

# Altered mesolimbocortical and thalamic dopamine in Tourette syndrome

**Abstract**—We used [F-18]fallypride PET in six adults with Tourette syndrome and age-matched controls to assess extrastriatal dopamine 2 (D2) receptors. D2 receptor availability was significantly lower in the orbitofrontal cortex, primary motor cortex, anterior cingulate gyrus, mediodorsal nucleus of thalamus, and hippocampus, areas important for motivation and reward, sensory gating, movement, and attention. Altered dopaminergic function in mesolimbocortical systems and thalamus may contribute to increased motivational salience of tics.

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Most research into dopaminergic transmission in Tourette syndrome (TS) has examined differences in the nigrostriatal system. Clinical observations also support involvement of extrastriatal structures. The thalamus (sensory urges), orbitofrontal cortex (abnormal motivational salience), anterior cingulate gyrus (attention), and motor cortex (tics) merit study, as fMRI and fluorodeoxyglucose (FDG)-PET report TS-linked differences in these regions.

Previously available tracers have only been optimal for striatum. However, a newer PET ligand, [F-18]fallypride, visualizes extrastriatal D2 receptors.<sup>1</sup> In this pilot study, we assessed the thalamic and mesolimbocortical dopamine system in adults with TS.

**Methods.** *Subject recruitment.* We recruited six healthy men with TS, ages 18 to 45, from the Cincinnati Children's Hospital Medical Center (CCHMC) TS clinic. Diagnoses of TS, obsessive-compulsive disorder (OCD), and attention-deficit/hyperactivity disorder (ADHD) were made using DSM-IV criteria. Tic sever-

ity was rated using the Yale Global Tic Severity Scale (YGTSS) Motor and Vocal Tic Scales, which rate tics 0 to 5 on five domains.<sup>2</sup> No subjects had ever taken dopamine receptor-blocking medication long term (>1 month), and none had taken these agents in the past 2 years. One subject currently took clonidine. One subject smoked cigarettes daily. Subjects taking stimulants or selective serotonin reuptake inhibitors were excluded. Healthy, age- and gender-matched subjects were used for comparison.

Approval for the PET studies was obtained from the investigational review boards of CCHMC and Kettering Medical Center (KMC), and informed consent was obtained.

*Radiopharmaceutical, PET scanning, MRI.* PET scans were acquired in the supine position, using an ECAT EXACT HR+ scanner in three-dimensional mode. A 5-minute transmission scan was first acquired using a <sup>68</sup>Ge/<sup>68</sup>Ga rod source to correct for photon attenuation. Dynamic acquisition of the PET dynamic data was initiated with the 30-second i.v. bolus injection of 6.4 mCi (range 5.1 to 7.0 mCi) [F-18]fallypride, produced according to previously reported methods.<sup>3</sup>

The dynamic scanning sequence was split into two 80- to 90-minute segments separated by a 10-minute break. Data were reconstructed using the ECAT v7.2.2 software. A filtered back projection algorithm (DIFT) was used with brain mode sinogram trimming, zoom = 2.8, and a 4-mm gaussian filter to a reconstructed image of 128 × 128 × 63 voxel matrix (pixel size = 1.84 × 1.84 × 2.43 mm). The PET data were corrected for the attenuation of annihilation radiation, scanner normalization, and scatter radiation.

*MRI acquisition.* For image coregistration, high-resolution, T1-weighted axial MR images were acquired with the GE Signa CVI system (General Electric, Milwaukee, WI) (repetition time [TR] = 7.6 msec, echo time [TE] = 3.1 msec, flip angle = 20 degrees, slice thickness = 1.5 mm, pixel matrix = 256 × 256, field of view = 23 cm, total slices = 124).

*PET image analysis.* The reconstructed images were tested for motion bias and corrected for patient motion using the realignment algorithm for the Statistical Parametric Mapping Software Package, SPM2 version (Wellcome Department of Cognitive Neurology, University College London, UK). The motion-corrected dynamic PET data sets were used to create voxel-by-voxel parametric images of [F-18]fallypride distribution volume ratio (DVR) using the linear regression spatial constraint method.<sup>4</sup> The cerebellum (no specific binding) was used as a reference region. The DVR serves as a metric that is proportional to the available D2/D3 receptor density. The analysis of the dynamic data set was limited to 120 minutes for all subjects.

