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Association of Pain Centralization and Patient-Reported Pain in Active Rheumatoid Arthritis

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Objective. Pain is a significant burden for patients with rheumatoid arthritis (RA) despite advancements in treatment. We undertook this study to examine the independent contribution of pain centralization to the pain experience of patients with active RA.

Methods. A total of 263 RA patients with active disease underwent quantitative sensory testing (QST), including assessment of extraarticular pressure pain thresholds (PPTs), temporal summation (TS), and conditioned pain modulation (CPM). The pain experience was assessed by a pain intensity numeric rating scale and the Patient-Reported Outcomes Measurement Information System pain interference computerized adaptive test. We examined associations between QST measures and pain intensity and pain interference. Multiple linear regression models were adjusted for demographic and clinical variables, including swollen joint count and C-reactive protein level.

Results. Patients with the lowest PPTs (most central dysregulation) reported higher pain intensity than patients with the highest PPTs (adjusted mean difference 1.02 [95% confidence interval (95% CI) 0.37, 1.67]). Patients with the highest TS (most central dysregulation) had higher pain intensity than those with the lowest TS (adjusted mean difference 1.19 [95% CI 0.54, 1.84]). CPM was not associated with differences in pain intensity. PPT and TS were not associated with pain interference. Patients with the lowest CPM (most centrally dysregulated) had lower pain interference than patients with the highest CPM (adjusted mean difference –2.35 [95% CI –4.25, –0.44]).

Conclusion. Pain centralization, manifested by low PPTs and high TS, was associated with more intense pain. Clinicians should consider pain centralization as a contributor to pain intensity, independent of inflammation.

INTRODUCTION

Pain is a prevalent symptom in patients with rheumatoid arthritis (RA) and is a high patient priority for improvement in care (1,2). While significant advancements have been made in the treatment of RA, pain continues to be a significant burden (3). Thus, a more complete understanding of the mechanisms underlying pain in RA is needed.

Pain in RA has been classically understood as a consequence of inflammation acting on peripheral nociceptors. However, recent observations have expanded the understanding of pain in RA to include a role for central nervous system (CNS) modulation of pain perception, termed "pain centralization" (4–7). For instance, the proinflammatory cytokines tumor necrosis factor and interleukin-6 have been shown in animal models to directly act on spinal cord neurons, eliciting development of spinal hyperexcitability to pain. In some cases, this hyperexcitability persists despite neutralization of inflammation (8–11). Similarly, in patients with RA, pain often persists despite objective evidence of improvement in inflammation demonstrated by normalization of inflammatory markers and reduced swollen joint counts (12,13). Increased sensitivity to pain in regions distant from joints has also been noted, providing

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SIGNIFICANCE & INNOVATIONS

- This is the first multicenter study to determine the association between pain centralization (assessed by pressure pain thresholds, temporal summation, and conditioned pain modulation) and patient-reported pain in patients with active rheumatoid arthritis (RA) necessitating change in therapy.
- Pain centralization is associated with increased patient-reported pain, independent of inflammation.
- Clinicians should consider pain centralization as a contributor to patient-reported pain when tailoring individualized therapy for patients with RA.

further support for the role of pain centralization in RA (14). Greater understanding of the role of pain centralization in RA is needed because patients with pain driven predominantly by pain centralization may be treated better by centrally acting agents (e.g., serotonin norepinephrine reuptake inhibitors and gabapentinoids) or cognitive behavioral therapy rather than changes in or escalation of treatment with disease-modifying antirheumatic drugs (DMARDs).

Quantitative sensory testing (QST) is a semiquantitative method that can detect abnormalities in pain processing. Three commonly used QST methodologies include pressure pain thresholds (PPTs), temporal summation (TS), and conditioned pain modulation (CPM). Decreased PPTs at swollen joints indicate increased pain sensitivity as a consequence of local inflammation, while decreased PPTs at nonarticular sites are thought to be indicative of pain centralization (15,16). Abnormal TS represents increased responsiveness of the dorsal horn neurons to peripheral stimulation, which is a specific mechanism of pain centralization (17). An additional mechanism of pain centralization is decreased activity of the descending analgesic pathways, which can be assessed by the CPM paradigm (18). We hypothesized that central dysregulation of pain processing, manifested by low extraarticular PPT, exaggerated TS, and blunted CPM, would be associated with patient-reported measures of pain in patients with active RA and that this association would be independent of inflammatory activity.

