# D2-Like Dopamine Receptor Density in Tourette Syndrome Measured by PET

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Tourette syndrome (TS) is a chronic neurologic disorder characterized by the presence of involuntary motor and phonic tics. There is evidence that TS is associated with an abnormality of the dopaminergic system, involving postsynaptic D2 receptors. We tested the hypothesis that D2-like dopamine receptors are elevated in TS. **Methods:** Twenty-nine adult patients with TS were studied by PET imaging with [$^{11}$C]3-N-methylspiperone ([$^{11}$C]NMSP). Two methods of data analysis were used. The first was a caudate-to-cerebellar ratio, measured at 45 min. The second method, applied in 20 subjects, was a two-PET scan procedure. Both used high specific activity [$^{11}$C]NMSP, but the second scan was preceded by a dose of unlabeled haloperidol, which partially occupied the D2-like dopamine receptors. This was done to provide an absolute measure of receptor density ($B_{max}$). All patients were compared to age- and sex-matched controls. **Results:** Neither group showed significant differences from their control group in caudate-to-cerebellar ratio. However, the two-PET scan $B_{max}$ measurement demonstrated that 4 of the 20 patients had significantly elevated D2-like receptors. In this group of 20 patients, multiple linear regression analysis revealed a trend between the severity of vocal tics and $B_{max}$ values. This $B_{max}$ measure also revealed a significant ($p < 0.05$) association with performance on the Wisconsin Card Sorting Test. **Conclusion:** These findings suggest that not all patients with TS have an abnormality of D2-like receptors, but a subgroup of TS subjects has a significant D2-like dopamine receptor elevation. These findings also support the importance of applying a more quantitative method for $B_{max}$ determination to PET imaging analysis. The $B_{max}$ findings in the subgroup do not exclude an effect of intrasynaptic dopamine competition, but this effect may be less likely due to the high affinity of [$^{11}$C]NMSP.

**Key Words:** PET; D2-like dopamine receptor density; Tourette syndrome; neuropsychology

**J Nucl Med 1997; 38:1243–1247**

Tourette syndrome (TS) is a chronic neurologic disorder characterized by the presence of involuntary motor and phonic tics. Pathophysiologically, there is evidence that TS is associated with an abnormality of the dopaminergic system, involving postsynaptic D2 receptors (*1–3*). In this study, which was performed over a period of 10 yr, we measured D2-like receptor binding and density in adults with TS using [$^{11}$C]3-N-methylspiperone ([$^{11}$C]NMSP) and two different PET scan techniques: a single-scan caudate-to-cerebellar ratio and a two-scan technique, with studies before and after the administration of unlabeled haloperidol.

Methods of data analysis for PET and, later, SPECT were originally based on quantitative estimates of receptor binding by comparing the ratio of radioactivity in brain regions with specific and nonspecific affinity for the radiotracer (*4–6*). More recently, methods have used multiple PET acquisitions and determined binding by mathematical analyses with plasma radioactivity as the input function (*7–9*). Receptor density ($B_{max}$) has also been determined by studying inhibition with either an unlabeled radiotracer (low specific activity) or a structurally analogous unlabeled inhibitor. These methodologies have been used successfully to evaluate several neuropsychiatric disorders, including schizophrenia, Parkinson's disease and Rett and Lesch-Nyhan syndromes (*10–13*).

## MATERIALS AND METHODS

### Patient Selection

The study population consisted of 29 patients with TS and 68 normal, healthy volunteers. All patients were neuroleptic-free for at least 6 mo before the PET study, and three had not received medication for at least 3 yr.

In nine patients (group I), the diagnosis of TS was based on the criteria proposed by Shapiro et al. (*14*). The mean age of this group at the time of scan was 27 yr (range, 19–35 yr). Their mean age of disease onset was 6.3 yr (range, 3–8.5 yr). Five subjects had been treated previously with dopamine-blocking agents, either haloperidol or fluphenazine, for periods ranging from 2 mo to 2.5 yr. Symptom severity rating at the time of the PET scan, by the Hopkins Motor and Vocal Tic Scale (HMVTS) (*15*), revealed that four subjects had mild symptoms, two had mild to moderate symptoms and three had moderately severe symptoms. Group I control subjects were neurologically normal (22 men and 22 women, ages 19–73 and 19–67, respectively) (*4*).

