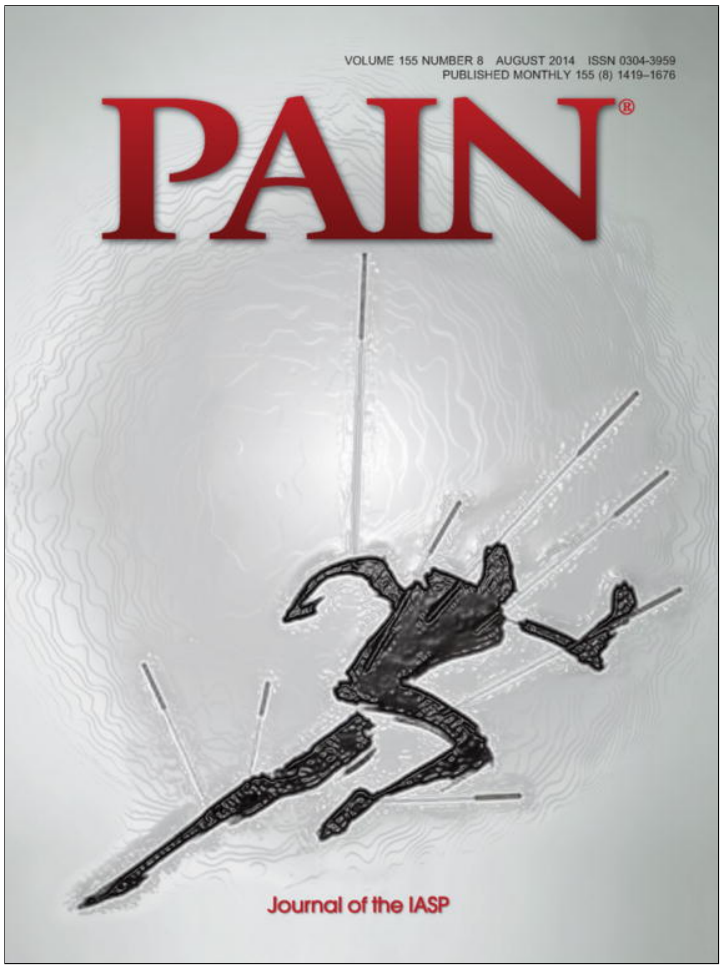

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The contribution of sensory system functional connectivity reduction to clinical pain in fibromyalgia

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ABSTRACT

Fibromyalgia typically presents with spontaneous body pain with no apparent cause and is considered pathophysiologically to be a functional disorder of somatosensory processing. We have investigated potential associations between the degree of self-reported clinical pain and resting-state brain functional connectivity at different levels of putative somatosensory integration. Resting-state functional magnetic resonance imaging was obtained in 40 women with fibromyalgia and 36 control subjects. A combination of functional connectivity-based measurements were used to assess (1) the basic pain signal modulation system at the level of the periaqueductal gray (PAG); (2) the sensory cortex with an emphasis on the parietal operculum/secondary somatosensory cortex (SII); and (3) the connectivity of these regions with the self-referential "default mode" network. Compared with control subjects, a reduction of functional connectivity was identified across the 3 levels of neural processing, each showing a significant and complementary correlation with the degree of clinical pain. Specifically, self-reported pain in fibromyalgia patients correlated with (1) reduced connectivity between PAG and anterior insula; (2) reduced connectivity between SII and primary somatosensory, visual, and auditory cortices; and (3) increased connectivity between SII and the default mode network. The results confirm previous research demonstrating abnormal functional connectivity in fibromyalgia and show that alterations at different levels of sensory processing may contribute to account for clinical pain. Importantly, reduced functional connectivity extended beyond the somatosensory domain and implicated visual and auditory sensory modalities. Overall, this study suggests that a general weakening of sensory integration underlies clinical pain in fibromyalgia.

1. Introduction

Pain originates from potentially noxious stimuli that are able to trigger a neural response in pain-dedicated systems. In abnormal circumstances, individuals may experience pain with no noxious stimulation as a consequence of concrete neural damage (ie, neuropathic pain) [4,15]. Nonetheless, pain may also appear spontaneously with no apparent neural lesion, as in fibromyalgia, a disorder characterized by chronic complaints of spontaneous widespread pain in the musculoskeletal system [75].

From a pathophysiological viewpoint, fibromyalgia is classed as a disorder of pain-related somatosensory signal processing [13]. Existing hypotheses propose that an alteration exists in

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physiological pain modulation mechanisms, in which enhanced pain facilitation may combine with defective inhibition of nociceptive signals to ultimately augment pain perception [25,44,65]. A key converging brain site for pain modulation is the periaqueductal gray (PAG) in the upper brainstem. The PAG acts as a gateway that serves to both attenuate and amplify pain signals, primarily via its projection to the rostral ventromedial medulla [5,47]. Potentially, alterations originating in different elements of the pain modulation pathways could alter activity in the PAG by virtue of its strategic placement.

It is also recognized that clinical pain in fibromyalgia is perceived as somatic unpleasant sensations, frequently reported as "pain all over" the body [75]. Body awareness is abnormally enhanced with both global spontaneous soreness and increased sensitivity to pressure [25]. Despite its subjective nature, painful somatosensation has anatomical correlates in the brain. The sensory body is largely represented in the cerebral cortex with all its major dimensions, including touch, proprioception, temperature, and nociception [42,68,69]. Therefore, the degree of spontaneous body pain may arguably be related to neural activity in the cortical representation of the body.

Neuroimaging research has made a unique contribution to our understanding of the functional status of the human brain at rest. Functional magnetic resonance imaging (fMRI) of spontaneous brain activity permits tests of the integrity of relevant functional networks on the basis of region activity synchronization – typically defined as "functional connectivity" [23]. Previous studies have already identified alterations in brain resting-state functional connectivity in patients with fibromyalgia. Specifically, abnormal functional connectivity has been demonstrated in the self-referential ("default mode") network and the "executive attention" network with regions relevant to somatosensory sensations and nociception (parietal operculum and insula), which positively correlated with the intensity of spontaneous pain [51]. In another study, resting-state functional connectivity disturbances were identified within elements of the pain-processing network [12].

In this study, we used resting-state fMRI to investigate the neural correlates of clinical pain in fibromyalgia at different levels of somatosensory processing. The PAG system was examined as representative of the basic pain modulatory system using a specific region-of-interest analysis based on previous studies. A novel approach based on mapping brain functional connectivity degree allowed us to identify alterations in cortical sensory areas. This approach served to guide further region-of-interest analyses to assess functional connectivity within the cortical sensory system (ie, somatosensory, visual, and auditory cortex) and between sensory integration cortex (ie, parietal operculum) and the self-referential network.

2. Materials and methods

2.1. Subjects

A total of 76 subjects participated in the study, including 40 women with fibromyalgia and 36 healthy control women with comparable age (mean ± SD for patients; 46.4 ± 7.5 years and control subjects; 44.0 ± 6.0 years, $t = 1.5$, $P = 0.134$), education level (patients; 14.3 ± 4.7 years and control subjects; 15.2 ± 4.6 years, $t = -0.9$, $P = 0.378$) and hand-dominance (all right-handed).

