# Cognitive-Pharmacologic Functional Magnetic Resonance Imaging in Tourette Syndrome: A Pilot Study

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**Background:** *Dopamine agonists and antagonists can reduce abnormal movements and vocalizations (tics) in Tourette syndrome (TS); however, dopamine-responsive abnormal function in specific brain regions has not been directly demonstrated in TS. We sought to identify dopamine-modulated brain regions that function abnormally in TS by combining functional magnetic resonance imaging (fMRI), a working memory (WM) task, and infusion of the dopamine prodrug levodopa (while blocking dopamine production outside the brain).*

**Methods:** *We obtained complete fMRI data in 8 neuroleptic-naive adults with a chronic tic disorder and in 10 well-matched tic-free control subjects.*

**Results:** *Different task-sensitive brain regions responded differently to the WM task depending on levodopa status and diagnostic group (analysis of variance [ANOVA], p < .001). Four regions showed interactions with diagnosis (ANOVA, p < .001). In TS subjects, the task induced excessive brain activity in parietal cortex, medial frontal gyrus, and thalamus. Levodopa normalized the excess activity. In left parietal cortex, the degree of normalization was greater in patients with higher levodopa plasma concentrations (n = 6; Spearman's r = −.84, p = .04) and a greater degree of diagnostic confidence of TS (r = −.71, p = .05).*

**Conclusions:** *These results are consistent with a dopamine-influenced functional abnormality of brain response in TS and suggest testable hypotheses about the mechanism by which dopamine antagonists and agonists alleviate tics.*

Tourette syndrome (TS) is defined by chronic tics, such as repetitive blinking or sniffing, that begin in childhood and are otherwise unexplained (American Psychiatric Association 1994). Although current diagnostic criteria rely on these motor and vocal manifestations, cognitive and sensory symptoms are also prominent in TS (e.g., inattention, obsessions, "just right" phenomena, or sensory tics), and tics often involve an interplay of compelling urge versus effortful suppression (Black and Webb 2004). The cause of TS remains unknown, and there is little understanding of the pathophysiology underlying the symptoms.

The discovery that dopamine antagonists substantially reduce tic severity (Bockner 1959) led to hypotheses of abnormal dopamine function in TS. In vivo and limited postmortem studies in TS have examined dopamine D2 receptors, dopamine precursor uptake, or monoamine transporters (Albin et al 2003; Anderson et al 1999; Peterson 2001; Singer and Wendlandt 2001; Swerdlow and Young 2001). No consistent abnormalities have emerged from these studies.

Another line of research has used neuroimaging techniques to identify cerebral correlates of tics (Peterson 2001; Peterson et al 1998; Stern et al 2000). Such studies have helped refine hypotheses about the anatomic pathophysiology of tics (Mink 2001b, 2001a; Swerdlow and Young 2001); however, functional imaging studies of tics themselves can be difficult to interpret. For instance, if TS patients show excess activity in a movement-related region of brain, it may be difficult to distinguish whether this is an important observation about regional brain dysfunction that causes tics or merely an expected correlate of increased movement.

Other variables can also limit interpretation of neuroimaging studies in TS. Ideally, control subjects should match TS patients on variables such as age and gender that can influence brain shape, cognitive performance, dopamine release, or receptor binding. Additionally, TS patients have often been treated with dopamine receptor antagonists, which have substantial effects on the brain and its dopaminergic system that can persist even years after exposure (Peterson et al 2003; Sachdev 2000). Combined with the relatively low prevalence of TS in adults, this has slowed research requiring neuroleptic-naive adults with TS. Finally, any task-elicited brain response is difficult to interpret if task performance is not matched between groups of interest (e.g., Schlaggar et al 2002).

This study addressed these methodologic challenges and used a novel approach. Dopamine antagonists improve tics, but, surprisingly, there is now increasing evidence that dopamine agonists also can improve tics (Anca et al 2001; Black and Mink 2000; Gilbert et al 2000, 2003). Thus dopaminergic tone in TS is unlikely to be simply too high or too low, yet clearly dopamine modifies brain function in TS. These observations provide the rationale to search for abnormal brain responses in TS that are modulated by dopamine.

We combined two disparate methods of stimulating activity in dopamine-influenced neuronal circuits—cognitive and pharmacologic activation—to detect dopamine-mediated abnormal brain responses in TS using functional magnetic resonance imaging (fMRI). Cognitive and pharmacologic stimuli have not been combined in functional neuroimaging studies of TS, but this approach has been useful in studying other conditions (Coull et al 2001; Mattay et al 2002).

In designing an experimental study of a neuropsychiatric disorder, one choice is to select a task for which performance is

**Table 1.** Tourette Syndrome Subject Demographic and Clinical Information

| Subject | Gender | Age | TSSG | DSM-IV | DCI Score | OCD (Lifetime) | ADHD (Lifetime) | Self Y-BOCS Current | Self Y-BOCS Worst Ever | Self-Rated Recent Tic Severity[a] | Psychoactive Oral Medications |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 56 | DTS | TD | 58 | Yes | No | 8 | —[b] | 21 | Carbidopa, levodopa[c] |
| 2 | M | 21 | DTS | TD | 61 | No | Yes | 0 | 0 | 13 | imipramine[c] |
| 3 | M | 43 | DTS | TD | 80 | No | Yes | 0 | 0 | 19 | — |
| 4 | F | 36 | DTS | —[d] | 43 | No | No | 0 | 0 | 20 | — |
| 5 | F | 32 | DTS | TD | 74 | Yes | Yes | 5 | 7 | 11 | — |
| 6 | M | 19 | CMMTD | — | 41 | No | No | 0 | 0 | 7 | — |
| 7 | M | 23 | DTS | — | 43 | No | No | 0 | 4 | 12 | — |
| 8 | M | 51 | CMMTD | — | 38 | No | Yes | 3 | 3 | 11 | — |
| Mean (SD) | | 35.5 (13.5) | | | 54.8 (16.1) | | | 2.0 (3.1) | 2.0 (2.7) | 14.3 (5.1) | |

M, male; F, female; TSSG, Tourette Syndrome Study Group diagnosis; DTS, definite tourette syndrome; CMMTD, definite chronic multiple motor tic disorder; DSM-IV, Diagnostic and Statistical Manual, 4th ed., diagnosis; TD, Tourette's disorder; OCD, obsessive–compulsive disorder; ADHD, attention-deficit/hyperactivity disorder; Y-BOCS, self-rated Yale–Brown Obsessive Compulsive Scale.

