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Reduced Cortico-Cortical Resting-State Connectivity in Sensory Systems is related to Bodily Pain in Juvenile Fibromyalgia

Maria Suñol, PhD[1,*], **Jon Dudley, PhD**[2], **Michael F. Payne, MA**[3], **Han Tong, PhD**[3,4,5], **Tracy V. Ting, MD, MSc**[6,7], **Susmita Kashikar-Zuck, PhD**[3,6,8], **Robert C. Coghill, PhD**[3,6,8], **Marina López-Solà, PhD**[1,*]

[1]Institute of Neurosciences, Department of Medicine, School of Medicine and Health Sciences, University of Barcelona, Barcelona, Spain

[2]Pediatric Neuroimaging Research Consortium, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

[3]Division of Behavioral Medicine and Clinical Psychology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

[4]Neuroscience Graduate Program, University of Cincinnati College of Medicine, Cincinnati, OH, USA

[5]Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL, USA

[6]Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA

[7]Division of Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

[8]Pediatric Pain Research Center, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

Abstract

Objectives: Juvenile-onset fibromyalgia (JFM) is a paradigmatic chronic pain condition for which the underlying neurobiological substrates are poorly understood. This study examined for the first time data-driven resting-state functional connectivity (rsFC) alterations in 37 female adolescents with JFM compared with 43 healthy female adolescents, and identified associations with bodily pain.

Methods: Whole-brain voxel-wise rsFC alterations were assessed using the intrinsic connectivity contrast, a measure of node centrality at each voxel, and seed-based analyses for interpretability. We studied the relationship between rsFC alterations in somatosensory systems and location and extension of bodily pain.

Results: Adolescents with JFM had voxel-wise rsFC reductions in the paracentral lobule (PCL)/primary somatosensory cortex (S1) (T=4.89, pFWE<.001) and left midcingulate cortex (T=4.67,

[*]Corresponding Authors: **Maria Suñol, PhD,** Address: Department of Medicine, School of Medicine and Health Sciences, University of Barcelona, Casanova, 143, Ala Nord, 5a planta, Barcelona, 08036, Spain. Telephone: +34 93 403 9299. msunol@ub.edu; **Marina López-Solà, PhD,** Address: Department of Medicine, School of Medicine and Health Sciences, University of Barcelona, Casanova, 143, Ala Nord, 5a planta, Barcelona, 08036, Spain. Telephone: +34 93 403 9299. mlopezsola@ub.edu.

CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

pFWE=.043). Post-hoc analyses revealed reduced rsFC spanning major cortical sensory hubs (T's>4.4, pFWE's<.030). Cortico-cortical rsFC reductions within PCL/S1 in JFM occurred in locations innervated by bodily areas where the pain was most frequent (F=3.15; pFDR=.029) and predicted widespread pain (T's>4.4, pFWE's<.045). Conversely, adolescents with JFM had increases in PCL/S1-thalamus (T=4.75, pFWE=.046) and PCL/S1-anterior insula rsFC (T=5.13, pFWE=.039).

Conclusion: Reduced cortico-cortical sensory integration involving PCL/S1 and spanning the sensory systems may underly critical pain sensory features in youth with JFM. Reduced sensory integration is paralleled by augmented crosstalk between sensory and affective/salience-processing regions, potentially indicating a shift towards more affectively colored sensory experiences to the detriment of specific sensory discrimination.

1. INTRODUCTION

Fibromyalgia is a widespread chronic pain condition, associated with fatigue, mood disturbances, and amplified sensitivity to sensory stimuli (1,2). Brain imaging research in adult fibromyalgia suggests that this condition is linked to altered brain structure, metabolism, and activity involving multiple brain circuits and spanning functional domains (3–8). Conversely, juvenile-onset fibromyalgia (JFM) is poorly understood and understudied, specifically from a pathophysiological perspective. JFM affects 2–6% of children, primarily adolescent girls, during a critical period for brain, body, and psychosocial development (9). JFM causes severe functional impairment, and over 80% of adolescents continue to experience symptoms into adulthood (9,10). There might be relevant differences between adults and youth with fibromyalgia. Primarily, they differ in brain developmental stage, which could entail meaningful differences in processing of external and internally generated stimuli, as suggested by a recent study on pain-evoked brain responses (11). Additionally, only two out of six meta-analytic brain structural alterations reported in adult fibromyalgia replicated in JFM (12). Thus, conclusions from adult fibromyalgia studies may not directly apply to adolescents with JFM, reinforcing the importance of studying this condition in youth.

Resting-state functional connectivity (rsFC) captures synchronous patterns in the fluctuation of blood oxygen level-dependent (BOLD) signal during rest, reflecting the functional organization of large-scale brain systems. To date, no studies have addressed rsFC in JFM. One study reported reduced rsFC in the primary somatosensory system of pediatric chronic pain patients (13), which concurs with rsFC reductions in somatosensory areas observed in adults with fibromyalgia (4,5). In fact, fibromyalgia has been classified as a disorder of pain-related somatosensory processing that may lead to increased pain facilitation and impaired inhibition (4,5). A previous study found reciprocal inhibitory influences between responses to noxious and tactile stimuli at the cortical level (14). The primary somatosensory cortex (S1) is the first cortical relay where nociceptive but mainly tactile and proprioceptive afference from different body locations converges (15). A lack of optimal nociceptive and non-nociceptive signal integration within S1 and surrounding somatosensory regions could contribute to amplified pain perception (4). In adults with fibromyalgia, sensory rsFC alterations extended beyond the somatosensory domain (4),

patients perceived non-painful multisensory stimuli as more unpleasant than controls and had altered visual and auditory cortical activation (6). Together, evidence suggests that fibromyalgia might be characterized by a broader alteration involving cortical sensory integration in the somatosensory cortex and other major sensory cortices in the posterior aspect of the brain. Whether this phenomenon characterizes JFM, a condition starting much earlier in development, coinciding with a developmental peak, and usually involving shorter periods exposed to disease symptoms, remains to be elucidated.

In this study, we examined differences in rsFC between female adolescents with JFM and healthy female adolescents for the first time using a voxel-wise, data-driven approach (16,17). We also assessed rsFC changes from regions that showed globally altered rsFC in JFM using a seed-based approach and emphasizing on the somatosensory system and its association with the location and extension of bodily pain. We hypothesized that adolescents with JFM would show reduced rsFC in somatosensory regions and spanning other sensory systems. We anticipated somatosensory rsFC alterations would be associated with bodily pain distribution.

