ORIGINAL ARTICLE

Regional Brain and Ventricular Volumes in Tourette Syndrome

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Background: The pathophysiology of Tourette syndrome (TS) is thought to involve disturbances in cortico-striato-thalamo-cortical circuitry. The morphological characteristics of the cortical and associated white matter portions of these circuits have not been previously examined in TS subjects.

Methods: High-resolution anatomical magnetic resonance images were acquired in 155 TS and 131 healthy children and adults. The cerebrums and ventricles were isolated and then parcellated into subregions using standard anatomical landmarks.

Results: For analyses that included both children and adults, TS subjects were found to have larger volumes in dorsal prefrontal regions, larger volumes in parieto-occipital regions, and smaller inferior occipital volumes. Significant inverse associations of cerebral volumes with age were seen in TS subjects that were not seen in healthy controls. Sex differences in the parieto-occipital regions of healthy subjects were diminished in the TS group. The age-related findings were most prominent in TS children, whereas the diminished sex differences were most prominent in TS adults. Group differences in regional ventricular volumes were less prominent than in the cerebrum. Regional cerebral volumes were significantly associated with the severity of tic symptoms in orbitofrontal, midtemporal, and parieto-occipital regions.

Conclusions: Broadly distributed cortical systems are involved in the pathophysiology of TS. Developmental processes, sexual dimorphisms, and compensatory responses in these cortical regions may help to modulate the course and severity of tic symptoms.

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TOURETTE SYNDROME (TS) is a chronic, childhood-onset neuropsychiatric illness. It is characterized by motor and vocal tics that fluctuate in severity, and it frequently co-occurs with obsessive-compulsive disorder (OCD), attention-deficit/hyperactivity disorder (ADHD), or other social and behavioral disturbances.[1,2] This structural imaging study of cerebral and ventricular volumes in 286 TS and healthy control subjects tests several previously formulated hypotheses that derive from studies of the natural history and pathophysiology of TS.

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First, we hypothesize that some but not all regional brain volumes will differ between TS and healthy control groups.[3] This hypothesis follows immediately from a model of TS pathophysiology that postulates anatomical and functional disturbances in particular components of the multiple circuits that loop between the cortex and subcortex (the cortico-striato-thalamo-cortical circuits).[3,4] Motor portions of these circuits are believed to subserve tic behaviors,[3,5] whereas other components are thought to modulate activity in motor circuits and thereby influence the severity of tic symptoms.[6-8] Components of these neuromodulatory circuits in subjects who voluntarily suppress their tics, for example, include the frontal, temporal, and parietal cortices.[9] Anatomic and functional variability in the brain regions that compose these circuits may contribute to between-subject variability in symptom severity and to differences between TS and control groups in regional brain volumes.

Second, we hypothesize age-specific differences in volume between TS and healthy control subjects (ie, group differences in some brain regions vary according to age of the subjects).[10] This hypothesis is based on studies of the natural history of TS that demonstrate a typical, gradual diminution in severity of tics during ado-

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SUBJECTS AND METHODS

SUBJECT RECRUITMENT AND CHARACTERIZATION

Tourette syndrome subjects were recruited from the Tic Disorders Specialty Clinic at the Yale Child Study Center. Normal controls were recruited from a list of 10 000 names purchased from a telemarketing company. They were identified by the company as having individuals in specified age ranges and as living in the same neighborhoods (based on ZIP code) as the TS subjects. Individuals from the list were selected for contact by the investigators using a random number generator. Introductory letters were followed by screening telephone calls. Of the eligible control families contacted, approximately 10% participated. Written informed consent was obtained for all participants.

Subjects were aged 6 to 63 years, and they were predominantly right-handed according to a standardized questionnaire.[39] Tourette syndrome subjects had to meet *DSM-IV* criteria for this diagnosis.[40] Exclusionary criteria for TS subjects included another movement disorder, or a major psychiatric disorder other than OCD or ADHD that antedated the onset of TS. For control subjects, exclusionary criteria included any history of tic disorder, OCD, ADHD, or 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 Syndrome and Other Behavioral Disorders,[41] a structured interview that has been used extensively in TS family studies. The Schedule for Tourette and Other Behavioral Syndromes includes the Kiddie-Schedule for Affective Disorders and Schizophrenia Epidemiologic Version for diagnoses in children,[42,43] the Schedule for Affective Disorders and Schizophrenia for diagnoses in adults,[44] 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.[45] Ratings of current and worst-ever severity of tic symptoms were obtained using the Yale Global Tic Severity Scale[46] and either the adult or child version of the Yale-Brown Obsessive Compulsive Scale.[47,48] Socioeconomic status was estimated with the Hollingshead Index of Social Status.[49]

MRI SCANNING

Magnetic resonance imaging scans were obtained using a single 1.5-T scanner (GE Signa; General Electric, 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; flip angle, 45°; 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).

MORPHOMETRIC PROCEDURES

Morphometric analyses were performed on Sun Ultra 10 workstations using ANALYZE 7.5 software (Rochester, Minn) while blind to subject characteristics and hemisphere (images were randomly flipped in the transverse plane before region definition). A second operator confirmed the accuracy of all procedures.

Preprocessing

Large-scale variations in image intensity were removed before the images were reformatted.[50,51] Head flexion/extension, rotation, and tilt were corrected before to region definition using the anterior-posterior (AC-PC) commissure and standard midline landmarks.

Cerebral Tissue

An isointensity contour function was used in conjunction with manual editing to isolate the cerebrum. The cerebrum (exclusive of cerebellum) was then parcellated into 8 anatomical subunits using orthogonal planes. The cerebral hemispheres were first divided using a curved Hermite spline surface interpolated from 100 points placed at standard midline landmarks. Each of the cerebral hemispheres was subdivided using 1 axial plane placed through the AC-PC line (tangent to the top of the AC and bottom of the PC) and 3 coronal planes—1 tangent to the genu of the corpus callosum, 1 tangent to the anterior border of the AC, and 1 through the PC at the midline.[52] These planes divided each hemisphere into 8 regions: dorsal prefrontal, orbitofrontal, premotor, subgenual, sensorimotor, parietooccipital, midtemporal, and inferior occipital (**Figure 1**). The validity of related parcellation schemes have been previously documented.[53-57] Parcellated cerebral tissue volumes included both gray and white matter but not cerebrospinal fluid (CSF).

Cerebral Ventricles

An isointensity contour function was used to define the contours of the cerebral ventricles. The ventricular system was subdivided by first manually isolating the third and fourth ventricles. Each of the lateral ventricles was then divided into 3 sections—the frontal horns, midbody, and occipital horns—using 2 coronal planes, one passing tangent to the

lescence. These studies indicate that the persistence of severe tics into adulthood is relatively unusual.[11,12] Studies that include adults as well as children can therefore yield clinically important information—they may, for example, point to the neural systems that change with age and that thereby influence the severity of symptoms and natural history of TS.

Third, we hypothesize that regional sex differences in brain volume will be seen in healthy controls and that those sex differences will be attenuated in TS subjects.[6] This hypothesis is based on the well-documented observation that TS is 4 to 10 times more common in males than in females.[7,13-15] Although the determinants of these sex-specific differences in rates of illness are unknown,

anterior-most point of the AC and the other through the PC as those commissures crossed midline.[52] The temporal horn was separated from the lateral bodies of the ventricles using an axial plane containing the AC-PC line (**Figure 2**). The interrater reliability of the measurements was assessed on 20 scans each measured by 4 raters. Intraclass correlation coefficients calculated using a 2-way random-effects model[58] were greater than 0.98 for each of the cerebral and ventricular subdivisions, with the exception of the third ventricle, which had an intraclass correlation coefficient of 0.88.