[a]Modified self-rated Yale Global Tic Severity Scale (maximum score = 50; see Methods and Materials).
[b]Subject did not complete.
[c]Discontinued 12 hours prior to study.
[d]See first paragraph of Methods and Materials.

abnormal in the patient group. That choice lends face validity to the task but also confounds interpretation of results because abnormal task performance itself may cause group differences in brain activity. An alternative is to find a pertinent task that can be performed normally in the patient group; then abnormal brain activation cannot be explained by poor performance. We prefer the latter approach, as have others (e.g., Schlaggar et al 2002; Tempel and Perlmutter 1990).

The cognitive stimulus in this study was a test of working memory (WM) (Braver et al 1997; Gray 2001). Working memory can be defined as the ability to hold and manipulate information online for short periods of time to guide future actions (Goldman-Rakic 1990). Dopamine agonists or antagonists can modulate WM function (Goldman-Rakic 1992), and WM is abnormal in conditions with dopamine deficiency such as Parkinson disease (Gabrieli et al 1996). Thus, WM-related brain activation is of interest in testing dopamine-influenced brain function in TS. Additionally, we expected that people with TS would perform the WM task with normal accuracy and speed, so that group differences in brain response would not be explained by simple group differences in performance.

The pharmacologic stimulus was levodopa. After intravenous administration, levodopa crosses the blood–brain barrier and is rapidly converted into dopamine in specific brain regions. In either normal or dopamine-depleted brain, this is followed by increased dopamine release at the synapse, altered electrical activity of striatal neurons, regional changes in metabolic rate, and other postsynaptic effects, as recently reviewed (Black et al 2003). With adequate inhibition of peripheral dopamine synthesis, however, levodopa causes no effect on whole-brain blood flow (Hershey et al 1998, 2000, 2003) and, in contrast to dopamine antagonists, levodopa causes minimal subjective effects (Black et al 2003). These characteristics make levodopa ideal as a dopaminergic challenge agent for functional MRI.

Local blood flow (and BOLD [blood oxygen level–dependent] MRI) responses to behavioral or dopaminergic challenges primarily reflect changes in axonal terminal fields or local interneurons (Azuma et al 1988; Gold and Lauritzen 2002; Hershey et al 2000; Lauritzen 2001; Logothetis et al 2001; McCulloch 1984; Schwartz et al 1979). Thus, a BOLD signal response could indicate a change of input to that region from anatomically connected regions or alterations in local interneuronal activity.

BOLD signal changes following dopaminergic challenges can determine how regions of the brain downstream from dopamine receptors are affected in disease states (Henriksen and Boas 1985; Kobari et al 1995; Leenders et al 1985; Melamed et al 1978; Montastruc et al 1987; Oishi et al 1996; Perlmutter and Raichle 1985) and how any alterations in function relate to clinical symptoms (Black et al 2001; Hershey et al 1998).

We combined levodopa and a WM task with fMRI to search for abnormal dopamine-modulated brain responses in neuroleptic-naive adults with TS.

## Methods and Materials

### Subjects

The Institutional Review Board at Washington University School of Medicine approved this study, and all subjects gave informed consent before participation. A board-certified psychiatrist and movement disorders expert examined all subjects for other psychiatric (Hudziak et al 1993), neurologic, or medical illness. Subjects with tics were included if they had otherwise unexplained vocal or motor tics that occurred many times a day for longer than 1 year, without 3 tic-free months, and if symptoms began before age 18. Tic disorders were diagnosed by DSM-IV (American Psychiatric Association 1994) and Tourette Syndrome Classification Study Group (1993) criteria. Discrepancies between the two sets of diagnostic criteria occurred solely because some subjects had no occupational or social impairment or "marked" distress. Nevertheless, subjects 1–7 (in Table 1) were all bothered by their symptoms and had sought medical advice.

One author retrospectively assigned Diagnostic Confidence Index (DCI) scores to each subject with tics, blind to subjects' imaging or task performance results (see Table 1). The DCI, which was published after this study began (Robertson et al 1999), is a clinician-rated scale intended to quantify diagnostic certainty for TS based on expert consensus weighting of lifetime symptoms and signs. In a large clinical sample diagnosed with TS by DSM-III-R criteria, scores ranged from 5 to 100 (mean 61, SD 20; Robertson et al 1999).

Control subjects were matched for age, gender, handedness, and educational attainment. Subjects with TS were excluded for comorbid neurologic or psychiatric illness except attention-deficit/hyperactivity disorder (ADHD), obsessive–compulsive

disorder (OCD), learning disabilities, or adjustment disorder. Control subjects were excluded for neurologic or psychiatric illness including ADHD and OCD. Subjects in both groups were excluded for any history of neuroleptic treatment.

