Orbito-frontal cortex and thalamus volumes in the patients with obsessive-compulsive disorder before and after cognitive behavioral therapy

Murad Atmaca¹, Hanefi Yildirim², Seda Yilmaz¹, Neslihan Caglar¹, Osman Mermi¹, Sevda Korkmaz¹, Unsal Akaslan², M Gurkan Gurok³, Yasemin Kekilli⁴, and Hakan Turkcapar⁵

Abstract

Background: The effect of a variety of treatment modalities including psychopharmacological and cognitive behavioral therapy on the brain volumes and neurochemicals have not been investigated enough in the patients with obsessive-compulsive disorder. Therefore, in the present study, we aimed to investigate the effect of cognitive behavioral therapy on the volumes of the orbito-frontal cortex and thalamus regions which seem to be abnormal in the patients with obsessive-compulsive disorder. We hypothesized that there would be change in the volumes of the orbito-frontal cortex and thalamus.

Methods: Twelve patients with obsessive-compulsive disorder and same number of healthy controls were included into the study. At the beginning of the study, the volumes of the orbito-frontal cortex and thalamus were compared by using magnetic
resonance imaging. In addition, volumes of these regions were measured before and after the cognitive behavioral therapy treatment in the patient group.

**Results:** The patients with obsessive-compulsive disorder had greater left and right thalamus volumes and smaller left and right orbito-frontal cortex volumes compared to those of healthy control subjects at the beginning of the study. When we compared baseline volumes of the patients with posttreatment ones, we detected that thalamus volumes significantly decreased throughout the period for both sides and that the orbito-frontal cortex volumes significantly increased throughout the period for only left side.

**Conclusions:** In summary, we found that cognitive behavioral therapy might volumetrically affect the key brain regions involved in the neuroanatomy of obsessive-compulsive disorder. However, future studies with larger sample are required.

**Keywords**
Obsessive-compulsive disorder, cognitive behavioral therapy, orbito-frontal cortex, thalamus

**Introduction**
Obsessive-compulsive disorder (OCD) is characterized by the existence of the obsessions and/or compulsions. OCD has been placed in the new category of the obsessive-compulsive and related disorders in the *DSM 5* which was published in 2013 by the American Psychiatric Association. The disorder lasts lifetime and causes to decrease in the quality of life. To date, the exact reason for the occurrence of the OCD has not been established. Probably, the heterogen nature of OCD’s clinical picture may be to contribute for this. Nowadays, a lot of knowledge on the etiopathogenesis of the OCD has been collected. An important part of this knowledge has been provided by biochemical studies. Apart from this, genetic, neurobiological, and neuroimaging investigations have also contributed.

In neuroimaging studies on OCD, there have been found important findings. In general, structural researches have emphasized the pathology on basal ganglia and frontal region. These studies revealed inconsistent reports, including increases, decreases, or no differences. Our study group also carried out important studies on the neuroimaging of OCD. For neuroimaging investigations of OCD, we started with studying key brain regions. We evaluated orbito-frontal cortex (OFC), thalamus, caudate nucleus, and anterior cingulate cortex volumes in the patients with OCD. In that study, we found that OCD patients had significantly smaller OFC and greater thalamus volumes compared to those of healthy control subjects. Our study group evaluated the OFC’s relation with traditional psychodynamic perspective. We examined the relationship between defense styles and OFC volumes. We did not find an association between the right OFC volumes of both the patient and control groups and their scores of
mature, neurotic, or immature defense mechanisms. However, for the left OFC, we detected that there was a significant relationship between the scores of immature defense mechanism and OFC volumes in the patient group. We suggested that the left OFC might be related to treatment resistance in the patients with OCD. In another study, our study group also performed a volumetric magnetic resonance imaging (MRI) study in the patients with refractory OCD, those with treatment responding OCD and healthy controls.\textsuperscript{15} In that study, OCD patients as a whole group had increased white matter volume than that of healthy controls. On the other hand, first applying patients had significantly smaller left and right 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 between the volume of first applying patients compared to that of refractory patients. We determined that anterior cingulate volumes exhibited a near-significant difference only between first applying patients and healthy controls on left side, with the finding that 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. We concluded that reductions in OFC and increase in thalamic volumes might be related to refractoriness of OCD and might not be due to changes in cingulate and caudate regions.