Whole Brain Volume

To control for generalized scaling effects within the brain,[59] we measured whole brain volume (WBV) for use as a covariate in statistical analyses.[60] This measure included cerebral tissue (gray and white matter), ventricular CSF, and CSF spaces within the brain (cisterns, fissures, and cortical sulci). The CSF spaces were added to the volume of cerebral tissue using a connected components analysis (the ANALYZE subroutine "delete holes"). These spaces were included to minimize the effects of age-related cortical atrophy on this covariate in older subjects and other possible neurodegenerative effects in the patient group. Covarying for WBV in the presence of these effects can either covary out similar effects in brain subregions or make volumes of unaffected subregions seem artifactually larger.[60,61]

STATISTICAL ANALYSES

A Priori Hypothesis Testing

All statistical procedures were performed in SAS version 8.0 (SAS Institute Inc, Cary, NC). A priori hypotheses were tested using a mixed models analysis (PROC MIXED) with repeated measures over a spatial domain (regional brain volumes).

The cerebral and ventricular parcellations were entered as dependent variables into 2 separate models. The model for the cerebrum included 2 within-subjects factors—"region," which had 8 levels (the 8 cerebral parcellations listed above) plus the cerebellum, and "hemisphere," which had 2 levels ("left" and "right" for the 8 cerebral parcellations) plus a "midline" specification for the cerebellum. The model for the ventricles also included a region factor with 4 levels (frontal, midbody, occipital, and temporal horns) plus the third and fourth ventricles; it also included a hemisphere factor with 2 levels (left and right for the 4 components of the lateral ventricles) plus a midline specification for the third and fourth ventricles. Diagnosis was a between-subjects factor, and covariates included age, sex, WBV, socioeconomic status, and lifetime-diagnoses OCD or ADHD.

In addition to the covariates described above, we considered for inclusion in the model all 2- and 3-way interactions of diagnosis, sex, hemisphere, region, and age, because these terms all had potential biological relevance and were readily interpretable. We also considered the 2-way interactions of WBV with hemisphere or region because these terms too were readily interpretable and seemed likely to be associated with parcellated volumes. Terms that were not 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 significance).[62]

Tests of the significance of 4 statistical interactions—TS × region, TS × age × region, sex × TS × region, and TS × hemisphere × region—were used to test the 4 respective a priori hypotheses. Applied to the analysis of cerebral and ventricular volumes in separate statistical models, these hypotheses required 8 tests of significance; therefore, values of $P<.006$ for each interaction to survive strict Bonferroni correction were required for multiple comparisons. Hypothesis testing was performed on volumes from all 286 subjects. However, results of identical analyses are presented for volumes from children and adults alone to help clarify whether significant effects derived from one or both age groups.

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 the final mixed models. Least squares means and SEs were calculated in the mixed models and plotted to assist in the interpretation of significant interactions (Figure 1).

Assessment of Possible Confounding Factors

We also included in the initial models minority status, height, weight, and handedness index.[39] However, these variables had negligible effects on the 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 regional volumes with the severity of tic symptoms, either at the time of 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. We anticipated that worst-ever ratings would be more strongly associated with regional brain volumes than ratings of current severity, as suggested in our prior TS structural imaging studies.[32,33]

they seem not to include sex-linked transmission of the putative TS vulnerability genes.[16-20] We and others[6,21] have hypothesized that these differences in rates of illness instead have their neural basis in regions of the brain that are sexually dimorphic. Anatomical and functional disturbances in these regions may be responsible for the more frequent expression of TS in males and for the overt expression of symptoms in the relatively few women who would otherwise not express their inherent genetic diathesis to TS.[6,21] This proposal is supported by findings that hormonal manipulations can influence the severity of tic and OCD symptoms.[6,22-25] Candidate regions where group differences in volumetric sexual dimorphisms might be expected to differ between TS and healthy subjects

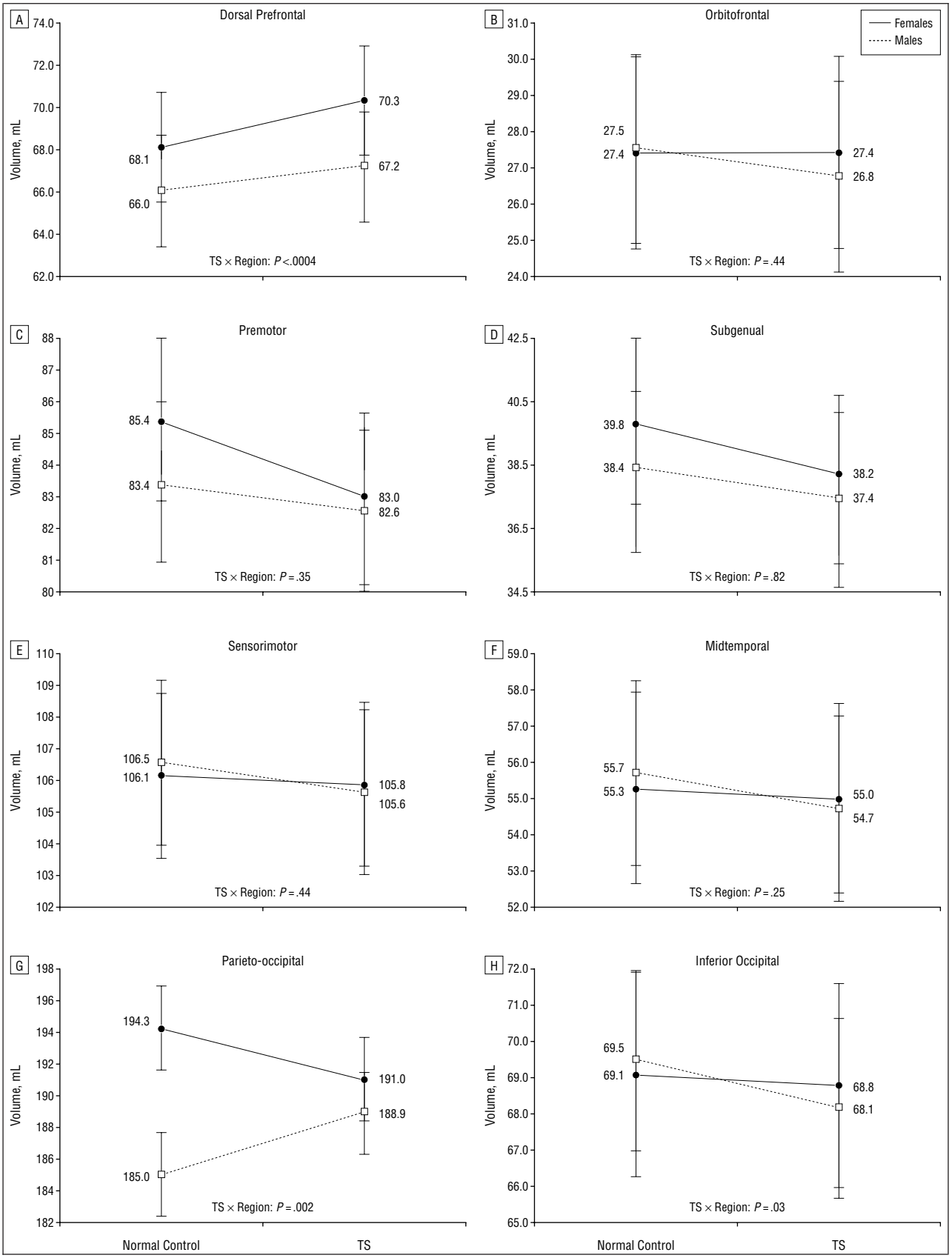

Figure 1. *The abscissa represents the dichotomous variable of diagnosis (Tourette syndrome [TS] or controls) and the ordinate represents regional volume. The graphs present, for each cerebral parcellation unit, the least squares mean values and SEs for males and females in each diagnostic group. The means are adjusted for all other terms of the statistical model (shown in Table 1). Significant effects for diagnosis are seen in the dorsal prefrontal, premotor, and subgenual regions. A significant TS× sex× region interaction is evident in the parieto-occipital region. The larger volumes for women in some brain regions are not absolute, but only proportional to the whole brain volume covariate used to correct for the smaller overall brains in women and for overall scaling effects in the statistical model.*

