Neuroscience Letters 640 (2017) 99–104

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Research article

Abnormal regional spontaneous neuronal activity associated with symptom severity in treatment-naive patients with obsessive-compulsive disorder revealed by resting-state functional MRI

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HIGHLIGHTS

- Decreased fALFF in thalamus was observed in treatment-naive OCD patients.
- Decreased fALFF in brain areas outside the CSTC circuits were also found.
- Decreased fALFF associated with symptom severity in treatment-naive OCD patients.
- Brain areas outside the CSTC circuits may play a role in the pathophysiology of OCD.

ARTICLE INFO

Article history:
Received 3 November 2016
Received in revised form
26 December 2016
Accepted 11 January 2017
Available online 16 January 2017

Keywords:
Obsessive-compulsive disorder
Resting-state
Functional magnetic resonance imaging (fMRI)
Fractional amplitude of low-frequency fluctuation (fALFF)
Spontaneous brain activity

ABSTRACT

A large number of neuroimaging studies have revealed the dysfunction of brain activities in obsessive-compulsive disorder (OCD) during various tasks. However, regional spontaneous activity abnormalities in OCD are gradually being revealed. In this current study, we aimed to investigate cerebral regions with abnormal spontaneous activity using resting-state functional magnetic resonance imaging (fMRI) and further explored the relationship between the spontaneous neuronal activity and symptom severity of patients with OCD. Thirty-one patients with OCD and 32 age-and sex-matched normal controls received the fMRI scans and fractional amplitude of low-frequency fluctuation (fALFF) approach was applied to identify the abnormal brain activity. We found that patients with OCD showed decreased fALFF not only in the cortical-striato-thalamo-cortical (CSTC) circuits like the thalamus, but also in other cerebral systems like the cerebellum, the parietal cortex and the temporal cortex. Additionally, OCD patients demonstrated significant associations between decreased fALFF and obsessive-compulsive symptom severity in the thalamus, the paracentral lobule and the cerebellum. Our results provide evidence for abnormal spontaneous neuronal activity in distributed cerebral areas and support the notion that brain areas outside the CSTC circuits may also play an important role in the pathophysiology of OCD.

1. Introduction

Obsessive-compulsive disorder (OCD) is a chronically disabling disorder marked by recurrent intrusive thoughts (obsessions) and repetitive behaviors (compulsions), which has a prevalence of 2–3% in the general population [1,2]. Although the exact etiology of OCD remains unknown, convergent evidence from neuro-imaging stud-

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http://dx.doi.org/10.1016/j.neulet.2017.01.024
0304-3940/

ies suggest that the dysfunction of cortico-striato-thalamo-cortical (CSTC) circuits play a core role in the pathophysiology of OCD [3,4]. The abnormal function of structures within the CSTC circuits has been proposed to be related to the neural basis for key symptoms in patients with OCD [5]. However, increasing evidence from recent studies have indicated that more extensive brain abnormalities including regions outside the CSTC circuits may also be involved in the pathophysiology of OCD [6–9].

Recently, great emphasis has been placed on the spontaneous low frequency fluctuations (LFF) in the blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI) signal, which have been suggested to be physiologically meaningful and reflect the intensity of regional spontaneous neuronal activity [10,11]. The resting-state fMRI has been proposed to be a promising approach to investigate intrinsic spontaneous brain activity [12], which has the advantage of identifying neural mechanisms that are not specific to the task employed [13]. Most of the resting-state fMRI studies focused on the functional connectivity between different cerebral areas, which have provided us with holistic information of patterns within brain networks from the perspective of functional integration [14,15]. There was also considerable advance in detection and localization of abnormal regional spontaneous neuronal activity in OCD [6,16]. For instance, Hou et al. [6] applied amplitude of low-frequency fluctuation (ALFF) to investigate spontaneous neuronal activity in OCD patients, and observed abnormalities of ALFF in the cerebellum and parietal cortex. Compared with the ALFF, the fractional amplitude of low-frequency fluctuation (fALFF) utilizes the distinct frequency properties of noise and signal and can improve the sensitivity and specificity in detecting regional spontaneous neuronal activity within the whole brain during the resting state [17]. The fALFF has been applied to directly reveal the spontaneous activity of each brain region and precisely demonstrate in which cerebral area the intrinsic activity is altered in many psychiatric disorders such as schizophrenia, depression and OCD [18–20]. According to Cheng et al. [20], they discovered alterations in the cingulate cortex, cerebellum, parietal lobe, brainstem and the precentral lobe in patients with OCD through the fALFF analysis.