There have been so limited number of investigations on the effects of pharmacologic and psychotherapeutic approaches on the brain volumes in the patients with OCD.\textsuperscript{16-18} So the effect of a variety of treatment modalities including psychopharmacological and cognitive behavioral therapy (CBT) on the brain volumes and neurochemicals have not been investigated enough. Therefore, in the present study, we aimed to investigate the effect of CBT on the volumes of the OFC and thalamus regions which seem to be abnormal in the patients with OCD. We hypothesized that there would be change in the volumes of the OFC and thalamus.

**Methods**

**Subjects and clinical evaluation**

This study was conducted at the Firat University, School of Medicine, Department of Psychiatry, out-patient clinics, and at the Yildirim Beyazit Diskapi Education and Investigation Hospital, Department of Psychiatry, out-patient clinics. Totally, 12 OCD patients were included into the study. The Diagnostic and Statistical Manual of Mental Disorders Fourth Version (DSM-IV)\textsuperscript{19} OCD diagnosis was done by using Turkish version of Structured Clinical Interview for DSM-IV.\textsuperscript{20} All patients were right-handed; 12 comparison volunteers were selected among healthy persons who had been recruited from the
hospital staff and had been invited to obtain their MRIs for our study. All comparison healthy subjects were also right-handed. This study was carried out under guidelines of Helsinki declaration. Written informed consent was obtained from all subjects. Apart from this, local ethics committee approval was obtained. Some criteria were used to exclude unavailable patients from the present study. They include the presence of any current or history of comorbid psychiatric disorder apart from depression which is frequently comorbid with OCD, the presence of current medical problems, or alcohol/substance abuse within the six months preceding the study, any contraindication for suffering from MRI investigation such as cardiac stent, and use of psychoactive medication within four weeks of the study. For healthy control subjects, exclusion criteria include the presence of any current or history of psychiatric disorder in self and in their first-degree relatives, the presence of current medical problems, or alcohol/substance abuse within the six months preceding the study, and any contraindication for suffering from MRI investigation such as cardiac stent.

**Procedure**

At the beginning of the present study, the course of the investigation and treatment process were told to all patients. All of them accepted to maintain the therapy program for 16 interviews. The period between the therapy sessions was planned to be one week. However, sometimes, some postponements sourced by both the clinicians and patients existed. Anyway, none of the sessions were postponed over one week. The sessions were carried out by academy of cognitive therapy-certified therapists, with several years of experience in cognitive and behavior therapy, MA, at the Firat University, School of Medicine, Department of Psychiatry, and HT, at the Yildirim Beyazit Diskapi Education and Investigation Hospital, Department of Psychiatry. The session protocol was structured as follows: Sessions 1–3—psychoeducation on OCD; sessions 4–6—arrangements of symptoms hierarchies and preparation to exposure and response prevention; session 7–12—studies on exposure and response prevention; sessions 12–16—maintaining exposure and response prevention, talking on recurrence of the OCD symptoms. Patients who missed more than two consecutive sessions were considered dropouts. The course of the severity of OCD was followed by using the Yale-Brown Obsession Compulsion Scale (Y-BOCS). Magnetic resonance imaging procedure

The MRI procedure before process was explained to the patients with OCD and healthy control subjects. They were told that we could give some anxiolytic agents for their worry. None of them required any anxiolytic agent.
MRI scans were obtained on a 1.5 Tesla General Electric signa Excite high speed scanner (Milwakuee, 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 three-dimensional spiral fast spin echo high-resolution images, with the following values: echo time (TE) = 15.6 ms, repetition time (TR) = 2000 ms, flip angle = 20°, field of view (FOV) = 240 mm, bandwidth = 20.8, slice thickness = 2.4 mm, echo spacing = 15.6 ms, 8 echoes, resolution = 0.9375 x 0.9375 x 1.328 mm. The data were stored on optical disc and loaded onto computer. The measurements were performed on a computer advanced workstation with the GE Volume Viewer voxel tool 4.2 program. The landmarks of the region of interest (ROI) were detected by using standard brain anatomy atlases and were adapted from Portas et al. and Riffkin et al. By using those guidelines, same procedure as in our previous studies was performed. The tracings of the thalamus and OFC were done by a single neuroradiologist (HY) who did not know about the diagnoses of the patients. When the OFC region was traced, some landmarks were used. The superior boundary of the OFC was defined by a line extending from the anterior commissure to the posterior commissure. The posterior boundary was accepted as the point when the olfactory sulcus was first appeared. The most inferior aspect of the cortex was accepted as the inferior boundary of the OFC. The most lateral edge of the cortex was accepted as the lateral boundary of OFC. On the other hand, the medial boundary of the OFC was accepted as the longitudinal fissure. Likewise, when the thalamus region was traced, some landmarks were used. The mammillary bodies of the hypothalamus were defined as the most anterior boundary. The point when the thalamus merged under the crus fornix was defined as the posterior boundary of the thalamus. Third ventricle was accepted as the medial boundary, whereas the inferior border was defined when the thalamus merged with the brain stem. The superior boundary was defined as the main body of the lateral ventricle. Scanning views owning to the OFC and thalamus are presented in Figure 1. As in our previous studies, all volumes for the ROIs were presented in cubic centimeters. The test–retest reliability for tracing was $r = 0.90$ for OFC and $r = 0.92$ for thalamus.

