Basal Ganglia Volumes in Patients With Gilles de la Tourette Syndrome

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Background: Despite strong circumstantial evidence that the pathophysiology of Gilles de la Tourette syndrome (TS) involves structural and functional disturbances of the basal ganglia, inconsistent findings from relatively small in vivo TS imaging studies have supported contradictory conclusions concerning the role of abnormal anatomical characteristics of the basal ganglia in the pathophysiology of TS.

Methods: Basal ganglia volumes were measured on high-resolution magnetic resonance images acquired for 154 children and adults with TS and 130 healthy control subjects. Repeated-measures analyses tested hypotheses concerning regional specificity, age effects, and abnormal asymmetries in the basal ganglia of subjects with TS. Subjects with prior neuroleptic exposure had larger basal ganglia volumes and were excluded from further statistical analyses.

Results: Caudate nucleus volumes were significantly (P = .008) smaller in children and adults with TS. Lenticular nucleus volumes also were smaller in adults with TS and in children with TS who were diagnosed as having comorbid obsessive-compulsive disorder. Regional anatomical asymmetries did not differ across groups. Regional volumes did not correlate significantly with the severity of tic, obsessive-compulsive disorder, or attention-deficit/hyperactivity disorder symptoms.

Conclusions: Reduced caudate nucleus volumes may be a good candidate marker for a trait abnormality in the structure of the basal ganglia in persons with TS. Smaller lenticular nucleus volumes may be an additional marker for the presence of comorbid obsessive-compulsive disorder and for the persistence of tic symptoms into adulthood. Brain regions other than the basal ganglia may have greater clinical relevance in determining the severity of tic symptoms.

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also tended to report abnormal asymmetries of the basal ganglia in persons with TS, although the basal ganglia subregions in which these were found varied between the lenticular,\textsuperscript{9,10} caudate,\textsuperscript{12} and globus pallidus nuclei, particularly in boys with TS who had comorbid attention-deficit/hyperactivity disorder (ADHD).\textsuperscript{13} The variability in these findings probably derived from the small numbers of subjects studied, the differences in ages and sex compositions of the study population, the variable characterization of and control for comorbid illnesses and medication use, and the technical limitations of the earlier magnetic resonance imaging (MRI) methods, which included relatively poor image resolution for measuring these small structures.\textsuperscript{14-16}

We report herein a high-resolution MRI study of basal ganglia volumes in persons with TS. The well-characterized sample of 154 individuals with TS and 130 healthy control subjects, the largest assembled thus far in a single TS imaging study, to our knowledge, is more than 5-fold larger than the largest prior morphological study of the basal ganglia in persons with TS. This sample and the use of state-of-the-art imaging techniques permit a much more detailed and more definitive assessment of abnormalities in volume and asymmetries across groups, and assessment of the effects on these volumes of age, sex, comorbid illnesses, and medication use. Based on prior studies of basal ganglia volumes in persons with TS, we hypothesized that we would detect reduced volumes of basal ganglia nuclei that would be regionally specific, and that these regional findings would likely vary as a function of the age of the subject. We also hypothesized that anatomical asymmetries would differ between the group with TS and the healthy control group.

**METHODS**

**SUBJECT RECRUITMENT AND CHARACTERIZATION**

Subjects with TS were recruited from the Tic and Obsessive-Compulsive Disorders Specialty Clinic at the Yale Child Study Center. Healthy controls were recruited from a list of 10000 names purchased from a telemarketing company. The names were identified by the company as representing individuals whose ages were within a specified range and whose residences were within particular ZIP codes (chosen to match the ages and ZIP codes for the subjects with TS). Individuals from the list were selected for contact by the investigators using a random number generator. Introductory letters were followed by screening telephone calls. Approximately 10% of the eligible control families who were contacted ultimately participated. Written informed consent was obtained for all participants.

Subjects were aged 6 to 63 years, and they were predominantly right-handed.\textsuperscript{17} Exclusionary criteria for subjects with TS included another movement disorder, or a major psychiatric disorder other than ADHD or obsessive-compulsive disorder (OCD), that antedated the onset of tics. Exclusionary criteria for control subjects included any history of tic disorder, OCD, ADHD, or psychotic disturbance, or a current Axis I disorder. Additional exclusionary criteria for both groups included any prior seizure, a history of head trauma with loss of consciousness, ongoing substance abuse or previous substance dependence, or an IQ below 80.