In 20 patients (group II), 16 men and 4 women, the diagnosis of TS was made based on DSM-IIIR criteria. These subjects were at least 18 yr of age (mean ± s.d., 36.2 ± 8.9 yr; range, 19–52 yr). Family history was positive for TS in 15 of these patients and positive for obsessive compulsive disorder (OCD) in 5 of the 20 subjects. Four patients had prior treatment with dopamine receptor antagonists, either haloperidol or thioridazine, with the duration of neuroleptic treatment ranging from 1 wk to 10 yr. All patients were neuroleptic-free for at least 6 mo before the PET scans. The Frankel Scale for OCD (*16*) was completed by the subjects and was abnormal (score greater than 70) in seven subjects. Tic severity was measured at the time of the PET scans by the HMVTS (*15*) and the Tourette Syndrome Severity Scale (*17*) and in 13 patients, using only the Yale Global Tic Severity Scale. (*18*) On the basis of these

Received Feb. 26, 1996; accepted Dec. 19, 1996.

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**TABLE 1**
Clinical Studies for 20 Patients with TS (Group II)

| | Mean ± s.d. | Range |
|---|---|---|
| Age of tic onset (yr) | 8.5 ± 2.3 | 5.0–14.0 |
| Combined motor tic score (HMVTS) | 2.6 ± 0.7 | 1.5–4.0 |
| Combined vocal tic score (HMVTS) | 2.1 ± 0.7 | 1.5–4.0 |
| TSSS | 3.0 ± 1.9 | 0.5–6.0 |
| Yale global Tic Severity Scale | 43 ± 8.2 (n = 13) | 26–63 |
| Frankel OCD inventory | 64.3 ± 36.5 | 15–138 |

TSSS = Tourette Syndrome Severity Scale.

three scales, eight subjects were rated mild, five mild to moderate, two moderate and five moderate to severe (Table 1). Group II controls consisted of 24 medically and neurologically normal subjects, ages 18–83 yr.

A battery of neuropsychological tests were administered within 4 wk of PET scanning for 12 of the 20 subjects. [Scheduling difficulties precluded testing of the other 8 subjects.] Tasks were chosen to assess behaviors associated with frontal and striatal brain function or to identify cognitive deficits previously associated with OCD and/or TS, such as impairments in visuomotor and visuoconstructional skills, abstraction and mental flexibility. The tests given were the Grooved Pegboard Test, Symbol Digit Modalities Test, Wechsler Adult Intelligence Scale (revised) (Vocabulary and Block Design subtests), Wechsler Memory Scale (revised), Controlled Oral Word Association, Design Fluency Test, Stylus Maze Test, Standardized Road-Map Test of Directional Sense, Trail-Making Test and Wisconsin Card Sorting Test (WCST).

### PET Imaging

Before PET scanning, subjects underwent an alignment and localizing x-ray computerized tomography scan. Structures of interest, including the basal ganglia and the cerebellum, were located by the method of Wong et al. (*4*). PET scanning was conducted after injection of approximately 740 MBq (20 mCi) of [$^{11}$C]NMSP (specific activity, approximately 1500-2000 mCi/$\mu$mole), synthesized by the method of Dannals et al. (*19*). For group I, the specific activities of the [$^{11}$C]NMSP administered were not significantly different between patients and controls. For group II, specific activities were similar for controls pre- and posthaloperidol (mean ± s.d.), 1369 ± 708 and 1548 ± 623 Ci/$\mu$mole, respectively, and for patients pre- and posthaloperidol, 1355 ± 676 and 1617 ± 702 Ci/$\mu$mole, respectively. All subjects received 7.5 mg of haloperidol orally, 4 hr before the second scan. For each group, the mass of NMSP ranged from 0.2 to 2.9 $\mu$g/kg.

All patients and controls underwent kinetic scanning on a CTI NeuroECAT scanner with an in-plane resolution of 8 mm and axial resolution of 12–14 mm, with the septa plane in place in the high-resolution mode. Twelve PET acquisitions of three planes were acquired over a 90-min period.