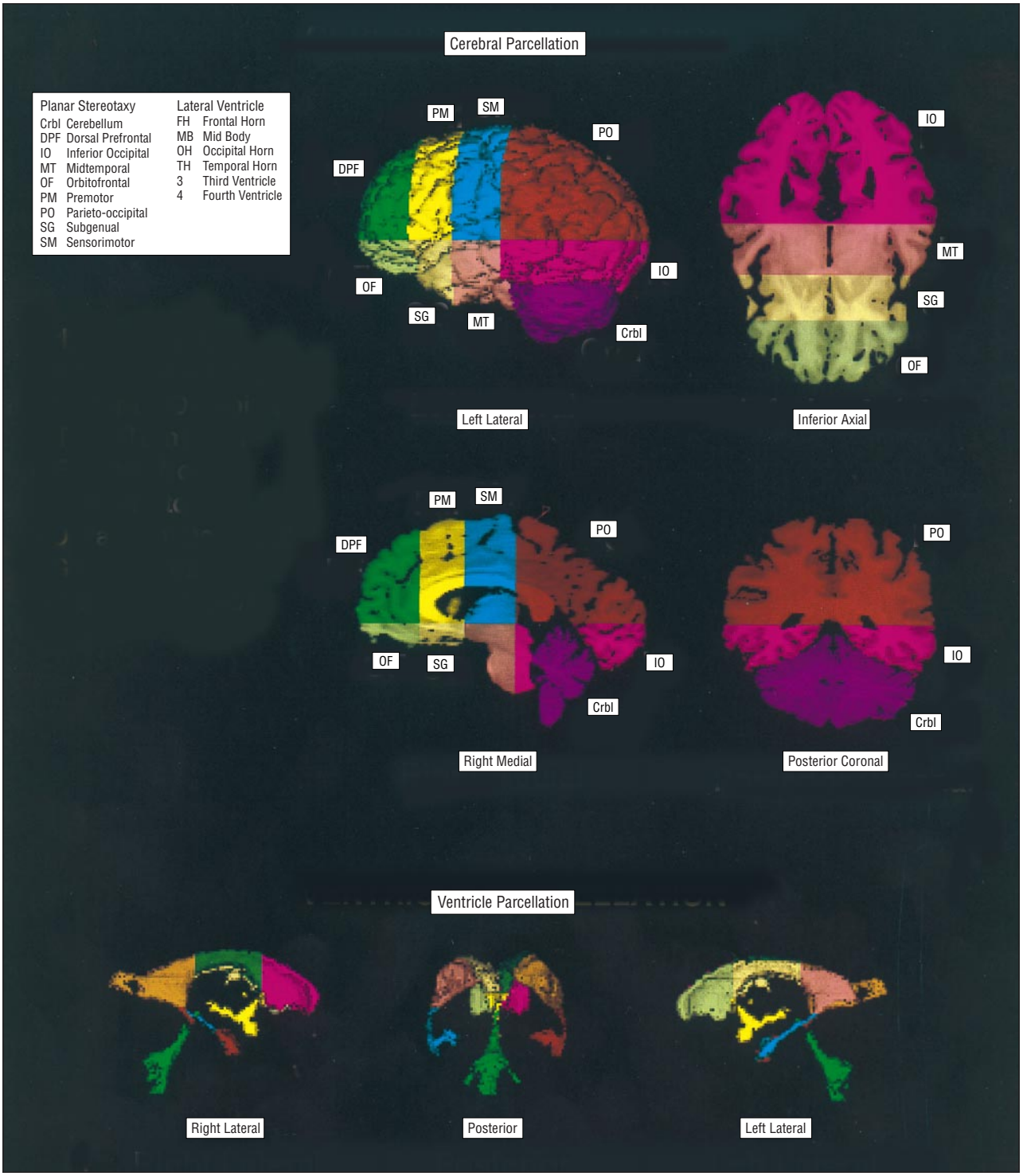

Figure 2. *The parcellation units defined using axial and coronal planes through standard anatomical landmarks of the reformatted brain, as described in the text. The medial view is a parasagittal slice (ie, lateral to the interhemispheric fissure and true midline) to permit visualization of structures within the cerebral hemisphere.*

include the parietal region. This area exhibits volumetric differences between sexes in normal individuals[26] and, based on the well-replicated finding that men on average perform better than women on a variety of visuospatial tasks that require an intact parietal lobe,[27-30] the region was hypothesized by some investigators to be functionally sexually dimorphic even before the anatomical sex differences were first described.[31]

Fourth, we hypothesize that hemispheric asymmetries will be observed in healthy subjects and that those asymmetries will be reduced in TS subjects in some brain regions.[32,33] This hypothesis is based on previous reports of altered basal ganglia asymmetries in TS.[32,34-36] These basal ganglia findings motivated the measurement of the corpus callosum in TS, which suggested the presence of disturbances in the structural integrity of in-

Table 1. A Priori Hypothesis Testing for the Parcellated Cerebrum*†

Source	NDF	All Subjects‡			Children Only§			Adults Only‖		
		DDF	$F_{Type\ 3}$	*P*	DDF	$F_{Type\ 3}$	*P*	DDF	$F_{Type\ 3}$	*P*
Hemisphere	1	561	3.58	.06	341	4.67	.03	217	0.11	.74
Region	7	2159	2.71	.01	1295	3.08	.003	833	3.54	.001
TS	1	270	0.07	.79	162	1.03	.31	99	1.5	.22
OCD	1	270	2.91	.09	162	3.14	.08	99	0.35	.56
ADHD	1	270	3.55	.06	162	3.56	.06	99	0.46	.50
Sex	1	270	2.25	.13	162	5.49	.02	99	0.37	.54
WBV¶	1	270	330.96	<.0001	162	225.83	<.0001	99	87.59	<.0001
Age	1	270	34.18	<.0001	162	0.53	.47	99	11.34	.001
SES	1	270	2.9	.09	162	2.27	.13	99	0.14	.71
Region × WBV	8	4304	136.89	<.0001	2576	98.16	<.0001	1664	40.58	<.0001
Region × hemisphere	7	1617	10.39	<.0001	965	5.02	<.0001	639	5.96	<.0001
Region × TS	*8*	*2159*	*6.15*	*<.0001*	*1295*	*4.48*	*<.0001*	*833*	*1.29*	*.24*
Region × sex	8	2159	3.08	.00	1295	2.82	.004	833	1.96	.05
Region × age	8	4304	33.33	<.0001	2576	2.81	.004	1664	13.30	<.0001
TS × age	1	270	0.41	.52	162	1.31	.25	. . .	. . .	. . .
Sex × age	1	270	0.24	.63	. . .	. . .	. . .	99	0.08	.77
TS × sex	1	270	0.38	.54	. . .	. . .	. . .	99	0.12	.73
Sex × age × region	8	4304	7.45	<.0001	. . .	. . .	. . .	1664	2.63	.007
TS × sex × region	*8*	*2159*	*3.69*	*.0003*	. . .	. . .	. . .	*833*	*4.21*	*<.0001*
TS × age × region	*8*	*4304*	*5.69*	*<.0001*	*2576*	*3.98*	*<.0001*	. . .	. . .	. . .

