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Disrupted Functional Connectivity of the Pain Network in Fibromyalgia

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Objective: To investigate the impact of chronic pain on brain dynamics at rest. **Methods:** Functional connectivity was examined in patients with fibromyalgia (FM) ($n = 9$) and healthy controls ($n = 11$) by calculating partial correlations between low-frequency blood oxygen level–dependent fluctuations extracted from 15 brain regions. **Results:** Patients with FM had more positive and negative correlations within the pain network than healthy controls. Patients with FM displayed enhanced functional connectivity of the anterior cingulate cortex (ACC) with the insula (INS) and basal ganglia (p values between .01 and .05), the secondary somatosensory area with the caudate (CAU) ($p = .012$), the primary motor cortex with the supplementary motor area ($p = .007$), the globus pallidus with the amygdala and superior temporal sulcus (both p values $< .05$), and the medial prefrontal cortex with the posterior cingulate cortex (PCC) and CAU (both p values $< .05$). Functional connectivity of the ACC with the amygdala and periaqueductal gray (PAG) matter (p values between .001 and .05), the thalamus with the INS and PAG (both p values $< .01$), the INS with the putamen ($p = .038$), the PAG with the CAU ($p = .038$), the secondary somatosensory area with the motor cortex and PCC (both p values $< .05$), and the PCC with the superior temporal sulcus ($p = .002$) was also reduced in FM. In addition, significant negative correlations were observed between depression and PAG connectivity strength with the thalamus ($r = -0.64$, $p = .003$) and ACC ($r = -0.60$, $p = .004$). **Conclusions:** These findings demonstrate that patients with FM display a substantial imbalance of the connectivity within the pain network during rest, suggesting that chronic pain may also lead to changes in brain activity during internally generated thought processes such as occur at rest.
Key words: fibromyalgia, chronic pain, resting state, functional connectivity, partial correlation analysis.

BOLD = blood oxygen level–dependent; **FM** = fibromyalgia; **HC** = healthy control; **WHYMPI** = West Haven-Yale Multidimensional Pain Inventory; **fMRI** = functional magnetic resonance imaging; **ACC** = anterior cingulate cortex; **PCC** = posterior cingulate cortex; **AMYG** = amygdala; **CAU** = caudate; **PUT** = putamen; **INS** = insula; **M1** = primary motor area; **SMA** = supplementary motor area; **SI** = primary somatosensory area; **SII** = secondary somatosensory area; **mPFC** = medial prefrontal cortex; **PAG** = periaqueductal gray; **STS** = superior temporal sulcus; **THA** = thalamus.

INTRODUCTION

The understanding of brain correlates involved in pain processing has increased significantly since the advent of neuroimaging techniques (1). Most studies have revealed that the processing of painful stimuli is associated with the increased activation of several brain regions, such as the insular cortex, anterior cingulate cortex (ACC), primary (SI) and secondary somatosensory cortices (SII), and thalamus (THA), which comprise the so-called pain network (2). This functional network has been viewed as a dynamic neural substrate of the subjective experience of pain modulated by sensory, cognitive, and affective factors. Little is known, however, about the dynamic properties of this pain network and its intrinsic functional connectivity during spontaneous pain as compared with chronic pain (3).

The study of spontaneous blood oxygen level–dependent (BOLD) activity when subjects are asked to rest quietly in the scanner has provided insight into the functional topography of the brain and the coherence patterns of functionally interconnected networks not related to specific tasks (4). In this sense, recent work has shown that spatial cross-correlations and the estimation of independent components in low-frequency spontaneous fluctuations (<0.1 Hz) of BOLD time series acquired under resting-state conditions are useful tools to analyze spatial patterns of coherent brain activity within different functional networks involved in somatosensory, motor, visual, auditory, or executive functions (5). Moreover, enhanced functional connectivity strength measured by positive or negative correlations across spontaneous BOLD fluctuations has been associated with increases in neuronal synchrony or asynchrony (6), respectively, suggesting that regions with similar functionality tend to be positively correlated in their spontaneous BOLD activity, whereas regions with apparently opposing functionality are negatively correlated or anticorrelated. Analyses of resting-state functional connectivity have also been applied in neuropsychiatric disorders such as major depression (7) or chronic pain (8–10), showing that persistent, emotionally laden, self-reflective tendencies in depressed subjects are linked to increased functional connectivity in the medial prefrontal cortex (mPFC) and that persistent pain is associated with greater connectivity of the insula (INS). Because these two brain regions are also relevant parts of the pain network and given the strong relationships between depression and chronic pain, it seems plausible that spontaneous and persistent pain as it occurs in chronic pain states

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could be affecting the brain dynamics of the pain network. Nevertheless, to our knowledge, there is no information about the intrinsic functional connectivity of all brain regions within the pain network in patients with chronic pain.

