

Volumetric MRI assessment of brain regions in patients with refractory obsessive–compulsive disorder

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Available online 9 May 2006

Abstract

No prior study to date has examined the comparisons of the structures that have been implicated in obsessive–compulsive disorder (OCD) in patients with refractory OCD, those who are treatment-responded and healthy controls concurrently. Therefore, we performed a volumetric MRI study in patients with refractory OCD, those with treatment responding OCD and healthy controls. Morphometric MRI was used to compare in thirty patients with OCD and ten healthy controls. Of the patient group, ten were first applying patients, ten were treatment-responded and the rest were refractory OCD patients. As a whole group, OCD patients had increased white matter volume than healthy controls. First applying patients had significantly smaller left and right orbito-frontal cortex (OFC) volumes compared with treatment-responded patients and healthy controls, with a significant difference between refractory patients and treatment-responded patients and with no significant difference was found between the volume of first applying patients compared to that of refractory patients. Anterior cingulate exhibited a near-significant difference only between first applying patients and healthy controls on left side. First applying patients had significantly greater left and right thalamus volumes compared with treatment-responded patients and healthy controls and there was a considerable difference in regard to thalamic volumes between refractory patients and treatment-responded patients. Taken together, our findings suggest that reductions in OFC and increase in thalamic volumes may be associated with refractoriness of OCD and may not be due to changes in cingulate and caudate regions.

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Keywords: Anterior cingulate; Brain regions; MRI; Orbito-frontal cortex (OFC); Refractory; Volume

1. Introduction

Obsessive–compulsive disorder (OCD) is characterized by intrusive unwanted thoughts, ideas, or images that are distressing (obsessions) and urges to perform ritualistic behaviors or mental acts (compulsions) to reduce this distress. The lifetime prevalence is estimated to be 2–3% around the world (Weissman et al., 1994). OCD is associated with impairment in occupational, academic, and social functioning (Koran et al., 1996), and can sometimes involve self-injury, such as skin damage from excessive hand washing. Although symptoms tend to wax and wane through the course of

the disorder, OCD symptoms rarely remit spontaneously. Given the prevalence, course, and functional interference associated with OCD, it is important to elucidate variables underlying this disorder.

Recent neurobiological models have postulated that abnormalities in brain activity underlie the etiology of OCD. Specifically, experts implicate dysfunction in the orbito-frontal–subcortical circuits. These circuits are thought to connect regions of the brain that process information involved in the initiation of behavioral responses that are implemented with little conscious awareness (Saxena et al., 2001). Neurobiological theories of OCD are largely derived from results of functional neuroimaging studies. Functional imaging techniques indirectly measure activity levels in specific brain areas and therefore are used to determine whether the structures thought to be involved in OCD are abnormally active in patients with this disorder. Despite abnormalities reported in neuropsychological and functional imaging literature, the findings from structural imaging studies have been inconsistent, with reports of increases (Scarone et al., 1992), decreases (Robinson et al., 1995; Szeszko et al., 1999) or no differences (Jenike et al., 1997;

Abbreviations: ANCOVA, analysis covariance; GAF, Global Assessment of Functioning Scale; MRI, magnetic resonance imaging; OCD, obsessive–compulsive disorder; OFC, orbito-frontal cortex; SSRI, selective serotonin reuptake inhibitor; Y-BOCS, Yale–Brown Obsessive–Compulsive Scale.

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O'Sullivan et al., 1997; Bartha et al., 1998) in the volumes of these key brain regions.

In summary, the studies examining the structures that have been implicated in OCD mostly had naturalistic design, and no OCD study to date has examined the comparisons of these regions in patients with refractory OCD, those with treatment responding and healthy controls. Therefore, we performed a volumetric MRI study in patients with refractory OCD, those with treatment responding and healthy controls patients focusing on the *in vivo* neuroanatomy of the whole brain, total gray and white matter volume, thalamus, caudate nucleus, anterior cingulate cortex, and orbito-frontal cortex (OFC) concurrently.

