Striatal [^{11}C]dihydrotetrabenazine and [^{11}C]methylphenidate binding in Tourette syndrome

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ABSTRACT

Objective: Tourette syndrome (TS) is a common neurodevelopmental disorder marked by tics and behavioral comorbidities. Clinical pharmacology suggests that dopaminergic signaling abnormalities are part of the pathophysiology of TS. Prior molecular imaging studies of nigrostriatal dopaminergic terminal markers report conflicting results. Our goal was to characterize the distribution of nigrostriatal dopaminergic terminals in subjects with TS.

Methods: Thirty-three adult subjects with TS were studied with PET using [^{11}C]dihydrotetrabenazine (DTBZ), a ligand for the type 2 vesicular monoamine transporter, and with [^{11}C]methylphenidate (MP), a ligand for the plasmalemmal dopamine transporter. Subjects were characterized with standard rating instruments for tic severity, obsessive-compulsive behaviors, and attentional deficits.

Results: We found no differences between subjects with TS and control subjects in DTBZ and MP binding in any striatal region. There was no correlation between binding measures and clinical variables. Ventral striatal DTBZ and MP binding distributions in subjects with TS were normal.

Conclusions: We found no evidence of increased striatal dopaminergic innervation in Tourette syndrome (TS). Discrepancy between our present results and those of other studies may be explained by heterogeneity of TS. ***Neurology*® 2009;72:1390–1396**

GLOSSARY

BP = binding potential; **CAARS-S:S** = Conners Adult ADHD Rating Scale-Self Report: Short version; **DAT** = dopamine transporter; ***DSM-IV*** = *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition; **DTBZ** = [^{11}C]dihydrotetrabenazine; **DVR** = ratio of volumes of distribution; **FDR** = false discovery rate; **MP** = [^{11}C]methylphenidate; **OCBs** = obsessive-compulsive behaviors; **TS** = Tourette syndrome; **VOI** = volume of interest; **YBOCS** = Yale-Brown Obsessive Compulsive Scale; **YGTSS** = Yale Global Tic Severity Scale.

Tourette syndrome (TS) is a common disorder marked by the presence of tics (fluctuating repetitive involuntary movements).[1-3] TS has a heritable polygenic component.[4,5] TS has a distinctive natural history with onset of tics in childhood, common exacerbation of tics before and around the onset of puberty, and frequent remission or moderation of tics as patients with TS enter adulthood. This natural history suggests a disorder of brain development. TS commonly is accompanied by obsessive-compulsive disorder and other psychiatric comorbidities.

Tics are ameliorated by treatment with dopamine D2 receptor antagonists, leading to speculation that dopaminergic signaling mechanisms are involved in the pathophysiology of tics. This clinical pharmacology and other data suggest that TS is a basal ganglia disorder.[1] Direct evidence for this inference is modest. TS is not fatal and only a small amount of postmortem material has been analyzed, without definitive conclusions.[6,7] PET and SPECT with tracers binding to dopaminergic terminal markers have been employed to search for evidence of striatal dopaminergic abnormalities in TS. These studies return conflicting results.[8,9]

Supplemental data at www.neurology.org

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Table 1 Clinical features of 33 subjects with Tourette syndrome

Characteristics	Values
Age, y, mean ± SD (range)	33.4 ± 11.3 (18–58)
Male/female	25/8
History of OCBs	21
Family history of tics	14
Goetz score, mean ± SD (range)	3.3 ± 1.8 (0–7)
Current YGTSS, mean ± SD	37 ± 20.5
Worst YGTSS, mean ± SD	54 ± 17.8
Current YBOCS, mean ± SD	10 ± 8.4
CAARS-S:S, mean ± SD	56.8% ± 9.7

Subjects rated with the Yale Global Tic Severity Scale (YGTSS), Yale-Brown Obsessive Compulsive Scale (YBOCS), and the Conners Adult ADHD Rating Scale-Self Report: Short version (CAARS-S:S) Scale. The Goetz Score, YGTSS, and YBOCS generate numerical ratings. The summary score of the CAARS-S:S is expressed as percentile compared to a set of normal controls.
OCBs = obsessive-compulsive behaviors.

