Day-to-day pain symptoms among patients with knee osteoarthritis: The contribution of psychological factors and dysfunctions in nervous system pain processing

Marc O. Martel, PhD [1], Jiaqi Bi [2], Claudia M. Campbell, PhD [3], Junie S. Carriere, PhD [4], Myrella Paschali, PhD [5], Asimina Lazaridou, PhD [5], Samantha M. Meints, PhD [5], Bethany Pester, PhD [5] ; Patrick H. Finan, PhD [3], Jennifer A. Haythornthwaite, PhD [3], Michael T. Smith, PhD [3], Robert R. Edwards, PhD [5]

[1] Faculty of Dental Medicine & Department of Anesthesiology, McGill University, Montreal, Canada

[2] Department of Epidemiology and Biostatistics, Schulich School of Medicine & Dentistry, Western University, London, Canada

[3] Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD 21224, USA.

[4] Faculty of Medicine and Health Sciences, Université de Sherbrooke, Longueuil, Canada

[5] Department of Anesthesiology and Pain Medicine, Harvard Medical School, Brigham & Women's Hospital, Boston, Massachusetts

Address correspondence to:

Marc O. Martel, PhD
Strathcona Anatomy & Dentistry building
3640 University street, room M-71
Montreal, Qc, Canada, H3A 2B2
Phone: 1-514-398-1662; Email: marc.o.martel@mcgill.ca

Funding and dislosure of interest

This research was supported by R01 AG034982 (Edwards, PI), a grant from the National Institutes of Health (NIH). The authors have no conflicts of interest to declare.

Abstract

Evidence indicates that dysfunctions in nervous system pain processing and maladaptive psychological factors contribute to pain among patients with knee osteoarthritis (OA). To date, however, the bulk of work in this area was based on cross-sectional studies, yielding only limited insights into how these factors contribute to day-to-day OA pain symptoms. Relatedly, little is known on the factors contributing to acute pain exacerbations as well as "recovery" from day-to-day pain exacerbations among patients with OA. **Objectives:** The first objective was to examine degree to which quantitative sensory testing (QST) measures of nervous system pain processing (i.e., joint pain sensitivity, endogenous pain modulation) contributed to daily pain intensity, acute pain exacerbations, and recovery from pain exacerbations among patients with knee OA. The contribution of psychological factors (i.e., negative affect, catastrophizing) to these daily OA pain outcomes was also examined. **Methods:** In this micro-longitudinal study, 158 patients with knee OA underwent QST procedures and then completed daily diaries assessing pain intensity and psychological function. **Results:** Measures of joint pain sensitivity and endogenous pain facilitation were associated with heightened pain intensity (both p's < .05). Subsequent analyses indicated that catastrophizing was associated with an increased likelihood of acute pain exacerbations ($p < .001$) as well as with a decreased likelihood of recovery on days following pain exacerbations ($p < .001$). **Conclusions**: Our study provides new insights into the factors that may increase susceptibility to acute pain exacerbations and interfere with the ability to recover from pain exacerbations in knee OA patients.

1.0. Introduction

Knee osteoarthritis (OA) is a degenerative joint disease characterized by cartilage loss in the knee. Pain is one of the primary symptoms associated with knee OA and the main reason for patients to seek treatment (1, 2). The experience of pain among patients with knee OA has long been viewed to result primarily from disease activity at the peripheral (i.e., joint) level. However, it is now well-documented that radiographic measures of disease activity are only modestly associated with patients' subjective reports of pain (2, 3), raising questions concerning the factors that contribute to pain intensity among patients with knee OA.

Over the past few decades, evidence from quantitative sensory testing (QST) studies has accumulated indicating that dysfunctions in nervous system pain processing contribute to pain among patients with knee OA (for reviews, see (4, 5)). For instance, compared to healthy controls, patients with OA have been found to exhibit heightened pain sensitivity at affected joint sites (6, 7), suggesting that local (i.e., peripheral) sensitization at least partly contributes to OA pain. Patients with OA have also been found to be more sensitive to pressure stimuli at distant (i.e., non-affected) joint sites than healthy controls (6, 7), suggestive of potential alterations in central nervous system pain processing (8, 9). The notion that patients with OA may be characterized by alterations in central nervous system pain processing is further supported by studies showing evidence of enhanced temporal summation of pain (6, 10) and deficits in conditioned pain modulation (6, 11) among these patients.

