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Running head: Pain sensitization as a mediator between sleep and pain

Title: Pain sensitization as a potential mediator of the relationship between sleep disturbance and subsequent pain in rheumatoid arthritis

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Objective: Many patients with rheumatoid arthritis (RA) suffer from sleep disturbances, commonly attributed to joint pain. Sleep disturbances could also influence pain. One mechanism may be through dysregulated pain processing, manifested by enhanced pain sensitivity. In this study, we examined the role of pain sensitization, measured by quantitative sensory testing (QST), as a mediator in the pathway of sleep disturbance leading to subsequent pain.

Methods: We used longitudinal data from 221 patients with active RA who were followed for 12 weeks after initiating a disease-modifying anti-rheumatic drug. Baseline QST included pressure pain thresholds at articular (wrists, knees) and non-articular (trapezius, thumbnails) sites, temporal summation (TS) at the wrist and forearm, and conditioned pain modulation (CPM). Baseline sleep disturbance and subsequent pain intensity were assessed using the Patient-Reported Outcomes Measurement Information System®. We evaluated correlations between sleep disturbance, QSTs, and subsequent pain intensity. Mediation analyses separately assessed each QST as a mediator, adjusting for baseline confounding factors.

Results: Sleep disturbance was correlated with all QST measures except wrist TS and CPM. Sleep disturbance significantly predicted subsequent pain (coefficient for a meaningful increase of 5-unit in sleep disturbance = 0.32, 95% confidence interval [CI] 0.11, 0.50) in multiple regression. QST mediated 10-19% of this effect.

Conclusion: Pain sensitization may be one mechanism through which sleep disturbance contributes to pain. The small magnitude of association indicates that unmeasured pathways

may contribute to this relationship. Intervention studies are needed to establish causality and determine whether improving sleep can improve pain in patients with RA.

Significance and Innovations

- This is the first multi-center study to examine the role of peripheral and central pain mechanisms as mediators of the relationship between sleep and subsequent pain among patients with active rheumatoid arthritis (RA).
- Sleep disturbance before the initiation of a disease-modifying anti-rheumatic drug significantly predicted pain intensity after 12 weeks of disease-modifying anti-rheumatic drug treatment.
- Quantitative sensory testing (QST) measures including trapezius pressure pain threshold (PPT), wrist PPT, knee PPT, and temporal summation at the forearm partially mediated the effect of sleep disturbance upon subsequent pain, with the proportion mediated ranging from 10-19%.
- Pain sensitization may be one mechanism through which sleep disturbance contributes to subsequent patient-reported pain intensity.

Among patients with rheumatoid arthritis (RA), a major cause of pain is peripheral joint inflammation; however, pain intensity may be out of proportion to the severity of inflammation assessed by the clinician (1). Pain management remains a priority for patients with RA even after effective control of inflammation by disease-modifying anti-rheumatic drugs (DMARDs) (2). Studies suggest that abnormalities in pain regulation may contribute to pain refractory to DMARD treatment (3).

Abnormalities in pain regulation can be divided into two broad categories: peripheral sensitization and central sensitization. For the purpose of this paper, we define central sensitization as any abnormality of the central nervous system pain processing pathways. To assess abnormalities in pain processing, researchers frequently use quantitative sensory testing (QST). Common QST modalities include pressure pain thresholds (PPTs), temporal summation (TS), and conditional pain modulation (CPM). PPTs at sites of localized inflammation or injury (such as articular sites in RA) are used to assess the combination of peripheral and central sensitization. PPTs at non-articular sites are used to measure central sensitization. Central sensitization can be further categorized as ascending facilitation and descending inhibition, which are assessed by TS and CPM respectively.

Sleep problems are common in patients with RA. More than half of patients with RA report problems with sleep, with a prevalence up to three-fold greater than that of the general population (4). Patients with RA frequently report fragmented sleep, difficulty falling asleep, and non-restorative sleep (5). Among patients with RA, sleep problems are associated with high pain intensity in cross-sectional analyses (6). While it is commonly accepted that RA-related

joint pain can disturb sleep, one study reported that sleep deprivation is associated with an increase in next day patient-reported pain intensity.(4)

One mechanism by which sleep disturbance could influence pain is through dysregulated pain processing, manifested by enhanced pain sensitivity. Our previous studies have shown that disturbed sleep was associated with low pain thresholds at both articular and non-articular sites, supporting an association between disturbed sleep and pain sensitization in RA (1). In this study, we used data from patients with active RA undergoing initiation of or change in DMARD therapy to evaluate relationships between sleep disturbance, pain sensitization, and subsequent pain intensity. Specifically, we hypothesized that pain sensitization mediates the association between baseline sleep disturbance (before starting a new DMARD) and subsequent patient-reported pain intensity (12 weeks after DMARD initiation).