2. Methods

2.1. Subjects and clinical evaluations

Thirty patients with OCD were recruited from Firat University School of Medicine Department of Psychiatry. Of them, ten were first applying patients who never had taken any drug for this condition, ten were treatment-responded and the rest were refractory patients. Treatment responding patients were selected among first applying OCD patients who were treated for an a selective serotonin reuptake inhibitors (SSRI) for eight weeks and demonstrated 50% or more reduction on the Yale–Brown Obsessive–Compulsive Scale (Y–BOCS) according to baseline. A group of healthy controls were matched on age, sex, education and handedness. Diagnoses were made according to the Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition (DSM-IV) and the Structured Clinical Interview for the Diagnostic Schedule for Mental Disorders—Fourth Edition (SCID) (First et al., 1997). Severity of OCD symptoms was assessed with the Y–BOCS (Goodman et al., 1989). Each treatment refractory patient was required to have had adequate trials (at least 10 weeks at the maximally tolerated dose) of at least three of the serotonin reuptake inhibitors (clomipramine, fluoxetine, sertraline, paroxetine, fluvoxamine, or citalopram) and augmentation of at least one of the previous drugs for 1 month with at least two of the following medications: lithium, clonazepam, buspirone, or a neuroleptic. In addition, they included (a) less than 35% decrease on the Yale–Brown Obsessive–Compulsive Scale (Y–BOCS) total score at final evaluation as compared to baseline or a final score of > 16 on the Y–BOCS and (b) no better than “minimally improved” on the Clinical Global Impression improvement item. Of the patients, 18 were females and 12 were males. The mean age was 27.1 ± 4.2 years (range, 18–46 years) for total OCD group (26.5 ± 5.2 years for drug-free patients, 27.6 ± 3.7 years for well-responding patients and 29.0 ± 4.7 years for refractory OCD patients). A group of healthy controls were matched on age (29.8 ± 6.4 years for the controls; range, 19–45 years), sex (six females and 4 males), and education. All of the patients and controls were Caucasian.

Patients with any comorbid psychiatric disorder, current or lifetime neurologic, current medical problems, history of head trauma, and alcohol/substance abuse within the 6 months preceding the study were excluded. Healthy control subjects had no DSM-IV Axis I disorders in self or in a first-degree relative, as determined by the SCID nonpatient version, no

current medical problems, neurologic or psychiatric histories, and no use of psychoactive medication within 2 weeks of the study.

Patients and control subjects were comparable regarding age and gender distribution ($t=1.56$, $p>0.05$; $\chi^2=0.78$, $p>0.05$; respectively). They did not differ significantly regarding educational background: eight patients and nine control subjects completed high school, eight patients and 16 control subjects completed college and/or a professional school [$\chi^2=0.54$, $p>0.05$]. The intelligence quotient was not measured in this study, but bipolar patients and healthy control subjects had no gross functional impairment, as suggested by the relatively high DSM-IV Global Assessment of Functioning scale (GAF) scores (GAF [mean \pm SD]= 74 ± 3.4 and 93 ± 2.6 , respectively, with 83.3% of patients having a score ≥ 70 at the point they entered the study) and by the relatively high educational level.

The procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 1983. All subjects provided written informed consent.

2.2. MRI procedure

Magnetic resonance imaging scans were acquired with a 1.5 T General Electric scanner. Spiral pulse sequences were employed because of insensitivity to subject motion. A high-resolution structural image of the entire brain was obtained using sagittally acquired 3D spiral fast spin echo high-resolution images (TR=2000 ms, TE=15.6 ms, TI=700 ms, FOV=240 mm, echo SPACING=15.6 ms, 8 echoes, RESOLUTION=0.9375 \times 0.9375 \times 1.328 mm, 128 contiguous slices, 8 min 36 s). Functional scans were acquired using spiral imaging in the axial plane (TR=4000 ms, TE=40 ms, flip ANGLE=90°, FOV=240 mm, 20 7-mm contiguous slices, 72 repetitions, 4 min 48 s) with a reconstructed in-plane resolution of 1.875 \times 1.875 mm.

