Volumetric MRI study of key brain regions implicated in obsessive–compulsive disorder

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Received 20 February 2006; received in revised form 12 June 2006; accepted 15 June 2006
Available online 20 July 2006

Abstract

Neuroanatomic abnormalities have been implicated in the pathophysiology of obsessive–compulsive disorder (OCD). To date, no study has measured the orbito-frontal cortex (OFC), anterior cingulate, caudate nucleus, and thalamus concurrently in first-episode patients. Thus, we performed a volumetric MRI study in patients who were treatment-naive and healthy controls focusing on the in vivo neuroanatomy of the whole brain, total gray and white matter volume, thalamus, caudate nucleus, anterior cingulate cortex, and OFC concurrently. The volumes of thalamus, caudate nucleus, anterior cingulate cortex, and OFC were measured in 12 OCD patients who were treatment-naive and 12 healthy control subjects. Anterior cingulate and OFC volumes included both white and gray matters. Volumetric measurements were made with T1-weighted coronal MRI images, with 1.5-mm-thick slices, at 1.5 T. The patients had increased white matter volume than healthy controls. The patient group had significantly smaller left and right OFC volumes and significantly greater left and right thalamus volumes compared with healthy controls. Anterior cingulate exhibited a near-significant difference between the patients and healthy controls on left side. Significant correlations were found between Y-BOCS scores and left OFC, and right OFC, and between Y-BOCS and left thalamus volumes in the patient group. In conclusion, our findings suggest that abnormalities in these areas may play an important role in the pathophysiology of OCD.

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Keywords: Anterior cingulate; MRI; OCD; OFC; Structural; Volume

1. Introduction

Obsessive–compulsive disorder (OCD) is a chronic and often disabling anxiety disorder. Data from the Epidemiological Catchment Area (ECA) survey and other epidemiological studies revealed the lifetime prevalence of OCD to be between 2% and 3% in the general population (Robins et al., 1985). 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. Although symptoms tend to wax and wane through the course of the disorder, OCD symptoms rarely remit spontaneously.

Recent brain imaging techniques have been particularly convincing in suggesting that specific circuits are responsible for the mediation of OCD symptoms (Stein et al., 2000). The predominant hypothesis is prefrontal–basal ganglia–thalamic–prefrontal circuits to be particularly important (Insel, 1992). Dysfunction in these circuits may be associated with implicit processing deficits and intrusive symptoms (Rauch and Savage, 1997). Structural imaging studies of OCD, for example, although not always consistent, have suggested basal ganglia and frontal pathology (Insel, 1992). The findings from structural imaging studies have been inconsistent, with reports of increases (Scarone et al., 1992), decreases (Robinson et al., 1995; Szaszko et al., 1999) or no differences (Jenike et al., 1996; O’Sullivan et al., 1997; Rosenberg et al., 2000a,b; Bartha et al., 1998; Riffkin et al., 2005)
in the volumes of these key brain regions. Recently, Pujol et al. (2004) found reduced gray matter volume in the medial frontal gyrus, the medial OFC, and the left insulo-opercular region. Likewise, Choi et al. (2004) showed volume reduction of the left anterior OFC in patients with OCD versus normal controls. In a very recent meta-analysis, Whiteside et al. (2004) reported that meta-analytic results partially support the conclusions drawn from previous narrative reviews that point to structures in the OFC, caudate nucleus, anterior cingulate, and thalamus as the key brain regions in the pathophysiology of OCD. Functional imaging studies have found altered activity in basal ganglia and prefrontal areas at rest and during behavioral challenge with feared stimuli in OCD patients (Rauch and Savage, 1997). Furthermore, there is evidence for alterations in basal ganglia and prefrontal cortex activity after both pharmacotherapy and behavioral psychotherapy (Baxter, 1992).