MATERIALS AND METHODS

Study Population

This study examined longitudinal data from the multisite, prospective, observational Central Pain in Rheumatoid Arthritis (CPIRA) study (7). CPIRA recruited 295 patients from five academic medical centers from January 2014 to July 2017: Massachusetts General Hospital, Brigham and Women's Hospital, John Hopkins University School of Medicine, University of Michigan Medical School, and Boston University Medical Center. Participants were required to meet American College of Rheumatology (ACR) 2010 criteria for RA (8) and be starting or switching a DMARD for active RA. Exclusion criteria included starting hydroxychloroquine as the new DMARD,

switching between DMARDs with the same mechanism of action (e.g., one TNF inhibitor to another), daily use of ≥10 mg prednisone, regular use of opioid pain medications, severe Raynaud's phenomenon, peripheral neuropathy, severe peripheral vascular disease, and/or diagnosis of another autoimmune disease. Institutional review board (IRB) approval was obtained from all participating sites by Partners IRB (for both Massachusetts General Hospital and Brigham and Women's hospital), Johns Hopkins Medicine IRB, University of Michigan Medical School IRB, and Boston University Medical Center IRB. Each participant provided written informed consent.

This analysis was restricted to 227 participants with 12-week follow-up measures of pain intensity and baseline measures of QST, sleep disturbance, and other examined covariates. Sixty participants were excluded because they were lost to follow-up. Five were excluded due to missing data in baseline sleep disturbance or QST measures, and three were excluded due to missing data in other baseline covariates. A comparison of baseline characteristics between the analysis sample (n=227) with those excluded (n=68) yielded no statistical differences.

Outcome – Subsequent Pain

Overall pain intensity at 12 weeks was assessed using the Global07 item on the Patient Reported Outcomes Measurement Information System (PROMIS®) Global Health v1.1 Short Form. This item asked patients to rate their average pain in the past 7 days on a 0-10 scale, with 0 indicating no pain and 10 the worst pain imaginable.

Exposure - Sleep Disturbance at Baseline

Sleep disturbance was assessed using the PROMIS sleep disturbance Computer Adaptive Test (CAT), which measures self-reported perceptions of sleep quality, depth, and restoration within the past 7 days. Raw scores were standardized to T-scores with a general population mean of 50 and standard deviation of 10 via PROMIS Assessment Center (http://www.assessmentcenter.net/acl/) (9). Higher scores indicate worse sleep disturbance. Based on previous literature, a half-standard deviation (5-unit) in sleep disturbance scores was considered an approximation of a moderate sized effect (10).

Potential Mediator – Quantitative Sensory Testing (QST) at Baseline

Trained research coordinators conducted QST at baseline study visits before patients started or added a new DMARD.(11) Training included a 1-day, in-person session, as well as assessment of intraclass correlations. The following three modalities of QST were performed: 1) pressure pain thresholds (PPTs), 2) temporal summation (TS), and 3) conditional pain modulation (CPM). The order of testing was randomized to eliminate order effects, except CPM procedures were conducted last due to potential carryover effects of the cold-water bath task. To minimize the likelihood of habituation, we required a minimum of 60 seconds between each type of pain test.

<u>Pressure Pain Thresholds (PPTs): overall pain sensitization</u>

PPTs assess overall sensitivity to pain. Low PPTs at articular sites represent a combination of peripheral and central mechanisms of sensitization, whereas low PPTs at non-articular sites indicate central mechanisms of sensitization (11, 12). PPTs were assessed using a Wagner Force 10 FDX Algometer (Wagner Instruments, Greenwich, CT) at articular (bilateral wrists and knees)

and non-articular (bilateral trapezius muscles and thumbnails) sites. Pressure was increased at a rate of approximately 0.50 kgf per second. The pressure reading (kgf) at which the participant first reported pain was recorded, and the average of three trials for each site was defined as the PPT for that site. Lower PPTs at the wrists and knees were considered indicators of greater overall sensitization (including both peripheral and central sensitization); whereas lower PPTs at the trapezius muscles and thumbnails were considered indicators of greater central sensitization.