PATIENTS AND METHODS

Study population. The Central Pain in Rheumatoid Arthritis study is an observational, multicenter study designed to examine the relationship between QST-assessed pain mechanisms and patient-reported measures of pain experience in patients with active RA undergoing initiation or change in DMARD therapy (19). A total of 295 subjects from 5 US academic medical centers were recruited from January 2014 through June 2017.

Participants meeting the following criteria were included for the study: a diagnosis of RA based on the American College of Rheumatology/European League Against Rheumatism 2010 classification criteria; active disease that necessitates initiation of or change in treatment with DMARDs; and the ability to participate in a baseline study visit prior to the change in or initiation of DMARDs (20). Subjects were excluded for the following reasons: peripheral neuropathy; peripheral vascular disease resulting in severe claudication or rest pain; Raynaud's phenomenon; chronic opioid use; changing dose of a centrally acting pain medication (e.g., amitriptyline, duloxetine, milnacipran, gabapentin, or pregabalin) within 3 months of study enrollment; or glucocorticoid use equivalent to >10 mg daily of prednisone.

QST. QST was performed as previously described (21). All assessors underwent a 1-day training session to ensure standardization of QST procedures across sites. We calculated a two-way, mixed, single-score, intraclass correlation coefficient (ICC) (1,3) to assess reproducibility of QST between assessors (22). According to Cicchetti et al, an ICC from 0.4 to 0.59 was considered fair, 0.6 to 0.74 was considered good, and 0.75 to 1 was considered excellent (23). ICCs ranged from 0.71 to 0.9 for PPTs and TS, whereas the ICC for CPM was 0.45 (19).

PPTs. A Force Ten FDX algometer (Wagner Instruments) was used to determine extraarticular PPTs at the bilateral trapezius muscles. The algometer probe was placed on the center of the trapezius muscle. Pressure on the algometer was increased at a rate of 0.5 kgf/second until pain was reported. Three trials were performed at each trapezius muscle. The mean PPT was determined by averaging the 3 trials on both sides. We chose the trapezius as the primary site to evaluate pain centralization for the following reasons: 1) the trapezius is a commonly used site for assessment of PPTs in the pain literature; 2) the literature supports standard values for PPT at the trapezius in normal adults; and 3) the trapezius is a site distant from joints commonly affected by RA, enabling assessment of pain centralization without the confounding effects of peripheral sensitization due to active joint inflammation (24–27).

TS. TS was assessed at the dorsal forearm using 6 calibrated probes of increasing weight. The probes were tested on the subject's forearm using sequentially increasing weight until the patient reported a pain level of 30–40 on a 100-point scale. We used the probe that generated a pain score of 30–40 for further testing. The probe was tapped 10 times with each tap lasting 0.5 seconds with a 1-second interval between taps. The subject rated the pain produced by the probe at taps 1, 5, and 10. TS was determined by subtracting the pain rating for tap 1 from the pain rating for tap 10. We repeated the test 3 times. The mean TS was calculated as the average of the 3 trials. We divided the resulting value by 10 to normalize TS to the units used in the standard pain scale. Higher TS was considered to be indicative of central sensitization. As with PPT, we chose the dorsal forearm due to its distance from articular sites to avoid confounding from peripheral sensitization.

CPM. CPM was assessed using a conditioning stimulus (a painful stimulus that activates the descending analgesic pain pathways) and a test stimulus (a painful stimulus used to assess pain sensitivity). The conditioning procedure involved placing the subject's right hand in a cold water bath between 5°C and 7°C. The test stimulus was produced by placing an algometer probe at the center of the left trapezius muscle (contralateral to the hand placed in the cold water bath) and applying a force of 0.5 kgf/second until pain was reported by the participant. PPT was measured immediately prior to cold bath immersion. PPT was again assessed at 20 seconds of cold bath immersion or immediately after removal of the hand if pain was intolerable before the 20 seconds had passed. CPM was calculated as the ratio of the second PPT to the first PPT. Values >1 represent efficient CPM, whereas values <1 represent inefficient CPM.

