Research Paper

PAIN 164 (2023) 2316–2326

PAIN®

OPEN

Augmented pain-evoked primary sensorimotor cortex activation in adolescent girls with juvenile fibromyalgia

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Abstract

Juvenile fibromyalgia (JFM) is a chronic widespread pain condition that primarily affects adolescent girls. Previous studies have found increased sensitivity to noxious pressure in adolescents with JFM. However, the underlying changes in brain systems remain unclear. The aim of this study was to characterize pain-evoked brain responses and identify brain mediators of pain hypersensitivity in adolescent girls with JFM. Thirty-three adolescent girls with JFM and 33 healthy adolescent girls underwent functional magnetic resonance imaging scans involving noxious pressure applied to the left thumbnail at an intensity of 2.5 or 4 kg/cm^2 and rated pain intensity and unpleasantness on a computerized Visual Analogue Scale. We conducted standard general linear model analyses and exploratory whole-brain mediation analyses. The JFM group reported significantly greater pain intensity and unpleasantness than the control group in response to noxious pressure stimuli at both intensities ($P < 0.05$). The JFM group showed augmented right primary somatosensory cortex (S1) activation to 4 kg/cm^2 ($Z > 3.1$, cluster-corrected $P < 0.05$), and the peak S1 activation magnitudes significantly correlated with the scores on the Widespread Pain Index ($r = 0.35$, $P = 0.048$) with higher activation associated with more widespread pain. We also found that greater primary sensorimotor cortex activation in response to 4 kg/cm^2 mediated the between-group differences in pain intensity ratings ($P < 0.001$). In conclusion, we found heightened sensitivity to noxious pressure stimuli and augmented pain-evoked sensorimotor cortex responses in adolescent girls with JFM, which could reflect central sensitization or amplified nociceptive input.

Keywords: Juvenile fibromyalgia, Pediatric pain, Brain activation, fMRI, Adolescent, Pain sensitivity, Noxious stimuli

1. Introduction

Juvenile-onset fibromyalgia (JFM) is a poorly understood chronic pain condition that affects up to 6% of children, primarily adolescent girls.[4,12,14] It is characterized by persistent widespread musculoskeletal pain and often accompanied by physical fatigue, nonrestorative sleep, headaches, anxiety, and depression.[24–26,61] Unfortunately, there is no known cure for JFM, and over 80% of adolescents with JFM continue to experience pain into adulthood.[22,23] Despite sharing many clinical features,[52] some differences exist between JFM and adult-onset fibromyalgia (FM). First, joint hypermobility and dysautonomia, rarely reported in adults with FM, are common in adolescents with JFM.[14,25,53] Second, the brain, which is critical for forming and regulating pain perception,[1] undergoes robust development during adolescence.[5] In a recent article, we were the first to report that brain processing of pain during adolescence differs from adulthood,[54] suggesting that the conclusions from adult fibromyalgia studies may not be directly applicable to JFM pathophysiology.

The past 2 decades have seen considerable advances in understanding the brain mechanisms of adult

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.painjournalonline.com).

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http://dx.doi.org/10.1097/j.pain.0000000000002933

fibromyalgia.[9,15–17,27,28,33,37,38,41,46,47] In particular, multiple functional magnetic resonance imaging (fMRI) studies have found that adult fibromyalgia is associated with augmented brain responses to acute experimental pain involving primary somatosensory cortex, secondary somatosensory cortex, posterior and anterior insula, and anterior midcingulate cortex.[9,15,27,28,38,46,47] Nevertheless, the brain mechanisms of pain processing in adolescents with JFM remain unclear. In a 2017 study using quantitative sensory testing, our group observed that adolescents with JFM were more sensitive to noxious pressure than their healthy peers,[29] suggesting a propensity for sensitization of peripheral or central nociception. In our group's recent structural MRI study, adolescents with JFM showed significantly less grey matter volume in the pain-associated midcingulate cortex than healthy controls.[51] To the best of our knowledge, only one preliminary study examined the brain activity related to pressure pain in adolescents with JFM.[40] However, this study was likely limited by the small sample size (ie, only 10 participants per group) and uncorrected statistics.

In this study, we investigated the brain correlates of the observed pain hypersensitivity in adolescent girls with JFM using an fMRI task involving noxious pressure stimulation. First, we conducted whole-brain massive univariate general linear model analyses to compare the pain-evoked brain responses between 33 adolescent girls with JFM and 33 healthy adolescent girls. Next, in adolescents with JFM, we correlated their altered brain responses to noxious pressure with measurements of clinical pain. Last, we performed exploratory whole-brain mediation analyses to identify the brain mediators of increased sensitivity to pain in adolescents with JFM.

2. Methods

2.1. Participants

This study involved 33 adolescent girls with JFM (13-18 years old, mean age of 15.85 ± 1.09 years) and 33 matched healthy girls (13-18 years old, mean age of 15.33 ± 1.31 years; 2-sample *t* test for age, $t = 1.73$, $P = 0.089$). Inclusion criteria for the JFM group included (1) having received a clinical diagnosis of JFM from a pediatric rheumatologist or a pain physician following the 2010 American College of Rheumatology (ACR) diagnostic criteria for fibromyalgia,[52,57] (2) reporting 5 or more tender points on the study day, (3) reporting an average pain intensity during the past week of at least 3 of 10, and (4) reporting a Functional Disability Inventory (FDI) score of 7 or higher of 60, indicating at least mild disability.[56] Inclusion criteria for the control group included (1) being healthy both physically and psychologically (ie, not diagnosed with chronic pain, psychiatric, neurological, or inflammatory disorders), (2) reporting an average pain intensity of 0 to 2 of 10 for the past week, and (3) reporting an FDI score below 7, indicating no disability. Those participants with a contraindication to MRI scanning, developmental delay, major neurological or psychiatric disorders, a positive pregnancy test, or taking opioid or psychotropic medication were excluded from the study. All participants included in the study were either not taking any medication or were under a stable medication regimen for a minimum of 3 weeks before the first MRI assessment. Before being enrolled in the study, legal guardians of the study participants provided written informed consent, and all participants provided informed assent. The study protocol and consent forms were approved by Cincinnati Children's Hospital Medical Center Institutional Review Board (Study ID: 2017-7771).

2.2. Study procedures

This study is part of a larger ongoing clinical study on brain mechanisms of juvenile fibromyalgia which has been registered on ClinicalTrials.gov (Study ID: NCT03612258).