Each subject with tics was videotaped before and as soon as possible after the fMRI session. Each videotape segment was > 5 min long (except two segments were ~4.5 min long). Severity ratings and number of body parts affected were rated after viewing the entire video segment (Black and Mink 2000). Each segment consisted of full body views and head-and-shoulder views, each done with the examiner in and out of the room. Tic counts were done on the portions with the examiner out of the room. The first technically adequate 60-sec period was used to count tics below the shoulders (full body view) and all other tics (head and shoulder view; Black and Mink 2000). Ratings were deferred until all subjects had been scanned. Pre- and postscan videotape segments were viewed in randomized order by a single rater who was not told the correct order and was blind to imaging results.

Subjects with TS also completed a detailed self-report of lifetime symptoms and treatment. Symptom severity, both "worst ever" and for the week before the scan, were rated using self-rated versions of the Yale–Brown Obsessive Compulsive Scale and a modified Yale Global Tic Severity Scale (self-rated tic severity only, for current week, maximum score 50; Findley et al 1999; Leckman et al 1989; Scahill et al 1999). See Table 1 for additional information. Finally, before and after the fMRI scan, subjects with TS indicated on a 100-mm visual analog scale the severity of their tics and their obsessive–compulsive symptoms "at this exact moment" (100 = severe symptoms, 0 = none).

### fMRI Acquisition

Magnetic resonance scans were performed on the boosted-gradient 1.5-T Siemens VISION system at the Research Imaging Center of the Mallinkrodt Institute of Radiology at Washington University Medical School. Tape and padding were used to restrict head movement, and headphones were worn to dampen the noise of the scanner and for communication between the experimenter and subject. Functional images were preceded by magnetization-prepared rapid acquisition gradient echo (MPRAGE) and T2-weighted anatomic images. The MPRAGE consisted of a three-dimensional T1-weighted sequence with 1.25 mm³ voxels. Functional images were collected using an asymmetric spin-echo echo-planar sequence sensitive to BOLD contrast (T2*) (repetition time = 2500 msec, echo time = 50 msec, field of vision = 24 cm, flip angle = 90°). During each functional run, 128 sets of 16 contiguous, 8-mm-thick axial images were acquired parallel to the anterior–posterior commissure plane (3.75 × 3.75 mm in-plane resolution), allowing complete brain coverage at high signal-to-noise ratio (Conturo et al 1996). Artifact removal, within-subject image alignment, and atlas registration were performed as described elsewhere (Braver et al 2001; Talairach and Tournoux 1988). Scans were smoothed spatially with a 6-mm full width at half maximum Gaussian filter.

### Working Memory Task

A block design was used contrasting task versus fixation. We chose a two-back letter task (WM task) that had been validated in previous work (Braver et al 1997; Gray 2001). This task provides robust activation of cortical and subcortical regions. Previous work has determined which regions are sensitive to the WM, general difficulty, and motor and visual demands of the task (Barch et al 1997; Braver et al 1997; Nystrom et al 2000). In this

study, our goal was to determine how disease and levodopa modulated brain responses to a WM task, not to parse out the precise relationship between cognitive components of the task and regions of BOLD response.

Subjects performed four blocks of 31 trials (10 fixation and 21 task trials) for each scan. Each scan lasted approximately 6 min. Visual stimuli were presented via a liquid crystal diode projector and a mirror. During a fixation trial, subjects fixated on a central cross. During the task trials, subjects watched a continuous series of letters presented one at a time (against a visual mask/background and in random spatial locations). Manual button presses were required for each stimulus, with a target button press made to denote a letter that was identical to the letter presented two trials back, and a nontarget button press made for all other letters. PsyScope was used to present all stimuli and record responses (Macwhinney et al 1997). Two scans were performed in the off levodopa (baseline) condition and two in the on levodopa condition.

### fMRI Analysis

The preprocessed functional images were analyzed in a manner designed to examine regions of WM task activation that were altered by group, drug condition, or both in a manner that protects the results from type I error and is unbiased toward any single condition. The first step in this strategy was to determine the task effect (WM vs. fixation) at each voxel within each run. We included BOLD runs 2–4 (see Task Performance in the Results section). We estimated the magnitude of the BOLD signal at each voxel within each run using a general linear model that included terms for task and fixation blocks (corrected for assumed hemodynamic response delay), linear trends, and intercepts.

Next, we determined the statistically significant clusters of task-related (WM vs. fixation) activation across the entire brain, collapsed across conditions and groups. By considering all task data, regardless of condition (baseline vs. drug) or group (TS vs. control), we avoided biasing the selection of task-related regions of interest (to be used in further analyses) toward any one group or condition (Keppel 1991). To identify these regions of task-related activation, we used a voxelwise three-way analysis of variance (ANOVA) with task (WM vs. fixation), drug (baseline vs. levodopa), and group (TS vs. control) as factors. In this first analysis, however, we were only interested in the main effect of task. We took the statistical image of the main effect of task and corrected it for multiple comparisons at the .05 level using a method validated by Monte Carlo simulation (McAvoy et al 2001). This method takes into account the volume of clusters of contiguous voxels passing a specified magnitude threshold. Clusters of task-related activation that survived this correction at the .05 level were identified as regions of interest (colored areas in Figure 2).

The mean regional BOLD responses for each of these clusters of task-related activation were entered in a single four-way ANOVA with region, task condition, drug condition, and diagnostic group as factors.

### Levodopa Administration

Carbidopa 200 mg was given by mouth at least 2 hours before levodopa administration (Hershey et al 1998). A plastic 20-g catheter was placed in an upper extremity vein for infusion of levodopa. We gave levodopa by the intravenous route to avoid variability and age and gender biases in oral absorption of levodopa (Kompoliti et al 2002; Robertson et al 1989). After the

baseline fMRI scans, we infused a loading dose of levodopa to reach an approximate steady state tissue concentration rapidly, followed by a slower infusion to balance losses by metabolism and excretion. Infusion rates were calculated using published pharmacokinetic parameters, individually adjusted based on age and body mass with a target steady-state concentration of 600 ng/mL (Black et al 2003). A 35-year-old, 70-kg subject would receive a total dose bioequivalent to ~150 mg oral levodopa. This infusion protocol is well tolerated and produces statistically significant motor benefit in patients with Parkinson disease (Black et al 2003). The on-levodopa cognitive scans began at least 35 min after the start of the levodopa infusion and ended by 90 min after the start of the levodopa infusion.

