Published in final edited form as:

Arthritis Care Res (Hoboken). 2020 August ; 72(8): 1122–1129. doi:10.1002/acr.23994.

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

Andrew C. Heisler, MD[1], **Jing Song, MS**[2], **Dorothy D. Dunlop, PhD**[3], **Alyssa Wohlfahrt, BA**[4], **Clifton O. Bingham III, MD**[5], **Marcy B. Bolster, MD**[6], **Daniel J. Clauw, MD**[7], **Wendy Marder, MD**[8], **Kristine Phillips, MD PhD**[9], **Tuhina Neogi, MD PhD**[10], **Yvonne C. Lee, MD MMSc**[1]

[1]Northwestern University Feinberg School of Medicine Ringgold standard institution - Medicine/ Rheumatology, 633 N. St. Clair Street 18th Floor, Chicago, Illinois, 60611, United States.

[2]Northwestern University - Feinberg School of Medicine, 339 E Chicago Ave Wieboldt 717, Chicago, Illinois, 60611, United States.

[3]Northwestern University - Institute for Healthcare Studies, 750 North Lake Shore Drive Tenth Floor, Chicago, Illinois, 60611, United States.

[4]Brigham and Women's Hospital - Rheumatology, 75 Francis Street, Boston, Massachusetts, 02115, United States.

[5]Johns Hopkins School of Medicine Ringgold standard institution - Division of Rheumatology, 5200 Eastern Ave MFL Center Tower Room 404, Baltimore, Maryland, 21224, United States.

[6]Massachusetts General Hospital - Division of Rheumatology, 55 Fruit Street Bulfinch 165, Boston, Massachusetts, 02114, United States.

[7]University of Michigan - Internal Medicine, 24 Frank Lloyd Wright Dr PO Box 385, Ann Arbor, Michigan, 48105, United States.

[8]University of Michigan - Internal Medicine, 7C27 North Ingalls Building 300 North Ingalls, SPC 5422, Ann Arbor, Michigan, 48109-5422, United States.

[9]Vanderbilt University School of Medicine - Rheumatology Nashville, Tennessee, United States.

[10]Boston University, School of Medicine - Clinical Epidemiology Research and Training Unit, 650 Albany St., X Bldg, Suite 200, Boston, Massachusetts, 02118, United States.

Abstract

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

Corresponding Author Address, Email, and Telephone Number: Northwestern University Feinberg School of Medicine, Medicine/ Rheumatology, 633 N. St. Clair Street, 18th Floor, Chicago, IL, USA 60611, andrew.heisler@northwestern.edu, Phone: 312-503-2962, Fax: 312-503-4939.

The authors have the following disclosures:

Yvonne C. Lee, MD, MMSc reports advisory board membership for Eli Lilly (unpaid), stock ownership in Express Scripts, and a research grant from Pfizer. Marcy Bolster reports educational grants from Abbvie and Pfizer, advisory board membership for Johnson and Johnson, and investments in Gilead. Daniel J. Clauw MD has received consulting fees from Aptinyx, Daiichi Sankyo, Intec Pharma, Eli Lilly, Pfizer, Samumed, Theravance, Tonix and Zynerba (less than $10,000 per single occurrence).

Methods—Two hundred and sixty-three RA patients with active disease underwent quantitative sensory testing (QST) including assessment of extra-articular 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 (PROMIS®) 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.

Results—Patients with the lowest PPTs (most central dysregulation) reported higher pain intensity than patients with the highest PPTs (adjusted mean difference (95% CI) 1.02 (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 (95% CI) 1.19 (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 (95% CI) −2.35 (−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 pro-inflammatory cytokines tumor necrosis factor alpha (TNFα) and interleukin-6 (IL-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 RA patients, 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 further support for the role of pain centralization in RA (14). Greater understanding of the role for pain centralization in RA is needed as patients with pain driven predominantly by pain centralization may better be treated by centrally-acting agents (e.g., serotonin norepinephrine reuptake inhibitors, gabapentinoids) or cognitive behavioral therapy, rather than DMARD change or escalation.