Patients were consecutively recruited during clinical follow-up to make up a homogeneous sample with severe and long-lasting symptoms. All patients met the American College of Rheumatology criteria for fibromyalgia [75]. Mean illness duration was 7.2 (±4.7) years. The number of tender points upon study assessment was 16.0 (±1.9). The Fibromyalgia Impact Questionnaire [8] total score was 66.2 (±14.2) (maximum score, 100), and the Functional Capacity score of the Fibromyalgia Impact Questionnaire was 4.8 (±1.9). The score for General Perception of Health according to the 36-item Short-Form Health Survey [72] was 30.6 (±18.1) (maximum score, 100). Hospital Anxiety and Depression Scale (HADS) ratings [60,77] were 8.9 (±4.8) for depression and 11.6 (±4.1) for anxiety.

Patients were allowed to continue with their stable medical treatment, which is described in Supplementary Table 1, but were required to refrain from taking occasional (rescue) analgesic drugs (ie, paracetamol and nonsteroidal antiinflammatory drugs) 72 hours prior to fMRI.

As to the control group, subjects with relevant medical or neurological disorder, any form of chronic or acute pain, substance abuse, or psychiatric disease were not considered for inclusion. None of the control subjects was undergoing medical treatment. Pregnancy was also an exclusion criterion for both study groups.

This study was conducted according to the principles expressed in the Declaration of Helsinki. The study was approved by the Ethics and Institutional Review Board of the Autonomous University of Barcelona (reference number SAF2010-19434). All patients and control subjects provided written informed consent for clinical and fMRI assessment and subsequent analyses.

2.2. Clinical pain assessment

The aim of the assessment was to obtain a subjective measurement of clinical (nonevoked) fibromyalgia pain before fMRI as a direct expression of the patient's current generalized pain sensation. Clinical pain was assessed using a 101-point numerical rating scale [36], which has been previously used in fibromyalgia patients [26]. A score of 0 represented no pain and a score of 100 the maximum bearable fibromyalgia-related pain perceived in the body as a whole, or in most of its extension, rather than referring to any focal tenderness. A specific anamnesis was performed to characterize current pain sensations. No patient was scanned who reported current pain that was unrelated to the fibromyalgia syndrome (eg, headache/migraine, low back pain, neuropathic pain). Patients were asked to report pain before fMRI assessment twice; at 1 hour (±10 minutes) before imaging and within the 10-minute period before imaging.

2.3. MRI acquisition

A Philips Achieva 3.0 Tesla magnet (Philips Healthcare, Best, The Netherlands), equipped with an 8-channel phased-array head coil and single-shot echo planar imaging (EPI) software, was used. Functional sequences consisted of gradient recalled acquisition in the steady state (time of repetition [TR] = 2.000 ms; time of echo [TE] = 35 ms; pulse angle = 90°) within a field of view of 23 cm, a 96 × 69-pixel matrix, slice thickness of 4 mm (plus interslice gap, 1 mm) and acquisition voxel size of 3.3 × 2.4 × 4 mm. Twenty-two slices parallel to the anterior-posterior commissure line covered the whole brain. A 6-minute continuous resting-state scan was acquired for each participant. Participants were instructed to relax, stay awake, and lie still without moving, while keeping their eyes closed throughout. This scan generated 180 whole-brain EPI volumes. The sequence included 4 additional dummy volumes to allow the magnetization to reach equilibrium.

2.4. Image preprocessing

Image data were processed using MATLAB version 2011b (The MathWorks Inc, Natick, MA, USA) and Statistical Parametric Mapping software (SPM8; The Wellcome Department of Imaging Neuroscience, London, UK). Preprocessing involved motion correction,

spatial normalization, and smoothing using a Gaussian filter (full-width half-maximum, 8 mm). Data were normalized to the standard SPM-EPI template and re-sliced to 2-mm isotropic resolution in Montreal Neurological Institute (MNI) space. All image sequences were inspected for potential acquisition and normalization artifacts. No subjects were excluded because of artifacts or head displacements (>2 mm for translations and >2° for rotations in any *x*, *y*, *z* axis). In addition, we compared both study groups for potential differences in movement for translations, rotations, and mean interscan motion and found no significant differences (all $P > 0.6$).

2.5. Image analysis

A combination of functional connectivity-based measurements was used involving connectivity degree maps and functional connectivity region-of-interest (seed) maps. The connectivity degree measurements [7,14,55,67] served to globally assess the functional status of sensory cortices (somatosensory, visual, and auditory) and to guide a subsequent region-of-interest functional connectivity mapping.

2.5.1. Regional connectivity degree mapping

The data-driven method described by Sepulcre et al. [62] was adopted to generate whole-brain maps of the degree of regional functional connectivity, but using study-specific parameters. The method measures the connectivity degree of each voxel with neighboring voxels as the sum of correlations above a given Pearson correlation coefficients threshold.

Specifically, connectivity degree maps were generated for each subject using the preprocessed EPI images, re-sliced to a voxel dimension of $6.32 \times 7.6 \times 6.8$ mm to increase signal-to-noise ratio and optimize computing speed. To remove low-frequency drifts, a high pass filter set at 128 seconds was applied before generating the correlation *r*-matrix, and the volume mean of global brain, cerebrospinal fluid (CSF), and white matter signal time courses were regressed from each voxel's time series also at this step to remove sources of physiological noise. Global brain, CSF, and white matter segments were thresholded at a probability of >70%. The CSF segment included the lateral, third, and fourth ventricles. Separate measurements were used for anterior (anterior to MNI $y = -15$) and posterior (posterior to MNI $y = -15$) white matter anatomy.

Each voxel's fMRI signal time series was then correlated with every other voxel's time series, resulting in a Pearson correlation coefficient *r*-matrix. The analysis was restricted to gray matter, which allowed us to define a total amount of 4097 gray matter voxels or brain nodes. From the correlation matrix data, regional connectivity degree of each voxel was computed by summing the number of correlations that a given voxel had above a threshold $r > 0.35$ within a region defined by a 30-mm-radius sphere. Connectivity degree was finally expressed in relative values as the ratio of total supra-threshold connections over all the possible connections within the region.

SPM8 was used to generate one-sample *t*-statistic maps for each group, and 2-sample *t*-tests were performed to map between-group differences.

2.5.2. Seed-based functional connectivity analysis

Functional connectivity maps were generated as detailed in previous studies [29,58]. The results of our connectivity degree mapping served as the basis for selecting seed coordinates within the sensory systems at the cortical level. Significant between-group sensory system differences involved the parietal operculum/secondary somatosensory cortex (SII), and the auditory, visual, and primary somatosensory cortices (Supplementary Table 3). Three maps were obtained using anterior (MNI; −59, −8, 23), middle (MNI; −59, −20, 16), and posterior (MNI; −46, −38, 22) parietal operculum seeds to comprehensively assess its functional connectivity, as the parietal operculum is made up of notably distinct functional subdivisions [9,21]. The auditory seed was placed at MNI; −56, −15, 8, the visual seed at MNI; −8, −91, 30, and primary somatosensory at MNI; −8, −30, 70 (Supplementary Table 3). The PAG system was explored using a specific region-of-interest analysis based on coordinates extracted from previous studies. The seed was placed at MNI coordinates; $x = 1$, $y = -29$, $z = -12$, which is the reported PAG peak activation likelihood estimate derived from fMRI data obtained in 2533 subjects [40]. This region also coincides with the activation likelihood peak from 40 pain experiments and includes the ventral PAG area that has been related to opioid-mediated analgesia [40].