**NDF indicates numerator degrees of freedom; DDF, denominator degrees of freedom; $F_{Type\ 3}$, F statistic for type 3 sum of squares; TS, Tourette syndrome; OCD, obsessive-compulsive disorder; ADHD, attention-deficit/hyperactivity disorder; WBV, whole brain volume; SES, socioeconomic status; and ellipses, not included. Model terms in italics represent the a priori hypotheses.*

†Final models for each age group were determined by backward stepwise elimination, with the constraint that models at each step would remain hierarchically well formulated. Formal testing of the hypotheses was performed for the all-subjects model; the children- and adults-only models were developed to determine which findings were most readily generalizable. Probability values are not corrected for multiple comparisons.

‡Order of elimination of nonincluded terms for all subjects: region × hemisphere × sex; region × hemisphere × age; hemisphere × TS × age; TS × sex × age; hemisphere × sex × age; region × hemisphere × TS; hemisphere × TS × sex; hemisphere × sex, hemisphere × TS; and hemisphere × age. All terms were excluded at P>.10.

§Order of elimination of nonincluded terms for children only: region × hemisphere × age; region × hemisphere × sex; region × hemisphere × TS; TS × sex × age; hemisphere × TS × age; hemisphere × sex × age; hemisphere × TS × sex; hemisphere × TS; hemisphere × sex; region × TS × sex; TS × sex; hemisphere × age; sex × age × region; and sex × age. All terms were excluded at P>.10.

‖Order of elimination of nonincluded terms for adults only: region × hemisphere × age; region × hemisphere × sex; hemisphere × sex × age; hemisphere × TS × age; hemisphere × age; region × hemisphere × TS; TS × sex × age; hemisphere × TS × sex; hemisphere × sex; hemisphere × TS; TS × age × region; and TS × age. All terms were excluded at P>.10, except the TS × age × region term in this model (P = .09).

¶The strength of WBV effects in each model indicates that general scaling within the brain accounted for the most variance in regional volumes.

terhemispheric connections.[33,37] Reasoning that altered structural lateralization would not be limited to the basal ganglia and corpus callosum, we have predicted that imaging studies will demonstrate disturbances in cortical asymmetry.[33,38]

To examine these hypotheses, we conducted a magnetic resonance imaging (MRI) study of 155 TS and 131 healthy children and adults. Subregions of the cerebrum were compared between groups using multivariate models that tested each of our hypotheses concurrently. Similar comparisons were conducted for subregions of the cerebral ventricles to complement these analyses, as abnormal ventricular volumes have long been thought to reflect abnormalities in the surrounding cerebral tissue.

RESULTS

SUBJECTS

We acquired high-resolution anatomical MRI scans on 155 TS and 131 normal control subjects. The TS and control groups were of comparable mean±SD ages (18.7±13.4 vs 20.8±13.4 years, respectively; $t_{284}=1.3$, $P=.18$). Of the 286 participants, 177 (61.9%) were children (age, <18 years) and 109 (38.1%) were adults, with a similar age distribution between groups. The TS group compared with the controls had a significantly higher percentage of males (114 [73%] vs 72 [55%]; $\chi^2_1=10.2$, $P=.002$) and significantly fewer minorities (7 [5%] vs 16 [12%]; $\chi^2=5.69$, $P=.02$). Socioeconomic status did not differ significantly between groups (45.5±11.5 vs 47.6±9.8; $t_{284}=1.67$, $P=.10$).

Based on the structured interviews, lifetime diagnoses in the TS cohort included OCD in 62 (40%) and combined-type ADHD in 36 (23%). At the time of the study, 72 TS subjects (46%) were taking medication, stimulants (N=3 [2%]), traditional neuroleptics (haloperidol or pimozide, N=20 [12.9%]), risperidone (N=7 [4.5%]), α-adrenergic agonists (clonidine or guanfacine) (N=29 [18.7%]), selective serotonin reuptake inhibitors (N=19 [7.5%]), or tricyclics (N=11 [4.3%]).

HYPOTHESIS TESTING

Cerebrum

Statistical tests for each term in the final models are presented in **Table 1**.

Table 2. Selected Fixed Effects for the Parcellated Cerebrum*†

Model Term	Hemisphere	Region‡	TS	Sex	Parameter Estimate (95% CIs)	*df*	*P*
Hemisphere	Left				−36 170 (−50 904.8 to −21 435.2)	561	<.0001
Hemisphere	Right				−32 872 (−47 607.3 to −18 136.7)	561	<.0001
Region		3			18 827 (6670 to 30 984)	2159	.002
OCD			NC		−666.8 (−1433.0 to 99.3)	270	.09
ADHD			NC		−847.6 (−1729.1 to 33.9)	270	.06
WBV					0.08 (0.07 to 0.09)	270	<.0001
Region × WBV		1			−0.0299 (−0.04 to −0.02)	4304	<.0001
Region × WBV		2			−0.02 (−0.03 to −0.01)	4304	<.0001
Region × WBV		3			−0.02 (−0.03 to −0.01)	4304	<.0001
Region × WBV		4			0.06 (0.05 to 0.07)	4304	<.0001
Region × WBV		5			−0.06 (−0.07 to −0.05)	4304	<.0001
Region × WBV		6			−0.05 (−0.06 to −0.04)	4304	<.0001
Region × WBV		7			−0.05 (−0.06 to −0.04)	4304	<.0001
Region × WBV		8			−0.03 (−0.04 to −0.02)	4304	<.0001
Region × hemisphere	Left	1			4845.4 (3087.6 to 6603.2)	1617	<.0001
Region × hemisphere	Left	2			4115.6 (2366.2 to 5865)	1617	<.0001
Region × hemisphere	Left	3			3706.6 (1957.2 to 5456)	1617	<.0001
Region × hemisphere	Left	5			3728.9 (1971.1 to 5486.7)	1617	<.0001
Region × hemisphere	Left	6			3742.4 (1993.0 to 5491.8)	1617	<.0001
Region × hemisphere	Left	7			3659.3 (1909.9 to 5408.7)	1617	<.0001
TS × region		*1*	*NC*	*M*	*−7312.3 (−11 377.7 to −3247.0)*	*2159*	*.0004*
TS × region		*1*	*NC*	*F*	*−6609.54 (−11 740.6 to −1478.5)*	*2159*	*.01*
TS × region		*2*	*NC*	*M*	*1946.46 (−2102.45 to 5995.37)*	*2159*	*.34*
TS × region		*2*	*NC*	*F*	*5363.05 (248.57 to 10 477.53)*	*2159*	*.04*
TS × region		*4*	*NC*	*M*	*−5489.5 (−9590.6 to −1388.5)*	*2159*	*.009*
TS × region		*4*	*NC*	*F*	*3406.42 (−1803.36 to 8616.19)*	*2159*	*.20*
TS × region		*8*	*NC*	*M*	*−4583 (−8684 to −482)*	*2159*	*.03*
TS × region		*8*	*NC*	*F*	*−3796.78 (−9006.56 to 1412.99)*	*2159*	*.15*
Sex × region		1		F	4543.5 (−367.6 to 9454.5)	2159	.06
Sex × region		8		F	7433.2 (2441.1 to 12 425.3)	2159	.004
Age × region		1			−235.4 (−360.8 to −110.0)	4304	.0002
Age × region		2			133.2 (8.0 to 258.4)	4304	.04
Age × region		4			−322.9 (−449.1 to −196.6)	4304	<.0001
Age × region		5			−113.7 (−239.1 to 11.8)	4304	.07
Age × region		7			119.7 (−5.5 to 244.8)	4304	.06
Age × region		8			233.1 (106.8 to 359.3)	4304	.0003
Sex × age × region		4		M	−154.1 (7.5 to −315.6)	4304	.06
Sex × age × region		8		M	318.4 (479.9 to 156.9)	4304	<.0001
TS × age × region		*1*	*NC*		*246 (86.3 to 405.8)*	*4304*	*.003*
TS × age × region		*8*	*NC*		*232.8 (72.1 to 393.5)*	*4304*	*.004*

**TS indicates Tourette syndrome; CI, confidence interval; OCD, obsessive-compulsive disorder; NC, normal control; ADHD, attention-deficit/hyperactivity disorder; WBV, whole brain volume; M, male; and F, female. Model terms in italics represent the a priori hypotheses.*

†Fixed effects with values of P<.10 in the final model for all subjects are shown; however, some less significant TS × region effects are also shown to better illustrate the sex differences.

