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Research report

Dopaminergic modulation of response inhibition: an fMRI study

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Abstract

Dopamine has been hypothesized to modulate response inhibition. To test this hypothesis, we used functional magnetic resonance imaging (fMRI) to measure the effects of the dopamine prodrug levodopa on the brain responses to a well-validated response inhibition task (go/no-go, or GNG). Since abnormalities of response inhibition and dopamine have been thought to underlie tics and other symptoms of Tourette syndrome, we studied 8 neuroleptic-naive adults with tic disorders as well as 10 well-matched healthy controls. Subjects were pretreated with the peripheral decarboxylase inhibitor carbidopa, then scanned during GNG and control blocks, both before and during i.v. levodopa infusion. Both groups had similar task performance and task-related regional brain activity before and during levodopa infusion. Levodopa did not affect reaction times or accuracy, so fMRI findings can be interpreted without concern that they simply reflect a performance difference between conditions. Levodopa did affect the magnitude of GNG-related fMRI responses in the right cerebellum and right parietal cortex, significantly reducing both. Pre-levodopa activity in the right cerebellum correlated with reaction times (higher magnitudes associated with faster reaction times), and pre-levodopa activity in the right parietal cortex correlated with false alarm rate (higher magnitudes associated with higher error). In summary, right parietal and cerebellar regions important in mediating specific aspects of the GNG task were modulated by levodopa, suggesting a region-specific role for dopamine in response inhibition.

Theme: Neural basis of behavior
Topic: Cognition

Keywords: Tourette syndrome; Chronic multiple motor tic disorder; Levodopa; fMRI; Dopamine; Inhibition (psychology); Cerebellum; Parietal cortex; Reaction time

1. Introduction

Response inhibition has been defined as the inhibition of contextually inappropriate, prepotent behavior [18,54]. Response inhibition may be mediated in part by the basal ganglia and its connections to frontal cortex [54], including anterior cingulate, dorso- and ventrolateral prefrontal cortex, and temporal and inferior parietal cortex [5,17]. Since dopamine clearly influences these circuits, it has been hypothesized to be involved in the regulation of response inhibition [54]. The cognitive neuroscience of response inhibition is an area of great interest [5,17,18], but the relationships between dopamine, response inhibition, and functional neuroanatomy are poorly understood.

People with tic disorders (TD) such as Tourette's syndrome and chronic multiple motor tic disorder comprise a clinical population thought to have faulty response inhibition. These disorders are characterized by nearly irresistible urges that culminate in movements and vocalizations, known as tics. Tics begin in childhood and can extend throughout life [8,45]. The frequency and character of tics can change dramatically over the course of days and months

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and can be influenced by environmental and internal factors (e.g. stress) [8,45]. Response inhibition deficits may explain tics and other symptoms associated with TD including compulsions, impulsivity, and complex socially inappropriate behavior [43,54]. Furthermore, obsessive-compulsive disorder (OCD) and attention deficit hyperactivity disorder (ADHD) are commonly comorbid with TD, and response inhibition is a major feature of these disorders as well [22,54,58]. Available behavioral studies of response inhibition in TD demonstrate mixed results. Baron-Cohen et al. [6] found that children with TS were greatly impaired on tests of verbal response inhibition and motor response set shifting. In addition, Straube et al. [70] reported that adults with TS were impaired on antisaccade and saccade sequence tasks. However, Ozonoff et al. [57] did not find any deficits on a go/no-go (GNG) response inhibition task in TS children. Unfortunately, some of these studies were confounded by medication (e.g. past or present use of anti-dopaminergic agents) or by comorbidity.

Another clinically motivated hypothesis about tic pathophysiology is based on the observation that dopamine D2 receptor antagonists and, paradoxically, some dopamine agonists can reduce tic severity [3,4,9,31,32,68]. These clinical observations support a model of tic pathophysiology that hypothesizes abnormal dopaminergic regulation of the basal ganglia and its projections to frontal cortex [54]. Efforts to clarify a dopaminergic abnormality underlying tics have not yet provided a coherent explanation of dopamine's role in regulating tics [4,61,62].