### Plasma Drug Concentrations

Blood samples for plasma levodopa and carbidopa concentrations were taken just after each on-levodopa cognitive scan through a plastic catheter previously placed in an upper extremity vein contralateral to the levodopa infusion site. Out of the total number of subjects with usable fMRI data, six TS and nine control subjects had adequate blood samples for examining the relationship between levodopa levels and other variables. Plasma concentrations of carbidopa and levodopa were measured by high-performance liquid chromatography with electrochemical detection (Baruzzi et al 1986; Carl and Perlmutter 1998).

### Results

### Subjects

Usable working memory fMRI data both before and after levodopa were acquired in 8 TS and 10 control subjects (3 subjects left the scanner before the postlevodopa scans). We were unable to obtain blood samples from two TS subjects and one control subject because of technical problems. Thus, analyses that involved levodopa measurements were performed on the remaining 6 TS and 9 control subjects. All other analyses (e.g., cognitive and fMRI) were performed on 8 TS and 10 control subjects. Mean age in each group was 35.5 years (SD = 13.5 for TS, SD = 12.4 for control) and mean education was 14.1 years in each group (SD = 1.4 for TS, SD = 1.2 for control). One subject in each group was left-handed. See Table 1 for TS patient information.

### Levodopa Plasma Concentrations

Plasma concentrations of carbidopa and levodopa did not differ significantly across groups (levodopa, TS mean = 503 ng/mL, SD = 80, $n$ = 6; control mean = 495 ng/mL, SD = 73, $n$ = 9; $t$ test, $t(13)$ = .20, $p$ = .85; carbidopa, TS mean = 508 ng/mL, SD = 228, $n$ = 6; control mean = 475 ng/mL, SD = 182, $n$ = 9; $t$ test, $t(13)$ = .32, $p$ = .76).

### Task Performance

Despite previous practice, subjects tended to improve their reaction times significantly between runs 1 and 2. There was no significant change between runs 2 and 4. Thus, we discarded run 1 from further consideration in behavioral or BOLD analyses. There were no significant differences between groups (TS: $n$ = 8, control: $n$ = 10) in reaction time or accuracy (reaction time: off levodopa, TS mean = 876 msec, SD = 289; control mean = 982 msec, SD = 170; on levodopa, TS mean = 791, SD = 280, control mean = 903, SD = 190; accuracy: off levodopa, TS mean = 88%, SD = 6, control mean = 85%, SD = 9; on levodopa, TS mean = 88%, SD = 5, control mean = 85%, SD = 9). By contrast,
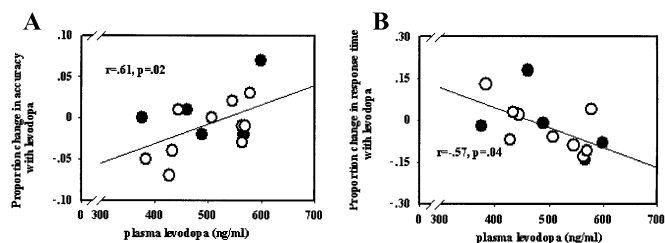


**Figure 1.** Relationship between plasma levodopa levels and working memory (WM) task performance. Plasma levodopa levels significantly correlated with improvements in accuracy and reaction time following levodopa administration. **(A)** Change in WM accuracy with levodopa correlates positively with levodopa levels such that higher accuracy is related to higher levodopa levels. **(B)** Change in WM reaction times with levodopa correlates negatively with levodopa levels such that faster reaction time is associated with higher levodopa levels. Subjects with Tourette syndrome (filled circles; $n$ = 6) and tic-free control subjects (empty circles; $n$ = 9) with adequate blood samples are depicted with different symbols; however, there were no group differences in levodopa levels or performance.

levodopa did affect performance. Although mean task accuracy did not change with levodopa in either the TS or the control group, there was a correlation between subjects' levodopa concentrations and their change in task accuracy when both groups were considered together. Accuracy tended to worsen (compared with prelevodopa performance) in subjects with lower levodopa concentrations but to improve in those with higher concentrations ($n$ = 15; $r$ = .61, $p$ = .02, Figure 1A). Higher levodopa levels also correlated with improvement in reaction time ($n$ = 15; $r$ = −.57, $p$ = .04, Figure 1B).

### Tics and Other Symptoms

Pre- and postlevodopa tic self-ratings (visual analog scale) and videotape tic counts were compared using Wilcoxon Signed Ranks tests (Table 2). None of these measures of tic severity and obsessive–compulsive symptom severity changed significantly across the course of the study (absolute $Z$ values 1.6 and below; $p$ values .11 and above). Side effects of levodopa were mild and reported at similar rates across the two groups (Fisher's Exact Test, $p$ values .31 and above; see Table 3).

### fMRI Results

Statistical analysis of the fMRI data had to account for several independent variables (diagnosis, pre- vs. postlevodopa, WM vs. fixation). We followed a multistep process designed to give us an unbiased assessment (not weighted toward any one condition) of significant regions of task-related activity that we could then examine for drug and group influences.