To map functional connectivity in this approach, the signal time course of a selected seed region was used as a regressor to be correlated with the signal time course of every voxel in the brain, and the obtained voxel-wise regression coefficients served to build first-level output (.con) images. For each map, seeds were defined as 3.5-mm radial spheres (sampling approximately 25 voxels) using MarsBaR region-of-interest toolbox in MNI stereotaxic space [6]. Signal values for the seeds were calculated as the average signal of the voxels included in the seed at each time point. As in the connectivity degree analysis, we derived estimates of global brain, CSF, and white matter signal fluctuations to be included as confounding ("nuisance") variables in the multiple regression SPM model together with the variable of interest (signal time course of a selected seed region).

First-level images, obtained in each participant, were then included in second-level (group) random-effects analyses. One-sample *t*-statistic maps were calculated to obtain sensory cortices and PAG functional connectivity maps for each group, and 2-sample *t*-tests were performed to map between-group differences for the contrasts: fibromyalgia < controls and fibromyalgia > controls. Voxel-wise analyses in SPM were performed to map the correlation between clinical pain and resting-state functional connectivity measurements. In order to assess the influence of anxiety and depression symptoms on the relationship between pain and functional connectivity, the correlation maps were re-estimated after covarying for patients' HADS scores.

Finally, a multiple regression analysis was performed to assess the combined contribution of functional connectivity measurements to clinical pain scores in the fibromyalgia group. Pain scores were included as the dependent variable, and potential predictors were functional connectivity measurements from those brain regions showing a significant correlation in bivariate correlation analyses (Supplementary Tables 2, 4, 5, and 6). To limit the number of predictive variables, a representative measurement was included from each analysis (7 in total) comprising one measurement of connectivity between the parietal operculum and other sensory cortices (averaged across the auditory, visual, and primary somatosensory areas with the strongest correlations) for each seed map (anterior, middle, and posterior). Additionally, connectivity between the parietal operculum and both posterior cingulate cortex (PCC; anterior and posterior seed maps) and lateral frontal cortex (middle seed map), and between the PAG and left insula was included. The step-wise multiple regression method was used.

2.5.3. Thresholding criteria

Spatial extent thresholds were determined by 2000 Monte Carlo simulations using AlphaSim [71] as implemented in the SPM REST toolbox [64]. Input parameters to AlphaSim included an individual voxel threshold probability of 0.005, cluster connection radius of 5 mm, 8-mm full-width half-maximum smoothness, incorporating a gray matter mask volume of 167,265 ($2 \times 2 \times 2$ mm) voxels. The estimated minimum cluster size extent was 1.032 mL (129 voxels

for seed maps and 4 voxels for connectivity degree maps) in order to satisfy a family-wise error (FWE) rate correction of $P_{FWE} < 0.05$. All maps in figures are displayed showing $t > 2.4$.

3. Results

3.1. Behavioral ratings

3.1.1. Clinical pain ratings in patients

Fibromyalgia patients reported moderate-to-severe clinical pain ratings before MRI acquisition (mean ± SD, 70.9 ± 15.9 in the first rating and 71.3 ± 14.7 in the second rating). The 2 recorded measurements were highly correlated showing $r = 0.80$ and $P < 0.000001$. In the fMRI correlation analysis, we therefore used the average of both measurements as representative of the current clinical pain (71.1 ± 14.6, range 40–90).

3.1.2. Anxiety and depression symptoms

Fibromyalgia patients had significantly higher anxiety and depressive symptom ratings than control subjects, as measured with the Hospital Anxiety and Depression Scale (anxiety: 11.6 ± 4.1 in patients, 5.6 ± 3.4 in controls, $t = 6.8$ and $P < 0.0001$; depression: 8.9 ± 4.8 in patients; 2.0 ± 2.3 in controls, $t = 8.1$ and $P < 0.0001$). These symptom ratings, however, showed a weak linear relationship with patient pain ratings (pain and anxiety: $r = 0.30$ and $P = 0.062$; pain and depression: $r = 0.35$ and $P = 0.028$).

3.2. Periaqueductal gray functional connectivity analysis

One-sample (group) seed maps showed that the PAG was functionally connected to a variety of structures mostly in the ventral aspect of the cerebrum (basal ganglia, thalamus, insula, parahippocampal gyrus, and amygdala) and in the upper brainstem in both