2. METHODS

2.1 Participants

The study sample included 37 cis-gender female adolescents diagnosed with JFM (16.26±1.07 years) and 43 healthy cis-gender female adolescents (15.88±1.32 years). We enrolled exclusively female participants because a) studies based on clinical samples show that JFM is significantly more prevalent in girls (18,19); b) 86% of eligible JFM participants from the parent clinical trial FIT-teens (20) were cis-females. Thus, including other genders would have resulted in too small a representation given the possibility of relevant sex/gender differences in pain processing (21–24) and brain developmental stage (25,26). Such differences could have led to relevant, non-addressable confounding effects in the present study. Inclusion and exclusion criteria are detailed in Supplement 1. All participants and their parent/legal guardians provided written informed consent/assent. The Cincinnati Children's Hospital Medical Center's Institutional Review Board approved the study protocol and consent forms (ID: 2017-7771).

2.2 Measures

Developmentally appropriate and validated self-report measures were used to assess demographic and clinical characteristics. Participants self-reported functional disability (i.e., physical difficulties in daily activities) using the Functional Disability Inventory (27). Participants completed the Fibromyalgia Symptom Severity, indicating symptoms experienced in the past week, and the Widespread Pain Index (WPI), reporting body areas where they had pain during the last three months (1,28). Since the WPI limits pain reports to 19 predefined body areas and requests a rating reflecting a wide time window (past three months), we asked JFM patients to freely mark body areas where they felt pain in that particular moment in a 2D body template from the Brief Pain Inventory-Short Form (BPI) (29), thus illustrating their bodily pain map at the moment of assessment. This template resembled the male body, which was also the case for a previous study assessing pain

distribution in adult female patients with fibromyalgia through a digital application (30). Here, we used the BPI template because this questionnaire is widely used in the chronic pain context regardless of sex/gender and has good psychometric properties (29). However, it is a limitation and future studies should incorporate templates that more closely represent the female anatomy.

2.3 Imaging Data Acquisition, Preprocessing and Denoising

We collected resting-state BOLD fMRI and structural T1-weighted data with a Philips Ingenia 3.0-Tesla MR System (Philips Healthcare, Best, Netherlands) equipped with a 32-channel head coil at the Cincinnati Children's Hospital Medical Center. Imaging data were preprocessed and denoised using standard pipelines from the CONN Toolbox-20.b (www.nitrc.org/projects/conn) (17) running on MATLAB-R2021a (Math Works Inc, Natick, MA). Imaging data acquisition, preprocessing and denoising are detailed in Supplement 2.

2.4 Data Analysis

2.4.1 Statistical analyses of demographic and clinical variables—Between-group differences in demographic and clinical variables were analyzed with $\chi 2$ and two-sample t-tests in SPSS v.26 (IBM Corp, Armonk, NY).

2.4.2 JFM bodily pain distribution at the moment of assessment—We converted hand-marked diagrams of pain into maps in a common body space. We plotted the number of JFM patients that reported pain in specific body areas (i.e., 2D pixels in the body space) and performed a one-sample t-test to identify body areas where patients significantly experienced pain at False Discovery Rate (FDR)-corrected and uncorrected levels (see Figure 1).

Bodily pain maps were also used to compute bodily pain distribution metrics. We binarized the bodily pain pixel map and calculated the fraction of pixels that patients marked as in pain, obtaining a summary of Pain Body Coverage. Next, we divided the template into 74 areas based on the CHOIR body map (31) and computed the fraction of pixels that JFM patients marked as in pain for each area. These measures were used to compute 5 normalized bodily pain distribution variables: Pain Centrality (1=pain only in the trunk, −1=only in limbs and head/neck); Pain Laterality (1=pain only on the left body side, −1=only on the right); Anterior-Posterior Pain Index (1=pain only on the anterior body side, −1=only on the posterior); Joint Pain Index (1=pain only in joints, −1=only in other regions); Knee-Hip-Shoulder Pain Index (1=pain only in joints where pain was more common -knees, hips, shoulders-, −1=only in other regions). Scores close to 0 indicated even pain distribution. The in-house coding used in this section is available at github.com/neuroPENlab. Finally, we assessed correlations between these bodily pain distribution metrics and clinical symptoms in JFM.

2.4.3 rsFC analysis—In first-level analyses, we estimated whole-brain, voxel-wise rsFC using the Intrinsic Connectivity Contrast (ICC) implemented in CONN (17). ICC is a measure of node centrality at each voxel that characterizes the rsFC strength by averaging the squared correlation coefficient values (r^2) of a given voxel with all the other voxels in

the brain (16). In second-level analyses, we assess between-group rsFC differences with a two-sample t-test.

ICC, as a measure of node centrality, does not provide information regarding what connections of such nodes are actually affected. Thus, we performed post-hoc seed-based analyses to gain knowledge regarding the specific rsFC patterns that were altered. We used the whole clusters of voxels that significantly differed between groups in voxel-wise rsFC as seeds of interest, as suggested by the ICC developers (16) and done in previous studies (e.g., 32,33). Next, we evaluated between-group differences in seed-based rsFC using two-sample t-tests. The statistical threshold of voxel-wise and seed-based analyses was set at Family-Wise Error (FWE) cluster-level corrected $p<.05$.

2.4.4 Assessment of rsFC alterations in the somatosensory cortex and associations with pain location and widespreadness in JFM—

Voxel-wise rsFC analyses showed that adolescents with JFM (*vs.* controls) had reduced rsFC in the paracentral lobule (PCL)/S1. S1 is functionally organized in somatotopic maps that represent specific body locations (34). We used this property to test whether S1 rsFC alterations in JFM specifically involved somatotopic areas representing body parts where patients reported pain. We built two connectivity matrices including S1 regions of interest (ROIs) representing a) the most frequently painful and b) the least frequently painful body areas in JFM based on the bodily pain maps. Bodily pain maps also showed that pain was more common in proximal -in or closer to trunk- rather than distal -away from trunk- body areas, except for the knees. Thus, we built two additional matrices including S1 ROIs representing a) proximal and b) distal body areas. The selection and construction of S1 ROIs is detailed in Supplement 3. Each matrix element was defined as the Fisher-transformed bivariate correlation coefficient between a pair of ROIs BOLD timeseries (17). Next, we assessed between-group differences with two-sample t-tests. The statistical significance was set using cluster-level inferences based on multivariate statistics (35) with an FDR-corrected $p<.05$ threshold. This correction method constitutes the standard CONN criterion for ROI-to-ROI analysis (17,35).