In the present study, we examined low-frequency fluctuations of resting-state BOLD signals in fibromyalgia (FM), a functional somatic syndrome characterized by widespread pain sensations and affective symptoms (11). Although the underlying etiology of FM still remains unclear, altered activations of several brain regions in the pain network (thalamic nuclei, somatosensory cortices, ACC, INS, and prefrontal cortices) have already been reported during the sensory processing of acute pain (12–15). Moreover, it has been suggested that abnormal pain processing in FM might be modulated by the patient's mood and the affective context in which body sensations are felt (16). On the basis of previous findings, we hypothesize that functional connectivity within the pain network should be altered in FM even when patients are experiencing spontaneous fluctuations of their pain at rest. We assumed that the intrinsic functional connectivity of brain regions within the pain network would be greater and much more extended in patients with FM than in controls, reflecting the diffuse and complex patterns of symptoms in these patients. In particular, we expected that brain regions involved in the processing of affective (i.e., ACC and INS) and sensory pain components (i.e., somatosensory cortex and THA) would show enhanced connectivity to other brain regions of the pain network in FM, whereas brain regions involved in pain modulation, such as the periaqueductal gray (PAG) matter, would display reduced connectivity.

MATERIALS AND METHODS

Participants

The study was conducted at the Research Center for Neurological Diseases (Madrid, Spain) between March 2009 and July 2009. Nine right-handed patients with FM (8 women, mean [standard deviation {SD}] age = 52.3 [8.9] years) and 11 right-handed healthy controls (HCs; 9 women, mean [SD] age = 49.0 [12.1] years) participated in the study. Patients with FM had to meet the American College of Rheumatology 1990 criteria for FM and to experience pain as their major complaint (11). Subjects were excluded from the study if they were pregnant and had a neurological disease or a psychiatric diagnosis. An experienced and external rheumatologist reviewed the patient's chart to exclude other origins of pain. All participants signed their informed consent before testing. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of the Balearic Islands (Spain).

Participants underwent a semistructured interview to identify subjective psychological factors contributing to the maintenance of chronic pain and completed the Beck Depression Inventory (17) and the West Haven-Yale Multidimensional Pain Inventory (WHYMPI) (18) (Table 1). The Beck Depression Inventory was used as a measure of mood because altered emotional states might influence pain processing (19). The WHYMPI evaluates the impact of pain on a patient's life through five subscales (pain intensity, pain interference, affective distress, social support, and life control), as well as through the assessment of the self-perceived responses of others to patients' pain behavior (solicitous, punishing, and distracting responses), and the extent to which patients participate in common daily activities. Scores on each item of the WHYMPI range from 0 (never or minimum level) to 6 (very frequently or maximum level) and are averaged to yield the different subscale scores.

TABLE 1. Data Obtained From Patients' and Healthy Controls' Questionnaires

	HC (n = 11)	FM (n = 9)	t
Age, y			−0.688
M (SD)	49.0 (12.1)	52.3 (8.9)	
Range	23–61	33–65	
Sex			
Male	2	1	
Female	9	8	
Pain beginning, M (SD), y	—	25.6 (16.6)	
Pain duration, M (SD), y	—	26.8 (17.4)	
Medication			
Antidepressants	—	8	
Analgesics/relaxants/ NSAIDs	—	4	
Anxiolytics	—	8	
BDI score			−4.992*
M (SD)	8.1 (6.3)	29.78 (12.07)	
Range	3–21	2–44	
WHYMPI, M (SD) (range = 0–6)			
Social support	—	4.0 (1.4) (1.5–6.0)	
Affective distress	—	4.1 (1.0) (2.3–5.5)	
Pain interference	—	4.0 (1.7) (1.3–5.7)	
Pain intensity	—	4.5 (0.9) (3.3–5.5)	
Life control	—	2.8 (0.5) (2.0–3.5)	
Distracting responses	—	4.1 (1.6) (1.0–6.0)	
Solicitous responses	—	3.1 (1.6) (0.2–4.8)	
Punishing responses	—	1.5 (1.4) (0.0–3.7)	
Household chores	—	3.2 (1.3) (1.2–5.2)	
Activities away from home	—	1.7 (1.3) (0.0–3.8)	
Outdoor work	—	0.9 (0.6) (0.0–2.0)	
Social activities	—	1.3 (0.8) (0.3–3.0)	

HC = healthy control; FM = fibromyalgia; M = mean; SD = standard deviation; NSAIDs = nonsteroidal anti-inflammatory drug; BDI = Beck Depression Inventory; WHYMPI = West Haven-Yale Multidimensional Pain Inventory.
WHYMPI scores go from 0, the lowest score of the scale, to 6, the highest score (e.g., 6 on pain interference means that pain interferes the maximum on patient's life).
*p = .05.