This study was designed to investigate whether dopamine alters either behavioral or brain responses to a response inhibition task and whether these responses are different in TD compared to normals. We used fMRI to measure brain responses to a well-described response inhibition task, GNG, before and during levodopa infusion in normals and those with TD. Pharmacologic and cognitive challenges have not previously been combined in neuroimaging studies of TD, but have been useful in neuroimaging studies of other dopamine-related disorders such as schizophrenia [26,29], Parkinson's disease [25,49], and ADHD [73].

We chose levodopa as a challenge agent for several reasons. First, levodopa is well tolerated in normal individuals and in TD [9,16], whereas dopamine antagonists such as haloperidol often cause akathisia or other distressing motor side effects. Second, when dopamine production outside the brain is adequately inhibited by a peripheral decarboxylase inhibitor like carbidopa, levodopa does not alter global cerebral blood flow [34,36,38]. This characteristic allows us to use qualitative measurements of blood flow such as blood oxygenation level-dependent (BOLD) signal in fMRI to determine the impact of levodopa on brain activity without misrepresenting an absolute change in local flow or neuronal activity [10,15,27]. Local blood flow (and BOLD signal) responses to behavioral or dopaminergic challenges primarily reflect changes in axonal terminal fields or local interneurons [33,44,47,52,67]. 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 normal or disease states [13,34,35,42,46,53,55,56,59].

In this study, we combined dopaminergic activation (infusion of the dopamine prodrug, levodopa, in the presence of carbidopa), a response inhibition task, and BOLD fMRI measures to test the hypothesis that dopaminergic stimulation would affect the neurophysiological substrates of response inhibition, and that these effects would differ in TD.

2. Methods

2.1. Subjects

We recruited individuals with a tic disorder (TD group) and individually matched controls. All subjects were screened carefully for psychiatric [39], neurological, or other medical illness by a movement disorders specialist and psychiatrist. Tic disorders were diagnosed by DSM-IV and Tourette Syndrome Study Group (TSSG) criteria [2,72]. Subjects with tics were included if they had one or more otherwise unexplained vocal or motor tic which occurred many times a day for longer than 1 year, without 3 months tic-free, and if symptoms began before age 18. Some subjects had a definite tic diagnosis by TSSG criteria but had no diagnosis by DSM-IV criteria (see Table 1). In these subjects, this was solely because they had no occupational or social impairment or "marked" distress. The judgment of "marked" distress is subjective, and all but one subject (#8) were bothered by their symptoms and had sought medical advice.

We retrospectively assigned Diagnostic Confidence Index (DCI) scores to each subject with tics (see Table 1). The DCI, which was published after this study began [63], is a clinician-rated scale intended to quantify diagnostic certainty for TD 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). DCI ratings were performed blind to imaging results.

Control subjects were matched for age, sex, handedness, and educational attainment. TD subjects were excluded for comorbid neurological or psychiatric illness except attention deficit hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD), learning disabilities, or adjustment disorder. Controls were excluded for neurological or psychiatric illness including ADHD and OCD. Subjects also were excluded for any history of neuroleptic treatment. Subjects on other psychoactive medications (e.g. Sinemet)

Table 1
TD subjects' demographic and clinical information

TD subject	Sex	Age	TSSG diagnosis	DSM-IV tic diagnosis	DCI score	OCD	ADHD	Self Y-BOCS current	Self Y-BOCS worst ever	Self-rated recent tic severity	Psychoactive medications at time of study
1	M	56	DTS	TD	58	yes	no	8	[a]	21	Sinemet[b], Lodosyn[b]
2	M	21	DTS	TD	61	no	yes	0	0	13	Imipramine[b]
3	M	43	DTS	TD	83	no	yes	0	0	19	none
4	F	36	DTS	None	45	no	no	0	0	20	none
5	F	32	DTS	TD	74	yes	yes	5	7	11	none
6	M	19	CMMTD	None	41	no	no	0	0	7	none
7	M	23	DTS	None	47	no	no	0	4	12	none
8	M	51	CMMTD	None	33	no	yes	3	3	11	none
Mean (SD)		35.5 (13.5)			55.3 (17.0)			2.0 (3.1)	2.0 (2.7)	14.3 (5.1)	

M=male; F=female; TSSG=Tourette Syndrome Study Group; DTS=Definite Tourette Syndrome; CMMTD=Definite Chronic Multiple Motor Tic Disorder; DSM-IV=Diagnostic Statistical Manual, 4th Edition; TD=Tourette's Disorder; OCD=obsessive-compulsive disorder; ADHD=attention deficit hyperactivity disorder; Y-BOCS=Yale-Brown Obsessive Compulsive Scale; YGTSS=Yale Global Tic Severity Scale.