Clinical variables. We assessed the subjects' pain experience using Patient-Reported Outcomes Measurement Information System (PROMIS) questionnaires. The PROMIS global health short form was administered, while pain interference, depression, anxiety, and sleep disturbance were assessed using computerized adaptive testing (CAT) (28–31). PROMIS sleep disturbance was stratified into categories of none, mild, and moderate/severe (32). Clinical variables were age, sex, race, educational status, RA duration, and body mass index (BMI). Blood serum was analyzed for C-reactive protein (CRP), rheumatoid factor (RF), and anti–citrullinated protein antibody at a single laboratory. A standardized joint count (28 swollen joints) was obtained by trained study staff members. Comorbidity was assessed using a modified Charlson comorbidity index score (33).

Statistical analysis. The primary outcome was overall pain intensity assessed on a 0–10 numeric rating scale (item Global07 on the PROMIS global health short form). The secondary outcome was the PROMIS pain interference CAT score. Pain interference measures the extent to which pain interferes with patients' physical, mental, and social activities (30). The primary predictor was the PPT at the trapezius muscle. Secondary predictors were TS and CPM. To avoid assumptions of linearity and to address differences in PPT responses between men and women, the QST measures were categorized by sex-specific tertiles. For ease of interpretation, the tertiles are presented by degree of central dysregulation (least, moderate, and most). More central dysregulation corresponded to decreasing PPT and CPM tertiles (T3, T2, T1) and increasing TS tertiles (T1, T2, T3).

Standard covariates included age, sex, race, and BMI. Education level, anxiety, and sleep disturbance were included as covariates due to their association with pain based on literature review (26,34,35). We included seropositivity (RF and/or citrullinated peptide positive), disease duration, and the modified Charlson comorbidity index score as covariates per clinical experience. Swollen joint count (SJC) and CRP level were included as covariates because our objective was to assess the role of pain centralization on pain experience independent of inflammation. Finally, we included a site variable to account for potential differences between patient populations across study sites. These variables were included in all statistical models. The relationship between QST tertiles and patient-reported pain outcomes was evaluated using multiple linear regression. All analyses were performed using SAS, version 9.4.

RESULTS

Clinical characteristics. This study sample of 263 patients with RA had a mean age of 57.4 years (range 18–81 years) and included primarily white (75%) and female (82%) patients with an average RA disease duration of 9.8 years (Table 1). Another 33 patients from the parent study did not contribute to these analyses due to missing data (4 with missing outcome data, 11 with missing predictor data, and 18 with missing covariate data). These patients were similar to those in the study sample with the exception of statistically significant differences in education (75.7% with some college or higher in the included sample versus 48.5% in the excluded sample), anxiety (mean PROMIS T score of 53.6 in the included sample versus 57.5 in the excluded sample), and sleep disturbance (25.1% with moderate/severe sleep disturbance in the included sample versus 43.3% with moderate/severe sleep disturbance in the excluded sample).

Patient-reported pain measures by QST tertile. The unadjusted mean pain intensity and pain interference scores for each QST tertile group are summarized in Tables 2–4. With increasing central dysregulation as defined by PPT, mean scores

Table 1. Clinical characteristics of the subjects (n = 263 patients)*

Characteristic	Value
Age, years	54.7 ± 13.8
Female sex, %	81.8
White race, %	74.9
BMI, kg/m^2	28.6 ± 6.8
Some college or higher, %	75.7
Seropositive, %	73.0
Disease duration, years	9.8 ± 11.9
CRP, mg/liter	7.9 ± 12.2
SJC	5.1 ± 5.0
PROMIS depression score	50.9 ± 9.1
PROMIS anxiety score	53.6 ± 8.9
PROMIS sleep disturbance score, %	
None	54.4
Mild	20.5
Moderate/severe	25.1
Modified Charlson comorbidity index score	1.3 ± 1.1
DAS28 score	3.8 ± 1.1
CDAI score	23.7 ± 13.9

* Values are the mean ± SD unless indicated otherwise. BMI = body mass index; CRP = C-reactive protein; SJC = swollen joint count; PROMIS = Patient-Reported Outcomes Measurement Information System; DAS28 = Disease Activity Score in 28 joints; CDAI = Clinical Disease Activity Index.