To further characterize the association between somatosensory rsFC alterations and pain widespreadness in JFM, we built a second-level whole-brain regression model with WPI score as the independent variable and seed-based rsFC from the PCL/S1 cluster as the dependent variable. Statistical significance was set at FWE cluster-level corrected $p<.05$.

2.4.5 Associations between rsFC alterations and clinical symptoms in JFM—

At an exploratory level, we assessed the associations between rsFC findings and clinical symptoms in JFM using a stepwise multiple regression model per symptom. All models included between-group rsFC differences as independent variables (i.e., beta values of voxel-wise and seed-based clusters and pairwise rsFC measures between S1 ROIs).

3. RESULTS

3.1 Demographic and clinical variables

JFM patients and controls did not differ in demographic variables. As anticipated, JFM patients reported higher functional disability (t=15.63, p<.001), pain widespreadness (t=16.77, p<.001), and symptom severity (t=16.36, p<.001) (Table 1).

3.2 JFM bodily pain distribution at the moment of assessment and clinical symptoms

Bodily pain maps showed that, at the moment of assessment, pain in JFM was more common in proximal areas -in or closer to the trunk- such as the neck, shoulders, upper and lower back, and hips, but also in the knees (Figure 1). Bodily pain distribution metrics expanded these findings by showing that pain was not centralized within the trunk, and was highly prevalent in joints, especially knees, shoulders, and hips. Pain was not lateralized and affected both the anterior and posterior axis (Figure 1). Correlations among these metrics are displayed in Supplementary Figure 1. We also explored correlations between these metrics and clinical symptoms. JFM patients with more pain on the left side of the body at the moment of the study had higher WPI scores (r=.399, p=.024; r=.436, p=.033 after excluding subjects scoring between −.01 and .01 on pain laterality). JFM patients with more joint and knee-hip-shoulder pain had less symptom severity (r=−.350, p=.049; r =−.374, p=.035). Functional disability did not correlate with any bodily pain distribution metric (Supplementary Figure 1).

3.3 rsFC alterations in female adolescents with JFM

JFM patients (*vs.* controls) showed reduced voxel-wise rsFC in bilateral PCL/S1 (T=4.89, pFWE<.001) and the left midcingulate cortex (MCC) (T=4.67, pFWE=.043) (see Figure 2 and Supplementary Table 1).

To identify the anatomy of rsFC alterations for these regions, we performed post-hoc seed-based analyses using the entire, FWE-corrected PCL/S1 and the left MCC clusters as seeds of interest. These analyses showed that JFM patients had reduced rsFC within these regions and between the MCC and the bilateral supplementary motor area (SMA), posterior insula/parietal operculum (S2), and auditory cortices (T's>4.4, pFWE's<.030). Conversely, JFM patients had increased PCL/S1-thalamus (T=4.75, pFWE=.046), and PCL/S1-right anterior insula (T=5.13, pFWE=.039) rsFC (see Figure 3 and Supplementary Table 2).

Following previous recommendations (36,37), we replicated voxel-wise and seed-based group-level analyses including mean framewise displacement as a confounder. All results remained significant (pFWE's<.05), with two exceptions bordering significance (pFWE's=.059 and .065), indicating that movement was not driving rsFC differences (see Supplementary Tables 3 and 4). Moreover, framewise displacement and global signal change did not differ between groups (t=1.61, p=.11; t=.80, p=.43, respectively) and did not correlate with any of the rsFC findings reported in this study (see Supplementary Table 5).

3.4 Reduced rsFC affects S1 subregions innervated by body locations frequently reported as painful in JFM

In agreement with our hypothesis, matrices including somatotopic S1 subregions representing most painful body areas according to the JFM bodily pain maps (neck, back, hip, and knees) and proximal body areas (neck, back, chest, and hip), were significantly different between JFM and controls (matrix of S1 subregions innervated by frequently painful body regions: F=3.15; pFDR=.029; matrix of proximal regions: F=6.37; pFDR<.001). JFM patients showed reduced rsFC between most of such S1 subregions. Correlation matrices for somatotopic S1 subregions innervated by least painful (face, chest, hand, and leg) or distal (face, hand, leg, knee) body areas did not differ between groups (pFDR's>.05) (Figure 4, Supplementary Table 6). Results remained significant after controlling for mean framewise displacement (Supplementary Table 7).

3.5 PCL/S1 rsFC alterations in JFM are parametrically associated with more widespread pain

Concurring with the rest of our findings, JFM patients with higher WPI scores had decreased PCL/S1-right S1 rsFC (T=4.48, pFWE=.042). Additionally, they had increased PCL/S1-SMA rsFC (T=5.01, pFWE=.035) (Supplementary Figure 2, Supplementary Table 8). Results remained significant after controlling for mean framewise displacement (see Supplementary Table 9).

3.6 Associations between rsFC alterations and clinical symptoms in JFM

The rsFC alterations observed in the JFM group (i.e., beta values of voxel-wise and seed-based clusters and pairwise rsFC measures between S1 ROIs) significantly contributed to explaining functional disability (F=5.15, p=.03); specifically, the rsFC between left MCC-right Rolandic operculum/right supramarginal gyrus (t=2.27, p=.03). rsFC alterations were associated with pain body coverage (F=11.81, p<.001) but not with the WPI. Reduced rsFC between right chest-right hip and right chest-left hip S1 ROIs contributed to explaining pain body coverage (t=−2.90, p=.007; t=−2.05, p=.05). Finally, rsFC alterations contributed to explaining symptom severity (F=5.54, p=.009); specifically, reduced rsFC between the right back-right knee S1 ROIs (t=−2.72, p=.011), and between PCL/S1-right anterior insula (t=−2.20, p=.035).

The main study findings are summarized in Figure 5. The overlap between clusters and ROIs located in somatosensory regions is displayed in Supplementary Figure 3.