All participants completed 2 study visits. Visit 1 involved collecting demographic information, administering clinical questionnaires and familiarizing the participants with the pressure pain fMRI task. Clinical questionnaires included Widespread Pain Index (0-18) which assesses the number of pain locations and Symptom Severity Scale (0-12) which assesses the severity of 3 cardinal symptoms of fibromyalgia (ie, fatigue, waking unrefreshed, and cognitive symptoms) and the presence of other somatic symptoms, as described in the 2010 ACR diagnostic criteria for FM.[52,57] These are 2 subscales from the Pain and Symptom Assessment Tool (PSAT), which was developed to enhance consistent classification of adolescents with JFM based on the 2010 ACR diagnostic criteria for FM.[11,39] Besides, the study participants were also asked to complete the Functional Disability Inventory[56] and the Children's Depression Inventory.[31] These 2 questionnaires were used to measure pain-related functional impairment and depressive symptoms in adolescents, respectively.

During visit 1, the experimenter explained the pressure pain task and demonstrated the pressure stimulation device to the participants. Then, participants were asked to practice the pain rating task on a computer. Noxious pressure was applied with a hand-held algometer using the same stimulus intensity, duration, and interval as the stimuli administered by the pressure pain device during the fMRI task.

Visit 2 immediately followed visit 1 and involved MRI data acquisition. During the pressure pain fMRI task, a computer-controlled pneumatic device, which could reliably transmit preset pressure to 1 cm^2 surface,[15,36,38,46,54] was used to deliver noxious pressure stimuli to the left thumbnail. We chose to stimulate the thumbnail because it is a body site that is relatively easy to stimulate with minimal head motion. We chose the left side for stimulation because this would allow our participants to submit their pain ratings using the trackball mouse with the right hand, as in previous studies.[6,34,35] Noxious pressure was applied at the intensity of either 2.5 kg/cm^2 or 4 kg/cm^2.

A block design was adopted for our pressure pain fMRI task, which was programmed and presented to the participants using the E-Prime 3.0 software (Psychology Software Tools, Pittsburgh, PA). As described in our previous paper,[54] the task consisted of 2 consecutive fMRI runs, each containing 6 trials in a mixed pseudorandom order, with 3 trials at each stimulus intensity. As shown in **Figure 1**, each trial began with a rest period with pseudorandom duration (range: 11-20 seconds), followed by a very brief auditory cue lasting 0.2 seconds, a 3-to-6-second pain anticipation period, and then a fixed 10-second pain period. After an 8 to 10 seconds postpain period, the participants were asked to rate the pain intensity ("How intense was the pain you just experienced?") and pain unpleasantness ("How unpleasant was the pain you just experienced?") on computerized Visual Analogue Scales (VAS) from 0 ("not painful or unpleasant at all") to 100 ("most painful or unpleasant imaginable").[44] The participants were instructed to move the cursor on the scales using an MRI-compatible trackball until the position that best describes their pain experience and click the button to submit their ratings. The numbers between 0 and 100 on the scales were not visible to the participants. At the end of each run, the participants were asked to rate the intensity of spontaneous bodily pain ("How much bodily pain did you experience during the task?") and extensiveness of spontaneous bodily pain ("How extensive was

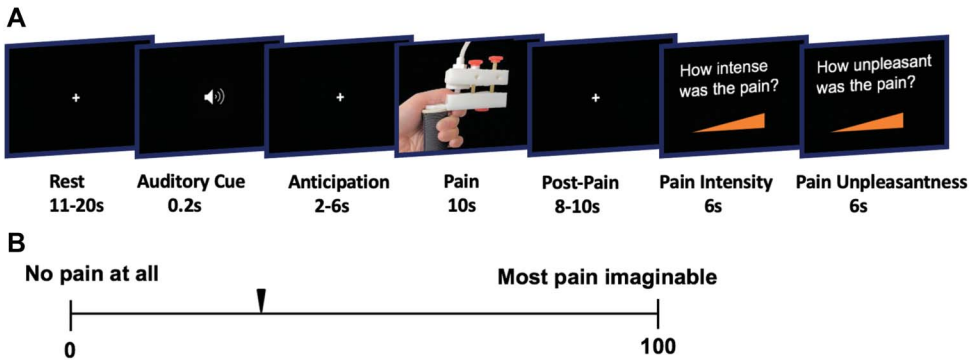

Figure 1. Noxious pressure stimulation task. (A) Details and timing of one stimulation cycle. Adapted from Tong et al., 2022.[54] (B) Illustration of the computerized Visual Analogue Scales used in the study.

the bodily pain you felt during the task?") unrelated to the noxious stimuli on a computerized VAS from 0 ("no pain at all" or "very localized pain") to 100("worst pain imaginable" or "pain all over my body"). Answers to these 2 questions represented the self-reported severity of spontaneous bodily pain during the task.

2.3. Magnetic resonance imaging data acquisition

Neuroimaging data for this study were acquired at Cincinnati Children's Hospital Medical Center using a Philips Ingenia 3T MR System (Philips Healthcare, Best, The Netherlands) with a 32-channel head coil. Structural MRI images of the brain were acquired using the standard T1-weighted gradient echo sequence and the following scan parameters: TR = 10 milliseconds, TE = 1.8, 3.8, 5.8, 7.8 milliseconds, field of view = 256 × 224 × 200 mm, voxel size = 1 × 1 × 1 mm, number of slices = 200, flip angle = 8°, slice orientation = sagittal, and scan duration = 4:42 minutes. Blood oxygen level-dependent (BOLD) fMRI data were collected using T2* weighted echo planar imaging sequence with the multiband sensitivity encoding (SENSE) technique.[45] Scan parameters for the pressure pain task were as follows: multiband acceleration factor = 4, repetition time (TR) = 650 milliseconds, echo time (TE) = 30 milliseconds, field of view = 200 mm, flip angle = 53°, voxel size =2.5 × 2.5 × 3.5 mm, slice orientation = transverse (parallel to the orbitofrontal cortex line), slice thickness = 3.5 mm, number of slices = 40 (provided whole-brain coverage), number of volumes = 522, number of dummy scans = 12, and scan duration = 5:42 minutes. Two consecutive fMRI runs of pressure pain task were acquired. Information regarding other fMRI scans acquired during the same MRI session can be found on ClinicalTrials.gov (Study ID: NCT03612258).

2.4. Data analyses

2.4.1. Statistical analyses of demographic and clinical variables

Differences in demographic and clinical variables between adolescents with JFM and healthy adolescents were analyzed using 2-sample *t* tests in R software (version 3.6.2, R Foundation for Statistical Computing, Vienna, Austria).

2.4.2. Statistical analyses of behavioral data

We built a mixed-design analysis of variance (ANOVA) model with "group" as the between-subject variable and "stimulus intensity" as the within-subject variable using R software to assess differences in pain intensity and unpleasantness between the JFM group and the healthy adolescent group under 2 experimental conditions (ie, noxious pressure stimuli at 2.5 kg/cm^2 and 4 kg/cm^2). Post hoc pairwise comparisons were made using the false discovery rate (FDR) correction method.