The DVR parametric images were transformed into Montreal Neurologic Institute (MNI) space using the SPM2 software. The regions of interest were automatically defined in MNI space using a predefined template image<sup>5</sup> within the SPM framework. A dilation of 1 was applied to the template mask regions prior to their application to the individual DVR images to account for the reduced image resolution of the PET images. No additional corrections were applied for the inherent resolution blurring (i.e., partial volume effects) in the PET images. Due to the dilation step, the regions of interest likely expanded

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**Table** Distribution volume ratios of [F-18]fallypride binding in Tourette syndrome vs control patients

Group	Orbitofrontal cortex		Mediodorsal nucleus thalamus		Hippocampus		Anterior cingulate gyrus		Motor cortex-BA4	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Control	1.62	0.08	3.61	0.32	1.99	0.08	1.41	0.13	1.37	0.09
Tourette	1.34	0.10	3.12	0.32	1.76	0.15	1.22	0.12	1.13	0.07
<i>p</i> Value	0.0004		0.024		0.010		0.028		0.0004	

outside the boundaries of the actual structures (particularly for the thalamic nuclei); therefore, a slight overlap of the regions is present. However, the mask placement was inspected for each individual to ensure the (PET) structure was properly centered in the mask image.

Voxel-based exploratory analysis was performed on the entire brain using a statistical nonparametric permutation test (SnPM).<sup>6</sup> SnPM maps were thresholded at  $p < 0.002$ . The DVR images were smoothed with an 8-mm gaussian smoothing filter prior to the voxel-based comparison.

The regions of interest compared the orbitofrontal cortex, mediodorsal thalamus, primary motor cortex, and anterior cingulate gyrus. Hippocampus was added based on the results of the SnPM test. Right- and left-sided DVR values, which were highly correlated (data not shown), were averaged. Multivariate analysis of variance was used to test for group differences in DVR values, with  $p < 0.05$  considered significant.

**Results.** Subjects with TS were men, ranging in age from 18 to 45 years (mean  $30.7 \pm 10.8$ ). Total YGTSS tic score ranges were 8 to 14 motor; 0 to 13 vocal; 8 to 27 total. Three subjects had ADHD and one had OCD. Control subjects were men, ranging in age from 20 to 44 years (mean  $30.2 \pm 10.0$ ).

There were no group differences in subject motion during the PET or in total injected mass of unlabeled ligand: TS  $1.54 \pm 0.64 \mu\text{g}$  vs controls  $1.52 \pm 0.53 \mu\text{g}$ .

D2 receptor binding DVR values for brain regions of interest were lower in TS than in healthy comparison subjects  $F(5,6) = 5.93$ ,  $p = 0.026$ . For the voxel-based nonparametric comparison, the region with the greatest significant difference in binding was the hippocampus, which had lower DVR values ( $p < 0.001$ ). Fallypride binding for individual regions are shown in table and figure E-1 (available on the *Neurology* Web site at [www.neurology.org](http://www.neurology.org)). Tic severity did not correlate with DVR, and the effect of age on DVR was not significant.

**Discussion.** TS adults had reduced D2 receptor availability in extrastriatal regions implicated in the phenomenology of TS and shown in prior FDG-PET and fMRI studies to exhibit TS-related signal differences. The orbitofrontal and motor cortex, hippocampus, anterior cingulate gyrus, and mediodorsal thalamus had lower DVR values. This may indicate primary reduced D2 (or D3) receptor density in these regions. Alternatively, chronic excess tonic or phasic mesolimbocortical dopamine release in TS patients may secondarily reduce D2 receptor expression. Last, higher acute levels of dopamine release during the PET scan, possibly related to suppressing tics during the scan, may have competed with [F-18]fallypride, reducing tracer binding.

Our findings in the thalamus may have clinical

relevance. Based on its neuroanatomic connections, the thalamus may play a crucial role in sensory, cognitive, limbic, and behavioral difficulties in TS. Severe and disabling adult TS cases have recently been treated with thalamic deep brain stimulation.<sup>7</sup>

Our findings in TS of aberrant dopaminergic systems in the orbitofrontal cortex are consistent with the clinical phenomenology of context-dependent compulsive tics in adults. Processes involving abnormal motivational salience involve dysfunction within the mesolimbocortical dopamine system.<sup>8</sup> Our finding in hippocampus may correspond to altered hippocampal activity found in FDG-PET studies in TS<sup>9</sup> and may relate to the cognitive features of this disorder.