Statistical analysis

All statistical analyses were carried out by using the Statistical Package for the Social Sciences for Windows software, version 13.0 (SPSS, Chicago, IL). Group differences in demographic variables involving continuous data were computed using independent $t$ test, whereas between-group comparisons involving categorical data were assessed using Chi-square test. Volumetric comparisons regarding the OFC and thalamus were performed by using General Linear Model in the SPSS. When the volumetric data of the patients with OCD at baseline were compared to those healthy control subjects, age and total
brain volume were used as covariates. On the other hand, when comparing the OFC and thalamus volumes of the patients before and after CBT, paired $t$ test was used. Correlational relationships were done by using the Spearman’s correlation test.

**Figure 1.** Anatomic landmarks for the tracing of the OFC.
Results

In regard to demographical characteristics, including age (for the patient group, mean age ± SD = 30.12 ± 4.91 vs. 29.46 ± 4.73 years), and sex distribution, no difference was determined between the patients with OCD and healthy control subjects (P > 0.05) (Table 1).

As expected, after treatment, the patients with OCD exhibited a statistically significant decrease in the severity of obsessive-compulsive symptoms, as determined by the Y-BOCS (mean ± SD pre- vs. posttreatment

### Table 1. Some characteristics of the patient and control groups and volumetric changes in OCD patients.

<table>
<thead>
<tr>
<th></th>
<th>Patients with OCD (n = 12)</th>
<th>Controls (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>30.12 ± 4.91</td>
<td>29.46 ± 4.73</td>
</tr>
<tr>
<td><strong>Gender (female/male)</strong></td>
<td>7/5</td>
<td>6/6</td>
</tr>
<tr>
<td><strong>Handedness (right)</strong></td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td><strong>Education level (years)</strong></td>
<td>10.83 ± 2.15</td>
<td>10.16 ± 3.71</td>
</tr>
<tr>
<td><strong>Y-BOCS score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretreatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>11.66 ± 1.79</td>
<td>14.56 ± 2.42</td>
</tr>
<tr>
<td>Right</td>
<td>10.74 ± 2.33</td>
<td>13.88 ± 2.65</td>
</tr>
<tr>
<td>Posttreatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>13.75 ± 1.34</td>
<td>–</td>
</tr>
<tr>
<td>Right</td>
<td>11.04 ± 1.11</td>
<td>–</td>
</tr>
<tr>
<td><strong>OFC volume (cm³)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretreatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>5.56 ± 0.82</td>
<td>5.02 ± 0.66**</td>
</tr>
<tr>
<td>Right</td>
<td>5.48 ± 1.06</td>
<td>4.89 ± 0.70**</td>
</tr>
<tr>
<td>Posttreatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>5.11 ± 0.77**</td>
<td>–</td>
</tr>
<tr>
<td>Right</td>
<td>5.01 ± 0.89**</td>
<td></td>
</tr>
</tbody>
</table>


No significant differences exist between groups in age, handedness, education, and gender composition.

*P < 0.001, **P < 0.05.
Y-BOCS: 22.7 ± 4.3 vs. 14.4 ± 5.3; decrements of 36.6%, with a paired t test; 
\( P < 0.001 \).