2.3. Tracing guidelines

MRI was obtained on a 1.5-Tesla GE signa Excite high speed scanner (Milwaukee, USA). Spiral pulse sequences were employed because of insensitivity to subject motion. A high-resolution structural image of the entire brain was obtained using sagittally acquired 3D spiral fast spin echo high-resolution images (repetition time [TR]=2000 ms, echo time [TE]=15.6 ms, field of view [FOV]=240 mm, flip angle=20°, bandwidth=20.8, slice thickness=2.4 mm, echo spacing=15.6 ms, 8 echoes, resolution=0.9375 \times 0.9375 \times 1.328 mm).

Anatomic measurements were conducted on a computer workstation with the GE Volume Viewer voxtool 3.0 64q program. Tracing was performed by one researcher (HY) blind to subject diagnosis, and independently verified by a second (HO) blinded investigator. Measured brain structures consisted of the whole brain, total gray and white matter volume, thalamus, caudate nucleus, anterior cingulate cortex, and OFC. The boundaries of structures evaluated were delineated on the coronal MR images according to standard brain atlases (Yuh et al., 1994; Jackson and Duncan, 1996; Patel and Friedman, 1997) and were adapted from Noga et al. (1995), Portas et al. (1998), Lacerda et al. (2003), Sassi

et al. (2004), and Riffkin et al. (2005). For the tracing of caudate nucleus, in the slice where the anterior commissure was most visible, a horizontal line underlying the lateral ventricles was drawn. The software automatically drew horizontal lines at the same level in all slices in order to exclude the nucleus accumbens. The posterior landmark was represented by the pontine cistern; tracings were performed on all slices moving anteriorly when the nucleus caudatus disappeared. The lateral ventricle and the internal capsule represented the medial and lateral boundaries. The most anterior boundary was identified using the mammillary bodies of the hypothalamus as a landmark. The ventralis anterior nucleus is just dorsal to the hypothalamus, bounded laterally by the third ventricle. The posterior boundary was defined when the thalamus merged under the crus fornix. The medial boundary was defined using the third ventricle. The inferior border was defined when the thalamus merged with the brain stem and the superior border, by the main body of the lateral ventricle. For the tracing procedure for measuring the OFC, a line from the anterior commissure (AC) to the posterior commissure (PC) defined the superior boundary, anterior to the genu of the corpus callosum, but the choice of an oblique line, used to define the more posterior slices, appeared to

eliminate a large portion of the lateral OFC. This problem was overcome by using the AC–PC line to define the superior boundary on all slices, thereby creating a fixed geometric boundary that incorporated the OFC to the superior extent of the lateral orbital sulcus. The posterior boundary of the OFC was located on the coronal image as the slice on which the olfactory sulcus first appeared. The inferior boundary was defined by the most inferior aspect of the cortex, the lateral boundary by the most lateral edge of the cortex, and the medial boundary of each hemisphere by the longitudinal fissure. The tracing was started with the anterior cingulate at two slices anterior to the most anterior slice where the genu of the corpus callosum was visible, with the cingulate sulcus as the upper limit and the callosal sulcus as the lower limit defining the cingulate gyrus. The tracing was maintained caudally on all slices until the slice where the anterior commissure was most apparent was reached. The anterior commissure indicated the posterior limit of the anterior cingulate. The subsequent slice marked the anterior border of the posterior cingulate, and the cingulate gyrus was traced in the same manner. Examples of the structures of coronal slices are presented in Fig. 1. All volumes were reported in cubic centimeters.