Our prior studies of striatal [^{11}C]dihydrotetrabenazine (DTBZ) binding, a ligand for the type 2 vesicular monoamine transporter (VMAT2), indicated increased ventral but not dorsal striatal dopaminergic innervation.[10,11] Most PET and SPECT imaging studies have been marked by small subject numbers, varying subject populations, use of tracers whose targets may undergo physiologic or pharmacologic regulation of expression, and inclusion of subjects receiving dopaminergic antagonists. In an effort to overcome these deficiencies, we report the largest study to date of striatal dopaminergic terminal markers in TS. We utilized both [^{11}C]DTBZ and [^{11}C]methylphenidate (MP), a ligand for the dopamine transporter (DAT), and studied well-characterized subjects not treated with dopamine antagonists.

METHODS

Subjects. We recruited 33 adult individuals (≥18 years) with TS (table 1). All subjects met *DSM-IV* criteria for TS with the severity criterion relaxed. Subjects taking dopamine antagonist or stimulant preparations within the 6 months before study were excluded. Almost all subjects with TS had not used dopamine antagonists for years or never used dopamine antagonists. There are limited data on the long-term effects of dopamine antagonist treatment. A prior PET study indicated that dopamine D2 receptor occupancy normalizes within weeks of cessation of oral dopamine antagonists.[12] Clinical experience with drug-induced parkinsonism indicates persistent pharmacodynamic effects of dopamine antagonists lasting as long as a year.[13] Current use of α-adrenergic agonists (clonidine, guanfacine) or serotonin selective reuptake inhibitors was acceptable. Exclusion criteria included presence of another primary neurologic disorder. Control subjects recruited were without neurologic or psychiatric disease. Control subjects were not rated but questioned for clinical histories of tics or comorbid psychiatric disorders. We studied 28 age-comparable controls (mean age = 36 years; SD = 13 years; 14 men, 14 women). All study procedures were approved by the Institutional Review Board at the University of Michigan School of Medicine. Informed consent was obtained from all subjects.

Clinical ratings. All subjects with TS were evaluated on the study day with a standard general medical and neurologic examination to exclude confounding medical or neurologic disease and administration of standard rating scales. We used the Yale Global Tic Severity Scale (YGTSS), the Yale-Brown Obsessive-Compulsive Scale (YBOCS), and a self-administered attention scale (the Conners Adult ADHD Rating Scale-Self Report: Short version [CAARS-S:S]). Current tic score was assigned with the rating scale of Goetz et al.[14] based on observation during the interview and examination. All subjects were evaluated by one experienced rater (R.L.A.). Four subjects with TS participated in our prior study but no data from that study were used.[11]

[^{11}C]DTBZ and [^{11}C]MP PET imaging. The [^{11}C]methylphenidate ([^{11}C]MP) PET studies were acquired as 17 scan frames over a total of 80 minutes as follows: four × 30 seconds; three × 1 minute; two × 2.5 minutes; two × 5 minutes; and six × 10 minutes. Radiotracer was administered as a bolus plus constant infusion using 60% as a slow bolus over 30 seconds, followed by constant infusion of the remaining 40% over the 80 minutes study duration. [^{11}C]DTBZ PET studies were performed identically except for the following: 15 frames were acquired over 60 minutes, omitting the last two 10-minute frames, and the bolus:infusion schedule was 55% as a bolus over 30 seconds, followed by infusion of the remaining 45% over 60 minutes. PET studies were acquired in three-dimensional mode with interplane septa retracted on a Siemens ECAT HR+ scanner (Siemens Medical Solutions USA, Malvern, PA). Two-dimensional transmission scans were acquired for measured attenuation correction followed by segmentation and reprojection. Standard corrections were made for dead-time, randoms, radioactive decay, scatter, and attenuation. Image reconstruction consisted of Fourier rebinning (FORE) of three-dimensional data into two-dimensional projections, followed by 2D-OSEM (ordered subsets expectation-maximization); 4 iterations, 16 subsets. No smoothing filters were used during or post reconstruction. Resultant images had both in-plane and axial resolution of approximately 5.0–5.5 mm full-width at half-maximum.