Image Acquisition and Preprocessing

Magnetic resonance imaging was done on a 3-T scanner (General Electric Signa HDx [General Electric Healthcare, Milwaukee, WI]). For each subject, 240 echo-planar volumes were acquired (repetition time, 2500 milliseconds; echo time, 35 milliseconds; matrix dimensions, 64 × 64; field of view, 200 mm; 32 transversal slices; slice thickness, 3 mm; flip angle, 90 degrees) over a period of 10 minutes with the eyes closed. The structural imaging data consisted of T1-weighted images (repetition time, 7176 milliseconds; echo time, 3150 milliseconds; matrix dimensions, 512 × 512; field of view, 240 mm; 176 slices; slice thickness, 1 mm; flip angle, 12 degrees).

Image processing was performed using FMRIB Software Library (FSL version 4.1.4) (20). The following preprocessing steps were consecutively applied: brain extraction using the Brain Extraction Tool multiple-iteration method (21), intensity normalization (equivalent to grand mean scaling), motion correction (22),

TABLE 2. Center of MNI Coordinates for Each Seed Within the Pain Network Extracted From Previous Studies on Experimental Pain and Anatomical Atlases

	Right Coordinates			Left Coordinates		
Seed	*x*	*y*	*z*	*x*	*y*	*z*
ACC	1	8	30[a]	−2	8	30[b]
AMYG	26	0	−22[b]	−24	−2	−22[b]
CAU	14	4	20[a]	−12	14	8[b]
GP	18	−2	−4[b]	−12	0	2[a]
INS	36	6	6[a]	−48	12	−2[a]
M1	10	−30	70[c]	−10	−26	68[c]
mPFC	2	46	−16[b]	−2	46	−16[d]
PAG	6	−32	−10[e]	−6	−32	−10[b]
PCC	12	−56	6[a]	−12	−56	6[b]
PUT	28	6	−2[a]	−22	8	−4[b]
SI	52	−16	44[a]	−48	−24	52[a]
SII	52	−20	16[a]	−58	−24	14[a]
SMA	12	2	68[a]	−12	2	68[b]
STS	60	−46	−4[e]	−60	−48	−4[b]
THA	20	−18	12[f]	−10	−22	6[b]

MNI = Montreal Neurological Institute; ACC = anterior cingulate cortex; AMYG = amygdala; CAU = caudate; GP = globus pallidus; INS = insula; M1 = primary motor area; mPFC = medial prefrontal cortex; PAG = periaqueductal gray; PCC = posterior cingulate cortex; PUT = putamen; SI = primary somatosensory area; SII = secondary somatosensory area; SMA = supplementary motor area; STS = superior temporal sulcus; THA = thalamus.
[a] Gracely et al. (13).
[b] Harvard-Oxford atlas FSLview.
[c] Juelich Histological Atlas FSLview.
[d] Baliki et al. (8).
[e] Zaki et al. (23).
[f] Burgmer et al. (12).

spatial smoothing using a Gaussian kernel of 5-mm full width at half maximum, interleaved slice timing correction, and high-pass temporal filtering (Gaussian-weighted least squares straight-line fitting). After preprocessing, functional images were coregistered to the Montreal Neurological Institute 152 standard space using affine linear registration (22), and all volumes were resampled to a 2 × 2 × 2-mm space. Data were also band-pass filtered (0.006–0.1 Hz) to avoid low-frequency noise (e.g., scanner drift) and high-frequency artifacts (e.g., respiration and cardiac function).

Selection of Seeds and Extraction of the BOLD Time Series

Previous functional magnetic resonance imaging (fMRI) studies on experimental pain in patients with chronic pain (8,12,13) and HCs (23) have consistently shown that several brain regions are involved in the so-called pain network. Hence, for our network analysis of the resting state, we chose to extract BOLD time series from the following 15 brain regions: ACC, posterior cingulate cortex (PCC), amygdala (AMYG), caudate (CAU), putamen (PUT), globus pallidus, INS, primary (M1) and supplementary motor areas (SMAs), SI and SII, mPFC, PAG matter, superior temporal sulcus (STS), and THA. Two brain regions of the auditory cortex (Brodmann areas 41 and 42) were also included to control the effects of the scanner noise on functional connectivity of the pain network. Each brain region consisted of a cube of 3 × 3 × 3 voxels (27 voxels) from each cerebral hemisphere and centered on Montreal Neurological Institute coordinates reported by previous studies (Table 2). The signal characteristic for each seed was then selected as the spatial average of the BOLD time series over all voxels within the region.