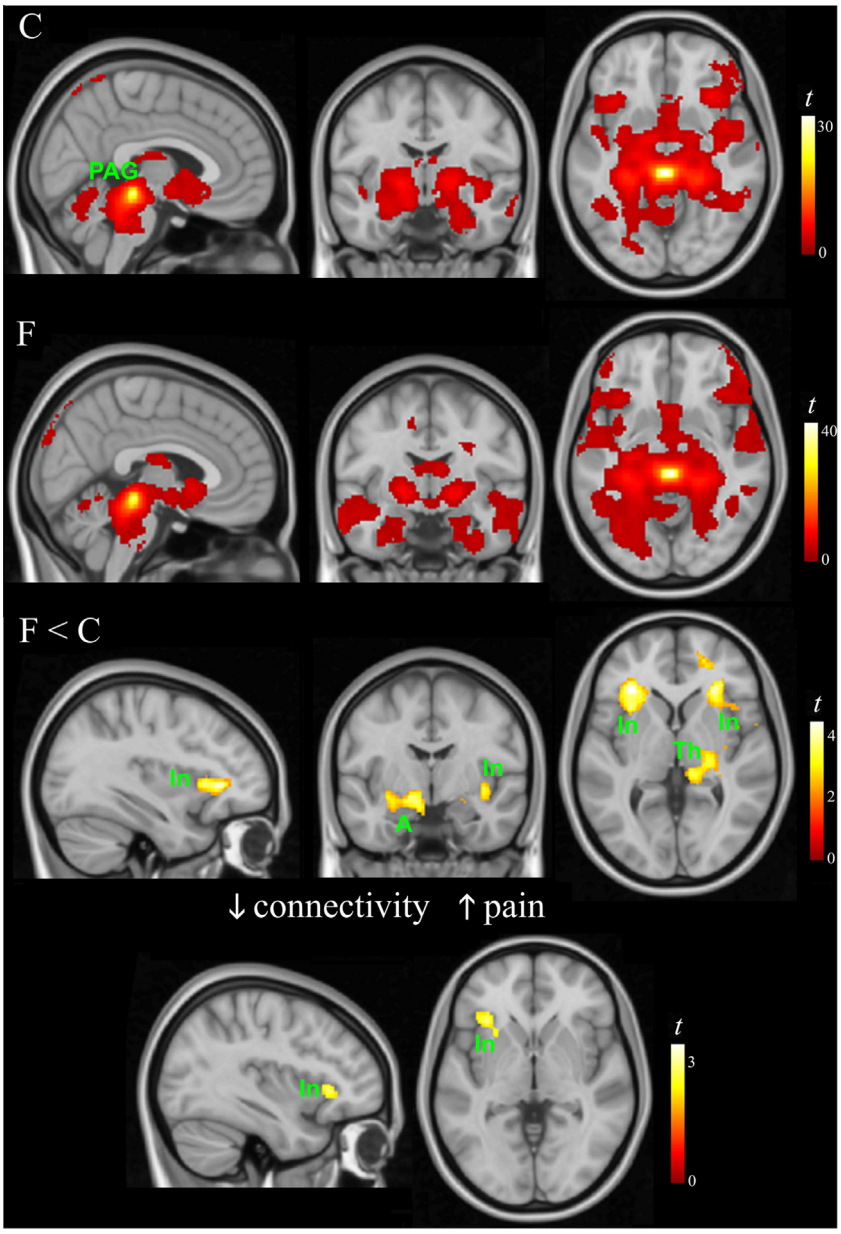

Fig. 1. Periaqueductal gray seed analysis. Within-group (one-sample) functional connectivity maps for controls (C) and fibromyalgia patients (F), between-group differences (F < C), and a specific correlation between functional connectivity measurements and clinical pain scores (bottom row) are presented. The right hemisphere corresponds to the right side of axial and coronal views. The region showing the highest correlation in one-sample maps indicates seed location. PAG, periaqueductal gray; In, insula; A, amygdala; Th, thalamus.

study groups (Fig. 1, Supplementary Table 2). Compared with control subjects, fibromyalgia patients showed a significant reduction of functional connectivity between the PAG and the anterior portion of the left and right insulae, left amygdala, and right thalamus. Subjective ratings of clinical pain showed a negative correlation with functional connectivity measurements between PAG and left anterior insula (more pain, less connectivity). This finding is below the general study threshold, but is reported as it closely coincides with the insula region showing significantly reduced functional connectivity (Fig. 1).

3.3. Somatosensory cortex functional connectivity analysis

3.3.1. Regional connectivity degree mapping

Significant reductions of regional connectivity in fibromyalgia patients compared with control subjects involved both the primary somatosensory cortex and secondary somatosensory cortex (SII). The largest changes were identified at the level of the parietal operculum, mostly in the left hemisphere (Fig. 2). Group differences were also significant for other brain locations (Supplementary Table 3). Of particular relevance, abnormal regional connectivity was observed in auditory and visual cortices. These results informed the selection of regions of interest for subsequent seed-based functional connectivity mapping. Six regions were selected from the analysis of between-group differences, including the anterior, middle, and posterior parietal operculum/SII, auditory cortex, visual cortex, and primary somatosensory cortex.

No significant increases of regional connectivity degree were found in fibromyalgia patients compared to controls (contrast fibromyalgia > control) in this whole-brain approach.

3.3.2. Region-of-interest functional connectivity mapping

Compared with the control group in the contrast fibromyalgia < controls, patients showed a reduction of functional connectivity between the parietal operculum/SII and auditory cortex, visual cortex, primary somatosensory cortex, and posterior insula (Supplementary Tables 4–6, and see Supplementary Fig. 1 for within-group maps). Figure 3 illustrates the pattern of between-group differences and shows the extent to which the identified alterations were restricted to sensory cortical areas. Auditory, visual, and primary somatosensory cortex connectivity maps reciprocally confirmed reduced functional connectivity between

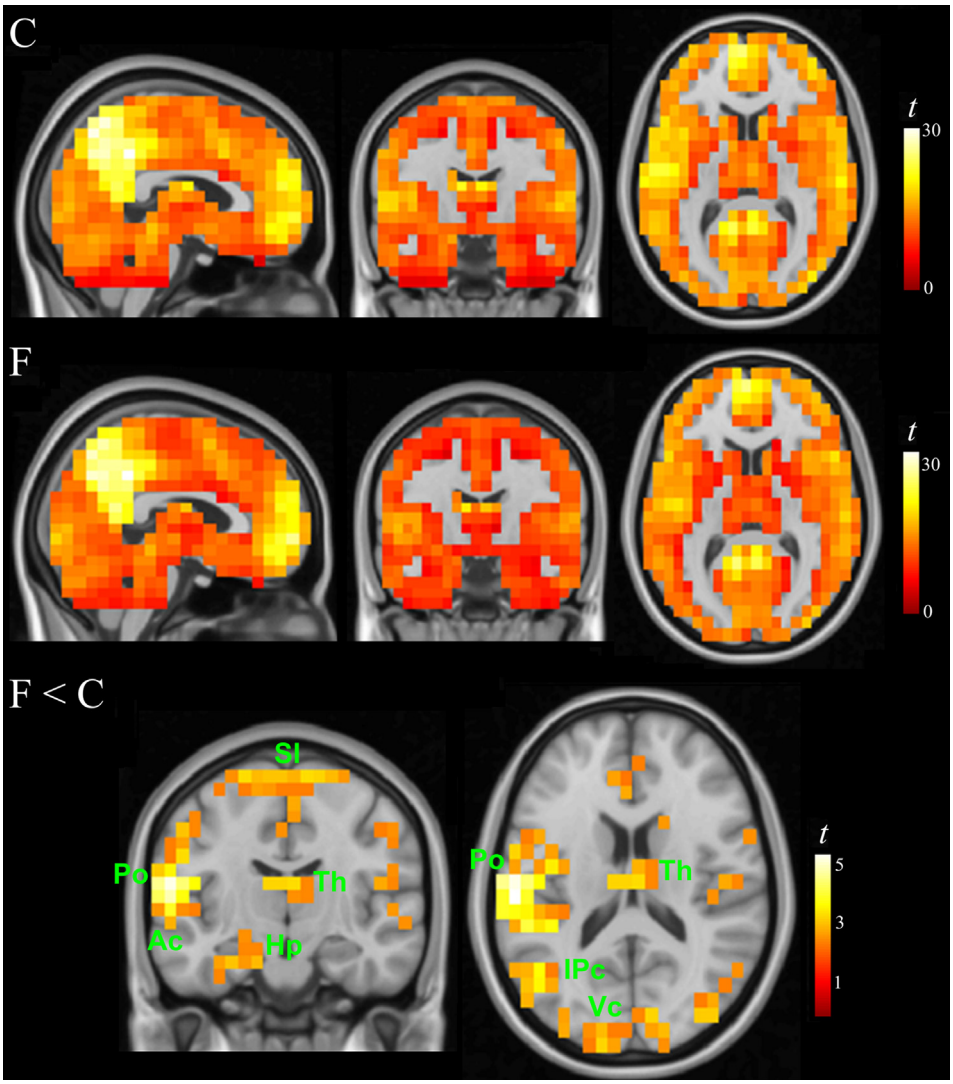

Fig. 2. Regional functional connectivity degree analysis. Within-group (one-sample) maps for controls (C) and fibromyalgia patients (F), and between-group differences (F < C). The most evident connectivity reductions were identified in the left parietal operculum involving the primary and secondary somatosensory cortex (SII). The right hemisphere corresponds to the right side of axial and coronal views. SI, primary somatosensory cortex; Po, parietal operculum; Th, thalamus; Ac, auditory cortex; Hp, hippocampus; IPc, inferior parietal cortex; Vc, visual cortex.