Neuropsychiatric diagnoses were established through clinical evaluation and administration of the Schedule for Tourette and Other Behavioral Syndromes.\textsuperscript{18} This diagnostic interview includes the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version for diagnoses in children,\textsuperscript{19,20} the Schedule for Affective Disorders and Schizophrenia for diagnoses in adults,\textsuperscript{21} and more detailed sections on TS and OCD for both age groups. Diagnoses were established through a best-estimate consensus procedure performed by 2 child psychiatrists (B.S.P and J.F.L.) using all available clinical and investigational materials.\textsuperscript{22} Ratings of current and worst ever severity of tic, OCD, and ADHD symptoms were obtained using, respectively, the adult or child version of the Yale Global Tic Severity Scale,\textsuperscript{23} the Yale-Brown Obsessive Compulsive Scale,\textsuperscript{24,25} and the DuPaul-Barkley ADHD rating scale.\textsuperscript{26} Intraclass correlation coefficients\textsuperscript{27} for clinicians who administered the Yale Global Tic Severity Scale and the Yale-Brown Obsessive Compulsive Scale were greater than 0.90 on videotaped training interviews. Estimates of full-scale IQs were made in the children using the Kaufman Brief Intelligence Test (American Guidance Services, Circle Pines, Minn)\textsuperscript{28,29} and in the adults using 2 performance (block design and object assembly) and 3 verbal (information, digit span, and vocabulary) subscale scores of the Wechsler Adult Intelligence Scale–Revised.\textsuperscript{30} Socioeconomic status was quantified using the Hollingshead Four-Factor Index of Social Status.\textsuperscript{31}

**MRI SCANNING AND BASAL GANGLIA VOLUMES**

The MRI scans were obtained using a single 1.5-T scanner (GE Signa, Milwaukee, Wis). Head positioning was standardized using canthomeatal landmarks. A 3-dimensional spoiled-gradient echo sequence was obtained for the morphometric analyses (repetition time, 24 milliseconds; echo time, 5 milliseconds; 45° flip; frequency encoding superior/inferior; no wrap; 256 × 192 matrix; field of view, 30 cm; 2 excitations; slice thickness, 1.2 mm; and 124 contiguous slices encoded for sagittal slice reconstructions to yield 1.17 × 1.17 × 1.2-mm voxels).

Morphometric analyses were performed on UNIX workstations (Sun Ultra 10) using standard computer software (ANALYZE 7.5; Biomedical Imaging Resource, Mayo Foundation, Rochester, Minn) while blind to subject characteristics and hemisphere (images were randomly flipped left-right before analysis). Large-scale variations in image intensity were removed before region definition.\textsuperscript{32,33} An isointensity contour function was used in conjunction with manual editing to isolate the cerebrum. The computer software module “delete holes” was used to combine gray and white matter tissues with ventricular, cisternal, and sulcal cerebrospinal fluid to provide a measure of whole brain volume (WBV) that could be used as a statistical covariate to control for scaling effects within the basal ganglia. The inclusion of cerebrospinal fluid spaces in this measure was intended to minimize the effects of age-related atrophy for this statistical covariate.

Basal ganglia were defined by hand tracing. Images were cropped down to the cortices surrounding the basal ganglia and then enlarged 8-fold in each image dimension to minimize mechanical tracing errors. Tissue contrast between structures having similar gray-scale values (such as the putamen and globus pallidus) was enhanced through optimization of the pixel intensity histogram. Caudate, putamen, and globus pallidus nuclei were traced initially in the transaxial plane, the accuracy of which was confirmed in the coronal and sagittal planes (Figure 1). If corrections were made in any of these latter 2 imaging planes, their accuracy had to be corroborated in the orthogonal views. The head of the caudate nucleus was distinguished from the accumbens nucleus by drawing a straight line in the coronal plane from the inferiormost tip of the internal...
capsule to the inferiormost tip of the lateral ventricles. The claustrum was excluded from the volume of the putamen using the axial and coronal views. The entire rostrocaudal extent of the caudate visible at this resolution was included in the region's definition (ie, external landmarks were not used to exclude the tail of the caudate, as in some prior studies), which was made possible by the high resolution of the images and the use of 3 orthogonal views of the caudate. An expert in these procedures (B.S.P.) reviewed the accuracy of all regional definitions.

The interrater reliability of volumes for each of the basal ganglia subregions was assessed blindly at nearly equal intervals on the same 10 scans measured by 2 raters (P.T. and M.J.K.) throughout the 3 years in which the morphometric analyses were performed. Volumes at each time point were comparable to the gold standard measures obtained at the beginning of the study (by B.S.P.). The intraclass correlation coefficients calculated using a 2-way random effects model were always greater than 0.95 for the caudate and putamen nuclei, greater than 0.90 for the globus pallidus nucleus, and greater than 0.99 for the WBV measurement. A repeated-measures analysis of variance of basal ganglia volumes in these 10 scans across these 4 time points revealed no significant systematic drift in volumes with time for any of the basal ganglia subregions (P > .60 for all).