Partial Correlation Analysis

Because of the very scarce information about the functional architecture of resting-state networks driven by intrinsic activity, partial correlations were used here to compute the functional connectivity between seeds (24–28). In brief, partial correlation analysis of a network composed of R regions consists of computing the conditional correlation between any pair of regions with respect to the remaining R-2 regions. As such, this approach provides a measure of functional connectivity between any two brain regions in a network of arbitrary size, allowing the removal of mutual dependencies originating from the common influences of other brain regions.

In the present study, the functional connectivity between two brain regions was calculated as the minimum first-order partial correlation between two seed time series (28,29). These calculations resulted in 30 × 30 correlation matrices including the left and right hemispheres. Differences between patients with FM and HCs for seed correlation matrices were compared by using nonparametric tests (uncorrected).

In addition, the number of positive and negative Pearson correlations between two seeds at different thresholds (0.1–0.9) was computed, and group differences in the balance of the functional connectivity within the pain network were statistically compared using a Wilcoxon signed rank test.

Finally, the relationship of functional connectivity strength with pain intensity and pain duration, as well as with psychological factors such as pain-related distress, depression, or anxiety, was examined by computing Pearson correlations.

RESULTS

Table 3 shows the cumulative number of positive and negative Pearson correlations for different thresholds. Significant group differences between patients with FM and HCs were found in the number of positive correlations above or equal to $r = 0.5$ and $r = 0.6$, whereas significant group differences were

TABLE 3. Number of Pearson Correlations Thresholding the Connectivity Matrix at a Certain Value

r Threshold	Healthy Controls	Patients With Fibromyalgia	*p*
No. correlations above the threshold			
0.1	617.4 (56.2)	617.0 (34.3)	.97
0.2	450.0 (60.5)	470.0 (33.5)	.56
0.3	294.4 (74.4)	328.8 (38.1)	.53
0.4	171.0 (62.7)	217.5 (43.6)	.25
0.5	**91.0 (42.0)**	**133.0 (47.9)**	**.046***
0.6	**45.4 (22.9)**	**76.8 (38.0)**	**.03***
0.7	21.0 (10.8)	35.8 (24.1)	.13
0.8	8.2 (3.6)	15.3 (10.7)	.14
0.9	3.2 (1.7)	4.0 (2.6)	.49
No. correlations below the threshold			
−0.1	501.3 (59.5)	503.0 (34.3)	.96
−0.2	326.4 (82.6)	358.5 (45.1)	.36
−0.3	180.9 (87.4)	233.7 (37.3)	.13
−0.4	91.1 (66.9)	147.0 (36.2)	.08
−0.5	**39.6 (39.9)**	**82.3 (31.5)**	**.03***
−0.6	**14.7 (18.1)**	**39.8 (23.8)**	**.02***
−0.7	**4.2 (6.2)**	**15.8 (15.1)**	**.03***
−0.8	0.4 (0.9)	4.3 (6.6)	.05
−0.9	0.0 (0.0)	0.0 (0.0)	—

Boldfaced data indicate those thresholds with significant group differences.
*$p = .05$.

observed in the number of negative correlations below or equal to $r = -0.5$, $r = -0.6$, and $r = -0.7$. In all cases, the number of positive and negative correlations was higher for patients with FM than for HCs.

Functional Connectivity Strength Within the Pain Network

Figure 1 displays the correlation networks for patients with FM and HCs. The strength of the functional connectivity within the pain network was measured as the partial correlation between two seed regions after removing the confounding effects of all other seed regions. Patients with FM showed increased connectivity of the ACC with the INS ($p = .046$), PUT ($p = .046$), and CAU ($p = .002$), as well as reduced connectivity with the AMYG ($p < .001$) and PAG ($p = .046$) matter in comparison with HCs. Reduced connectivity of the THA with the INS ($p = .003$) and PAG ($p = .002$) matter, the INS with PUT ($p = .038$), and PAG matter with CAU ($p = .038$) was also found in patients with FM when compared with HCs.