Quantitative sensory testing (QST) is a semi-quantitative 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 non-articular 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 extra-articular 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 (CPIRA) 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 of disease modifying anti-rheumatic drug (DMARD) therapy (19). Two hundred and ninety-five subjects from 5 US academic medical centers were recruited from January 2014 through June 2017.

Participants meeting the following criteria were included for study: a diagnosis of RA based on the ACR/EULAR 2010 classification criteria; active disease necessitating initiation or change of DMARD; and ability to participate in a baseline study visit prior to change or initiation of the new DMARD (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 corticosteroid use equivalent to >10 mg daily of prednisone.

Quantitative Sensory Testing (QST).

QST was performed as previously described (21). All assessors underwent a 1-day training session to assure standardization of QST procedures across sites. We calculated a two way mixed single score ICC (3,1) to assess reproducibility of QST between assessors (22). Per 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). Intraclass correlation coefficients (ICCs) ranged from 0.71 to 0.9 for PPTs and TS, whereas the ICC for CPM was 0.45 (19).

Pressure Pain Thresholds (PPTs).—A Wagner Force 10 FDX algometer was used to determine extra-articular 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 because: 1) the trapezius is a

commonly used site for assessment of PPTs in the pain literature; 2) literature supports standard values for PPT 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).

Temporal Summation (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 generating a pain score between 30 and 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 choose the dorsal forearm due to its distance from articular sites to avoid confounding from peripheral sensitization.

Conditioned Pain Modulation (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° to 7° Celsius. The test stimulus was pressure produced by an algometer probe placed at the center of the left trapezius muscle (contralateral to the hand placed in the cold water bath). 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 greater than 1 represent efficient CPM, whereas values less than 1 represent inefficient CPM.

Clinical Variables.

We assessed the subjects' pain experience using Patient-Reported Outcomes Measurement Information System (PROMIS®) questionnaires. PROMIS Global Health was administered as a short form, while pain interference, depression, anxiety, and sleep disturbance were assessed using Computerized Adaptive Tests (CATs) (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-cyclic citrullinated peptide antibody (anti-CCP) 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 medical co-morbidities scale (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. 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 CCP positive), disease duration, and the modified Charlson medical co-morbidities scale as covariates per clinical experience. Swollen joint count (SJC) and CRP were included as covariates as 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 were evaluated using multiple linear regression. All analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Clinical Characteristics.

This study sample of 263 patients with RA had a mean age of 57.4 years (range of 18 to 81 years) and was primarily Caucasian (75%) and female (82%), 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 the study sample with the exception of statistically significant differences in education (75.7% with some college or higher in included sample vs. 48.5% in the excluded sample), anxiety (mean PROMIS t-score 53.6 in included sample vs. 57.5 in the excluded sample), and sleep disturbance (25.1% with moderate/severe sleep disturbance in the included sample vs. 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 Table 2. As PPT tertile decreased from least to most central dysregulation, mean scores increased for both pain intensity (least: 4.51, moderate: 5.11, most: 5.95) and pain interference (least: 58.66, moderate: 60.32, most: 62.13). Similarly, as TS tertile increased from least to most central dysregulation, mean scores increased for both pain intensity (least: 4.24, moderate: 5.55, most: 5.71) and pain interference (least: 58.58, moderate 60.69, most: 61.79). However, as CPM tertile decreased from least to most central dysregulation, no trend was observed in pain intensity or pain interference.

Associations between QST Tertile and Measures of Patient-Reported Pain.

Trapezius pressure pain thresholds (PPT).—In both unadjusted and adjusted analyses, greater central pain dysregulation, assessed by trapezius PPT, was significantly associated with higher pain intensity (P for trend ≤ 0.002) (Table 3). 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 were all significantly associated with greater pain interference in the PPT model.

Temporal summation (TS).—In both unadjusted and adjusted analyses, greater central pain dysregulation, assessed by TS, was significantly associated with higher pain intensity (P for trend < 0.001) (Table 3). 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 for trend = 0.004). However, the trend was attenuated in the adjusted analysis (P for trend = 0.205). In addition, sleep disturbance, anxiety, CRP, and less education, were all significantly associated with greater pain interference in the TS model.

