Decrease in Thalamic Volumes of Pediatric Patients With Obsessive-compulsive Disorder Who Are Taking Paroxetine

Andrew R. Gilbert, MD; Gregory J. Moore, PhD; Maher S. Keshavan, MD; Lori Anne D. Paulson; Vikram Narula; Frank P. Mac Master; Carol M. Stewart, RNC; David R. Rosenberg, MD

Background: Thalamic dysfunction has been implicated in obsessive-compulsive disorder (OCD). While OCD frequently has its onset during childhood, to our knowledge, no prior study has measured neuroanatomical changes in the thalamus of patients with OCD near the onset of illness, and before and after treatment.

Methods: Volumetric magnetic resonance imaging studies were conducted in 21 psychotropic drug-naive children, aged 8 to 17 years, with OCD and 21 case-matched healthy comparison subjects. Magnetic resonance imaging studies were also conducted in 10 of the 21 patients with OCD after 12 weeks of monotherapy with the selective serotonin reuptake inhibitor, paroxetine hydrochloride.

Results: Thalamic volumes were significantly greater in treatment-naive patients with OCD than in controls but declined significantly after paroxetine monotherapy to levels comparable with those of controls. Decrease in thalamic volume in patients with OCD was associated with reduction in OCD symptom severity.

Conclusions: Our findings provide new evidence of thalamic abnormalities in pediatric OCD and further suggest that paroxetine treatment may be paralleled by a reduction in thalamic volume. These reductions may, however, not be specific to paroxetine treatment and could be due to a more general treatment response, and/or spontaneous improvement in symptoms. Our findings are preliminary given the small sample size and our inability to measure discrete thalamic nuclei.

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OBSESSIVE-COMPULSIVE disorder (OCD) has a lifetime prevalence of 2% to 3%1-3 with pediatric onset in as many as 80% of cases.4 Investigation of the developmental neurobiology of the disorder is, therefore, best accomplished by studying early onset illness in childhood to minimize potentially confounding factors of long-term illness duration and treatment intervention.

Abnormalities in the thalamus, a sensory and motor gateway to the cortex, are believed to be involved in the expression and pathophysiological mechanisms most often implicated in the formation of OCD symptoms.5-7 Neurosurgical interventions such as partial thalamotomy that decrease OCD symptoms in treatment-refractory patients with OCD provide indirect support for this hypothesis.5 More direct evidence comes from functional neuroimaging studies in adult patients with OCD that demonstrate metabolic abnormalities within the thalamus that have been correlated with OCD symptom severity and subsequent treatment response.6,8-11 Serotonin is the neurotransmitter most implicated in the pathophysiology of OCD. Pharmacological treatment studies have demonstrated the effectiveness of the selective serotonin reuptake inhibitors (SSRIs) in the treatment of OCD.12 This selective serotonergic response has led to the “serotonin hypothesis” of OCD.

The thalamus is a densely serotonergic region.13 Serotonin is also a complex modulator of thalamocortical development and activity.14-19 Chugani et al20 reported high regional serotonin synthesis in the thalamus. Baxter et al21 have reported decreases in thalamic metabolic activity in adult patients with OCD after SSRI treatment. The preferential therapeutic effects of SSRIs in OCD may arise principally from their potent actions on serotonin neurotransmission within thalamocortical circuits.22

Jenike et al23 reported no thalamic volumetric differences between adult patients with OCD and control subjects. Most of these patients had long-term illness duration and had been treated with SSRIs and other central nervous system–active medi-
SUBJECTS AND METHODS

SUBJECTS

Twenty-eight right-hand dominant, psychotropic-naïve, pediatric outpatients with OCD, aged 8 to 17 years, and 28 healthy controls matched pairwise for age, sex, handedness, weight, height, and parental socioeconomic status were studied. All patients recruited were referred to our child psychiatry outpatient clinic at Wayne State University, Detroit, Mich. Two patients with OCD refused to undergo MRI scanning; 5 patients with OCD and 2 controls were also excluded because of motion artifact and magnetic field inhomogeneities. Thus, 21 case-control pairs were analyzed (Table 1).