Table 2. Pain measures by PPT trapezius tertile, n = 263 patients*

	Least central dysregulation (PPT tertile 3; n = 90)	Moderate central dysregulation (PPT tertile 2; n = 90)	Most central dysregulation (PPT tertile 1; n = 83)
PPT trapezius, kgf/second	4.62 ± 1.58	2.70 ± 0.69	1.48 ± 0.57
Pain intensity (NRS 0–10)	4.51 ± 2.38	5.11 ± 2.17	5.95 ± 2.08
Pain interference, T score	58.66 ± 8.05	60.32 ± 6.53	62.13 ± 6.32

* Values are the mean ± SD. PPT = pressure pain threshold; NRS = Numeric Rating Scale.

increased for both pain intensity (least: 4.51, moderate: 5.11, and most: 5.95) and pain interference (least: 58.66, moderate: 60.32, and most: 62.13). Similarly, with increasing central dysregulation as defined by TS, mean scores increased for both pain intensity (least: 4.24, moderate: 5.55, and most: 5.71) and pain interference (least: 58.58, moderate 60.69, and most: 61.79). However, as central dysregulation defined by CPM increased, no trend was observed in pain intensity or pain interference.

Associations between QST tertile and measures of patient-reported pain. *Trapezius PPTs*. In both unadjusted and adjusted analyses, greater central pain dysregulation, assessed by trapezius PPT, was significantly associated with higher pain intensity ($P \leq 0.002$ for trend) (Table 5). Compared to the least dysregulated group (highest tertile of PPT), mean pain intensity was 0.48 points higher in the group with moderate central dysregulation (middle tertile of PPT) and 1.02 points higher in the group with the most central dysregulation (lowest tertile of PPT) in adjusted analyses. Covariates in the PPT model associated with greater pain intensity included sleep disturbance and less education. Greater central pain dysregulation was also significantly associated with more pain interference in unadjusted analyses (P for trend = 0.001). However, the trend was attenuated in the adjusted analysis (P for trend = 0.066). In addition, sleep disturbance, anxiety, and CRP level were all significantly associated with greater pain interference in the PPT model.

TS. In both unadjusted and adjusted analyses, greater central pain dysregulation, assessed by TS, was significantly associated with higher pain intensity ($P < 0.001$ for trend) (Table 5). Compared to the least dysregulated group (lowest tertile of TS), mean pain intensity was 0.96 points higher in the group with moderate central dysregulation (middle tertile of TS) and 1.19 points higher in the group with the most central dysregulation (highest tertile of TS) in adjusted analyses. Covariates in the TS model associated with greater pain intensity included sleep disturbance and less education. Greater central pain dysregulation was also significantly associated with more pain interference in unadjusted analyses ($P = 0.004$ for trend). However, the trend was attenuated in the adjusted analysis ($P = 0.205$ for trend). In addition, sleep disturbance, anxiety, CRP level, and less education were all significantly associated with greater pain interference in the TS model.

CPM. CPM was not associated with pain intensity in unadjusted analyses or after adjusting for covariates, nor was a trend observed. Only sleep disturbance and less education were significantly associated with pain intensity in the CPM model. However, lower CPM, thought to be indicative of greater central pain dysregulation, was significantly associated with lower pain interference in adjusted analyses ($P = 0.016$ for trend). Compared to the least dysregulated group (highest tertile of CPM), mean pain interference was 1.18 points lower in the group with moderate central dysregulation (middle tertile of CPM) and 2.35 points lower in the group with the most central dysregulation (lowest tertile of CPM). Sleep disturbance, anxiety, CRP level, and white race were also associated with greater pain interference.