Patients with FM and HCs also showed significant differences regarding the strength of functional connectivity between areas involved in motor and somatosensory processes. Thus, patients with FM displayed increased connectivity of the M1 with SMA ($p = .007$) when compared with HCs. Nevertheless, patients with FM showed reduced connectivity of the SII with M1 ($p = .046$) and the PCC ($p = .038$), as well as increased connectivity of the SII with the CAU ($p = .012$) when compared with HCs. Decreased connectivity of the globus pallidus with the CAU ($p = .046$), as well as enhanced connectivity with the AMYG ($p = .046$) and STS ($p = .012$), was also found in

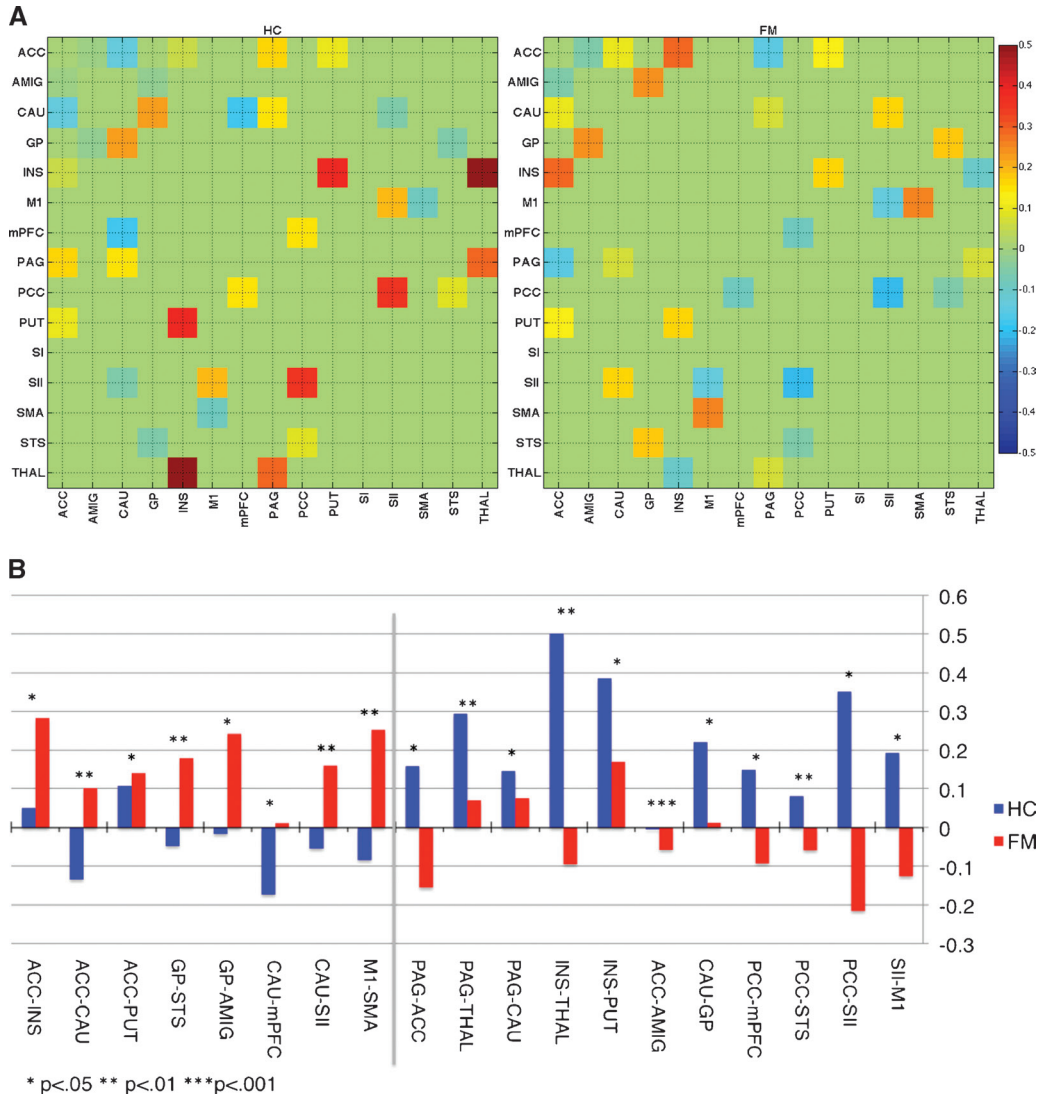

Figure 1. A, Differences in functional connectivity of the pain network between patients with fibromyalgia (FM) and healthy controls (HCs). Correlation matrices for each group were constructed by extracting the blood oxygen level–dependent time series from the 15 seed regions (over the left and right hemispheres) defined in Table 1 and calculating partial correlations between each pair of seeds. B, Group differences in the functional connectivity strength between patients with FM and HCs. The bars display the partial correlation values for pairs of seeds with significant differences. ACC = anterior cingulate cortex; AMYG = amygdala; CAU = caudate; GP = globus pallidus; INS = insula; M1 = primary motor area; mPFC = medial prefrontal cortex; PAG = periaqueductal gray; PCC = posterior cingulate cortex; PUT = putamen; SI = primary somatosensory area; SII = secondary somatosensory area; SMA = supplementary motor area; STS = superior temporal sulcus; THAL = thalamus.