[a] Subject did not complete.

[b] Discontinued 12 h prior to study.

discontinued treatment the evening prior to the start of our study.

2.2. Protocol

Subjects fasted and avoided caffeine for at least 8 h prior to their scheduled scan. Subjects were pretreated with 200 mg oral carbidopa, given at least 2 h before levodopa infusion [16,38]. TD subjects also completed a detailed self-report of lifetime symptoms and treatment [65]. Symptom severity, both "worst ever" and for the week prior to the scan, were rated using self-rated versions of the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) and the modified Yale Global Tic Severity Scale (self-rated recent tic severity; tic ratings only, for current week, maximum score 50) [65]. Finally, before and after the fMRI scan, TD subjects indicated on a 100-mm visual analogue scale the severity of their tics and their obsessive-compulsive symptoms "at this exact moment." The scales were demarcated on the left with the words "no tics" or "no O/C" and on the right with "severe tics" or "severe O/C." Subjects placed a mark on the line in between the two extremes to indicate current severity. The placement of this mark was then measured in millimeters.

Each subject with tics was also 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, as previously described [9]. 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-s period was used to count tics below the shoulders (full body view) and all other tics (head-and-shoulder view). Vocal tics, eye or eyebrow tics, other face and shoulder tics, and body tics below the shoulders were counted separately, but we analyzed only vocal tics per minute and motor tics (the sum of all other tics) per minute, as before [9]. All ratings were done after this study ended and independently of the clinical diagnosis. Prescan and postscan videotape segments were viewed in randomized order by a rater who was not told the correct order and was blind to imaging results. To test adequacy of blinding for scan order, the videotape rater recorded for each segment a guess as to its timing (prescan, postscan, or unknown) and confidence (unsure, confident). Due to unplanned cues in the videotape segments (e.g. antecubital band-aid visible after the scans), the rater was confident in guessing one pre- and two postscan segments and was correct in each of these three cases. Overall, of true prescan segments, the rater guessed five as prescan, one as postscan, and two as unknown. Of true postscan segments, he guessed three as postscan and five as unknown.

Plastic intravenous catheters were placed in each arm for levodopa infusion and for blood sampling. The subjects were then taken to the MRI suite and had baseline imaging studies and then imaging after intravenous loading of levodopa, as described in subsequent paragraphs. After the scans were completed, all subjects were asked if they had noticed side effects, including nausea, sleepiness, or lightheadedness. They were asked if they had difficulty with any of the cognitive tasks, whether they thought they may have fallen asleep during any of the scans, and whether they were uncomfortable during any of the scans. Tic patients were asked whether they noticed any changes in tics or OCD symptoms and completed the VAS ratings for TD and OCD symptom severity. Lastly, TD subjects were videotaped again.

The scanning protocol included anatomical images, followed by functional images during two cognitive tasks: a GNG task and a verbal working memory task (two-back letter; [37]) at baseline and again during a levodopa infusion. Details of this protocol are as follows.

2.2.1. Levodopa infusion

We chose a dose of levodopa known to be biologically active (e.g. antiparkinsonian effects in Parkinson disease patients) and an administration method designed to hold levodopa levels at a relatively consistent level during on-levodopa scanning [16]. An intravenous loading dose of levodopa, followed by a slower maintenance infusion, rapidly achieved and maintained a clinically relevant concentration of levodopa, with doses adjusted for age and body mass [16]. Levodopa was infused using a programmable infusion pump (Model 44, Harvard Apparatus, Holliston, MA) in an RF-shielded box. During a typical study, a 35-year-old, 70-kg volunteer would receive an intravenous levodopa dose bioequivalent to ~150 mg oral levodopa [16]. The second set of cognitive scans started at least 25 min after the end of the loading dose. Blood samples for later levodopa and carbidopa plasma level measurements were taken just after each on-levodopa cognitive scan through a second venous catheter, previously placed distal or contralateral to the infusion site.

