











Correlation of Fibromyalgia Survey Questionnaire and Quantitative Sensory Testing Among Patients With Active Rheumatoid Arthritis

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ABSTRACT. **Objective.** Patients with rheumatoid arthritis (RA) commonly demonstrate disordered pain processing associated with high pain sensitization. Pain sensitization is often assessed using quantitative sensory testing (QST), which is burdensome to patients. The self-administered Fibromyalgia Survey Questionnaire (FSQ) has been proposed as a low-burden, surrogate measure of central pain sensitization. We examined the correlation between FSQ and QST in patients with active RA.

Methods. Participants in the Central Pain in Rheumatoid Arthritis (CPIRA) cohort underwent FSQ and QST evaluation at enrollment. QST measures included pressure pain threshold (PPT) at the thumb, trapezius, wrist, and knee; temporal summation (TS) at the wrist and arm; and conditioned pain modulation (CPM). Partial Spearman correlation between FSQ and each QST measure was assessed, adjusted for demographic factors, study site, disease characteristics, and pain catastrophizing. Sensitivity analyses included (1) stratified analysis by sex and (2) evaluation of how each component of FSQ associates with the QST measures.

Results. Among 285 participants with active RA, FSQ was weakly but statistically significantly correlated with PPT (r range = -0.31 to -0.21), and TS (r range = 0.13 – 0.15) at all sites in unadjusted analyses. After adjustment, statistically significant correlations persisted for TS at the wrist and PPT at all sites (except the thumb). Sensitivity analyses did not identify differences in association based on sex or with individual FSQ components.

Conclusion. FSQ and QST were correlated among participants with active RA, but the strength of association was weak. QST and FSQ are not interchangeable measures of pain sensitization.

Key Indexing Terms: central nervous system sensitization, fibromyalgia, pain measurement, rheumatoid arthritis

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Patients with rheumatoid arthritis (RA) frequently experience heightened sensitivity to pain in a widespread distribution, suggestive of abnormalities in peripheral and central pain processing.¹ Abnormalities in central pain processing, termed *central pain sensitization*, are associated with worse functional outcomes and reduced response to disease-modifying treatment.²⁻⁴ In the research context, quantitative sensory testing (QST) assessments of allodynia, temporal summation (TS), and conditioned pain modulation (CPM) are often considered proxies for pain sensitization.⁵ While QST has been used to characterize pain sensitization in RA,^{1,6,7} it poses a substantial burden to patients and assessors, as it is time-consuming and requires a trained operator to administer the tests in a controlled setting.

The self-administered Fibromyalgia (FM) Survey Questionnaire (FSQ) has been proposed as a low-burden surrogate for QST assessment.⁸⁻¹⁰ The FSQ assesses widespread pain and somatic symptoms such as fatigue, poor sleep, and cognitive difficulty.¹¹ However, there are limited data evaluating the relationship between the clinical symptoms measured using FSQ and the neurologic abnormalities measured by QST. Previous studies in noninflammatory pain conditions, and in patients with well-controlled RA, suggest a low-to-moderate correlation between these measures ($r = 0.27-0.44$), which may be limited to certain subpopulations (ie, female patients).^{8,12,13} Further, widespread pain and somatic symptoms may be driven by other processes beyond pain sensitization, and therefore may reflect distinct domains contributing to the pain experience in RA.

To our knowledge, no data exist regarding the relationship between pain sensitization (assessed by QST) and the patient-reported symptoms of pain sensitization (assessed by FSQ) among patients with active RA. The assessment of pain sensitization is particularly important in this subgroup because pain sensitization may inflate composite disease activity measures, making it seem as if some patients have active inflammatory disease when they do not.¹ Identification of pain sensitization in these patients could affect treatment decisions about escalating disease-modifying antirheumatic drug (DMARD) therapy and may inform alternative management approaches to target chronic pain.^{14,15} To address this gap in knowledge, we aimed to examine the correlation between FSQ and QST in a cohort of participants who were starting or intensifying DMARD treatment for active RA.