We first identified clusters of contiguous voxels significantly activated by the WM task after correction for multiple comparisons (colored areas in Figure 2; 20 such clusters were identified). We then examined the mean regional BOLD signal for all clusters of task-related activation in a single four-way repeated-measures ANOVA with region, task condition, drug condition, and diagnostic group as factors. This analysis revealed a significant four-way interaction [region × task × drug × group, $F(19,304)$ = 5.62, $p$ < .001], and two significant three-way interactions [region by task by drug, $F(19,304)$ = 2.40, $p$ = .001 and region by task by group, $F(19,304)$ = 2.75, $p$ < .001]. These significant omnibus tests allowed us to proceed to examine each region independently for significant task, drug, and group interactions. These analyses revealed one region with a significant interaction between task and drug, and four regions with significant interac-

**Table 2.** Pre- and Postlevodopa Tic Counts and Visual Analog Scale Results for Tics and Obsessive–Compulsive Symptoms in Subjects with Tourette Syndrome

| Subject | Pre Motor Tic Count | Post Motor Tic Count | Pre Vocal Tic Count | Post Vocal Tic Count | Pre VAS for Tics (mm) | Post VAS for tics (mm) | Pre VAS for OCD (mm) | Post VAS for OCD (mm) |
|---|---|---|---|---|---|---|---|---|
| 1 | 83 | 35 | 6 | 10 | 17 | 2 | 16 | 2 |
| 2 | 7 | 11 | 1 | 2 | 3 | 5 | 1 | 1 |
| 3 | 38 | 28 | 3 | 2 | 61 | 50 | 0 | 0 |
| 4 | 29 | 9 | 5 | 0 | 42 | 13 | 0 | 0 |
| 5 | 97 | 79 | 2 | 4 | 2 | 4 | 2 | 3 |
| 6 | 6 | 5 | 0 | 3 | — | — | — | — |
| 7 | 10 | 8 | 3 | 2 | 6 | 15 | 1 | 5 |
| 8 | 16 | 8 | 0 | 0 | 0 | 22 | 1 | 0 |
| Mean (SD) | 29.5 (29.9) | 22.9 (25.1) | 2.5 (2.2) | 2.9 (3.2) | 18.7 (23.7) | 15.9 (16.6) | 3.0 (5.8) | 1.6 (1.9) |

VAS, visual analog scale; OCD, obsessive-compulsive disorder.

tions between task, drug, and group (Figure 2). See Table 4 for an anatomic description of each region, Talairach coordinates, and ANOVA values.

The region with a task by drug effect was in the left parietal-occipital cortex. This region had a decreased fMRI BOLD response to the task, which was attenuated in the presence of levodopa (Figure 3D). This pattern was similar across groups. The regions with task by drug by group interactions were in medial frontal, left and right parietal cortex, and left thalamus. In three of these regions (medial frontal, left parietal, and left thalamus), the TS group had an elevated fMRI response to the WM task at baseline. With levodopa, these differences disappeared, because activity in the TS group decreased to control levels in all three regions (see Figure 3, A–C). In left parietal cortex, this normalization was correlated to levodopa plasma concentration ($p < .05$) and a greater degree of diagnostic confidence of TS ($p < .05$). Specifically, the reduction with levodopa in the left parietal fMRI response to the WM task was greater in subjects with higher levodopa levels (Figure 4A) and in subjects with more severe symptoms and more prototypical course (Figure 4B). Supporting the relevance of this region to WM task performance, left parietal reaction times correlated significantly with fMRI responses, both at baseline and during the on levodopa scans ($p < .02$); faster reaction times were associated with greater fMRI response to the WM task (Figure 5).

Similarly, in the right parietal region, the TS group decreased activation with levodopa and the control subjects increased activation with levodopa; however, in this region the task-related fMRI response in the two groups was more similar at baseline so that there was no significant group difference either before or during the levodopa infusion.

**Table 3.** Number of Subjects Reporting Side Effects Following Levodopa Infusion[a]

| Side Effect | TS (n = 8) | Control (n = 10) |
|---|---|---|
| Any | 5 | 8 |
| Nausea | 1 | 4 |
| Sedation | 4 | 5 |
| Dizziness | 0 | 1 |
| Miscellaneous | 5 | 5 |

TS, Tourette Syndrome.
[a] No significant differences were found between groups.

## Subgroups

The small number of TS subjects precludes statistically valid comparison of subgroups with ADHD, with OCD, or those recently exposed to (nonneuroleptic) neuroactive medication (see Table 1); however, the fMRI results were similar when excluding any of these subgroups, suggesting that our findings are not likely driven by these subgroups.

## Discussion

### Overview

In four of the brain regions activated by the WM task, the fMRI response differed significantly depending on levodopa administration and diagnostic group. In the medial frontal, left thalamus, and left parietal regions, the TS group had higher WM task responses than control subjects at baseline that reduced to normal levels during levodopa infusion. The data from left parietal cortex are especially compelling. In this region, fMRI responses correlated significantly with measures of task performance, levodopa concentration, and lifetime severity of TS (Figures 4 and 5). These correlations strengthen the conclusion that the fMRI results relate specifically to WM, to levodopa, and to diagnosis.

In interpreting these results, the study design and subject characteristics allow us to reasonably exclude important confounds such as group differences in age, gender, drug absorption, task performance, levodopa effects on task performance, or exposure to neuroleptic treatment. The simplest and most plausible explanation is that these regions respond abnormally to WM demands in TS and are modulated by dopamine.