2.2.2. Levodopa measurements

We measured levodopa and carbidopa plasma levels with high-performance liquid chromatography and electrochemical detection according to published methods [7,19].

2.2.3. Go/no-go (GNG) task

We chose a validated measure of inhibitory function, the GNG task. This task has been well characterized in fMRI studies, and an understanding of its component processes and their neural basis has developed [5,17,21]. The task required subjects to monitor a visual display while single uppercase letters are presented one at a time (250-ms duration, 1000-ms intertrial interval) on a black background. Participants were instructed to push a response button as quickly as possible at the occurrence of every letter except the letter X. Non-X's occurred 83% of the time, requiring a button press, and X's occurred for the remainder (17%), requiring the withholding of a response [17].

2.2.4. fMRI methods

MRI 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 MPRAGE and T2-weighted anatomical images. The MPRAGE consisted of a 3D T1-weighted sequence with 1.25-mm^3 voxels. Functional images were collected using an asymmetric spin-echo echo-planar sequence sensitive to blood oxygenation level-dependent (BOLD) contrast (T2*) (TR=2500 ms, TE=50 ms, FOV=24 cm, flip=90°). During each functional run, 102 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 [24].

Two scans were performed during the GNG task approximately 6 min apart at baseline and again during the levodopa maintenance infusion, at least 25 min after the end of the levodopa loading dose. Each scan consisted of seven blocks, with four task blocks and three fixation blocks in alternating order. Task blocks lasted 40 s and fixation blocks lasted 25 s. During fixation blocks, subjects were told to fixate on a cross-hair presented in the center of the screen. Visual stimuli were generated by an Apple PowerMac and PsyScope [48] and projected to subjects onto a screen placed at the head end of the bore. Subjects viewed the screen through a mirror. A fiber-optic, light-sensitive key press interfaced with a PsyScope Button box was used to record subject's accuracy and reaction times.

2.2.5. fMRI preprocessing

Movement correction was applied to all frames in all runs of the functional images using a rigid-body rotation and translation correction [69]. These images were normalized across runs by scaling the whole-brain modal signal intensity to 1000. Functional images were transformed into atlas space [71] and resampled into 3-mm isotropic voxels using the T2 and MPRAGE images and a validated method [14]. Scans were smoothed with a 6-mm Gaussian filter.

2.2.6. fMRI analysis

The preprocessed functional images were analyzed in a manner designed to examine regions of GNG activation that are altered by group, drug condition, or both, in a manner that protects the results from Type I error and is unbiased towards any single condition. The first step in this strategy was to determine the task effect (GNG vs. fixation) at each voxel within each run. We estimated the magnitude of the BOLD signal at each voxel within each run using a general linear model (GLM) that included terms for task and fixation blocks (corrected for assumed hemodynamic response delay), linear trends, intercepts, and a high pass filter.

Next, we determined the statistically significant clusters of task-related (GNG vs. fixation) activation across the entire brain, collapsed across drug condition and group. By considering all task data, regardless of drug condition (baseline vs. levodopa) or group (TD vs. control), we avoided biasing the selection of task-related regions of interest (to be used in further analyses) towards any one group or drug condition [41]. To identify these regions of task-related activation, we used a voxel-wise three-way ANOVA with task (GNG vs. fixation), drug condition (baseline vs. levodopa), and group (TD vs. C) as factors. However, in this analysis, 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 0.05 level using a method, validated by Monte Carlo

Table 2
Number of subjects in each group reporting side effects following levodopa infusion

Side effect	TD (n=8)	Control (n=10)
Any	5	8
Nausea	1	4
Sedation	4	5
Dizziness	0	1
Miscellaneous	5	5

simulation [50], that sets the number of contiguous voxels that exceed a specified magnitude threshold to achieve a p-value of <0.05. For this analysis, we used a z threshold of 4.25 which requires a cluster threshold of eight voxels to achieve a corrected p<0.05. Clusters of task-related activation that survived this correction were identified as regions of interest.

To help protect against Type I error, we next performed an omnibus four-way ANOVA on these multiple-comparison correction-generated task-related regions, with region, task (task vs. fixation), drug condition (baseline vs. levodopa), and group (TD vs. controls) as factors. Significant interactions involving region were then followed up with ANOVAs on each region to determine which of them were responsible for driving the interaction from the omnibus ANOVA. For illustration and correlational purposes, we obtained the average task-related signal change for each region with significant effects on a subject-by-subject basis. This task-related signal change could then be correlated with levodopa levels, task behavior, and clinical ratings.