Parametric imaging. Standard parametric image calculations were performed using equilibrium analysis.[15] This analysis is based on a reference region assumed to be devoid of specific binding to normalize radiotracer binding measures, yielding estimates of the ratio of volumes of distribution (DVR) between any target region (voxel) and the reference region. The binding potential, BP, is DVR-1, effectively subtracting the nonspecific binding assumed to be the same between target and reference tissues. Occipital cortex was used as the reference region for both tracers. Cerebellum has been used previously as the reference region for MP; however, there is DTBZ-specific binding in cerebellum.[16] An estimate of relative transport parameters (K_1R; K_1 ratio) between target and reference tissues was also calculated.

Estimates of the equilibrium ratio of the tracer's tissue concentrations in a given voxel (vox) and in the reference region (rr) are used to estimate the BP of the given voxel.

$$BP_{vox} = [C_{vox(eq)} - C_{rr(eq)}]/C_{rr(eq)}$$

where $C_{vox(eq)}$ and $C_{rr(eq)}$ are the concentrations of tracer in a given voxel and reference region measured at equilibrium. For [^{11}C]MP, data from 50 to 80 minutes postinjection was used to estimate BP. For [^{11}C]DTBZ, data from 30 to 60 minutes was used for BP. K_1R for both tracers were estimated by a simple ratio from the early data postinjection (0 to 4 minutes):

$$K_1R_{vox} = K_{1vox}/K_{1rr} \approx C_{vox(0-4\ min)}/C_{rr(0-4\ min)}$$

Volume of interest analysis. After calculation of functional parametric images for each subject, these maps were anatomically reoriented to the anterior commissure–posterior commissure line. Linear scaling was followed by nonlinear deformation to the reference coordinate system defined by the anatomic atlas of Talairach and Tournoux.[17-19] These anatomic transformations were determined on the basis of each subject's K_1R parametric images, and were then applied to that subject's DVR images.

Volumes of interest (VOIs) for subregions of the basal ganglia were extracted from the anatomically standardized parametric images. We previously digitized the anatomic atlas of Talairach and Tournoux and created a full set of brain regions including both cerebral cortical and subcortical areas. Binding values corresponding to VOIs from both left and right hemispheres were extracted from caudate nucleus, anterior putamen, posterior putamen, and ventral striatum for each subject.

We also created a ventral striatal volume based on the voxel-wise analysis from our prior study.[11] An irregular VOI of ~3 cm^3 was determined from the peak *t* values for the statistical *t* test of TS vs control subjects. This volume was created in the right hemisphere (hemisphere of greatest significance in the prior study) and an equivalent VOI created for the left hemisphere by mirroring the volumes across the sagittal midline.

Statistical analysis. For the VOI analyses, two-sample Student *t* tests were used for comparison of TS and NC subjects, using two-tailed tests with unequal variances between groups. Significance values are reported of these tests without correction for multiple comparisons.

For voxel-wise analysis, a generous striatal mask was found based on thresholding the average MP or TBZ data, resulting in a 4,275 voxel analysis. SPM2 (Wellcome Department of Imaging Neuroscience, http://www.fil.ion.ucl.ac.uk/spm) with 5% false discovery rate (FDR) thresholding was used for all analyses.[20] In each case, four datasets were considered: DVR and K_1R from the MP data, and DVR and K_1R from the TBZ data. For the two-group analysis comparison, the TS and NC groups were compared with a two-sample *t* test. Average striatum VOI intensity was also computed and analyzed with a two-sample *t* test. In each case, the result was computed for MP and TBZ separately. The regression analysis on the patients with TS consisted of voxel-wise multiple linear regressions using five covariates: Goetz Tic Rating scores, current YGTSS scores, worst YGTSS scores, YBOCS scores, and CAARS scores. These five regressors were assessed with six *F*-statistic images (5 individual *F*-tests, as well as one omnibus *F*-test), resulting in a total of 24 *F* images over the four datasets.

To assess whether ventral striatal VOI DTBZ and MP binding was distributed normally, binding data for these VOIs were analyzed with the Kolmogorov-Smirnov test. No correction for multiple comparisons was applied.