In addition, we compared the intensity and extensiveness of bodily pain between the 2 groups using 2-sample *t* tests and computed Pearson correlations between pain ratings to noxious pressure stimuli (2.5 kg/cm^2 and 4 kg/cm^2) and bodily pain ratings (intensity and extensiveness), respectively.

Last, we examined whether the perception of spontaneous bodily pain in our participants significantly changed from run 1 to run 2 using paired *t* tests in R software.

2.4.3. Preprocessing of neuroimaging data

We preprocessed the neuroimaging data using FSL (FMRIB Software Library version 6.0.3, the Analysis Group, FMRIB, Oxford, United Kingdom)[50] and AFNI (Analysis of Functional Neuroimages version 20.3.02, Medical College of Wisconsin, WI).[10] For the structural images, we performed brain extraction using the Brain Extraction Tool (BET)[49] in FSL. We performed bias correction and segmentation using FMRIB's Automated Segmentation Tool (FAST) in FSL.[64] Then we normalized and resampled the brain-extracted image to the 2-mm isotropic MNI ICBM 152 nonlinear sixth generation template[13] using FSL's FMRIB's Linear Image Registration Tool (FLIRT).[18,19] We preprocessed each participant's functional scans in the following steps: First, brain extraction was performed using FSL's BET.[49] Next, outlying functional volumes (ie, spikes) were detected using the DVARS metric within FSL's "fsl_motion_outliers."[43] We performed motion correction of the functional time series using MCFLIRT.[18] The motion corrected data were then high pass filtered at 0.00556 Hz (180 seconds) and smoothed with a 6-mm full width at half maximum (FWHM) filter using AFNI 3dBandpass. To minimize pain-induced global cerebral blood flow fluctuations,[7,8] we applied intensity normalization by scaling each fMRI volume by its mean global intensity.[54,62,63] The intensity-normalized data were first coregistered with the participant's T1 image using FSL FLIRT (6-parameter rigid body model),[18] then aligned to the MNI template.[13]

2.4.4. General linear model analyses

We used the general linear model (GLM) approach as implemented in FSL's "fsl_glm"[59] to estimate each participant's brain

responses to noxious stimuli. Specifically, we modeled the 3 pain periods associated with 2.5 kg/cm^2 stimuli and the other 3 pain periods associated with 4 kg/cm^2 stimuli as 2 separate regressors. In addition to the pain period regressors, our GLM model included regressors for the anticipatory periods, postpain periods, and pain rating periods. The remaining "rest" period was used as the implicit baseline. Finally, 6 motion parameters (3 for translational motion and 3 for rotational motion) and outlying volumes ("spikes") were included as nuisance regressors. The 2 runs of each participant's first-level GLM results, which included estimated contrasts of parameter estimates (COPEs) and their variances (VARCOPEs), were combined at the single-subject level using the fixed effects modeling in FSL with "flameo."[58] Then at the group level, mixed effects modeling (FLAME 1 + 2)[58] was used to compute each group's mean brain responses to pressure pain (one-sample *t* test) and between-group differences (2-sample *t* test) for each condition (2.5 kg/cm^2 and 4 kg/cm^2). The group-level GLM analyses for between-group differences were repeated with age added as a covariate in the model to verify that the observed group difference was not explained by age. The results of group-level analyses were corrected for multiple comparisons across the whole brain using the FSL "cluster" tool. Clusters of voxels were identified using a threshold of $Z > 3.1$, and their statistical significance ($P < 0.05$) was estimated by cluster-based inference according to the Gaussian random field theory.[60]

Next, we conducted a post hoc analysis to determine if changes in spontaneous bodily pain from run 1 to run 2 were potentially confounding the group differences in pressure pain activation (ie, the significant cluster we identified in GLM analyses). We extracted the contrast parameter estimates for the 2.5 kg and 4 kg pressure pain conditions for each run for each subject (ie, for each contrast image generated in first-level models in FSL) and computed the correlation between the change in activation from run 1 to run 2 and the change in bodily pain from run 1 to run 2 for each group.

To further understand the clinical implications of our neuroimaging findings, we extracted the maximum Z score within the brain region representing the between-group difference in brain responses to noxious stimuli in adolescents with JFM and correlated it with their scores of Widespread Pain Index and Symptom Severity Scale, clinically validated measures of extensiveness of bodily pain and JFM symptom severity during the past week, respectively.[11,39] Likewise, we also tested the correlations between the peak between-group difference in pain-evoked brain responses in adolescents with JFM and their ratings of bodily pain intensity and extensiveness during the fMRI task.

2.4.5. Exploratory whole-brain mediation analyses

First-level contrast images for the pain period regressors were carried forward to a whole-brain mediation analysis model. We tested relationships between group (adolescents with JFM vs healthy adolescents), single-subject pain-evoked brain responses (contrast images for each trial), and single-subject pain intensity ratings to stimuli at 4 kg/cm^2 using mediation analysis found in the multilevel mediation and moderation (M3) toolbox[55] and implemented in MATLAB (version R2019b, MathWorks, MA).[2,30,34] Mediation analysis identifies brain regions that show partially independent, but not orthogonal, effects: (1) between-group differences in pain-evoked brain responses (path a), (2) brain activity that predicts changes in pain intensity ratings (path b) controlling for group, and (3) brain activity mediating the between-group differences in pain intensity ratings (path a × b). The resulting activation maps were shown at uncorrected $P < 0.001$, as implemented in our previous study.[54] To facilitate interpretation of the functional maps, adjacent voxels to the identified clusters were also displayed in a different color at a lower threshold of uncorrected $P < 0.005$.

3. Results

3.1. Demographic and clinical variables

Adolescents with JFM and healthy controls did not differ in sex (all female), age, race, ethnicity (all non-Hispanic), and household income (all $P > 0.05$) (**Table 1**). As expected, compared with healthy adolescents, adolescents with JFM reported significantly higher scores in Functional Disability Inventory, Widespread Pain Index, Symptom Severity, and Children Depression Inventory (all $P < 0.001$, as shown in **Table 1**), suggesting worse functional impairment, fibromyalgia symptoms, and depressive symptoms. Data regarding medication use are also summarized and presented in **Table 1**. Pain and psychiatric medications were the most used categories in adolescents with JFM (42.42%).