‡The 8 regions are numbered as follows: dorsolateral prefrontal (region 1); premotor (region 2); sensorimotor (region 3); parieto-occipital (region 4); orbitofrontal (region 5); subgenual (region 6); midtemporal (region 7); and inferior occipital (region 8).

Region-Specific Differences

The TS × region interaction was significant, confirming our first hypothesis. The fixed effects (**Table 2**) and least squares means (Figure 1) indicated that the strongest contributions to this effect came from larger dorsal prefrontal volumes in TS males (1.7%, *P*=.0004) and females (3.3%, *P*=.01), smaller premotor volumes in TS females (−3.0%, *P*=.04), larger parieto-occipital volumes in TS males (2.1%, *P*=.0002), and smaller inferior occipital volumes (−1.9%, *P*=.03) in TS males.

Children Only. Compared with normal children of the same sex, the fixed effects and least squares means indicated larger dorsal prefrontal volumes in TS boys (5.7%, *P*=.0007) and TS girls (5.8%, *P*=.003), smaller premotor volumes in TS boys (−4.8%, *P*=.02), larger parieto-occipital volumes in TS boys (0.5%, *P*<.0001) and TS girls (0.5%, *P*=.002), smaller orbitofrontal volumes in TS boys (−4.8%, *P*=.001), smaller subgenual volumes in TS boys (−5.5%, *P*=.03), and larger inferior occipital volumes in TS boys (2.4%, *P*=.05) and TS girls (2.5%, *P*=.02).

Adults Only. Compared with normal adults of the same sex, the fixed effects and least squares means indicated smaller dorsal prefrontal volumes in TS women (−3.4%, *P*=.06), larger premotor volumes in TS men (3.4%, *P*=.01), larger parieto-occipital volumes in TS men (2.8%, *P*=.0008), and smaller parieto-occipital volumes in TS women (−2.7%, *P*=.005).

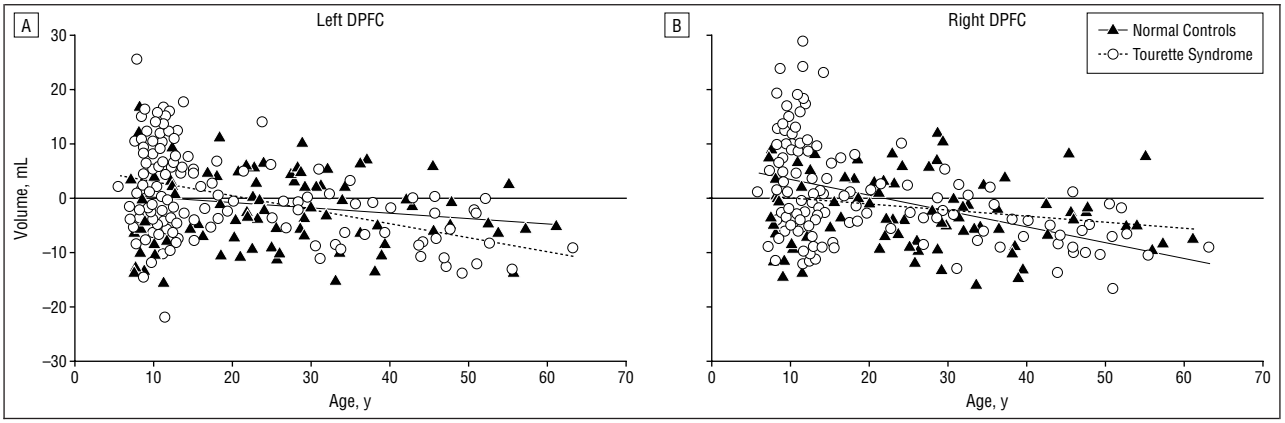

Figure 3. *Significant age × diagnosis × region interactions in post hoc testing were seen in the dorsal prefrontal (DPFC) region. The residual volumes of those regions after partialling out whole brain volume, sex, socioeconomic status, obsessive-compulsive disorder, and attention-deficit/hyperactivity disorder in a repeated-measures analysis of variance are plotted against age. Because these are residual volumes, they can take positive or negative values.*

Age-Specific Differences

The TS × age × region interaction was significant, confirming our second hypothesis. The fixed effects indicated the greatest contributions from the dorsal prefrontal ($P=.003$) and inferior occipital ($P=.004$) regions. Graphical representation (**Figure 3**) indicated that dorsal prefrontal volumes in TS children were larger than those in controls, but by midadulthood those volumes were smaller in TS than in control subjects. In inferior occipital regions, volumes were positively associated with age in the normal controls and negatively associated with age in the TS group (data not shown).

Age-specific group differences in volume were more prominent in children than in adults, and they were especially strong in dorsal prefrontal, orbitofrontal, and parieto-occipital regions (Tables 1 and 2). In the TS children, the associations of age with regional volumes were in the same direction as those in the combined age groups (Figure 3); inverse associations with age were present in all 3 regions in the TS group, but negligible age effects were detected in normal controls.

Sex-Specific Differences

The TS × sex × region term was significant. Fixed effects indicated the strongest contributions from parieto-occipital regions ($P=.0002$). Here, volumes in healthy females were considerably larger than in healthy males, whereas volumes in TS females and males were similar to one another (Figure 1). Sex-specific group differences were more prominent in adults than in children (Tables 1 and 2), with sex differences in healthy adult subjects absent in the TS adults. In the prefrontal area of adults, reduced sex differences were largely caused by reduced volumes in TS women (3.5%, $P=.02$), whereas in the premotor region it was mostly caused by larger volumes in TS men (3.4%, $P=.02$) (data not shown). The findings in the parietal region of adults were nearly identical to those when all subjects were included ($P<.0001$) (Figure 1).

Hemisphere-Specific Differences

The TS × hemisphere × region term was not significant in any of the age groups examined.

Ventricles

Multivariate statistical testing is presented in **Table 3**. The TS × region, TS × age × region, and TS × hemisphere × region interactions were not significant and therefore did not support the first, second, or fourth hypotheses for the ventricles. The significant TS × sex × region interaction ($P=.002$), however, confirmed the third hypothesis. The fixed effects (**Table 4**) (**Figure 4**) indicated a sex difference in the occipital horns of TS subjects (larger volumes in males) that was not present in normal controls ($P=.03$).

Associations With Tic Severity

Ratings of worst-ever tic severity correlated more robustly and consistently with regional volumes than did ratings of current tic severity (data not shown). For the cerebral parcellations, correlations were strongest in the left ($\beta=-0.26$, $P=.002$) and right ($\beta=-0.20$, $P=.02$) orbitofrontal region, and in the left ($\beta=-0.20$, $P=.03$) and right ($\beta=-0.29$, $P=.002$) parieto-occipital region, where increasing volumes were associated with fewer symptoms. Weaker, positive associations were seen between tic severity and volumes of the left sensorimotor and left midtemporal regions ($\beta=0.17$, $P=.05$) (**Figure 5**). For the cerebral ventricles, correlations with symptom severity were uniformly positive and strongest with the volumes of the midbodies of the lateral ventricles ($\beta=0.21$-0.23, $P=.02$ to $P=.008$) and with volumes of the third ($\beta=0.19$, $P=.03$) and fourth ventricles ($\beta=0.24$, $P=.004$). These correlations of tic severity with regional volumes were more robust in adults (eg, orbitofrontal and parieto-occipital β –0.44 to –0.46, $P=.01$ to $P=.009$) and they were negligible in children.