RESULTS

Subject characteristics. The mean age of subjects was 33.4 years (SD, 11.3 years; range, 18–58 years). There were 25 men and 8 women. Two thirds described a history of obsessive thinking or compulsive behavior and approximately half had a family history of tics. The mean Goetz score was 3.3 (SD, 1.8; range, 0–7). The mean YGTSS summary score for current tics was 37 (SD, 21) and mean summary score for worst tics was 54 (SD, 18); $p < 0.001$, Wilcoxon signed-rank test. The mean YBOCS was 10.2 (SD, 8.4) and the mean CAARS-S:S was 15.2 (SD, 5.1; mean cumulative percentile, 56.8). Subject characteristics are summarized in table 1.

Routine VOIs and ventral striatal VOI analysis. Subtraction of control from TS images suggested increased [^{11}C]DTBZ and [^{11}C]MP binding bilaterally in TS ventral striatum (figure 1). For standard striatal VOIs, however, there were no significant differences between TS and control subjects using standard VOIs (figure 2, table 2). With the ventral striatal VOI derived from our prior study, no significant differences were found between TS and control groups (data not shown).

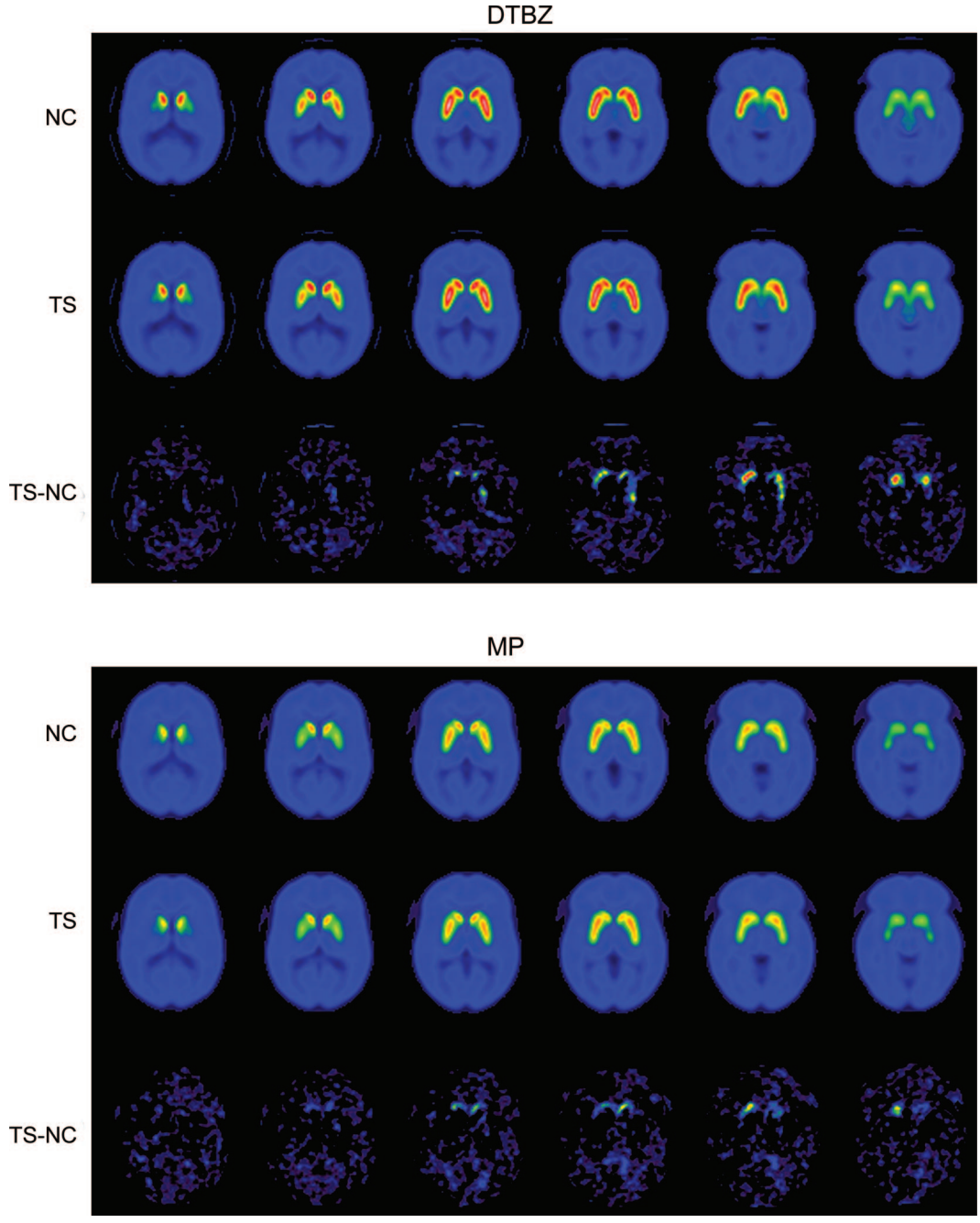
TS and control subjects were comparable in age but not in gender distribution (Pearson χ^2 test; $p = 0.03$). There were no differences between female and male TS subjects in any VOI (data not shown).