Although previous studies using QST have advanced our understanding of the pathophysiological mechanisms underlying OA pain, questions remain concerning the

degree to which alterations in nervous system processing contribute to pain symptoms among patients with knee OA. In previous studies conducted in this population, associations between QST measures of nervous system pain processing and reports of clinical pain intensity have been found to be modest, at best (for a review, see (12)). These associations, though, have most often been based on studies that involved long time intervals between QST and patients' reports of clinical pain intensity (13, 14), or cross-sectional studies that involved single retrospective reports of OA pain intensity (6, 15). The memory and/or recall biases associated with retrospective reports of pain have been well-documented (16), and these biases could have weakened the magnitude of associations observed between QST measures and patients' reports of clinical pain intensity.

In addition to the methodological shortcomings of previous cross-sectional studies on the determinants of OA pain, these studies have yielded only limited insights into our understanding of how OA pain symptoms unfold in everyday life. Patients with knee OA are susceptible to experiencing day-to-day fluctuations in pain as well as acute pain exacerbations (i.e., “pain flares”), which are known to be distressing (17, 18) and to have a deleterious impact on patients’ function (1, 17, 19). Given that previous cross-sectional studies among OA patients were not suited to capture potential fluctuations in pain, the factors contributing to acute pain exacerbations among patients with OA also remain largely unexplored. Importantly, the factors influencing patients’ ability to “recover” from pain exacerbations have also remained unexplored. For instance, in the absence of disease progression, the intensity of a patient’s pain is expected to return to its “usual” or "average" level at some point following the pain exacerbation. Given the potentially

frequent occurrence of OA pain exacerbations (1, 17, 19), recovering from pain exacerbations represents an important aspect of patients' adjustment to osteoarthritis (20-22).

The first objective of the present study was to examine the degree to which QST measures of nervous system pain processing (i.e., pain sensitivity, endogenous pain modulation) contributed to daily pain intensity, acute pain exacerbations, and recovery from pain exacerbations among patients with knee OA. The second objective was to examine the contribution of psychological factors (i.e., negative affect and catastrophizing) to these daily OA pain outcomes. Negative affect and catastrophizing have been linked to heightened daily reports of clinical pain intensity among OA patients (for a review, see (23)), but little is known about the contribution of these psychological variables to acute pain exacerbations as well as recovery from day-to-day pain exacerbations among patients with OA.

2.0. Patients and Methods

2.1. Participants

Patients included in the present study (n = 158) were part of a larger multisite study in which patients were scheduled to undergo unilateral total knee arthroplasty (TKA) (24). Data included in the present report were collected before patients underwent TKA. Although some data from the broader parent study have been previously published (24, 25), this is our first report examining knee pain exacerbations using daily diaries within this sample of knee OA patients.

Participants were recruited through printed advertisements posted within Brigham and Women's Hospital and Johns Hopkins University School of Medicine communities.

All participants underwent a telephone screening to ensure they met eligibility criteria. Patients included in the broader parent study met the following inclusion criteria: 1) age of 45 or older, 2) diagnosis of knee osteoarthritis based on the American College of Rheumatology criteria with a score of 3 or 4 on the Kellgren/Lawrence (KL) scale, 3) scheduled to undergo unilateral total knee arthroplasty, 4) ability to understand English to a sufficient degree in order to complete study procedures.

2.2. Measures and procedures

The institutional review boards of Brigham and Women's Hospital and Johns Hopkins University approved all study procedures, and written informed consent was obtained from all participants. The present observational study involved baseline assessment procedures (see 2.2.1) and a micro-longitudinal daily diary phase (see 2.3).

2.2.1. Baseline self-report measures

During the baseline visit, participants completed a demographic questionnaire, provided information on medical history, and were asked to report all the medications they were currently taking. Patients were also asked to complete the Brief Pain Inventory (BPI (26)) and the Western Ontario McMaster Universities Osteoarthritis Scale (WOMAC (27)).