3.2. Adolescents with juvenile fibromyalgia show greater pain sensitivity to noxious pressure

As shown in **Figure 2**, pain intensity and pain unpleasantness ratings in response to noxious stimuli at 2.5 kg/cm^2 were 31.64 ± 20.72 (mean ± SD) and 33.72 ± 22.44 in adolescents with JFM and 20.66 ± 13.12 and 19.31 ± 11.82 in healthy adolescents, respectively. Pain intensity and pain unpleasantness ratings to noxious stimuli at 4 kg/cm^2 were 41.38 ± 21.07 (mean ± SD) and 44.43 ± 20.86 in adolescents with JFM and 28.49 ± 16.61 and 29.58 ± 17.22 in healthy adolescents, respectively (measured using a VAS ranging from 0 to 100). Using a group-by-stimulus intensity mixed-design ANOVA, we found a significant main effect of group (pain intensity: $F = 7.48$, $P = 0.008$; pain unpleasantness: $F = 11.16$, $P = 0.001$) and a significant main effect of pressure on pain ratings (pain intensity: $F = 77.97$, $P < 0.001$; pain unpleasantness: $F = 65.96$, $P < 0.001$) but did not find an interaction between group and stimulus intensity (pain intensity: $F = 0.92$, $P = 0.34$; pain unpleasantness: $F = 0.03$, $P = 0.865$). Post hoc pairwise comparisons showed that, in response to stimuli at either 2.5 or 4 kg/cm^2, adolescents with JFM reported greater pain intensity (2.5 kg/cm^2: $t = 2.57$, FDR-corrected $P = 0.013$; 4 kg/cm^2: $t = 2.76$, FDR-corrected $P = 0.010$) and pain unpleasantness (2.5 kg/cm^2: $t = 3.26$, FDR-corrected $P = 0.002$; 4 kg/cm^2: $t = 3.15$, FDR-corrected $P = 0.003$) than healthy adolescents. These results indicate that adolescents with JFM have greater pain sensitivity to noxious pressure stimuli than their healthy peers for both intensities of noxious stimuli.

3.3. Experimental pain ratings and spontaneous bodily pain ratings are significantly correlated in adolescents with juvenile fibromyalgia

As expected, adolescents with JFM reported significantly greater intensity ($t = 9.42$, $P < 0.001$) and extensiveness ($t = 8.04$, $P < 0.001$) of spontaneous bodily pain during the task (ie, pain unrelated to the noxious stimuli) than healthy adolescents (**Fig. 3**).

In both groups of participants, there was no significant difference in intensity and extensiveness of bodily pain ratings between run 2 and run 1 of the pressure pain task ($P > 0.05$ in all paired *t* tests, Figure S1, available at http://links.lww.com/PAIN/B822),

Table 1

Demographic and clinical characteristics of adolescents with juvenile fibromyalgia and healthy controls.

	Adolescents with JFM	Healthy controls	t-score	*P*
Demographics				
Age, y	15.85 ± 1.09	15.33 ± 1.31	1.73	0.089
Race, White (%)	31 (93.94)	31 (93.94)	—	—
Ethnicity, non-Hispanic	33 (100)	33 (100)	—	—
Annual household income*	5.21 ± 1.92	5.24 ± 1.95	−0.06	0.95
Clinical variables				
Widespread pain index	11.34 ± 3.68	0.09 ± 0.29	17.23	<0.001
Symptom severity	8.63 ± 2.27	1.00 ± 1.34	15.36	<0.001
Functional disability inventory	22.30 ± 9.15	0.48 ± 1.30	13.56	<0.001
Children's depression inventory	19.43 ± 9.75	4.68 ± 5.68	7.1	<0.001
Medication use, no. (%)				
Pain-related drugs†	14 (42.42)	—	—	—
Psychiatric drugs‡	14 (42.42)	—	—	—
Gastrointestinal drugs	7 (21.21)	—	—	—
Antihistamines	3 (9.09)	—	—	—
Melatonin	3 (9.09)	—	—	—
Vitamins/minerals	3 (9.09)	—	—	—
Birth control	2 (6.06)	1 (3.03)	—	—
Steroids	1 (3.03)	—	—	—
Diuretics	—	1 (3.03)	—	—
Statins	—	1 (3.03)	—	—

* Annual household income is shown using a scale of 1 to 7, where 1 = <$24,999; 2 = $25,000 to $49,999; 3 = $50,000 to $74,999; 4 = $75,000 to $99,000; 5 = $100,000 to $124,999; 6 = $125,000 to $14999; 7 = >$150,000.

† Pain-related drugs included antiepileptic drugs, nonsteroidal anti-inflammatory drugs, muscle relaxants, acetaminophen, or acetylsalicylic acid.

‡ Psychiatric drugs included antidepressants, anxiolytics, and attention deficit hyperactivity disorder drugs.

JFM, juvenile fibromyalgia.

suggesting their perception of spontaneous bodily pain did not significantly change during the pressure pain task.

In adolescents with JFM, average pain intensity ratings to 2.5 kg/cm^2 (a total of 6 trials) were positively correlated with the intensity (t = 3.61, P = 0.001, r = 0.54) and extensiveness (t = 2.29, P = 0.029, r = 0.38) of spontaneous bodily pain (unrelated to the noxious stimuli) experienced during the fMRI scan and reported at the end of the scan also using a VAS. The average pain intensity ratings to 4 kg/cm^2 (6 trials) also showed a positive correlation with the intensity of spontaneous bodily pain experienced along the course of the scan (t = 2.56, P = 0.016, r = 0.42) and a trend towards a positive correlation with extensiveness of spontaneous bodily pain (t = 1.76, P = 0.088, r = 0.30) (**Fig. 4**).

3.4. Adolescents with juvenile fibromyalgia show augmented pain-evoked activation in primary somatosensory cortex and activation in such region correlates with widespreadness of spontaneous bodily pain

Adolescents with JFM showed pain-evoked brain activation in regions similar to those found in healthy adolescents, including bilateral insular cortex and operculum, parietal operculum (S2), supramarginal gyrus, primary sensorimotor cortex (S1/M1),

