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Neurobiologic Features of Fibromyalgia Are Also Present Among Rheumatoid Arthritis Patients

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Objective. **Many patients with rheumatoid arthritis (RA) report pain despite excellent control of inflammation with immunotherapies. Variable degrees of coexisting fibromyalgia (FM) may explain this disparity. FM has been characterized by aberrant brain functional connectivity, especially between the default mode network (DMN) and insula. We undertook this study to test the hypothesis that RA patients with the highest 2011 American College of Rheumatology FM survey criteria scores—a continuous measure of the degree of FM also known as "fibromyalgianess" (FMness)—would demonstrate functional connectivity abnormalities similar to those in FM.**

Methods. **RA patients underwent an 11-minute functional connectivity magnetic resonance imaging (MRI) brain scan and a clinical evaluation which included a measure of FMness. Brain networks were isolated from functional connectivity MRI data. Individual patient network-to–whole brain connectivity analyses were then conducted, followed by group-level regression, which correlated the connectivity of each network with FMness. Results were significant on the cluster level with a family-wise error (FWE) rate *P* value less than 0.05 derived from an uncorrected voxel-level *P* value less than 0.001.**

Results. **A total of 54 patients participated (mean age 54.9 years, 75.9% women, mean FMness score 13.2 [range 1–29]). From the whole brain analyses, a single significant positive correlation between DMN connectivity to the left mid/posterior insula and FMness (r = 0.58, FWE-corrected *P* = 0.001) was demonstrated.**

Conclusion. **RA patients who have increased levels of FMness appear to share neurobiologic features consistently observed in FM patients. This study is the first to provide neuroimaging evidence that RA is a mixed pain state, with many patients' symptoms being related to the central nervous system rather than to classic inflammatory mechanisms.**

Rheumatoid arthritis (RA) is an archetypal chronic inflammatory disorder which is principally characterized by peripheral joint pain, stiffness, and swelling. Recently, management of RA has been revolutionized by the early and aggressive application of antiinflammatory therapies. These advances have led to tremendous average improvements in objective outcomes and even disability, but as many as 50% of patients continue to report clinically significant levels of pain despite excellent control of their peripheral inflammation (1,2).

This disconnect between improvements in inflammation and improvements in pain suggests that there is a likely contribution of pain mechanisms that are in addition to and distinct from peripheral inflammation. Central sensitization—a consequence of dysfunctional central nervous system (CNS) pain processing which defines the primary chronic pain syndrome of fibromyalgia (FM)—may represent one such mechanism (3). This possibility is supported by clinical epidemiologic research which has revealed evidence of coexisting FM in 13–25% of RA patients (4). This compares to a prevalence of 1–5% in the general population (5). An additional 7–15% of RA patients have hallmark features of FM (which include somatic symptoms such as fatigue as well as chronic pain) without meeting the American College of Rheumatology (ACR) 1990 classification criteria (4,6). Wolfe and colleagues derived a continuous scale from the ACR FM survey criteria (7) and found that it predicted pain and disability in RA even

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among patients who did not fully satisfy the FM criteria. The term fibromyalgianess (FMness) was subsequently introduced to reflect this wide phenotypic range (8).

Very few studies have examined whether the prevalent FMness phenotype in RA is underpinned by the same central sensitization pathways as demonstrated in "primary" FM. If this is true, it would greatly enhance the argument for "primary" FM therapeutic approaches (which are quite distinct from current peripherally directed antiinflammatory RA therapies) to benefit RA patients who have clinical features of FMness.

Advanced neuroimaging techniques have been crucial in delineating the neurobiologic features of central sensitization in "primary" FM, but these have not previously been applied to concomitant FM in RA. Recent studies have used functional connectivity magnetic resonance imaging (MRI), an adaptation of functional MRI data that examines temporal correlations in the MRI signal across various brain networks and regions. These connections are thought to be important for the maintenance of synaptic connectivity, and as such they modulate the efficiency and extent of neuronal transmission in the brain.