DISCUSSION

This study implicates pain centralization as a contributor to pain in patients with RA independent of the effects of inflammation. Specifically, we observed an association between low extraarticular PPTs and high TS with pain intensity, which persisted

Table 3. Pain measures by TS tertile, n = 263 patients*

	Least central dysregulation (TS tertile 1; n = 85)	Moderate central dysregulation (TS tertile 2; n = 102)	Most central dysregulation (TS tertile 3; n = 76)
TS (range 0–100)	0.11 ± 2.68	8.78 ± 4.64	31.37 ± 12.82
Pain intensity (NRS 0–10)	4.24 ± 2.12	5.55 ± 2.34	5.71 ± 2.09
Pain interference, T score	58.58 ± 7.41	60.69 ± 6.99	61.79 ± 6.72

* Values are the mean ± SD. TS = temporal summation; NRS = Numeric Rating Scale.

Table 4. Pain measures by CPM tertile, n = 263 patients*

	Least central dysregulation (CPM tertile 3; n = 84)	Moderate central dysregulation (CPM tertile 2; n = 99)	Most central dysregulation (CPM tertile 1; n = 80)
CPM	1.79 ± 0.36	1.31 ± 0.07	1.10 ± 0.10
Pain intensity (NRS 0–10)	5.21 ± 2.27	4.86 ± 2.24	5.51 ± 2.33
Pain interference, T score	61.89 ± 7.40	59.93 ± 7.21	59.18 ± 6.57

* Values are the mean ± SD. CPM = conditioned pain modulation; NRS = Numeric Rating Scale.

after adjustment for CRP level and SJC. We additionally assessed aberrant descending pain modulation manifested by abnormal CPM but did not find consistent evidence of an association between CPM and increased pain.

Low PPTs at extraarticular sites are thought to represent pain centralization (15). Fischer et al established normal values for PPTs at the trapezius in a study of 50 healthy volunteers (24). In comparison, our population of patients with active RA had lower PPTs at the trapezius, which is consistent with other studies showing lower extraarticular PPTs in patients with RA compared to healthy control subjects (36). For instance, Gerecz-Simon et al compared PPTs at multiple sites in healthy control subjects and patients with RA, osteoarthritis, and ankylosing spondylitis and noted the lowest PPTs in RA patients (37). Löfgren et al noted similar results in a study showing lower PPTs in 45 patients with RA compared to 20 healthy control subjects (38).

To our knowledge, only 1 study has examined the association between PPTs and pain in RA. Joharatnam et al reported an association between PPTs at the medial knee, tibia, and sternum with pain measured by the McGill Pain Questionnaire in a population of 50 patients with RA, but this study did not account for potential confounding from inflammatory activity (39). Our study

Table 5. Regression results for the association between quantitative sensory testing parameters and pain (n = 263 patients)*

	Quantitative sensory testing tertile†		
	Moderate central dysregulation‡	Most central dysregulation§	*P* for trend
Pain intensity outcome			
PPT trapezius			
Unadjusted	0.60 (−0.05, 1.25)	1.44 (0.78, 2.11)¶	<0.001¶
Adjusted#	0.48 (−0.15, 1.11)	1.02 (0.37, 1.67)¶	0.002¶
TS			
Unadjusted	1.31 (0.68, 1.95)¶	1.48 (0.79, 2.16)¶	<0.001¶
Adjusted#	0.96 (0.36, 1.56)¶	1.19 (0.54, 1.84)¶	<0.001¶
CPM			
Unadjusted	−0.36 (−1.02, 0.31)	0.30 (−0.40, 1.00)	0.420
Adjusted#	−0.14 (−0.75, 0.47)	0.37 (−0.27, 1.01)	0.251
Pain interference outcome			
PPT trapezius			
Unadjusted	1.66 (−0.40, 3.72)	3.48 (1.37, 5.58)¶	0.001¶
Adjusted#	1.11 (−0.79, 3.02)	1.84 (−0.12, 3.80)	0.066
TS			
Unadjusted	2.12 (0.08, 4.16)¶	3.21 (1.02, 5.40)¶	0.004¶
Adjusted#	0.49 (−1.36, 2.35)	1.29 (−0.71, 3.28)	0.205
CPM			
Unadjusted	−1.96 (−4.03, 0.11)	−2.71 (−4.89, −0.53)¶	0.014¶
Adjusted#	−1.18 (−3.00, 0.64)	−2.35 (−4.25, −0.44)¶	0.016¶