2.2.2. Quantitative sensory testing (QST)

During the QST session, participants were seated comfortably in a reclining chair while they underwent a standardized battery of psychophysical pain testing procedures, which first included testing of pressure pain thresholds (PPThs) at the patella of the affected knee (i.e., knee for which surgery was indicated). Patients then underwent testing of mechanical temporal summation of pain (TSP (28)), which involved repeated administration of pinprick stimulators around the affected knee (28). Finally, patients

underwent testing of conditioned pain modulation (CPM) testing based on protocol recommendations (29). The TSP and CPM values were used as proxies for endogenous pain-facilitatory and pain-inhibitory processing, respectively (28, 29). All these QST procedures have been described elsewhere (28, 29) and full details on these procedures are also included in Supplementary file 1.

2.3. Daily reports of pain intensity, negative affect, and catastrophizing

Following the QST session, prior to beginning the daily diary period, patients received a personal digital assistant (PDA; Hewlett Packard, Palo Alto, CA). During the week preceding their surgery, patients were asked to provide reports of pain intensity, negative affect, and pain catastrophizing using visual analogue scales (VAS). Patients were prompted to make diary reports every evening based on the past 24 hours. Diary reports were date- and time-stamped to ensure validity, to record specific times when reports were made, and to monitor patients' compliance with the diary protocol.

2.3.1. Daily reports of pain intensity

Patients were asked to rate the average level of pain they experienced over the past 24 hours using a VAS that ranged between 0 (no pain) and 100 (pain as bad as could be). This measure is an adaptation of the standard VAS item commonly used in the Brief Pain Inventory (BPI; (26)) to assess pain intensity among patients with chronic pain (26, 30).

2.3.2. Daily reports of negative affect

Patients were asked to rate how much they felt various negative emotions (i.e., anxious, unhappy, annoyed) in the past 24 hours using a VAS that ranged from 0 (not at all) to 100 (extremely). These negative emotion items appear on the Positive and

Negative Affect Scale (PANAS; (31)). Consistent with previous research, negative emotion items were averaged to create a daily composite measure of negative affect (32).

2.3.3. Daily reports of pain catastrophizing

Patients were asked to report on the following thoughts and emotions associated with their pain over the past 24 hours: 1) “I felt I couldn’t stand the pain”, 2) “I felt like the pain was never going to get any better”, 3) “I couldn't stop thinking about how much it hurt”. These items appear on the diary version of the Pain Catastrophizing Scale (PCS) (33) and were rated using a VAS that ranged from 0 (not at all) to 100 (very much).

2.3.4. Daily reports of physical activity

As part of the diary protocol, patients were also asked to provide, once daily, end-of-day reports of physical activity (i.e., “How physically active were you today”) on a VAS that ranged from 0 (not at all) to 100 (extremely). This item is similar to those used to assess global physical activity among pain populations, including patients with osteoarthritis (25).

3.0. Data reduction and analysis

Primary analyses were conducted using multilevel modeling given the hierarchical data structure of the present study, in which repeated daily assessments (Level 1 units) were nested within participants (Level 2 units). Multilevel modeling was also well-suited to handle the unequal number of data points across participants due to missing data. Given that multilevel modeling can account for unbalanced data set and/or missing data (34), all 158 participants could be included in multilevel analyses without using any data imputation procedure. Among all patients who were invited to complete diaries (n = 248), a total of 178 (72 %) agreed. Among those, 89 % (n = 158) provided more than 3 days of

diaries (mean = 6.3 days; SD = 1.7). Analyses indicated that patients with and without missing data did not differ significantly on any of the main study variables (all p's > .05).

Before conducting primary study analyses, the potential confounding influence of patient demographics and biomedical variables on primary study outcomes was first examined. The influence of daily physical activity levels on study outcomes was also examined given the impact of physical activity on OA-related outcomes (1, 2). Variables associated with main study outcomes were retained as covariates in subsequent analyses.

To examine the factors associated with daily pain intensity, analyses were first conducted using Level 1 pain intensity (i.e., daily pain intensity ratings) as the outcome variable, and pain sensitivity (i.e., PPThs), endogenous pain modulation (i.e., TSP, CPM), and psychological factors (i.e., NA, catastrophizing) as independent variables (IVs) in separate multilevel linear models. The contribution of each IV to daily pain intensity was then examined after controlling for covariates (i.e., adjusted models).

