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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) experience 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. The present study was undertaken to examine 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 antirheumatic drug. Baseline QST included pressure pain thresholds at articular (wrists, knees) and nonarticular (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 (PROMIS). 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 units in sleep disturbance = 0.32 (95% confidence interval 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.

INTRODUCTION

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 antirheumatic 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 2 broad categories: peripheral sensitization and central sensitization. For the purpose of this article, we define central sensitization as any abnormality of the pain-processing pathways of the central nervous system. 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 conditioned 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 nonarticular 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.

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SIGNIFICANCE & INNOVATIONS

- This is the first multicenter 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 antirheumatic drug significantly predicted pain intensity after 12 weeks of treatment with disease-modifying antirheumatic drugs.
- Quantitative sensory testing 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% to 19%.
- Pain sensitization may be one mechanism through which sleep disturbance contributes to subsequent patient-reported pain intensity.

Sleep problems are common in patients with RA. More than one-half of patients with RA report problems with sleep, with a prevalence up to 3-fold greater than that of the general population (4). Patients with RA frequently report fragmented sleep, difficulty falling asleep, and nonrestorative 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 nonarticular 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).

PATIENTS AND METHODS

Study population. This study examined longitudinal data from the multisite, prospective, observational Central Pain in Rheumatoid Arthritis (CPIRA) study (3). CPIRA recruited 295 patients from 5 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 the American College of Rheumatology 2010 criteria for RA (7) and to 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 tumor necrosis factor [TNF] inhibitor to another), daily use of ≥10 mg of 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 3 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 version 1.1 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 an SD of 10 via the PROMIS Assessment Center (http://www.assessmentcenter.net/acl/) (8). Higher scores indicate worse sleep disturbance. Based on previous literature, one-half of an SD (5 units) in sleep disturbance scores was considered an approximation of a moderate-sized effect (9).

Potential mediator (QST at baseline). Trained research coordinators conducted QST at baseline study visits before patients started or added a new DMARD (10). Training included a 1-day, in-person session, as well as assessment of intraclass correlations. The following 3 modalities of QST were performed: 1) PPTs, 2) TS, and 3) 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.

PPTs (overall pain sensitization). 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 nonarticular sites indicate central mechanisms of sensitization (10,11). PPTs were assessed using a Wagner Force 10 FDX algometer (Wagner Instruments) at articular (bilateral wrists and knees) and nonarticular (bilateral trapezius muscles and thumbnails) sites. Pressure was increased at a rate of ~0.50 kgf per second. The pressure reading (kgf) at which the participant first reported pain was recorded, and the average of 3 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.

TS (pain facilitation). TS is considered a measure of the pain facilitatory pathways of the central nervous system (11,12). 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 of 100 on a visual analog scale or the heaviest probe (if pain ratings were <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 (10,12,13).

CPM (pain inhibition). CPM is considered a measure of endogenous descending pain inhibition (10,14,15). 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 (16–20). Higher values reflected efficient descending modulation of pain, while lower values reflected inefficient descending pain inhibition (10).

Baseline confounders. We considered baseline age, sex, body mass index (BMI), RA disease duration, comorbidity, depressive symptoms, swollen joint count, glucocorticoid 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 ≤ BMI <30 kg/m^2 and BMI ≥30 kg/m^2, respectively. Comorbidity was assessed using a modified Charlson comorbidity index (21). Depressive symptoms were measured using the T score from the PROMIS depression CAT (8). 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 (22). For this purpose, we calculated Spearman's 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) (22,23). 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 (22). 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 5,000 replicates were used to estimate the 95% confidence intervals (95% CIs) 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

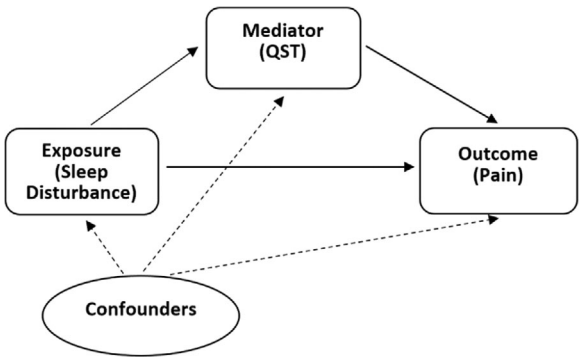

Figure 1. Diagram for the mediation effect of quantitative sensory testing (QST) in the relationship between sleep disturbance in the past week and subsequent pain at 12 weeks.

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

Characteristic	Value
Age, years	54.88 ± 14.14
Female sex, %	81.1
BMI	28.75 ± 6.84
Overweight, %	31.3
Obese, %	37.4
RA disease duration, years	10.18 ± 12.27
PROMIS depression T score	51.04 ± 9.32
Modified Charlson comorbidity score	1.29 ± 1.00
Pain intensity score	5.14 ± 2.30
Swollen joint count	5.14 ± 5.33
Glucocorticoid use, %	42.3
QST scores	
Peripheral and central pain sensitization	
Wrist PPT, kgf	2.96 ± 1.59
Knee PPT, kgf	5.36 ± 2.81
Central pain sensitization	
Trapezius PPT, kgf	2.90 ± 1.58
Thumbnail PPT, kgf	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
PROMIS sleep disturbance score	54.58 ± 8.96

* Values are the mean ± SD unless indicated otherwise. BMI = body mass index; CPM = conditioned pain modulation; PPT = pressure pain threshold; PROMIS = Patient-Reported Outcomes Measurement Information System; TS = temporal summation.
† N = 222 for CPM.

used in the statistical tests. All statistical analyses were conducted using SAS, version 9.4.