Conditioned pain modulation (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 for trend = 0.016). 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, and Caucasian 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 extra-articular PPTs and high TS with pain intensity, which persisted after adjustment for CRP 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 extra-articular 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 extra-articular PPTs in RA patients compared to healthy controls (36). For instance, Gerecz-Simon *et al* compared PPTs at multiple sites in healthy controls and patients with RA, osteoarthritis, 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 RA patients compared with 20 healthy controls (38).

To our knowledge, only one study has examined the association between PPTs and pain in RA. Joharathnam *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 confirms this association and adds to this finding by showing that this relationship persists after adjusting for multiple clinical variables including SJC and CRP.

To evaluate the clinical implications of the association between PPTs and pain intensity, we considered the minimal clinically important difference (MCID) in pain intensity. Salaffi *et al* reported a 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 group, which was not statistically significant. To provide clinical context, Chen *et al* established that the minimally important difference (MID), a measure similar to the MCID, in 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 RA patients compared with 20 healthy controls (27). Additionally, Vladimirova *et al* noted greater TS in 38 RA patients with active disease, compared to 38 healthy female controls (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 0–10 scale in the most centrally dysregulated TS group compared to the least dysregulated group. Again, this increase is above the MCID for pain intensity in RA patients. For pain interference, we noted a higher 1.29 point higher t-score in the most centrally dysregulated group compared

to the least, which was not statistically significant nor clinically important based on the MID of 2 to 3.

In addition to TS, we studied CPM as a potential mechanism of pain regulation in active RA. The CPM paradigm involves use of a conditioning stimulus to activate the descending analgesic pathways (44). We previously showed that RA patients have lower CPM than pain-free controls, 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 pre-existing 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 3021 DMARD-naïve 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 DMARD initiation (35).

Lastly, we noted no association between measures of inflammation and our primary outcome of pain intensity. While there was a statistically significant association between CRP 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 as these values are well below the MID. This is consistent with two recent studies showing minimal correlation between pain and markers of inflammation (CRP, grey scale, and (Ultrasound) power Doppler) (47, 48).

This study has several strengths. The overall sample size is larger than prior studies of QST and pain in RA. Additionally, the study was conducted at five different medical centers across the United States, which makes the results more generalizable to the general RA population. This study also studied multiple QST measures, including extra-articular 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 two different noxious stimuli and the assessment of two 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 RA. Further study should be performed to assess the optimum CPM protocol in RA patients 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, limiting 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 DMARD change. As 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 DMARD change, subjecting the patient to delay in appropriate treatment of pain as well as to unnecessary exposure to potential DMARD-related toxicities. These findings highlight the need for research into 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.

Acknowledgments

Grants and other Financial Support:

This work is supported by the NIH/ National Institute of Arthritis and Musculoskeletal and Skin Diseases (grants R01-AR064850, R01-AR054155, P30-AR070254, and P60-AR48098). Andrew C. Heisler M.D. is supported in part by Grant Number T32 AR007611–13 from the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

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Significance and Innovations

- This is the first multi-center 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.

Table 1:

Clinical Characteristics of Subjects, n=263 patients

Characteristic	% or Mean (SD)
Age, years	54.7 (13.8)
Female	81.8%
Caucasian	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/L	7.9 (12.2)
SJC	5.1 (5.0)
PROMIS Depression	50.9 (9.1)
PROMIS Anxiety	53.6 (8.9)
PROMIS Sleep Disturbance[1]	
No	54.4%
Mild	20.5%
Mod/Severe	25.1%
Modified Charlson Comorbidity Score	1.3 (1.1)
DAS28	3.8 (1.1)
CDAI	23.7 (13.9)

*BMI = Body Mass Index; CRP = C-Reactive Protein; SJC = Swollen Joint Count; PROMIS = Patient-Reported Outcome Measurement Information System