Among FM patients, the dorsal attention, sensorimotor, and salience brain networks have been implicated in having increased connectivity to pronociceptive brain areas and decreased connectivity to antinociceptive brain areas (9–11). However, currently the most convincing and reproducible functional connectivity MRI evidence relates to the association between the default mode network (DMN) and the insular cortex, which are otherwise implicated in self-referential mental activity (12) and multimodal sensory processing (13), respectively. This specific connection is cross-sectionally associated with FM and pain intensity (14) and longitudinally associated with change of FM pain following both efficacious pharmacologic (pregabalin) and nonpharmacologic (acupuncture) treatments (15,16). The robustness of this finding is further corroborated by magnetoencephalography (a more direct measure of brain connectivity) (17–19). These same patterns have been noted in other conditions known to be accompanied by central sensitization, such as irritable bowel syndrome and low back pain (18,19). Taken together, these data indicate that functional connectivity—and specifically DMN–insular cortex hyperconnectivity—may be a key biologic marker of both the presence and the severity of FM-related pain and central sensitization.

As yet, no studies have investigated whether functional connectivity MRI features of FM are observed in RA patients with co-occurring FM. Specifically, we hypothesized that RA patients reporting the highest levels of FMness would demonstrate functional connectivity MRI features of FM.

PATIENTS AND METHODS

Patients. A total of 335 RA patients were approached through a UK regional rheumatology service. Of those, 193 indicated interest in the study. Participants were considered eligible if they met the 2010 ACR/European League Against Rheumatism classification criteria (20) and had a clinically significant level of fatigue for at least 3 months (defined as a score of >3 on the Chalder Fatigue Binary Scale) (21). Exclusion criteria were contraindications to MRI and left-handedness. A total of 73 patients fulfilled these criteria, and ultimately 54 RA patients completed the study.

All consenting participants underwent a clinical evaluation. This included a measure of FMness using the ACR FM survey criteria, which combine a measure of widespread pain (number of painful sites [0–19]) with a symptom severity scale (e.g., fatigue, subjective cognitive problems, headache, poor mood; scores range from 0 to 12) (7). In addition, their levels of systemic inflammation (C-reactive protein [CRP] level), disease activity (Disease Activity Score in 28 joints [DAS28]) (22), current overall fatigue and pain severity (numerical rating scales of 0–10), sleep disturbance (Jenkins' sleep problems scale [23]), and depression (Hospital Anxiety and Depression Scale [24]) were recorded. Participants then underwent a functional MRI (fMRI) brain scan.

Ethical approval. Ethical approval for the study was obtained from the North of Scotland Research Ethics Committee. All participants provided written informed consent according to the Declaration of Helsinki.

Data acquisition. Each participant underwent an 11-minute functional scan while completing the Paced Auditory Serial Addition Test (PASAT), a validated measure of cognitive function (auditory processing, calculation, working memory, attention) that has been previously used in an fMRI context (25). The PASAT was given in a block design with three 3-minute "on" periods interspersed with four 30-second rest periods. The functional images were acquired by an Achieva 3T X-series MR system (Philips Medical Systems) with an 8-channel phased-array head coil using a T2-weighted gradient-echo single-shot echo-planar imaging pulse sequence with the following parameters: repetition time (TR) 3,000 msec, echo time (TE) 30 msec, flip angle 90°, in-plane SENSE acceleration 2, 128 × 128–pixel matrix size with 30 slices, field of view (FOV) 240 mm, voxel dimensions 1.88 mm × 1.88 mm × 5 mm, and 226 volumes. The first 4 volumes were discarded to avoid equilibration effects. A high-resolution T1-weighted fast-field echo 3-dimensional structural scan was collected for normalization (TR 8.2 msec, TE 3.8 msec, inversion recovery time 1,018 msec, flip angle 8°, FOV 240 mm, 240 × 240–pixel matrix size with 160 slices, and voxel dimensions 0.94 mm × 0.94 mm × 1 mm).

Preprocessing. All data were checked for motion > than 3.76 mm and 5° rotation and visually inspected for artifacts. No participants were excluded for these reasons. Functional connectivity MRI data were preprocessed using SPM8 (Wellcome Department of Cognitive Neurology, London, UK) running on MatLab R2014a (MathWorks), as previously described (25). Briefly, the functional images were realigned, and the structural image was

Table 1. Clinical characteristics of the patients*

RA disease activity†	3.62 ± 1.30
CRP, mg/liter	7.78 ± 8.54
Current fatigue‡	4.59 ± 2.19
Depression§	6.89 ± 3.92
Sleep disturbance¶	15.67 ± 5.46
Current overall pain‡	3.81 ± 2.38

* Values are the mean ± SD. RA = rheumatoid arthritis; CRP = C-reactive protein.
† Disease Activity Score in 28 joints.
‡ On a numerical rating scale of 0–10.
§ Hospital Anxiety and Depression Scale.
¶ Jenkins' sleep problems scale.

coregistered to mean functional image and then segmented. The structural and functional scans were normalized to the standard statistical parametric mapping Montreal Neurological Institute template gray prior probability map via the individuals' segmented gray matter image. Functional scans were smoothed with an 8-mm full width at half maximum Gaussian kernel.