METHODS

Study population. Central Pain in Rheumatoid Arthritis (CPIRA) comprised participants enrolled prospectively with active RA who are changing DMARD therapy due to uncontrolled disease activity, determined by their treating rheumatologist.¹ Between January 2014 and July 2017, 295 participants at 5 academic medical centers in the United States enrolled in CPIRA. Exclusion criteria included the following: (1) failure to meet 2010 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology criteria for RA diagnosis (www.rheumatology.org); (2) a coexisting diagnosis of any other systemic autoimmune disease, severe Raynaud phenomenon, peripheral vascular disease, or peripheral neuropathy; and (3) use of chronic opiates, changing dose of centrally acting pain medications in the past 3 months, or prednisone ≥ 10 mg/day. This study complies with the Declaration of Helsinki. The institutional review boards at each site (Boston University H-32334,

Brigham and Women's Hospital 2013P000951, Johns Hopkins University NA_00085841, Northwestern University STU00206528, University of Michigan HUM00081289) approved the study. Informed consent was obtained from all subjects prior to enrollment.

We used baseline data from CPIRA for this study. Analyses were restricted to 285 participants with data in at least 1 of the 7 QST measures as well as complete data in FSQ and covariates. Ten participants were excluded due to missing data in covariates (ie, race or C-reactive protein [CRP]).

Assessment of clinical variables. Variables including age, sex, RA disease duration, RA serostatus, BMI, and enrollment site were assessed at the baseline study visit. BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Presence of rheumatoid factor (> 14 IU/mL) and cyclic citrullinated peptide antibody (> 17 U) was assessed through serum analysis performed at a central laboratory. Patient-reported questionnaires provided demographic and RA disease duration information. Pain catastrophizing was assessed using the Pain Catastrophizing Scale.¹⁶ An assessment of clinical pain intensity was captured using a 0 to 10 numeric rating scale of overall pain.

Assessment of RA disease activity and inflammation. RA disease activity was assessed through measurement of CRP and calculation of the Clinical Disease Activity Index (CDAI), which includes tender joint count, swollen joint count (SJC), patient global assessment (PtGA) and physician global assessment (PGA).^{17,18} Trained study staff members performed standard 28-joint counts and PGA. Responses for PtGA were measured on a 100-point scale and converted to a 10-point scale.

Assessment of pain sensitization: QST. We evaluated 3 baseline QST measures: pressure pain threshold (PPT), TS, and CPM. We performed interrater reliability assessments for both PPT and TS. Intraclass correlation coefficients (ICC) for both measures ranged from 0.71 to 0.90, which is considered good to excellent.¹⁹ The ICC for CPM was 0.45, which is considered fair.

PPT, which assesses hyperalgesia, was measured using a Force 10 FDX (Wagner Instruments) algometer with a 1-cm² probe placed at the bilateral trapezius muscles, wrists, knees, and thumbnails. PPTs assess overall sensitivity to pain. Low PPTs at joint sites represent a combination of peripheral and central mechanisms of sensitization, whereas low PPTs at nonjoint sites indicate central mechanisms of sensitization. Pressure was increased by 0.5 kilogram force (kgf) per second until the participant reported pain at each assessment site. PPT was defined as the pressure at which the participant reported pain, with lower values suggesting more sensitivity.

TS assesses amplification of painful inputs in response to repeated stimuli and is considered a specific measure of pain facilitation. We measured TS using 6 weighted probes (8-256 mN) placed on the participant's wrist and forearm. Probe weight was increased until the participant reported a pain score of 30 to 40 of 100, or the heaviest weight was reached. The probe registering a pain score of 30 to 40 out of 100 was then tapped against the wrist and dorsal forearm 10 times, with 1 second between taps. After taps 1, 5, and 10, the participant rated pain on a scale of 0 to 100. We subtracted the participant's pain score at tap 1 from the score at tap 10, then divided by 10 to provide a TS score from 0 to 10. Higher TS scores represent higher pain amplification.

CPM is believed to be a measure of descending inhibitory pain modulation. The conditioning stimulus engages the descending (inhibitory) analgesic pathway, whereas the test stimulus assesses the effect of this inhibition. In an appropriately functioning pathway, the inhibition results in a lessened pain response to the second stimulus. Our conditioning stimulus was a cold water bath at 5 °C to 7 °C, into which participants placed their right hand. We assessed PPT at the left trapezius muscle at 2 timepoints: before the cold water bath, and 20 seconds after initiation of the cold water bath. CPM was reported as the ratio of PPT at the second timepoint to PPT at the first timepoint, with lower values suggesting inefficient descending analgesic inhibition.