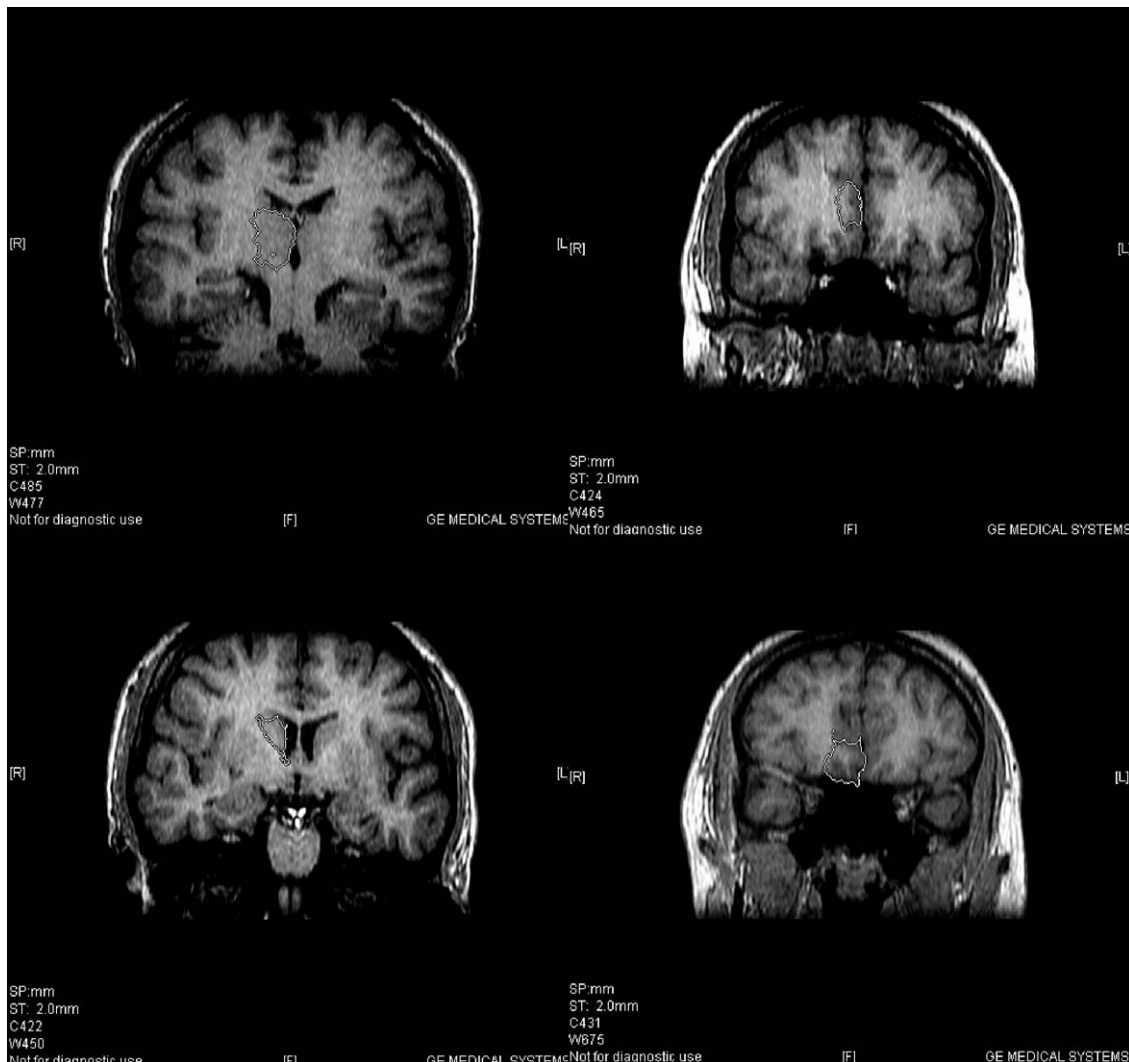


Fig. 1. Anatomic landmarks for the tracing of the structures evaluated.

2.4. Statistical analysis

Analysis of covariance (ANCOVA), analysis of variance (ANOVA), chi-square and partial correlation analyses were conducted using SPSS for Windows software, version 10.0 (SPSS, Chicago, IL).

3. Results

There were no significant differences in demographic variables of age, gender composition, educational level, and intracranial volume (ICV) among drug-free patients, those with well-responding OCD, refractory OCD patients and healthy controls ($p > 0.05$).