To examine the factors associated with acute pain exacerbations, a model-building approach identical to that described above was followed using the same IVs. For this analysis, an acute pain exacerbation (APE) index was first computed based on absolute (Δ) changes in patients' reports of pain intensity across successive days. An *acute pain exacerbation* (= 1) was indicated on days when patients reported any increase of 20 points (or more) in pain intensity on the 0-100 visual analogue scale (VAS) over the preceding day. *No acute pain exacerbation* (= 0) was indicated if the change in pain intensity was $<$ 20 points on the VAS. This cutoff is consistent with previously established operationalizations of clinically significant changes in clinical pain intensity among chronic

pain populations (35, 36), including patients with osteoarthritis (37, 38). Multilevel logistic regression analyses were then conducted separately for each of the independent variable (IVs) using the binary (i.e., 0/1) APE index as the outcome variable. The contribution of each IV to acute pain exacerbations was then examined after controlling for covariates (i.e., adjusted models).

To examine the factors associated with patients' recovery from pain exacerbations, a model building approach identical to that described above was followed using the same IVs, and by deriving a recovery from pain exacerbation (RPE) index. To derive the RPE index, the average level of pain intensity (VAS: 0-100) reported across all diary days was first computed separately for each patient. A *pain exacerbation* (= 1) was indicated on days when pain intensity was above patients' own (i.e., within-person) average pain intensity levels. *No pain exacerbation* (= 0) was indicated if pain intensity was equal (or below) patients' own average pain intensity levels. On days following a pain exacerbation, *recovery* (= 1) was indicated if pain intensity returned at (or below) patients' own average pain intensity levels. *No recovery* (= 0) was indicated if pain intensity remained above patients' own average pain intensity levels. The RPE index was derived based on pain exacerbations that were above patients' within-person average pain intensity levels rather than based on APE (i.e., increases of ≥ 20 points on the VAS) to maximize the number of pain exacerbation events. This data analytic decision allowed to prevent statistical underpowering and to minimize the risk of Type II error. Multilevel logistic regression analyses were then conducted separately for each of the independent variable (IVs) using the binary (i.e., 0/1) RPE index as the outcome variable. The contribution of each IV to

the outcome (i.e., RPE) was then examined after controlling for covariates (i.e., adjusted models).

4.0. Results

4.1. Factors associated with daily pain intensity

To examine the factors associated with daily pain intensity, a multilevel model was first built using Level 1 pain intensity as the outcome variable, and pressure pain thresholds at the affected knee as a Level 2 independent variable; results indicated that higher PPThs were associated with lower daily pain intensity, B = -.02, p = .001. Two distinct multilevel models were subsequently built using the same outcome variable but using TSP and CPM as Level 2 independent variables. Results indicated that higher levels of TSP were associated with higher daily pain intensity, B = .17, p = .036. CPM, however, was not significantly associated with daily pain intensity, B = -.02, p = .659.

Multilevel analyses also examined the association between psychological factors (i.e., NA, catastrophizing) and daily pain intensity. Results indicated that day-to-day elevations in negative affect (B = .08, p = .004) and catastrophizing (B = .36, p = .000) were both associated with heightened reports of pain intensity. Results subsequently revealed that catastrophizing was the only psychological variable that remained significantly associated with daily pain intensity after adjusting for other covariates (B = .34, p = .000).

4.2. Factors associated with acute pain exacerbations

Acute pain exacerbations (i.e., increases of ≥ 20 points on the 0-100 VAS) occurred on 16.7 % of all pain exacerbation days, and the average increase in pain on these days was 30.5 points (SD = 10.6) on the 0-100 VAS. To examine the factors

associated with acute pain exacerbations, a series of multilevel logistic regression models were built using the APE index as the outcome variable (see Table 2). Results indicated that PPThs (B = -.001, OR = 0.99, p = .110), TSP (B = -.01, OR = 0.98, p = .122), and CPM (B = .001, OR = 1.00, p = .848) were not significantly associated with acute pain exacerbations. Results, however, indicated that day-to-day elevations in negative affect (B = .02, OR = 1.02, p = .003) and catastrophizing (B = .04, OR = 1.04, p = .000) were associated with a greater likelihood of experiencing acute pain exacerbations. Results subsequently revealed that catastrophizing was the only psychological variable that remained significantly associated with acute pain exacerbations after adjusting for other covariates (B = .03, p = .000). The odds of experiencing acute pain exacerbations as a function of daily catastrophizing levels are displayed in Figure 1.