4. DISCUSSION

To our knowledge, this is the first study assessing rsFC and bodily pain distribution in JFM. Female adolescents with JFM had voxel-wise rsFC reductions in the PCL/S1, a sensorimotor cluster (15,38,39), and left MCC, central to pain-related processing (40). Post-hoc analyses revealed reduced rsFC spanning major cortical sensory hubs. Sensorimotor rsFC reductions in JFM may be clinically relevant since they predicted pain widespreadness and involved S1 somatotopic areas innervated by body areas reported as painful, which contributed to explaining pain body coverage and symptom severity. Conversely, in JFM,

PCL/S1 was hyperconnected to the thalamus, first relay of most sensory afference to the cortex (41), and the right anterior insula, implicated in salience and affective processing (42). All findings were independent of symptom duration (2.4 years on average, significantly shorter than in adults), highlighting the need for longitudinal studies to determine whether reduced signal integration in cortical sensory systems during rest is an early marker of JFM pathophysiology and severity.

Bodily pain maps revealed that pain (at the moment of the study) in JFM was not evenly distributed in the body, but rather concentrated on the neck, shoulders, back, hips, and knees. Importantly, the topographic distribution of JFM pain almost perfectly matched that of adult fibromyalgia (30). We computed pain distribution metrics from the bodily pain maps and assessed their association with clinical symptoms. Given the sample size, these correlations should be interpreted with caution and require replication. Functional disability did not correlate with any metric, suggesting it was not strongly related to the distribution of bodily pain. Functional disability may be more closely related to other fibromyalgia symptoms, such as fatigue, pain unpleasantness or affective symptoms. JFM patients who had more pain on the left side of the body at the moment of the study had also experienced greater pain widespreadness (WPI) during the previous three months. The lack of other correlations between the WPI and bodily pain distribution metrics such as pain body coverage may be explained by the discrepancy in temporal scales (i.e., pain during the last 3 months *vs.* pain at the moment of the study), and by the fact that the WPI does not assess regions where we found pain to be common in JFM, such as the knees. We also found that JFM patients with more joint pain at the moment of assessment had less symptom severity. Since symptom severity encompasses a broad range of symptoms (e.g., fatigue, sleep disturbances, cognitive and physical symptoms), our finding may indicate that subjects who predominantly experience pain more localized in the joints rather than more widespread, have less severe symptoms in other related domains. This finding together with the high within-group variability that we observed in most metrics derived from the bodily pain maps suggest that JFM patients experience a wide range of symptoms and different degrees of bodily pain extent, which highlights the importance of further understanding and considering individual differences in symptom presentation and severity in JFM.

At the brain level, we found that female adolescents with JFM had reduced voxel-wise rsFC in the left MCC, central to acute pain processing and pain-related affective encoding, cognitive interpretation, anticipation, and response selection (40). This finding is consistent with adult fibromyalgia studies reporting disrupted rsFC and volume reductions in the MCC (3,43), and with a recent JFM study showing reduced volume in this area (12). Although the cluster of reduced rsFC presented here and the one of reduced volume (12) in the MCC found in adolescents with JFM did not overlap, these findings suggest that functional and structural alterations in the MCC may be a key feature of fibromyalgia, already present in pediatric patients and independent of symptom duration. Here, we also observed that left MCC-right Rolandic operculum/supramarginal gyrus rsFC, involved in cross-modal sensory integration, contributed to explaining functional disability in JFM.

The rest of the observed rsFC reductions in JFM point toward a weakening of cortical sensory signal processing during rest. Female adolescents with JFM had reduced voxel-

wise rsFC in a region encompassing S1, a primary somatosensory region receiving and encoding information related to touch, proprioception, and pain (15), and the PCL, a cortical sensorimotor area crucial for the integration of sensory and motor signals from the lower limbs, allowing for coordinated movement execution, and body and spatial awareness (38,39). Post-hoc analyses showed that hypoconnectivity in JFM involved the left MCC and PCL/S1 regions and expanded from the MCC to cortical regions processing multiple sensory modalities, including somatosensory and auditory, and motor responses. Previous studies have observed reduced S1 rsFC in adult fibromyalgia (4,5) and pediatric chronic pain (13). Adult fibromyalgia studies have also reported reduced rsFC in somatosensory, auditory, and visual cortices at rest (4), and altered activation in visual and auditory cortices during multisensory stimulation, accompanied by increased unpleasantness (6). These findings may be interpreted within the classical framework that postulates pain perception emerging from augmented nociceptive signals and reduced opponent processing of non-nociceptive sensory information (4,14,44). Reciprocal inhibitory influences between responses to painful and non-painful sensory stimuli have been demonstrated at the spinal cord (44) and cortical levels (14). Thus, reduced non-painful sensory information processing may enhance pain experience. Crucially, our findings show first evidence that the prominent alteration of sensory processing observed in adult fibromyalgia is already present in adolescent patients and extends beyond the somatosensory domain involving other sensory modalities.

Another set of findings add to the interpretation that reduced processing of non-painful sensory information at the cortical level may contribute to enhancing pain experience. We found that S1 hypoconnectivity in JFM matched the bodily pain. Kim and colleagues observed decreased rsFC between somatotopic S1 subregions in adult fibromyalgia (5). Here, we expanded this finding by showing a relationship between S1 dysfunction and the specific somatic localization of bodily pain. S1 is the first cortical relay where somatic afference from different body locations converges, including nociceptive but mainly tactile and proprioceptive information, and contributes to providing a first brain representation of body schema (15,45). Thus, reduced cortical signal crosstalk within S1 could reflect lower tactile and proprioceptive information integration, which may directly support pain in this part of the body schema. In agreement, we found that reduced rsFC between specific pairs of S1 ROIs contributed to explaining pain body coverage and symptom severity in JFM. Moreover, patients with higher pain widespreadness (WPI) had reduced PCL/S1-right S1 rsFC but increased PCL/S1-SMA rsFC. SMA helps execute movements to produce a behavioral response to pain (46), such as moving away from its source. We interpret this finding as patients with greater pain widespreadness having heightened sensory-motor communication that may facilitate planning and executing avoidant responses rather than allocating attention to pain-related sensory appraisal. Combined, our findings suggest that JFM is linked to an alteration in the sensorimotor network expanding to other sensory systems but specifically involving S1, the PCL and SMA, which were intimately linked to the spatial distribution of bodily pain. Thus, cortical sensorimotor systems could be a therapeutic target in JFM. In adults, treatments aimed at improving tactile acuity have shown clinical benefit in chronic pain (47) through mechanistic changes in somatosensory processing. Similar strategies may be effective in JFM. However, multisensory hypersensitivities have been described in adult fibromyalgia (6,7) and proposed

for inclusion in JFM medical classification systems (48). Considering this evidence and the present findings, we hypothesize that tackling multisensory integration, possibly using virtual reality and non-painful stimulation from different modalities, may progressively reduce perceived pain. No trial has assessed multisensory acuity training on pain reduction in pediatric patients, which opens fascinating venues for clinically oriented research.

