Thalamic Volume in Pediatric Obsessive–Compulsive Disorder Patients before and after Cognitive Behavioral Therapy

David R. Rosenberg, Nili R. Benazon, Andrew Gilbert, April Sullivan, and Gregory J. Moore

Background: Neurobiologic abnormalities in the thalamus have been implicated in the pathophysiology of obsessive–compulsive disorder. We recently reported increased thalamic volume in treatment-naive pediatric obsessive–compulsive disorder patients versus case-matched healthy comparison subjects that decreased to levels comparable to control subjects after effective paroxetine therapy. To our knowledge, no prior study has measured neuroanatomic changes in the thalamus of obsessive–compulsive disorder patients near illness onset before and after cognitive behavioral therapy.

Methods: Volumetric magnetic resonance imaging studies were conducted in 11 psychotropic drug-naive 8–17-year-old children with obsessive–compulsive disorder before and after 12 weeks of effective cognitive behavioral therapy monotherapy (≈30% reduction in obsessive–compulsive disorder symptom severity).

Results: No significant change in thalamic volume was observed in obsessive–compulsive disorder patients before and after cognitive behavioral therapy.

Conclusions: Our findings suggest that reduction in thalamic volume after paroxetine therapy may be specific to paroxetine treatment and not the result of a general treatment response or spontaneous improvement. These results are preliminary in view of the small sample studied.

Introduction

Obsessive–compulsive disorder (OCD) is a severe, prevalent (Flament et al 1988; Hanna 1995; Valleni-Basile et al 1994), and often chronically disabling illness with onset in childhood or adolescence in up to 80% of all cases (Pauls et al 1995). Investigation of early-onset OCD is therefore critical, as it can minimize potential confounds of illness duration and treatment intervention (Chakos et al 1994; Keshavan et al 1994).

The thalamus is a site of integration and relay and is thought to be involved in the pathophysiology of OCD (Baxter 1992; Insel 1992; Modell et al 1989). Partial thalamotomy, for example, can reduce symptom severity in treatment-refractory OCD patients (Chiocca and Martuza 1990). Metabolic abnormalities in the thalamus of adult OCD patients associated with symptom severity and response to treatment (Baxter 1992; Cottraux et al 1996; Lucey et al 1995; McGuire et al 1994; Perani et al 1995; Rauch et al 1994) provide more direct evidence for involvement of the thalamus in OCD. More recently, Gilbert et al (2000) reported increased thalamic volume in 21 treatment-naive pediatric OCD patients versus 21 case-matched healthy comparison subjects.

Pharmacologic treatment studies have repeatedly demonstrated the effectiveness of the selective serotonin re-uptake inhibitors (SSRIs) in treating OCD (Grados et al 1999) and have spawned the “serotonin hypothesis” of OCD. Baxter et al (1996) have hypothesized that the preferential response of OCD patients to SSRIs may be a result of thalamocortical alterations in serotonergic neurotransmission, as the thalamus has a particularly dense serotonergic innervation (Chugani et al 1998; Oke et al 1997). Serotonin has been shown to play a critical role in modulating thalamocortical function (Bennett-Clarke et al 1995, 1996; Chubakov et al 1986; Lebrand et al 1996; Rhoades et al 1994; Salt and Eaton 1996). In adult OCD patients, reduction in metabolic activity has been observed after SSRI treatment (Baxter 1992). Using volumetric magnetic resonance imaging (MRI), Gilbert et al (2000)
Table 1. Demographic and Clinical Data from Children with Obsessive–Compulsive Disorder (OCD)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>OCD Patients (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>12.89 ± 3.23 (8.33–16.83)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>6</td>
</tr>
<tr>
<td>Females</td>
<td>5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>44.46 ± 15.06 (24.09–72.73)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>147.55 ± 24.37 (96.52–175.26)</td>
</tr>
<tr>
<td>Parental SES*</td>
<td>2.09 ± 0.70 (1.00–3.00)</td>
</tr>
<tr>
<td>Age of onset of first clinical presentation (years)</td>
<td>10.52 ± 2.24 (7.50–15.17)</td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>2.38 ± 2.28 (0.08–6.83)</td>
</tr>
</tbody>
</table>

*Parental socioeconomic status was measured by assessing parental education level and the highest level of occupational functioning of the parents on a scale of 1 to 5, with 1 representing highest parental SES and 5 representing lowest parental SES (Hollingshead 1978).

reported a reduction in thalamic volume in 10 pediatric OCD patients associated with reduction in OCD symptom severity after treatment with the SSRI paroxetine. These reductions may not be specific to paroxetine therapy, however, as they could reflect a more generalized treatment response or even spontaneous improvement. It is also possible that the reduction in thalamic volume associated with paroxetine treatment in OCD patients represented a nonspecific drug effect that was independent of the subject’s symptomatic improvement, as can be seen with basal ganglia volume increases associated with neuroleptic treatment in schizophrenic patients (Chukos et al 1994; Keshavan et al 1994).