Patients were diagnosed using DSM-IV criteria using the Schedule for Affective Disorders and Schizophrenia for School-aged Children–Present and Lifetime (K-SADS-PL) versions. All subjects and their parent(s) were interviewed by a board-certified child and adolescent psychiatrist (D.R.R.). Exclusion criteria for patients and controls were lifetime history of unipolar or bipolar disorder, psychosis, eating disorders, substance abuse or dependence, Sydenham chorea, Tourette syndrome and other tic-related conditions, conduct disorder, significantly debilitating medical or neuropsychologic conditions, pervasive developmental disorders, mental retardation or learning disorders. Seven of the 21 patients had comorbid anxiety disorders, 2 had dysthymia, 2 had oppositional defiant disorders, 1 had attention-deficit disorder without hyperactivity, 1 had trichotillomania, and 10 had OCD as their sole diagnosis. There was no history of psychiatric illness in controls or in any of their first-degree relatives. Familial psychopathology was assessed using Family History Research Diagnostic Criteria. The child's parents served as informants. Prior to all studies, legal guardians gave written informed consent, and all subjects provided written assent.

CLINICAL ASSESSMENTS

The Children’s Yale-Brown Obsessive Compulsive Scale (CYBOCS) measured OCD symptom severity (obsessive symptoms, mean [SD] score, 14.10 [3.77]; compulsive symptoms, mean [SD] score, 14.10 [3.45]; total mean [SD] score, 28.19 [5.99]). All patients with OCD had a pretreatment total CYBOCS score of at least 19. The 17-item Hamilton Depression Rating Scale measured severity of depression (mean [SD] score, 9.37 [6.67]) and the Hamilton Anxiety Rating Scale measured severity of anxiety (mean [SD] score, 10.24 [6.4]). Tic severity was measured with the Yale Global Tic Severity Scale (mean [SD] score 1.67, [4.12]). A neuropsychological screening examination assessed general intelligence, cerebral dominance, manual dexterity, and attention. No significant differences were noted between case-control pairs on any of these measures. One patient with OCD was unable to complete the neuropsychological screening examination because of severity of illness.

MRI STUDIES

All volumetric MRI scans were conducted at the Children’s Hospital of Michigan Imaging Center (1.5-T, Horizon 5.7, General Electric, Milwaukee, Wis). Image acquisition and analysis have been described in detail previously. Briefly, image quality and clarity as well as patient head position and cooperation were determined with a sagittal scout sequence. A 3-dimensional spoiled gradient echo pulse sequence obtained 124 1.5-mm-thick contiguous coronal images (echo time = 5 milliseconds, repetition time = 25 milliseconds, acquisition matrix = 256 × 256 pixels, field of view = 24 cm, and flip angle = 40°). To facilitate image orientation, coronal slices were obtained perpendicular to the anterocommissure-posterocommissure line. Axial proton density and T2-weighted images were obtained to exclude structural abnormalities on MRI scans. National Institutes of Health image software (version 1.61) was used to measure anatomical data. This technique yields valid and reliable neuroanatomical measurements with a semiautomated segmentation approach.

Neuroanatomical boundaries were determined by reference to standard neuroanatomical atlases and detailed definitions (available on request) were adapted from previously published psychiatric neuroimaging studies of the thalamus. Intracranial volume measurement has been described in our previous investigations.

VOLUMETRIC COMPARISONS BETWEEN TREATMENT-NAÏVE PATIENTS WITH OCD AND CONTROLS

Psychotropic-naïve patients with OCD had significantly larger thalamic volumes than controls (t0 = 2.71, P = .01; F1,36 = 5.65, P = .02; 16% difference between groups) (Table 2). A moderate effect size (df = 0.86) for abnormality in thalamic anatomy was observed in pediatric patients with OCD. Case-matched control pairs did not differ in intracranial volume (t0 = 1.26, P = .22; F1,39 = 1.59, P = .21). No significant correlations were observed between thalamic volumes and clinical or neuropsychological inventories, illness duration, or age of onset of illness.

TREATMENT RESPONSE

After 12 weeks of paroxetine therapy, patients with OCD showed a significant decrease in OCD symptom severity as reflected by their total CYBOCS scores, obsessive subscale scores, and compulsive subscale scores (Table 3). Seven of the 10 subjects were considered treatment responders (>30% improvement on the CYBOCS score) and 3 nonresponders (<30% improvement on the CYBOCS score). There was a significant reduction in anxiety but no significant change in severity of depression or tics.
Separate measurements were obtained for the left and right thalami using a manual tracing technique. The mamillary bodies and interventricular foramina were used as the anterior boundaries. The internal capsule was considered the lateral boundary, the third ventricle the medial boundary, and the hypothalamus the inferior boundary. The posterior boundary was defined by where the thalamus merged under the crus fornix. The superior boundary was the main body of the lateral ventricle (Figure 1).43

The number of coronal slices used to quantify the thalamus ranged from 14 to 20 slices, with an average of 17.5 slices.

