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·Original Article·

Structural changes in the gray matter of unmedicated patients with obsessive-compulsive disorder: a voxel-based morphometric study

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ABSTRACT

The aim of the current study was to use whole brain voxel-based morphometry (VBM) to assess the gray matter (GM) changes in unmedicated patients with obsessive-compulsive disorder (OCD) compared with normal controls. We compared the GM volumes in 28 patients with 22 matched healthy controls using a 1.5T MRI. Three-dimensional T1-weighted magnetic resonance images were obtained from all participants. VBM was performed to detect GM volume differences between the two groups. We detected increased regional GM volumes in the bilateral middle temporal gyri, bilateral middle occipital gyri, bilateral globus pallidus, right inferior parietal gyrus, left superior parietal gyrus, right parahippocampus, right supramarginal gyrus, right medial superior frontal gyrus, and left inferior frontal opercular cortex in the OCD patients relative to controls (P <0.001, uncorrected, cluster size >100 voxels). No decreased GM volume was found in the OCD group compared with normal controls. Our findings suggest that structural changes in the GM are not limited to fronto-striato-thalamic circuits in the pathogenesis of OCD. Temporo-parietal cortex may also play an important role.

Keywords: obsessive-compulsive disorder; magnetic resonance imaging; voxel-based morphometry; gray matter

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a common psychiatric disorder, with a prevalence rate of 2–3%[1]. OCD may begin in either childhood or adulthood, and may manifest in a variety of ways. It is marked by chronic disability with concomitant impairments in interpersonal and occupational functioning[2]. Obsessions are recurrent, persistent, and intrusive ego-dystonic thoughts, impulses, or images; compulsions are repetitive behaviors or mental acts that are executed with the goal of preventing or reducing distress or preventing some dreaded event or situation (American Psychiatric Association, 2000). Due to the high prevalence, chronic course, and impaired social functioning, OCD was among the top 10 disorders in terms of years lived with illness-related disability named by the World Health Organization in 1996[3].

Morphometric MRI studies, especially the voxel-based morphometry (VBM) methods, have recently been widely used to analyze structural changes in the brain in psychiatric diseases. VBM, which is an automated technique, has allowed the investigation of between-group differences in regional gray matter (GM) volumes across the entire brain with no need to define anatomical borders. Different psychiatric disorders have GM abnormalities in different regions. For example, patients with autism spectrum disorder have a significant reduction in GM

volume in the medial temporal gyrus, fusiform and cerebellar regions[4]. Patients with schizophrenia have a significant decrease in GM volume in the right anterior cingulate, right medial frontal lobe, left middle temporal gyrus, left postcentral gyrus, and the left limbic lobe[5].

Several studies have revealed patterns of structural brain abnormalities in OCD, particularly involving fronto-striato-thalamic circuitry[6-8], but the results of the numerous papers have been inconsistent and even contradictory across investigations. For example, Valente *et al.*[9] found an increased GM volume in the posterior orbitofrontal and parahippocampal regions and decreased GM volume in the left anterior cingulate cortex in OCD patients compared with controls. Gilbert *et al.*[10] reported lower GM density in the left anterior cingulate cortex and bilateral medial superior frontal gyri in OCD patients. Christian *et al.*[11] revealed that OCD patients had significantly more GM in the left thalamus than healthy volunteers. Yoo *et al.*[12] detected a significant reduction of GM volume in the inferior frontal gyrus, medial frontal gyrus, insula, cingulate gyrus, and superior temporal gyrus. Rotge *et al.*[13] found that thalamic volumes were significantly negatively correlated with orbital frontal cortex volume in OCD patients. These varied findings may, partly, be accounted for by the heterogeneity of the illness, differences in illness duration, psychotropic medication exposure, and the diversity of neuroimaging methods.

The main purpose of our study was to determine the extent to which GM volume abnormalities are present in unmedicated OCD patients without a concomitant psychiatric disease compared with healthy controls. The results from these two groups avoided the influence of medication and comorbidity. Due to the complexity of OCD, we assumed that the GM volume change might not be confined to the fronto-striato-thalamic circuitry.

PARTICIPANTS AND METHODS

Participants

Twenty-eight unmedicated OCD patients (10 with age at onset <18 years and 18 with first course) and 22 sex-, age- and education-matched healthy controls were enrolled. All participants were Chinese and right-handed. The patients were recruited from the outpatient clinic at Shanghai Mental Health Center, Shanghai, China. The controls were recruited through print advertising. This study was approved by the Review Board of Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine. Written informed consent was given by all participants after the interview procedure and before the MRI scan.