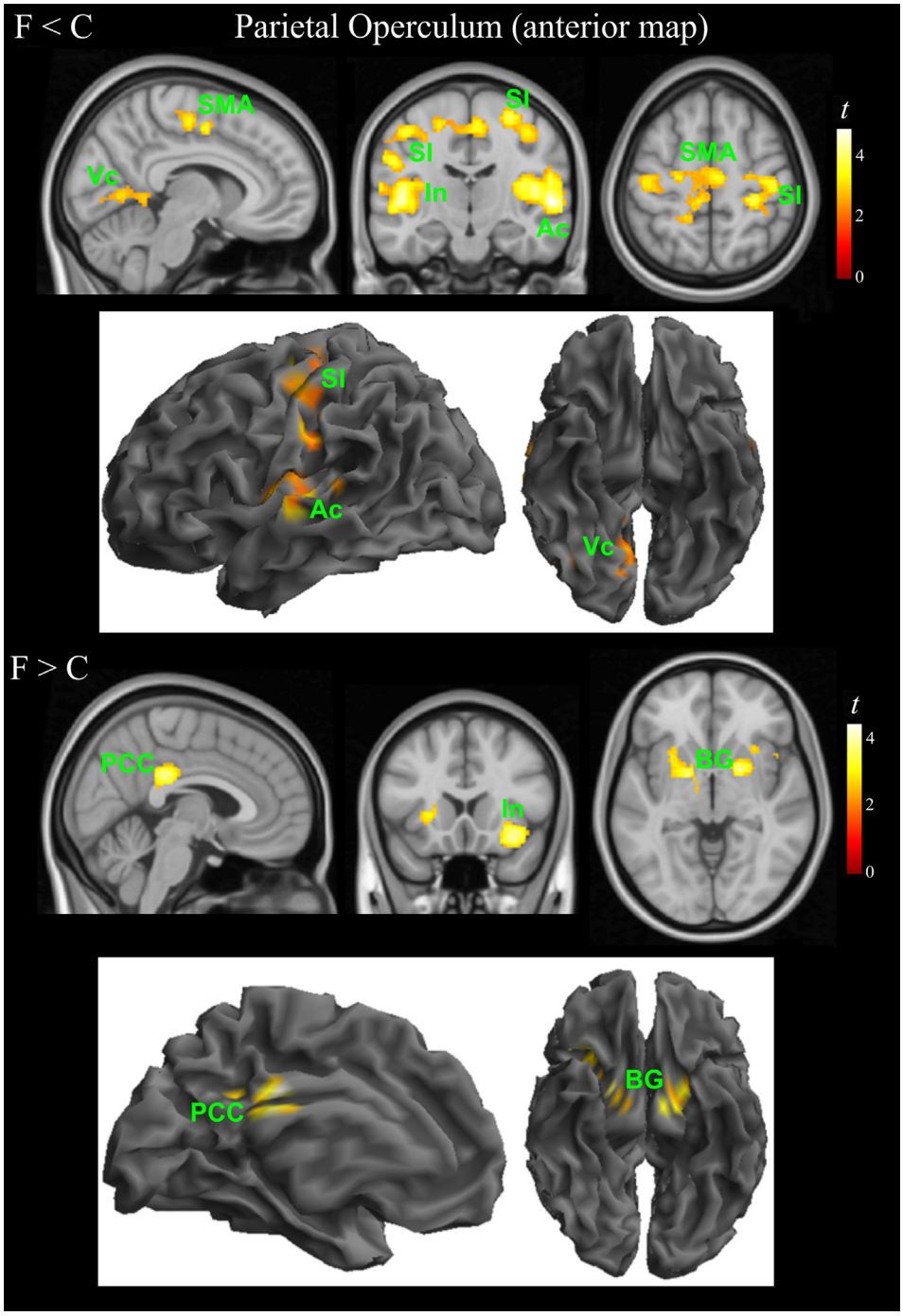

Fig. 3. Between-group differences in the functional connectivity of the left parietal operculum. Findings from the parietal operculum anterior seed map best illustrated the general pattern. Compared with control subjects (C), fibromyalgia patients (F) showed a reduction in functional connectivity between the parietal operculum/SII and primary somatosensory, visual and auditory cortices (top panels). The 3D picture shows the anatomical specificity of the pattern. Regions showing a functional connectivity increase in fibromyalgia (bottom panels) involved the posterior cingulate cortex, insula, and basal ganglia. The right hemisphere corresponds to the right side of axial and coronal views. SMA, supplementary motor area; SI, primary somatosensory cortex; Vc, visual cortex; In, insula; Ac, auditory cortex; PCC, posterior cingulate cortex; BG, basal ganglia.

each sensory cortex modality and the parietal operculum/SII region, which was very consistent and notably specific (Fig. 4, Supplementary Table 7).

Within the fibromyalgia group, subjective pain scores showed a significant negative correlation with measurements of functional connectivity between the parietal operculum and the other sensory cortices (more pain, less connectivity). Clusters of significant correlation were found in auditory, visual, and primary somatosensory cortices (Fig. 5, Supplementary Tables 4–6). In general terms, the correlation pattern showed a notable resemblance with the pattern of group functional connectivity differences (compare Figs. 5 and 3). A similar pattern of correlations was obtained after the inclusion of patients' HADS scores as covariates (Supplementary Tables 4–6).

Fibromyalgia patients showed significant increases of functional connectivity (fibromyalgia > controls) between the parietal operculum/SII and the posterior cingulate cortex, precuneus, ventral putamen, and ventral insula (Fig. 3 and Supplementary Tables 4–6).