ICV ($1438.4 \pm 140.5 \text{ mm}^3$ for drug-free patients, $1440.8 \pm 151.2 \text{ mm}^3$ for well-responding patients, $1451.0 \pm 142.9 \text{ mm}^3$ for refractory patients and $1448.5 \pm 145.2 \text{ mm}^3$ for controls), whole brain volume ($1149.1 \pm 120.6 \text{ mm}^3$ for drug-free patients, $1158.8 \pm 149.3 \text{ mm}^3$ for well-responding patients, $1150.6 \pm 143.7 \text{ mm}^3$ for refractory patients and $1133.4 \pm 138.1 \text{ mm}^3$ for controls), and gray matter volumes ($777.6 \pm 62.2 \text{ mm}^3$ for drug-free patients, $763.5 \pm 71.2 \text{ mm}^3$ for well-responding patients, $759.3 \pm 57.9 \text{ mm}^3$ for refractory patients and $797.2 \pm 79.2 \text{ mm}^3$ for controls) did not differ among drug-free patients, those with well-responding OCD, refractory OCD patients and healthy controls ($p > 0.05$) (Table 1). However, as a whole group, OCD patients had increased white matter volume compared to healthy controls ($p < 0.05$). There were no difference in regard to whole brain and gray matter volumes among groups ($p > 0.05$). First applying patients had significantly smaller left ($F = 6.01$, $p < 0.05$) and right ($F = 5.09$, $p < 0.05$) OFC volumes compared with treatment-responded patients and healthy controls. In addition, there was a significant difference between refractory patients and treatment-responded patients for both sides ($p < 0.05$). No significant difference was found between the volume of first applying patients compared to that of refractory patients. In

regard to OFC volumes, no other differences were determined (Table 1). Anterior cingulate exhibited a near-significant difference only between first applying patients and healthy controls on left side ($p = 0.08$). There was no difference in regard to caudate volumes for both sides among groups ($p > 0.05$). First applying patients had significantly greater left ($F = 5.59$, $p < 0.05$) and right ($F = 6.56$, $p < 0.05$) thalamus volumes compared with treatment-responded patients and healthy controls. There was a considerable difference in regard to thalamic volumes between refractory patients and treatment-responded patients ($p < 0.05$), or health controls ($p < 0.05$); however no difference was found between refractory patients and first applying patients ($p > 0.05$) (Table 1). Patients who had positive ($n = 13$) and negative ($n = 17$) familial history of mood disorder did not demonstrate significant differences with regard to any of the structure evaluated.

Whole brain volume, gray and white matter volumes did not differ between drug-free patients, those with well-responding OCD and refractory OCD after covarying for age ($p > 0.05$). After covarying for age and whole brain volume, first applying patients had still increased white matter volume compared to healthy controls ($p < 0.05$ for both covariates). On the other hand, first applying patients had significantly smaller left ($F = 4.91$, $p < 0.05$ for age, and $F = 4.05$, $p < 0.05$ for whole brain volume) and right ($F = 4.18$, $p < 0.05$ for age, and $F = 5.23$, $p < 0.05$ for whole brain volume) OFC volumes compared with treatment-responded patients and healthy controls even after covarying for age and whole brain volume. After covarying for whole brain volume, statistical significant difference still lasted among first applying patients and treatment-responded patients and healthy controls in between refractory patients and treatment-responded patients ($p < 0.05$), or health controls ($p < 0.05$) in regard to left thalamus.

The following significant correlations were found in first-applying patients: Y-BOCS scores and left OFC ($r = -0.71$, $p < 0.01$) or right OFC ($r = -0.51$, $p < 0.05$); and Y-BOCS and left

Table 1
Volumetric measurements of the bipolar patients and healthy control subjects