At the beginning of the study, volumetric comparisons regarding the OFC and thalamus were performed by using General Linear Model, as controlling for age and total brain volume. It indicated that the patients with OCD had greater left and right thalamus volumes compared to those of healthy control subjects (for left thalamus, 5.56 ± 0.82 cm\(^3\) for the patients with OCD vs. 5.02 ± 0.66 cm\(^3\) for healthy control subjects, \( P < 0.05 \); for right thalamus, 5.48 ± 1.06 cm\(^3\) for the patients with OCD vs. 4.89 ± 0.70 cm\(^3\) for healthy control subjects; \( P < 0.05 \)). General Linear Model with controlling for age and total brain volume revealed that the patients with OCD had smaller left and right OFC volumes compared to those of healthy control subjects (for left OFC, 11.66 ± 1.79 cm\(^3\) for the patients with OCD vs. 14.56 ± 2.42 cm\(^3\) for healthy control subjects, \( P < 0.05 \); for right OFC, 10.74 ± 2.33 cm\(^3\) for the patients with OCD vs. 13.88 ± 2.65 cm\(^3\) for healthy control subjects; \( P < 0.05 \)).

When we compared baseline volumes of the patients with posttreatment ones, as controlling for the age and total brain volume, we detected that thalamus volumes significantly decreased throughout the period for both sides (for the left thalamus, from 5.56 ± 0.82 cm\(^3\) to 5.11 ± 0.77 cm\(^3\), \( P < 0.05 \); for the right thalamus, from 5.48 ± 1.06 cm\(^3\) to 5.01 ± 0.89 cm\(^3\), \( P < 0.05 \)). On the other hand, the mean left and right posttreatment thalamus volumes in OCD patients who completed the treatment protocol was not different than those of healthy control subjects (\( P > 0.05 \)). When we compared baseline volumes of the patients with posttreatment ones, as controlling for the age and total brain volume, we detected that the OFC volumes significantly increased throughout the period for only left side (for the left OFC, from 11.66 ± 1.79 cm\(^3\) to 13.88 ± 1.34 cm\(^3\), \( P < 0.05 \); for the right OFC, from 10.74 ± 2.33 cm\(^3\) to 11.04 ± 1.11 cm\(^3\), \( P > 0.05 \)). On the other hand, while the mean left posttreatment OFC volumes in OCD patients who completed the treatment protocol was not different than those of healthy control subjects (\( P > 0.05 \)), the mean right posttreatment OFC volumes was significantly smaller than those of healthy control subjects (\( P < 0.05 \)).

When we used Spearman’s correlation test to detect the relationship between the severity of obsessions and compulsions, and volumetric change in the OFC and thalamus, some important data were obtained: There was a significant positive relationship between the decrease in Y-BOCS scores and change in the volumes of thalamus in both sides (for the left thalamus, Spearman’s rho = 0.65, \( P < 0.01 \); for the right thalamus, Spearman’s rho = 0.49, \( P < 0.05 \)). On the other hand, decrease in Y-BOCS scores was negatively correlated with the change in left OFC volumes (for the left OFC, Spearman’s rho = −0.47, \( P < 0.05 \); for the right OFC, Spearman’s rho = −0.11, \( P > 0.05 \)). No other significant correlation was detected.
Discussion