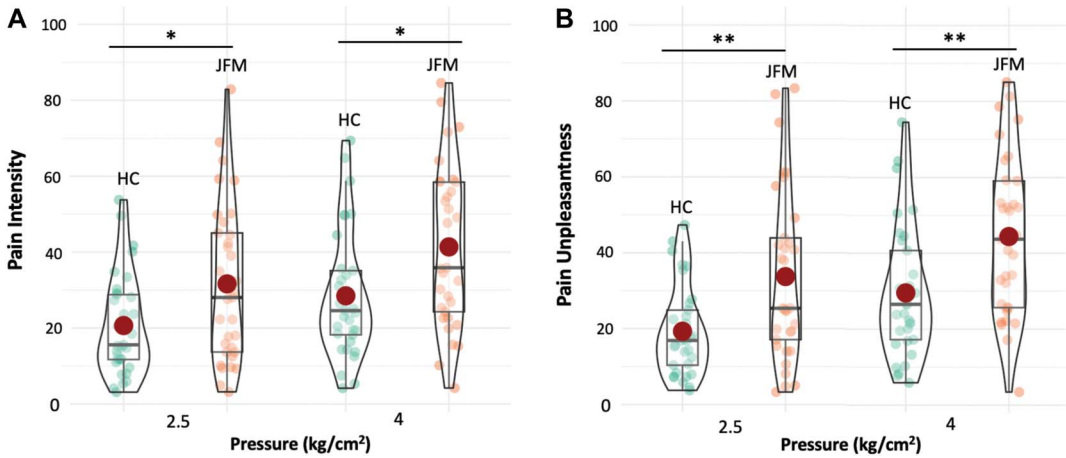

Figure 2. Pain intensity (A) and unpleasantness (B) ratings to noxious pressure stimuli by different pressure (2.5 kg/cm^2 and 4 kg/cm^2) in healthy adolescents and adolescents with JFM. Using mixed-design ANOVA tests, we found a significant main effect of group and a significant main effect of pressure on pain ratings but did not find an interaction between group and stimulus intensity neither for pain intensity nor for pain unpleasantness. Dark red dots represent the group mean. *P < 0.05 in post hoc t tests (FDR corrected); **P < 0.01 in post hoc t tests (FDR corrected). ANOVA, analysis of variance; FDR, false discovery rate; HC, healthy controls; JFM, juvenile fibromyalgia.

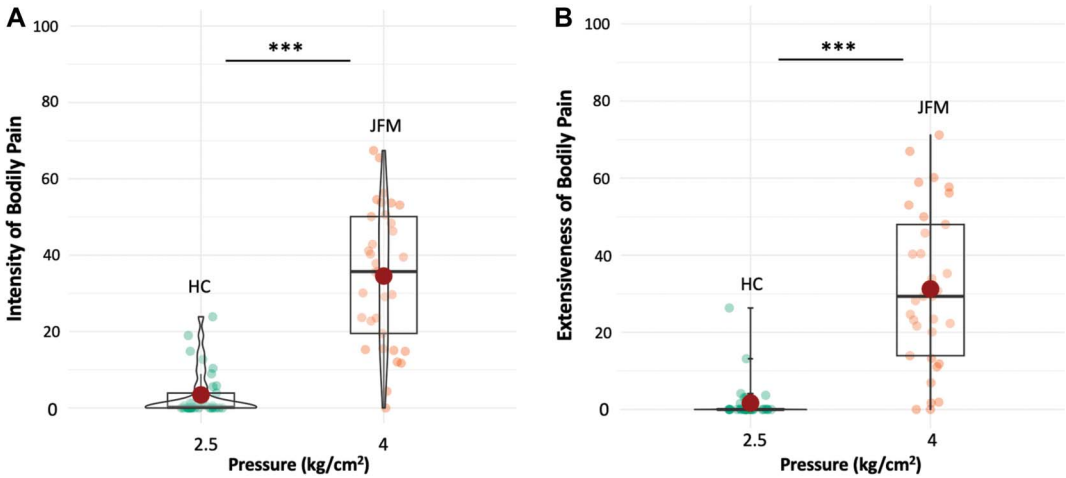

Figure 3. Intensity (A) and extensiveness (B) of bodily pain in healthy adolescents and adolescents with JFM. Dark red dots represent the group mean. ***$P < 0.001$ in 2-sample t tests. HC, healthy controls; JFM, juvenile fibromyalgia.

anterior cingulate cortex, supplementary motor area, dorsolateral prefrontal cortex, superior temporal gyrus, basal ganglia, thalamus, and amygdala (**Fig. 5** and Tables S1-S4, available at http://links.lww.com/PAIN/B822). Both groups of adolescents showed pain-evoked deactivations in the fusiform gyrus, precuneus cortex, and occipital visual cortex. In both groups, the cerebellum was deactivated in response to 2.5 kg/cm^2 and became activated in response to stimuli at 4 kg/cm^2. When compared statistically, adolescents with JFM exhibited significantly augmented activation ($Z > 3.1$, $P < 0.05$ corrected for multiple comparisons) in the right primary somatosensory cortex (S1, postcentral gyrus) in response to