4.3. Factors associated with recovery from pain exacerbations

To examine the factors associated with recovery from pain exacerbations, a series of multilevel logistic regression models were built using the recovery from pain exacerbation (RPE) index as the outcome variable (see Table 3). Results indicated that PPThs (B = .489, OR = 1.00, p = .973), TSP (B = .001, OR = 1.00, p = .774), and CPM (B = .002, OR = 1.02, p = .640) were not significantly associated with recovery from pain exacerbations. Negative affect was also not significantly associated with recovery from pain exacerbations (B = -.002, OR = 0.99, p = .824). Results, however, indicated that elevations in daily levels of catastrophizing were associated with a decreased likelihood of recovery on days following pain exacerbations, even after multivariate adjustment for other putative predictors such as negative affect (B = -.05, OR = 0.94, p = .000). The odds

of recovering from pain exacerbations as a function of daily catastrophizing levels are displayed in Figure 2.

5.0. Discussion

The main objective of the present study was to examine the contribution of psychological factors and QST measures of nervous system pain processing to daily pain outcomes among patients with knee OA. More specifically, analyses examined the contribution of these variables to daily pain intensity, acute pain exacerbations, and recovery from pain exacerbations.

Consistent with previous research among patients with OA (39, 40), significant associations were found between psychological factors and patients' daily reports of pain intensity. More specifically, results indicated that day-to-day elevations in catastrophizing and negative affect were associated with heightened reports of pain intensity. We also found that lower pressure pain thresholds at the affected knee were associated with higher daily levels of pain intensity. This finding is consistent with previous studies among OA patients that have observed associations between measures of local (i.e., joint) pain sensitivity and patients' reports of clinical pain intensity (for a review, see (12)). Results indicated that endogenous pain inhibition, assessed using the CPM paradigm, was not significantly associated with patients' daily pain intensity levels. A significant association, however, was found between temporal summation of pain and daily pain intensity, with patients exhibiting higher TSP reporting heightened daily levels of pain. Higher TSP is assumed to reflect hyperexcitability in nociceptive pathways and enhanced pain-facilitatory function (4, 5). Under real-life conditions, temporal summation of pain is expected to occur with repeated stimulation of affected joints, such as during physical

activity (41) or weight-bearing activities (42). In our study, the association between TSP and daily pain intensity was not influenced by patients' overall daily levels of physical activity. It remains possible, though, that summation processes contributed to heightened pain intensity due to patients' engagement in low intensity weight-bearing activities that are repeatedly performed on a daily basis, such as walking around the home or climbing stairs.

Of particular interest in the present study was to examine the contribution of psychological factors, pain sensitivity, and endogenous pain modulation to the occurrence of acute pain exacerbations. Acute pain exacerbations were operationalized as any 20-point increase in pain intensity (on a 0-100 VAS) across successive days, which is consistent with previously established cutoffs for clinically significant changes in pain intensity among chronic pain populations (35, 36), including patients with OA (38, 43). In the present study, we found that daily elevations in catastrophizing were associated with greater odds of experiencing acute pain exacerbations, which parallels findings from a recent study conducted among hip OA patients (38). None of the other variables included in our study were found to be associated with acute pain exacerbations.

Although speculative, a number of factors could explain why catastrophic thinking contributed to the occurrence of acute pain exacerbations among patients with OA. First, catastrophic thinking involves a tendency to ruminate on pain and to magnify the threat value of pain (44). In the context of our study, it is thus possible that some relatively mild day-to-day increases in pain were appraised as threatening as well as magnified, contributing to exacerbations in pain perception. It is also possible that catastrophic thinking contributed to the occurrence of acute pain exacerbations through an

amplification of neural activity in brain regions involved in pain processing. In previous research, catastrophic thinking has been found to be associated with enhanced activity in multiple cortical and subcortical brain regions involved in pain perception (23). It is possible that some relatively mild day-to-day increases in pain were accompanied by elevations in catastrophic thinking, which in turn led to acute pain exacerbations through enhanced pain-related brain activity. Finally, catastrophic thinking has been found to be associated with enhanced systemic levels of inflammation among patients with arthritic conditions (23, 45). Given that inflammation is known to play a role in OA pain symptoms (2, 23), there is reason to believe that catastrophic thinking might contribute to acute pain exacerbations in part through an impact on pro-inflammatory activity.