Assessment of FM severity. All participants completed the 2010/2011 FSQ at

baseline.¹¹ This instrument is composed of a widespread pain index (WPI) that assesses self-reported pain at 19 prespecified sites, and a symptom severity scale (SSS) of 0 to 12. The SSS measures the sum of self-reported fatigue, nonrestorative sleep, and cognitive symptoms on a 1- to 3-point Likert scale, and the presence of headache, abdominal pain, and depression assessed as binary variables. This questionnaire has been previously used to measure severity of FM, the prototypical centralized pain condition, in the general population as well as in disease-specific cohorts, including the CPIRA cohort.^{1,20} Previous studies have suggested that a FSQ score ≥ 12 be considered the threshold for diagnosis of FM.^{11,21} However, previous studies suggest that the concept of FM is more appropriately viewed as a continuum rather than a discrete entity.²²⁻²⁴

Statistical analysis. Descriptive statistics were used to evaluate demographic and clinical data. The primary analysis evaluated Spearman correlations between each QST measure (PPT, TS, CPM) and overall FSQ score. Partial correlations were adjusted for age, sex, race, BMI, study site, seropositivity, CRP, SJC, and pain catastrophizing. We performed a sex-stratified sensitivity analysis to examine the possibility suggested from literature that sex may modify the correlation between FSQ and QST measures.⁸ A second sensitivity analysis evaluated the correlation between QST and each FSQ component: WPI to assess the extent of pain, and SSS to assess the severity of comorbid symptoms. We did not adjust for multiple testing because the objective of this study was only to describe the relationship between various QST measures and FSQ, as opposed to confirming a specific hypothesis about the relationship between QST measures in general and FSQ.

RESULTS

We describe the characteristics of the 285 participants included in this study in Table 1. Mean age was 54.70 (SD 13.74) years, 82.1% were female, 74.7% were White, and 78.3% were seropositive. Mean (SD) baseline CDAI score was 24.56 (14.25), representing high RA disease activity.¹⁸ Mean (SD) baseline FSQ score was 11.22 (6.08) out of a total possible score of 31, with 32% of the study population meeting the ACR 2011 modified diagnostic criteria for FM.¹¹

In unadjusted analyses, FSQ had a statistically significant, but weak inverse correlation between FSQ and PPT at all sites, including the thumb ($r = -0.21$, 95% CI -0.32 to -0.10), trapezius ($r = -0.25$, 95% CI -0.35 to -0.13), wrist ($r = -0.27$, 95% CI -0.37 to -0.16), and knee ($r = -0.31$, 95% CI -0.41 to -0.20 ; Figure). Negative correlation coefficient values indicate that increasing FSQ score is associated with a decrease in pain threshold (measured by PPT), representing higher pain sensitization. Weak correlations were also found between FSQ and TS at the wrist ($r = 0.15$, 95% CI 0.03 - 0.26), and arm ($r = 0.13$, 95% CI 0.01 - 0.24). Adjusting for covariates reduced the magnitude of these correlations, but correlations between FSQ and PPT at the trapezius ($r = -0.13$, 95% CI -0.25 to -0.01), wrist ($r = -0.16$, 95% CI -0.27 to -0.04), and knee ($r = -0.20$, 95% CI -0.32 to -0.09), as well as TS at the wrist ($r = 0.13$, 95% CI 0.01 - 0.24) remained statistically significant. No significant correlation was found between FSQ and CPM (Figure).

To examine the previously reported effect of sex on the relationship between FSQ and QST, we examined Spearman correlations of FSQ and QST by sex.⁸ Individually, correlations for men and women were similar in magnitude and statistical significance to the overall analysis. The largest difference occurred in the correlations of FSQ with PPT of

Table 1. Baseline characteristics (N = 285).^a

	Mean (SD) or %
Age, yrs	54.70 (13.74)
Female	82.1
White	74.7
BMI, kg/m ²	28.58 (6.62)
Seropositive, %	78.3
RA duration, yrs	9.97 (11.88)
bDMARD use	24.9
Site, % of enrolled	
Brigham/MGH	51.9
Boston University	10.2
Michigan University	19.3
Johns Hopkins	18.6
Pain Catastrophizing Scale	18.67 (13.56)
Pain intensity (NRS 0-10)	5.25 (2.29)
CDAI	24.56 (14.25)
PtGA	4.23 (2.44)
PGA	3.68 (2.28)
SJC	5.26 (5.25)
TJC	10.89 (8.60)
CRP (mg/L)	8.15 (12.45)
FSQ score	11.22 (6.08)
WPI score	5.95 (4.32)
SSS score	5.27 (2.65)
QST	
Thumb PPT, kgf	3.67 (1.95)
Trapezius PPT, kgf	2.93 (1.65)
Wrist PPT, kgf	2.93 (1.59)
Knee PPT, kgf	5.41 (2.84)
Wrist TS	13.06 (14.78)
Arm TS	12.54 (14.63)
CPM	1.40 (0.35)