Structure volumes (cm ³)	First applying (n=10)	Treatment-responding patients (n=10)	Refractory patients (n=10)	Healthy control group (n=10)	p
ICV*	1438.4±140.5	1440.8±151.2	1451.0±142.9	1448.5±145.2	p>0.05
Whole brain volume	1149.1±120.6	1158.8±149.3	1150.6±143.7	1133.4±138.1	p>0.05
Gray matter volume	777.6±62.2	763.5±71.2	759.3±57.9	797.2±79.2	p>0.05
<i>OFC* volumes</i>					
Left	11.2±1.5	13.9±2.2	11.5±2.1	14.8±2.6	p<0.05
Right	10.5±2.5	13.3±1.7	10.9±1.6	13.3±2.2	p<0.05
<i>Anterior cingulate volumes</i>					
Left	1.6±0.2	1.7±0.2	1.7±0.4	1.9±0.3	p>0.05
Right	1.7±0.2	2.0±0.4	1.8±0.5	1.9±0.5	p>0.05
<i>Caudate volumes</i>					
Left	3.9±0.2	3.5±0.3	3.6±0.8	3.6±0.3	p>0.05
Right	3.7±0.5	4.1±0.7	3.9±0.6	3.8±0.2	p>0.05
<i>Thalamus volumes</i>					
Left	5.6±0.7	5.0±0.8	5.5±0.4	4.8±0.9	p<0.05
Right	5.5±0.9	4.9±0.6	5.4±0.5	4.6±0.6	p<0.05

Data are presented as mean±SD.

*ICV=Intracranial volume; OFC=Olfacto-frontal cortex.

thalamus ($r=0.50$, $p<0.05$). Significant correlations found in treatment-responded patients were: Y–BOCS scores and left OFC ($r=-0.51$, $p<0.05$). The following significant correlations were found in refractory patients: Y–BOCS scores and left OFC ($r=-0.55$, $p<0.05$); Y–BOCS scores and right thalamus ($r=0.48$, $p<0.05$); length of illness and thalamus ($r=0.49$, $p<0.05$ for left).

4. Discussion

This is the first study regarding structural investigation of brain regions in refractory OCD patients. Thus, we would like to emphasize the main findings found in the present study: (i) As a whole group, OCD patients had increased white matter volume than healthy controls, (ii) first applying patients had significantly smaller left and right OFC volumes compared with treatment-responded patients and healthy controls. In addition, there was a significant difference between refractory patients and treatment-responded patients. (iii) Anterior cingulate exhibited a near-significant difference only between first applying patients and healthy controls on left side. (iv) First applying patients had significantly greater left and right thalamus volumes compared with treatment-responded patients and healthy controls and there was a considerable difference in regard to thalamic volumes between refractory patients and treatment-responded patients, or healthy controls; however no difference was found between refractory patients and first applying patients. Our first important finding is that as a whole group, OCD patients had increased white matter volume than healthy controls. Increased white matter volume, in the absence of increased gray matter volume, may reflect increased amount of myelin or glia cells. On the other hand, these abnormalities can be due to primary developmental processes, as mentioned in the study by Rauch et al. (2001) in which patients with body dysmorphic disorder (BDD) had increased white matter volume compared to healthy controls. In addition, this may be further support for the conceptualization of BDD as an obsessive–compulsive spectrum disorder. Although the pathophysiology of OCD remains controversial, there are some evidences that the OFC may be implicated in the pathophysiology of OCD. Previous functional neuroimaging studies have shown that the OFC activity of OCD patients is increased versus that of normal control subjects in resting states (Rubin et al., 1992; Kwon et al., 2003), and that this is decreased after successful treatment (Swedo et al., 1992; Saxena et al., 1999), which suggests that this area may be involved in mediating the expression of obsessive–compulsive symptoms. In addition, there is evidence of morphological changes in the OFC in OCD. Szeszko et al. (1999) reported using MRI that patients with OCD had significantly reduced bilateral OFC volumes as compared with healthy subjects. Kim et al. (2001) investigated gray matter abnormalities in patients with OCD using voxel-based morphometry (VBM). Moreover, the OFC was found to play a role in mobilizing strategies during a novel and ambiguous verbal learning task, and in directing strategic memory processes (Savage et al., 2001). Savage et al. (1999, 2000) previously reported that verbal and nonverbal episodic memory deficits in OCD were affected by impaired strategic processing. Thus, it has been hypothesized that OFC abnormality may be involved in the clinical and cognitive expression of OCD. In the present study, we found that first

applying patients had significantly smaller left and right OFC volumes compared with treatment-responded patients and healthy controls and that there was a significant difference between refractory patients and treatment-responded patients but no difference between the volume of first applying patients compared to that of refractory patients. These results support the findings of aforementioned studies indicating that OFC volumes were reduced in OCD patients and suggest that OFC volumes increase to healthy controls' levels and that decreased OFC volumes seem to be associated with refractoriness to available treatment.