To our knowledge, no prior study of OCD patients has measured thalamic volume before and after cognitive behavioral therapy (CBT) monotherapy in early-onset patients. Therefore, we performed a volumetric MRI study in treatment-naive pediatric OCD patients focusing on the in vivo neuroanatomy of the thalamus before and after CBT to determine whether reductions in thalamic volume were specific to paroxetine therapy or due to a more general treatment response.

Methods and Materials

Subjects

Seventeen right hand–dominant, psychotropic drug–naive, 8–17-year-old OCD patients were recruited after being referred to our child psychiatry outpatient clinic at Wayne State University. Four patients recruited into this study required psychopharmacologic intervention before completing CBT and did not have a follow-up MRI scan. One patient refused follow-up MRI (his baseline scan also had considerable motion artifact), whereas another patient and family refused MRI scanning. Thus, 11 patients were analyzed before and after CBT (Table 1).

Patients and their parents were interviewed with the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version (Kaufman et al 1997). Exclusion criteria included any lifetime history of psychosis, bipolar disorder, major depressive disorder, eating disorders, substance abuse or dependence, Tourette’s syndrome or other tic-related conditions, attention-deficit/hyperactivity disorder, significant medical or neurologic disorders, autism, mental retardation, or learning disabilities. Three patients had comorbid anxiety disorders, two had dysthymia, one had attention-deficit disorder without hyperactivity, one had trichotillomania, and five had OCD as their sole diagnosis. Legal guardians provided written informed consent and children gave written assent before initiation of all studies.

Clinical Assessments

The children’s version of the Yale–Brown Obsessive Compulsive Scale (CY-BOCS; Scahill et al 1997) assessed OCD symptom severity (range 0–40; obsessive symptoms, mean score = 11 [SD 3]; compulsive symptoms, mean score = 12 [SD 2]; total mean score = 22 [SD 4]). All patients with OCD had a pretreatment CY-BOCS score of at least 17. The 17-item Hamilton Depression Rating Scale (Hamilton 1967) was used to measure severity of depression (mean score = 7 [SD 5]), whereas severity of anxiety was assessed by the Hamilton Anxiety Rating Scale (Hamilton 1959; mean score = 8 [SD 6]). A neuropsychologic screening examination measured general intelligence (Ammons and Ammons 1962), motor coordination (Knights and Norwood 1980), and attention (Wechsler 1991) and revealed no abnormalities.

MRI Studies

Volumetric MRI studies were performed at the Children’s Hospital of Michigan Imaging Center (1.5 T, Horizon 5.7, General Electric, Milwaukee), which is dedicated to scanning only children. Image acquisition and analysis were identical to the methods used in our previous study of thalamic volume in pediatric OCD patients before and after paroxetine therapy and case-matched healthy comparison subjects (Gilbert et al 2000) and are not described here.

Neuroanatomic boundaries for the left and right thalami were adapted from published neuroimaging studies of the thalamus (Andreason et al 1994; Buchsbaum et al 1996; Pakkenberg 1992; Portas et al 1998; Staal et al 1998). A manual tracing technique was utilized to acquire discrete measurements from the left and right thalami (see Figure 1 [Gilbert et al 2000] for a representative multislice series of coronal images of thalamic measurement with boundary delineation). The anterior boundary was the mammillary bodies and interventricular foramen, and the posterior boundary was where the thalamus merged under the crus fornix. The lateral boundary was defined as the internal capsule and the third ventricle was considered the medial boundary. The inferior boundary was the hypothalamus, and the superior boundary was the main body of the lateral ventricle (Portas et al 1998). The number of coronal slices used to quantify the thalamus ranged from 13 to 22 slices, with an average of 17.5. Detailed definitions are available upon request. Intracranial volume mea-
All patients were treated with CBT only and did not receive any psychotropic medication during the course of the study, nor through the behavioral hierarchy of anxiety-provoking situations. Obsessions in a goal-oriented manner, allowing them to progress provide patients with specific tools with which to respond to their fears. The four steps (relabel, reattribute, refocus, and revalue) activities and situations that they avoid doing because of their compulsions was assigned a value that indicated a subjective unit of distress on a scale of 0 to 100, in which the item at 100 is the performance of compulsive behaviors. Each obsession and compulsion was assigned a value that indicated a subjective unit of distress on a scale of 0 to 100, in which the item at 100 is the most anxiety provoking to confront. Behavioral hierarchies were constructed. With the support and assistance of the therapist, patients were directed to confront their fears in a graduated fashion. Parents were invited to attend four of the 12 sessions and were offered psychoeducation and coaching on how to cope more effectively with their child’s symptoms. To supplement and enhance E/RP, Schwartz’s Four-Step Self-Treatment Method (Schwartz et al 1996) was utilized to help patients cultivate a sense of control and mastery by their total CY-BOCS scores and obsessive and compulsive subscale scores (Table 2). There was also a significant decrease in anxiety and depressive symptom severity.