RESULTS

Participant characteristics. The study cohort was primarily female (81.1%) with a mean ± SD age of 54.9 ± 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 mean ± SD disease duration of 10.2 ± 12.3 years and 5.1 ± 5.3 swollen joints with a mean ± SD pain intensity of 5.1 ± 2.3. Forty-two percent of participants reported glucocorticoid use. The baseline mean ± SD PROMIS sleep disturbance score was 54.6 ± 9.0. At the second visit, most of this cohort had an improved C-reactive protein level and/or swollen joint count (84%), but >94% of these participants still reported subsequent pain, with a mean ± SD pain intensity of 3.8 ± 2.4.

Associations between baseline pain sensitization with the exposure and the outcome. The Spearman's 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's 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% 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%

Table 2. Spearman's correlations of quantitative sensory testing (QST) with sleep disturbance during the past week and subsequent pain in 12 weeks (n = 227)*

QST	Sleep disturbance and QST correlation coefficient	*P*	QST and pain correlation coefficient	*P*
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	–0.2	<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

* CPM = conditioned pain modulation; PPT = pressure pain threshold; TS = temporal summation.
† N = 222 for CPM.

Table 3. Results from a mediation analysis adjusted for confounding factors for the effect of an increase of one-half SD (5 units) in the sleep disturbance scale on subsequent pain intensity at 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)

* Adjusted for age, sex, body mass index, duration of rheumatoid arthritis, comorbidity, depression symptoms, swollen joint count, glucocorticoid use, and study site. 95% CI = 95% confidence interval; PPT = pressure pain threshold; QST = quantitative sensory testing; TS = temporal summation.

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; although, 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 (24). Several studies of healthy subjects have shown that experimentally induced sleep deprivation leads to enhanced pain sensitivity, assessed by PPTs (25). In addition, a few studies have reported that sleep deprivation is associated with significant increases in pain facilitation, assessed by TS (26,27), as well as impaired pain inhibition, assessed by CPM (26,28). Large, longitudinal cohort studies also have reported associations between sleep disturbances and an increased risk for incident chronic pain disorders (29–32).

In the context of RA, patients and health care 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, although cross-sectional studies suggest that 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 nonarticular sites, providing support for a link between sleep disturbance and abnormal central nervous system 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 (33).

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 nonarticular 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 versus 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 (33). 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 intraclass correlation coefficient (10). 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 >1 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 TNF, which have been shown to increase after sleep restriction in healthy young adults (34). IL-6 and TNF are capable of inducing allodynia and hyperalgesia in animal models (35). 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 (4,36,37). 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 3 time points, but we only have assessments at 2 time points in this study. Finally, sleep disturbance was only assessed by self-report rather than objectively (e.g., polysomnograms or actigraphy).

In conclusion, this study suggests that 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 TS 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.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Lee had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Song, Muhammad, Neogi, Dunlop, Bolster, Bingham, Clauw, Marder, Lee.

Acquisition of data. Wohlfahrt, Lee.

Analysis and interpretation of data. Song, Muhammad, Dunlop, Lee.

REFERENCES

1. Lee YC, Chibnik LB, Lu B, et al. The relationship between disease activity, sleep, psychiatric distress and pain sensitivity in rheumatoid arthritis: a cross-sectional study. Arthritis Res Ther 2009;11:R160.
2. Ten Klooster PM, Veehof MM, Taal E, et al. Changes in priorities for improvement in patients with rheumatoid arthritis during 1 year of anti-tumour necrosis factor treatment. Ann Rheum Dis 2007;66:1485–90.
3. Heisler AC, Song J, Dunlop DD, et al. Association of pain centralization and patient-reported pain in active rheumatoid arthritis. Arthritis Care Res (Hoboken) 2020;72:1122–9.
4. Irwin MR, Olmstead R, Carrillo C, et al. Sleep loss exacerbates fatigue, depression, and pain in rheumatoid arthritis. Sleep 2012;35:537–43.
5. Taylor-Gjevre RM, Gjevre JA, Nair B, et al. Components of sleep quality and sleep fragmentation in rheumatoid arthritis and osteoarthritis. Musculoskeletal Care 2011;9:152–9.
6. Wolfe F, Michaud K, Li T. Sleep disturbance in patients with rheumatoid arthritis: evaluation by medical outcomes study and visual analog sleep scales. J Rheumatol 2006;33:1942–51.
7. Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569–81.
8. Wohlfahrt A, Bingham CO III, Marder W, et al. Responsiveness of patient-reported outcomes measurement information system measures in rheumatoid arthritis patients starting or switching a