Temporal Summation (TS): pain facilitation

TS is considered a measure of the CNS's pain facilitatory pathways (12, 13). TS was measured at the wrist and forearm. A series of weighted, wire-tipped probes with increasing weights were tapped at the skin at each site. The probe eliciting a pain rating of 30-40 out of 100 on a visual analog scale or the heaviest probe (if pain ratings were less than 30) was chosen for further testing. The selected probe was tapped 10 times in a row at each site, and the subject rated the pain at the first and the tenth taps for each of 3 trials. TS was calculated as the mean difference between the tenth and the first pain ratings. Larger TS values indicated greater pain facilitation (11, 13, 14).

Conditioned Pain Modulation (CPM): pain inhibition

CPM is considered a measure of endogenous descending pain inhibition (11, 15, 16). CPM was assessed using a noxious conditioning stimulus (to activate endogenous analgesia) and a test stimulus (a painful stimulus to test analgesic response to the conditioning stimulus). The conditioning stimulus was immersion of the right hand in a cold-water bath at 7°C. The test

stimulus was pressure applied by an algometer probe to the left trapezius muscle. CPM was defined as the ratio of the PPT measured at the trapezius after 20 seconds of cold-water submersion to the PPT before cold-water submersion. The exposure time of 20 seconds was determined based on established CPM protocols for patients with chronic pain (17-21). Higher values reflected efficient descending modulation of pain, while lower values reflected inefficient descending pain inhibition (11).

Baseline Confounders

We considered baseline age, sex, body mass index (BMI), RA disease duration, comorbidity, depressive symptoms, swollen joint count, corticosteroid use, and study site as potential confounders of the relationship between baseline sleep disturbance and subsequent patient-reported pain intensity. BMI (kg/m^2) was calculated using body weight and height at the time of the study visit. Overweight and obese were defined as 25 $kg/m^2 \leq$ BMI <30 kg/m^2 and BMI ≥ 30 kg/m^2, respectively. Comorbidity was assessed using a modified Charlson Comorbidity Index (22). Depressive symptoms were measured using the T-score from the PROMIS Depression CAT (9). A standardized swollen and tender joint count (28 joints) was obtained by trained study staff members. Glucocorticoid use was assessed by self-report.

Statistical Analysis

Descriptive means and frequency distributions were calculated for baseline characteristics. To assess the likelihood of each QST measure as a potential mediator, we first examined the association between each potential mediator with both the exposure and the outcome (23). For this purpose, we calculated Spearman correlations between sleep disturbance, each QST

measure, and subsequent pain intensity. QST measures associated with both the exposure and the outcome were evaluated further in mediation analyses.

We tested for evidence that QST-based measures of pain sensitization acted as potential mediators along the pathway from the exposure variable (baseline sleep disturbance) to the outcome variable (subsequent pain intensity) using causal mediation analysis with linear models (Figure 1) (23, 24). This approach decomposes the total exposure effect on outcome into indirect and direct effects. Total effect is the effect of the exposure on the outcome, including any potential effects of the mediator (23). The direct effect is the exposure effect on outcome, controlling for the mediator (i.e., the effect of exposure directly on the outcome that does not go through the mediator). The remaining effect is the indirect effect, which is the effect of the exposure on the outcome that operates through the mediator. The percent mediated is the proportion of the indirect effect relative to the total effect. Since mediation analysis only provides point estimates of the effects, bootstrapping methods with 5000 replicates were used to estimate the 95% confidence intervals of the total effect, direct effect, indirect effect, and percent mediated. Potential confounders included baseline measures of age, sex, BMI, RA disease duration, comorbidity, depressive symptoms, swollen joint count, glucocorticoid use, and study site. A sensitivity analysis was conducted by including baseline pain intensity as an additional confounder. A nominal 5% alpha significance level was used in the statistical tests. All statistical analyses were conducted using SAS 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