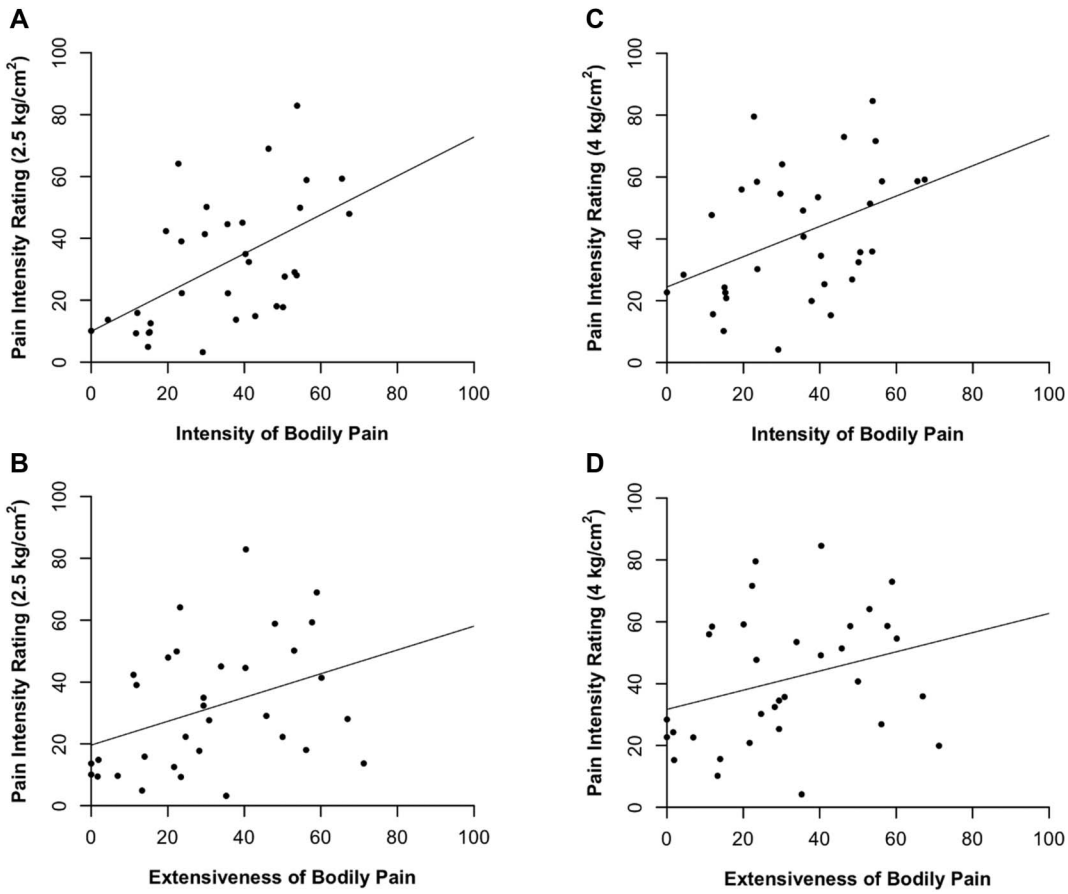

Figure 4. Associations between pressure pain and bodily pain in patients with JFM. Pain intensity ratings to 2.5 kg/cm^2 (left column) were positively correlated with (A) intensity of bodily pain ($t = 3.61$, $P = 0.001$, $r = 0.54$) and (B) extensiveness of bodily pain ($t = 2.29$, $P = 0.029$, $r = 0.38$). Pain intensity ratings to 4 kg/cm^2 (right column) also showed a positive correlation with (C) intensity of bodily pain ($t = 2.56$, $P = 0.016$, $r = 0.42$) and a trend towards a positive correlation with (D) extensiveness of bodily pain ($t = 1.76$, $P = 0.088$, $r = 0.30$). JFM, juvenile fibromyalgia.

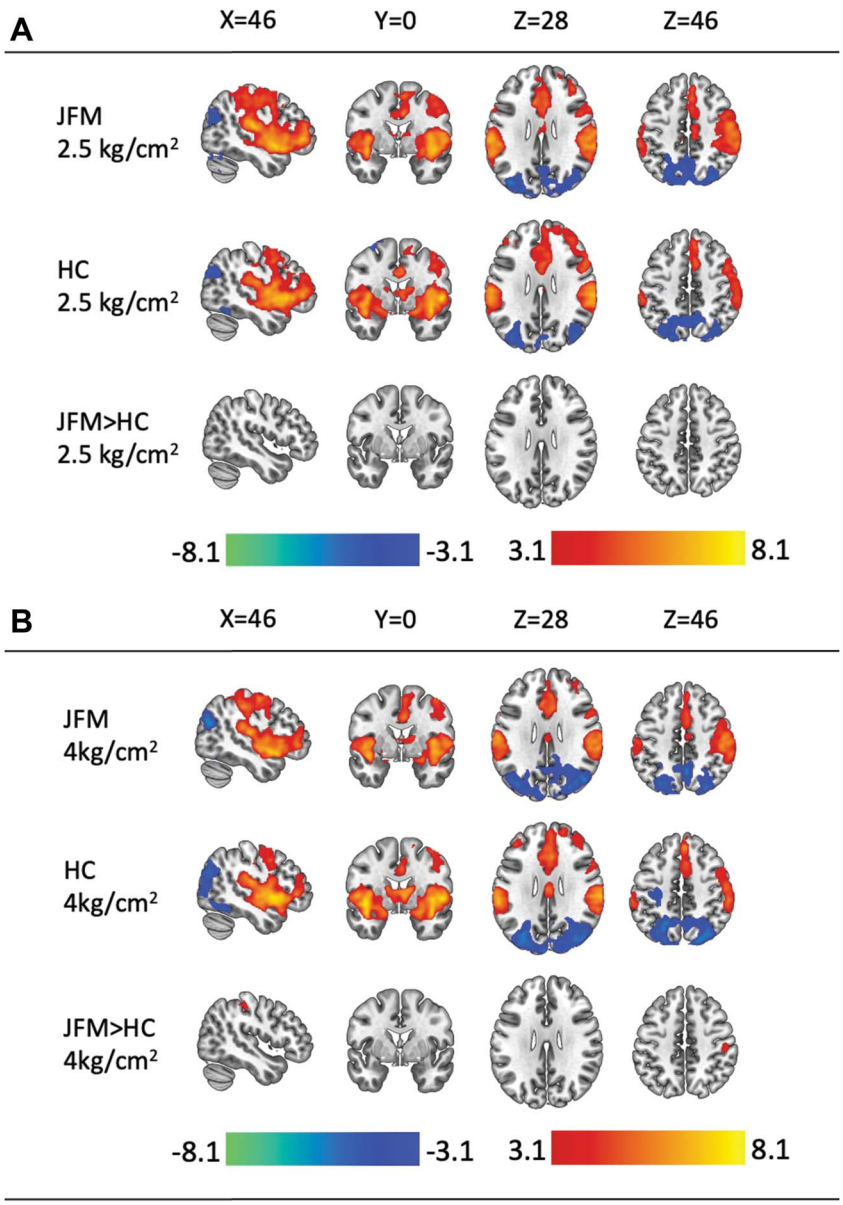

Figure 5. Pain-evoked brain responses in adolescents with JFM (top rows), healthy adolescents (middle rows), and between group comparisons (bottom rows). (A) Brain responses to 2.5 kg/cm^2 were not significantly different between the groups. (B) Adolescents with JFM had significantly greater activation in right primary somatosensory cortex (postcentral gyrus, S1) in response to stimuli at 4 kg/cm^2. Statistical significance was estimated using cluster-based inference at $Z > 3.1$, cluster-corrected $P < 0.05$. HC, healthy controls; JFM, juvenile fibromyalgia.

noxious stimuli at 4 kg/cm^2 (**Fig. 5** and Table S5, available at http://links.lww.com/PAIN/B822). Brain responses to noxious stimuli at 2.5 kg/cm^2 were not significantly different between groups after correcting for multiple comparisons (**Fig. 5**). After adjusting for age, between-group differences in S1 remained significant for stimuli at 4 kg/cm^2 and became significant for stimuli at 2.5 kg/cm^2 as well (Tables S6-S7, available at http://links.lww.com/PAIN/B822).

To determine whether changes in spontaneous bodily pain from run 1 to run 2 were potentially confounding the group differences in pressure pain activation (ie, the significant cluster we identified in right S1), we correlated the change in right S1 activation from run 1 to run 2 with the change in bodily pain from run 1 to run 2 for each group and each stimulus intensity. None of the correlations were statistically significant (Figure S2, available at http://links.lww.com/PAIN/B822), suggesting changes in spontaneous bodily pain did not confound our neuroimaging finding.