Independent component analysis (ICA). We performed group ICA using a Group ICA of fMRI Toolbox to create group-specific network masks (26). Component estimates were validated using ICASSO software (27) over 20 iterations to ensure the accuracy and reliability of results. Subject-specific spatial maps and time courses were generated using a GICA3 back-reconstruction method. The networks of interest were the DMN, dorsal attention, sensorimotor, and salience brain networks. These components were verified by spatial correlation between the component maps and previously identified templates (28). Spatial masks of the mean component map for each network were created using a MarsBaR Toolbox (http://matthew.dynevor.org/research/abstracts/marsbar/marsbar.pdf) for seed-based connectivity analyses.

Network-to–whole brain connectivity analysis. The preprocessed functional data were entered into a Functional Connectivity Toolbox (CONN; Cognitive and Affective Neuroscience Laboratory, Massachusetts Institute of Technology, Cambridge [www.nitrc.org/projects/conn]) version 15 in SPM8 (29). A nuisance regression using a CompCor method (30) was performed with 6 subject-specific motion parameters, the signal from white matter and cerebrospinal fluid, and their first-order derivatives included as confounders. A band pass filter (0.01–0.1 Hz) was applied to remove linear drifts and high-frequency noise in the data. The mean component maps generated from ICA were used as seeds. Beta maps for each individual representing connectivity between the network of interest and the rest of the brain were generated. The task beta maps were then passed onto second-level group analyses in SPM8. Using a multiple regression model, we assessed the association between network–whole brain connectivity and FMness with age and sex originally included as covariates of no interest, followed by additional corrections for the putative confounders of CRP level and amitriptyline use. The resulting maps were thresholded at an uncorrected voxelwise $P < 0.001$, and significance was set at $P < 0.05$ family-wise error (FWE) cluster corrected for multiple comparisons. The average Fisher-transformed r values of significant clusters were extracted from the first-level beta maps for each subject using MarsBaR. These values were brought into Stata version 12.1