^a CDAI: n = 243; PtGA: n = 243; thumbnail PPT, trapezius PPT, wrist PPT: n = 284; knee PPT: n = 283; wrist TS: n = 282; arm TS: n = 281; CPM: n = 279. bDMARD: biologic disease-modifying antirheumatic drug; CDAI: Clinical Disease Activity Index; CPM: conditioned pain modulation; CRP: C-reactive protein; FSQ: Fibromyalgia Survey Questionnaire; MGH: Massachusetts General Hospital; kgf: kilogram force; NRS: numeric rating scale; PGA: physician global assessment; PPT: pressure pain threshold; PtGA: patient global assessment; QST: quantitative sensory testing; RA: rheumatoid arthritis; SJC: swollen joint count; SSS: symptom severity scale; TJC: tender joint count; TS: temporal summation; WPI: widespread pain index.

the trapezius, but no meaningful pattern related to sex was observed (Table 2).

To evaluate for differences in the strength of relationship between QST and each component of the FSQ, we examined how each QST measure correlated with WPI and SSS (Table 3). For PPT, the magnitude of the observed correlations for SSS (range $r = -0.31$ to -0.25) was similar to those seen in the primary analysis, while those for WPI were lower than those seen in the primary analysis (range $r = -0.24$ to -0.13). Weak correlations were found between SSS and TS of wrist ($r = 0.16$, 95% CI 0.04 - 0.27) and TS of the arm ($r = 0.13$, 95% CI 0.01 - 0.24), while no significant correlations were found between WPI and TS. No significant correlations were found between either FSQ component (WPI or SSS) and CPM.