### $B_{max}$ Calculation (Group II Subjects Only)

*In Vivo Receptor Binding Theory and Kinetic Modeling Assumptions.* Quantification of D2 dopamine receptors in brain is based on a four-compartment model described previously (*9,20*). The plasma radioactivity is corrected for labeled metabolites of [$^{11}$C]NMSP by using a modeling procedure and by high-performance liquid chromatography (HPLC) (described below). The model yields $K_1$, the rate of clearance of ligand from the circulation, $k_2$, the fractional clearance of ligand from the region of interest to the plasma, and $k_3$, the rate constant of binding to the D2 dopamine receptor. For the duration of this [$^{11}$C] PET study $k_4$ is negligible. This rate constant is estimated twice, once before and again after a blocking dose of haloperidol, which is given 4 hr before the second PET scan. Thus, $k_3$ is calculated under two conditions of receptor occupancy, unblocked and partially blocked by haloperidol.

The calculation of receptor density ($B_{max}$) is

$$B_{max} = D_w \frac{[H]}{\left(\frac{1}{k_3^i} - \frac{1}{k_3^u}\right)}, \qquad \text{Eq. 1}$$

where $k_3^u$ is the estimate of the rate constant in the unblocked case, and $k_3^i$ is the estimate when the receptor is blocked by the unlabeled inhibitor. [H] is the plasma haloperidol concentration, and $D_w$ is a constant derived from the ratio between $\lambda$, the partition coefficient, and $k'_{off}$, the haloperidol dissociation rate (*10,21*). This formula assumes the blood–brain partition coefficient and dissociation rate of haloperidol to be known in patients and normal controls. The partition coefficient for [$^{11}$C]NMSP is measured in each PET study from the kinetic analysis of tracer uptake in the cerebellum, which is devoid of D2 dopamine receptors.

This model assumes that the tracer and haloperidol available for the brain precursor pool do not vary systematically between patients and normal subjects, and the assessment of the metabolism of [$^{11}$C]NMSP is accurate. The input function into the brain for [$^{11}$C]NMSP is corrected for the metabolism of the tracer by measuring the fall of the cerebellar volume of distribution for [$^{11}$C]NMSP (*9*). To determine the metabolism of [$^{11}$C]NMSP, we used a reverse-phase HPLC C-18 column assay adapted from Wong et al. (*21*). In a series of studies before and after haloperidol administration in patients and controls, the labeled plasma metabolites of [$^{11}$C]NMSP were determined and compared to the results of the cerebellar curves used to correct for metabolism (*9*). On average, four to six radioactivity samples per PET scan were obtained 5, 12, 20, 30, 45 and 60 min after injection.

The fraction of free [$^{11}$C]NMSP in plasma was measured with ultrafiltration devices after patient plasma was "spiked" with the radioligands in concentrations similar to those reached in a PET study for [$^{11}$C]NMSP (1–5 $\mu$Ci/ml).

### Data Analysis

*Caudate-to-Cerebellum Ratio Comparisons.* Caudate-to-cerebellar ratios were measured at 43 min postinjection in these analyses; all group I scans and the first scan from group II were used. In addition, $B_{max}$ measurements were performed in group II only (see below). The estimated receptor binding was then compared to age- and gender-specific (95%) prediction limits (PLs) and confidence limits (CLs) derived from 22 healthy men and 22 healthy women (*4*). [The 95% CLs on a regression line of dependent variable Y on independent variable X, at a given value (say) X* of X, are defined such that the probability that the limits cover the population regression line at X* is 95%. Such CLs obtained by letting X* range over the values of X in the data will trace out the 95% confidence bands. In the above setting, the 95% PLs at X* are defined such that, if a new value of Y is to be obtained with X fixed at X*, the probability that the limits will contain the value of the new Y is 95%. (The new (X*,Y) pair is not part of the data used to fit the regression line of Y on X.) As with confidence bands, prediction bands can be traced out.] Individual subjects were considered to have significant elevations in receptor binding if their caudate-to-cerebellar ratios fell outside the PLs.