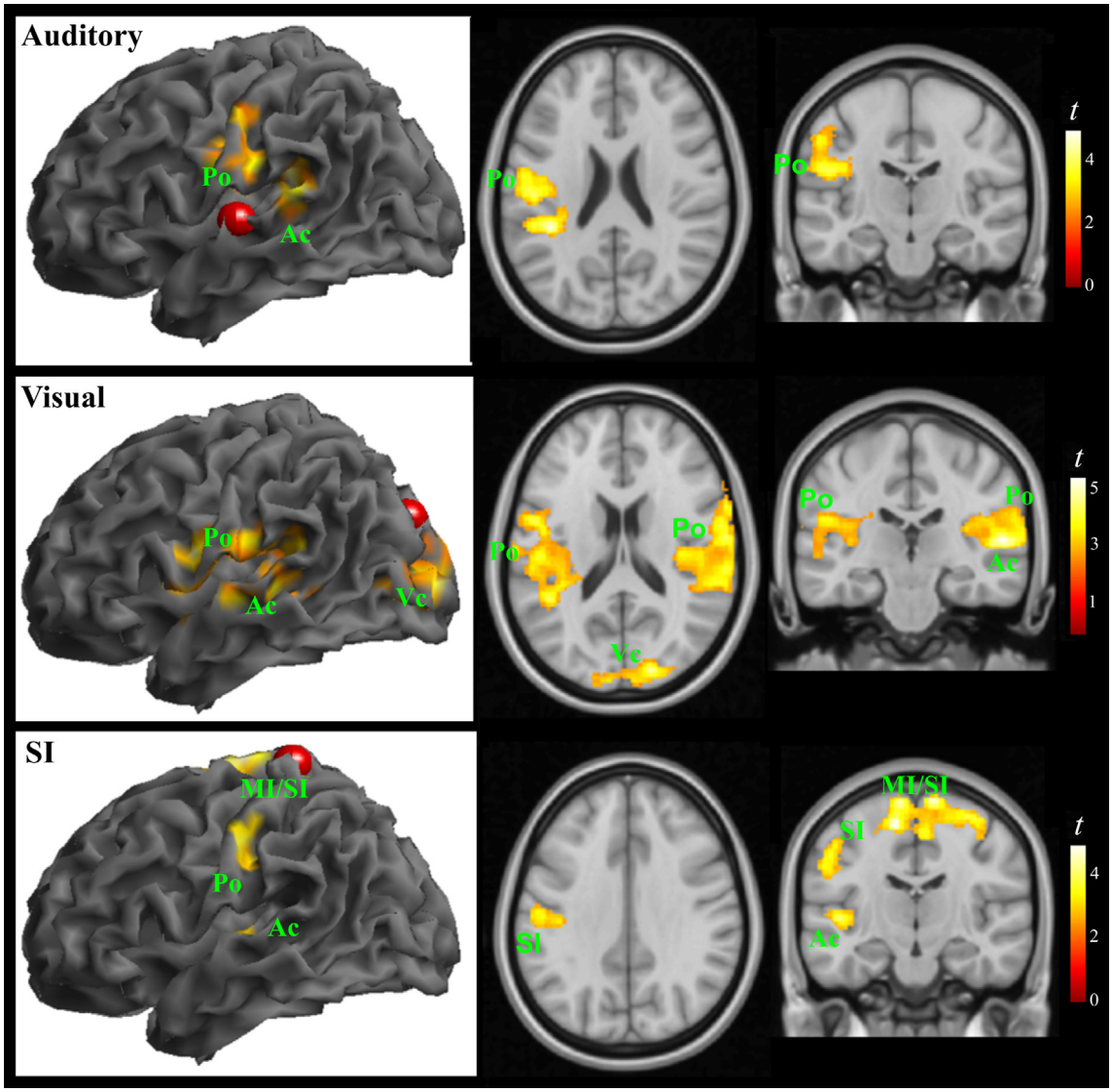

Fig. 4. Functional connectivity between-group differences in the auditory, visual, and primary somatosensory seed maps (fibromyalgia < controls). The overall pattern illustrates the reciprocal reduction of connectivity between these regions and the left parietal operculum. Red spheres indicate seed locations. The right hemisphere corresponds to the right side of axial and coronal views. Po, parietal operculum; Ac, auditory cortex; Vc, visual cortex; SI, primary somatosensory cortex; MI, primary motor cortex.

Within the fibromyalgia group, subjective pain ratings showed a significant positive correlation (more pain associated with more connectivity) with measurements of functional connectivity between the parietal operculum and PCC, anterior cingulate cortex, left angular gyrus (elements of the default mode network), and the left prefrontal cortex (Fig. 5 and Supplementary Tables 4–6). Again, similar correlational results were obtained after the inclusion of patients' HADS scores as covariates.

3.4. Multiple regression analysis

The results overall indicate that clinical pain was associated with functional connectivity disturbances at (1) basic levels of pain modulation involving the PAG; (2) cortical sensory areas; and (3) parietal operculum/default-mode network interaction. A multiple regression analysis including the measurements from the 3 levels showed that each accounted for significant, unique pain score variance in patients (Fig. 6). In a stepwise approach, (1) a measurement representing the average connectivity between parietal operculum and the other sensory cortices (middle seed map); (2) connectivity between parietal operculum and PCC (posterior seed map); and (3) connectivity between PAG and left insula entered the equation, accounting for 71% of pain score variance (adjusted *R* square, 0.71).

4. Discussion

We have investigated the association between the degree of clinical pain and resting-state functional connectivity measurements at different levels of sensory integration. A combination of changes was identified, accounting for a relevant part of pain score variance. Clinical pain correlated with reduced connectivity between PAG and anterior insula, reduced connectivity between the parietal operculum and primary somatosensory, visual and auditory cortices, and increased connectivity between the parietal operculum and elements of the default mode network. Overall, the data suggest a strong association of clinical pain with a general weakening of sensory integration in fibromyalgia.

Although high levels of anxiety and depression are common in fibromyalgia patients, in this study, both symptom domains exhibited a weak linear relationship with pain ratings and were not