Measurements were made by a single well-trained and reliable rater (A.R.G.). Pretreatment and posttreatment patients and controls were measured concurrently with the rater unaware of time or of the identity of MRI scans. In- terrater (F.P.M. and A.R.G.) and intrarater reliabilities for thalamic measurements (r = 0.98-0.99) and intracranial volume (r = 0.99) were very high.

PAROXETINE TREATMENT

After completion of the clinical assessment and baseline volumetric MRI study, 13 of the 21 patients with OCD were given paroxetine hydrochloride, 10 mg/d. Eight of the 21 patients and their parents chose nonmedication therapy and/or rejected medication intervention. Paroxetine hydrochloride was titrated to a maximum of 60 mg/d (mean [SD] paroxetine hydrochloride dose, 51.00 ± 8.76 mg/d; range, 40-60 mg/d). Patients were monitored for medication side effects and adverse experiences during the 12-week treatment trial. After 12 weeks of paroxetine therapy, 10 patients with OCD underwent a second follow-up MRI scan. Two patients refused the follow-up MRI scan and, in 1 patient, excess motion artifact precluded measurement. None of the patients had significant side effects during the 12-week paroxetine trial. The same clinical rating scales were used to compare patients with OCD and controls on neuropsychological screening measures, age, height, weight, and parental socioeconomic status (Table 1).

Paired t tests and ANCOVAs with intracranial volume as a covariate were then conducted to assess differences in thalamic volumes between patients with OCD before and after treatment. Paired t tests were used to compare intra- cranial volume in patients with OCD before and after treatment. Paired t tests compared pretreatment vs post- treatment CYBOCS, Hamilton Depression Rating Scale, Hamilton Anxiety Scale, and Yale Global Tic Severity Scale scores before and after paroxetine treatment. Pearson and partial correlations were used to determine the association between thalamic and intracranial volumes and age, clinical and neuropsychological inventories, and illness duration. Two-way sex by diagnosis ANCOVAs were conducted to delineate sex effects. Differences in left and right thalamic volumes were also examined using repeated-measures ANOVAs in which the main effects of side, diagnostic group, and group by side interaction were tested. Because no significant differences in laterality interaction effects were detected in case-control pairs, right and left thalamic volumes were pooled (Table 2). Two-tailed significance tests (P < .05) are presented throughout.

### Table 1. Clinical and Demographic Characteristics of Pediatric Patients With OCD and Healthy Control Subjects*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients With OCD (n = 21)</th>
<th>Healthy Control Subjects (n = 21)</th>
<th>t†</th>
<th>df‡</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>12.35 ± 2.93 (8.08-17.33)</td>
<td>12.47 ± 2.64 (8.33 ± 17.17)</td>
<td>0.14</td>
<td>40</td>
<td>.99</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of males</td>
<td>7</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of females</td>
<td>14</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>43.83 ± 16.18 (17.27-79.55)</td>
<td>51.52 ± 15.56 (27.27-79.55)</td>
<td>0.65</td>
<td>40</td>
<td>.56</td>
</tr>
<tr>
<td>Height, cm</td>
<td>151.67 ± 12.58 (121.92-172.72)</td>
<td>155.06 ± 14.11 (121.92-180.34)</td>
<td>0.82</td>
<td>40</td>
<td>.42</td>
</tr>
<tr>
<td>Parental SES§</td>
<td>2.52 ± 0.75 (1.00-4.00)</td>
<td>2.71 ± 0.56 (2.00-4.00)</td>
<td>0.93</td>
<td>40</td>
<td>.36</td>
</tr>
<tr>
<td>Age of onset of first clinical presentation, y</td>
<td>10.49 ± 2.92 (5.25-15.33)</td>
<td>...</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of illness, y</td>
<td>1.86 ± 1.84 (0.25-7.00)</td>
<td>...</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Pediatric patients with obsessive-compulsive disorder (OCD) were psychotropic naïve. Data are presented as mean ± SD, unless otherwise indicated. Numbers in parentheses indicate reference ranges. Ellipses indicate not applicable.
†Indicates independent statistic using the paired t test.
‡df indicates degrees of freedom.
§Parental SES indicates parental socioeconomic status that assesses parental education and occupational functioning on a scale of 1 (highest) to 5 (lowest).24
Significant differences in thalamic volumes were observed between treatment-naïve patients with OCD and case-matched controls (t18 = 2.19, P = .01, F1,16 = 6.19, P = .02; 10.10 ± 1.86 cm³ vs 7.91 ± 1.72 cm³, respectively). Thalamic volume decreased significantly in patients with OCD after paroxetine treatment (t9 = 2.95, P = .02, F1,16 = 8.15, P = .01; 19% reduction). A large effect size (df = 1.28) was observed for reduction in thalamic volume after paroxetine treatment. Thalamic volume did not differ significantly between patients with OCD after paroxetine treatment and controls (t18 = .39, P = .70, F1,16 = .10, P = .76; 8.18 ± 1.26 cm³ vs 7.91 ± 1.72 cm³, respectively) (Figure 2). Intra-cranial volume did not differ significantly between patients with OCD before and after paroxetine therapy (t9 = 1.37, P = .21; 1211.25 ± 84.51 cm³ vs 1190.30 ± 104.78 cm³, respectively). Reduction in thalamic volume was correlated with reduction in OCD symptom severity as measured by the CYBOCS (r = 0.74, P = .02) (Figure 3). Change in thalamic volume was not associated with a change in depressive, anxiety, or tic symptom severity. Paroxetine dosage was also not correlated with thalamic volume or change in thalamic volume after treatment.