*Group II $B_{max}$ Comparisons.* Group II receptor densities ($B_{max}$) were calculated using serum haloperidol measurements and the unblocked and blocked binding rates to the D2 receptor ($k_3$),

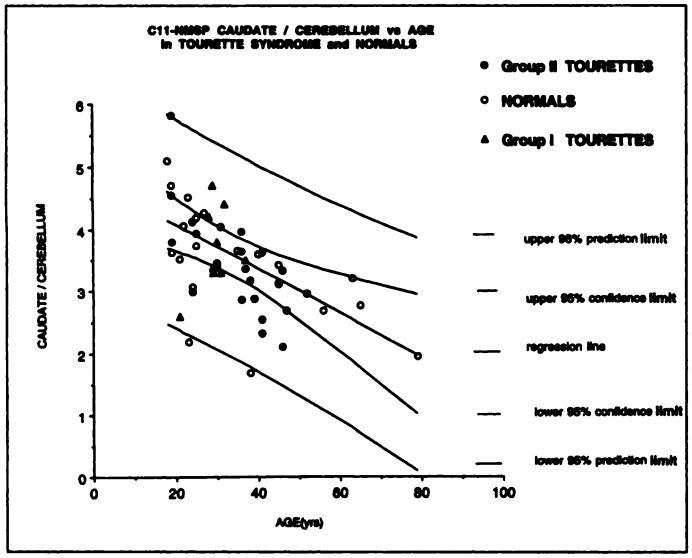


**FIGURE 1.** Caudate-to-cerebellum ratio versus age for groups I and II. Ordinate, caudate-to-cerebellum ratios at 43 min postinjection; abscissa, age (yr). The long middle line represents the normal control linear regression of caudate-to-cerebellum ratio on age [$Y = 4.8 - (0.003)(age)$; $R^2 = 0.4$] for the group II controls. The innermost curved lines directly above and below the regression line are the upper and lower 95% CLs, and the outermost upper and lower lines are the 95% PLs. ○, control caudate-to-cerebellum ratio data; ●, TS subjects for groups I and II. None of the TS subjects at any age have ratios above the upper PL.

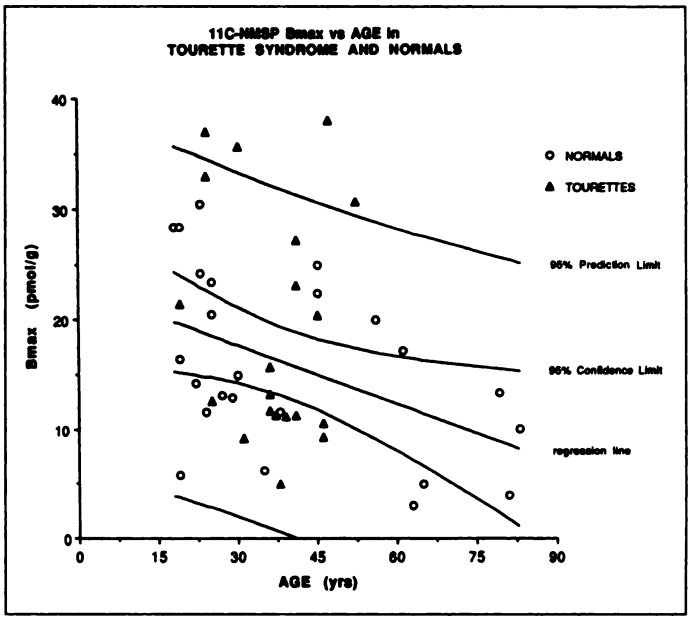


**FIGURE 2.** Receptor density versus age. Ordinate, receptor density ($B_{max}$) in pmole/g; abscissa, age (yr). ○, $B_{max}$ values at various ages for the control subjects. The central line is the linear regression of $B_{max}$ on age for the controls only [$Y = 22.9 - (0.18)(age)$, $R^2 = 0.2$]. The two curved lines immediately above and below the regression lines are the 95% CLs on the regression line. The outermost upper and lower lines are the 95% PLs. ▲, TS subjects. Four TS subjects are outside the PLs and have elevated $B_{max}$ values.

according to the method of Wong et al. and others (*9,21*). Measurements of $B_{max}$ in the TS patients were compared to $B_{max}$ values of the control subjects. $B_{max}$ values for 24 normal volunteers were subjected to regression against age, using a linear function of $B_{max}$ on age. [Although the maximum age in the TS patients was 52, we used all normals to construct the regression line and PLs because the lot with all normal controls shows that a straight line is the best relationship over the entire age range. Thus, the best estimate of the line is that based on all normal controls.] From this, 90% and 95% CLs and PLs were obtained, respectively.