3. Results

We scanned 11 TD patients and 12 controls. Three TD patients and two controls did not complete all their scans due to discomfort or claustrophobia. Thus, we analyzed complete data from 8 TD and 10 control subjects and all subsequent analyses describe these subjects. Mean age in these analyzed groups was 35.5 years (SD=13.5 for TD and 12.4 for controls) and mean education was 14.1 years in each group (SD=1.4 for TD and 1.2 for controls). One subject in each group was left-handed. See Table 1 for additional diagnostic information for the TD subjects.

3.1. Levodopa and carbidopa plasma levels

We were unable to withdraw adequate blood samples from two of the TD subjects' and one of the control subject's i.v.s. However, we did obtain adequate samples from 15 of the 18 subjects (6 TD, 9 C) and were able to measure levodopa and carbidopa plasma concentrations in these samples. In these subjects, levodopa concentrations peaked near the end of the loading dose of levodopa and then stabilized approximately 30 min later [16]. Furthermore, mean levodopa levels remained above levels known to have an antiparkinsonian effect [23] during collection of the on-levodopa fMRI scans. There were no significant differences between groups in levodopa levels at the time of the post-levodopa scans (TD mean=502.8 ng/ml, SD=79.8; C mean=494.8 ng/ml, SD=73.1). Carbidopa concentrations remained stable across the study and were not different between groups (TD mean=505.1 ng/ml, SD=208.5; C mean=474.9 ng/ml, SD=181.9).

3.2. Tics and other behavior

Side effects of levodopa were mild and were reported at similar rates across the two groups (Fisher's Exact Test, p-values 0.31 and above) (see Table 2). Pre- and post-levodopa self-ratings (visual analogue scales) and total motor and vocal tic counts from videotapes were compared using Wilcoxon Signed Ranks tests (Table 3). 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 0.11 and above). Of the eight subjects with TD, none reported that tics worsened with levodopa, whereas one reported that tics improved with levodopa.

3.3. GNG task performance

No significant main effects of drug condition (baseline vs. levodopa) or group, or interactions between the two

Table 3
Pre- and post-levodopa tic counts and visual analogue scale (VAS) results for tics and obsessive-compulsive symptoms (OCD)

TD subjects	Premotor tic count	Postmotor tic count	Prevocal tic count	Postvocal 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)

There were no statistically significant changes across condition for any variable.

Table 4
Mean (SD) GNG task performance for each group and each condition

Mean (SD) proportion correct	Baseline		Levodopa	
	TD	Control	TD	Control
No-Go Trials	0.81 (0.14)	0.81 (0.20)	0.78 (0.20)	0.84 (0.13)
Go Trials	1.00 (0.01)	1.00 (0.004)	0.99 (0.01)	1.0 (0.01)
Discriminability index (d')	3.5 (0.6)	3.6 (0.8)	3.4 (0.8)	3.6 (0.5)

Performance on No-Go trials was significantly worse than Go trials ($p<0.05$), but no other comparisons were significantly different.

variables, were found on response accuracy or median reaction time. There was an effect of trial type (Go vs. No-Go) on accuracy [$F(1,15)=20.2$, $p<0.001$], such that overall subjects were more accurate on Go trials (pressing for letters other than X's) than No-Go trials (withholding a response for X's; errors are false alarms). In addition, reaction time and false alarm rate correlated well ($rs=-0.90$, $p<0.001$), suggesting that at baseline, the faster subjects respond to targets, the more likely they are to fail to inhibit a response to a nontarget. Furthermore, there were no significant main effects of drug condition (baseline vs. levodopa) or group or interactions between the two variables on a measure of discriminability (d' ; p's>0.30) (Table 4).

3.4. Cognitive correlates of levodopa concentration

There were no significant correlations between level of plasma levodopa achieved during the on-levodopa BOLD scans and change in accuracy or reaction time between baseline and on-levodopa scans.