Participant characteristics

The study cohort was primarily female (81.1%) with mean age of 54.9 (standard deviation [SD] 14.1) years (Table 1). At baseline, more than two thirds were overweight or obese (31.3% and 37.4%). On average, these participants had a disease duration of 10.2 (SD 12.3) years and 5.1 (SD 5.3) swollen joints with mean pain intensity of 5.1 (SD 2.3). Forty-two percent of participants reported glucocorticoid use. The baseline mean PROMIS sleep disturbance score was 54.6 (SD 8.9). At the second visit, most of this cohort had improved CRP and/or swollen joint count (84%), but more than 94% of these participants still reported subsequent pain with mean pain intensity of 3.8 (SD 2.4).

Associations between baseline pain sensitization with the exposure and the outcome

The Spearman correlation between the exposure (baseline sleep disturbance) with each QST measure of pain sensitization was statistically significant except for wrist TS and CPM (Table 2). Similarly, the Spearman correlation between each QST measure of pain sensitization with the outcome (subsequent pain intensity) was statistically significant except for CPM (Table 2). Due to lack of evidence for a relationship with sleep disturbance, wrist TS and CPM were not further analyzed as potential mediators.

Mediation analyses

QST measures partially mediated the effect of sleep disturbance on subsequent pain intensity, controlling for potential confounders. The total effect (prior to mediation) of sleep disturbance (5-unit increase) on subsequent pain intensity was 0.32 (95% confidence interval [CI] 0.11, 0.50)

(Table 3), which indicates that every 5-unit worsening in sleep disturbance was associated with 0.32-unit increase in subsequent pain intensity. The mediated proportion of the total effect ranged from 11.6% to 19.1% for measures of combined peripheral and central pain sensitization: wrist PPT 11.6% (95% CI: 0.7%, 47.6%) and knee PPT 19.1% (95% CI: 3.4%, 58.3%). The proportion mediated of central pain sensitization ranged from 10.0% to 15.5%: thumbnail PPT 10.0% (95% CI: -0.4%, 44.4%) and trapezius PPT 15.5% (95% CI: 0.9%, 54.8%). Finally, the proportion mediated for pain facilitation measured by arm TS was 19.5% (95% CI: 5.1%, 58.5%).

A sensitivity analysis showed that, after additionally controlling for baseline pain intensity, the total effect of sleep disturbance on subsequent pain intensity diminished, but the mediation effects remained relatively stable (from 32% reduced to 26% stronger).

DISCUSSION

We examined the role of pain sensitization as a potential mediator of the relationship between sleep disturbance and subsequent pain intensity among patients with active RA. QST measures of pain sensitization partially mediated the effects of sleep disturbance on pain intensity by 10-19%. No specific type of abnormality appeared more influential than others; though, we found no relation of descending inhibition with sleep disturbance.

It is well documented that sleep disturbance is associated with pain in healthy subjects and in patients with chronic pain conditions (25). Several studies of healthy subjects have shown that experimentally induced sleep deprivation leads to enhanced pain sensitivity, assessed by PPTs (26). In addition, a few studies reported that sleep deprivation is associated with significant increases in pain facilitation, assessed by TS (27, 28), as well as impaired pain inhibition,

assessed by CPM (27, 29). Large, longitudinal cohort studies also reported associations between sleep disturbances and an increased risk for incident chronic pain disorders (30-33).

In the context of RA, patients and healthcare providers often assume that disturbed sleep is due to pain from joint inflammation, but data on this relationship are sparse. In a laboratory-based study, patients with RA reported a larger increase in self-reported pain after partial night sleep deprivation than controls who were pain-free prior to partial night sleep deprivation (4). These patients also reported an increase in joint pain severity and the number of painful joints post sleep deprivation. These findings were further supported by an increase in clinician-assessed tender or swollen joint count. Taken together, these results support a role for sleep deprivation inducing increased self-reported pain in patients with RA.

The mechanisms underlying the association between sleep disturbances and self-reported pain intensity in patients with RA have not been well established, though cross-sectional studies suggest pain sensitization may play a role. In a cohort of 59 female patients with established RA, sleep disturbance was associated with low PPTs at both articular and non-articular sites, providing support for a link between sleep disturbance and abnormal CNS regulation of pain in RA (1). A subsequent study showed that patients with RA had impaired CPM and impaired sleep, compared to pain-free controls, and mediation analyses indicated that the relationship between RA and impaired CPM might partially be attributed to sleep problems (34).