### Results

After 12 weeks of CBT, patients with OCD showed a significant decrease in OCD symptom severity as reflected by their total CY-BOCS scores and obsessive and compulsive subscale scores (Table 2). There was also a significant decrease in anxiety and depressive symptom severity.

**Data Analysis**

Thalamic volume and intracranial volume were analyzed using paired t tests before and after CBT. Paired t tests were also used to compare pre- and posttreatment CY-BOCS and Hamilton Depression and Anxiety scores before and after CBT. An unpaired t test was also used to compare all 15 pretreatment thalamic volumetric measurements in OCD patients (including study noncompleters) to the 11 post-CBT scans. Two-way gender by diagnosis analyses of covariance were conducted to delineate gender effects. Two-tailed significance tests (p < .05) are reported throughout.

### CBT

After completion of the clinical assessment and baseline volumetric MRI study, the patients started a 12-week course of CBT by a cognitive behavioral psychologist (NRB). Patients received 14 60-min sessions of CBT over a period of 12 weeks. Treatment was derived from two similar therapy manuals (March and Mulle 1998; Schwartz et al 1996). Standardized exposure and response prevention (E/RP) techniques were used to disrupt the association between 1) the obsessions and anxiety and 2) the anxiety and the performance of compulsive behaviors. Each obsession and compulsion was assigned a value that indicated a subjective unit of distress on a scale of 0 to 100, in which the item at 100 is the most anxiety provoking to confront. Behavioral hierarchies were constructed. With the support and assistance of the therapist, patients were directed to confront their fears in a graduated fashion. Parents were invited to attend four of the 12 sessions and were offered psychoeducation and coaching on how to cope more effectively with their child’s symptoms. To supplement and enhance E/RP, Schwartz’s Four-Step Self-Treatment Method (Schwartz et al 1996) was utilized to help patients cultivate a sense of control and mastery by their total CY-BOCS scores and obsessive and compulsive subscale scores (Table 2). There was also a significant decrease in anxiety and depressive symptom severity.

**Table 2. Clinical Assessment Data from Psychotropic Medication–Naive Pediatric Patients with Obsessive–Compulsive Disorder (OCD) before and after Cognitive Behavioral Therapy (CBT)**

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Patients with OCD before treatment (mean ± SD)</th>
<th>Patients with OCD after CBT (mean ± SD)</th>
<th>p</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total score CY-BOCS</td>
<td>22.45 ± 4.16</td>
<td>10.45 ± 5.48</td>
<td>.000</td>
<td></td>
</tr>
<tr>
<td>Obsessive subscale score</td>
<td>10.82 ± 2.64</td>
<td>4.73 ± 2.87</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>Compulsive subscale score</td>
<td>11.64 ± 2.34</td>
<td>5.64 ± 2.80</td>
<td>.000</td>
<td></td>
</tr>
<tr>
<td>HAM-A</td>
<td>7.91 ± 5.99</td>
<td>2.00 ± 2.72</td>
<td>.01</td>
<td></td>
</tr>
<tr>
<td>HAM-D</td>
<td>7.09 ± 4.91</td>
<td>2.18 ± 2.82</td>
<td>.008</td>
<td></td>
</tr>
<tr>
<td>Brain region</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial volume (cm³)</td>
<td>1208.17 ± 115.27</td>
<td>1203.34 ± 122.20</td>
<td>.69</td>
<td></td>
</tr>
<tr>
<td>Right thalamic volume (cm³)</td>
<td>4.37 ± 0.95</td>
<td>4.32 ± 1.10</td>
<td>.90</td>
<td></td>
</tr>
<tr>
<td>Left Thalamic volume (cm³)</td>
<td>4.39 ± 1.04</td>
<td>4.46 ± 1.15</td>
<td>.85</td>
<td></td>
</tr>
</tbody>
</table>

CY-BOCS, children’s version of the Yale–Brown Obsessive Compulsive Scale; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale.