3.5. fMRI

Fifteen separable regions reflecting a significant task effect (GNG vs. fixation) were identified (colored regions, Fig. 1). We then performed an omnibus ANOVA with region, task, drug condition, and group as factors. This ANOVA revealed a significant three-way interaction for region by task by drug condition [$F(14, 224)=3.91$, $p<0.001$]; that is, the levodopa modulation of GNG-related BOLD signal differed significantly across regions. No interactions with group (TD vs. control) as a factor were significant.

3.6. fMRI: GNG×drug interaction

Examination of the data on a subject level revealed one outlier in the TD group whose baseline task activation data were greater than 3 SDs away from the mean for all regions. This individual, for unknown reasons, had no task activation in any condition or regions. After removing this individual from consideration, we performed three-way ANOVAs on each region separately, looking for significant drug condition by task interactions. We found two regions with a significant effect of drug condition on task activation. Table 5 lists each region's anatomical description, Talairach coordinates, and ANOVA results. Drug condition affected the magnitude of GNG activation in the right cerebellum [$F(1,15)=9.53$, $p=0.008$] and right parietal cortex [$F(1,15)=9.57$, $p=0.007$]. At baseline, BOLD signal in these regions increased during the GNG task. On levodopa, this increase was attenuated for both groups (see Fig. 1A and B for the locations of these regions; see Fig. 2A and B for change in task effect with levodopa).

3.6.1. Levodopa level correlates

There were no significant correlations between levodopa plasma concentration and percent signal change in either region.

3.6.2. Task performance correlates

Change in GNG task effect in these two regions did not correlate with change in performance across drug condi-

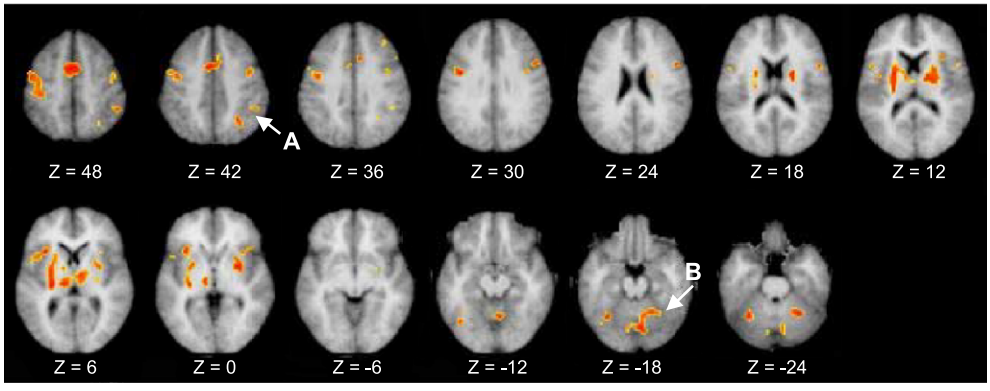

Fig. 1. Multiple-comparison corrected statistical map of GNG task effect. Colored regions shown consist of eight or more contiguous voxels with z scores of 4.25 or greater and are overlaid on a composite MRI in atlas space. Labeled regions are those that behaved differently across the variables of task (GNG vs. fixation) and drug status (baseline vs. on levodopa) in subsequent analyses. (A) Right parietal cortex; (B) right cerebellar region. See Table 5 for additional anatomical information.

Table 5
Anatomical description and *x*,*y*,*z* coordinates [71] for regions of GNG task activation tested for drug condition by task interactions

