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Increased power spectral density in resting-state pain-related brain networks in fibromyalgia

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ABSTRACT

Fibromyalgia (FM), characterized by chronic widespread pain, is known to be associated with heightened responses to painful stimuli and atypical resting-state functional connectivity among pain-related regions of the brain. Previous studies of FM using resting-state functional magnetic resonance imaging (rs-fMRI) have focused on intrinsic functional connectivity, which maps the spatial distribution of temporal correlations among spontaneous low-frequency fluctuation in functional MRI (fMRI) resting-state data. In the current study, using rs-fMRI data in the frequency domain, we investigated the possible alteration of power spectral density (PSD) of low-frequency fluctuation in brain regions associated with central pain processing in patients with FM. rsfMRI data were obtained from 19 patients with FM and 20 age-matched healthy female control subjects. For each subject, the PSDs for each brain region identified from functional connectivity maps were computed for the frequency band of 0.01 to 0.25 Hz. For each group, the average PSD was determined for each brain region and a 2-sample *t* test was performed to determine the difference in power between the 2 groups. According to the results, patients with FM exhibited significantly increased frequency power in the primary somatosensory cortex (S1), supplementary motor area (SMA), dorsolateral prefrontal cortex, and amygdala. In patients with FM, the increase in PSD did not show an association with depression or anxiety. Therefore, our findings of atypical increased frequency power during the resting state in pain-related brain regions may implicate the enhanced resting-state baseline neural activity in several brain regions associated with pain processing in FM.

1. Introduction

Fibromyalgia (FM) is a disorder characterized by chronic widespread pain [27]. Although the mechanisms behind this chronic pain syndrome remain unclear, studies using stimuli-evoked functional magnetic resonance imaging (fMRI) have demonstrated an apparent association of FM with altered central pain processing, which produces heightened responses to painful stimuli (hyperalgesia) and painful responses to nonpainful stimuli (allodynia) [2,6,12,26]. In addition, recent studies of FM using resting-state fMRI (rs-fMRI) have demonstrated a dysfunction of central pain processing in patients with FM at rest. A recent study using rs-fMRI delineated the increased connectivity between the insula and the default mode network, a brain region related to evoked pain processing, hyperexcitability, and elevated intrinsic connectivity to the insula, which is linked to increasing spontaneous pain in patients with FM [21]. A more recent longitudinal study using rs-fMRI demonstrated that intrinsic connectivity between the insula and the default mode network was reduced, and this reduction showed a correlation with reductions in pain [20].

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rs-fMRI examines intrinsic spontaneous low-frequency fluctuations of the blood oxygen level–dependent (BOLD) signal, which is characterized as ongoing neural and metabolic activity that occurs in the resting state [9]. Spontaneous low-frequency fluctuations of the BOLD signal can be analyzed in either time-space or frequency-space. In analyzing fMRI resting-state data in time-space, previous rs-fMRI studies of FM have focused on intrinsic functional connectivity, which maps the spatial distribution of temporal correlations among spontaneous low-frequency fluctuation (LFF) in fMRI resting-state data [4,6,20,21].

In the current study, we investigated the impact of chronic pain in FM using a new approach. We studied rs-fMRI in frequency-space using a BOLD signal of 0.01 to 0.25 Hz oscillatory band (corresponding to 1 cycle per 4 to 100 s). Although the slow fluctuation of BOLD signal in the healthy subjects is usually below 0.1 Hz (corresponding to 1 cycle per 10 s), we investigated this frequency band because a recent observation showed abundant activity at 0.12 to 0.25 Hz in patients with chronic pain [16]. In contrast to functional connectivity, which measures temporal correlations between brain regions in time-space, the amplitude of LFF, which is often measured in terms of power spectral density (PSD), provides valuable information on regional characteristics of spontaneous LFF [8,10,33,34]. A recent study using rs-fMRI and PSD analysis demonstrated stronger spectral power at 0.12 to 0.25 Hz in the insula cortices of both hemispheres in patients with chronic pain when compared with that of control subjects [19]. In addition, accumulating evidence has indicated that the amplitude of LFF may reflect regional spontaneous neural activity and cerebral metabolic rate (such as glucose or oxygen consumption) during resting baseline state [11,29,34].

The aim of the current study was to compare the PSD of low-frequency fluctuation among brain regions associated with pain processing in patients with FM and control subjects. Specifically, we focused on the possible alteration of PSD in brain regions composing pain-related brain networks, including affective-cognitive and sensory-discriminative components.