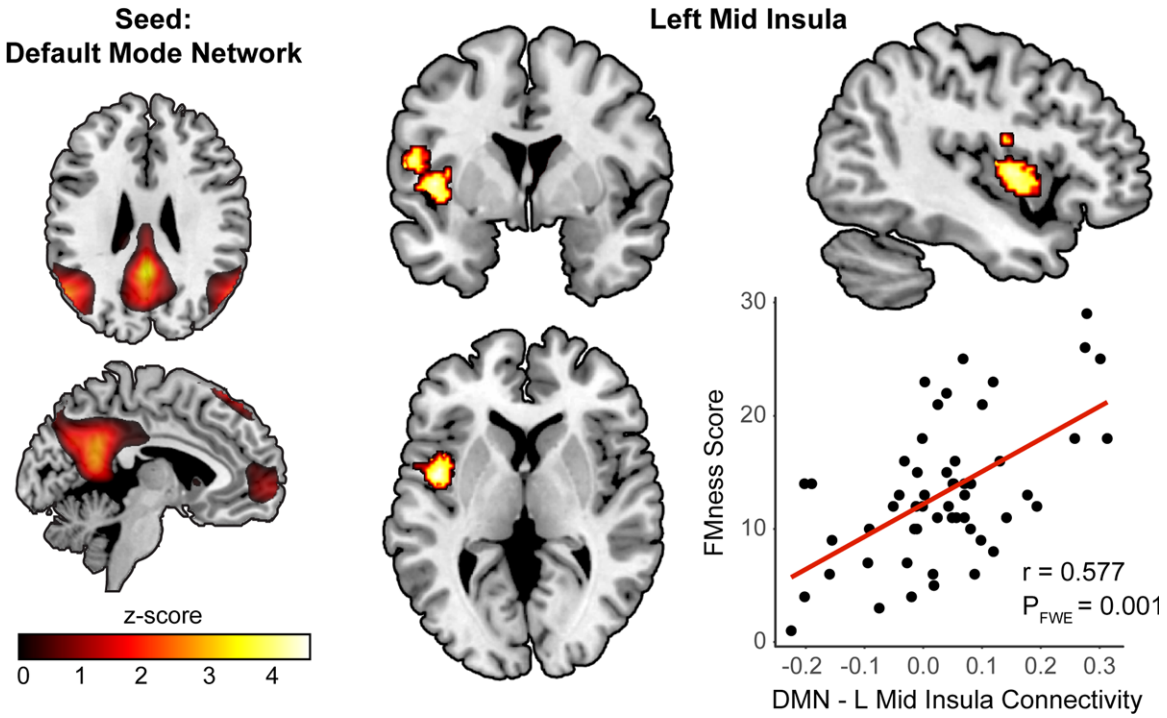

Figure 1. Increased brain connectivity between the default mode network (DMN) and left mid/posterior insula in rheumatoid arthritis patients is associated with fibromyalgianess (FMness). Scatterplots show positive correlations for interindividual differences in brain connectivity (Fisher-transformed r values) with the total FMness score. FWE = family-wise error.

(StataCorp) to enable sensitivity analyses and test post hoc correlations analyses with disease and symptom measures.

RESULTS

Clinical characteristics. A total of 54 patients completed the study. Their mean ± SD age was 54.9 ± 11.41 years, 41 were women, and their mean ± SD disease duration was 11.49 ± 8.64 years. Their mean ± SD FMness score was 13.20 ± 6.21 (range 1–29), and 5 were receiving pharmacologic treatment for FM (all low-dose amitriptyline). Other characteristics of the patients are displayed in Table 1. Correlations of FMness scores with these characteristics are shown in Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40451/abstract.

DMN–insula functional connectivity is associated with FMness in RA. There was a significant positive correlation between DMN connectivity to the left mid/posterior insula and the FMness score (r = 0.572, FWE-corrected $P = 0.001$) in RA patients. The association remained significant after controlling for age and sex (r = 0.577, FWE-corrected $P = 0.001$) (Figure 1). Furthermore, analyses correcting for the putative confounding factors of inflammation (CRP level) and amitriptyline use did not alter this observation (r = 0.568, FWE-corrected $P = 0.001$ and r = 0.556, FWE-corrected $P = 0.009$, respectively). No significant correlations with any of the other networks of interest were identified. Furthermore, a sensitivity analysis of only those patients (n = 27) who did not fulfill the ACR preliminary criteria for FM (31) (total score <13) again yielded a highly significant correlation of DMN–insula connectivity with the FMness score (r = 0.51, $P = 0.006$).

We then examined correlations with phenotypic features (Table 2). First, the individual components of the FMness score were examined, the widespread pain index and the symptom severity scale, in order to determine whether the DMN–insula connectivity relationship was directed by one or both components. Both the widespread pain index (r = 0.50, $P = 0.0001$) and the symptom severity scale (r = 0.41, $P = 0.002$) were significantly associated, indicating important contributions from both. This was further corroborated by significant associations with chronic fatigue ($P = 0.002$) and sleep disturbance ($P = 0.02$), although interestingly, there was no association between DMN–insula connectivity and pain reported at the time of the scan ($P = 0.52$). We next explored correlations between the identified functional connection and RA disease features. Overall disease activity (the DAS28) was significantly correlated ($P = 0.002$), although CRP level was not ($P = 0.19$).

Table 2. Disease and symptom correlations with default mode network–insula connectivity*

Phenotypic feature	Correlation†	*P*
FM widespread pain index	0.50	0.0001
FM symptom severity scale	0.41	0.002
Disease duration	0.03	0.83
RA disease activity‡	0.41	0.002
Swollen joint count	0.25	0.07
Tender joint count	0.32	0.02
CRP	0.18	0.19
Current overall pain§	0.09	0.52
Current fatigue§	0.26	0.06
Chronic fatigue¶	0.40	0.002
Depression#	0.10	0.46
Sleep disturbance**	0.31	0.02

* FM = fibromyalgia; RA = rheumatoid arthritis.
† All are Pearson's correlation coefficient (r) except for C-reactive protein (CRP), for which Spearman's rho was used due to distribution.
‡ Disease Activity Score in 28 joints.
§ On a numerical rating scale of 0–10.
¶ Chalder Fatigue Binary Scale.
# Hospital Anxiety and Depression Scale.
** Jenkins' sleep problems scale.