All patients were interviewed by a licensed psychiatrist and recruited according to the DSM-IV criteria for OCD and had no relevant medical, neurological, or other major psychiatric diseases. All patients were drug-naïve or without medication for a minimum of 8 weeks before the day of scanning (10 of the 28 OCD patients had never been treated with psychotropic drugs). All patients with comorbid Axis I psychiatric disorders and a history of neurologic disorders were excluded.

The mean age of patients (n = 28) was 25.4 ± 7.2 years and of healthy controls (n = 22) was 27.9 ± 8.0 years. The mean age at onset was 19.3 ± 8.1 years (range 12–50) and the mean illness duration in the OCD group was 4.5 ± 4.1 years. There were no statistically significant differences in age, sex, education and marital status between patients and controls (Table 1).

MRI Acquisition and Image Processing

All imaging studies were performed on a 1.5-Tesla MRI scanner (GE Medical Systems, Milwaukee, WI) in Ruijin Hospital, Shanghai, China. For each participant a set of 232, 1-mm thick, contiguous axial T1-weighted images encompassing the whole brain were acquired using a three-dimensional spoiled gradient recalled echo sequence. Acquisition parameters were as follows: repetition time,

Table 1. Demographic and clinical characteristics of OCD patients and controls

	OCD group n = 28	Control group n = 22	t/χ^2	P
Age (years)	25.35 ± 7.24	27.88 ± 8.02	–1.055	0.298
Education (years)	13.73 ± 2.99	15.06 ± 4.07	–1.220	0.230
Sex			0.001	0.981
Male	19 (67.9%)	15 (68.2%)		
Female	9 (32.1%)	7 (31.8%)		
Marital status			0.010	0.919
Married	8 (28.6%)	6 (27.3%)		
Unmarried	20 (71.4%)	16 (72.7%)		

8.1 ms; echo time, 1.6 ms; flip angle, 20°; field of view, 24 cm; matrix size, 256 × 192 pixels; number of excitations, 2. Acquisition time was 7 min 14 s.

Imaging data were processed on a workstation using Matlab 2009 (MathWorks Inc., Natick, MA) and SPM software (SPM5; Wellcome Department of Imaging Neuroscience, London, UK).

DICOM files were first converted to NIFT-1 format (http://nifti.nimh.nih.gov) using the DICOM import tool of SPM5. Second, we segmented the T1-weighted images from each participant using the unified segmentation method in SPM5. This method provides a probabilistic framework to combine image registration, tissue classification, and bias correction into a generative model, and performs better than separately applying registration and tissue classification[14]. We next acquired modulated and normalized GM images in standard Montreal Neurological Institute space. Finally, these normalized GM images were smoothed with an 8-mm Gaussian kernel to render the data more normally distributed.

Statistical Analyses

We compared the normalized and smoothed GM images in the OCD and healthy control groups using the two-sample *t*-test (SPM 5). Total intracranial volume and sex were set as covariates in the statistical analysis. We used a threshold of P <0.05 FDR (false discovery rate)-corrected and another threshold of P <0.001 uncorrected with cluster size >100 voxels. The P <0.001 value is commonly used in VBM-based OCD studies[9, 12, 15]. Multiple regression models were applied to assess the relationship between clinical variables and regional GM brain volume changes in OCD patients.

RESULTS

All patients were unmedicated at the time of the scan. No significant difference was detected between the two groups under the threshold of P <0.05 FDR-corrected. Compared with healthy controls, patients with OCD showed increased regional GM volume in the bilateral middle temporal gyri, bilateral middle occipital gyri, bilateral globus pallidus, right inferior parietal gyrus, left superior parietal gyrus, right parahippocampus, right supramarginal gyrus, right medial superior frontal gyrus and left inferior frontal opercular cortex (P <0.001, uncorrected, cluster size >100 voxels; Table 2, Fig. 1). However, no decrease in GM volume was found in the OCD group compared with normal controls. In

Table 2. Regional changes in gray matter volume between OCD patients and healthy controls

Regions	MNI coordinates			Voxels	*t*	Z
	x	y	z			
Right middle temporal gyrus	54	–71	9	163	4.84	4.33
Left middle temporal gyrus	–50	–59	–1	265	4.65	4.19
Right middle occipital gyrus	41	–80	28	248	4.37	3.98
Left pallidum	–9	4	1	130	4.22	3.86
Right parahippocampal gyrus	22	–36	–13	334	4.14	3.80
Right inferior parietal gyrus	58	–37	49	130	4.14	3.79
Right supramarginal gyrus	54	–25	41	166	4.01	3.69
Right pallidum	18	–4	–5	163	3.99	3.68
Left superior parietal gyrus	–13	–74	54	135	3.90	3.60
Left middle occipital gyrus	–38	–83	32	148	3.84	3.56
Right medial superior frontal gyrus	9	32	36	141	3.81	3.54
Left inferior frontal opercular gyrus	–42	5	9	120	3.80	3.53

P <0.001, uncorrected, cluster size >100 voxels. MNI, Montreal Neurological Institute.

