns were associated with different underlying pain mechanisms as assessed by commonly used QST. We found that higher levels of sensitization were associated with 1) higher ICOAP intermittent (by PPT and TS) and constant subscale values (by PPT) and total scores (by PPT); and 2) a greater likelihood of constant +/− intermittent pain compared with intermittent pain only (by PPT), and more frequent unpredictable pain (by PPT and TS). Interestingly and in contrast to our hypothesis, we found that the presence of adequate CPM, thought to be protective for the development of chronic pain (14), was also associated with higher ICOAP constant subscale scores and a higher likelihood of having constant +/− intermittent pain vs intermittent pain only.

As per our initial hypotheses, we found a stronger association between PPTs and the ICOAP intermittent subscale than for the constant subscale, however the clinical relevance of these differences is unknown. We have previously reported on the importance of PPT sensitivity to the development of persistent pain (1). These current findings provide new support for the role of PPT sensitivity in the development of constant pain (defined as pain that is there all the time) compared to intermittent pain (pain that comes and goes). However, these cross-sectional data suggests no difference in peripheral or central facilitatory input, as results were similar for PPTs tested at local (the knee) and remote (the wrist) sites, respectively, on ICOAP scores and risk of pain patterns. Conversely, TS, a phenomenon representative of windup in the central nervous system, produced a smaller increase in ICOAP pain scores (subscales and total) and this was only significant for the intermittent subscale, though this association was no longer significant once adjusted for pain medications. This may also be in part due to the inherently smaller variance observed in TS compared to PPTs. On the other hand, TS was not associated with greater risk of having constant +/− intermittent pain versus intermittent pain only, contrary to our hypothesis that TS may increase likelihood of having constant pain. These findings suggest that TS may not drive pain patterns *per se*, but rather may contribute to the pain severity experienced. Of note, the association with increased intermittent pain severity complements previous work that shows TS is associated with knee pain severity (7). Collectively these findings support the existing literature of clinical studies implicating the role of local peripheral nociceptive input as an important driver of pain in knee OA, at least initially, and contributing to the well-recognized intermittent, activity/weight-bearing related pain (15). Longitudinal analyses will be needed to confirm the strength of these relationships with intermittent and constant pain

and whether they may differ in their contribution from the peripheral or central nervous systems.

We found that those with greater ascending facilitation either peripherally (i.e., PPT at the knee) or centrally (i.e., PPT at the wrist) were more likely to have constant +/− intermittent pain compared with intermittent pain only. This is in line with evidence supporting the association of greater facilitation, regardless of origin, with widespread pain that is often constant in nature (16). Unexpectedly, we found that the presence of adequate CPM was associated with increases in the constant pain subscale total and with a greater likelihood of constant +/− intermittent pain vs intermittent pain. We had initially hypothesized that poor descending modulation would be associated with more constant pain. This is a novel finding and is contrary to prior studies reporting reduced or absent CPM in those with higher sensitization in people with knee OA (17), as well as collective evidence in the pain literature suggesting that CPM is an important factor in determining if pain becomes chronic or not (14). One potential reason for our findings is that to our knowledge we are the first to measure CPM in those with knee OA with pain defined as either intermittent or constant. For example, previous studies have sampled symptomatic people (18), with moderate or high pain severity (9), but the nature of their pain as being intermittent or constant has not been specified. It may be that defining pain in this way and trying to understand its relation with measures of pain sensitivity and modulation, as well as progression of disease severity, will shed new light on our understanding of underlying pain mechanisms. Certainly, the pathways involved in pain sensitization are distinct from descending inhibition, thus it is not necessarily surprising that our findings differed somewhat between QST measures. Others have suggested that people may be either pain inhibitors or pain facilitators and speculated that among the variability and range of CPM responses found in healthy volunteers, those in the lowest quartile maybe vulnerable to the development of chronic pain (16). On the other hand, our current study was cross-sectional, so there is a possibility of reverse causation in that individuals with chronic pain may be activating their descending inhibitory pathways as an appropriate response. That is, those with constant pain may have adequate CPM activated due to the presence of that constant pain. The results of our sensitivity analysis support this supposition, as the effect of having adequate CPM increased with increased severity of constant pain. Further longitudinal studies of endogenous modulation are needed in people with knee OA, specifically to address how endogenous modulation of pain may change with disease progression.

Finally, we found that higher ascending facilitation by PPT (locally or remotely) and TS were associated with more frequent unpredictable pain, (however this was no longer significant when adjusted for pain medications) but not so for CPM. In keeping with our finding of greater association with constant pain, it may be that intermittent pain, regardless of severity (as per our sensitivity results), whether predictable or unpredictable, is not sufficient to activate CPM. Unpredictable pain has been rarely studied in people with knee OA; however, a study of a similar but different concept, ‘movement-evoked’ versus resting pain has shown that pain associated with movement is related to greater sensitization (19). The difference is that movement evoked pain is not necessarily unpredictable; in fact it is common that pain increases with activity acutely (20) and yet exercise may reduce sensitization acutely (21) and be an effective treatment for pain long-term (22). Given that

the unpredictability of pain has been described as a feature of progressive disease and one of the more bothersome aspects of OA pain, it will be important to disentangle the concepts of pain, its unpredictability and triggers, as well as its relationship to movement and flares in future work.