2. Methods

2.1. Subjects

We included 19 patients with FM (all female subjects; mean age 40.89 ± 6.72) and 20 age-matched female healthy control subjects (mean age 38.10 ± 8.16) in this study. Patients were diagnosed with FM using classification criteria proposed by the American College of Rheumatology in 1990 [28]. The control subjects were recruited volunteers, all of whom had undergone screening for chronic widespread pain, generalized weakness, sleep disturbance, and specific tender points. Patients with FM were recruited from outpatient rheumatic clinics at 4 university-based hospitals and from 1 general hospital. All subjects in the fMRI study gave written informed consent and the local Institutional Review Board approved the protocol for this study.

2.2. Clinical and psychological measurements for FM

Demographic, psychological, and clinical data, including age, education, intelligence quotient, disease duration, and tender-point count were acquired from medical records and an interview with each subject at the time of enrollment in the study. The patients with FM underwent a manual tender-point survey to calculate the number of tender points based on direct palpation of 18 specific anatomical positions using a force of 4.0 kg/m^2. The patients completed the Korean version of fibromyalgia impact questionnaire (FIQ) that was used for evaluation of the functional abilities of patients with FM. The brief fatigue inventory (BFI) was used for fatigue assessment [31]. The Beck depression inventory (BDI) and the Beck anxiety inventory (BAI) were used for evaluation of the severity of depression [15] and the severity of anxiety [30], respectively.

2.3. Resting state BOLD fMRI data acquisition

All MRI data were acquired with a 3.0T MR scanner (HD, General Electric Healthcare, Milwaukee, WI, USA) equipped with a transmit-receive body coil and a commercial 8-element head coil array. High-resolution T1-weighted anatomical images were obtained using a 3D-fast spoiled gradient echo sequence (repetition time TR = 8.1 ms, echo time TE = 3 ms, flip angle = 20, matrix = 256 × 256, FOV = 22 mm, and 1.3 mm thickness with no gap). Resting-state BOLD images were obtained using an echo planar-imaging sequence (repetition time TR = 2000 ms, echo time TE = 30 ms, flip angle = 90, matrix = 64 × 64, FOV = 22 mm, and 4 mm thickness with no gap). Total scan time was 8 m to obtain 240 volumes. During the scan, subjects were given no task but were instructed to stay alert and keep their eyes closed.

2.4. Data preprocessing

Preprocessing and statistical analyses of rs-fMRI data were carried out with the statistical parametric mapping software SPM5 (http://www.fil.ion.ucl.ac.uk/spm/), including slice-timing, realignment, normalization into a Montreal Neurological Institute template based on the standard stereotaxic coordinate system, and spatial smoothing with an 8-mm (full-width at half-maximum) Gaussian kernel. Rs-fMRI data were then prepared for further seed correlation mapping and analysis of PSD of low-frequency BOLD fluctuations.

2.5. Resting-state functional connectivity

Functional connectivity was determined using a seed-based method similar to that described previously [25]. In brief, using the Functional Connectivity SPM5 toolbox (http://web.mit.edu/swg/software.htm), the functional connectivity, which had strong temporal correlation with a seed point of anterior insula, was calculated. The functional connectivity, which had strong temporal correlation with posterior insula was also calculated. Anterior and posterior insular, which are key nodes in the processing of the affective (emotional) aspects of pain and in the processing of the sensory-discriminative aspects of pain, respectively, were identified using MarsBaR toolbox (Marseilles, France; http://marsbar.sourceforge.net/). To correct for cofluctuations in BOLD signal due to noise, cerebrospinal fluid, white matter, motion parameters, and global signals were used as nuisance covariates. For head motion, there was no significant difference in mean motion between groups. Additionally a band-pass filter (0.01 to 0.25 Hz) was used. For within-group analysis, the SPM{t}s was given a threshold of $P < 0.05$; the false discovery rate was corrected for multiple comparisons across the whole brain statistical parametric mapping SPM{t}. A 2-sample t test was performed for direct comparison of the connectivity between the patients with FM and controls. SPM{t}s were assigned the threshold of $P < 0.05$, false discovery rate–corrected for multiple comparisons across the whole brain.

2.6. Power spectral density analysis

PSDs were calculated at the anatomically defined brain regions, which were identified from a functional connectivity anchored by anterior insula and a functional connectivity anchored by posterior insula using MarsBaR toolbox (Supplemental Table S1). In addition, as a control brain region, PSD was also calculated at the visual