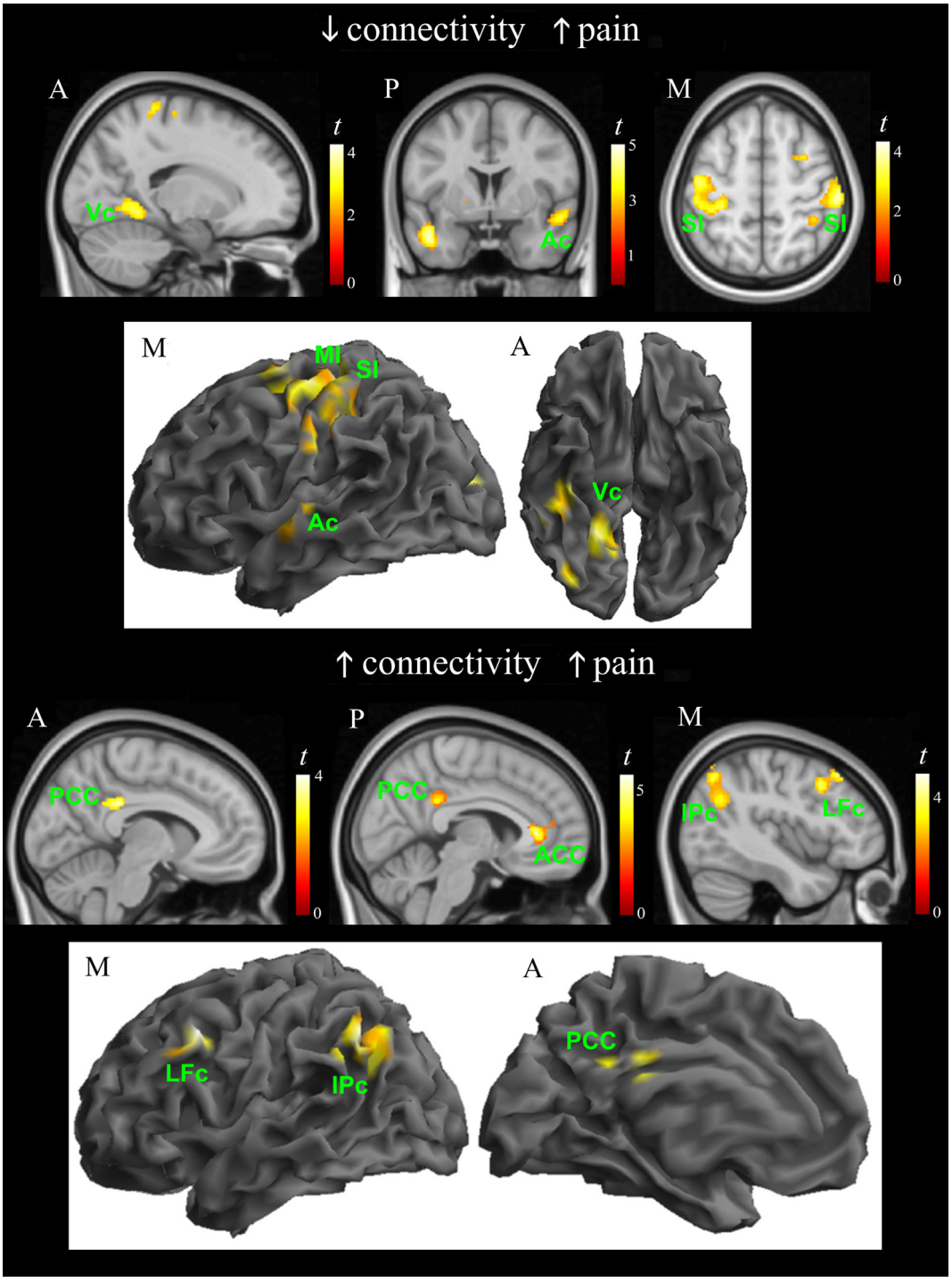

Fig. 5. Correlation analysis results in patients. The severity of clinical pain was associated with functional connectivity reduction (top panels) and increase (bottom panels) between the left parietal operculum and specific brain areas. A combination of findings is shown from the 3 parietal operculum seed maps (A, anterior; M, middle; P, posterior) in order to illustrate the approximate resemblance between the pattern of between-group differences (Fig. 3) and the pattern of correlations. The right hemisphere corresponds to the right side of axial and coronal views. Vc, visual cortex; Ac, auditory cortex; SI, primary somatosensory cortex; MI, primary motor cortex; PCC, posterior cingulate cortex; ACC, anterior cingulate cortex; IPc, inferior parietal cortex; LFc, lateral frontal cortex.

found to mediate the correlation between pain and functional connectivity at rest. These results are consistent with the study by Jensen et al. [35] and suggest, overall, that the interaction between negative affect and pain in fibromyalgia is likely a complex one.

The amygdala and the insula are 2 major components of the descending limbic input to the PAG [40]. We have identified a reduction in functional connectivity within this early pain modulation pathway, which may suggest downregulation of the cerebral influence upon the PAG. In normal circumstances, the PAG exerts tonic inhibition on the ascending sensory system [47,65]. A reduction of this tonic effect is thought to be a contributor to many chronic pain conditions and to fibromyalgia, specifically [44,53,65]. Thus, the abnormal PAG connectivity pattern observed here gives further support for a deficient sensory signal filtering in fibromyalgia, which may concur with alterations in other relevant (non-PAG-mediated) endogenous analgesia pathways [25].

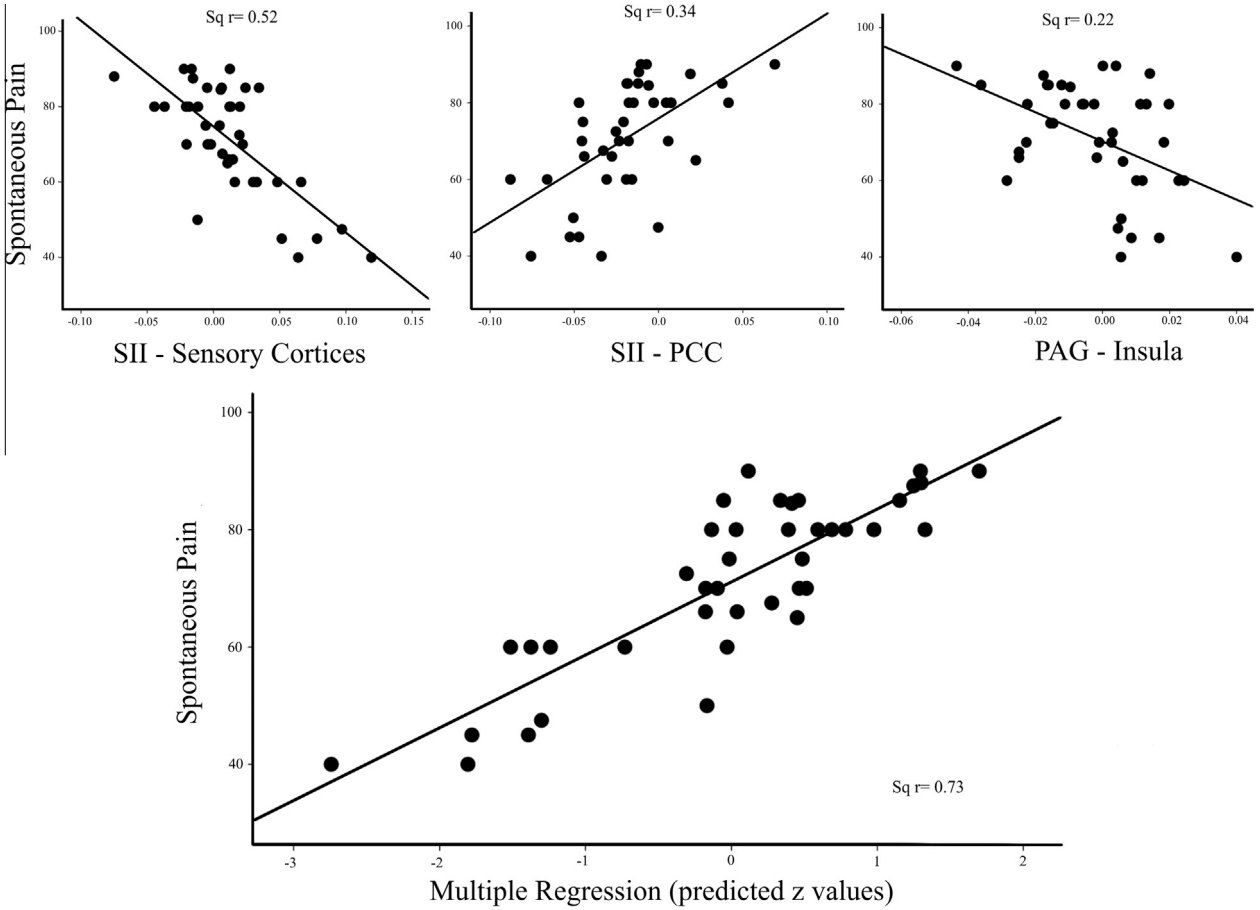

Fig. 6. Plots of the correlations between clinical pain and functional connectivity measurements. Clinical pain was measured using a 101-point numerical rating scale and functional connectivity with ".con" values representative of the correlation between the "seed region" and the functionally connected regions. SII, secondary somatosensory cortex; PCC, posterior cingulate cortex; PAG, periaqueductal gray. All correlations were significant at $P < 0.005$.