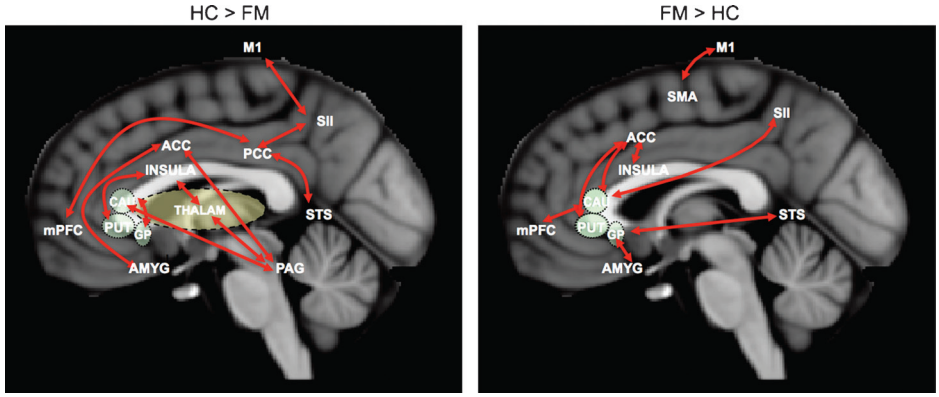

Figure 2. Differences in functional connectivity within the pain network. Schematic summary of changes in pain network connectivity among patients with FM. The figure represents the HC>FM (left) and the FM>HC contrasts (right). HC = health control; FM = fibromyalgia; ACC = anterior cingulate cortex; AMYG = amygdala; CAU = caudate; GP = globus pallidus; M1 = primary motor area; mPFC = medial prefrontal cortex; PAG = periaqueductal gray; PCC = posterior cingulate cortex; PUT = putamen; SII = secondary somatosensory area; SMA = supplementary motor area; STS = superior temporal sulcus; THALAM = thalamus.

patients with FM when compared with HCs. Finally, patients with FM displayed increased connectivity of the mPFC with the PCC ($p = .020$) and CAU ($p = .046$) when compared with HCs, as well as reduced connectivity of the PCC with STS ($p = .002$). A summary of the increased and reduced connectivity in patients with FM, as compared with HCs, is displayed in Figure 2.

Correlation of Functional Connectivity With Self-Report Measures

The relationships between functional connectivity within the pain network and data from self-report questionnaires were also analyzed by Pearson correlation. The functional connectivity of PAG matter with the THA and with the ACC was negatively correlated with depression (Pearson $r = -0.62$, $p = .003$ and $r = -0.60$, $p = .004$, respectively; Fig. 3). No significant relationship was found with pain scores or the WHYMPI questionnaire.

DISCUSSION

In the present study, we examined the intrinsic functional connectivity of specific brain structures or seeds that were previously identified as belonging to the so-called pain network (2,8,12,13,23): INS, ACC, PCC, basal ganglia, THA, PAG matter, mPFC, STS, somatosensory cortices (SI and SII), primary motor cortex (M1), SMA, and AMYG. For this purpose, low-frequency fluctuations of resting-state BOLD signals were extracted from the previously mentioned seeds, and individual functional connectivity matrices were constructed by using mutual partial correlations between seeds.