Each scan was rated blindly on a 6-point ordinal scale with descriptive anchors for the severity of motion artifact, ranging from a score of 0 (none) to 5 (severe). Scores of 4 or 5 (occurring in 10 subjects with TS and 9 control children) mandated exclusion of the scan from morphometric analyses. Excluded scans were not included in the subject numbers reported herein. A series of 2 \times 4 contingency tables demonstrated that the severity of motion artifact in nonexcluded scans did not differ significantly between the healthy control group and the patient group, or between children and adults in either diagnostic group (x^2 values, <1.39; P > .70 for all).

**STATISTICAL ANALYSIS**

A Priori Hypothesis Testing

All statistical procedures were performed using SAS statistical software (SAS v.8.0; SAS Institute Inc, Cary, NC). A priori hypotheses were tested using a mixed-model analysis (PROC MIXED) with repeated measures over a spatial domain (regional basal ganglia volumes). The model included the within-subjects factors of hemisphere, with 2 levels (left and right), and region, with 3 levels (caudate, putamen, and globus pallidus). Diagnosis (TS or healthy control) was a between-subjects factor. Covariates included age, sex, lifetime diagnoses of ADHD or OCD, and WBV to control for scaling effects within the brain.

In addition to the independent variables previously described, we considered for inclusion in the model the covariate of socioeconomic status; all 2-, 3-, and 4-way interactions of diagnoses (TS, OCD, or ADHD), sex, hemisphere, region, and age; and the 2-way interactions of WBV with hemisphere or region. Terms that were not statistically significant were eliminated via backward stepwise regression, with the constraint that the model at each step had to be hierarchically well formulated (ie, all possible lower-order terms had to be included in the model, regardless of their statistical significance).

The hypothesized regionally specific reduction in volume of the basal ganglia of subjects with TS was tested with assessment of the statistical significance of the TS-by-region term in the model. Whether these regional differences varied with...
age was tested with the TS-by-region-by-age 3-way interaction term. Possible abnormalities in basal ganglia asymmetries in subjects with TS were tested with a TS-by-region-by-hemisphere interaction. To reduce the likelihood of false positives when testing these 3 hypotheses, \( P < .02 \) was considered statistically significant. Reported \( P \) values have not been corrected for multiple comparisons, and all \( P \) values were 2-sided.

**Tests of Fixed Effects**

To identify the component terms that contributed most to the significance of higher-order interactions, we examined the parameter estimates, 95\% confidence intervals, and \( P \) values of the component terms in an analysis of fixed effects for each basal ganglia subregion individually. The statistical models were the same as the final mixed models used for hypothesis testing, with the exception that the main effects for region and its interactions were removed. Least squares means and SEs were calculated in the mixed models and plotted to assist in the interpretation of significant interactions.

**Assessment of Possible Confounds**

Also included in the initial statistical models were minority status, height, weight, and handedness index. These variables, however, had negligible effects on the findings and parameter estimates. Consequently, they were not included in the final models for hypothesis testing.

**Associations With Symptom Severity**

In the TS group, we explored the associations of basal ganglia volumes with the severity of tic symptoms, either at scanning or when the symptoms were at their worst in the patient’s lifetime. Associations of symptom severity with regional volumes were performed using linear regression with WBV and sex as covariates.

**Medication Effects**

The possible effects of medication use on basal ganglia volumes in subjects with TS were assessed by including in the final model for hypothesis testing the main effects and the 2- and 3-way interactions of current medication use, dichotomously coded as 0 (no) or 1 (yes). This was done for any medication used and for the medication classes of traditional neuroleptic agents (eg, haloperidol or pimozide), risperidone, and for the medication classes of traditional neuroleptic medications compared with healthy controls and subjects with TS not taking those medications (main effect for typical neuroleptic agents: \( F_{1,273} = 7.44, P = .007 \); and region-by-medication effect for atypical neuroleptic agents: \( F_{2,273} = 3.67, P = .03 \)). Least squares means indicated that, in subjects taking typical neuroleptic medications, volumes were significantly larger in the caudate (3854.5 vs 3598.3 mm\(^3\); \( F_{1,273} = 5.19, P = .03 \)) and globus pallidus (1945.6 vs 1818.2 mm\(^3\); \( F_{1,273} = 11.0, P < .001 \)), and they tended to be larger in the putamen (5125.0 vs 4934.2 mm\(^3\); \( F_{1,273} = 2.75, P = .09 \)). In subjects taking atypical neuroleptic medications, in contrast, the region \( X \) medication effect derived from slightly smaller volumes in the caudate (3713.1 vs 3737.7 mm\(^3\); \( F_{1,273} = 0.02, P = .90 \)) and putamen (4913.2 vs 5146.0 mm\(^3\); \( F_{1,273} = 1.56, P = .21 \)), but larger volumes in the globus pallidus (1925.5 vs 1818.2 mm\(^3\); \( F_{1,273} = 2.22, P = .14 \)). No significant associations with basal ganglia volumes (as either main effects or interactions) were noted with the use of \( \alpha \)-adrenergic agonists, specific serotonin reuptake inhibitors, or tricyclic medications.