Region name	Center of magnitude	Peak magnitude	ANOVA condition × task	
			F	*p*
Right parietal	28 −57 42 right parietal, BA 7	26 −54 42 right parietal, BA 7	9.57	0.007
Right cerebellum	14 −63 −21 right cerebellum, posterior lobe	8 −72 −18 right cerebellum, posterior lobe	9.53	0.008
Left cerebellum	−32 −60 −21 left cerebellum, posterior lobe	−31 −60 −21 left cerebellum, posterior lobe	2.96	0.106
Left temporal	−38 −54 −15 left temporal lobe	−37 −54 −15 left cerebellum, posterior lobe	3.24	0.092
Left thalamus	−4 −9 9 left thalamus, medial dorsal nucleus	−25 −24 3 left thalamus, extranuclear	0.21	0.657
Left insula	−38 9 6 left insula, BA 13	−31 15 3 left insula	0.53	0.476
Right insula	34 15 3 right insula	32 15 12 right insula, BA 13	0.31	0.588
Left insula 2	−40 −6 9 left insula	−40 −6 12 left insula, BA 13	0.38	0.549
Right frontal	50 9 24 right inferior frontal	50 15 33 right inferior frontal	0.72	0.411
Right frontal 2	40 −3 42 right precentral gyrus	41 0 42 right precentral gyrus, BA 6	0.03	0.860
Left frontal	−40 −15 48 left precentral gyrus	−37 −27 54 left postcentral gyrus	0.03	0.865
Right frontal 3	34 33 36 right middle frontal gyrus	35 30 33 right middle frontal gyrus	0.06	0.806
Midline frontal	−2 3 51 left medial frontal gyrus	8 15 36 right cingulate gyrus	2.86	0.111
Right parietal 2	46 −42 45 right inferior parietal, BA 40	53 −42 48 right inferior parietal, BA 40	2.60	0.128
Left frontal 2	−26 −9 60 left middle frontal gyrus, BA 6	−25 −9 60 left middle frontal gyrus, BA 6	4.13	0.060

One outlier subject was removed from all analyses.

tions. However, the baseline GNG task effect in the right parietal region correlated significantly with baseline false alarm rate (incorrectly hitting the button for a no-go trial; r=0.48, p=0.05; see Fig. 3A), such that higher magnitudes were related to higher false alarm rates. In addition, the baseline GNG task effect in the right cerebellum correlated significantly with baseline reaction times (r=−0.65, p=0.007; see Fig. 3B), such that higher magnitudes were related to faster reaction times. A measure of discriminability, d', did not correlate significantly with the GNG task effect in either region.

4. Discussion

Levodopa infusion significantly affected regional BOLD responses to a GNG task in 2 of 15 GNG task-related regions: right parietal cortex and right cerebellum. In these regions, task activation at baseline was associated differentially with reaction time and false alarm rates at baseline. Higher task activation in the right cerebellar region was related to faster reaction times, whereas higher task activation in the right parietal region was related to higher false alarm rates. In these task-related regions, levodopa significantly reduced the BOLD response to the GNG task even though it did not appreciably affect task performance. One advantage of this pattern of findings is that it allows us to interpret levodopa's effects on task-related brain activation without being hampered by the confound of behavioral differences across drug conditions; a similar rationale has been used by others [66]. TD and control groups also had similar task performance and brain activation.

The pattern of GNG task-related BOLD responses observed in this study is very similar to previously published results [5,17,20]. In addition, both of the levodopa-modulated regions identified by our study are reliably activated by GNG tasks. The parietal cortex is consistently activated by GNG or other similar response inhibition tasks [17,18,30,64] and is more commonly activated in the right hemisphere, leading in part to hypotheses about right hemisphere dominance for response inhibition [17,30]. In one previous study, task-related BOLD response in the right inferior parietal cortex was associated with response speed [30]. However, we found a relationship between task-related BOLD response in right parietal cortex and false alarm rate at baseline. Others have hypothesized that the parietal cortex

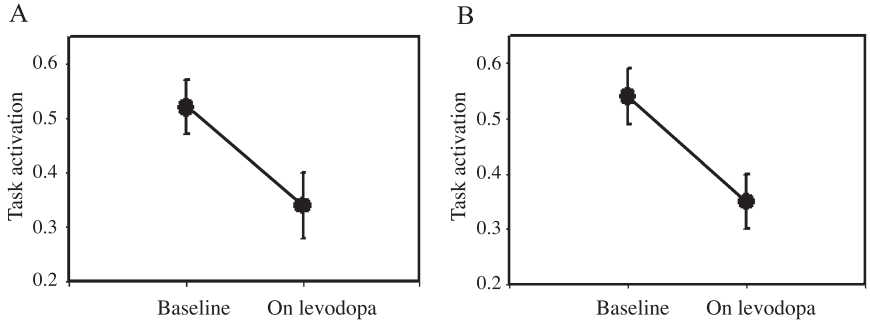

Fig. 2. Mean (±S.E.M.) GNG task-related activation at baseline and during i.v. levodopa infusion in (A) right parietal cortex and (B) right cerebellum. Both regions had a significant condition by task interaction (p<0.05).