Previously, Kang et al. (2004) measured volumes of the orbitofrontal cortex, anterior cingulate gyrus, thalamus, and caudate nucleus, which are the main components of the frontal subcortical circuitry in patients with OCD and in normal subjects. These may be key brain regions in the pathophysiology of OCD. Since psychotherapeutic approaches and pharmacotherapy can affect brain volumes, it is very important to evaluate these key regions in medication-naive patients. However, to date, no study has examined the OFC, anterior cingulate, caudate nucleus, and thalamus concurrently in medication-naive patients. Thus, we performed a volumetric MRI study in patients who first applied 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 OFC concurrently.

2. Materials and methods

2.1. Subjects and clinical evaluations

Twelve patients with OCD (6 females and 6 males) who were first episode treatment-naive were recruited from Firat University School of Medicine Department of Psychiatry. 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). On the other hand, severity of depressive symptoms was assessed with the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960). A group of healthy controls were matched on age, sex, education and handedness.

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. With respect to comorbidity in the patient group, as assessed by the SCID and clinical interviews, nobody met criteria for current any psychiatric disorder. Additional comorbid lifetime Axis I psychiatric diagnoses were tic disorder (n=1), major depressive disorder (n=1), panic disorder (n=1), and dysthymia (n=1). 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. None of healthy controls already had not taken any psychotropic agent. Of the patients, while mothers of two had subclinic OCD and father of one had subclinic panic disorder; mothers of one had history of specifc phobia but now she had been in remission for 7 years.

There were no significant group differences in age, years of education, lifetime weeks of alcohol intoxication, and sex and handedness ratio. OCD 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±S.D.] = 70±5.1 and 91±2.9, respectively and by the relatively high educational level.

The procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 1983.

2.2. MRI procedure

MRI was obtained on a 1.5-T 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=0.9375×0.9375×2.4 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
Fig. 1. A, B, C. Anatomic landmarks for the tracing of the structures evaluated.
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. 1A, B, C. All volumes were reported in cubic centimeters. The interrater reliability (intraclass correlation coefficient), established by two different evaluators tracing, was $r = 0.84$ for thalamus, $r = 0.88$ for caudate nucleus, $r = 0.82$ for anterior cingulate cortex, and $r = 0.90$ for OFC.

### 2.3. Statistical analysis

Analysis of covariance (ANCOVA), t-test and partial correlation analyses were conducted using SPSS for Windows software, version 10.0 (SPSS, Chicago, IL). In ANCOVA analyses, age and whole brain volumes were covariates. Correlation analyses was done by using Spearman’s rank test. Statistical significance was defined as $P<0.05$ by a two-tailed test.

### Table 1
Clinical and demographic characteristics

<table>
<thead>
<tr>
<th>Item</th>
<th>Patients group $(n=12)$</th>
<th>Control group $(n=12)$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>26.9±2.64</td>
<td>28.78±2.66</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Gender (female/male)</td>
<td>6/6</td>
<td>7/5</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>High school</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Elementary school</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>First school</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Handedness (right)</td>
<td>12</td>
<td>12</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Length of illness (months)</td>
<td>0.4±0.3</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Total Y-BOCS Score</td>
<td>27.3±4.9</td>
<td>4.1±2.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Y-BOCS Obsession Score</td>
<td>15.2±5.3</td>
<td>2.5±1.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Y-BOCS Compulsion Score</td>
<td>12.1±4.4</td>
<td>1.9±1.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hamilton Depression Rating Score</td>
<td>12.3±3.1</td>
<td>2.7±1.4</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

### 3. Results

There were no significant differences in demographic variables of age, gender composition, educational level, and intracranial volume (ICV) between OCD patients (1432.3±134.8) and healthy controls (1443.4±140.7) ($P>0.05$). In patient group, mean Y-BOCS and HDRS scores were 27.3±4.9 and 12.3±3.1, respectively (Table 1).

Whole brain volume, and gray matter volumes did not differ between patients and healthy controls ($P>0.05$). However, OCD patients had increased white matter volume compared to healthy controls ($P=0.037$). There were no difference in regard to whole brain and gray matter volumes among groups ($P>0.05$). The patient group had significantly smaller left ($P=0.024$) and right ($P=0.031$) OFC volumes compared with healthy controls. Anterior cingulate exhibited a near-significant difference between the patients and healthy controls on left side ($P=0.071$). There was no difference in regard to caudate volumes for both sides between groups ($P>0.05$). The patients had significantly greater left ($P=0.044$) and right ($P=0.041$) thalamus volumes compared with healthy controls (Table 2).