To evaluate the significance of our findings, test-retest reliability of thalamic volumetric measurements were obtained in 8 healthy pediatric controls who received a baseline MRI scan and were then rescreened approximately 12 weeks later. Controls did not receive medication. The temporal stability of the in vivo measure of thalamic volume in healthy children was ±5.6% of the initial measure on repeated scanning (7.70 ± 1.84 cm³ vs 8.16 ± 1.93 cm³, respectively). Thus, the observed differences in thalamic volumes between patients with OCD before treatment and controls and the decrease in thalamic volume seem to be statistically significant.

SEX

Comparable ages were observed in male (mean ± SD age, 11.13 ± 1.49 years) and female patients (11.42 ± 3.19 years) with OCD. Age of onset of illness did not differ between

Figure 1. Representative multislice composite series of coronal images demonstrating the boundaries delineating measurement of thalamic volume.
male and female patients with OCD (t₀ = .643, P = .54; 10.64 ± 1.43 years vs 9.83 ± 1.93 years, respectively). No sex-related differences were noted in thalamic and intracranial volumes between patients with OCD before and after treatment or controls.

To our knowledge, this is the first neuroimaging study of treatment-naıve patients with OCD to demonstrate increased thalamic volumes that decrease following treatment with the SSRI, paroxetine. Our results suggest that abnormalities in thalamic anatomy may represent a central neurobiological deficit in this illness and may be reversible with effective paroxetine treatment. Reductions in thalamic volume may, however, not be specific to paroxetine treatment and might be the result of a general treatment response or spontaneous improvement.

While most studies of pediatric patients with OCD report an approximately 2:1 prevalence of males to females,¹⁰ twice as many female subjects were enrolled in this study. Tic-related OCD is especially common in young

**COMMENT**

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date volumetric abnormalities were not observed be-
tabolism in animals. Increased thalamic volumes in
14-17,19 Serotonin agonists decrease brain glucose me-
latory role in thalamocortical development and activ-
recruitment, the male-female ratio would more closely
also a small sample so that perhaps with additional
matched controls studied at the University of Pittsburgh
naı¨ve patients with OCD are consistent with previous find-
ing brain anatomy.

The increased thalamic volumes in psychotropic-naı¨ve patients with OCD may be consistent with prior reports of hypermetabolism and in-
creased regional cerebral blood flow in the thalamus of adult patients with OCD6,8,10,50 that decreased after SSRI intervention. This may, in part, explain the finding of Jenike et al23 of no thalamic volumetric differences be-
tween adult patients with OCD and controls. Most of the patients they had studied was treated with psychoac-
tive medications, particularly SSRIs. This underscores the
importance of controlling for treatment intervention as well as illness duration and comorbidity when measuring
brain anatomy.

The increased thalamic volumes in psychotropic-naı¨ve patients with OCD are consistent with previous find-
ings in a similar sample of patients with OCD and case-
matched controls studied at the University of Pittsburgh Medical Center51 and elsewhere23,32 demonstrating in-
creased ventral prefrontal cortical volumes in patients with

Ventral prefrontal cortex sends dense efferent projec-
tions to the thalamus and caudate nucleus. While cau-
date volumetric abnormalities were not observed be-
tween patients with OCD (7.69 ± 1.31 cm³) and controls
(7.49 ± 1.10 cm³) in our study, metabolic activity in ven-
tral prefrontal cortex is very closely coupled with that in the caudate nucleus and thalamus in patients with
OCD.21 The thalamus serves as the final subcortical in-
put to frontal cortex and as such stimulates cortical out-
put when released from the inhibitory tonic influence of the striatum. As such, the thalamus may be exquisitely
sensitive to SSRI intervention resulting in the volumet-
ric changes observed in the present study.