## RESULTS

### D2-Like Dopamine Receptors

*Caudate-to-Cerebellum Ratio.* The group I ratio estimates of receptor binding were, in general, not significantly different between TS patients and controls when comparisons were made between age- and sex-appropriate control groups. The mean ± s.d. estimates of receptor binding were for TS men, 4.0 ± 0.7, and for TS women, 3.6 ± 1. All but two men and one woman were within the 95% PLs of the function relating caudate-to-cerebellar ratio to age (*4*). The remaining subjects were within the 95% PLs.

The group II subjects were also all within the 95% PLs compared to their control values. In this case, because fewer control subjects were available (20 versus 44), the men and women were pooled. Like group I patients, all group II patients were not significantly different from normal controls, and all were within the 95% PLs. The results for group I and group II are shown in Figure 1 for the same controls as those used in the $B_{max}$ measurements (group II).

*$B_{max}$ (Receptor Densities).* The results for group II are shown in Figure 2. The average $B_{max}$ value did not reveal a significant difference between patients and controls. However, in 4 of the 20 subjects, the $B_{max}$ was elevated well beyond the 95% PLs for the normal data.

The [$^{11}$C]NMSP free fraction in plasma was obtained for TS subjects and controls. The mean percents of free fraction were 4.2 ± 0.3% (s.e.m.) and 4.6 ± 0.3% (s.e.m.) for TS and controls, respectively, and were not significantly different ($p > 0.05$ by Student's t-test).

The metabolite corrections estimated from the model were compared with HPLC corrections in five subjects. In all five, there is an excellent correlation ($r = 0.95$) between the HPLC analysis and the values derived from the models across 60 points (six points/scan, two scans/subject).

*Relationship of $B_{max}$ with Clinical Parameters.* In 4 of the 20 subjects with TS, the $B_{max}$ values were elevated as compared to age-matched regression PLs for controls. We identified these as group IIa. The remaining patients, whose $B_{max}$ values were similar to controls, were identified as group IIb. A summary of the individual test results for group IIa (elevated $B_{max}$) and group IIb means is given in Table 2. The score on only one of the scales, the HMVTS (*15*), shows a Pearson correlation with $B_{max}$ as a dichotomous variable (95% cutoff) of $r = 0.50$ ($n = 20$, $p = 0.04$).

Post hoc testing revealed that group IIa patients ($n = 4$) had a higher mean vocal tic scale [2.8 ± 0.6 (s.e.m.)] than did the group IIb patients ($n = 16$), who had a mean vocal tic scale of 2.0 ± 0.1 (s.e.m.) ($t = 2.2$, $df = 18$, $p < 0.04$) (equal variance assumption).

Multiple linear regression ($n = 19$) on the group II patients (one subject did not have Frankel test), with $B_{max}$ as the dependent variable (continuous) and with age, motor and vocal tic scores, age of onset and Frankel scores (dichotomized with a cutoff of 70) yielded the equation: $B_{max} = 6.35$ (vocal) + 5.81 pmole/g ($p < 0.075$).

A similar multiple linear regression with backward elimination was also performed with only the men (16 of 19) of group II. This analysis yielded the equation $B_{max} = 9.46$ (vocal) − 2.18 pmole/g. Thus, the variable left in the regression was vocal tics ($p < 0.01$).

The Pearson product–moment correlation coefficients were computed between the neuropsychological variables and $B_{max}$

