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Research paper

Abnormal resting-state functional connectivity of the left caudate nucleus in obsessive-compulsive disorder

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HIGHLIGHTS

- OCD showed decreased functional connectivity within CSTC circuit at rest.
- OCD displayed increased functional connectivity outside CSTC circuit at rest.
- Functional connectivity within CSTC circuit related with OCD illness duration.

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ABSTRACT

Altered brain activities in the cortico-striato-thalamocortical (CSTC) circuitry are implicated in the pathophysiology of obsessive-compulsive disorder (OCD). However, whether the underlying changes occur only within this circuitry or in large-scale networks is still not thoroughly understood. This study performed voxel-based functional connectivity analysis on resting-state functional magnetic resonance imaging (fMRI) data from thirty OCD patients and thirty healthy controls to investigate whole-brain intrinsic functional connectivity patterns in OCD. Relative to the healthy controls, OCD patients showed decreased functional connectivity within the CSTC circuitry but increased functional connectivity in other brain regions. Furthermore, decreased left caudate nucleus-thalamus connectivity within the CSTC circuitry was positively correlated with the illness duration of OCD. This study provides additional evidence that CSTC circuitry may play an essential role and alteration of large-scale brain networks may be involved in the pathophysiology of OCD.

1. Introduction

Although the pathophysiology of obsessive-compulsive disorder (OCD) remains unclear, most neuroimaging studies tend to emphasize abnormalities in the cortico-striato-thalamo-cortical (CSTC) circuitry, which includes the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), prefrontal cortex (PFC), striatum and thalamus, and associates with the cognitive, affective, and behavioral symptoms of OCD [1,2]. Nonetheless, structural and functional changes in large-scale brain regions including the temporal, occipital, and cerebellar cortices have also been reported in OCD [3–7]. Therefore, an important question remains unanswered as to whether underlying OCD pathophysiology is driven by functional connectivity changes only within the CSTC circuitry or in large-scale networks.

Multiple OCD neuroimaging studies have consistently reported abnormalities in the caudate nucleus [3,8–10], some even suggested that these abnormalities may be an OCD-specific feature [3,11]. The caudate nucleus receives inputs from the OFC, ACC, and PFC. It selects, mediates, and produces new activity patterns that are forwarded to the basal ganglia and then projected back to the OFC, ACC, and PFC via the thalamus [12]. These brain regions influence each other via parallel corticostriatal loops [12]. Previous OCD resting-state functional magnetic resonance imaging (RS-fMRI) studies that have used the caudate nucleus as a region-of-interest (ROI) in seed-based analyses have reported increased functional connectivity between the caudate nucleus and the OFC,

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Table 1
Demographic and clinical data of subjects.

	OCD patients (n = 30)	Healthy controls (n = 30)	p Value
Age (years)	26.23 ± 5.69	28.17 ± 7.65	0.27
Sex (male/female)	24/6	23/7	1.00
Education (years)	13.10 ± 2.67	13.13 ± 4.10	0.97
Illness duration (months)	66.43 ± 48.53	NA	
Y-BOCS,			
Total score	23.77 ± 6.85	0.20 ± 0.41	0.00
Obsession score	14.03 ± 3.33	0.20 ± 0.41	0.00
Compulsion score	9. 73± 6.18	0.00 ± 0.00	0.00
HAMD total score	10.80 ± 5.72	2.33 ± 0.92	0.00
HAMA total score	12.80 ± 6.70	1.40 ± 0.67	0.00

OCD, obsessive compulsive disorder; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale; HAMD, 17-item Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale. Data are presented as mean ± standard deviation or number or frequency.

dorsolateral prefrontal cortex (DLPFC), and ventral medial prefrontal cortex [13,14]. Interestingly, the level of altered functional connectivity between the OFC and ventral caudate nucleus was positively correlated with OCD symptoms [14]. These findings suggest that the caudate nucleus plays an important role in the pathophysiology of OCD and can be used effectively as a ROI for a resting-state functional connectivity analysis in OCD.

RS-fMRI measures spontaneous changes in the blood-oxygen-level dependent (BOLD) activation signal, which indirectly reflects changes in the intrinsic neuronal activity at rest. Regional homogeneity (ReHo) measures synchronization of local BOLD signal fluctuations in neighboring voxels, based on the assumption that a common functional brain unit will have temporally homogeneous variations in the BOLD signal in all of its encompassing voxels [15]. ReHo permits the exploration of these unpredictable hemodynamic responses, which can help identify the underlying characteristics of the resting-state brain activity [15].