*There were 11 OCD patients studied before and after cognitive behavioral therapy

*Paired t test, df = 10.

Measurement has also been described previously (Rosenberg et al 1997).

All measurements were made by a single well-trained and reliable rater (AS). Pre- and posttreatment patients were measured at the same time with the rater blind to the time or identity of the scans. Interrater (AS, AG) and intrarater reliabilities for thalamic measurements (r = .97–.99) and intracranial volume (r = .99) were high.

### Results

After 12 weeks of CBT, patients with OCD showed a significant decrease in OCD symptom severity as reflected by their total CY-BOCS scores and obsessive and compulsive subscale scores (Table 2). There was also a significant decrease in anxiety and depressive symptom severity.

Left [t(20) = 0.16, p = .88, confidence interval (CI) = 1.05–0.9] and right thalamic volumes [t(20) = 0.12, p = .91, CI = 0.86–0.97] did not change significantly in the 11 OCD patients after CBT (Figure 1). No significant differences were observed between pretreatment right
[t(24) = 0.22, p = .79, CI = 0.71–0.89, 4.40 cm³ ± 0.88 cm³ vs. 4.32 cm³ ± 1.10 cm³, respectively] and left thalamic volumes [t(24) = 0.28, p = .79, CI = 1.00–0.77, 4.34 cm³ ± 1.03 cm³ vs. 4.46 cm³ ± 1.15 cm³, respectively] in the 15 patients studied at baseline (including study noncompleters) and the 11 patients after 12 weeks of CBT (study completers). Intracranial volume also did not differ significantly in OCD patients before and after CBT [t(20) = 0.10, p = .93, CI = 100.82–110.49).

Comparable ages were observed in male (12 ± 3) and female patients (14 ± 3) with OCD [t(9) = 0.87, p = .41]. Age of onset of illness did not differ in male and female OCD patients [t(9) = 0.22, p = .83; 11 ± 3 years vs. 10 ± 1.5 years]. There were no gender-related differences in OCD patients before or after treatment in thalamic and intracranial volumes.

Discussion
To our knowledge, this is the first neuroimaging study of treatment-naive OCD patients investigating thalamic volume before and after CBT. Our results suggest that abnormalities in thalamic anatomy may not be reversible with effective CBT. The observed differences between right and left thalamic volumes in pediatric OCD patients before and after CBT were ±1% and ±2%, respectively. When baseline right and left thalamic volumes for the 15 OCD patients (including study noncompleters) were compared to the 11 post-CBT thalamic measures (study completers), comparable differences between right (±1%) and left (±1%) thalamic volumes were observed. The temporal stability of the in vivo measure of thalamic volume before and after CBT is, therefore, comparable to the temporal stability of thalamic volume observed in healthy children scanned at 12-week intervals (Gilbert et al 2000). In contrast, a 19% reduction in thalamic volume was observed in 10 OCD patients studied before and after paroxetine therapy. This suggests that the preferential therapeutic effects of SSRIs such as paroxetine in OCD may be related to their impact on serotonin neurotransmission in thalamocortical circuitry (Baxter et al 1996). Reductions in thalamic volume may also be specific to paroxetine treatment rather than the result of a general treatment response or spontaneous improvement; however, nonspecific drug effects independent of symptom improvement cannot be ruled out.

Given the small sample size, our findings of no change in thalamic volume after CBT in OCD patients must be considered preliminary and require replication; however, a much larger effect size (d = 1.28) was observed for reduction in thalamic volume in 10 OCD patients after paroxetine treatment (Gilbert et al 2000) compared with change in thalamic volume in 11 OCD patients after CBT (d = 0.07). Although mean pretreatment total CY-BOCS OCD scores were higher in the patients treated with paroxetine than in those who received CBT [28.19 ± 5.99 vs. 22.45 ± 4.16, t(30) = 3.83, p = .001], pretreatment thalamic volumes were comparable in both groups [4.65 ± 1.05 vs. 4.37 ± 1.10, respectively, for the right thalamus, t(30) = 0.34 p = .74, CI = 0.65–0.91; 4.52 ± 1.01 vs. 4.39 ± 1.04, respectively, for the left thalamus, t(30) = 0.73, p = .47, CI = 0.50–1.05]. Mean pretreatment Hamilton Depression Rating Scale scores [7.09 ± 4.91 vs. 7.80 ± 4.64, respectively, t(19) = 0.34, p = .74], Hamilton Anxiety Rating Scale scores [7.91 ± 5.99 vs. 8.30 ± 4.99, respectively, t(19) = 0.16, p = .87], Yale