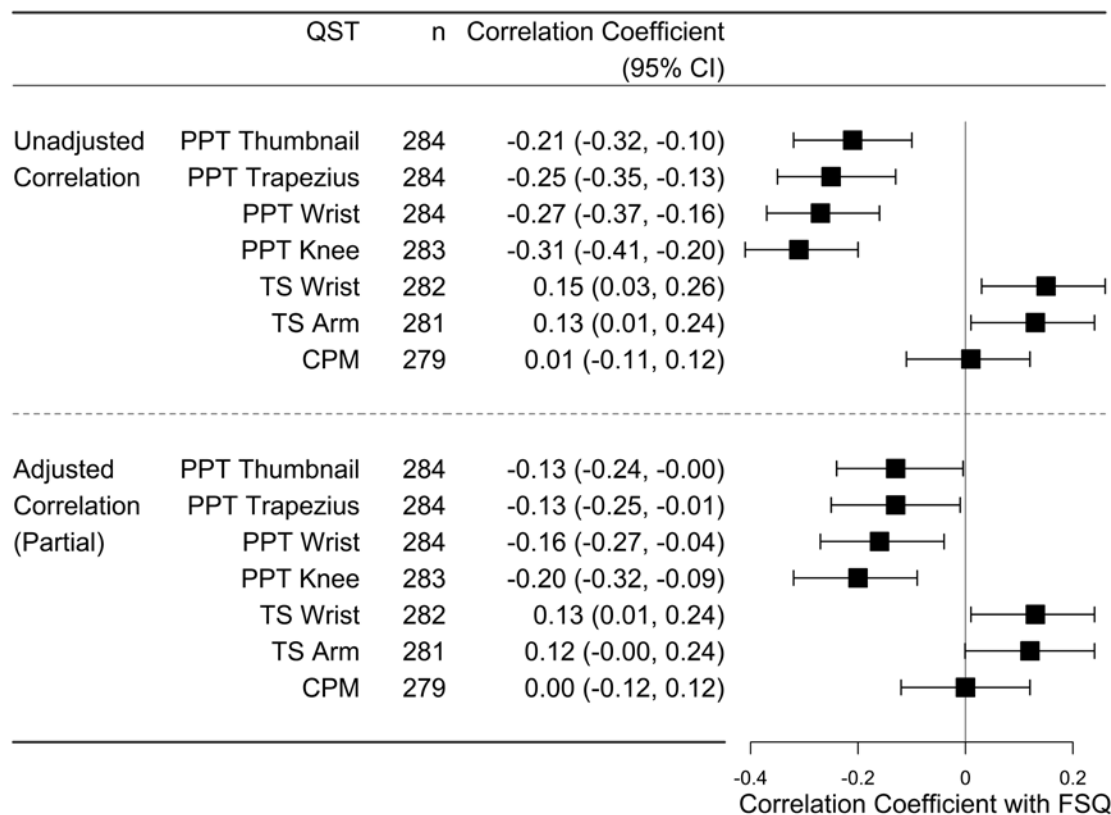


Figure 1. Spearman correlations of QST with FSQ, adjusted for age, sex, race, BMI, seropositivity, swollen joint count, CRP, pain catastrophizing, and site. CPM: conditioned pain modulation; CRP: C-reactive protein; FSQ: Fibromyalgia Survey Questionnaire; PPT: pressure pain threshold; QST: quantitative sensory testing; TS: temporal summation.

Table 2. Unadjusted correlations between QST measures and FSQ after stratification by sex.

QST	Men Correlation Coefficient (95% CI)	Women Correlation Coefficient (95% CI)
Thumb PPT	-0.15 (-0.41, 0.13)	-0.22 (-0.34, -0.09)
Trapezius PPT	-0.36 (-0.57, -0.09)	-0.20 (-0.32, -0.08)
Wrist PPT	-0.23 (-0.48, 0.05)	-0.26 (-0.38, -0.14)
Knee PPT	-0.31 (-0.54, -0.03)	-0.30 (-0.41, -0.18)
Wrist TS	0.08 (-0.20, 0.35)	0.15 (0.02, 0.27)
Arm TS	0.07 (-0.21, 0.34)	0.14 (0.01, 0.27)
CPM	0.00 (-0.28, 0.28)	-0.01 (-0.14, 0.12)

CPM: conditioned pain modulation; FSQ: Fibromyalgia Survey Questionnaire; PPT pressure pain threshold; QST: quantitative sensory testing; TS temporal summation.

DISCUSSION

In a cohort of patients with RA escalating DMARD therapy due to uncontrolled disease activity, FSQ was weakly correlated with PPT and TS, and not correlated with CPM. These relationships did not differ by sex. In a sensitivity analysis, the correlations between both components of FSQ (SSS and WPI) and QST measures were minimally different. These results indicate that, among patients with active RA, the patient-reported symptoms measured by FSQ are not strongly associated with quantitative measurements of pain sensitization assessed by QST. Thus, while

Table 3. Unadjusted correlations between QST measures and the individual components of FSQ, the WPI, and SSS.

QST	WPI Correlation Coefficient (95% CI)	SSS Correlation Coefficient (95% CI)
Thumb PPT	-0.13 (-0.24, -0.01)	-0.26 (-0.36, -0.14)
Trapezius PPT	-0.18 (-0.29, -0.07)	-0.25 (-0.36, -0.14)
Wrist PPT	-0.20 (-0.31, -0.08)	-0.29 (-0.39, -0.18)
Knee PPT	-0.24 (-0.34, -0.12)	-0.31 (-0.41, -0.20)
Wrist TS	0.12 (0.00, 0.23)	0.16 (0.04, 0.27)
Arm TS	0.10 (-0.02, 0.22)	0.13 (0.01, 0.24)
CPM	0.01 (-0.11, 0.13)	0.01 (-0.11, 0.13)

CPM: conditioned pain modulation; FSQ: Fibromyalgia Survey Questionnaire; PPT pressure pain threshold; QST: quantitative sensory testing; SSS: symptom severity scale; TS temporal summation; WPI: widespread pain index.

the FSQ may reflect severity of FM in terms of symptoms, it may not provide additional insights into altered nociceptive signal processing.

