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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.

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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

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