A particularly interesting objective of the present study was to examine the factors associated with patients' recovery from pain exacerbations. Given the potential day-to-day fluctuations in OA pain symptoms (17, 38, 43), patients' ability to recover from pain exacerbations represents an important aspect of patients' adjustment to osteoarthritis (20-22). In the present study, catastrophizing was the only variable significantly associated with patients' recovery from pain exacerbations. More specifically, results indicated that patients reporting daily elevations in catastrophizing were less likely to return to (or below) their own average level pain intensity on days following pain exacerbations. None of the other variables assessed in the present study were associated with patients' recovery from pain exacerbations. In previous work, it has been suggested that certain psychological factors, such as coping or resilience, might influence patients' ability to recover from pain exacerbations (46, 47). These factors might contribute to explaining why, in our study, patients who engaged in catastrophic thinking were less

likely to recover from day-to-day pain exacerbations. For instance, catastrophic thinking is known to be accompanied by helpless cognitions (44, 48) and low self-efficacy beliefs (23, 44) , two cognitive features associated with lower resilience (46, 47, 49) that could have impeded patients' ability to recover from day-to-day pain exacerbations. Catastrophic thinking has also been found to interfere with the use of adaptive pain-coping strategies that may be potentially effective for decreasing pain intensity, such as distraction, cognitive reinterpretation, and positive self-statements (50). On days when catastrophic thinking increased, patients might have been less likely to rely on these types of coping strategies, which in turn could have interfered with their ability to recover from pain exacerbations.

Although preliminary, findings from the present study could have some implications for the management of pain among patients with OA. First, our findings suggest that a substantial number of patients with knee OA are likely to experience clinically significant exacerbations in pain as they go about their daily lives, and that psychological factors such as negative affect and catastrophizing may increase patients' susceptibility to experiencing these pain exacerbations. Minimizing the occurrence of pain exacerbations or "pain flares" has been identified as an important treatment target (17) (1, 19), as these episodic pain exacerbations may lead to psychological distress (17, 19) as well as functional limitations (1, 17, 19). Our findings suggest that interventions specifically aimed at reducing patients' negative affect and catastrophizing might contribute to minimizing the occurrence of pain exacerbations among patients with OA. Findings from the present study also suggest that catastrophizing might interfere with patients' ability to recover from

pain exacerbations, which further supports the potential utility of targeting this psychological variable as part of treatment efforts to improve OA outcomes.

There are limitations to the present study that must be considered when interpreting our findings. First, this study included only patients with severe OA (i.e., KL scores of 3 or 4) who were scheduled to undergo knee surgery. Therefore, our study sample is not representative of all patients with OA and those with less severe forms of knee OA. Second, despite the use of a longitudinal study design, the time period for the assessment of daily pain outcomes was relatively short (i.e., 7 days) and our primary study outcomes were assessed only once daily. Third, we could not tease out the directionality of associations between some of the study measures. For instance, it is certainly plausible that catastrophic thinking contributes to heightened pain intensity, as reported in our study, but day-to-day elevations in pain intensity could also have contributed to increases in catastrophizing. Future diary studies involving multiple within-day assessments and lagged analyses could shed light on the directionality of interrelations between psychological variables and daily OA pain symptoms.

Despite these limitations, the present findings provide new insights into our understanding of factors that may increase patients' susceptibility to acute pain exacerbations, an important aspect of daily OA pain that has received little attention in previous research. To our knowledge, this was also the first study to systematically examine the factors that may influence patients' recovery from pain exacerbations. A key finding is that catastrophic thinking might increase patients' susceptibility to experiencing acute pain exacerbations and interfere with patients' ability to recover from pain exacerbations. It is our hope that findings from the present study will also stimulate further

research on the biological and psychological factors contributing to the daily pain experience among patients with knee OA. Advances in this area might ultimately contribute to improving pain-related outcomes in these patients.