disease-modifying antirheumatic drug. Arthritis Care Res (Hoboken) 2019;71:521–9.
9. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. New York (NY): Routledge; 1988.
10. Lee YC, Bingham CO III, Edwards RR, et al. Association between pain sensitization and disease activity in patients with rheumatoid arthritis: a cross-sectional study. Arthritis Care Res (Hoboken) 2018;70: 197–204.
11. Graven-Nielsen T, Arendt-Nielsen L. Assessment of mechanisms in localized and widespread musculoskeletal pain. Nat Rev Rheumatol 2010;6:599–606.
12. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain 2011;152 Suppl:S2–15.
13. Rolke R, Magerl W, Campbell KA, et al. Quantitative sensory testing: a comprehensive protocol for clinical trials. Eur J Pain 2006;10:77–88.
14. Yarnitsky D. Role of endogenous pain modulation in chronic pain mechanisms and treatment. Pain 2015;156 Suppl 1:S24–31.
15. Boyden SD, Hossain IN, Wohlfahrt A, et al. Non-inflammatory causes of pain in patients with rheumatoid arthritis. Curr Rheumatol Rep 2016;18:30.
16. Martel MO, Petersen K, Cornelius M, et al. Endogenous pain modulation profiles among individuals with chronic pain: relation to opioid use. J Pain 2019;20:462–71.
17. Goodin BR, McGuire L, Allshouse M, et al. Associations between catastrophizing and endogenous pain-inhibitory processes: sex differences. J Pain 2009;10:180–90.
18. Edwards RR, Fillingim RB, Ness TJ. Age-related differences in endogenous pain modulation: a comparison of diffuse noxious inhibitory controls in healthy older and younger adults. Pain 2003;101:155–65.
19. Edwards RR, Ness TJ, Weigent DA, et al. Individual differences in diffuse noxious inhibitory controls (DNIC): association with clinical variables. Pain 2003;106:427–37.
20. Edwards RR, Grace E, Peterson S, et al. Sleep continuity and architecture: associations with pain-inhibitory processes in patients with temporomandibular joint disorder. Eur J Pain 2009;13:1043–7.
21. Katz JN, Chang LC, Sangha O, et al. Can comorbidity be measured by questionnaire rather than medical record review? Med Care 1996;34:73–84.
22. Valeri L, Vanderweele TJ. Mediation analysis allowing for exposure-mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros. Psychol Methods 2013;18:137–50.
23. SAS Institute. SAS/STAT 14.3 user's guide. Carey (NC): SAS Institute; 2017.
24. Finan PH, Goodin BR, Smith MT. The association of sleep and pain: an update and a path forward. J Pain 2013;14:1539–52.
25. Schrimpf M, Liegl G, Boeckle M, et al. The effect of sleep deprivation on pain perception in healthy subjects: a meta-analysis. Sleep Med 2015;16:1313–20.
26. Staffe AT, Bech MW, Clemmensen SL, et al. Total sleep deprivation increases pain sensitivity, impairs conditioned pain modulation and facilitates temporal summation of pain in healthy participants. PLoS One 2019;14:e0225849.
27. Simpson NS, Scott-Sutherland J, Gautam S, et al. Chronic exposure to insufficient sleep alters processes of pain habituation and sensitization. Pain 2018;159:33–40.
28. Smith MT, Edwards RR, McCann UD, et al. The effects of sleep deprivation on pain inhibition and spontaneous pain in women. Sleep 2007;30:494–505.
29. Mork PJ, Nilsen TI. Sleep problems and risk of fibromyalgia: longitudinal data on an adult female population in Norway. Arthritis Rheum 2012;64:281–4.
30. Nitter AK, Pripp AH, Forseth KO. Are sleep problems and non-specific health complaints risk factors for chronic pain? A prospective population-based study with 17 year follow-up. Scand J Pain 2012; 3:210–7.
31. Odegard SS, Sand T, Engstrom M, et al. The long-term effect of insomnia on primary headaches: a prospective population-based cohort study (HUNT-2 and HUNT-3). Headache 2011;51:570–80.
32. Boardman HF, Thomas E, Millson DS, et al. The natural history of headache: predictors of onset and recovery. Cephalalgia 2006;26: 1080–8.
33. Lee YC, Lu B, Edwards RR, et al. The role of sleep problems in central pain processing in rheumatoid arthritis. Arthritis Rheum 2013;65: 59–68.
34. Vgontzas AN, Zoumakis E, Bixler EO, et al. Adverse effects of modest sleep restriction on sleepiness, performance, and inflammatory cytokines. J Clin Endocrinol Metab 2004;89:2119–26.
35. Ji RR, Nackley A, Huh Y, et al. Neuroinflammation and central sensitization in chronic and widespread pain. Anesthesiology 2018;129: 343–66.
36. Lyne L, Akerstedt T, Alfredsson L, et al. Sleep problems in rheumatoid arthritis over 12 years from diagnosis: results from the Swedish EIRA study. RMD Open 2022;8:e001800.
37. Purabdollah M, Lakdizaji S, Rahmani A. Relationship between sleep, pain and inflammatory markers in patients with rheumatoid arthritis. J Caring Sci 2017;6:249–55.