Whole brain volume and gray matter volumes did not differ between patients and healthy controls after covarying for age ($P>0.05$). After covarying for age and whole brain volume, patients with OCD had still increased white matter volume compared to healthy controls ($P<0.05$ for both covariates). On the other hand, they had significantly smaller left ($F=4.91, P=0.028$ for age, and $F=4.05, P=0.035$ for whole brain volume) and right ($P=0.034$ for age, $P=0.042$ for whole brain volume) OFC volumes compared with healthy controls even

### Table 2
The volumes of the structures evaluated in patients with OCD versus controls subjects (mean±standard error)

<table>
<thead>
<tr>
<th></th>
<th>OCD patients $(n=12)$</th>
<th>Healthy controls $(n=12)$</th>
<th>$F_{1,19}$</th>
<th>Effect size</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole brain volume</td>
<td>1143.72±112.03</td>
<td>1131.78±129.6</td>
<td>2.28</td>
<td>0.34</td>
<td>0.67</td>
</tr>
<tr>
<td>Gray matter volume</td>
<td>784.17±73.57</td>
<td>807.11±66.57</td>
<td>2.61</td>
<td>–0.40</td>
<td>0.74</td>
</tr>
<tr>
<td>White matter volume</td>
<td>359.55±24.44</td>
<td>324.67±69.34</td>
<td>5.37</td>
<td>1.38</td>
<td>0.037</td>
</tr>
<tr>
<td>OFC volumes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>11.66±1.79</td>
<td>14.56±2.42</td>
<td>6.08</td>
<td>–1.61</td>
<td>0.024</td>
</tr>
<tr>
<td>Right</td>
<td>10.74±2.33</td>
<td>13.88±2.65</td>
<td>5.81</td>
<td>–1.45</td>
<td>0.031</td>
</tr>
<tr>
<td>Anterior cingulate volume</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>1.68±0.11</td>
<td>1.96±0.16</td>
<td>4.18</td>
<td>–0.92</td>
<td>0.071</td>
</tr>
<tr>
<td>Right</td>
<td>1.84±0.09</td>
<td>1.90±0.25</td>
<td>1.76</td>
<td>–0.27</td>
<td>0.80</td>
</tr>
<tr>
<td>Caudate volumes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>3.94±0.13</td>
<td>3.88±0.34</td>
<td>1.89</td>
<td>0.45</td>
<td>0.79</td>
</tr>
<tr>
<td>Right</td>
<td>3.76±0.17</td>
<td>3.94±0.22</td>
<td>2.12</td>
<td>–0.30</td>
<td>0.72</td>
</tr>
<tr>
<td>Thalamus volumes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>5.56±0.82</td>
<td>5.02±0.66</td>
<td>5.02</td>
<td>1.03</td>
<td>0.044</td>
</tr>
<tr>
<td>Right</td>
<td>5.48±1.06</td>
<td>4.89±0.70</td>
<td>5.12</td>
<td>1.14</td>
<td>0.041</td>
</tr>
</tbody>
</table>

Volumes presented are in cm$^3$. 
after covarying for age and whole brain volume. After covarying for whole brain volume, statistical significant difference still lasted between patients and healthy controls ($P = 0.039$) in regard to left thalamus.

The following significant correlations were found in the patients: Y-BOCS scores and left OFC ($r = -0.71, P = 0.0072$) or right OFC ($r = -0.51, P = 0.036$); and Y-BOCS and left thalamus ($r = 0.50, P = 0.038$). No correlation for any parameter was found in healthy controls.