DISCUSSION

To our knowledge, this study is the first to provide objective neuroimaging evidence that RA is a mixed pain state displaying characteristics of central sensitization. RA patients who reported high levels of FMness demonstrated significantly higher functional connectivity between the DMN and insula—a recognized neurobiologic feature of "primary" FM. Furthermore, the ACR FM survey appears to be a strong surrogate for this neurobiologic marker of central sensitization and could be a useful future tool to support clinicians' evaluation of pain and inform subsequent management.

Our group and others have previously identified significant alterations in DMN–insula connectivity in FM. The insula is a highly connected region of the brain with multiple functional features that routinely involve the integration and conversion of physiologic inputs into higher-level outputs (32). Numerous studies have implicated the insula's involvement in different disorders and dimensions of pain, including FM (33). Its purported role as a key relay station in pain processing has been supported by direct electric stimulation studies of the region, which have effected painful sensations in some patients (34). The DMN comprises synchronously functioning regions—including the posterior cingulate cortex, medial prefrontal cortex, and lateral parietal lobes—that are commonly associated with activities of introspection and are also found to be disrupted in chronic pain (35). It is not known whether this network is a modulator of pain (potentially via descending inhibitory pathways [36]) and/

or related somatic features or whether it is exclusively a consequence of chronic pain exposure (35). Given these possible complementary roles in pain processing, it is plausible to speculate that the DMN and the insula may be functionally connected in FM (14–17).

In the current study, we expanded on these findings by identifying a significant alteration of the very same functional connection in relation to phenotypic features of FM coexisting in another chronic pain disorder (with a distinct primary pathophysiology relating to inflammation). The presence of this connection despite the apparent absence of an association with significant concurrent peripheral inflammation or overall levels of pain further supports the apparent specificity of the DMN–insula connection as a marker of a distinct pain subtype. It is, however, interesting to consider the significant correlation with the DAS28, which appears to be principally driven by tender joint counts and not swollen joint counts. This is consistent with studies that have demonstrated worse DAS28 scores in patients with both RA and FM, which in turn leads to more frequent use of biologic therapies (37,38). That said, we cannot discount the possibility that inflammation may have some role in driving central sensitization.

Although no other study has applied neuroimaging to characterize FM in a coexisting disorder, dysfunctional DMN–insula functional connectivity has been observed in irritable bowel syndrome (18), chronic back pain (19), and migraine (39), all of which are pain conditions in which central sensitization has been implicated (40). Interestingly, these conditions are also associated with somatic symptoms (41,42), which is consistent with our post hoc analysis indicating that the DMN–insula functional connection relates not only to pain but also to symptoms such as fatigue and cognitive dysfunction (as measured by the Symptom Severity Index [7]). One notable discrepancy with previous non-RA studies is the absence of a correlation with current pain severity (which we have further confirmed with a voxelwise search of the insula). We speculate that patients with RA have more ongoing nociceptive input due to inflammation compared to other studied clinical populations in which central sensitization contributes more to current pain. A final point is that this connection remains significant even among those RA patients who do not fulfill ACR criteria for FM, providing further evidence that FM is a continuous construct rather than a discrete construct.

Our findings indicate that centralized pain pathways coexist with more established peripheral inflammation–driven pathways in RA. This is corroborated by quantitative sensory testing studies that suggest the existence of dysfunctional CNS pain pathways in RA by consistently showing hyperalgesia and allodynia (43). Specifically, lower pain–pressure thresholds have been measured across both diseased joints and nonjoint sites in RA patients with concomitant FM than in RA patients without concomitant FM (44).

Our study builds on the few functional neuroimaging studies that have been conducted in RA. Although previous studies have been small and limited to provoking acute experimental pain at the site of joints (rather than sites without disease), they have provided evidence supporting a role of mixed CNS mechanisms in RA-related pain. Using positron emission tomography, Jones and Derbyshire originally reported differential cortical responses to acute pain between 6 RA patients and a population of patients with chronic pain who had depression and dysfunctional coping. They subsequently speculated that the CNS mechanisms of inflammatory pain were distinct from those of other types of pain (45). More recently, Rech and colleagues conducted evoked pain fMRI in 10 RA patients before and after anti–tumor necrosis factor therapy, and they observed differences in brain activation between responders and nonresponders (46). This again implies the possible existence of different neural signatures for different types of pain, since responders are more likely than nonresponders to have pain originating from inflammation.