**HYPOTHESIS TESTING**

In light of the previous evidence suggesting that basal ganglia volumes varied systematically with exposure to typi-
interactions that tested a priori hypotheses. P
hierarchically well formulated. Interactions up to the fourth order were considered. All NR terms were excluded at
variable selection procedure; OCD, obsessive-compulsive disorder; TS, Gilles de la Tourette syndrome; WBV, whole brain volume.
effects detected in the entire sample, modeling of basal
mally with age (Figure 2). To clarify further the age
the caudate nucleus of subjects with TS varied mini-
adults than in children, whereas volume reductions in
regionally specific effects varied with age, supporting
this reduction in volume varied significantly by basal
ganglia subregions to be smaller in subjects with TS
main effect of TS reflected a tendency for all basal gan-
alysis indicated that the TS main effect derived from
volume reductions in the group with TS
region interaction indicated that the
reduction in volume varied significantly by basal ganglia subregion—reductions in subjects with TS were
relatively greater in the caudate (3477.0 vs 3656.6 mm3,
or −4.3%; F1,94 =4.3, P =.04) than in the putamen
(4988.6 vs 5034.4 mm3, or −0.9%; F1,94 =2.0, P =.16) or
globus pallidus (1755.1 vs 1775.2 mm3, or −1.1%;
F1,94 =1.1, P =.31), thus confirming our first hypothesis.
The TS × region × age interaction indicated that the
regionally specific effects varied with age, supporting
our second hypothesis. Plots of regional volumes demon-
strated that this interaction with age arose from reduced volumes in the putamen and globus pallidus of subjects with TS that were of greater magnitude in
adults than in children, whereas volume reductions in
the caudate nucleus of subjects with TS varied mini-
Figure 2. To clarify further the age
effects detected in the entire sample, modeling of basal ganglia volumes across groups was performed sepa-
rationally in the child (aged <18 years) and adult (aged
≥18 years) subjects who had not been exposed to neuro-
leptic medications (Table 2).

**Children Only**

Modeling in children demonstrated only a TS × region
effect. Post hoc analyses indicated that this effect
derived from volume reductions in the group with TS
that were greater in the caudate (3471.3 vs 3633.0
mm3, or −4.5%; F1,145 =3.4, P =.06) than in the puta-
men (5099.8 vs 5164.5 mm3, or −1.3%; F1,145 =1.1,
P =.30), and from slightly larger volumes in the globus pallidus (1776.6 vs 1764.0 mm3, or 0.7%; F1,145 =2.9,
P =.09). Age, sex, and hemisphere effects were not
significantly associated with a diagnosis of TS in the children.

**Adults Only**

Modeling in adults demonstrated a TS main effect and a
trend toward a TS × age effect (Table 1). Post hoc
analyses indicated that the TS main effect derived from
volume reductions in the TS group across all basal ganglia subregions, including the caudate (3492.8 vs
3648.3 mm3, or −4.3%; F1,145 =4.3, P =.04), putamen
(4729.5 vs 4900.3 mm3, or −3.5%; F1,145 =2.6, P =.11),
and globus pallidus (1668.4 vs 1762.3 mm3, or −5.3%;
F1,145 =2.3, P =.13). The absence of a significant TS × region effect indicated that volume reductions were not significantly different across subregions, although unlike the significant reductions in caudate

<table>
<thead>
<tr>
<th>Table 1. Hypothesis Testing*</th>
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<tbody>
<tr>
<td><strong>Variable</strong></td>
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<td>Hemisphere</td>
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<tr>
<td>Region</td>
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<td>TS</td>
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<td>OCD</td>
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<td>ADHD</td>
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<td>Sex</td>
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<td>WBV</td>
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<tr>
<td>Age</td>
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<td>WBV by Region</td>
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<td>TS by Region</td>
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<tr>
<td>OCD by Region</td>
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<tr>
<td>Sex by Region</td>
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<tr>
<td>Age by Region</td>
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<td>Age by Sex</td>
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<tr>
<td>Age by Region by Sex</td>
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<tr>
<td>Age by Region by TS</td>
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</tbody>
</table>