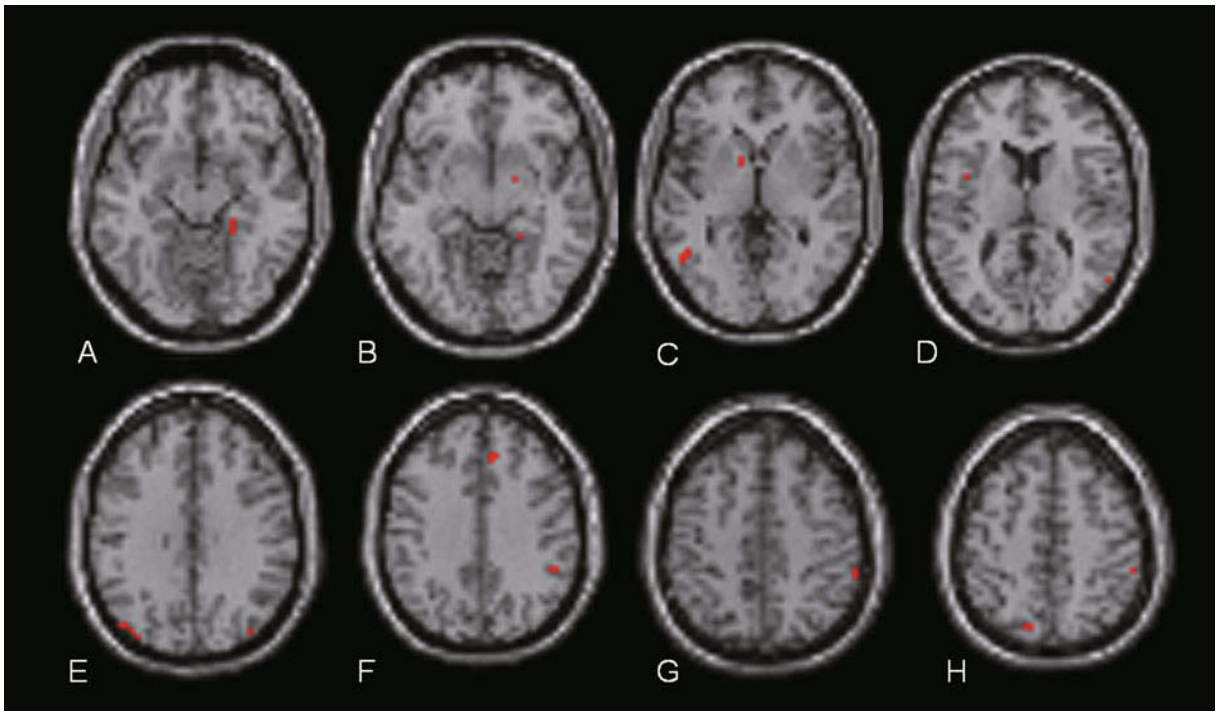

Fig. 1. Increased gray matter volumes in patients with OCD compared with normal controls. (A) Right parahippocampus, (B) right globus pallidus and right parahippocampus, (C) left globus pallidus and left middle temporal gyrus, (D) left inferior frontal opercular gyrus and right middle temporal gyrus, (E) bilateral middle occipital gyri, (F) right medial frontal gyrus and right inferior parietal gyrus, (G) right inferior parietal gyrus, and (H) right inferior parietal gyrus and left superior parietal gyrus.

addition, the GM volume changes had no relationship with the age of onset or illness duration.

DISCUSSION

Numerous papers have reported structural abnormalities in OCD patients with different MRI methods, but the results are inconsistent and even contradictory. The results might be affected by various factors. In our study, the enrolled patients were drug-naïve or without medication for a minimum of 8 weeks before the day of scanning. In addition, all patients were recruited according to the DSM-IV criteria for OCD and the absence of other major psychiatric disease. These inclusive criteria eliminated the influence of medication and coexisting psychiatric diseases.

The etiology of OCD is still uncertain. Many studies over the last 20 years have provided strong evidence that abnormalities in the fronto-striato-thalamic circuitry are involved in the pathophysiology of OCD[16-18]. However, we found GM volume abnormalities in the bilateral middle temporal gyri, bilateral middle occipital gyri, bilateral globus pallidus, right inferior parietal gyrus, left superior parietal gyrus, right parahippocampus, right supramarginal gyrus, right medial superior frontal gyrus and left inferior frontal opercular cortex in OCD patients compared with healthy controls.