* Values are the mean difference (95% confidence interval). PPT = pressure pain threshold; TS = temporal summation; CPM = conditioned pain modulation.
† Least central dysregulation is the reference.
‡ Values represent the mean pain intensity/interference difference between the moderate central dysregulation group and the least central dysregulation group.
§ Values represent the mean pain intensity/interference difference between the most central dysregulation group and the least central dysregulation group.
¶ Significant.
# Adjusted models used the following covariates: age, sex, race, education level, seropositivity (rheumatoid factor and/or anti–citrullinated peptide positive), disease duration, swollen joint count, C-reactive protein level, body mass index, depression, anxiety, sleep disturbance, modified Charlson comorbidity index score, and site.

confirms this association and adds to this finding by showing that this relationship persists after adjusting for multiple clinical variables, including SJC and CRP level.

To evaluate the clinical implications of the association between PPTs and pain intensity, we considered the minimum clinically important difference (MCID) in pain intensity. Salaffi et al reported an MCID for pain intensity of 1 on a 0–10 numeric rating scale in a study of 825 patients with RA (n = 290) and other chronic musculoskeletal conditions, including osteoarthritis and ankylosing spondylitis (40). In our study, we report an adjusted difference in pain intensity of 1.02 between the most and least centrally dysregulated PPT groups, which is above the MCID, indicating that this change is of clinical importance.

We also examined the relationship between PPTs and pain interference. In adjusted analyses, we observed a 1.84-point higher pain interference T score in the most centrally dysregulated PPT group compared to the least dysregulated group, which was not statistically significant. To provide clinical context, Chen et al established that the minimum important difference (MID), a measure similar to the MCID, in the PROMIS pain interference T score is between 2 and 3 (41).

To further clarify the mechanism of pain centralization in RA, we investigated a relationship between TS and pain. TS is thought to represent central sensitization due to increased responsiveness of the second order neurons of the dorsal horn of the spinal cord. Increased TS has been implicated as a specific mechanism of pain centralization in the prototypical central pain disorder, fibromyalgia (42). Higher TS was observed by Hermans et al in 11 patients with RA compared to 20 healthy control subjects (27). Additionally, Vladimirova et al noted greater TS in 38 RA patients with active disease compared to 38 healthy female control subjects (43).

Our study is the first to report an association between TS and patient-reported pain in RA. In adjusted analyses, we show a higher pain intensity of 1.19 points on a scale of 0–10 in the most centrally dysregulated TS group compared to the least dysregulated group. Again, this increase is above the MCID for pain intensity in patients with RA. For pain interference, we noted a 1.29-point higher T score in the most centrally dysregulated group compared to the least centrally dysregulated group, which was not statistically significant nor clinically important based on an MID of 2–3.

In addition to TS, we studied CPM as a potential mechanism of pain regulation in active RA. The CPM paradigm involves the use of a conditioning stimulus to activate the descending analgesic pathways (44). We previously showed that patients with RA have lower CPM than pain-free control subjects, which is indicative of abnormalities in the descending analgesic pathways (26). However, in the current study, we found no association between CPM and pain intensity. When examining the association between CPM and pain interference, we noted that the group with greatest central dysregulation (manifested by the lowest CPM) had a lower average pain interference T score of 2.35 points compared to the group with least central dysregulation. These results were unexpected given that dysregulation of the CNS pain regulatory pathways would be expected to enhance pain intensity and pain interference. The absence of association between CPM and pain intensity suggests that dysfunction of the descending analgesic pathway may not be implicated in the pathogenesis of pain in RA or that CPM may be a poor measure of the descending analgesic pathway in some settings. For example, in patients with preexisting clinical pain, the descending analgesic pathways may already be activated, complicating the experimental assessment of pain using the CPM paradigm (45). Finally, of the QST measures used in this study, CPM was the least reproducible, and heterogeneity in measurement may have impacted our results.