Although our findings are consistent with serotonin-
mediated thalamic involvement in OCD, our findings are
preliminary given the limitations of our study. One ma-
jor confound of this study was our inability to disting-
uish specific regions of the thalamus to identify volu-
metric changes within a particular thalamic target field. The dorsomedial nucleus of the thalamus may be es-
pecially relevant to the study of OCD. Fitzgerald et al33 have also identified abnormalities in the putative neuronal
marker N-acetyl-aspartate, localized to medial and not
lateral thalamus. Indeed, localization of abnormalities in
other brain regions in patients with OCD has been ob-
erved with ventral prefrontal cortex more affected than
dorsal prefrontal cortex51 and putamen more affected than
caudate.37

In this study, we chose to treat patients openly with
paroxetine. A double-blind, placebo-controlled study
would have been superior for delineating the specificity
of neuroanatomical change in relation to paroxetine
therapy. Since maximal anti-OCD treatment interven-
tion effects may in some cases be delayed several months,12
volumetric assessment after 12 weeks of paroxetine
therapy is indicated.

Paroxetine was administered in a flexible dosage de-
sign since we were measuring treatment response not the
dose-response curve. There is no known single optimal
dose for paroxetine in treating OCD.12,55 Paroxetine dos-
age was unassociated with posttreatment thalamic vol-
umes or with reduction in thalamic volumes.

We were also unable to ethically give healthy pedi-
atriac comparison subjects paroxetine for 12 weeks. We
believe that the critical study questions were addressed
without our administering an SSRI to children who did
not need medication. Thalamic volumetric reductions may
be due to a general effect of paroxetine although reduct-
ion in thalamic volumes was associated with the reduc-
tion in OCD symptom severity. The changes in thal-
amic volume after paroxetine treatment also did not seem
to reflect scan-rescan effects.

Together, our findings suggest that serotonergic ab-
normalities in patients with OCD may lead to volumet-
ric abnormalities in the thalamus that may be reversible
with effective SSRI treatment. Alternatively, it is pos-
sible that the observed thalamic changes with parox-
etine treatment are epiphenomena of the underlying neu-
ropathology and treatment intervention. The observed
change could, for example, be secondary to hemody-
namically mediated medication treatment effects. Sec-
ond, paroxetine also has dopamine-blocking effects, ie,
extrapyramidal side effects including tardive dyskine-
 sia. Therefore, other neurotransmitter alterations such
as those in the dopaminergic system may also be related
to the observed neuroanatomical changes. While, to our
knowledge, direct evidence for a dopamine-blocking ef-
efct of paroxetine treatment is lacking, there may be an
indirect effect of serotonin causing dopamine inhibi-
tion.38 These preliminary findings must be viewed with
cautions but demonstrate how volumetric MRI can be used

Figure 3. Decrease in thalamic volume associated with reduction
in obsessive-compulsive score of the Children’s Yale-Brown
Compulsive Scales (CYBOCS).

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for the in vivo, noninvasive measurement of the impact of psychotropic medication on brain neuroanatomy in OCD.

Acute studies earlier in treatment and longitudinal studies of patients beyond 12 weeks are critical to identify mechanisms of response to SSRIs in OCD and their relationship to thalamic volumetric measures. Future neuropathological and in vivo neuroanatomical studies before and after SSRI treatment in brain regions other than the thalamus, ie, ventral prefrontal cortex and striatum, are indicated. For example, neuroleptics increase caudate nucleus volumes in patients with schizophrenia.\(^5,5^8\) Baxter et al\(^\text{11}\) also found that metabolic relationships between ventral prefrontal-striatal-thalamic circuits were altered after fluoxetine treatment. Recent functional MRI studies in adult patients OCD\(^5\) suggest the potential feasibility of noninvasive investigation of cortico-striatal-thalamic function in pediatric patients with OCD. Such studies must control for volumetric differences in these circuits between patients with OCD and controls as well as treatment-induced neuroanatomical changes.

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Reprints: David R. Rosenberg, MD, Psychiatry 9B, 4201 St Antoine Blvd, Detroit, MI 48201. (e-mail: drosen@med.wayne.edu).

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