4. Discussion

This is the first regarding structural investigation which evaluates the brain regions of OFC, anterior cingulate, caudate nucleus, and thalamus volumes concurrently in medication-naive OCD patients. The volume changes found in the present study may be implicated in the pathophysiology of OCD. Thus, we would like to emphasize the main findings of this study: (i) OCD patients had increased white matter volume than healthy controls, (ii) the patient group had significantly smaller left and right OFC volumes compared with healthy controls, (iii) anterior cingulate exhibited a near-significant difference between the patients and healthy controls on left side, (iv) the patients had significantly greater left and right thalamus volumes compared with healthy controls, and (v) significant correlations were found between Y-BOCS scores and left OFC, or right OFC, and between Y-BOCS and left thalamus volumes in the patient group. Our first important finding is that OCD patients had increased white matter volume compared to healthy controls. Increased white matter volume, in the absence of increased gray matter volume, may reflect increased amount of myelin or glia cells. Likewise, Rauch et al.' study (2003) 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 is much evidence to support a role for the frontal–subcortical circuitry, including the OFC, cingulate cortex and caudate nucleus (Insel, 1992; Baxter, 1992; Kwon et al., 2003), in a neurobiologic model of 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). Valente et al. (2005) found increased gray matter in OCD subjects relative to control subjects in posterior orbitofrontal and parahippocampal regions. In Pujol et al.'s study (2004), the brains of patients with OCD showed reduced gray matter volume in the medial frontal gyrus, the medial orbitofrontal cortex, and the left insulo-opercular region. In addition, there is evidence of activity changes in the OFC in OCD. Functional neuroimaging studies, which have compared OCD patients with controls reported inconsistent results on anterior cingulate and caudate abnormalities in OCD, while relatively more consistent findings have been reported on abnormalities of the OFC in OCD patients (Saxena et al., 1998). 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 is decreased after successful treatment (Saxena et al., 1999), which suggests that this area may be involved in mediating the expression of obsessive–compulsive symptoms. In the present study, we found that OCD patients had significantly smaller left and right OFC volumes compared with healthy controls. These results support the findings of aforementioned studies indicating that OFC volumes were reduced in OCD patients. Meanwhile we should emphasize that significant correlations were found between Y-BOCS scores and both sides of OFC.

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 between OCD patients and healthy controls on left side. This difference do not support the results aforementioned but suggests that the volumetric reduction may be related in some way to the disorder but by itself it is unlikely to be important to the clinical presentation, or yield any useful diagnostic information. Inconsistent with other studies of the caudate nucleus (Jenike et al., 1996; Bartha et al., 1998; Riffkin et al., 2005; Stein et al., 1997), our investigation did not demonstrate any statistically significant differences in OCD.

Various studies have implicated the thalamus in the pathophysiology of OCD. The fact that partial thalamotomy could reduce symptom severity in treatment-refractory OCD patients (Chiocca and Martuza, 1990) provided further evidence on its role of of pathophysiology 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-naïve, pediatric OCD patients (Gilbert et al., 2000). Gilbert et al. (2000) reported increased thalamic volume in 21 treatment-naïve 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. The same scientific group (Rosenberg et al., 2000a,b) conducted a volumetric MRI study in 11 psychotropic-drug-naïve patients with OCD before and after 12 weeks of effective cognitive behavioral therapy as 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. Our present study in which was found the patients with OCD to have significantly greater left and right thalamus volumes compared...
with healthy controls supports the findings aforementioned and emphasizes the importance of thalamic changes in the neurophysiology of OCD.

There are several important limitations to this study that should not be overlooked or underestimated. First, the number of subjects is small; especially given the condition whether we generalize these findings, replication of the current findings is essential. Future studies will also need to examine whether our findings are applicable to cases of OCD with psychotic features that were not examined individually in this study. Second, as we acknowledged, the statistical threshold applied is somewhat liberal, further underscoring the need for replication. Third, we did not perform a segmentation for anterior cingulate and OFC volumes. In addition, other limitations including the lack of consideration of the effects of OCD symptom dimensions, gender differences, and IQ effects should be mentioned.

In conclusion, this morphometric MRI study of medication-naive OCD patients shows that OCD patients had increased white matter volumes, smaller left and right OFC volumes, and significantly greater left and right thalamus volumes compared with healthy controls. Taken together, our findings suggest that abnormalities in these areas may play an important role in the pathophysiology of OCD.

References