References

1. Hawker GA, Stewart L, French MR, Cibere J, Jordan JM, March L, et al. Understanding the pain experience in hip and knee osteoarthritis--an OARSI/OMERACT initiative. Osteoarthritis Cartilage. 2008;16(4):415-22.
2. Neogi T. The epidemiology and impact of pain in osteoarthritis. Osteoarthritis Cartilage. 2013;21(9):1145-53.
3. Neogi T, Felson D, Niu J, Nevitt M, Lewis CE, Aliabadi P, et al. Association between radiographic features of knee osteoarthritis and pain: results from two cohort studies. Bmj. 2009;339:b2844.
4. Lee YC, Nassikas NJ, Clauw DJ. The role of the central nervous system in the generation and maintenance of chronic pain in rheumatoid arthritis, osteoarthritis and fibromyalgia. Arthritis Res Ther. 2011;13(2):211.
5. Arendt-Nielsen L. Pain sensitisation in osteoarthritis. Clinical and experimental rheumatology. 2017;35 Suppl 107(5):68-74.
6. 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(3):573-81.
7. 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(10):1424-31.
8. Graven-Nielsen T, Arendt-Nielsen L. Assessment of mechanisms in localized and widespread musculoskeletal pain. Nat Rev Rheumatol. 2010;6(10):599-606.
9. Arendt-Nielsen L, Skou ST, Nielsen TA, Petersen KK. Altered Central Sensitization and Pain Modulation in the CNS in Chronic Joint Pain. Curr Osteoporos Rep. 2015;13(4):225
10. 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 Rheum. 2012;64(9):2907-16.
11. 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(1):69-78.
12. Georgopoulos V, Akin-Akinyosoye K, Zhang W, McWilliams DF, Hendrick P, Walsh DA. Quantitative sensory testing and predicting outcomes for musculoskeletal pain, disability, and negative affect: a systematic review and meta-analysis. Pain. 2019;160(9):1920-32.

13. 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(1):55-61.
14. 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(1):47-54.
15. 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(9):1588-94.
16. Stone AA, Broderick JE, Schneider S, Schwartz JE. Expanding options for developing outcome measures from momentary assessment data. Psychosom Med. 2012;74(4):387-
17. Murphy SL, Lyden AK, Kratz AL, Fritz H, Williams DA, Clauw DJ, et al. Characterizing Pain Flares From the Perspective of Individuals With Symptomatic Knee Osteoarthritis. Arthritis Care Res (Hoboken). 2015;67(8):1103-11.
18. Thomas MJ, Neogi T. Flare-ups of osteoarthritis: what do they mean in the short-term and the long-term? Osteoarthritis Cartilage. 2020;28(7):870-3.
19. Cross M, Dubouis L, Mangin M, Hunter DJ, March L, Hawker G, et al. Defining Flare in Osteoarthritis of the Hip and Knee: A Systematic Literature Review; OMERACT Virtual Special Interest Group. The Journal of Rheumatology. 2017;44:1920-7.
20. Affleck G, Tennen H, Pfeiffer C, Fifield J. Appraisals of control and predictability in adapting to a chronic disease. Journal of personality and social psychology. 1987;53(2):273-9.
21. Zautra AJ, Burleson MH, Matt KS, Roth S, Burrows L. Interpersonal stress, depression, and disease activity in rheumatoid arthritis and osteoarthritis patients. Health Psychol. 1994;13(2):139-48.
22. Keefe FJ, Caldwell DS. Cognitive behavioral control of arthritis pain. Med Clin North Am. 1997;81(1):277-90.
23. Edwards RR, Cahalan C, Mensing G, Smith M, Haythornthwaite JA. Pain, catastrophizing, and depression in the rheumatic diseases. Nat Rev Rheumatol. 2011;7(4):216-24.
24. Nandi M, Schreiber KL, Martel MO, Cornelius M, Campbell CM, Haythornthwaite JA, et al. Sex differences in negative affect and postoperative pain in patients undergoing total knee arthroplasty. Biology of sex differences. 2019;10(1):23.
25. Lazaridou A, Martel MO, Cornelius M, Franceschelli O, Campbell C, Smith M, et al. The Association Between Daily Physical Activity and Pain Among Patients with Knee Osteoarthritis: The Moderating Role of Pain Catastrophizing. Pain Med. 2019;20(5):916-
26. Tan G, Jensen MP, Thornby JI, Shanti BF. Validation of the Brief Pain Inventory for chronic nonmalignant pain. J Pain. 2004;5(2):133-7.
27. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient

relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. The Journal of rheumatology. 1988;15(12):1833-40.
28. Rolke R, Baron R, Maier C, Tolle TR, Treede RD, Beyer A, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. Pain. 2006;123(3):231-43.
29. Yarnitsky D, Bouhassira D, Drewes AM, Fillingim RB, Granot M, Hansson P, et al. Recommendations on practice of conditioned pain modulation (CPM) testing. Eur J Pain. 2014.
30. Turk DC, Fillingim RB, Ohrbach R, Patel KV. Assessment of Psychosocial and Functional Impact of Chronic Pain. J Pain. 2016;17(9 Suppl):T21-49.
31. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. Journal of personality and social psychology. 1988;54(6):1063.
32. Kratz AL, Davis MC, Zautra AJ. Pain acceptance moderates the relation between pain and negative affect in female osteoarthritis and fibromyalgia patients. Ann Behav Med. 2007;33(3):291-301.
33. Darnall BD, Sturgeon JA, Cook KF, Taub CJ, Roy A, Burns JW, et al. Development and Validation of a Daily Pain Catastrophizing Scale. J Pain. 2017;18(9):1139-49.
34. Hoffman L. Longitudinal analysis : modeling within-person fluctuation and change. 1 edition. ed. New York: Routledge; 2015.
35. Farrar JT, Young JP, Jr., LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain. 2001;94(2):149-58.
36. Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain. 2008;9(2):105-21.
37. Parry E, Ogollah R, Peat G. 'Acute flare-ups' in patients with, or at high risk of, knee osteoarthritis: a daily diary study with case-crossover analysis. Osteoarthritis Cartilage. 2019;27(8):1124-8.
38. Fu K, Metcalf B, Bennell KL, Zhang Y, Deveza LA, Robbins SR, et al. The association between psychological factors and pain exacerbations in hip osteoarthritis. Rheumatology (Oxford). 2021;60(3):1291-9.
39. Keefe FJ, Lefebvre JC, Egert JR, Affleck G, Sullivan MJ, Caldwell DS. The relationship of gender to pain, pain behavior, and disability in osteoarthritis patients: the role of catastrophizing. Pain. 2000;87(3):325-34.
40. Carriere JS, Lazaridou A, Martel MO, Cornelius M, Campbell C, Smith M, et al. The moderating role of pain catastrophizing on the relationship between partner support and pain intensity: a daily diary study in patients with knee osteoarthritis. J Behav Med. 2019.
41. McPhee M, Graven-Nielsen T. Alterations in Temporal Summation of Pain and Conditioned Pain Modulation Across an Episode of Experimental Exercise-Induced Low Back Pain. J Pain. 2019;20(3):264-76.
42. 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(4):703-11.

43. Hutchings A, Calloway M, Choy E, Hooper M, Hunter DJ, Jordan JM, et al. The Longitudinal Examination of Arthritis Pain (LEAP) study: relationships between weekly fluctuations in patient-rated joint pain and other health outcomes. J Rheumatol. 2007;34(11):2291-300.
44. Sullivan MJ, Thorn B, Haythornthwaite JA, Keefe F, Martin M, Bradley LA, et al. Theoretical perspectives on the relation between catastrophizing and pain. Clin J Pain. 2001;17(1):52-64.
45. Kojima M, Kojima T, Suzuki S, Oguchi T, Oba M, Tsuchiya H, et al. Depression, inflammation, and pain in patients with rheumatoid arthritis. Arthritis Care & Research. 2009;61(8):1018-24.
46. Sturgeon JA, Zautra AJ. Resilience: a new paradigm for adaptation to chronic pain. Curr Pain Headache Rep. 2010;14(2):105-12.
47. Sturgeon JA, Zautra AJ. Psychological resilience, pain catastrophizing, and positive emotions: perspectives on comprehensive modeling of individual pain adaptation. Curr Pain Headache Rep. 2013;17(3):317.
48. Thorn BE, Boothby JL, Sullivan MJL. Targeted treatment of catastrophizing for the management of chronic pain. Cognitive and behavioral practice. 2002;9(2):127-38
49. Ong AD, Zautra AJ, Reid MC. Psychological resilience predicts decreases in pain catastrophizing through positive emotions. Psychology and aging. 2010;25(3):516-
50. Keefe FJ, Affleck G, France CR, Emery CF, Waters S, Caldwell DS, et al. Gender differences in pain, coping, and mood in individuals having osteoarthritic knee pain: a within-day analysis. Pain. 2004;110(3):571-7.