### Implications for Pathophysiology

We propose two alternative explanations for the altered fMRI responses in the TS group. One possibility is that TS subjects have a primary abnormality of dopamine signaling that alters task-related cortical and thalamic BOLD signal and is corrected by exogenous levodopa. The abnormality in function could occur at various points: brain uptake of levodopa, conversion of levodopa to dopamine, dopamine release by the presynaptic neuron, dopamine metabolism or clearance from the synapse, postsynaptic dopamine receptors, or signal transduction. Studies of dopamine receptors in TS have shown no consistent abnormality; several studies reported a striatal increase in presynaptic dopamine markers, although other reports are contradictory (Albin et al 2003; Meyer et al 1999; Peterson 2001; Singer et al
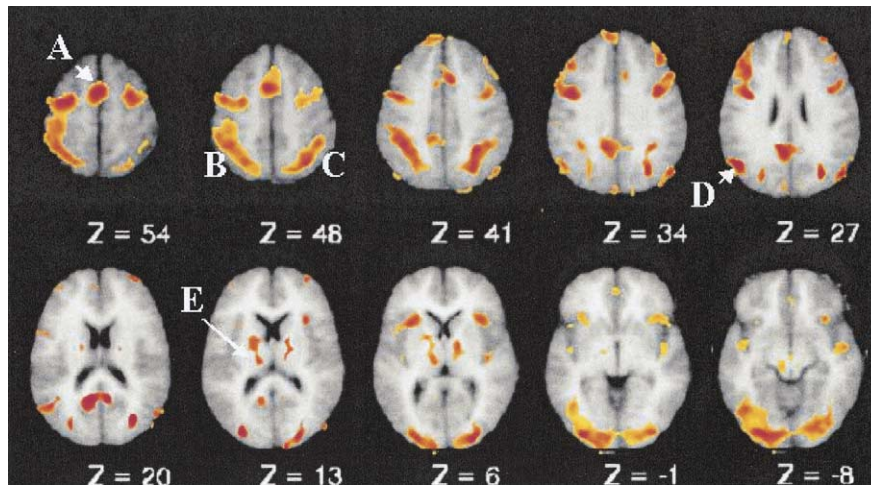
**Figure 2.** Multiple-comparison corrected statistical map of working memory (WM) task effect. Labeled regions are those that behaved differently across the variables of task (WM vs. fixation), drug status (baseline vs. on levodopa), and group (Tourette syndrome vs. control subjects). **(A)** Medial frontal region with a group × drug × task interaction; **(B)** left parietal region with a group × drug × task interaction; **(C)** right parietal region with a group × drug × task interaction; **(D)** left parietal-occipital region with a drug × task interaction; **(E)** left thalamus region with a group × drug × task interaction. See Table 4 for additional anatomical information.

2002; Stamenkovic et al 2001; Wong et al 1994). Our results could indicate a baseline, tonic abnormality of dopamine function but may be more consistent with a WM-task-related, phasic abnormality. In support of this view, the [$^{11}$C]raclopride PET study by Singer et al (2002) suggests normal dopamine release at baseline in TS but altered dopamine release in response to a pure pharmacologic challenge (amphetamine).

Alternatively, dopamine function per se may be normal, and the exaggerated baseline fMRI response to the WM task in TS may arise from primary abnormalities in "downstream" brain regions influenced by dopamine. In this case, the altered response to dopamine might be viewed as an appropriate compensation. For example, the baseline overactivation of specific regions in TS may relate to the use of an alternative cognitive strategy (e.g., greater use of phonologic rehearsal) or greater required effort, ultimately sustaining normal WM performance. With levodopa, the strategy or effort level may be altered (e.g., rehearsal becomes less effortful), producing neural activation more consistent with control subjects while preserving normal task behavior.

Either of these hypotheses proposes that levodopa corrects or ameliorates regional brain dysfunction in TS. This idea is not new given that dopamine agonists can improve tics, probably acting through postsynaptic mechanisms (Black and Mink 2000; Anca et al 2001; Gilbert et al 2000, 2003); however, our findings do provide an anatomic framework for understanding the brain pathways through which levodopa may exert its beneficial effects. We studied a cognitive rather than a motor task to minimize concerns that neuroimaging results could reflect only excessive movement. Consequently, this study shows levodopa-related normalization of fMRI responses in brain regions activated by a cognitive task; however, a similar design can now be applied to movement in TS. Our results suggest that abnormal brain activation by a motor task might similarly be normalized by levodopa. This hypothesis can be tested using a motor task that produces abnormal fMRI responses in TS (Biswal et al 1998; Peterson 2001).

Our finding that levodopa levels were correlated with improvements in WM performance is new. Other studies have shown an overall effect of levodopa on WM accuracy in control subjects and PD patients (Kimberg et al 1997; Lange et al 1992), but none has demonstrated a linear relationship between blood levels and performance. In dopamine denervation models, WM improves with dopaminergic stimulation but worsens either with dopamine antagonists or with higher doses of agonists (Arnsten et al 1994; Cools et al 2001). Consequently, some researchers

**Table 4.** Regions of Interactions for Working Memory Task

| Region Name | ANOVA Results | Center of Region[a] | Peak Magnitude[a] |
|---|---|---|---|
| Medial Frontal | Task × drug × group $F_{(1,16)} = 5.62, p = .03$ | −2, 6, 51 Medial frontal gyrus, BA6 | 11, 18, 30 Cingulate gyrus |
| Left Parietal | Task × drug × group $F_{(1,16)} = 10.43, p = .005$ | −34, −48, 45 Inferior parietal lobule | −28, −75, 15 Middle occipital gyrus |
| Right Parietal | Task × drug × group $F_{(1,16)} = 5.27, p = .035$ | 32, −60, 39 Parietal lobe, subgyral | 32, −72, 15 Middle occipital gyrus |
| Left Parietal-Occipital | Task × drug × group $F_{(1,16)} = 6.62, p = .02$ | −46, −66, 26 Angular gyrus/inferior parietal lobule | −49, −63, 12 Angular gyrus/inferior parietal lobule |
| Left Thalamus | Task × drug × group $F_{(1,16)} = 5.39, p = .03$ | −14, −12, 9 Ventrolateral nucleus of the thalamus | −13, −15, −6 Midbrain |