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; F, F statistic for type III sum of squares; NR, not retained in the backward stepwise elimination variable selection procedure; OCD, obsessive-compulsive disorder; TS, Gilles de la Tourette syndrome; WBV, whole brain volume.
*These were the final models used in the mixed-model analysis (PROC MIXED) statement after backward stepwise elimination. The models at each step were hierarchically well formulated. Interactions up to the fourth order were considered. All NR terms were excluded at P > .10. Data in boldface indicate main effects or interactions that tested a priori hypotheses.
Regional basal ganglia volumes. A, The least squares means for caudate, putamen, and globus pallidus volumes in neuroleptic-free subjects in the entire sample. The significant Gilles de la Tourette syndrome (TS)–by–region effect ($P < .001$) derived primarily from reductions in volume of the caudate nuclei in the subjects with TS ($P = .01$). B, The corresponding volumes in children only. The significant regionally specific effects ($P < .008$) again derive primarily from reduced volumes of the caudate nuclei in the TS group ($P = .07$). C, The volumes in adults only. Volumes are reduced throughout all basal ganglia subregions without regional specificity, as evidenced by the significant main effect of a TS diagnosis ($P = .02$), but no significant ($P = .51$) TS $\times$ region effect.

### Table 2. Selected Fixed Effects

<table>
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<tr>
<th>Variable</th>
<th>PE (95% CI)</th>
<th>$df$</th>
<th>$t$</th>
<th>Value</th>
<th>PE (95% CI)</th>
<th>$df$</th>
<th>$t$</th>
<th>Value</th>
<th>PE (95% CI)</th>
<th>$df$</th>
<th>$t$</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Hemisphere</td>
<td>-21.3 (-44.2 to 1.6)</td>
<td>253</td>
<td>1.8</td>
<td>.07</td>
<td>54.1 (21.1 to 87.1)</td>
<td>253</td>
<td>3.2</td>
<td>.002</td>
<td>85.1 (38.5 to 91.6)</td>
<td>253</td>
<td>4.8</td>
<td>&lt;.001</td>
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<tr>
<td>TS</td>
<td>291.2 (72.9 to 590.5)</td>
<td>245</td>
<td>2.6</td>
<td>.01</td>
<td>164.4 (-62.4 to 391.2)</td>
<td>245</td>
<td>1.4</td>
<td>.16</td>
<td>-42.3 (-123.1 to 38.5)</td>
<td>245</td>
<td>1.0</td>
<td>.31</td>
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<td>OCD</td>
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<td>0.6</td>
<td>.57</td>
<td>194.5 (6.7 to 382.2)</td>
<td>245</td>
<td>2.0</td>
<td>.04</td>
<td>-3.2 (-70.1 to 63.7)</td>
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<td>.93</td>
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<td>-1.4</td>
<td>-130.3 (-326.8 to 66.2)</td>
<td>245</td>
<td>-1.3</td>
<td>.19</td>
<td>-21.2 (-91.2 to 48.8)</td>
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<td>-0.6</td>
<td>.55</td>
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<tr>
<td>Sex</td>
<td>-85.6 (-316.8 to 145.7)</td>
<td>245</td>
<td>0.7</td>
<td>.47</td>
<td>-75.0 (-315.1 to 165.0)</td>
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<td>-0.6</td>
<td>.54</td>
<td>54.7 (-30.9 to 140.2)</td>
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<td>1.3</td>
<td>.21</td>
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<td>WBV</td>
<td>0.0019 (0.0014 to 0.0025)</td>
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<td>6.7</td>
<td>&lt;.001</td>
<td>0.0023 (0.0018 to 0.0029)</td>
<td>245</td>
<td>7.9</td>
<td>&lt;.001</td>
<td>0.0010 (0.0008 to 0.0012)</td>
<td>245</td>
<td>9.4</td>
<td>&lt;.001</td>
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<td>Age</td>
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<td>0.1</td>
<td>-10.3 (-17.8 to -2.9)</td>
<td>245</td>
<td>-2.7</td>
<td>.01</td>
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<td>1.6</td>
<td>.12</td>
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<td>Sex $\times$ Age</td>
<td>-5.1 (-13.7 to 3.5)</td>
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<td>-0.9</td>
<td>-2.0 (-5.2 to 1.2)</td>
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<td>.22</td>
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<tr>
<td>TS $\times$ Age</td>
<td>-12.1 (-25.8 to 1.6)</td>
<td>245</td>
<td>1.2</td>
<td>-10.1 (-30.0 to 9.9)</td>
<td>245</td>
<td>-1.0</td>
<td>.30</td>
<td>-53.6 (-115.2 to 8.1)</td>
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<td>1.0</td>
<td>.30</td>
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<tr>
<td>Sex $\times$ Age</td>
<td>12.1 (-0.0 to 24.3)</td>
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<td>1.2</td>
<td>2.2</td>
<td>-10.0 to 4.2</td>
<td>245</td>
<td>1.2</td>
<td>0.2</td>
<td>-0.5 (-6.5 to 6.8)</td>
<td>245</td>
<td>0.1</td>
<td>.96</td>
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</table>

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; OCD, obsessive-compulsive disorder; PE, parameter estimate; TS, Gilles de la Tourette syndrome; WBV, whole brain volume.