The relationship between patient-reported outcome measures like FSQ, and quantitative assessments like QST, may be influenced by a patient's underlying disease state and associated type of pain pathology. Prior work has shown moderate correlations between PPT and self-reported pain measures (ie, McGill Pain Questionnaire) among patients with noninflammatory

conditions such as FM and chronic fatigue syndrome.^{25,26} In contrast, reported widespread pain was not associated with PPT in a study of patients with knee osteoarthritis (OA).²⁷ Our work shows that patients with active RA, a highly inflammatory condition, demonstrate weak correlations between FSQ and QST. One explanation for this finding may be that the FSQ, in addition to detecting widespread muscle pain typical of central pain sensitization, is capturing inflammatory joint pain in patients with active RA. This explanation is supported by our group's previous finding that SJC and CRP increase with higher FSQ scores.²⁸

In our secondary analysis, we did not see differences in the correlation between QST and FSQ when stratified by sex. This is in contrast to a prior study of patients with knee OA, where there was a strong correlation between FSQ and PPT among female patients, but no correlation among male patients.⁸ The authors hypothesized that this finding may be related to sex differences in pain characteristics because females in their study had higher FSQ scores, higher pain hypersensitivity measured by PPT, as well as higher rates of depression, anxiety, and pain catastrophizing.⁸ While our analysis is limited by the small percentage of men (17.9%), prior work has revealed mixed results regarding the influence of sex on experimental pain models.²⁹ It is also possible that the role of sex as a modifier of the relationship between FSQ and QST depends on other factors, such as disease type (eg, OA vs RA).

We also considered the hypothesis that the separate components of the FSQ may be differentially associated with QST measures. The SSS component of the FSQ assesses symptoms (fatigue, waking unrefreshed, cognitive symptoms, headaches, lower abdominal pain, depression), which are a part of the syndrome of FM but may not be directly related to pain sensitivity and may also be due to other causes. In contrast, the WPI component of the FSQ focuses specifically on pain distribution. Thus, we performed a sensitivity analysis to separately examine associations between QST and the 2 subcomponents of the FSQ (WPI and SSS). However, the strengths of the correlations between QST and each component of the FSQ were not meaningfully different (Table 3).

Our study has notable strengths. To our knowledge, this is the first study to evaluate the relationship between examiner-derived and patient-reported measurements of pain sensitization in patients with an active inflammatory condition. Patients with coexisting inflammatory pain have historically been understudied in pain research,³⁰ despite the high prevalence and well-documented morbidity caused by disorders of central pain sensitization in this population.^{31,32}

There are several limitations to our work. First, the study is cross-sectional, and causation cannot be determined from these observational data. While our correlations were statistically significant, they reflect weak-to-moderate associations. The clinical significance of these associations relies on how well we understand the mechanism of the phenomenon being measured, how well the measures capture that phenomenon, and the similarities and differences between the correlated measures. Second, the goal of this study was to assess the correlation between FSQ

and QST-assessed pain sensitization in patients with active RA. Thus, our results do not necessarily extend to patients with well-controlled inflammatory arthritis. Understanding how these measures may perform in different patient populations may help researchers in judging the performance of their own studies. Third, although QST is commonly used to assess pain sensitivity and thereby yield inferences about peripheral and central pain pathways, there is no gold standard for assessing pain sensitization. Prior work has questioned the use of QST as a reference standard. For example, in patients with low back pain, QST had limited prognostic value for predicting the development of chronic symptoms or treatment failure after surgery.^{33,34} Both QST and FSQ measures typically correlate only modestly with functional neuroimaging techniques that are considered by some experts to be superior to either measure.^{35,36} These results do not mean that FSQ or QST do not provide useful information, only that the 2 measures are capturing different concepts. QST may be most useful when used in conjunction with other measures of pain that may include patient-reported questionnaires and neuroimaging. The idea of using different diagnostic tools to capture specific aspects of the FM experience is highlighted by the recently proposed Nociceptive-based Fibromyalgia Features tool.³⁷ While its psychometric properties have not yet been established, this tool is interesting in that it deemphasizes the somatic symptoms included in the 2016 diagnostic criteria²¹ in favor of specific features of pain, such as aggravation with physical or emotional stress, pain migration, and the description of pain as excruciating. Fourth, while a cut-off value for characterizing patients with FM using FSQ scores has been published, such cut-offs have not yet been established for QST measures. Some have argued that it is, in fact, not appropriate to establish these cut-offs given that pain sensitization is a continuum, as opposed to a condition defined by a clinically meaningful cut point.

In conclusion, these results do not support the use of FSQ as a proxy measurement for QST among patients with active RA. The difference between our results and results from noninflammatory pain conditions suggests that population-specific characteristics may affect the performance of these measures. While FSQ and QST each provide valuable information, they do not appear to assess the same construct in this population with high levels of inflammatory pain.

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