The globus pallidus and the medial frontal cortex are key components of the fronto-striato-thalamic circuits implicated in the pathogenesis of OCD. Mataix-Cols *et al.*[19] reported that OCD patients have significantly greater activation than controls in the globus pallidus when viewing checking-related pictures. The globus pallidus has a high concentration of stored iron. Correia *et al.*[20] found higher iron content in the bilateral globus pallidus of OCD patients and that iron deposition might be related to the age of OCD onset. Yucel *et al.*[21] detected abnormally high medial frontal cortex activity in functional neuroimaging studies of OCD. Ramnani and Owen[22] proposed that dysfunction of the prefrontal cortex results in deficits in cognitive flexibility which might contribute to the maintenance of repetitive

behaviors. Our findings regarding medial frontal cortical abnormalities in OCD patients are inconsistent with several morphometric studies[23-25]. These conflicting results may be partly due to the outcome of different methodologies and differences in sample size.

In our study, the GM changes were not limited to the fronto-striato-thalamic circuits. There were additional regions of increased GM volume in the OCD group compared with healthy controls.

The temporal cortex plays important roles in memory, language, vestibular function, and visceral sensory/motor inputs[26, 27]. In this study, increased volumes of the bilateral middle temporal gyri and right parahippocampus were detected. Kim *et al.*[15] reported increased volume of the right middle temporal gyrus in OCD patients. Narayan *et al.*[28] also indicated that the middle temporal cortex is thicker in patients with OCD than in healthy controls. Niki and Luo[29] observed robust and dominant middle temporal lobe activity when recent memories were contrasted with remote memories. It was initially thought that the repetitive thoughts and behaviors of OCD reflected impaired memory functioning, as patients were simply unable to recall that they had already checked the stove or washed their hands[30]. Brascamp *et al.*[31] suggested that disruption of a memory trace depends on the integrity of the middle temporal cortex. Abnormality of the middle temporal lobe could cause reduced confidence in memory in patients, which might lead to compulsive behavior. The parahippocampal gyrus is thought to play a central role in memory recollection. It receives perceptual information from association cortices, such as the language areas, and forwards this information to the hippocampus in order to be "recognized"[32]. Valente *et al.*[9] also found an increased GM volume in parahippocampal regions in OCD patients relative to controls.

Parietal cortex is not a region traditionally implicated in OCD, but recent reports suggest that its importance may have been overlooked. Lazaro *et al.*[33] detected abnormality of the supramarginal gyrus in OCD patients. Valente *et al.*[9] proposed that parietal lobe dysfunction might interact with frontal-subcortical circuits through an anatomical connection between the parietal associative areas and the lateral orbitofrontal cortex, striatum and thalamic nucleus. Evidence suggested that activity in the parietal lobe is related to sustained attention and attentional set-shifting[34]. Menzies *et al.*[35] suggested that the cognitive impairments in some patients with OCD might be related to dysfunction of the parietal cortex. Alvarenga *et al.*[36] reported that OCD patients scored higher on the "aggression" dimension and this was positively correlated with a bilateral parietal cluster including the supramarginal gyri. A meta-analysis suggested that changes in the parietal region are particularly apparent in individuals with OCD but without comorbid depression[37]. This is in line with our result, as our patients had no concomitant psychiatric diseases. All of these structural and functional imaging findings suggest that the parietal cortex also plays an important role in the pathophysiology of OCD.

The volumetric changes in the bilateral occipital cortex were unexpected. However, several previous studies suggested that the occipital cortex might also play a role in OCD[38-40]. Further study is required to understand the role of the occipital cortex in OCD.

Our results of GM volumetric changes in the temporo-parietal area were outside the fronto–striato–thalamic circuitry. However, the results are in line with some current studies showing the importance of dorsal cortical regions in OCD[23, 32].

Our study has some limitations. First, we did not find significant differences between the two groups under the threshold of P <0.05 FDR-corrected in this preliminary study. Nonetheless, we still used the stringent P-value threshold of <0.001 and a relatively large cluster of 100 voxels to indicate statistical confidence. This may mean that the GM changes in OCD patients were not very evident compared with normal controls in our study. Our current results may contain false-positives. This may be due to the subjects we enrolled and the small sample size. The small sample size is due to the difficulty of finding drug-naïve OCD patients. Future assessment of a large group of patients and normal controls will be important to reduce the potential for both Type I and Type II errors. Second, although GM abnormalities were detected in OCD patients, it is still difficult to tell whether the GM changes lead to the OCD or the OCD leads to GM changes. Continued studies of children are important. Third, the overall sample was too small to examine the relationship between symptom scores and GM volume changes.

In summary, our findings suggest that structural GM changes are not restricted to the fronto-striato-thalamic

circuits in OCD. Temporal-parietal regions may also be involved in the pathogenesis of OCD.

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