Limitations of this pilot study include small sample size and involve the tradeoffs between validity and generalizability. In excluding medicated patients to eliminate this source of confounding, we thereby excluded patients with significantly impairing OCD, depression, and the most severe tics. In addition, our adult subjects may be distinct from most TS children whose tics diminish over time. Last, due to long equilibration times of fallypride in the striatum ( $\approx 2$  hours), the caudate and putamen were not included in the analysis of this study.

Despite these limitations, [F-18]fallypride PET may yield novel and important insights into the complex neuroanatomic substrate of TS.

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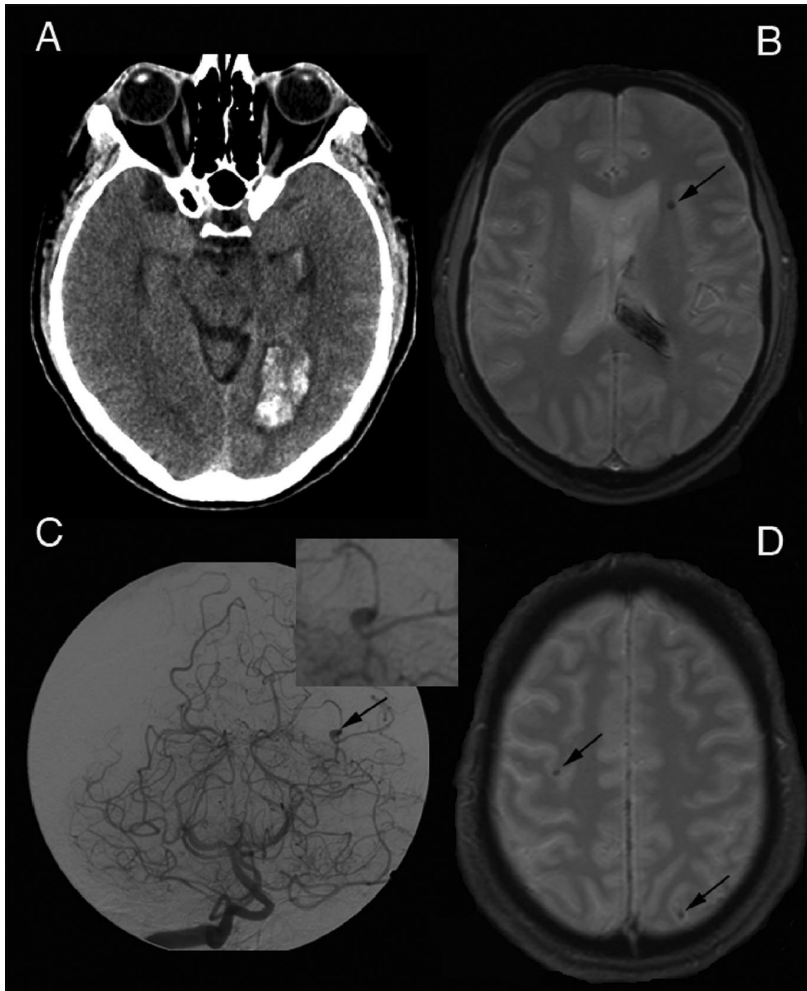
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## NeuroImages



*Figure. (A) CT scan with left occipital hemorrhage with left lateral intraventricular and convexity subarachnoid hemorrhage. (B, D) T2-gradient recall echo imaging suggestive of multifocal hemorrhage (arrow) in both cerebral hemispheres. (C) Cerebral angiogram showing 3 mm mycotic aneurysm (arrow and inset) involving the posterior temporal branch of the left posterior cerebral artery.*

### **Cerebral microhemorrhages in a patient with mycotic aneurysm: Relevance of T2-GRE imaging in SBE**

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A 43-year-old man presented with sudden onset left hemispherical headache and right superior quadrantanopia after 5 weeks of treatment with antibiotics for subacute bacterial endocarditis (SBE). Head CT (figure, A) showed left occipital ICH with intraventricular and convexity subarachnoid hemorrhage. Cerebral angiogram (figure, C) revealed a 3-mm mycotic aneurysm of the posterior temporal branch of the left PCA. MRI showed occipital ICH and microhemorrhages secondary to mycotic aneurysm rupture on T2-weighted–gradient recall echo (T2-GRE) imaging (figure, B and D). GRE imaging in SBE may have a potential role in diagnosing subclinical microhemorrhages, monitoring treatment effect, and perhaps identifying patients at risk for developing mycotic aneurysms.

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