1. Stratified into none, mild, and moderate or severe (32)

Table 2

Pain Measures by Quantitative Sensory Testing Tertiles, n = 263 patients

	PPT Trapezius Tertiles		
	Least Central Dysregulation (PPT Tertile 3)	**Moderate Central Dysregulation (PPT Tertile 2)**	**Most Central Dysregulation (PPT Tertile 1)**
	N = 90 Mean (SD)	**N = 90 Mean (SD)**	**N = 83 Mean (SD)**
PPT Trapezius	4.62 (1.58)	2.70 (0.69)	1.48 (0.57)
Pain Intensity	4.51 (2.38)	5.11 (2.17)	5.95 (2.08)
Pain Interference	58.66 (8.05)	60.32 (6.53)	62.13 (6.32)
	TS Tertiles		
	Least Central Dysregulation (TS Tertile 1)	**Moderate Central Dysregulation (TS Tertile 2)**	**Most Central Dysregulation TS Tertile 3)**
	N = 85 Mean (SD)	**N = 102 Mean (SD)**	**N = 76 Mean (SD)**
TS	0.11 (2.68)	8.78 (4.64)	31.37 (12.82)
Pain Intensity	4.24 (2.12)	5.55 (2.34)	5.71 (2.09)
Pain Interference	58.58 (7.41)	60.69 (6.99)	61.79 (6.72)
	CPM Tertiles		
	Least Central Dysregulation (CPM Tertile 3)	**Moderate Central Dysregulation (CPM Tertile 2)**	**Most Central Dysregulation CPM Tertile 1)**
	N = 84 Mean (SD)	**N = 99 Mean (SD)**	**N = 80 Mean (SD)**
CPM	1.79 (0.36)	1.31 (0.07)	1.10 (0.10)
Pain Intensity	5.21 (2.27)	4.86 (2.24)	5.51 (2.33)
Pain Interference	61.89 (7.40)	59.93 (7.21)	59.18 (6.57)

Table 3:

Regression Results for the Association between QST Parameters and Pain, n=263 patients

Pain Intensity Outcome					
QST Measure	**Model**	**Quantitative Sensory Testing Tertile**			**Trend-test P-value**
		Least Central Dysregulation	**Moderate Central Dysregulation[1]**	**Most Dysregulation[2]**	
PPT Trapezius	Unadjusted	Reference	0.60 (−0.05, 1.25)	**1.44 (0.78, 2.11)**	**<0.001**
	Adjusted[3]	Reference	0.48 (−0.15, 1.11)	**1.02 (0.37, 1.67)**	**0.002**
TS	Unadjusted	Reference	**1.31 (0.68, 1.95)**	**1.48 (0.79, 2.16)**	**<0.001**
	Adjusted[3]	Reference	**0.96 (0.36, 1.56)**	**1.19 (0.54, 1.84)**	**<0.001**
CPM	Unadjusted	Reference	−0.36 (−1.02, 0.31)	0.30 (−0.40, 1.00)	0.420
	Adjusted[3]	Reference	−0.14 (−0.75, 0.47)	0.37 (−0.27, 1.01)	0.251
Pain Interference Outcome					
QST Measure	**Model**	**Quantitative Sensory Testing Tertile**			**Trend-test P-value**
		Least Central Dysregulation	**Moderate Central Dysregulation[1]**	**Most Central Dysregulation[2]**	
PPT Trapezius	Unadjusted	Reference	1.66 (−0.40, 3.72)	**3.48 (1.37, 5.58)**	**0.001**
	Adjusted[3]	Reference	1.11 (−0.79, 3.02)	1.84 (−0.12, 3.80)	0.066
TS	Unadjusted	Reference	**2.12 (0.08, 4.16)**	**3.21 (1.02, 5.40)**	**0.004**
	Adjusted[3]	Reference	0.49 (−1.36, 2.35)	1.29 (−0.71, 3.28)	0.205
CPM	Unadjusted	Reference	−1.96 (−4.03, 0.11)	**−2.71 (−4.89, −0.53)**	**0.014**
	Adjusted[3]	Reference	−1.18 (−3.00, 0.64)	**−2.35 (−4.25, −0.44)**	**0.016**

[1]Values represent mean pain intensity/interference difference between the moderate central dysregulation group and the least central dysregulation group. 95% CI in parentheses.

[2]Values represent mean pain intensity/interference difference between the most central dysregulation group and the least central dysregulation group. 95% CI in parentheses.

[3]Adjusted models used the following covariates: age, sex, race, education level, seropositivity (RF and/or CCP positive), disease duration, swollen joint count (SJC), CRP, BMI, depression, anxiety, sleep disturbance, the modified Charlson medical co-morbidities scale, and site.