Figure 1. Left (A) and right (B) thalamic volumes before and after treatment. Lines indicate means. OCD, obsessive–compulsive disorder; CBT, cognitive behavioral therapy.
Global Tic Severity Scale (Leckman et al 1989) scores
[3.45 ± 7.71 vs. 2.20 ± 5.69, respectively, t(19) = 0.42, p = .68], illness duration [2.37 ± 2.28 vs. 1.31 ± 1.37, respectively, t(19) = 1.28, p = .22], and mean age of onset of OCD [10.52 ± 2.24 vs. 10.08 ± 1.76, respectively, t(19) = 0.50, p = .62] were also comparable in both groups.

It should be noted that, as in our prior study comparing thalamic volume before and after paroxetine therapy (Gilbert et al 2000), we were unable to distinguish discrete thalamic nuclei. Using proton magnetic resonance spectroscopy, Fitzgerald et al (2000) demonstrated localized functional neurochemical marker abnormalities in the medial thalamus but not the lateral in a similar sample of treatment-naive pediatric OCD patients, as compared with healthy control subjects. Specifically, reductions in N-acetyl-aspartate, a marker of neuronal viability, in the medial thalamus but not the lateral in pediatric OCD patients were observed. Neurobiological abnormalities in the dorsomedial nucleus of the thalamus are believed to be critically involved in the pathogenesis of OCD (Modell et al 1989). Our prior volumetric studies have identified localized abnormalities in other regions of interest in OCD including the prefrontal cortex, with case–control differences observed in the ventral prefrontal cortex but not the dorsal (Rosenberg and Keshavan 1998) and the putamen but not the caudate nucleus (Rosenberg et al 1997).

In this study patients were not randomly assigned to CBT or pharmacotherapy. Treatment cell was based on clinician and parent/patient decision. A controlled, randomized study would have been superior for delineating the specificity of neuroanatomic change in the thalamus in relation to paroxetine therapy versus CBT. Moreover, full treatment effects can be delayed beyond 12 weeks and up to several months (Grados et al 1999) so that volumetric assessment after 12 weeks of CBT is indicated.

Recent investigation also suggests that more sophisticated neuroimaging techniques such as positron emission tomography (PET), functional MRI, and magnetic resonance spectroscopy may be superior to standard volumetric MRI for measuring abnormalities in OCD (Bartha et al 1998). Using PET, Schwartz et al (1996) observed a significant decrease in caudate metabolic activity after CBT in adult OCD patients comparable to changes reported after pharmacotherapy (Baxter 1992). Although putative radiation risks make PET studies more difficult in pediatric populations, functional MRI studies in adult OCD patients (Breiter et al 1996) suggest that this technique may prove viable in pediatric OCD patients. In fact, in vivo functional MRI studies that actively drive the system and magnetic resonance spectroscopy studies of brain chemistry may be superior to standard neuroanatomic MRI studies in neuropsychiatric conditions such as OCD (Bartha et al 1998; Rauch et al 1994).

Taken together, our findings suggest that reductions in thalamic volume may be relatively specific to effective SSRI treatment and may not be due to a more general treatment response or spontaneous resolution of symptoms. Longitudinal studies of patients treated with paroxetine and CBT beyond 12 weeks are critical to tease apart mechanisms of response to treatment in OCD and their relationship to thalamic volumetric measures. Equally critical are future studies before and after SSRI treatment and CBT in brain regions other than the thalamus, particularly the prefrontal cortex and striatum.

This work was supported in part by the Joe Young Sr. Foundation and grants from the National Institute of Mental Health, Rockville, Maryland (Nos. MH01372 and MH59299) and the National OCD Foundation, Milford, Connecticut, to DRR.

We are grateful to Dr. Judith Rapoport for her consultation on this data, Dr. Joel Ager for statistical consultation, and Shauna MacMillan and Carla Nolan for assistance with manuscript production.

References