Analysis of the correlation between the covariates in our model and pain is notable for additional findings. First, moderate-to-severe sleep disturbance was significantly associated with pain intensity. Patients with moderate-to-severe sleep disturbance reported an average of 1.46 points higher pain intensity than those without sleep disturbance in the PPT model. This observation is consistent with previous studies implicating a role for sleep disturbance in pain perception in healthy subjects as well as patients with RA (14,26,34,46). Second, we noted that lower education was significantly associated with pain in RA. Jiang et al noted in a study of 3,021 DMARD-naive patients with RA that achieving a college or university degree was associated with a lower risk of reporting higher than median levels of pain at 3, 6, and 12 months following initiation of DMARDs (35).

Last, we noted no association between measures of inflammation and our primary outcome of pain intensity. While there was a statistically significant association between CRP level and our secondary outcome of pain interference, the magnitudes of association were small (mean increase in pain interference T scores of 0.08, 0.07, and 0.07 for each unit of CRP in the PPT, TS, and CPM models, respectively) and unlikely to be of clinical significance because these values were well below the MID. This is consistent with 2 recent studies showing minimal correlation between pain and markers of inflammation (CRP level and gray-scale and power Doppler ultrasound evaluations) (47,48).

This study has several strengths. The overall sample size is larger than that in prior studies of QST and pain in RA. Additionally, the study was conducted at 5 different medical centers across the US, which makes the results more generalizable to the general RA population. This study also studied multiple QST measures, including extraarticular PPTs, TS, and CPM, while adjusting for important potential confounders implicated in pain, including inflammation. Strengths of the chosen QST protocol include prior experience with its use, a well-established protocol for reference, and similarities to other protocols used in RA research allowing for comparisons.

Study limitations include the cross-sectional design, which does not permit assessment of causality or directionality of relationships between QST measures and pain. Another limitation is

the heterogeneity of QST assessments across assessors at different sites. To minimize these effects, rigorous training and standardization methods were employed, resulting in overall ICCs in the good to excellent range (19,23). However, reproducibility of the CPM measure was notably lower than the other QST measures likely due to the complexity of the paradigm, which involves 2 different noxious stimuli and the assessment of 2 PPTs over time. A 2016 systematic review examined the reliability of CPM among various testing conditions (49). ICCs ranged from 0.1 to 0.59 in patients with painful conditions, similar to the ICC of 0.45 noted in this study. Additionally, simultaneous application of multiple conditioning stimuli has been noted to result in lower CPM compared to application of a single conditioning stimuli (45). It is possible that this phenomenon could interfere with the measurement of CPM in patients with existing pain such as that from RA. Further studies should be performed to assess the optimum CPM protocol in patients with RA using a variety of conditioning and testing stimuli. Finally, 33 patients were excluded from the study due to missing data. These patients had lower education and higher levels of anxiety and sleep disturbance than the study population, which limited generalizability.

In conclusion, this study has important clinical implications. While pain in patients with RA has traditionally been attributed to peripheral inflammation, our study suggests that CNS dysregulation of pain enhances pain intensity independent of inflammatory activity. In a practice environment where treat-to-target is becoming increasingly the standard of care, these results should encourage physicians to carefully evaluate the factors contributing to pain in patients with active RA prior to changes in treatment with DMARDs. Because pain plays an important role in the subjective components of many composite measures of disease activity, it is possible that patients with centralized pain in the absence of significant inflammation would have high composite disease activity scores that would erroneously prompt a change in the treatment with DMARDs, subjecting the patient to a delay in the appropriate treatment of pain as well as to unnecessary exposure to potential DMARD-related toxicities. These findings highlight the need for research into the means of identifying pain mechanisms to help guide treatment decisions. Further areas of research include longitudinal studies to establish the directionality of the relationship between QST measures and clinical pain assessments, as well as assessment of the efficacy of centrally acting agents on controlling pain in 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. Heisler 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.

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