Importantly, we found a statistically significant positive correlation between pain-evoked responses in the region of S1 showing the largest between-group effects and the Widespread Pain Index scores in adolescents with JFM ($r = 0.35$, $P = 0.048$, **Fig. 6**). By contrast, there was no such association between S1 activity and Symptom Severity Scale scores ($P = 0.93$, $r = -0.01$). We also tested the correlations between peak activation in S1 during evoked pressure pain and intensity and extensiveness of spontaneous bodily pain during the pressure pain task, respectively. Neither intensity ($r = 0.07$, $P = 0.688$) nor extensiveness ($r = -0.01$, $P = 0.963$) of bodily pain during the pressure pain task was significantly correlated with peak activation in right S1 in adolescents with JFM (Figure S3, available at http://links.lww.com/PAIN/B822).

3.5. Augmented pain-evoked sensorimotor activation mediates greater pain sensitivity in adolescents with juvenile fibromyalgia

We performed an exploratory whole-brain mediation analysis to investigate brain activity underlying the observed group difference in pain intensity ratings between adolescents with JFM and healthy adolescents. As illustrated in **Figure 7**, the mediation model included "group (JFM vs Control)" as the independent variable X, "pain intensity ratings to stimuli at 4 kg/cm^2" as the dependent variable Y, and "brain responses to stimuli at 4 kg/cm^2" as the mediator M. Path a (X→M) represents the between-group differences in brain responses to noxious pressure stimuli. In line with the results of the GLM analyses, we found that adolescents with JFM had greater pain-evoked responses than healthy adolescents in the right primary sensorimotor cortex (precentral and postcentral gyrus), contralateral to the side of body receiving noxious stimuli. A subregion of the left primary sensory cortex and the right superior parietal lobule also showed greater responses in JFM. Path b (M→Y) represents pain-evoked brain activity predicting higher pain intensity ratings controlling for group. Significant path b effects were found in the following regions: cerebellum, thalamus, precuneus, ventromedial prefrontal cortex, and primary sensorimotor cortex. Path a × b (X→M→Y) represents the mediation effect. We found that the brain activity in the primary sensorimotor cortex–mediated group effects on pain intensity ratings. In other words, these results suggest that augmented pain-evoked sensorimotor responses in adolescents with JFM account for their augmented pain sensitivity compared with healthy adolescents.

4. Discussion

This is the first study that directly compares pain-evoked brain responses between adolescents with JFM and healthy adolescents using a relatively large sample size. We found that, compared with healthy adolescents, adolescents with JFM were more sensitive to noxious pressure at both low (2.5 kg/cm^2) and medium (4 kg/cm^2) stimulus intensities and exhibited significantly augmented pain-related activation in the primary somatosensory cortex, whose activation magnitude correlated with greater widespreadness of clinical pain. We also found that amplified primary sensorimotor cortex activation in adolescents with JFM mediated their hyperalgesia compared with healthy adolescents. Taken together, these findings suggest that adolescents with JFM have greater pain sensitivity and greater sensorimotor cortical responses to evoked noxious stimulation, which may reflect sensitization of the cortical somatosensory system, reduced intracortical inhibition of S1 during noxious input or augmented peripheral nociceptive input to the brain. Evidence favoring each of these options is discussed later in greater detail. Overall, our findings highlight the primary somatosensory cortex, S1, as a key driver of pressure-evoked hyperalgesia in adolescents with JFM, as opposed to other brain regions that are involved in affective, cognitive, or motivational aspects of the pain experience. Our findings suggest that acute hyperalgesia in patients is specifically associated with the sensory-discriminative aspect of pain processing at the brain level. Future studies are warranted to ascertain to which extent the brain circuits underlying affective, cognitive, or motivational processing may be involved in explaining other symptoms of JFM.

First, we compared pain intensity and unpleasantness ratings between adolescents with JFM and healthy controls using mixed-design ANOVA. We found significant main effects of group and stimulus intensity but no interaction, suggesting that adolescents with JFM are similarly hypersensitive to noxious pressure stimuli at low and medium intensities. This finding is in line with previous observations by our group in the 2017 King et al's study.[29] In that study, mechanical pressure was applied to the forehead and the palm using a hand-held algometer using a method of limits (ie, pressure pain thresholds), and adolescents with JFM rated higher pain intensity of the pressure stimulus than healthy adolescents. In the current study, suprathreshold pressure was applied using a computer-controlled pressure pain device to the thumbnail bed, one of the most distal parts of the body, as well as the most commonly used site in comparable imaging studies on adult fibromyalgia.[15,20,21,28,38,46] Our finding not only confirmed that adolescents with JFM are hypersensitive to noxious pressure but also added experimental evidence to the widespreadness of this increased pain sensitivity. The rest of the study sought to understand the underlying brain mechanisms.

The massive univariate GLM analyses showed that adolescents with JFM exhibited greater pain-evoked activation in the right S1, contralateral to the side of stimulation. The S1 region is almost always activated during acute experimental pain and is associated with sensory-discriminative aspects of pain perception.[1] Our finding is consistent with previous studies showing augmented S1

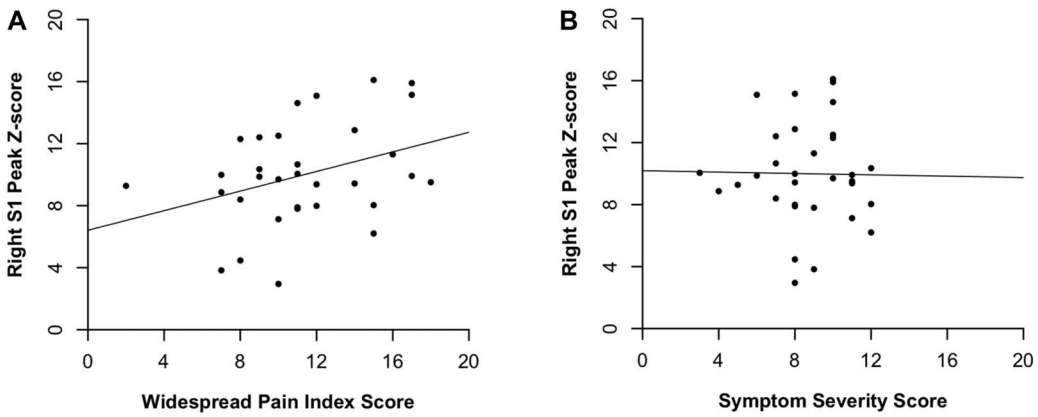

Figure 6. Association of peak pain-evoked activation in right S1 with 2 Pain and Symptom Assessment Tool subscales in adolescents with JFM. (A) Widespread Pain Index score was positively correlated with peak activation magnitude (Z-score) within right primary somatosensory cortex (S1), corresponding to the between-group difference in brain responses to 4 kg/cm^2 stimuli (t = 2.06, $P = 0.048$, $r = 0.35$). (B) Symptom Severity score was not correlated with peak S1 brain activation (t = 0.08, $P = 0.93$, $r = -0.01$). JFM, juvenile fibromyalgia.

