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Research report

Cortico-striato-thalamo-cortical circuit abnormalities in obsessive-compulsive disorder: A voxel-based morphometric and fMRI study of the whole brain

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HIGHLIGHTS

- There is a consistent trend between structural and functional brain images in OCD.
- In OCD higher cortical structures showed increased gray matter volume.
- In OCD subcortical structures showed decreased gray matter volume.
- SSRIs play an important role in improving brain structure in OCD.

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ABSTRACT

The primary aim of this study was to identify structural and functional abnormalities in the brains of obsessive-compulsive disorder (OCD) patients. Another aim was to assess the effect of serotonin selective reuptake inhibitors (SSRIs) on brain structure of OCD patients. All subjects underwent brain magnetic resonance imaging (MRI) and resting functional MRI (fMRI). High-resolution three-dimensional images were processed using the voxel-based morphometry (VBM) method. The final analysis included 18 OCD patients and 16 healthy controls. In the OCD patients there was a decrease in gray matter volume in the bilateral cingulate cortex and bilateral striatum. In some cortical structures including the cerebellar anterior lobe, left orbital frontal gyrus, right middle frontal gyrus, left middle temporal gyrus, precentral gyrus, and postcentral gyrus, there was an increase in gray matter volume. On fMRI the OCD patients had overactivation of the right cerebellum and right parietal lobe and reduced activation of the left cingulate gyrus, putamen, and caudate nucleus. Eleven OCD patients who improved during 12 weeks of drug treatment with sertraline hydrochloride had a significant increase in gray matter volume in several brain structures but no significant differences were found on resting fMRI. The results indicated a consistent trend between structural and functional images. Higher cortical structures showed increased gray matter volume and increased activation as did the cerebellum whereas subcortical structures showed decreased gray matter volume and decreased activation. And brain structure improvement consisted with symptom improvement after SSRIs treatment in OCD patients.

Abbreviations: CSTC, cortico-striato-thalamo-cortical; OCD, obsessive-compulsive disorder; SSRIs, erotonin selective reuptake inhibitors; MRI, magnetic resonance imaging; fMRI, resting functional MRI; VBM, oxel-based morphometry; lOFC, lateral orbitofrontal cortex; mOFC, medial orbitofrontal cortex; dACC, dorsal anterior cingulated cortex; CBT, cognitive behavioral treatment; HAMD, Hamilton Depression Scale; FSPGR, fast spoiled gradient recalled; ACC, anterior cingulate cortex; OFC, orbitofrontal cortex.

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1. Introduction

Obsessive-compulsive disorder (OCD) is a neuropsychiatric disorder with a worldwide prevalence between 1 and 3% [1]. While many OCD patients respond to the first line of available treatment, some cases are found to be treatment resistant. With the rapid development of neuroimaging techniques, a growing number of studies indicate that dysfunction of the "cortico-striato-thalamo-cortical" (CSTC) circuits is the main pathological basis of OCD [2–4]. In recent years, it has also been reported that the pathological basis of OCD is not limited to dysfunction of CSTC circuits, because more and more evidence has demonstrated that other structures such as lateral orbitofrontal cortex (lOFC), medial orbitofrontal cortex (mOFC), dorsal anterior cingulated cortex (dACC), and the amygdalo-cortical circuits, are also important components of the pathogenesis of OCD [3].

As one of the brain imaging techniques, voxel-based morphometry (VBM) has been widely used in OCD research since it was introduced in 2000 [5]. Although all the studies focused on the structural changes of the brain regions involving the CSTC circuits, the findings are inconsistent. For example, the orbitofrontal cortex volume has been reported to be increased [6], decreased [7,8], and unchanged [9,10]; the anterior cingulate cortex volume mostly to be decreased [7,11]; the thalamus volume mostly to be increased [6]; and the striatal volume to be increased [12,13], decreased [10,14], and unchanged [15]. The inconsistency in findings may be attributed to insufficient sample size, or to some studies not excluding patients in the process of drug treatment or having comorbidities. In addition, the number of OCD patients in our country is very large, while studies reporting abnormalities in brain structures in Chinese OCD patients are very few. So far, the structural changes of the key brain regions in Chinese OCD patients remain unknown.