The present study is strengthened by its large sample size (54 patients). To our knowledge, ours is the largest neuroimaging investigation of any inflammatory rheumatic disease, thus reducing the risk of the false-positive results that are endemic in neuroscience. The robustness of these results is further enhanced by our conservative analytic methodology. Despite our using a data-driven global scan approach, only the key DMN–insula functional connection was identified. Furthermore, these data were acquired using a scanner in a center that has not previously contributed to the literature, which shows the importance of this connection. Finally, replication of this specific pattern of coactivation in the context of a task (rather than with patients in a resting state, as with previous studies) not only strengthens validity but also enhances existing views that functional connectivity MRI largely reflects intrinsic communication networks that are unrelated to conscious activities (47).

Certain limitations to this study should also be considered. First, although the study population included a demographically representative cohort of RA patients with a mixture of disease activity states, there was a bias toward selecting patients with significant levels of fatigue. However, this sample enrichment enabled greater power to detect the mechanistic associations inherent in the research question. It also cannot be assumed that these findings may generalize to other rheumatic conditions, and the intriguing possibility that they may so generalize should be the subject of future experiments.

Second, due to the cross-sectional design, no assumption can be made regarding whether DMN–insula functional connectivity has a causal role in FMness. However, these data do reinforce previous studies that propose this connection, at least as a biologic marker of the FM construct, and so they are adequate to address our primary research question.

Third, although this is the largest study of its kind, the sample size cannot allow us to confidently exclude the existence of other relevant network-to-region connections (which most likely exist), and the study still lacks sufficient power to fully and independently correct for the multiple putative confounding variables that are implicated in FM. That said, our results remained significant following individual adjustments for age and sex. The latter is of particular interest because previous studies of functional connectivity in "primary" FM have included female subjects almost exclusively. Since numerous sex differences in FM biology have been reported (48), the generalizability observed here serves to further enhance the usefulness of the DMN–insula marker.

We have shown that central sensitization is not confined to individuals with "primary" FM and coexists in patients with the biologically distinct disorder of RA. Such evidence for shared mechanisms could inform future clinical decision-making. It is challenging for physicians to distinguish different pain states in patients, particularly those with a preexisting chronic pain disorder. This is especially true since the centralized pain state of FMness is not only common but also artificially inflates routinely used measures of peripherally based inflammatory pain states (e.g., the DAS28) (8) that are pivotal in guiding clinicians' prescriptions of antiinflammatory treatment. As a consequence, inappropriate prescribing of antiinflammatory therapies for pain that is actually not inflammatory in origin is likely common and is probably a principal reason why many RA patients continue to report pain following antiinflammatory therapy despite apparent resolution of inflammation (1). RA patients who report significant pain and who have evidence of high levels of functional connectivity between the insula and DMN are more likely to benefit from centrally acting therapies which are effective for FM, instead of or in addition to antiinflammatory therapies. These currently include both pharmacologic agents (e.g., neuroleptics) and nonpharmacologic agents (e.g., cognitive-behavioral therapy) (49).

Unfortunately, limited access, expense, and specialized analysis requirements will likely prohibit implementation of functional connectivity MRI in routine practice; however, this technology may not be essential given the demonstrated relationship with the ACR FM survey score. Instead, application of this measure as a point-of-care tool may enable clinicians to quantify the contribution of central sensitization to their patients' pain and subsequently inform management choices. Future refinements and abbreviations of this tool will hasten translation. Moreover, since coexisting FM is a common issue among many diseases (musculoskeletal and beyond) (50–54), such a tool may be generically applicable, and therefore testing across the spectrum of chronic pain disorders may finally move the pain field into the era of personalized medicine.

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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 published. Dr. Basu had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Basu, Kaplan, Ichesco, Larkin, Harris, Murray, Waiter, Clauw.

Acquisition of data. Basu, Murray, Waiter.

Analysis and interpretation of data. Basu, Kaplan, Ichesco, Larkin, Harris, Murray, Waiter, Clauw.

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