Voxel-wise analysis. The voxel-wise two-group analysis was negative, with no voxels surviving a 5% threshold in any of the four analyses. Likewise, none of the two-group VOI analyses were significant. Of the 24 *F* images used for regression analysis, only one had any positive voxels (MP K_1R had one suprathreshold voxel), though this is roughly consistent with the 1-in-20 false-positive results expected with total noise data. (FDR has weak control of family-wise error, meaning that with a 5% FDR threshold with completely null data, the per-image chance of any false-positive results is 5%.)

To further detect possible subthreshold effects in the regression analysis, an arbitrary $\alpha = 0.001$ uncorrected threshold was used and the number of suprathreshold voxels were counted. With 4,275 voxels, fraction 4,275 $\times$ 0.001 = 4.275 voxels would be expected by chance. Only 2 of the 24 voxel counts exceed the expected count of 4.275 voxels (table e-1 on the *Neurology*® Web site at www.neurology.org). Owing to the smoothness of the images, *p* values for these numbers are not available; however, the small number of voxels exceeding the expected count of 4.275 voxels seems consistent with a null hypothesis of no effect. In summary, several voxel-wise tests were completed, both using 5% FDR corrected and 0.1% uncorrected, and in all cases the results were consistent with chance.

Normality of striatal [^{11}C]DTBZ and [^{11}C]MP binding. Because TS is a syndrome that may result from heterogeneous underlying pathophysiologies, we searched for heterogeneity in ventral striatal TS or

Figure 1 Average parametric images of [^{11}C]DTBZ and [^{11}C]MP binding in Tourette syndrome (TS) and normal control (NC) subjects

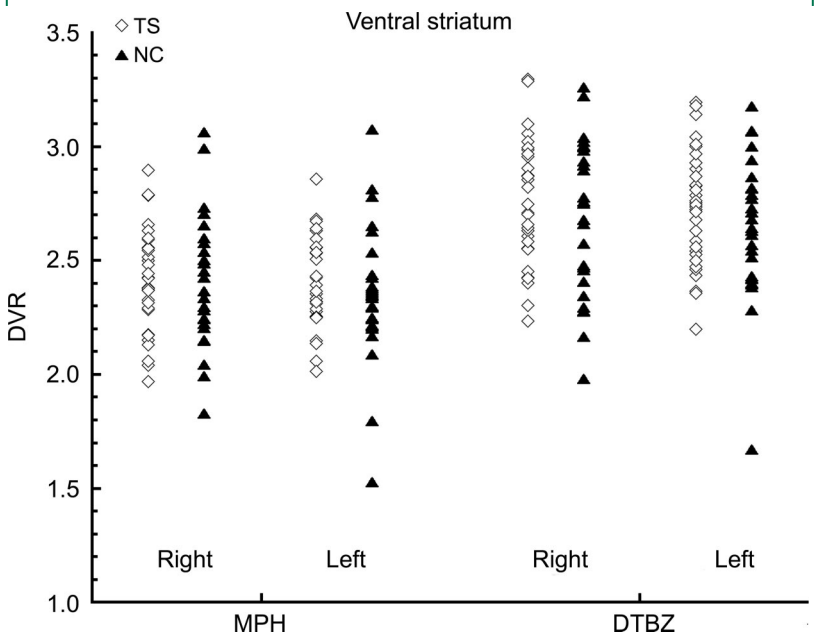


Six brain levels through the striatum for both controls (first and fourth rows) and subjects with TS (second and fifth rows) for DTBZ (top) and MP (bottom). Each slice represents the average DVR of the entire subject group (NC = 28, TS = 33). Subtraction images of TS minus control (third and sixth rows) with modest increases in some voxels in TS ventral striatum.

control subject DTBZ and MP binding. Analysis of ventral striatal standard VOI data indicated normal distribution of DTBZ and MP binding in these regions with the exception of MP binding in control left ventral striatum ($p = 0.042$; Kolmogorov-Smirnov test; uncorrected for multiple comparisons).