ANOVA, analysis of variance.
[a]Talairach coordinates (x, y, z) and anatomic description.
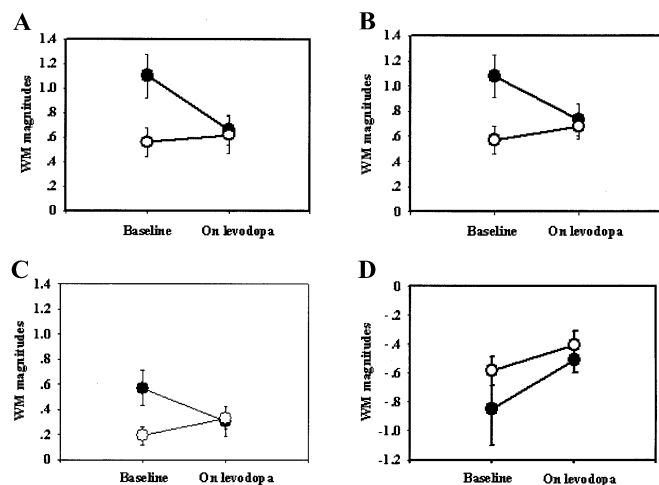
**Figure 3.** Modulation of working memory (WM) task activation by levodopa and diagnosis. Levodopa significantly altered WM task activation (mean ± SEM) differentially across groups in **(A)** medial frontal, **(B)** left parietal, and **(C)** left thalamus regions. Levodopa reduced the negative WM task activation (mean ± SEM) in the **(D)** left parietal-occipital region similarly across groups. Filled circles, subjects with Tourette syndrome; empty circles, control subjects.



**Figure 5.** Relationship between working memory (WM) task performance and WM task activation. Reaction time on the WM task correlated significantly with WM activation in the left parietal region at **(A)** baseline and **(B)** on-levodopa conditions. Groups are depicted with different symbols (filled circles, subjects with Tourette syndrome; empty circles, control subjects); however, there were no differences between groups in reaction times. There were significant differences between groups in baseline left parietal WM magnitudes, as depicted more clearly in Figure 3A.

have hypothesized that there is an inverted U-shaped function describing the effects of dopamine on WM function (Arnsten 1997; Desimone 1995; Zahrt et al 1997). This has been attributed to selective activation of inhibitory presynaptic receptors at low doses (Cooper et al 1996; Ruzicka et al 1994), which is less likely with the blood levels achieved in this study. The optimal level of dopamine may also depend on the memory demands of the task (Arnsten 1997; Granon et al 2000). Our study in TS and healthy control subjects also suggests a nonmonotonic dopamine dose-response curve, but in the opposite direction: WM performance correlated with plasma levodopa concentrations, but subjects with lower levodopa levels performed worse than before levodopa administration. The differences between dose-response curves in this study versus the studies in Parkinson disease or nonhuman primate models may relate to differences in the pharmacologic stimulus (levodopa vs. selective D1 receptor agents) or the population (chronic denervation and chronic dopamimetic treatment in Parkinson disease). The opposing effects of lower and higher levodopa concentrations on WM task performance could relate to possible differences in dose-re-
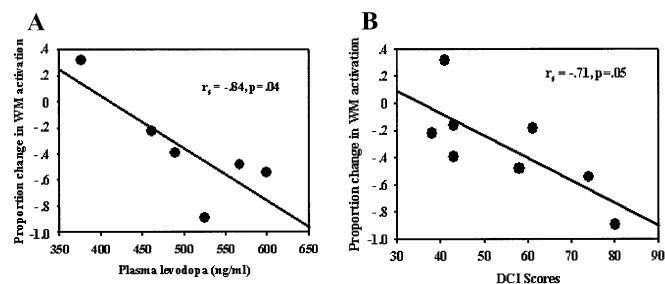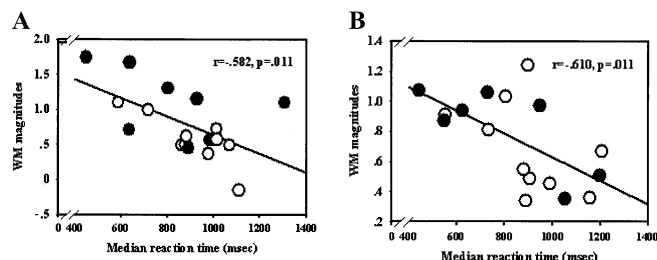
sponse curves for various clinical effects (e.g., sedation vs. WM efficiency), for the various receptor subtypes (D1–D5), or for various dopamine-influenced circuits (e.g., DLPFC vs. motor cortex vs. medial orbital cortex). We cannot resolve this issue from the available data.

Because tics improve either with dopamine antagonists or with agonists, they may follow a similar dopamine dose-response curve. Tic suppression by dopamine agonists has been attributed to preferential activation of inhibitory autoreceptors, but at the doses used here, this explanation is unlikely. Our subjects had levodopa plasma concentrations that produce motor benefit in treated Parkinson disease (Black et al 2003; Contin et al 1994). Similarly, tic suppression by pergolide was accompanied by decreased prolactin release, consistent with a postsynaptic effect (Gilbert et al 2000).

## Comparison to Past Studies

Previous investigations have used neuroimaging techniques to study working memory, dopamine, and Tourette syndrome individually. Those studies implicated some of the same brain regions identified in this report. Our research links all three factors for the first time and clarifies how they interact to affect brain function.