However, the abnormality of spontaneous neuronal activity in patients with OCD has not been totally elucidated. Information obtained from existing studies of OCD using the ALFF or fALFF approach is insufficient and inconsistent [6,20]. Divergence in the results from previous studies could be attributed to the inclusion of medicated patients, the influence of psychotherapy, co-morbidity, and small sample size. It is therefore necessary to determine abnormal spontaneous neuronal activity based on treatment-naive OCD patients and bigger sample size. In our previous study, we demonstrated abnormal functional connectivity of brain network in treatment-naive patients with OCD with a voxel-based graph analysis [8]. In the present study, we employed a different approach using resting-state fMRI and fALFF analysis to examine regional spontaneous brain activity changes and the relationship between symptoms and local brain spontaneous activity in said patients. We aimed to explore whether there would be any other dysfunctional cerebral areas outside the traditional CSTC circuits in patients with OCD, and further investigate the relationship between fALFF values and clinical symptoms.

2. Methods

2.1. Subjects

Thirty-one OCD diagnosed patients were recruited from the outpatient clinic of Wuxi Mental Health Center, Nanjing Medical University, China, and 32 age-and sex-matched healthy controls (HCs) were recruited from the local community participated in this study. The study was approved by the Medical Ethics Committee of Wuxi Mental Health Center, Nanjing Medical University, China. Subjects were required to give written informed consent before participating in the study. All patients had a current diagnosis of OCD according to DSM-IV-TR criteria [21] and none had been treated with psychotropic drugs or psychotherapy. The severity of OCD symptoms was evaluated using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) [22]. The 24-item Hamilton Rating Scale for Depression (HDRS-24) and the Hamilton Anxiety Rating Scale (HARS) were used to rate the severity of depressive and anxious symptoms, respectively [23,24]. All participants were right-handed when assessed by Edinburgh Handedness Inventory [25]. Exclusion criteria were intracranial pathology, brain injury, neurological illness, substance abuse, contraindications of MRI, and excessive head motion in the subsequent data analysis (see 2.3 Data processing). Eventually, twenty-nine treatment-naive patients with OCD and 29 demographically matched HCs were included in the imaging analysis, and their demographic and clinical characteristics were summarized in Table 1. All participants were enrolled in our previous fMRI study which approached a different issue using a different method [8].

2.2. Data acquisition

Imaging data were acquired using a 3.0-Tesla Magnetom Trio Tim (Siemens Medical System, Erlangen, Germany) at the Department of Medical Imaging, Wuxi People's Hospital, Nanjing Medical University. Foam pads were used to reduce head motion and scanner noise. Prior to the scan, subjects were instructed to keep their eyes closed, relax but not to fall asleep, and move as little as possible during data acquisition. A 3D magnetization-prepared rapid acquisition gradient-echo sequence was used to obtain high-resolution whole brain volumetric T1-weighted images with the following parameters: time repetition (TR) = 2530 ms, time echo (TE) = 3.44 ms, flip angle = 7°, matrix size = 256 × 256, field of view (FOV) = 256 × 256 mm^2, 192 sagittal slices, slice thickness = 1 mm, acquisition voxel size = 1 × 1 × 1 mm^3, total acquisition time = 649 s. After structural MRI scans, resting-state fMRI scans were obtained using a gradient-echo planar imaging sequence with the following parameters: TR = 2000 ms, FOV = 220 × 220 mm^2, TE = 30 ms, flip angle = 90°, matrix size = 64 × 64, 33 axial slices, slice thickness = 4 mm, acquisition voxel size = 3.4 × 3.4 × 4 mm^3, resulting in 240 vol.

2.3. Data processing

MRI data analysis was executed using the standard pipeline integrating SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) and REST (http://restfmri.net/forum/REST_V1.8) as implemented in DPARSF [26]. For image preprocessing, the first 10 vol were discarded to allow the magnetization to reach equilibrium. The remaining 230 fMRI images were corrected for slice-timing, and realigned for head movement correction. Two patients with OCD and 3 HCs were excluded due to excessive head motion cumulatively in any direction more than 3 mm and/or 3°. Regarding the confounding influence of micro-movements in intrinsic functional connectivity, mean framewise displacement was computed and compared between remaining 29 OCD patients and 29 HCs [27] providing comparable evidence ($P > 0.05$). Each subject's T1-weighted image was coregistered to the mean functional image and segmented into gray matter, white matter, cerebrospinal fluid tissue maps and nonlinearly registered into the Montreal Neurological Institute (MNI) space using a unified segmentation algorithm which also provided the transformation parameters from individual native space to standard MNI space for functional images. Next,