Table 3. A Priori Hypothesis Testing for the Parcellated Ventricles*†

Source	NDF	All Subjects‡			Children Only§			Adults Only‖		
		DDF	$F_{Type\ 3}$	*P*	DDF	$F_{Type\ 3}$	*P*	DDF	$F_{Type\ 3}$	*P*
Hemisphere	1	567	11.42	.0008	347	0.94	.33	215	6.62	.01
Region	4	1401	2.22	.07	858	1.35	.25	521	1.13	.34
TS	1	274	0.31	.58	164	1.66	.20	99	0.99	.32
OCD	1	274	0.48	.49	164	0.6	.44	99	1.07	.30
ADHD	1	274	3.36	.07	164	2.04	.16	99	0.37	.54
Sex	1	274	0.3	.58	164	0.24	.63	99	1.33	.25
WBV	1	274	0.33	.57	164	0.01	.94	99	0.87	.35
Age	1	274	77.83	<.0001	164	4.8	.03	99	13.05	.0005
SES	1	274	2.97	.09	164	1.99	.16	99	0.78	.38
Region × WBV	5	2520	8.76	<.0001	1537	5.2	<.0001	941	3.85	.002
Hemisphere × TS	1	. . .	. . .	. . .	347	6.17	.01	. . .	. . .	. . .
Hemisphere × sex	1	. . .	. . .	. . .	347	6.85	.009	. . .	. . .	. . .
Hemisphere × age	1	. . .	. . .	. . .	1537	0.33	.57	. . .	. . .	. . .
Region × TS	*5*	*1401*	*1.5*	*.19*	*858*	*1.32*	*.26*	*521*	*0.53*	*.76*
Region × sex	5	1401	1.96	.08	858	1.15	.33	521	1.61	.15
Region × age	5	2520	39.34	<.0001	1537	4.65	.001	941	4.32	.0007
TS × sex	1	274	1.16	.28	164	0.27	.60	99	1.14	.29
TS × age	1	. . .	. . .	. . .	164	1.75	.19	. . .	. . .	. . .
Sex × age	1	274	1.1	.29	164	0.03	.85	. . .	. . .	. . .
TS × age × hemisphere	2	. . .	. . .	. . .	1537	4.81	.008	. . .	. . .	. . .
Sex × age × hemisphere	2	. . .	. . .	. . .	1537	3.63	.03	. . .	. . .	. . .
Sex × age × region	5	2520	3.88	.002	. . .	. . .	. . .	. . .	. . .	. . .
TS × sex × region	*5*	*1401*	*3.95*	*.002*	*858*	*2.15*	*.05*	*521*	*2.18*	*.05*

**NDF indicates numerator degrees of freedom; DDF, denominator degrees of freedom; $F_{Type\ 3}$, F statistic for type 3 sum of squares; TS, Tourette syndrome; OCD, obsessive-compulsive disorder; ADHD, attention-deficit/hyperactivity disorder; WBV, whole brain volume; SES, socioeconomic status; and ellipses, not included. Model terms in italics represent the a priori hypotheses.*

†The nonincluded terms were eliminated in a backward stepwise elimination selection procedure. Age was strongly and positively associated with ventricular volume, and was especially prominent in the midbody and temporal horns.

‡Order of elimination of nonincluded terms for all subjects; region × hemisphere × sex; TS × age × hemisphere; sex × age × hemisphere; TS × sex × age; region × hemisphere × age; hemisphere × TS × sex; region × hemisphere × TS; TS × age × region; TS × age; hemisphere × sex; hemisphere × TS; hemisphere × age; and hemisphere × region. All terms were excluded at P>*.10.*

§Order of elimination of nonincluded terms for children only: region × hemisphere × sex; region × hemisphere × age; region × hemisphere × TS; sex × age × region; TS × sex × age; hemisphere × sex; hemisphere × region; and TS × age × region. All terms were excluded at P>*.10, except the TS × age × region term in this model (*P = *.09).*

‖Order of elimination of nonincluded terms for adults only: TS × age × hemisphere; region × hemisphere × age; region × hemisphere × TS; region × hemisphere × sex; sex × age × hemisphere; sex × age × region; hemisphere × TS × sex; hemisphere × sex; hemisphere × TS; hemisphere × region; TS × age × region; hemisphere × age; TS × sex × age; sex × age; and TS × age. All terms were excluded at P>*.10.*

FURTHER EXPLORATORY ANALYSES

Cerebrum

Diagnoses of OCD or ADHD in the TS subjects were associated as covariate main effects with larger volumes at trend levels of significance ($P=.09$ and $P=.06$, respectively) (Table 1).

Ventricles

A diagnosis of ADHD in TS subjects was associated with smaller ventricular volumes at a trend level of significance ($P=.06$).

Medication Effects in the TS Group

Medication effects on regional volumes were tested separately for the current use of neuroleptics, selective serotonin reuptake inhibitors, or α-adrenergic agonists using the same statistical models as those employed for the post hoc testing of diagnostic effects. In no regions were medication effects significant at a value of $P<.05$.

Neuroleptic-Naïve, "Pure" TS Children

In a separate mixed-model analysis of children (age <18 years), 42 pure TS subjects (no lifetime diagnosis of OCD or ADHD) who had no prior exposure to typical or atypical neuroleptics were compared with 67 healthy controls. Results were similar to those obtained for the comparison of all TS and control children (Table 1), suggesting that these comorbidities and prior neuroleptic exposure did not significantly influence the findings.

COMMENT

We were able to confirm region, age, and sex differences, but not hemisphere-specific differences in cerebral volume between TS and healthy control subjects. Group differences were much less prominent for ventricular volumes.

Table 4. Selected Fixed Effects for the Parcellated Ventricles*†

Model Term	Region‡	TS	Sex	Parameter Estimate (95% CIs)	*df*	*P*
Region	1			−979.9 (−1911.9 to −47.9)	1401	.04
Region	3			−1065.7 (−1997.8 to −133.7)	1401	.03
ADHD		NC		190.7 (−13.2 to 394.7)	274	.06
Age				23.4 (14.2 to 32.7)	274	<.0001
WBV × region	1			0.001 (0.0004 to 0.002)	2520	.003
WBV × region	2			0.001 (0.0001 to 0.002)	2520	.03
WBV × region	3			0.002 (0.001 to 0.003)	2520	<.0001
Sex × region	2		F	−385.6 (−771.2 to −0.1)	1401	.05
Sex × region	3		F	−665.0 (−1050.7 to −279.3)	1401	.0007
Age × region	1			12.1 (3.7 to 20.6)	2520	.005
Age × region	2			19 (10.5 to 27.4)	2520	<.0001
Age × region	4			−13.0 (−21.4 to −4.5)	2520	.003
Age × region	5			−11.5 (−21.3 to −1.7)	2520	.02
Age × sex			F	−14.6 (−28.4 to −0.8)	274	.04
TS × sex × region	*3*	*NC*	*F*	*397.8 (37.6 to 757.9)*	*1401*	*.03*
Age × sex × region	3		F	23.5 (10.8 to 36.2)	2520	.0003

*TS indicates Tourette syndrome; CI, confidence interval; ADHD, attention-deficit/hyperactivity disorder; NC, normal control; WBV, whole brain volume; and F, female. Model terms in italics represent the a priori hypotheses.

†Fixed effects with values of P<.10 in the final model for all subjects are shown. Significant fixed effects for a priori hypotheses in children only: TS × age × hemisphere (P=.006). There were no significant effects for a priori hypotheses in adult only.

‡The regions are numbered as follows: frontal horn (region 1); midbody of lateral ventricles (region 2); occipital horns (region 3); temporal horns (region 4); and fourth ventricle (region 5).