**TABLE 2**
Demographics, Clinical Scales and $B_{max}$ (Group II)

| | $B_{max}$ | Age (yr) | Sex | HMVTS, motor tic | HMVTS, vocal tic | TSSS | Frankel OCD Inventory | Medications |
|---|---|---|---|---|---|---|---|---|
| Group IIa | | | | | | | | |
| 1 | 30.7 | 52 | M | 3.5 | 3.5 | 6.0 | 56 | None |
| 2 | 37 | 24 | M | 3.5 | 4.0 | 5.0 | N/A | Haloperidol, clonidine |
| 3 | 38 | 47 | F | 2.0 | 1.5 | 2.0 | 26 | Clonidine, clomipramine, imipramine |
| 4 | 35.6 | 30 | M | 2.0 | 2.0 | 1.5 | 15 | None |
| Mean ± s.d. | 35.3 ± 3.2 | 38 ± 13 | | 2.8 ± 0.9 | 2.8 ± 1.2 | 3.6 ± 2.2 | 32.3 ± 21.2 | |
| Group IIb* (n = 16) | | | | | | | | |
| Mean ± s.d. | 15.3 ± 7.6 | 36.3 ± 7.9 | 13 M, 3F | 2.5 ± 0.7 | 2.0 ± 0.4 | 2.8 ± 1.9 | 74.9 ± 40.8 | |
| Range | (4.9–33.0) | (19–46) | | (1.5–4.0) | (1.5–3.0) | (0.5–6.0) | (15–138) | |

TSSS = Tourette Syndrome Severity Scale; M = male; F = female; N/A = not applicable.
*Group IIB before study: 13 neuroleptic-naive, 3 neuroleptic-free for 6 mo, 2 anti-anxiety and 1 anti-epileptic.

values for 12 patients in the TS group. There were significant correlations between $B_{max}$ and long-term retention of Stylus Maze learning ($r = 0.54$, $p = 0.036$) and performance on the WCST (cards needed: $r = 0.54$, $p = 0.035$; perseverative errors: $r = 0.61$, $p = 0.017$; nonperseverative errors: $r = 0.64$, $p = 0.013$).

## DISCUSSION

Although the precise neuropathology of TS is unknown, increasing evidence supports an abnormality within the basal ganglia system (*3*). Several neurotransmitter systems have been proposed to be abnormal in TS, although a preponderance of evidence favors the involvement of dopamine (*22*). One hypothesis is that TS is due to supersensitive (increased number or affinity) postsynaptic dopamine receptors. Support for this proposal comes from the clinical response of TS patients to dopamine receptor antagonists (haloperidol, fluphenazine and pimozide); the appearance of a tardive Tourette-like syndrome after withdrawal of neuroleptic drugs (*23,24*); reduced cerebral spinal fluid baseline and turnover levels of homovanillic acid (*25–27*); clinical improvement with restoration of cerebral spinal fluid homovanillic acid levels into the normal range (*27*); and limited studies of postmortem striatal tissue that have shown slight (but not significant) increases of D2 receptor binding (*2*).

We used two methods to examine dopamine D2 receptor binding in TS subjects. Using the caudate-to-cerebellar ratio to examine receptor binding, we found no significant differences between TS patients and controls in our earlier studies, nor for our later sample (*4,28*). George et al. (*29*) and Turjanski et al. (*30*) examined tissue ratios and binding potential, respectively, in patients and found results similar to those reported here for group I patients.

The results of our two-PET scan $B_{max}$ procedure revealed significant increases in a subgroup of TS subjects. This procedure has been successfully used to study and measure receptor density ($B_{max}$) through the use of a saturation technique analogous to that previously used (*12*) and validated (*5,31,32*) in other studies. With this method, most $B_{max}$ values did not show overall significant differences between patients with TS and controls, consistent with postmortem data (*2*). In 4 of 20 of the subjects, however, the $B_{max}$ values were elevated compared to the age-matched regression PLs for controls. The corresponding caudate-to-cerebellar ratios for these subjects were not outside the PLs. Thus, the two-scan procedure appears to be more sensitive in identifying abnormalities in 20% of the patients. This lack of difference seen in the overall mean $B_{max}$ between controls and TS subjects is compatible with single-point measurements of D2 receptors in postmortem striatal tissues from three adults with a lifetime diagnosis of TS (*3*).

The validation of several important assumptions of the two-PET scan model was an important feature of this study. We have shown that the model-derived metabolite correction is valid in TS subjects. For example, there was excellent agreement with our direct comparison of HPLC measures and the model correction procedures. Our studies of the free fraction of [$^{11}$C]NMSP in the TS subjects suggests that a systematic bias in free fraction is not occurring in any of these subjects. Furthermore, the four TS subjects with elevated $B_{max}$ (group IIa) would not be expected to be any different in their free fraction or partition coefficients. Indeed, the free fraction measures with [$^{11}$C]NMSP were the same in the four TS patients with elevated $B_{max}$ values as in the remaining TS patients and controls.