There are two main treatments for OCD: drug treatment (mainly serotonin selective reuptake inhibitors, SSRIs) and cognitive behavioral treatment (CBT). SSRI treatment is occasionally assessed for its efficacy by evaluation of the changes in clinical symptoms, but very few studies have tried to explore whether drugs cause changes in brain structure or function in OCD patients and reverse the course of OCD at the physical level, and thereby promote rehabilitation [16]. Therefore, the use of resting functional magnetic resonance (fMRI) should provide more structural information than assessment of clinical symptoms alone. It has been demonstrated that SSRIs may play a significant role in reversing brain structural abnormalities in OCD patients [17–19]. And adolescent OCD patients in a stable state after SSRIs showed no significant difference in brain morphology compared with control subjects [15].

The differences between Chinese and American or European cultures means that research in other populations may not be directly relevant to China; therefore, in order to address the unknown structural changes in the brain of Chinese OCD patients, the present study aimed to compare the differences in brain structures between OCD patients and healthy individuals by optimized voxel-based morphometry combined with fMRI, and to also compare the differences in brain structures before and after patients were given an SSRI.

2. Methods

2.1. Clinical data

2.1.1. Study design

This was a prospective observational study of a single cohort case group, and data from healthy individuals were used for normal reference values. The study was approved by the Ethics Committee of Hangzhou Mental Health Center and all enrolled patients signed an informed consent form before the study.

2.1.2. OCD group

Patients with severe OCD who received treatment or were hospitalized in the Hangzhou Mental Health Center in Zhejiang Province (China) from January 2012 to June 2014 were enrolled in this study. All OCD enrolled patients met the following inclusion criteria: (1) the OCD diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV); (2) the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) total score ≥ 25 and the Hamilton Depression Scale (HAMD-17) score < 18; (3) aged from 18 to 60 years, right-handed, education level at junior high school degree or above; (4) did not take SSRIs or other psychotropic drugs for 4 weeks prior to the enrollment; (5) had no metal implants. Patients were excluded if they had organic brain diseases, alcohol or drug addiction, other mental disorders in DSM-IV. Those with poor-quality MR images due to excessive head movements were not included in the statistical analysis.

After undergoing MRI examination, all OCD patients received sertraline hydrochloride treatment. The initial dose was 50 mg/day and it was increased up to 200 mg/day over 2 weeks. And after a 12-week treatment, the patients with a reduction in Y-BOCS score of not less than 50% upon reexamination were classified as having good improvement ($n = 11$) and received a second head fMRI reexamination, and the other patients with a reduction in Y-BOCS score of less than 50% were classified has having poor improvement ($n = 6$, and one lost follow-up after 3 weeks' treatment was not classified). 50% reduction was the cut-off value because this is the point at which the improvement in symptoms is considered significant.

2.1.3. Control group

All the subjects in the control group lived in the community, and met the same inclusion and exclusion criteria as patients in the OCD group, except they were not diagnosed with OCD so they did not fulfill the OCD diagnostic criteria in the DSM-IV and the Y-BOCS score > 25 categories.

2.2. Image acquisition

All subjects underwent a 3.0 T MRI examination according to the same criteria. During scanning, the subjects lied on the scanning table with their head placed in a comfortable position and fixed by a foam pad to reduce head movement. First, the positioning images were scanned, and then T1 and T2 images were scanned to confirm that there was no structural abnormality. Thereafter, three-dimensional structural MRI was performed using fast spoiled gradient recalled (FSPGR) (TR/TE = 10.5/2 ms, FOV = 240 mm, matrix size = 256×256, slice thickness = 1.8 mm) and then a resting state fMRI scan examination was performed (TR/TE = 5500/78 ms, FOV = 240 mm, matrix size = 512×512, 20 slices, slice thickness = 6.00 mm). The fMRI images were obtained by analysis of the DICOM files burned onto a CD. The images collected were read by radiologists, and no morphological abnormalities were found in any subject.

2.3. Data processing and analysis

The resulting high-resolution 3D-T structural images were processed using the optimized VBM method (Gaussian kernel = $4 \times 4 \times 4$ mm, voxel size = $3 \times 3 \times 3$) [5]. The resting state functional images were processed by the ALFF method (0.01–0.08 Hz). The data processing and statistical analysis were performed using MRIcro software (http://www.mricro.com), statistical parametric mapping SPM8 software (statistical parametric mapping, http://