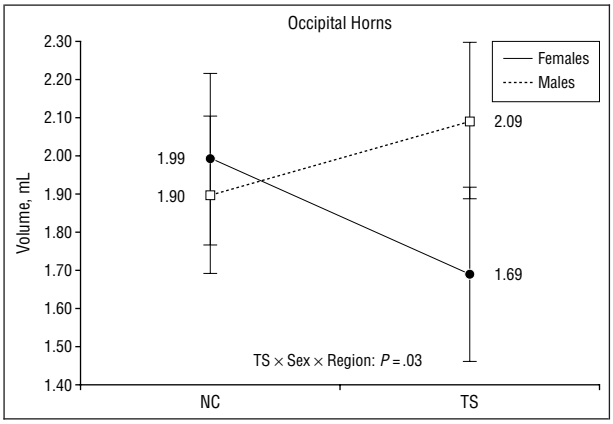

Figure 4. *Only the Tourette syndrome (TS) × sex × region interaction was significant, and this effect derived primarily from the parieto-occipital region.*

HYPOTHESES

Region Specificity

The most prominent regional effect in TS subjects was a larger dorsal prefrontal volume. However, this effect derived primarily from larger prefrontal volumes in TS children. Group differences were less prominent in older children because of an inverse association of age with prefrontal volumes in the TS group. In fact, by adulthood, the TS subjects tended to have smaller dorsal prefrontal volumes, an effect that reached significance in TS women. Similar effects that were specific to age group were observed in the parieto-occipital region, where volumes were larger in younger TS children but negligibly larger by late adolescence. In adults, parieto-occipital volumes were still significantly larger in TS men but were significantly smaller in TS women. Group differences in inferior occipital regions were similar to those in parieto-occipital regions, except that volumes were not significantly larger in TS men.

Separate analyses of children and adults revealed additional group differences that were more widespread and generally of larger magnitude in the children. Effects were significant for TS boys, who had smaller orbitofrontal, subgenual, and premotor volumes. In adults, effects in the premotor region were opposite in direction and were significantly larger in TS men. Group effects were therefore opposite in direction for TS children and adults in dorsal prefrontal, premotor, and parieto-occipital regions, and contributed to age-specific regional differences in the analysis of the combined age groups (below). Of these various regions, parieto-occipital and orbitofrontal volumes in the TS group were significantly and negatively associated with the severity of tic symptoms.

These various brain regions subserve diverse functions. The prefrontal region is believed to mediate performance in tasks that require decisions of whether, when, and how to act across a time delay, as needed for working memory, go–no go, and behavioral inhibition tasks.[63] The premotor region defined here includes the supplementary motor area, the cortical recipient of motor pathways in the cortico-striato-thalamo-cortical circuits that participate in planning and executing motor tasks. Electrical stimulation of this region produces complex movements, vocalizations, and urges to move a contralateral body part,[64,65] urges similar to those that accompany tics.[66] The subgenual region defined here contains inferior, dysgranular cortices that connect the orbitofrontal cortex, temporal pole, and amygdala with the ventral striatum and hypothalamus.[67] It is regarded as an anatomical crossroad that contributes to affective and motivational processing.[63,68-70] The premotor, prefrontal, and subgenual regions therefore together contribute, among other things, to the motivation, planning, and execution of normal behavioral repertoires, of the sort that have gone awry in

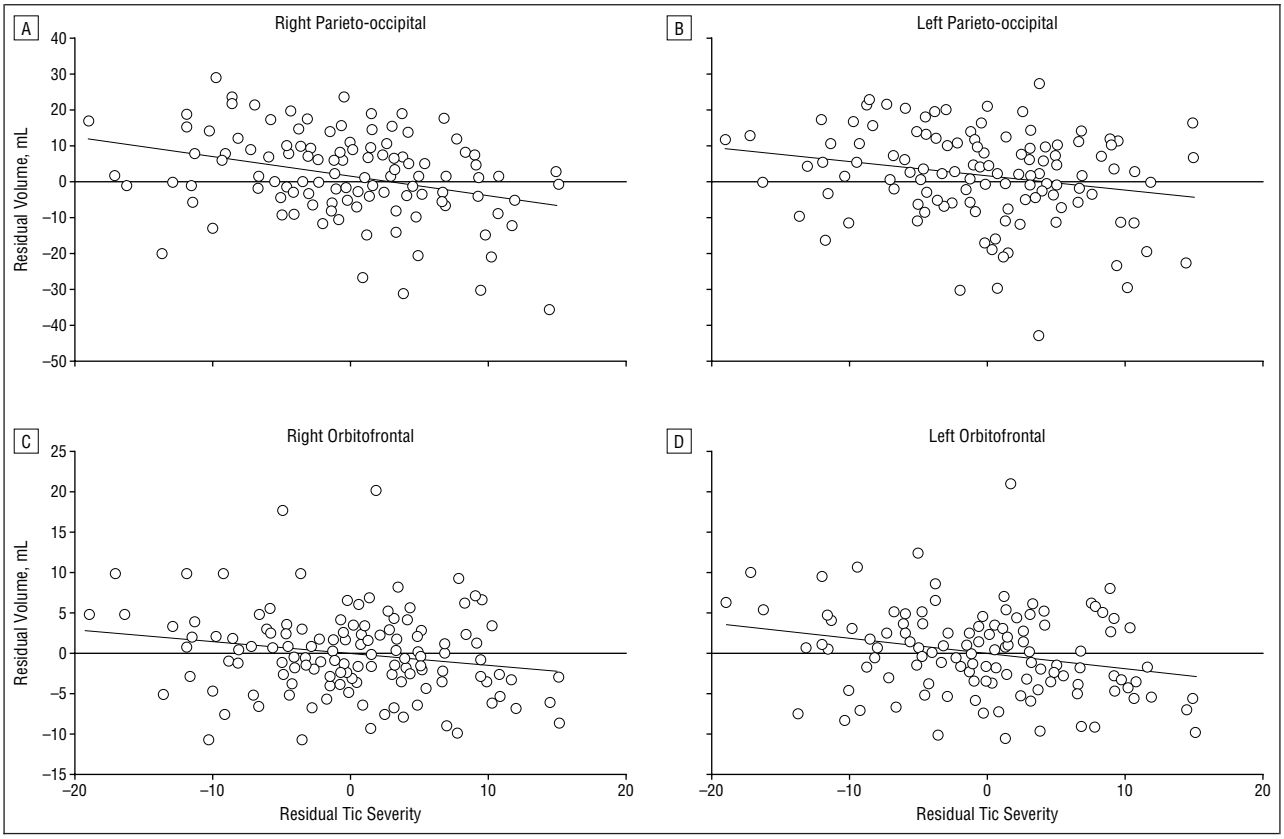

Figure 5. *Regions where the associations of volume with symptom severity were strongest are shown. Whole brain volume and sex were first partialed out of both volume and symptom severity, so that the associations of the residual values plotted here represent partial correlations. Because these are residual volumes and severity ratings, they can take positive or negative values.*

persons with TS. Functions of the parietal and occipital regions include visuospatial and attentional processing, disturbances of which are the most reliable findings in neuropsychological studies of TS subjects, particularly when these functions must be integrated with motor performance.[71]

Age Specificity

The associations of dorsal prefrontal and inferior occipital volumes with age differed significantly between TS and healthy controls because of inverse associations with age in the dorsal prefrontal, parieto-occipital, and inferior occipital regions of TS subjects (Figure 3). These group-specific age associations were strongest in children. Premotor volumes, in contrast, were significantly smaller in TS boys and larger in TS men. In the ventricular system, strong associations with age were seen throughout all subregions, but especially in the frontal horns, midbodies, and temporal horns of the lateral ventricles. These age effects, however, did not affect the TS group disproportionately.