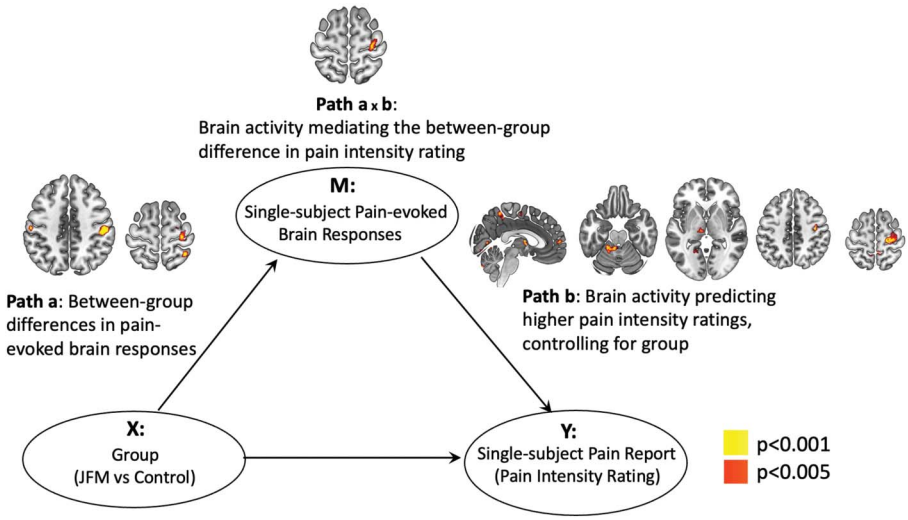

Figure 7. The model and results of exploratory whole-brain mediation analysis, which examines the relationships between group (X), single-subject pain-evoked brain responses to stimuli at 4 kg/cm^2 (M), and single-subject pain intensity ratings to stimuli at 4 kg/cm^2(Y). Pain-evoked brain responses in primary sensorimotor cortex mediate the between-group differences in pain intensity ratings. JFM, juvenile fibromyalgia.

responses during pain in adult fibromyalgia,[15] suggesting a potential common brain mechanism between juvenile and adult forms of fibromyalgia. S1 hyperactivation during pain in adolescents with JFM could reflect central sensitization or disinhibition. For example, compromised intracortical inhibition in S1 has been observed in adults with fibromyalgia using magnetoencephalography.[32] A review of neuroimaging literature also revealed that experimental pain increased the functional connectivity between S1 and insula in adults with fibromyalgia but not in controls, and this strengthened S1-to-insula connectivity was positively correlated with temporal summation of pain.[27] Another possibility is that S1 hyperactivation results from increased or amplified nociceptive input to the brain. For instance, a recent study found that about half of adolescents with JFM have skin biopsy findings suggesting small-fiber neuropathy,[3] consistent with findings in adults with FM.[42] Another study found that some adults with FM have silent nociceptors exhibiting hyperexcitability.[48] Although we cannot exclude the possibility that S1 hyperactivation is driven by augmented peripheral input to the central nervous system, we did not observe the expected accompanying hyperactivation of the thalamus, the first major brain relay station of peripheral noxious input.

We also found that S1 activation positively correlated with the Widespread Pain Index score but not the Symptom Severity Scale score. This finding suggests that S1 hyperactivation in adolescents with JFM may be particularly associated with the sensory component of pain perception but not with the overall severity of JFM symptoms. Interestingly, we did not find a correlation between S1 activation and intensity or extensiveness of bodily pain during our fMRI task involving pressure pain. This might suggest that S1 hyperactivation is associated with clinical pain averaged over a relatively long period of time (eg, 1 week in widespread pain ratings) but not with clinical pain measured over the short duration (ie, about 5 minutes) of our fMRI task. It is also worth mentioning that S1 activation is derived from periods when patients were experiencing acute noxious pressure and their brain probably allocated more resources to the processing of the acute noxious input as opposed to spontaneous bodily pain. Hence, S1 hyperactivation during these periods is unlikely to be related to spontaneous bodily pain.

Finally, using whole-brain mediation analysis, we found that the brain activity in primary sensorimotor cortex mediated the between-group difference in pain-intensity ratings, which implies that sensorimotor responses in adolescents with JFM may account for their greater pain sensitivity compared with healthy adolescents.

Collectively, the findings of brain correlates of pain hypersensitivity and the link between S1 hyperactivation and greater spatial spread of pain across multiple body sites are clinically relevant and important because they support JFM patients' self-reports of widespread pain, which are sometimes viewed with skepticism in a healthcare setting. Our findings could be helpful in enhancing pain neuroscience understanding amongst medical professionals so that they are better able to assure patients that there is a neurophysiological basis of their pain sensitivity.

This study has several limitations that should be considered when interpreting the results. First, only female adolescents, who represent most patients with JFM, were included in our study. Therefore, our findings might not be applied to male adolescents and children with JFM. Although quite rare, they could have distinct characteristics of pain processing in the brain and warrant further research. Second, we did not collect data regarding the specific locations of spontaneous bodily pain during the pressure pain task in our participants. Pain in the thumbnail or hand region, although uncommon in adolescents with JFM, could affect the perception of acute experimental pain and confound the results. Third, medication use in patients with JFM could have acted as a confounding factor, although all participants were required to maintain a stable regimen for at least 3 weeks before their fMRI scan. Last, our study is cross-sectional and included 33 participants per group. Future research is needed to reproduce our findings in larger samples and investigate whether the observed functional alterations in the brain differ in subgroups of adolescents with JFM identified based on clinical features (eg, joint hypermobility) and respond to treatments targeting sensorimotor system such as physical exercise and transcranial magnetic stimulation.

In conclusion, this study provides the first evidence of greater pain-evoked brain responses in adolescents with JFM involving primary sensorimotor regions important for sensory-discriminative aspect of pain perception, which may account for their augmented pain sensitivity compared with healthy adolescents.

Conflict of interest statement

The authors have no conflict of interest to declare.

Acknowledgements

This work was funded by Cincinnati Children's Hospital Medical Center's Trustee Grant Award and NIH/NIAMS Grants R01 AR074795 and P30 AR076316. Marina López-Solà, PhD is hired as part of the Serra Hunter Programme of the Generalitat de Catalunya. The authors gratefully thank Matt Lanier, Kaley Ireland, Kelsey Murphy, Brynne Williams, Sarah Miozzi, and Lacey Haas (Imaging Research Center, Department of Radiology, Cincinnati Children's Hospital Medical Center) for their assistance in collecting MRI data.

Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/B822.

Article history:
Received 7 September 2022
Received in revised form 17 January 2023
Accepted 7 February 2023
Available online 16 June 2023

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