In contrast, female adolescents with JFM showed augmented PCL/S1-thalamus rsFC. This finding may reflect augmented subcortical sensory input reaching the somatosensory cortex potentially accompanied by reduced cortico-cortical integration of such input in PCL/S1. Alternatively, it may reflect altered cortico-thalamic top-down inhibition -either reflective of an attempt for hyper-inhibiting activity in the thalamus or possibly suggesting defective inhibition (49). The second option would imply impaired top-down cortico-thalamic control, leading to disrupted modulation and filtering of ascending sensory signal to the cortex, which may contribute to the amplified pain perception observed in JFM both during spontaneous and experimentally evoked pain (50). In adult fibromyalgia, applying repetitive transcranial direct current stimulation to the motor cortex improved symptom severity and reduced S1-thalamus rsFC, possibly through the thalamic inhibition via descending cortico-thalamic fibers (49). If replicated, our findings may indicate that PCL/S1-thalamus rsFC could also be a treatment target in JFM.

Female adolescents with JFM also had increased PCL/S1-anterior insula rsFC, and connectivity between these areas contributed to explaining symptom severity. The anterior insula is involved in salience and affective processing (42). Thus, increased PCL/S1-anterior insula rsFC may reflect enhanced salience and emotional coloring of the somatosensory experience at the expense of fine sensory discrimination features -given the rest of the findings. Similarly, enhanced S1-anterior insula rsFC has been observed in adults with fibromyalgia during rest (49) and evoked pain (5).

This study has several limitations. First, we exclusively enrolled cis-females. Thus, our findings cannot be generalized to other genders. This choice was based on our primary aim of investigating rsFC in a well-characterized sample that represents the population group predominantly affected by JFM. We considered the potential influence of sex/gender differences in pain processing (21–24) and brain developmental stage (25,26). Future studies should include adequately powered samples of cis-male and transgender/non-binary individuals, which will allow examining between-sex/gender differences in JFM. Second, the use of the BPI male-resembling body template may interfere in the precise characterization of pain distribution in females. We encourage future studies to use templates that better represent the study sample. Third, our sample had a low representation of different ethnicities and participants with low socioeconomic status. Community-oriented research is crucial to overcome the predominance of white patients with medium/high socioeconomic status in research samples. Last, this is the first study evaluating rsFC in JFM. Thus, our findings should be replicated to determine robustness and translational utility.

In conclusion, our findings provide novel evidence that the weakening of cortico-cortical sensory integration, observed in adult fibromyalgia, may be a central feature of JFM, and

highlight the role of sensory processing alterations when studying, diagnosing, and treating JFM. Crucially, we found extensive similarities between juvenile and adult fibromyalgia in pain distribution and compromised brain circuitry. Longitudinal studies are warranted to define the temporal dynamics of such neurobiological alterations across the lifespan. In all, the study opens fascinating research venues and emphasizes the need for early, neurobiologically-informed interventions to prevent the transition from juvenile to adult forms of chronic pain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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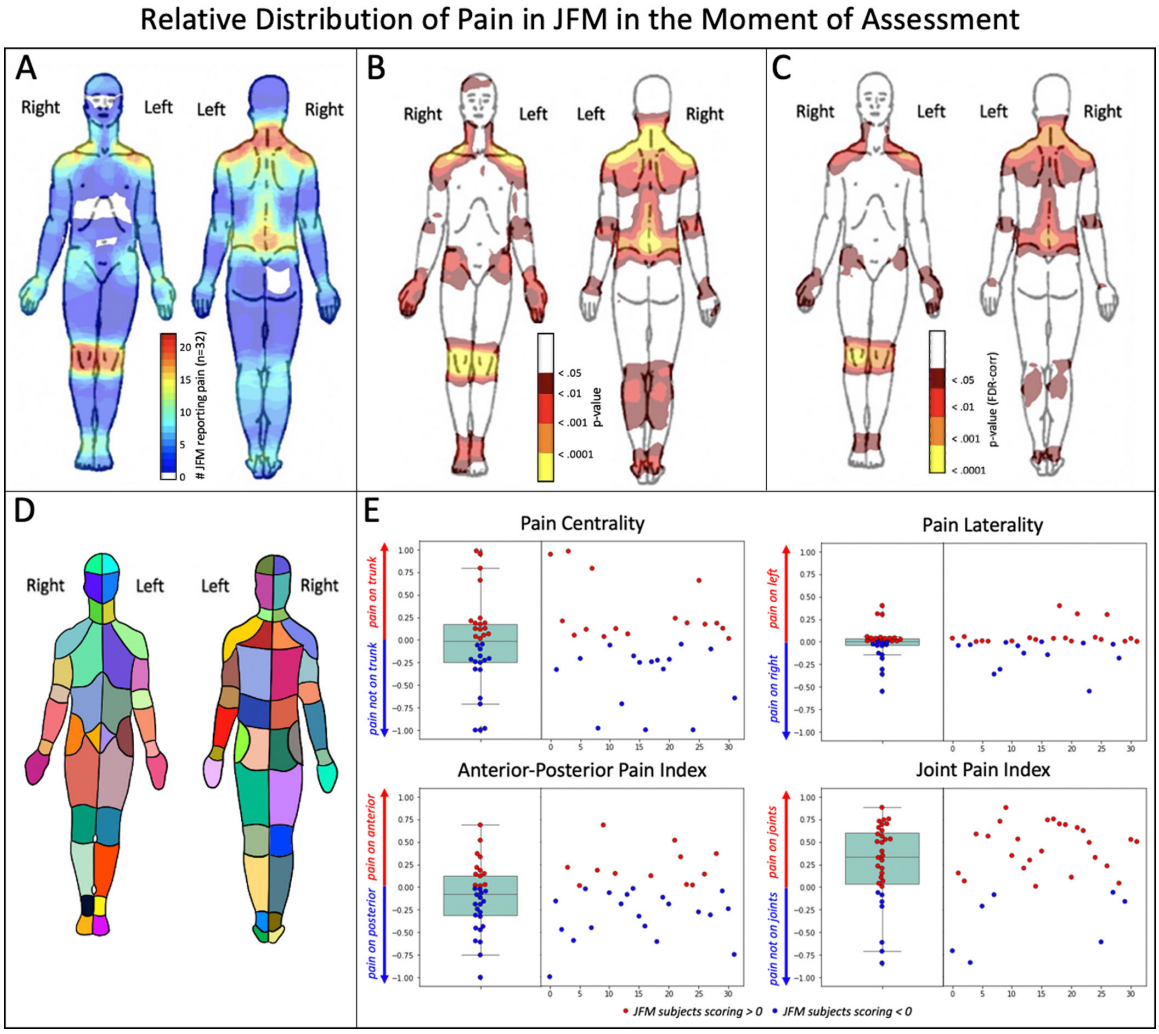