The structural variability and complexity of anterior cingulate cortex makes the identification and selection of boundaries difficult. Only several studies have evaluated the structure of the anterior cingulate cortex in OCD, and to date no volumetric abnormalities have been reported (Grachev et al., 1998). However, Szeszko et al. (1999) found a non-significant downward trend and a significant effect of hemisphere ($R>L$) in patients with OCD. In addition, though not significant, the rightward bias in anterior cingulate cortex volume was also observed in another OCD group (Riffkin et al., 2005) and was concluded this subtle asymmetry might provide a starting point for further pathophysiological investigations of OCD. In the present study, anterior cingulate cortex exhibited a near-significant difference only between first applying patients and healthy controls on left side. We suggest that this difference we found does not support the results aforementioned but suggests that the volumetric reduction may be related in some way to pathophysiology of the disorder but by itself it is unlikely to be important to the clinical presentation, and refractoriness or yield any useful diagnostic information. However, meanwhile, we should emphasize that the present study had small number of patients, limiting the strength of statistical power and the generalizability of the study findings. In consistent with other studies of the caudate nucleus (Jenike et al., 1997; Stein et al., 1997; Riffkin et al., 2005), our investigation did not demonstrate any statistically significant differences in OCD.

The thalamus is of particular interest in OCD, because it is thought to play a pivotal role in integrating interoceptive and exteroceptive information relayed to cortical areas (Alexander et al., 1986) and is thought to be involved in the pathophysiology of OCD. The fact that partial thalamotomy can relieve symptom severity in treatment-refractory OCD patients (Chiocca and Martuza, 1990) further supports this notion. Numerous studies have implicated the thalamus in the pathology of OCD. Structurally MRI studies have shown increased thalamic gray matter in medication-free adult OCD patients compared with control subjects (Kim et al., 2001). This finding has been extended to psychotropic-naive, pediatric OCD patients (Gilbert et al., 2000). Gilbert et al. (2000) reported increased thalamic volume in 21 treatment-naive pediatric OCD patients versus 21 case-matched healthy comparison subjects that decreased to levels comparable to control subjects after effective paroxetine therapy. The latter study reported a reduction in thalamic volume in 10 pediatric OCD patients associated with reduction in OCD symptom severity after treatment with the SSRI paroxetine. However, the same scientific group (Rosenberg et al., 2000) conducted a volumetric MRI study in 11 psychotropic drug-naive patients with OCD before and after 12 weeks of effective cognitive behavioral therapy monotherapy and found no significant

change in thalamic volumes before and after cognitive behavioral therapy and concluded that reductions in thalamic volume seem to be associated with relatively specific to effective SSRI treatment and may not be due to a more general treatment response or spontaneous resolution of symptoms. In the present study, first applying patients had significantly greater left and right thalamus volumes compared with treatment-responded patients and healthy controls and there was a considerable difference in regard to thalamic volumes between refractory patients and treatment-responded patients, or healthy controls; however no difference was observed between refractory patients and first applying patients. Given the last finding, that is, the fact that no difference was found between the thalamic volumes of refractory patients and first-applying patients, we suggest that increase in thalamic volumes seems to be associated with refractoriness of OCD.

Several limitations exist with the current study. The small sample size of the current study groups limits the generalizability of the study findings. With a population of this size, it is possible that other factors unique to the two groups may have influenced the outcome measures. Nevertheless, this is a relatively sample of a well-characterized patient group.

5. Conclusion

This initial morphometric MRI study of refractory OCD patients shows that first applying OCD patients had significantly smaller left and right OFC volumes compared with treatment-responded patients and healthy controls but similar with refractory patients as well as considerable greater left and right thalamus volumes in first applying patients compared with treatment-responded patients and healthy controls with no difference between refractory patients and first applying patients. Taken together, our findings suggest that reductions in OFC and increase in thalamic volumes may be associated with refractoriness of OCD and may not be due to changes in cingulate and caudate regions. Longitudinal studies with larger sample are required.

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