Our study builds upon these studies and adds information about the mechanisms underlying the relationship between sleep disturbances and patient-reported pain. The observation that PPTs at articular and non-articular sites partially mediated the sleep-pain relationship suggests

that sleep may influence pain via both peripheral and central sensitization. The observation that TS at the forearm partially mediated the sleep-pain relationship suggests that the specific mechanism of central sensitization may occur, in part, through ascending pain facilitation. Interestingly, however, sleep disturbance was not significantly associated with TS at the wrist, suggesting that the role of central facilitation is complex and may vary depending on other factors, such as inflammation and/or joint vs. muscle activation. For example, it is possible that inflammation at the wrist may confound the relationship between sleep disturbance and TS at the wrist.

Contrary to previous studies indicating a potential role for endogenous pain inhibition in the relationship between sleep disturbances and pain intensity, we did not observe significant associations between CPM and either sleep disturbance or patient-reported pain intensity. The interpretation of results from the CPM paradigm in patients with mixed pain states, such as RA, is challenging. In a previous study, we showed that patients with established RA have impaired CPM, compared to healthy controls, which likely contributes to the development and/or maintenance of chronic pain, even when joint inflammation is controlled (34). However, acute pain from active joint inflammation may increase CPM as pain induces endogenous pain inhibition. This possibility is supported by previous analyses from the CPIRA cohort, showing that patients with low CPM reported less pain interference than patients with high CPM (3). Thus, the measured CPM value may reflect multiple driving forces, which differ from patient to patient. In addition, CPM measurement was more variable than other QST measures in CPIRA indicated by a lower ICC (11). This might explain the lack of association between CPM and sleep disturbance as well as pain intensity. Further studies are needed to elucidate the role of

descending pain inhibition in the relationship between sleep disturbance and patient-reported pain in patients with RA.

While our analyses revealed that, the proportion of the effect of sleep disturbances on subsequent pain intensity was statistically significant for trapezius PPT, wrist PPT, knee PPT, and arm TS, the magnitudes of associations were small, ranging from 11.6% to 19.5%. This observation suggests that more than one pathway is likely involved in the association between sleep disturbance and patient-reported pain intensity. Other potential pathways could involve proinflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) which have been shown to increase after sleep restriction in healthy young adults (35). IL-6 and TNF-α are capable of inducing allodynia and hyperalgesia in animal models (36). Further studies are needed to investigate this possibility in humans, particularly those with systemic inflammatory conditions, such as RA.

This study has notable strengths. The study population included longitudinal data from both female and male patients with active RA who were comprehensively phenotyped using multiple QST modalities to assess pain sensitization. This study also has several limitations. First, the total and direct effects of sleep disturbance on subsequent pain were small, and the beta-coefficients for the indirect effects were low. Prior studies reporting associations between sleep disturbance and pain intensity have either been cross-sectional analyses or analyses examining next-day pain (4, 37, 38). It is possible that the magnitude of association would be higher if the duration between sleep assessment and pain intensity assessment were shorter. In addition, confounding by unmeasured factors may have impacted observed relationships. Second, causality cannot be determined from this observational study. The exposure (baseline sleep

disturbance) and the mediator (baseline QST) were both assessed at the baseline visit, limiting our understanding of the causal relationship between the exposure and mediator. While the measure of sleep disturbance was based on recall over the past 7 days, the ideal mediation analysis design would sequentially assess the exposure, mediator, and outcome at different time points. Third, we were not able to control for confounding due to changes in clinical characteristics (such as change in swollen joint count, etc.). To satisfy the temporal ordering of a mediation analysis, we would need measurements from at least three time points, but we only have assessments at two time points in this study. Finally, sleep disturbance was only assessed by self-report rather than objectively (e.g., polysomnograms or actigraphy).

In summary, this study suggests pain sensitization may be one mechanism through which sleep disturbance contributes to subsequent pain intensity. We observed that trapezius PPT, wrist PPT, knee PPT, and temporal summation at the forearm were statistically significant mediators of the relationship between baseline sleep disturbance and patient-reported pain at 12 weeks after initiating a new DMARD. However, the magnitudes of association were small, indicating that other, unmeasured pathways likely contribute to this relationship. Intervention studies are needed to establish causality and determine whether improving sleep can improve pain in patients with RA.