DISCUSSION Prior PET or SPECT studies of striatal dopamine terminal markers in TS return conflicting results. Different tracers have been used, including [^{18}F]fluorodopa, PET and SPECT DAT ligands, and the VMAT2 ligand [^{11}C]DTBZ. SPECT imaging studies with DAT ligands have reported diffusely increased or unchanged striatal DAT expression compared with control subjects.[21-27] Correlations between striatal DAT binding and some clinical variables have been reported but these findings are not reproducible.[22,23,25] One study of un-

Figure 2 Scatterplots of [11C]DTBZ and [11C]MP binding in Tourette syndrome and control ventral striatum



DTBZ = [11C]dihydrotetrabenazine; DVR = ratio of volumes of distribution; MP = [11C]methylphenidate.

treated children describes diffuse, marked increase in striatal DAT binding.[26] A small number of studies report subregional changes in striatal dopamine terminal markers, including increased [18F]fluorodopa uptake within the left caudate and right midbrain.[28]

Our present data indicate small, nonsignificant differences in dopamine terminal markers in TS striatum. Our prior study, employing comparable methodology, described significantly increased VMAT2 binding within the ventral striatum, on the order of 12–17%.[11] Neither dataset shows any change in VMAT2 binding in the dorsal striatum.

Several features distinguish our present study from prior work, including our own prior study. The present study is based on a relatively large subject number and no subjects were receiving treatment with dopamine antagonists or stimulants. Our subjects were all adults (≥18 years), which is true of most other studies, although one [18F]fluorodopa PET study studied 11 untreated adolescents (12–17 years) and a [123I]IPT SPECT study studied untreated children (ages 6–12).[26,28] While most symptomatic subjects with TS are children and adolescents, our subject pool has most of the features of TS in typical childhood cases; male predominance, a high percentage of subjects with a family history of tics, and the presence of comorbid obsessive-compulsive behaviors (OCBs). YGTSS ratings revealed that current tic burden is lower than worst-ever (generally during adolescence) tic burden, a result consistent with the known natural history of TS.

Table 2 Results of [11C]DTBZ and [11C]MP PET in Tourette syndrome (TS) and normal control (NC) subject striatum

	R caudate nucleus	L caudate nucleus	R anterior putamen	L anterior putamen	R posterior putamen	L posterior putamen	R ventral striatum	L ventral striatum
DTBZ								
TS mean	3.23	3.27	3.77	3.76	3.82	3.78	2.75	2.73
TS SD	0.34	0.35	0.37	0.38	0.38	0.38	0.27	0.25
TS COV, %	10.4	10.6	9.8	10.1	10.1	10.1	9.8	9.2
NC mean	3.25	3.26	3.80	3.72	3.85	3.76	2.70	2.67
NC SD	0.40	0.38	0.45	0.42	0.50	0.49	0.34	0.31
NC COV, %	12.4	11.5	11.7	11.4	13.0	13.0	12.5	11.5
t Test	0.845	0.834	0.791	0.679	0.799	0.883	0.338	0.218
TS/NC, %	99.4	100.6	99.2	101.2	99.2	100.5	101.9	102.3
MP								
TS mean	2.65	2.68	2.97	2.96	2.85	2.85	2.41	2.40
TS SD	0.22	0.19	0.24	0.25	0.25	0.25	0.22	0.19
TS COV, %	8.2	7.2	7.9	8.5	8.7	8.6	9.3	8.1
NC mean	2.67	2.70	3.04	2.97	2.91	2.88	2.40	2.37
NC SD	0.29	0.25	0.30	0.30	0.35	0.34	0.28	0.29
NC COV, %	10.8	9.3	10.0	10.0	12.2	11.7	11.9	12.4
t Test	0.719	0.779	0.329	0.979	0.465	0.752	0.637	0.426
TS/NC, %	99.1	99.4	97.7	99.9	98.0	99.2	100.7	101.4

Values are the ratio of total volumes of distribution.
COV = coefficient of variation.