*These are fixed effects with $P < .10$ in the final model for all subjects (given in Table 2). The least squares means are given in Figure 2. Data in boldface indicate fixed effects for component terms of higher-order interactions that tested a priori hypotheses in Table 1.

The volumes, the putamen and globus pallidus effects in post hoc analyses were not statistically significant in themselves. The TS–by–age trend reflected a tendency for volumes in adults with TS not to decline with age as rapidly as they did in control subject across all basal ganglia subregions, although univariate analyses suggested that this tendency was more evident in the caudate ($F_{1,47} = 3.0$, $P = .09$) and putamen ($F_{1,47} = 1.8$, $P = .31$). B, The corresponding volumes in children only. The significant regionally specific effects ($P < .008$) again derive primarily from reduced volumes of the caudate nuclei in the TS group ($P = .07$). C, The volumes in adults only. Volumes are reduced throughout all basal ganglia subregions without regional specificity, as evidenced by the significant main effect of a TS diagnosis ($P = .02$), but no significant ($P = .51$) $TS \times$ region effect.
**Asymmetries**

Other effects in the modeling of basal ganglia volumes included a significant hemisphere main effect and trends toward a region $\times$ hemisphere interaction in children and in all subjects combined (Table 1). The main effect of hemisphere represented larger right hemisphere volumes in the basal ganglia overall. The interaction term indicated a trend toward regionally specific differences in asymmetries, with right hemisphere volumes being larger in the putamen (5034.0 vs 4999.9 mm$^3$, or 1.1%, $F_{1,145}=10.32$, $P = .002$) and globus pallidus (1768.3 vs 1703.3 mm$^3$, or 3.8%, $F_{1,235}=22.98$, $P < .001$), but marginally smaller in the caudate (3572.0 vs 3593.3 mm$^3$, or −0.6%, $F_{1,235}=3.3$, $P = .07$). The hemisphere $\times$ diagnosis $\times$ region interaction was not significant ($F_{2,505}=0.94$, $P = .40$), however, and it therefore did not support our third hypothesis concerning abnormal asymmetries across groups. When we applied this same model to the analysis of asymmetries in the subjects (comprising 70.3% of the total sample) whose score on a standard handedness inventory was 100 (the greatest possible score, indicating extreme right-hand dominance),$^{17}$ findings were unchanged from those when modeling effects in all subjects.

**ADDITIONAL EFFECTS**

**OCD and ADHD Comorbidities**

Attention-deficit/hyperactivity disorder as a comorbid illness was not significantly associated with basal ganglia volumes as either a main effect ($P = .11$) or an interaction ($P > .20$ for all interactions). Obsessive-compulsive disorder, however, was associated with basal ganglia volumes in a regionally specific way in the entire sample (OCD $\times$ region interaction, $P = .006$). Volumes were slightly reduced in subjects with OCD in the caudate (3556.6 vs 3608.8 mm$^3$, or −1.4%; $F_{1,245}=0.01$, $P = .93$) and significantly so in the putamen (4977.6 vs 5300.9 mm$^3$, or −6.1%; $F_{1,235}=7.8$, $P = .006$) relatively more than the caudate (3514.7 vs 3630.5 mm$^3$, or −3.2%; $F_{1,235}=0.8$, $P = .39$) or globus pallidus (1722.5 vs 1767.7 mm$^3$, or −2.6%; $F_{1,235}=1.1$, $P = .30$) (Table 2 and Figure 3).

**Sex Effects**

The age $\times$ region $\times$ sex interaction that was significant in adults (Table 1) reflected tendencies toward a greater age-related decline in caudate volume in men than in women and a greater age-related decline in putamen volume in women than in men, regardless of diagnosis (data not shown). These regional associations with age were not significant in the regions individually—the 3-way interaction was significant because the associations of age with sex varied across basal ganglia subregions. The associations of volume with age did not differ between sexes in the globus pallidus.

**Scaling Effects**

Whole brain volume correlated significantly (Table 1) with basal ganglia volumes as a main effect across all age groups, indicating the presence of significant scaling effects within the basal ganglia. In addition, the significant WBV $\times$ region interaction suggested that this scaling effect differed significantly within basal ganglia subregions, independent of age. Scatterplots (not shown) and calculation of regression coefficients for WBV and the residuals of regional basal ganglia volumes (for the model shown in Table 1 for all subjects, except WBV terms were not entered) indicated that the scaling with WBV was similar between the caudate ($r = 0.30$; 95% confidence interval, 0.05-0.52) and putamen ($r = 0.35$; 95% confidence interval, 0.06-0.12). The scaling of globus pallidus volumes with WBV ($r = 0.39$; 95% confidence interval, 0.19-0.53) was significantly stronger than the scaling of either the caudate or the putamen.