We found important regional connectivity degree reduction in the parietal operculum involving SII. The seed-based approach reciprocally demonstrated a specific alteration in functional connectivity between the parietal operculum and visual, auditory, and primary somatosensory areas. This result suggests a general weakening of sensory cortex connectivity in patients at rest that showed a consistent correlation with the severity of clinical pain. To some extent, this association may appear paradoxical if one expects pain to correlate with upregulation in sensory cortices. However, our results may perhaps be best interpreted in line with a classical perspective on how pain perceptions are generated [30].

In 1920, Head [30] proposed that pain might result from an imbalance between protopathic (poorly localized pain) and epicritic (fine discriminations of touch) sensory functioning. In this framework, there is no debate that the nociceptive system processes pain signals and that pain is proportional to the nociceptive input, but the tone of activity in the opponent epicritic module may have a role in enhancing or attenuating pain experience. A balance mechanism at the spinal cord was later a fundamental component of the "gate control" theory of mutual competition between pain and tactile signals [45]. Importantly, the existence of reciprocal inhibitory influences between responses to noxious stimuli and tactile stimuli has been recently demonstrated at the cortical level in humans [34]. Therefore, arguments exist to suggest how spontaneous pain may correlate with downregulation of the nonnociceptive component of somatosensory processing. Reduced (effective) connectivity between left-hemisphere primary and secondary somatosensory cortices was recently identified as the most striking difference between fibromyalgia patients and control subjects during heat painful stimulation [16].

In provocation studies, the parietal operculum is regularly involved in the response to painful stimulation [41,59,68]. The role of the parietal operculum, however, is not limited to pain processing. This area, mostly including SII, participates in the integration of sensory information, both within the somatosensory modalities (fine touch and pain) and across sensory modalities (somatosensory, visual, and auditory) in combination with posterior insula [39,46,57,69]. In the current study, we have shown that SII is functionally connected with the major sensory cortical domains in healthy subjects, and that the functional connectivity of SII is reduced in fibromyalgia patients. Abnormal response to nonsomatic (visual, auditory, and olfactory) sensory stimulation has been reported in clinical and experimental studies in fibromyalgia [24,32,43,73,74], which together suggest a poor integration of general sensory information.

To what extent may reduced sensory cortex connectivity be considered a primary pathophysiological factor in fibromyalgia? Using the analogy of neuropathic pain, spontaneous pain may be a consequence of partial damage in the nociceptive system, with a subsequent nociceptive system hyperexcitability [4,15] and a secondary inhibition of the transmission of tactile signals [1,33,48,56]. In this context, primarily sensitized fibromyalgia patients would show a hyperreactive nociceptive system (with enhanced response to pressure stimuli) and secondary tonic inhibition of general sensory processes (allowing spontaneous pain to

emerge in the absence of painful stimulation). The scenario may also be more complex. A number of studies suggest that nociceptive pathway damage may not be sufficient for the development of neuropathic pain [15,20,22], and that alteration in the touch pathway may be necessary in this circumstance [18,52]. Moreover, cortical sensitization to pain can be generated experimentally with dorsal column (touch) pathway deafferentation with no spinothalamic (pain) pathway damage [76]. Therefore, the question of primary pathophysiological correlates in fibromyalgia appears to remain open. The possibility exists that both enhanced nociception and reduced opponent sensory processes contribute primarily to pain sensitization in a different proportion in different patients.

Functional connectivity alterations associated with clinical pain appear to additionally involve the interaction between sensory cortex and other neural systems. Based on a different data analysis approach, Napadow et al. [51] identified abnormal functional coupling between the operculum-insula region and both the default mode network and the executive attentional network, that correlated with spontaneous pain severity. The default mode network, relevant to situational self-awareness, is a highly active network during resting-state conditions and is normally negatively correlated with the operculum-insula region, relevant to somatic body awareness [11,27,28,37,58,63]. We have previously shown that both default and operculum-insula systems may synchronize when attentional demands increase [27]. Our current findings and those from Napadow et al. [50,51] both show a shift from negative to positive correlation in fibromyalgia as seen in the high attention states [27]. This alteration pattern may be relevant to the proposal of fibromyalgia as a hypervigilance condition with sustained attention to pain sensation [17,32,43]. A similar change in the coupling between the default network and anticorrelated networks was identified in chronic back pain, which was interpreted as a lasting effect of pain on brain function [3]. It may be relevant to test in future studies whether such a connectivity alteration specifically corresponds to enhanced attention to spontaneous pain perceptions.

Aside from the discussion of their primary/secondary pathophysiological role, our findings may be relevant in the context of pain treatment. Some pain-relieving procedures are founded on the competition between nociceptive and nonnociceptive (touch, proprioception, and vibration) sensory modalities, whereas other strategies aim at normalizing higher-order sensory representations [31,49,61]. Procedures tested to treat fibromyalgia with a range of success include peripheral nerve stimulation [19], vibrotactile stimulation [66], whole-body vibration therapy [54], heated water body stimulation, aerobic exercise [10], body awareness therapy [38], and cognitive behavioral therapy [10]. Therefore, a variety of tested treatments are primarily focused on increasing the tone of nonnociceptive sensory activity. Importantly, our results may contribute to provide a stronger rationale to empirical treatment approaches.

We have used one of several possible approaches to explore the correlates of clinical pain that allowed us to establish the relationships of overall pain severity with functional connectivity changes. Other procedures permit one to assess the dynamic coupling of pain fluctuations with brain activity. Interestingly, a study using a continuous rating of ongoing back pain showed the association of current pain with sustained activity in brain areas concerning the self [2]. Our approach and direct dynamic assessments may complement each other to characterize brain changes associated with fibromyalgia pain. Another limitation is that most patients were taking antidepressants or other psychoactive drugs at the time of the assessment. Given that these drugs affect neural function, a contribution of medication to the identified functional connectivity alterations cannot be excluded. Also, although global brain, CSF, and white matter signal fluctuations were used as confounding variables to remove physiological noise as a conventional approach, a more optimal correction would have been to incorporate actual cardiac and respiratory physiological data. Finally, we used a relatively short acquisition time (6 minutes) that may reduce the consistency of functional connectivity measurements. However, we also note evidence suggesting that resting-state connectivity strengths appear to stabilize with acquisition times as brief as 5 minutes [70].

4.1. Conclusion

Our results agree with previous research demonstrating abnormal functional connectivity in fibromyalgia patients, and suggest that weakening of sensory integration occurs at different levels of processing. Reduced functional connectivity in these patients extended beyond the somatosensory domain and implicated visual and auditory sensory modalities. Overall results suggest that a disturbance in the balance between nociceptive and nonnociceptive sensory tone may be relevant to spontaneously perceived pain. Future research will be necessary to reveal the origin of the identified functional connectivity alterations and their role in the maintenance of fibromyalgia.

Conflicts of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.pain.2014.04.028.

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