Cross-sectional, age-related differences between groups in regional cerebral volumes have several possible interpretations. One is that they represent pathological associations of volume with age that are representative of the longitudinal trajectories of regional brain volumes in most TS subjects. This seems unlikely, given the nonrepresentativeness of clinically identified TS adults who remain symptomatic (such as the subjects in this study) and given the inherent difficulty of inferring longitudinal course from a cross-sectional study such as this.[72] A second interpretation, which we favor, is that the group differences in adulthood represent regional markers for morphological traits that contribute to the relatively unusual persistence of symptoms into late adolescence and adulthood, and that contribute to the clinical identification and study of these still-symptomatic subjects. These traits might be long-standing from childhood (and would therefore constitute a marker of risk for future symptom persistence) or they might be acquired in adolescence or adulthood (and thereby represent a second process that influences the natural history of the primary tic disorder).[73] Longitudinal studies could help to confirm this explanation directly, and they would help to assess the utility of regional volumes as putative developmental markers for symptom persistence. A third possible explanation of the age associations is that they represent long-term activity-dependent plastic changes (presumably adaptive or compensatory in nature) caused by the lifelong presence of tics. Long-term, activity-dependent effects may include the larger dorsolateral prefrontal volumes in TS children and larger premotor volumes in TS men. Again, a longitudinal study would help to address these possibilities more directly. A fourth explanation is that the age-related changes are nonspecific responses to the presence of chronic illness.

Most TS imaging studies thus far have been of adult subjects. In radioligand and radiotracer studies, the ex-

clusive study of adults has been necessary because of the ethical concerns of exposing children to the radioactivity of tracers. The age-related findings of the present study, however, suggest that findings of prior adult studies may not generalize to pediatric populations or to TS adults who are less symptomatic.[10]

Sex Differences

Group-specific sex differences derived largely from the parieto-occipital region, where prominent sex differences were seen in normal but not in TS subjects. This group-specific sex difference was caused by relatively larger volumes in TS males and smaller volumes in TS females (Figure 1). In the ventricles, a sex difference in occipital horn volume was seen in TS subjects but not in normal subjects. It derived from larger volumes in TS males but smaller volumes in TS females (Figure 4). Altered sex differences in TS subjects therefore involved primarily posterior brain regions, where the directional effects of abnormalities in cerebral tissue and ventricular CSF paralleled one another—volumes of each were larger in TS males and smaller in TS females than in their healthy control counterparts. In the posterior compartment of TS subjects, this may have reduced sex differences that would otherwise have been prominent, and in the posterior ventricular system, it may have introduced sex differences that would not have otherwise existed.

Altered Asymmetries

Our hypothesis concerning altered cerebral and ventricular asymmetries was not supported by the present findings. This suggests that the prior findings of altered asymmetries in the basal ganglia do not generalize to cortical regions, that the cortical regions defined here were too coarse to detect altered asymmetries, or that the basal ganglia findings represented type I errors in studies with small numbers of subjects.

AN INTEGRATIVE MODEL: THE NEUROMODULATION OF TIC SYMPTOMS

The greatest group differences in this study were found in dorsal prefrontal, parieto-occipital, and inferior occipital regions. We suspect that these regional abnormalities in TS subjects derived in part from the participation of the heteromodal frontal and parietal regions in a broadly distributed action-attentional system that must be engaged for the successful inhibitory control of tic symptoms.[9,63,74-76] This network also includes the orbitofrontal and midtemporal regions, which, along with volumes of the parieto-occipital regions, correlated significantly with the severity of tic symptoms.

Smaller orbitofrontal and parieto-occipital volumes were associated with worse tic symptoms, suggesting that smaller volumes in this portion of the action-attentional system may provide insufficient inhibitory reserve to help suppress these unwanted behaviors. Larger prefrontal volumes in the TS subjects may represent an activity-dependent structural plasticity that could help to suppress tics. Consistent with this hypothesis are numerous preclinical and clinical studies suggesting that the orbitofrontal region in particular plays an important role in inhibitory control.[63,77-84] Also consistent is the prior finding that as TS subjects suppress tics, activation of the ventral prefrontal cortex is signficantly correlated with decreases in activity of basal ganglia nuclei, the putative neural substrate of tics.[9] Larger premotor regions in men compared with smaller volumes in TS boys may represent long-term, activity-dependent effects in the motor system associated with the presence of tics.

The inverse association of parieto-occipital volumes with age in TS subjects was disproportionately represented in TS females, and in the TS group this resulted in a reduced volume difference between sexes compared with normal controls. Neuroimaging and behavioral studies together suggest that sexual dimorphisms in the parietal region may contribute to sex differences in visuospatial task performance and other sexually dimorphic behaviors. The most robust sexually dimorphic behavior in normal children and adults is a reduced inhibitory control in males compared with females that is manifested as an innate predisposition to more aggressive behavior,[85,86] a frequently reported difficulty in TS clinic populations.[2] Because smaller volumes in the parieto-occipital region were associated with more severe tic symptoms in TS subjects, it is possible that a profile more like normal males (smaller volumes) in this portion of the action-attentional system predisposes TS subjects to more severe tics. This is consistent with our previously stated hypothesis that sexually dimorphic brain regions may contribute to symptom expression.[6]

As noted above, the stronger inverse association of dorsal prefrontal volumes with age in the TS group may have resulted from the presence in the TS adults of a morphological trait (smaller prefrontal volumes) that predisposes to more severe or more chronic symptoms. Smaller prefrontal volumes could have contributed to the relatively unusual persistence of their symptoms in adulthood and to the subsequent clinical identification and inclusion of the adults in this study. The age-specificity of regional findings thus further supports the possibility that larger prefrontal regions in TS subjects are an adaptive, compensatory response that helps to attenuate tic symptoms. Smaller prefrontal volumes might then constrain the magnitude of those adaptive reserves and, if present in childhood, would then be a promising marker for predicting the future course of illness.

Identifying neuromodulatory systems such as these may be more clinically relevant in TS than defining the neural basis of the origin of tics per se. Many younger children, for example, have transient or chronic tics,[87-90] but few will have tics of sufficient number or severity to cause functional impairment. Relatively few of the children who have severe tics, moreover, will continue to have severe tics into early adulthood. Neuromodulatory systems may therefore determine whether and for how long tics have a functional impact on a child's life.

LIMITATIONS AND FUTURE DIRECTIONS

Localization of the morphological correlates of TS was no doubt impaired in this study by the relative coarseness of the cerebral parcellation scheme. Regional cerebral volumes included both gray and white matter, and the region definitions all subsumed numerous cytoarchitectonic and functional areas. The coarseness did provide the advantage, however, of reducing the number of statistical comparisons and the risk of type I error, while also helping to guide future hypothesis-driven studies using finer-grained parcellation schemes.[56,91] The parcellation also relied on landmarks (the AC-PC line and the anterior border of the corpus callosum) that are assumed to be anatomically invariant between diagnostic groups, and this is an untested assumption. Nevertheless, the same parcellation scheme has been applied in the study of other conditions where the size of the corpus callosum is reduced by more than 30%, without producing patterns of group difference in regional volume that resembled those seen here.[92] In addition, the effects of prior medication use on regional brain volumes in the TS group cannot be entirely discounted by the absence of discernible effects of medication on the statistical analyses. Nevertheless, tests of a priori hypotheses and the parameter estimates for those subjects who had no prior medication use were similar to estimates for the entire group, suggesting that medication exposure did not unduly influence the findings.

The most limiting feature of this study is its cross-sectional design. The static view of the brain provided by cross-sectional imaging studies insufficiently constrains the possible interpretation of the correlation analyses that are needed to understand the direction of group differences.[72] In the present study, for example, it is impossible to say decisively whether observed group differences in regional volume contributed to the production of tics or whether they were somehow a plastic or compensatory response to the presence of the unwanted behaviors. If we are to be confined to study designs that are naturalistic and observational, as the vast majority of imaging studies are, then longitudinal studies should be undertaken to generate change scores that will at least help to further constrain the interpretation of critical brain-behavior associations.

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