Recent studies have successfully tested the combined relationship between changes in the amplitude of low-frequency fluctuations and functional connectivity in both seasonal affective disorder and healthy aging [16,17]. ReHo changes may be related to altered levels of neurotransmitters in local brain regions, which may subsequently alter information transmission to more distant brain regions and thus the functional organization of large-scale functional networks [17]. As a result, ReHo analysis can be used in conjunction with a voxel-based whole-brain functional connectivity analysis to explore the effects of regional dysfunction on the large-scale architecture of whole-brain functional networks. Applying this analysis to OCD could yield greater insights about the functional changes underlying OCD pathology.

This study used ReHo analysis to identify local regions of altered resting-state synchrony in OCD patients. Following this initial step, we used the most functionally relevant region from the ReHo analysis (the left caudate nucleus) as a ROI to investigate its voxel-based whole-brain intrinsic functional connectivity patterns in OCD. We tested the following three hypotheses: (1) OCD patients will exhibit increased functional connectivity within the CSTC circuitry (in particular in the OFC, ACC and DLPFC); (2) the altered functional connectivity (i.e., the caudate nucleus-OFC connectivity) will be correlated with the clinical presentation of OCD; and (3) the ReHo of the caudate nucleus will be correlated with altered functional connectivity in OCD.

2. Materials and methods

2.1. Participants

Thirty-two outpatients with OCD were recruited from the Qiqihar Mental Health Center and the Fourth Affiliated Hospital of Qiqihar Medical University. The Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 4th edition was used to confirm the diagnosis of OCD [18]. The Yale-Brown Obsessive Compulsive Scale (Y-BOCS) [19], the 17-item Hamilton Rating Scale for Depression (HAMD) [20], and the Hamilton Anxiety Rating Scale (HAMA) [21] were used to rate the severity of the OCD symptoms, depression, and anxiety symptoms respectively. Only patients with a score of 16 or more on the Y-BOCS scale, and a score of less than 18 on the HAMD-17 scale were included in the study. All clinical volunteers enrolled in the study were right-handed and 18–60 years of age. Patients with a history of neurological disorders, major physical diseases, or any history of psychiatric disorders other than OCD were excluded. Data from two patients was excluded because of poor quality (see image preprocessing). For the remaining 30 patients, four had never taken any medications for OCD; six had not taken medications for OCD in the past month; and 20 were on stable doses of selective serotonin reuptake inhibitors (SSRIs) at the time of the scan.

Thirty healthy controls were also recruited from the local community using the Structured Clinical Interview for DSM-IV Axis I Disorders-Non-patient Edition [22]. None of the healthy controls had any neurological illness, major physical diseases, psychiatric disorders, or any family history of major psychiatric disorders. The 30 case-control pairs were matched for age, sex, and years of education (Table 1). This study was approved by the Research Ethics Committee at Qiqihar Medical University. All participants provided an informed consent.

2.2. Imaging data acquisition

The RS-fMRI images were acquired using a 3.0-T GE 750 Signa-HDX scanner (General Electric Healthcare, Waukesha, Wisconsin) at the Third Affiliated Hospital of Qiqihar Medical University. During scanning, all subjects were instructed to relax, close their eyes, lay as still as possible, and avoid falling asleep. RS-fMRI scans were obtained using an echo-planar imaging (EPI) sequence. The parameters were: 33 axial slices, TR = 2000 ms, TE = 30 ms, FA = 90°, thickness/gap = 3.5/0.6 mm, FOV = 200 × 200 mm, in-plane resolution = 64 × 64, and 240 vols in total (8 min). For quality assurance purposes, all of the scans were visually inspected by two independent neuroradiologists. None of the data exhibited any clinically significant structural abnormalities in anatomical or RS-fMRI volumes.

2.3. Image data preprocessing

We used Data Processing Assistant for RS-fMRI (DPARSF) [23] for image preprocessing. The first 10 time points were discarded to ensure signal stabilization. Slice timing and head motion correction were conducted. After head motion correction, the functional images were normalized to the standard EPI template in Statis-