Figure 1.

Relative distribution of pain in the moment of assessment in JFM based on bodily pain maps (n = 32). **A**. Number of participants that had pain in each body area (i.e., each pixel); **B**. One sample t-test of the bodily pain maps, the color bar represents uncorrected p-values; **C**. One sample t-test of the bodily pain maps, the color bar represents False Discovery Rate (FDR)-corrected p-values. The FDR-corrected version is Benjamini-Hochberg step-up applied to the number of pixels within the body template (1,314,551 pixels); **D**. Segmentation of the body template into 74 regions of interest based on the CHOIR map (31). We used the fraction of pixels that participants marked as in pain for each area to compute normalized pain specificity variables; **E**. Box and scatterplots of the main normalized bodily pain distribution variables displaying the relative distribution of pain for the 32 JFM participants. Knee-Hip-Shoulder Pain Index is not displayed because the distribution was highly similar to the Joint Pain Index.

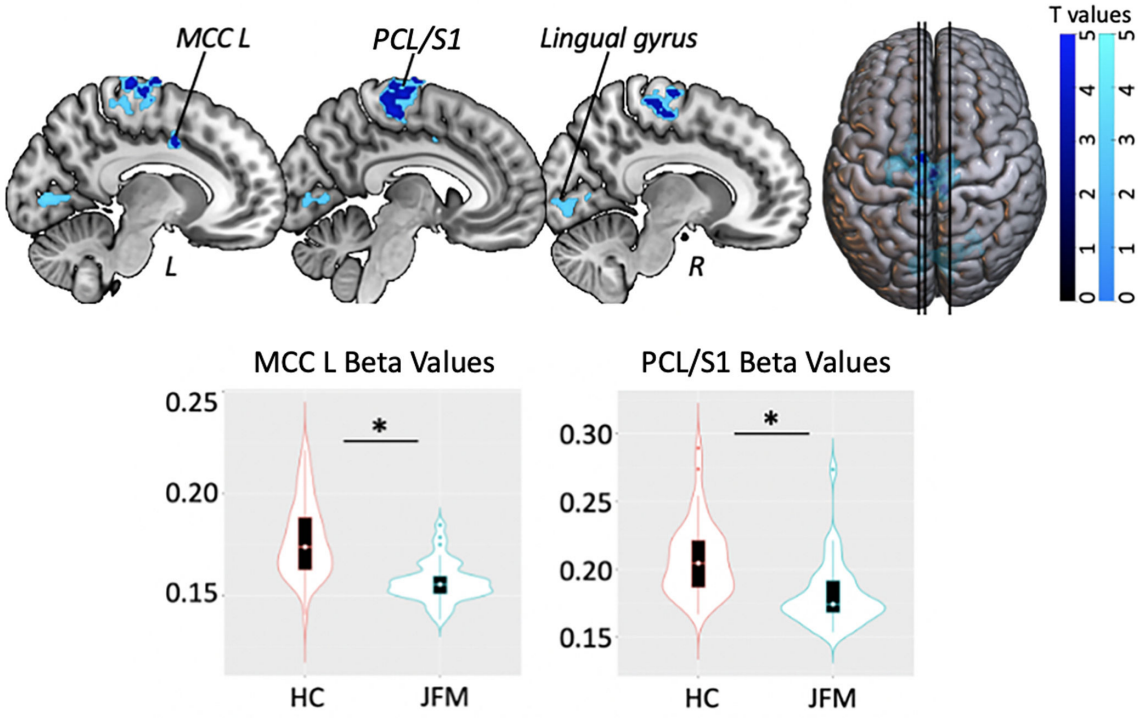

Figure 2.

Voxel-wise resting-state functional connectivity differences between juvenile fibromyalgia (JFM) and healthy control groups. **Top**: Clusters in cool colors represent connectivity reductions in JFM. Clusters in deep blue survive Family-Wise Error correction at $p_{FWE}<.05$. Clusters in cyan survive an uncorrected statistical threshold of $p<.005$, $Ke>100$ voxels. **Bottom**: violin plots of the beta weights of the left midcingulate cortex (MCC L) and paracentral lobule (PCL)/primary somatosensory cortex (S1) in healthy controls and JFM participants. Each box represents the 25th to 75th percentiles. Lines inside the boxes represent the median. Lines outside the boxes represent the 10th and 90th percentiles. Dots indicate outliers.