Limitations of this work include the fact that this is a cross-sectional analysis, therefore restricting any inferences about causation or time progression per se. We were also unable to ascertain any information regarding triggers in regards to unpredictable pain and this may be an important aspect to include to help clarify relationships in the future. In addition, we were unable to discern how long participants have had symptoms for, nor account for the variable course of the disease, which may not uniformly progress as suggested by qualitative research. Strengths of our study include the examination of ICOAP-defined pain patterns with indicators of sensitization and endogenous pain modulation with adjustment for known confounders, in addition to our use of standardized and validated questionnaires.

Taking a mechanistic approach to understanding pain in knee OA may provide the basis for a targeted and personalized approach to pain management, particularly when paired with validated clinical symptoms (23). We found that different pain sensitization-related mechanisms were associated with different pain patterns, particularly intermittent vs. constant pain. These pain patterns can evolve over the course of OA and appear to be related to peripheral +/− central facilitated ascending pain mechanisms, and descending modulatory mechanisms. These findings highlight the need for a broader approach to understanding pain and its mechanisms that may differ by disease symptomology. Importantly, ascending pain facilitation appears to be associated with constant pain and unpredictable pain, and may therefore be an important mechanism in the transition from intermittent to persistent/constant pain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Significance and Innovations

- In a cross-sectional analysis of a prospective cohort of people with or at risk of knee osteoarthritis, quantitative sensory tests (pressure pain thresholds, temporal summation and conditioned pain modulation) were associated with knee pain patterns (intermittent pain, constant pain or constant + intermittent pain).
- These findings highlight the importance of understanding pain mechanisms more broadly by symptomatic disease progression.

Table 1.

Participant characteristics

Characteristic	N= 2794 (5557 knees)
Age, years, (mean (SD))	63.9 (10.6)
Female (%)	57
BMI, kg/m^2 (mean (SD))	29.5 (5.7)
Low back pain (%)	45
Pain medications (%)	35
ICOAP totals (mean (SD)	
Intermittent pain subscale /24 ×100	10.3 (16.1)
Constant pain subscale /20 × 100	2.2 (10.0)
Total (Total pain score / 44) x 100	6.6 (11.1)
ICOAP pain patterns N (%) (knees)	
No intermittent or constant pain	3728 (67)
Intermittent pain only	1474 (26)
Constant pain only	157 (3)
Both constant and intermittent pain	198 (4)
Unpredictable pain	987 (18)

Table 2.

Association of QST with ICOAP scale totals

	ICOAP Intermittent score ß Est (95% CI)	ICOAP Constant score ß Est (95% CI)	ICOAP Total score ß Est (95% CI)
Temporal Summation per SD unit increase	*0.53 (0.03, 1.04)*	−0.03 (−0.38, 0.31)	0.28 (−0.08, 0.63)
PPT – patella per SD unit increase	*−1.60 (−2.06, −1.14)*	*−0.80 (−1.10, −0.51)*	*−1.24 (−1.54, −0.93)*
PPT – wrist per SD unit increase	*−1.44 (−1.92, −0.97)*	*−0.64 (−0.92, −0.36)*	*−1.08 (−1.40, −0.76)*
Presence of Adequate CPM (ratio > 1 vs. ≤1)	−0.74 (−1.73, 0.24)	*0.83 (0.25, 1.40)*	−0.03 (−0.69, 0.63)

Linear regression models adjusted for age, sex, BMI, race, pain catastrophizing, depressive symptoms, site. Significant results italicized.

Table 3.

Association of QST with ICOAP pain patterns

	ICOAP Constant +/− intermittent pain vs intermittent pain only *Adjusted OR (95% CI)	ICOAP Pain without warning Sometimes/often vs. rarely/never *Adjusted OR (95% CI)
Temporal Summation per SD unit increase	0.96 (0.84, 1.09)	*1.08 (1.00, 1.18)*
PPT – patella per SD unit increase	*0.80 (0.68, 0.93)*	*0.76 (0.70, 0.83)*
PPT – wrist per SD unit increase	*0.80 (0.66, 0.96)*	*0.82 (0.74, 0.90)*
Presence of adequate CPM (ratio > 1 vs. ≤1)	*1.45 (1.10, 1.92)*	0.96 (0.81, 1.13)

Linear regression models adjusted for age, sex, BMI, race, pain catastrophizing, depressive symptoms, site. Significant results italicized.