The relationship of these regions to WM function is particularly well described. The inferior parietal cortex has direct connections to the dorsolateral prefrontal cortex (DLPFC; Friedman and Goldman-Rakic 1991), and both regions bilaterally are consistently activated in WM tasks (Barch et al 1997), are sensitive to WM load (Barch et al 1997), and, if damaged, can cause WM deficits (Smith and Jonides 1998). The role of the inferior parietal cortex in WM is complex and not yet fully defined but may include computing comparisons, updating contents of the WM store, and performing rehearsal or storage operations (Smith and Jonides 1998). The left thalamus may be involved in the sensory, attentional, or motor aspects of WM task performance. The medial frontal region, which extends into anterior cingulate, may be important in motor planning, response inhibition, or error-monitoring aspects of WM (Braver et al 2001).

Dopamine is known to modulate brain activity in some of these regions, although the mechanisms are not well understood. Levodopa modulates left parietal response to WM tasks in Parkinson disease (Mattay et al 2002). In addition, levodopa or a dopamine agonist decreases baseline blood flow in parietal cortex in patient with Parkinson disease, healthy humans (Hershey et al 1998), and baboons (Black et al 2002).



**Figure 4.** Relationship between working memory (WM) task activation and plasma levodopa levels and tic severity. Correlates of change in WM activation induced by levodopa in left parietal region. **(A)** Plasma levodopa levels. Subjects with Tourette syndrome with adequate blood sampling shown (n = 6). **(B)** Diagnostic Confidence Index (DCI) scores for lifetime severity of tics.

Most of these regions also have been identified as abnormal in previous studies of TS. Men with TS have larger parietal-occipital volumes than control subjects (Peterson et al 2001). There may also be increased resting metabolic activity in the superior parietal cortex (Braun et al 1993) and decreased activity with active tic suppression (Peterson et al 1998). Additionally, there are known visuoperceptual and visuomotor deficits in TS, and these skills are linked to parietal cortex (Schultz et al 1998). Supplementary motor area (including medial frontal gyrus) over-activity has been reported in TS at rest (Biswal et al 1998; Braun et al 1993) or during a motor task (Biswal et al 1998). Drug effects in this region may reflect levodopa's effects on the motor system and on basal ganglia pathways that innervate the medial frontal gyrus or the subjacent anterior cingulate cortex (Alexander and Crutcher 1990; Peterson et al 2003).

Systemic dopaminergic effects on WM performance can be mimicked by applying dopamine directly to DLPFC (Goldman-Rakic 1992). Thus, we might also have expected robust effects of levodopa on WM activation of DLPFC. Instead, only by greatly reducing our statistical threshold could we identify any voxels that responded to task, diagnostic group, and drug. Dopaminergic modulation of DLPFC may require greater baseline dopaminergic deficiency (as in Parkinson's disease), more pharmacologic specificity, or greater dopaminergic stimulation (Cools et al 2002; Mattay et al 2002). Alternatively, dopaminergic stimulation of DLPFC could act directly at receptors on pyramidal neurons; preferential effects on firing of cortical projection neurons might produce greater effects on BOLD signal at the axon termini (e.g., in the thalamus).

## Limitations

Limitations of this pilot study include the relatively small sample size, heterogeneity of the sample, limited measures of symptom severity, and possible order effects. The TS group was composed of adults without past neuroleptic exposure, considerably limiting the pool of appropriate subjects. In addition, some subjects in our TS group also had ADHD or OCD, which could influence our results in unintended ways. These diagnoses did not significantly affect task performance, but we cannot entirely exclude such effects; the number of subjects is small, and for ADHD we did not use a standardized diagnostic interview or ratings of symptom severity. Thus, the results from this study need to be replicated in a larger sample of neuroleptic-naive patients with TS. Ideally, this larger sample would include enough TS patients without comorbid conditions to examine the impact of ADHD or OCD on fMRI and task responses to dopaminergic challenge. Extending this relatively invasive study to children presents challenges, yet would be important given known interactions of diagnosis and age in studies of brain structure (Peterson et al 2001).

Because we did not measure tic phenomenology during each fMRI scan, interpretation of our results could be affected by any changes in tic frequency between task or drug conditions; however, this seems unlikely to explain our findings. Our results and those from a tic suppression study overlap anatomically only in the right parietal cortex, where BOLD signal decreased during tic suppression (Peterson et al 1998). By contrast, in our study the TS group showed an increased BOLD signal response during the WM task blocks, when tic suppression would likely be more pronounced. Because levodopa, if anything, decreases tic severity slightly (Black et al 2003), the decreased parietal BOLD response with levodopa could be attributed to tic suppression only by presuming increased intentional tic suppression during

levodopa infusion. This contradicts the subjective response to levodopa in people with tics (Black and Mink 2000).

Finally, without a placebo control condition, it is difficult to exclude an effect of time or practice on our results; however, levodopa levels did correlate with BOLD signal changes in left parietal task activation for the TS group, suggesting that level of levodopa exposure was relevant to changes in brain activation. In summary, results from this pilot study could provide the basis for hypothesis-driven, larger-scale studies that may resolve some of these methodologically and theoretically important issues.

## Relevance

Our results directly demonstrate for the first time abnormal brain activation, modulated by dopamine, in TS. These findings also tie together three previously unrelated lines of research. Further studies may clarify whether these findings apply to TS patients with a wider range of age, severity, and comorbidity or whether similar results are seen with other domains of working memory or with motor tasks. The dopaminergic system and its effects on basal ganglia–thalamocortical pathways are implicated not only in TS but also in other disorders including Parkinson disease, dystonia, Huntington disease, attention-deficit disorder, cocaine abuse, and schizophrenia. When cognitive skills thought to rely heavily on prefrontal cortex (e.g., WM, response inhibition, planning) are altered in these disorders, it is often speculated that dysfunction of the dopaminergic system has affected the prefrontal targets of these pathways. This study illustrates that by combining dopaminergic and cognitive activation techniques we can test more focused and potentially disorder-specific hypotheses about the functional neuroanatomy and pharmacology of higher-order cognitive function.

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