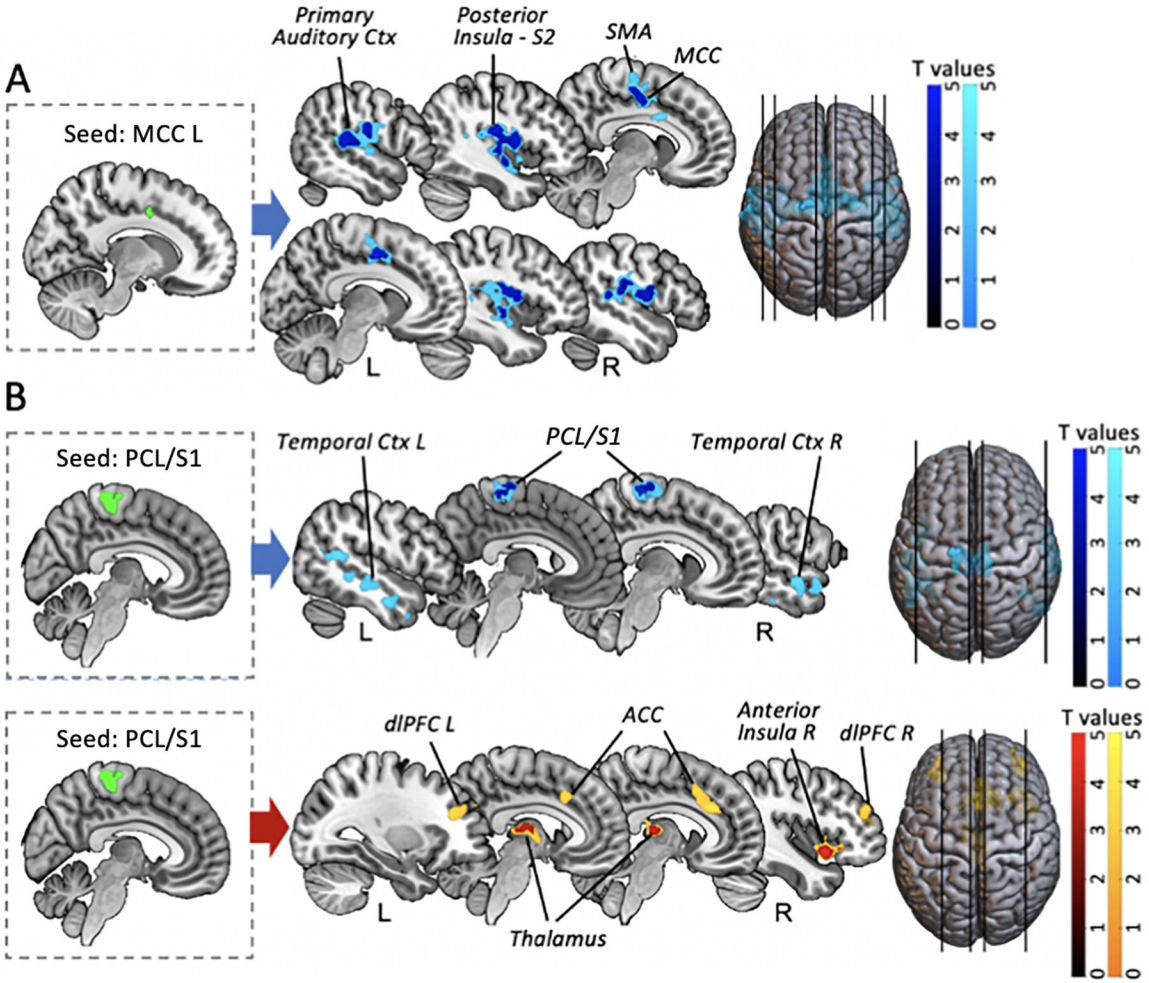

Figure 3.

Seed-based resting-state functional connectivity differences between juvenile fibromyalgia (JFM) and healthy control groups. **A.** Findings using the left midcingulate cortex (MCC L) cluster form the intrinsic connectivity contrast (ICC) analysis as the seed of interest. **B.** Findings using the paracentral lobule (PCL)/primary somatosensory cortex (S1) cluster from the ICC analysis as the seed of interest. Clusters in warm colors represent connectivity increases in JFM, clusters in cool colors represent connectivity reductions in JFM. Clusters in red and deep blue survive Family-Wise Error correction at $p_{FWE}<.05$. Clusters in yellow and cyan survive an uncorrected statistical threshold of $p<.005$, $Ke>100$ voxels.

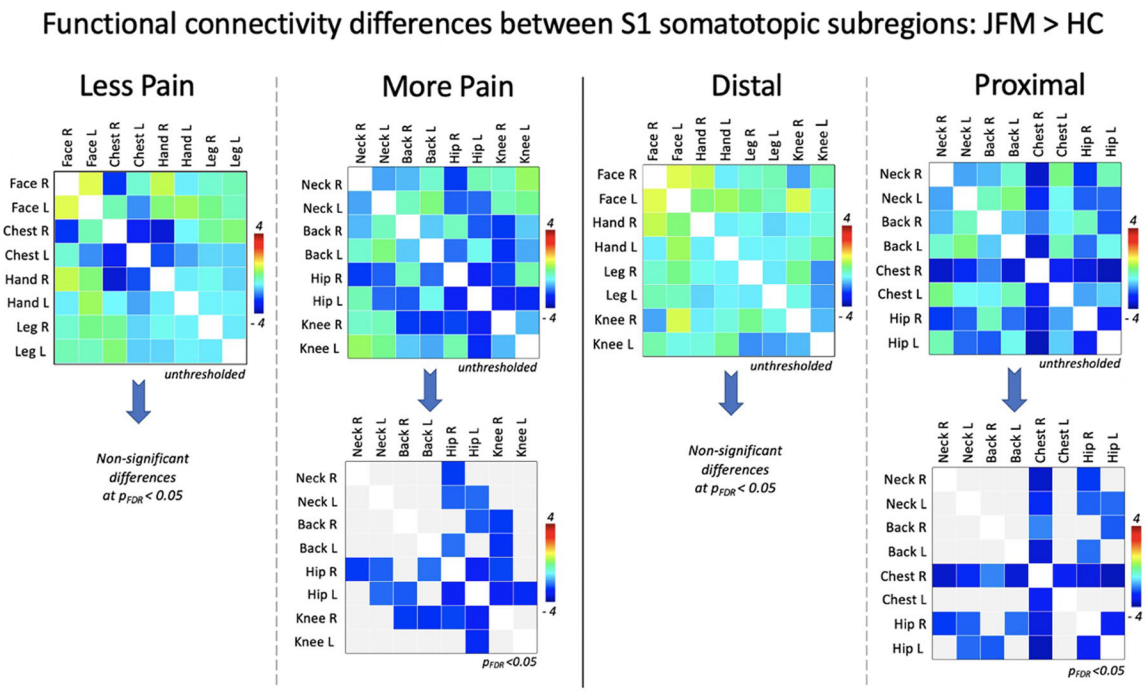

Figure 4.