Our study revealed that the dynamics of resting-state brain activity within the pain network were significantly altered in FM. Indeed, the number of positive (above $r = 0.5$ and $r = 0.6$) and negative (below $r = -0.5$, $r = -0.6$, and $r = -0.7$) correlations between the seeds of the pain network was 1.5 to 4 times higher in patients with FM than in HCs. Although the physiological significance of positive and negative correlations of spontaneous BOLD activity still remains unknown, previous studies have consistently demonstrated that regions with similar functionality tend to be correlated for their spontaneous BOLD activity, whereas regions with apparently opposing functionality are negatively correlated or anticorrelated (4). Moreover, increases in the number of positive correlations have been interpreted as relative increases in neuronal synchrony and/or activity, whereas negative correlation could be seen as a result of asynchronous neuronal firing or increased inhibitory drive (8). Such anticorrelations might be more accurately referred to as manifestations of ensemble inhibition between brain areas (4). In this context, our data seem to suggest that extensive changes in resting-state functional connectivity could have led to a disruption of the balance between excitatory and inhibitory mechanisms within the pain network in FM. This finding is in agreement with previous research showing that functional brain connectivity of other resting-state networks (such as the default mode

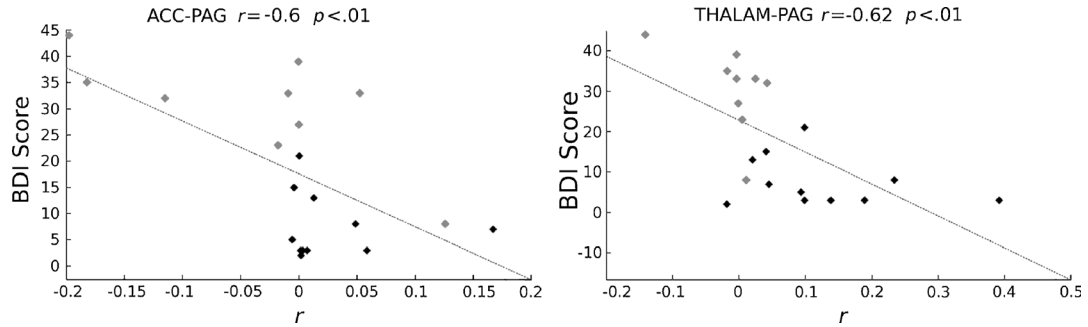

Figure 3. Significant correlations between the connectivity strength of anterior cingulate cortex-periaqueductal gray (ACC-PAG) (left) and thalamus (THALAM)-PAG (right) and depression (Beck Depression Inventory [BDI]) for patients with fibromyalgia (black diamonds) and healthy controls (gray diamonds).

network) might be altered in patients with chronic pain at rest (8–10,29–31) and suggests that ongoing and persistent pain may have led to the widespread disruption of brain function. It seems that enduring pain for a long time affects brain function in response to rest or even to minimally demanding attention tasks completely unrelated to pain. Given that patients with chronic pain, including those with FM, report a persistent pain sensation rendering their brain never truly at rest, it is reasonable to expect them to have altered resting-state functional connectivity of the pain network as described here.

Increased Resting-State Functional Connectivity in FM

We observed that resting-state functional connectivity of the ACC, basal ganglia, and sensorimotor cortices was increased in patients with FM as compared with HCs, suggesting that these seeds could represent relevant nodes or hubs within the pain network at rest. In this sense, the increased connectivity of the ACC with basal ganglia (CAU nucleus and PUT) and the ACC with the INS in patients with FM seems to be in concordance with previous neuroimaging studies demonstrating that these regions are transiently activated in experimental pain tasks (2,32) or during persistent pain (33) and that they play a key role in affective processing (ACC and INS) and in the integration of motor, emotional, autonomic, and cognitive aspects of pain signals (basal ganglia) (34). Moreover, increased connectivity of the INS has been observed in diabetic neuropathic pain (9), together with higher spectral power of BOLD fluctuations (at 0.12–0.25 Hz) in the ACC and INS during rest (30). Thus, our data seem to indicate that patients with FM maintain a high level of synchronization among these areas as compared with HCs, even in the absence of any painful task. This interpretation is also supported by previous work indicating that both the ACC and INS might be involved in the subjective evaluation of internal conditions, such as pain (35,36) and cardiac functions (37). Moreover, a significant functional connectivity of pregenual ACC and anterior INS at rest has been recently found in healthy volunteers (32), suggesting the existence of a system responsible for integrating interoceptive information with emotional salience, forming a subjective image of our bodily state. In this sense, our finding of increased connectivity between the ACC and the INS at rest would provide support for the relevance of emotional factors in the development and maintenance of chronic pain in FM.

Previous studies have also observed a significant activation of SMA during the processing of acute pain in HCs (38,39) and patients with FM (40). In those studies, subjective pain intensity elicited by acute pain stimuli was positively correlated with activation in the somatosensory cortices, INS, THA, ACC, and SMA. Moreover, it has been further suggested that stronger SMA activation might be related to C-fiber rather than to Aδ-fiber activation and that SMA could be more involved in the processing of the affective rather than the sensory-discriminative component of pain (41). Thus, considering the predominance of the affective pain component in FM and the presence of cutaneous C-fiber pain abnormalities in these patients, one could speculate that our observation of increased connectivity of the SMA and M1 at rest might be the result of the widespread central sensitization in FM.