Despite self-report among our subjects of a high frequency of OCBs, the mean YBOCS score revealed only a mild to moderate burden of OCBs in our subjects. Similarly, the mean CAARS-S:S score was only slightly elevated. It is possible that by excluding subjects treated with dopamine antagonists, we excluded a subgroup with more marked tics and psychiatric comorbidities and more marked changes in striatal dopamine terminal marker binding. The mean Goetz score for this group of subjects with TS was 3.3. This is identical to the mean Goetz score for the subjects with TS in our initial study, despite the fact that approximately one third of those individuals were using a dopamine antagonist.[11] The identity of mean Goetz scores between our initial and present study groups suggests that our initial group had greater tic intensity. Our present subjects span a range of individuals with mild to marked tics and there was no evidence of a subgroup with increased striatal dopamine terminal binding. Application of the Kolmogorov-Smirnov test to ventral striatal VOI [^{11}C]DTBZ and [^{11}C]MP binding indicates that binding site density was distributed normally. This is evidence in favor of a relatively uniform population of subjects in this cohort. Reanalysis of ventral striatal VOI DTBZ binding in our original study cohort indicates non-normal distribution of ventral striatal DTBZ binding (data not shown). This finding suggests a heterogeneous group of subjects in our prior study.

Multiple factors might account for apparent discrepancies between various studies. Studies with small subject numbers might be prone to overrepresentation of a TS subtype. Studies to date have used subject populations of varying ages. The natural history of TS indicates some developmentally regulated change in brain function. Differences between studies might reflect also differences in brain development. One SPECT imaging study examined nine untreated children (6–12 years) and described a substantial increase in striatal DAT binding, the largest increase described in any recent study.[26] Haycock et al.[29] suggested that striatal dopaminergic innervation is developmentally regulated, peaking in preadolescence and declining in the adult years. A difference in the timing or magnitude of the development of the striatal dopaminergic innervation is a plausible component of the pathophysiology of tics. Differences might be present at one age and then disappear with aging and development. Recent analyses suggest as well that TS is a heterogeneous condition with varying underlying pathophysiologies.[30]

There are other data suggesting abnormal dopamine signaling in TS. A recent study reports enhanced putaminal dopamine release following amphetamine infusion in a small group of subjects with TS.[31] This group subsequently reported a larger group of subjects with enhanced ventral striatal dopamine release following amphetamine infusion.[32]

Clinical data and our understanding of the role of the basal ganglia in natural repetitive movements and habit formation support the hypothesis of a developmental basal ganglia abnormality in TS.[1] Direct evidence for this hypothesis is modest. Recent postmortem work suggests a change in the number of striatal interneurons and pallidal projection neurons.[8] Like most imaging studies, this work is based on a small N and requires replication. An MRI morphometric study of a substantial number of both pediatric and adult TS and control subjects indicates reduced caudate volume and some changes in cortical volumes.[33,34] Longitudinal follow-up of children participating in these studies indicated that reduced caudate volume in childhood predicted persistence and severity of TS and OCBs in early adulthood.[34] These studies used observer-specified basal ganglia volumes. Recent, though smaller, morphometric studies using voxel-based morphometry and other methods have returned disparate results, with one study reporting increased midbrain gray matter, another reporting increased ventral putaminal volumes, and another reporting no change in TS basal ganglia volumes.[35-37] Another recent MRI study of children with TS (ages 7–18 years) reports widespread changes in cortical thickness.[38] Other forebrain regions and neurochemical systems have been implicated in TS.[39,40] Our experience with molecular imaging in TS stresses the need for systematic, large studies in well-characterized TS and control subject populations. Large-scale, systematic longitudinal analyses with morphometric and molecular brain imaging in TS are needed to understand the neurobiological bases of TS.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by R.A.K., Department of Radiology; W.Z., Department of Biostatistics; T.N., Department of Biostatistics; and K.A.F., Department of Radiology, University of Michigan.

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