Functional connectivity differences between somatotopic subregions of the primary somatosensory cortex (S1). Contrast: juvenile fibromyalgia (JFM) > healthy controls (HC). Differences between JFM and healthy control groups in connectivity correlation matrices including S1 somatotropic subregions representing body areas with less or more pain (**left**) or matrices including S1 somatotropic subregions representing distal and proximal body areas (**right**). Color bars indicate T values. L: left; R: right.

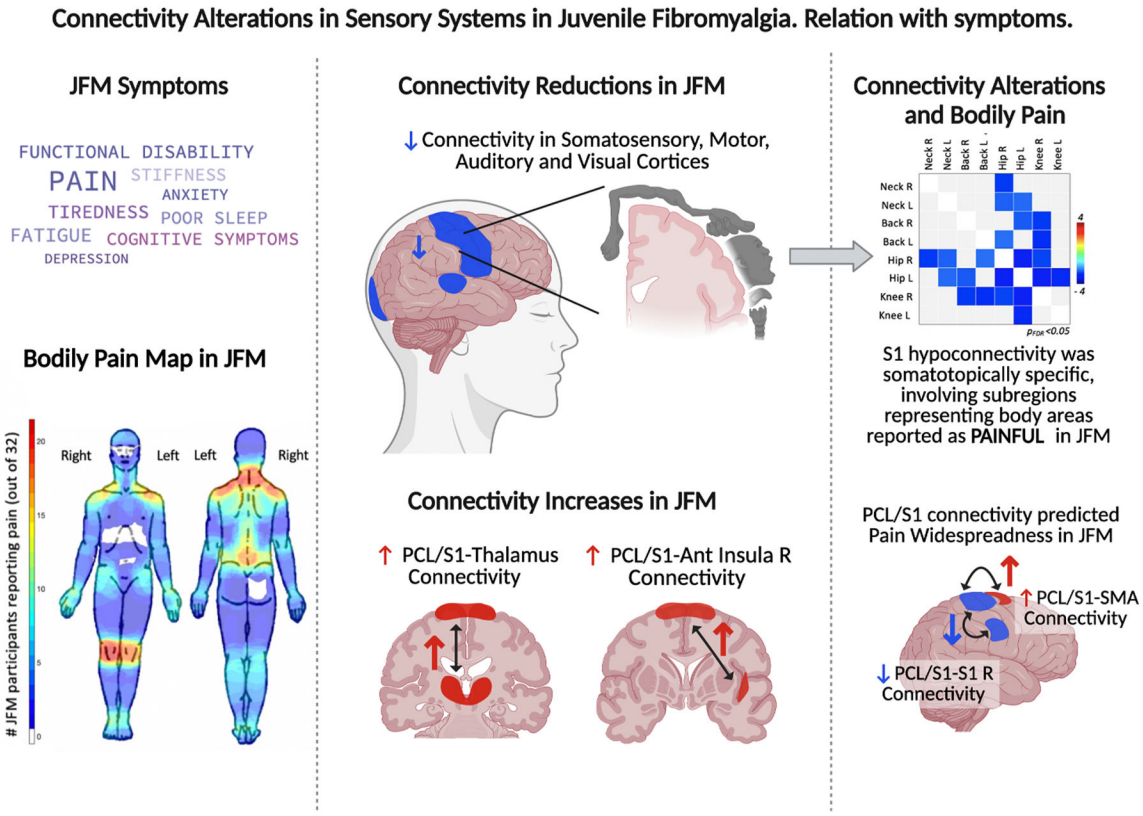

Figure 5.

Summary of findings. **Left/Top**: More frequent symptoms of juvenile fibromyalgia (JFM) displayed in a word cloud; **Left/Bottom**: Bodily pain distribution based on the number of participants with JFM (n=32) that reported pain in each body area -see figure 1 for further details-. **Middle**: Main resting-state connectivity differences between female adolescents with JFM and healthy controls at family-wise error (FWE)-corrected level (see Figures 2 and 3 for further details on these findings). **Right/Top**: Between-group connectivity differences within somatotopic regions of the primary somatosensory cortex (S1) (see Figure 4). **Right/Bottom**: Associations between PCL/S1 connectivity and widespreadness of bodily pain in the JFM group at FWE-corrected level (see Supplementary Figure 2 for further details). Created with BioRender.com.

Table 1.

Differences in demographic and clinical variables between female adolescents with juvenile fibromyalgia and matched healthy controls

	Controls (n = 43)	JFM (n = 37)	Statistics	
DEMOGRAPHIC VARIABLES	***Mean ± SD***	***Mean ± SD***	***T / X²***	***p-value***
Age (years)	15.88 ± 1.32	16.26 ± 1.07	1.44	.15
Race (C / NC)	40 / 3	35 / 2	.08	.77
Yearly Household Income (1–7)	5.14 ± 1.99	4.89 ± 2.03	.69	.49
Education Level of the Primary Caregiver (1–5)	4 ± 0.84	3.86 ± 0.88	.70	.49
Education Level of the Secondary Caregiver (1–5)	3.85 ± 0.74	3.71 ± 1.03	.54	.59
CLINICAL VARIABLES	***Mean ± SD***	***Mean ± SD***	***T***	***p-value***
Functional Disability (0–60)	0.51 ± 1.24	22.32 ± 9.06	15.63	<.001*
Pain Widespreadness (0–19)	0.30 ± 1.12	11 ± 3.39	16.77	<.001*
Symptom Severity (0–12)	1.21 ± 1.56	8.79 ± 2.07	16.36	<.001*
Symptom Duration (months)	–	29.42 ± 29.91	–	–

Note: **Yearly household income** is shown using a scale of 1–7, where 1 = <$24,999; 2 = $25,000 to $49,999; 3 = $50,000to $74,999; 4 = $75,000 to $99,999; 5 = $100,000 to $124,999; and 6 = $125,000 to $149,999; 7 > $150,000. **Primary caregiver** refers to the person who is primarily responsible for meeting the child's daily needs (mother in 74 cases, father in 6 cases); **Secondary caregiver** refers to the person who also plays a significant role in the child's care and well-being but may not have the primary responsibility (father in 67 cases, mother in 6 cases, not assigned for 7 cases). **Caregiver education level** is shown using a scale of 1–5, where 1 = less than high school; 2 = high school/GED;3 = partial college or trade school; 4 = college graduate; 5 = postgraduate degree.

*Significant values p < .001. C: Caucasian; JFM: juvenile fibromyalgia; NC: Non-Caucasian; SD: standard deviation.