The four subjects with elevated $B_{max}$ were distributed throughout the 3 yr of the second phase of the study, so fortuitous scheduling of these patients was not a factor. A possible confounding issue could be the prior use of neuroleptics in 1 of 4 in group IIa and 3 of 16 subjects in group IIb, but this is unlikely because the neuroleptic-free period before PET scanning exceeded 6 mo in all subjects. Thus, the differences seen in these four TS patients are probably due to receptor density and/or extracellular dopamine and not due to a bias of the modeling procedure. We cannot entirely exclude the possibility of differences in extracellular or intrasynaptic dopamine affecting the $B_{max}$ measures. Laruelle et al. (*33*) has suggested that $B_{max}$ may be affected by dopamine depletion as by AMPT or reserpine. But Young et al. (*34*) showed that these changes occurred primarily with benzamides as raclopride but not with NMSP, so it is unclear if this will be an important factor.

D2 receptor binding has been previously studied in patients with TS. A recent study of five sets of identical twins has shown that dopamine D2 binding, as measured by SPECT with [$^{123}$I]iodobenzamide, predicts phenotypic severity. More specifically, increased binding in the head of the caudate nucleus was associated with increased tic severity (*35*). In other studies

of D2 receptors, including [$^{123}$I]IBZM SPECT to determine an index of receptor availability and a PET study with [$^{11}$C]raclopride, no significant differences have been identified [George et al. (*29*); Turjanski et al. (*30*)]. Lastly, limited studies of D1 and D2 receptor binding in postmortem striatal tissue have shown no significant differences between TS and control membranes [Singer et al. (*2*)].

## CONCLUSION

Two methods of data analysis were applied to 29 adult patients with TS. For the first nine subjects, no significant differences were obtained between the outcome parameter, the caudate-to-cerebellar ratio. However, when a second PET scan $B_{max}$ measurement was made, 4 of the 20 patients had significantly elevated D2-like receptors.

There were higher vocal tic scores in the four TS subjects with elevated $B_{max}$ as compared to the other TS subjects. This suggests that disease severity may be associated with higher levels of D2-like dopamine receptors. Nonverbal concept formation (WCST) and long-term retention of planning and skill learning appeared to be associated with $B_{max}$ values. These findings could possibly have therapeutic implications for TS patients with elevated $B_{max}$ determinations.

## APPENDIX

### Comparison of the Caudate-to-Cerebellar Ratio to the $k_3$ Measurements

The slope of the caudate-to-cerebellar ratio versus normalized time is

$$K = \frac{k_2 k_3}{k_2 + k_3}. \qquad \text{Eq. 2}$$

Multiplying the numerator and denominator by the partition coefficient $\lambda = K_1/k_2$ yields the slope of the relationship between the caudate-to-cerebellar ratio and time,

$$L = \frac{K_1 k_3}{\lambda(k_2 + k_3)}. \qquad \text{Eq. 3}$$

It is evident that if the forward binding rate to the receptor, $k_3$, is small compared to the efflux ($k_3 \ll k_2$), then the slope of the caudate-to-cerebellar ratio versus time is actually proportional to the rate of binding, $k_3$. Conversely, if the rate of binding is very rapid, i.e., when $k_2$ is on the order of or much less than $k_3$, then the slope loses its dependence on binding and becomes proportional to $K_1$ divided by the partition coefficient, $\lambda$. If the receptor densities or affinities are low, i.e., $k_2 \gg k_3$ (as may be the case in older subjects), the dependence on blood flow will be greater if the receptor densities or affinities are high (as may be the case in young normal controls), then the slope has more or less of a dependence on blood flow. This relationship may explain why the caudate-to-cerebellar ratio was not different within groups, but the fall in the ratio with age is seen in all groups.

## ACKNOWLEDGMENTS

This work was supported by U.S. Public Health Service grants NS 15080, 2R01MH42821 and 5P30-HD24061 and the Tourette Syndrome Association. We especially thank Madge Murrell, Boon Chan, Traci Folio, Elynne Minkin, Laura Halliday, Laura Krafft and Judy Buchanan for technical assistance.

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