Reduced Resting-State Functional Connectivity in FM

In addition, we observed that functional connectivity of the THA with the INS and PAG, as well as connectivity of the ACC with PAG, was reduced in patients with FM as compared with HCs. Previous research has provided abundant evidence that a variety of brain regions, such as the PAG, INS, frontal lobe, AMYG, hypothalamus, nucleus cuneiformis, and rostral ventromedial medulla, are also involved in the descending pain modulatory system (1). Moreover, recent studies have suggested that connectivity among these brain areas might be fundamental in understanding inhibitory pain modulation (42). In agreement with previous research showing an abnormal reduction of activity in thalamic and CAU nuclei in FM (13,43–46), we believe that reduced connectivity of the THA, PAG, basal ganglia, ACC, and INS could be linked to a dysregulation of this inhibitory pain mechanism in these patients.

We also found decreased connectivity of the SII with the primary motor cortex (M1) and with the PCC in patients with FM. These regions have been involved in attention capture and orientation toward painful stimuli, as well as in the control of action and withdrawal reactions (1,2). Furthermore, stimulation of the motor cortex in neuropathic pain has also been demonstrated to induce analgesic effects by the release of endogenous opioids in the medial cingulate cortex and PAG (47). Thus, it seems that reduced connectivity among these brain regions would reflect the removal of inhibitory tone from the primary motor system onto the corticolimbic pain areas. Basically, our findings provide support for the central role of this brain inhibitory mechanism in the maintenance of chronic pain disorders (38,48) and suggest a need to strengthen the brain connectivity of somatomotor brain structures in future treatments for chronic pain (e.g., through neurofeedback training).

Finally, we observed that spontaneous BOLD fluctuations from the mPFC and PCC were significantly less positively correlated in patients with FM as compared with HCs. These two brain regions have been implicated in processes that are important for the resting-state default mode function of the brain and are known to be synchronously activated at rest in HCs (4). Thus, our finding that the seed correlations between the mPFC and PCC were significantly reduced in FM could be interpreted as a disruption of the default mode network involved in self-referential thinking as it has been described in other chronic pain syndromes (8,10,30,31). Furthermore, our study clearly demonstrates that enduring pain specifically alters the functional connectivity of brain regions beyond those involved in pain processing.

The present study has some clear limitations that should warrant caution in the interpretation of the current results. FM is known to exhibit substantial variability in somatic and cognitive symptoms. Thus, it is expected that this heterogeneity translates into fMRI brain phenomenology, limiting the precision and specificity of the interpretations of generalizations. Our results reflect this enormous variability and diffuse course

of symptoms, making any single area interpretation of fMRI data difficult. The different medication intake between groups may have also contributed to the observed differences in the present study. However, the use of antidepressants typically involves brain networks other than the one examined here (49). Furthermore, the fact that pain medication used in the patients with FM was not effective in reducing pain and affective symptoms speaks against a substantial influence on our connectivity results. Another potential limitation of the study is the relatively small size of the sample. However, the sample sizes here were comparable to others reported in previous neuroimaging studies (ranging between 8 and 18 patients) (8–10,30). Finally, it should also be stressed that, although partial correlation analysis provides estimates of functional interactions, it does not provide information regarding causality (25).

In sum, the present study revealed that FM is associated with significant changes in the functional connectivity of pain-related brain structures when participants were instructed to rest. These results are in line with functional brain abnormalities described previously in FM during experimental situations involving task performance or nociceptive stimulation (12,13,23). In particular, we observed that patients with FM displayed a substantial imbalance of the functional connectivity within the pain network, showing strengthened connectivity of relevant brain regions involved in pain processing, as well as significantly reduced connectivity of areas involved in pain inhibitory modulation. Thus, the present study provides further evidence of abnormal brain function in patients with FM, suggesting that chronic pain may lead to brain changes not only during externally driven information processing but also during internally generated thought processes such as those that occur in FM during the perception of ongoing pain at rest. Furthermore, our findings suggest that chronic pain is associated with extensive changes in functional connectivity in a small-world neuronal network such as the human brain, creating a substantial imbalance in the delicate equilibrium among different parts of the pain network. Whether the heterogeneous and extremely variable symptoms of FM is causally related to this imbalance of connectivity within the pain system remains to be determined, although the present study constitutes a first step in that direction and at least suggests such a possibility.

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