In fact, this is the first investigation that examines morphometric changes of the thalamus and OFC on the patients with OCD under the CBT program. There have been obviously limited number of studies investigating the effect of therapeutic methods on brain’s neurochemical and volumetric changes in psychiatric disorders. For this reason, the studies examining this relationship are so important. First of all, we can start the discussion with the presentations of important results of this study: As expected, after treatment period, the patients with OCD exhibited a statistically significant decrease in the severity of obsessive-compulsive symptoms, as determined by the Y-BOCS (mean ± SD pre- vs. post-treatment Y-BOCS: 22.7 ± 4.3 vs. 14.4 ± 5.3; decrements of 36.6%). This finding supports the notion that regular CBT treatment shows an important efficacy in reducing obsessive-compulsive symptoms in the patients with OCD. General Linear Model indicated that the patients with OCD had greater left and right thalamus volumes compared to those of healthy control subjects and revealed that the patients with OCD had smaller left and right OFC volumes compared to those of healthy control subjects. On the other hand, when we compared baseline volumes of the patients with posttreatment ones, as controlling for the age and total brain volume, we detected that thalamus volumes significantly decreased throughout the period for both sides, with the finding that the mean left and right posttreatment thalamus volumes in OCD patients who completed the treatment protocol was not different than those of healthy control subjects. When we compared baseline volumes of the patients with posttreatment ones, as controlling for the age and total brain volume, we detected that the OFC volumes significantly increased throughout the period for only left side, with the finding that while the mean left posttreatment OFC volumes in OCD patients who completed the treatment protocol was not different than those of healthy control subjects, the mean right posttreatment OFC volumes was significantly smaller than those of healthy control subjects. To date, only three studies have been performed to evaluate the effects of psychotropic drugs and psychotherapy on brain volumes. In a randomized clinical trial, Hoexter et al. investigated the structural brain abnormalities in the patients with OCD who were treatment-naive and to detect the effects of pharmacological and CBT on regional brain volumes. As primary, they found that the patients with OCD had smaller gray matter volumes in the left putamen, bilateral medial orbito-frontal, and left anterior cingulate cortices than those of healthy control subjects. As secondary, they determined that gray matter volume abnormalities in the left putamen did not last after treatment with either fluoxetine or CBT, with a within-group comparisons demonstrating that the mean gray matter volume significantly increased in fluoxetine-treated group, while it did not change in CBT-treated group. They suggested that CBT and fluoxetine might have different mechanisms of action in the treatment of OCD. In another study, 29 pediatric patients with OCD and
same number of control subjects were compared in regard to brain volumes by using voxel-based morphometry before and after CBT. The authors found that orbito-frontal gray matter and capsula externa white matter volumes increased after CBT compared to healthy control subjects. They also determined that orbito-frontal gray matter volumes were positively correlated with changes in symptom severity after CBT period and emphasized the importance of the ventral frontal-striatal circuit in the occurrence of pediatric OCD and that of plasticity of this circuit in response to the modulatory effects of CBT. In another study on pediatric OCD patients, Gilbert et al. examined thalamic volumes in 21 patients and same number of healthy control subjects before and after 12 weeks of treatment with paroxetine. The authors found that thalamus volumes of the patients with OCD at first had significantly greater than those of healthy control subjects and that those greater volumes significantly reduced to comparable values after paroxetine treatment, with a correlation between decreases in thalamus volumes and reductions in symptom severity. They suggested that paroxetine treatment might be associated with volume reductions in thalamus and that this effect could be related to general treatment effect beyond paroxetine’s direct effect. As seen in these limited studies, pharmacological agents and psychotherapeutic interventions may lead to structural changes in the patients with OCD. This was supported by our findings. In our previous study, we determined that first applying OCD patients had significantly smaller left and right 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 and found that 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 and concluded that reductions in OFC and increase in thalamic volumes might be related to refractoriness to OCD and might not be due to changes in cingulate and caudate regions. This is why we particularly select the regions of OFC and thalamus. Previously, it has been shown that modulations in serotonergic neurotransmission by using selective serotonin reuptake inhibitors have the effect of neuroplasticity in a variety of cortical and subcortical regions involved in OCD. In the present study, as much we showed that CBT affected both sides of thalamus and left side of OFC volumes and changed them to comparable levels with those of healthy control subjects, we do not exactly know whether these changes are associated with the direct therapeutic effects of CBT or not. Our finding that we found volume reductions of only left side of OFC by using CBT can be associated with our previous result suggesting that the left OFC might be related to treatment resistance in the patients with OCD.
On the other hand, it can be speculated that overall effects of clinical improvement itself might have affected the volumes of thalamus and OFC. As for the limitations of the present study, the findings given here should be interpreted with caution because of some factors. First of all, limited number of the subjects is main limitation of the study as much regularly follow up under the CBT program is very difficult to maintain. Second, we have no placebo group to compare with the results of the CBT. Third, we performed two MRI scans for the patients with OCD as pretreatment and posttreatment but only one scanning for healthy control ones. Fourth, some sessions were halted by some patients, this might have affected our findings. Fifth, the ROI approach in volumetric investigations has the risk of interindividual variations and depends on interrater/intrarater skills and reliability, with another situation that anatomical boundaries are often defined by arbitrary criteria and may not correspond to regions associated with the illness. These factors may lead to a potential for great variability in the volumetric findings. Sixth, the fact that one radiologist did all the tracings is another limitation of our study. Seventh, we did not measure IQ values in the groups. Finally, we evaluated the changes in volumetry for only OFC and thalamus regions but not in other brain regions.

In summary, we found that CBT might volumetrically affect the key brain regions involved in the neuroanatomy of OCD. However, future studies with larger sample are required.

Declaration of Conflicting Interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by FUBAP and Yildirim Beyazit Diskapi Egitim Hastanesi Research Unit.

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