None of the basal ganglia measures, after adjustment for the effects of scaling with WBV or after covarying with age, correlated with measures of tic, OCD, or ADHD symptom severity beyond levels that would be expected by chance.

**COMMENT**

The major finding of this study is that the volume of the caudate nucleus is decreased across all age groups in persons with TS, whereas the volumes of the putamen and globus pallidus nuclei are on average decreased primarily in adults with TS. The finding of reduced caudate nucleus volumes across age groups is consistent with the previous prediction, based on findings in a functional MRI study of tic suppression,$^{36}$ that the primary disturbance...
in cortico-striato-pallidal-thalamo-cortical circuits may be centered in the projections into or out of the caudate nucleus. It is also consistent with findings from a study\textsuperscript{11} of monozygotic twins, in which both members of each twin pair had either chronic tics or TS and in which caudate nucleus volumes were smaller in the more severely affected co-twin. Although tics are highly heritable,\textsuperscript{37-39} nongenetic determinants are thought to be important in determining disease expression,\textsuperscript{40-41} and these nongenetic determinants presumably contributed to the morphological differences within the monozygotic twin pairs. Thus, the similarity of the present morphological findings in singletons with TS with those in twins with TS suggests that the reduced caudate nucleus volumes detected in the present study may arise in part from nongenetic determinants in otherwise genetically predisposed individuals.\textsuperscript{42}

The larger reductions in volume of the putamen and globus pallidus nuclei in adults with TS compared with children with TS are consistent with the findings of prior morphological studies of the basal ganglia in persons with TS. Reduced putamen and globus pallidus volumes (10.7\% on the left side and 3.8\% on the right side) were first reported in adults with TS.\textsuperscript{9} A statistical trend toward reduced caudate volumes (11\%) was also reported in that study (P = .07). A subsequent study\textsuperscript{10} of children with TS reported, however, that lenticular nucleus volumes were on average only 2.9\% smaller on the left side and 2.8\% larger on the right side in the TS group, neither of which were statistically significant. Our findings help to reconcile these apparently discrepant previous reports by suggesting that the differing ages of the samples were responsible for the detection of reduced lenticular nucleus volumes in adults but not in children. Small numbers of subjects and inadequate statistical power likely contributed to detecting only trends toward smaller caudate volumes in the prior adult study.

The reduced caudate volumes across age groups in the present study suggest that the caudate nucleus may be a good candidate marker for a trait morphological abnormality in persons with TS. This is in contrast to the reduced volumes across all basal ganglia subregions, including the putamen and globus pallidus nuclei, that were seen only in our adult subjects with TS. By definition, the finding of abnormal lenticular nucleus volumes in adults with TS is not generalizable to the larger population of all subjects with TS, because children with TS in this study did not have significantly smaller lenticular nuclei. Although children with TS do not have significantly smaller lenticular nuclei, it is nevertheless possible that children with TS on average develop smaller lenticular nuclei when they become adults. If this is true, then the adult development of smaller lenticular nuclei would presumably represent either a degenerative process or an activity-dependent plastic response to the presence of tics. Smaller lenticular nucleus volumes seem unlikely to be a plastic response to the presence of tics, however, because volumes of this nucleus did not correlate with the severity of tic symptoms, as would have been expected if the tics were producing smaller volumes. Moreover, the presence of a degenerative process that would be typical of all subjects with TS seems equally implausible, in that tic symptoms typically improve in severity during late adolescence and early adulthood,\textsuperscript{43-46} and this is not characteristic of a degenerative disorder.

An alternative explanation for the smaller volumes of lenticular nuclei in adults, but not children, with TS is that, rather than representing the typical developmental course for this structure in the larger population of all patients with TS, smaller lenticular volumes may instead represent a unique feature of the atypical, still-symptomatic adults with TS who were successfully recruited for this brain imaging study. It is possible, for instance, that smaller lenticular nuclei may represent dysfunction of neuroregulatory systems that would otherwise help to attenuate the severity of tic symptoms during adolescent and early adult development. Dysfunction of a neuroregulatory system such as this would then predispose to a continuing or worsening of symptoms in adulthood. The possibility that smaller lenticular nuclei represent dysfunctional neuroregulatory systems could be tested relatively easily, because children with TS who have relatively reduced volumes of their lenticular nuclei, when compared with children who have larger lenticular nuclei, will be more likely to have enduring or more severe tic symptoms when they are followed up into adulthood.