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FIGURE LEGEND

Figure 1. Diagram for the mediation effect of QST in the relationship between sleep disturbance in the past week and subsequent pain in 12 weeks

TABLES

Table 1. Baseline characteristics of demographic and health factors, quantitative sensory testing (QST), and sleep disturbance, n=227*

Demographic and Health Characteristics	**Mean (SD) or %**
Age (yrs)	54.88 (14.14)
Female sex, %	81.1%
BMI	28.75 (6.84)
Overweight, %	31.3%
Obese, %	37.4%
RA disease duration (yrs)	10.18 (12.27)
Depression	51.04 (9.32)
Comorbidity	1.29 (1.00)
Pain intensity	5.14 (2.30)
Swollen joint count	5.14 (5.33)
Glucocorticoid use, %	42.3%
QST	
Peripheral and central pain sensitization	
Wrist PPT	2.96 (1.59)
Knee PPT	5.36 (2.81)
Central pain sensitization	
Trapezius PPT	2.90 (1.58)

Thumbnail PPT	3.61 (1.86)
Pain facilitation	
Arm TS	12.99 (14.81)
Wrist TS	13.33 (14.45)
Pain inhibition	
CPM*	1.41 (0.35)
Sleep disturbance during the past week	54.58 (8.96)

BMI = Body mass index, PPT = pressure pain threshold, TS = temporal summation, CPM = conditional pain modulation

*n=222 for CPM

Table 2. Spearman correlations (P-value) of QST with sleep disturbance during the past week and subsequent pain in 12 weeks, n=227*

QST	Sleep Disturbance and QST Correlation Coefficient (P-value)	QST and Pain Correlation Coefficient (P-value)
Peripheral and central pain sensitization		
Wrist PPT	-0.24 (<0.01)	-0.28 (<0.01)
Knee PPT	-0.27 (<0.01)	-0.33 (<0.01)
Central pain sensitization		
Trapezius PPT	-0.25 (<0.01)	-0.30 (<0.01)
Thumbnail PPT	-0.17 (0.01)	-0.23 (<0.01)
Pain facilitation		
Arm TS	0.17 (0.01)	0.30 (<0.01)
Wrist TS	0.10 (0.12)	0.23 (<0.01)
Pain inhibition		
CPM*	-0.05 (0.55)	0.04 (0.53)

PPT = pressure pain threshold, TS = temporal summation, CPM = conditional pain modulation

*n=222 for CPM

Table 3. Results from mediation analysis adjusted for confounding factors* for half standardized deviation (5-unit) increase in sleep disturbance scale on subsequent pain intensity in 12 weeks, n=227

Mediator	Total effect of sleep disturbance (5-unit) on pain intensity (95% CI)	Direct effect of sleep disturbance (5-unit) on pain intensity (95% CI)	Indirect effect of sleep disturbance (5-unit) on pain intensity mediated by QST (95% CI)	% Mediated (95% CI)
Peripheral and central pain sensitization				
Wrist PPT	0.32 (0.11, 0.50)	0.28 (0.08, 0.48)	0.04 (0.00, 0.10)	11.57 (0.67, 47.56)
Knee PPT	0.32 (0.11, 0.50)	0.25 (0.12, 0.50)	0.06 (0.01, 0.13)	19.13 (3.35, 58.34)
Central pain sensitization				
Trapezius PPT	0.32 (0.11, 0.50)	0.27 (0.06, 0.46)	0.05 (0.00, 0.12)	15.54 (0.89, 54.77)
Thumbnail PPT	0.32 (0.11, 0.50)	0.28 (0.09, 0.49)	0.03 (0.00, 0.09)	9.98 (-0.37, 44.37)
Pain facilitation				
Arm TS	0.32 (0.11, 0.50)	0.26 (0.07, 0.44)	0.06 (0.02, 0.14)	19.46 (5.08, 58.52)

PPT = pressure pain threshold, TS = temporal summation, CPM = conditional pain modulation

* Adjusted for age, sex, body-mass index, RA duration, comorbidity, depression symptoms, swollen joint count, glucocorticoid use, and study site.