The absence of significant associations of basal ganglia volumes with the severity of tic symptoms in this study essentially replicates similar findings in prior basal ganglia studies of TS,\textsuperscript{9,10} and it stands in stark contrast to the findings\textsuperscript{47} of significant inverse associations of tic severity with prefrontal and parieto-occipital volumes in the same subjects as those studied herein. These differing associations of symptom severity with basal ganglia or cortical volumes imply that if a predisposition to having tics is represented within the basal ganglia (and this is still an unproved premise), then prefrontal and parieto-occipital volumes are likely to be relatively more important than basal ganglia volumes in determining whether that predisposition is manifested within a given individual. Moreover, if that predisposition to tic is indeed manifested, the correlations with symptom severity indicate that cortical volumes seem to be more important in determining how severe the tic symptoms are likely to be. In other words, the morphological and functional integrity of cortical neuroregulatory systems may be clinically more salient for these patients than are putative trait vulnerabilities in the basal ganglia, such as the hypoplastic caudate nuclei identified herein. Through dense projections from prefrontal and parietal cortices to the striatum,\textsuperscript{48} these cortical regulatory systems interact directly with the basal ganglia nuclei, where the trait vulnerabilities to develop tics are presumably based.

A diagnosis of comorbid OCD in the subjects with TS was associated with significantly smaller volumes of the putamen, particularly in children with TS. This finding supports the previously stated contention that the spatial extent of abnormalities in a common set of basal ganglia–based circuits may distinguish those individuals who have TS alone from those who have either TS with comorbid OCD or TS with comorbid ADHD.\textsuperscript{35} Findings from
this and related studies, for example, suggest that subjects with TS alone have smaller caudate nucleus volumes, whereas those with TS and comorbid OCD have, in addition, smaller lenticular nucleus volumes. Individuals with TS and comorbid ADHD, in addition to having smaller caudate nuclei, tend to have larger volumes across all cortical portions of those circuits, as previously reported in the present sample. The finding of smaller volumes of the putamen in children with TS and comorbid OCD, together with the finding of smaller volumes of this same nucleus in still symptomatic adults with TS, raises the possibility that children who have TS and comorbid OCD may be at an increased risk for having tic symptoms that fail to remit in adulthood. This possibility is supported by findings from a prospective longitudinal study of epidemiologically ascertained children in whom the presence of OCD symptoms in adolescence predicted the persistence of tics into adulthood.

Individuals with TS who were taking neuroleptic medications had larger basal ganglia volumes than did other persons with TS or healthy subjects, consistent with previous reports of medication effects on basal ganglia volumes. The use of typical neuroleptic medications was associated with larger caudate and globus pallidus volumes, whereas atypical neuroleptic medications were associated only with larger globus pallidus volumes. The smaller volumes in medication-free subjects with TS and the larger volumes in subjects with TS who were taking neuroleptic agents suggest that these medications could possibly exert their beneficial effects on tics by altering structural features of the basal ganglia. These medication effects might correct and eventually overcorrect (in an anatomical sense) the reduced volumes observed in subjects with TS who were not taking medications. This correction may occur in either the caudate nucleus, the putative trait vulnerability marker for TS that we may have identified in this study, or the globus pallidus, the major motor output structure of the basal ganglia. The association of neuroleptic use with larger basal ganglia volumes could also represent characteristics of the subjects with TS or their illness that systematically predisposed them to having neuroleptic medications prescribed in the first place. What these characteristics could possibly be are unknown.

No abnormalities in lateralization of the basal ganglia were observed in the present study, suggesting that the explicitly post hoc findings of aberrant asymmetries reported in earlier, much smaller, studies of basal ganglia volumes in persons with TS were likely erroneous and attributable to chance. Finally, no abnormalities in the differences between sexes in basal ganglia volumes were detected in this study, suggesting that prominent sex differences in the prevalence of TS do not have their basis in basal ganglia nuclei. They may instead be represented in parieto-occipital cortices, where significant volume differences between sexes were observed in healthy individuals, but not in individuals with TS.

In conclusion, the findings from this study have several important implications for our understanding of the neural basis of TS symptoms. Smaller caudate nucleus volumes, for example, seem to be a good candidate marker for trait vulnerabilities in persons with TS. Smaller lenticular nucleus volumes, in contrast, may be a marker for the presence of comorbid OCD and for the persistence of tic symptoms into adulthood. Neuroleptic medications, in turn, may weaken or reverse some of these morphological abnormalities. Although these seem to be the most plausible interpretations of the cross-sectional findings from this study, prospective longitudinal imaging studies of children at high risk for TS are necessary to confirm whether anatomical abnormalities of the basal ganglia in persons with TS represent epiphenomena, trait or state abnormalities, or chronic compensatory responses to the presence of tics.

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