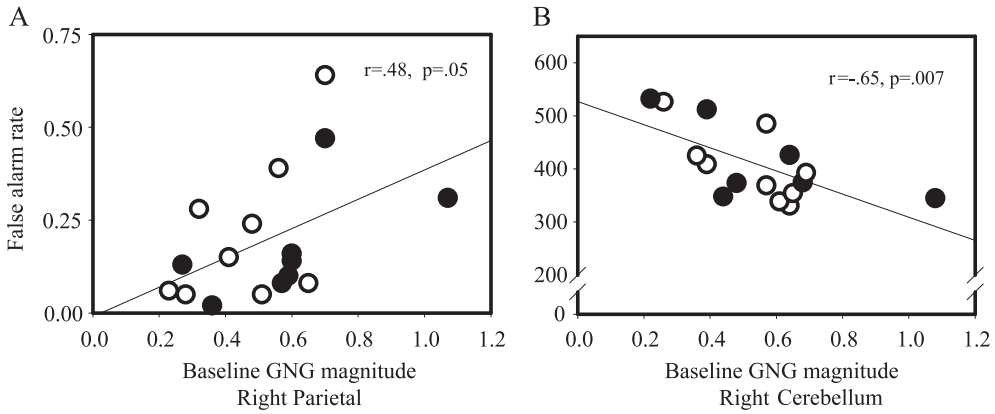

Fig. 3. Behavioral correlates of baseline GNG activation in regions with significant interactions between condition and task. (A) Baseline task activation in right parietal cortex correlated significantly with false alarm rate ($p<0.05$) and (B) baseline task activation in the right cerebellum correlated significantly with reaction time ($p<0.05$). Black circles are subjects from the TD group and white circles are subjects from the control group; however, no group differences were seen.

may play a role in regulating attention or withholding the motor response during response inhibition tasks [17,30]. Our finding could indicate that parietal overactivity is either an underlying cause of poor inhibition or a response to failures of inhibition (e.g. increased attention or error monitoring following false alarms). A few studies have noted cerebellar activation during response inhibition tasks, one on the left [17] and one on the right [18], but there are no prevailing hypotheses concerning its role in response inhibition. Our finding that greater cerebellar activation is correlated with faster reaction times in the GNG task is novel.

Parietal cortex and cerebellum do not have large concentrations of dopamine receptors. However, they receive input from brain regions with more obvious dopamine influences, and their activity changes in response to systemic administration of dopaminergic agonists. Parietal cortex is closely associated anatomically with regions such as lateral prefrontal cortex that receive input from the internal segment of the globus pallidus via thalamic nuclei [1,28]. In addition, resting blood flow in the posterior temporal/parietal region is affected by a dopamine challenge. Levodopa decreased rCBF in Parkinson's disease patients and normal controls [38], and, in a nonhuman primate model, inferior parietal regions showed decreased rCBF after acute doses of D1- or D3-preferring dopamine agonists [12,15]. The cerebellum has few dopamine receptors, but it has long been known to change its metabolic activity after a dopaminergic challenge [11,51]. Additionally, the cerebellum receives minor dopaminergic innervation from the ventral tegmental area [40]. Thus, anatomical and functional studies support the validity of *downstream* effects of levodopa for both regions. However, our study cannot confirm the specific anatomical pathways through which dopamine may modulate the BOLD response to the GNG task.

The absence of group differences in task performance, task activation, or response to levodopa was unexpected given prior studies in TD. The absence of group differences in this pilot study could of course reflect low power with small samples. This problem would be remedied with a larger, more diverse sample of TD subjects. Subjects were carefully screened for previous neuroleptic exposure, which eliminated potential confounds, but also likely excluded severely affected individuals. Thus, we cannot comment on brain function in people with more severe TD who may also be more likely to perform poorly on the GNG task (and who are also more likely to have used neuroleptics). Second, the task employed here has several virtues as a model of inhibitory processes, yet its simplicity may remove it too far from the complex symptoms of TD: inhibition of a prepotent button press response may differ in important ways from inhibition of an urge to yell or to touch someone. Third, comorbid ADHD may affect performance or brain activation, and we did not quantify ADHD severity. However, in our sample, there were no differences at baseline or with levodopa on GNG performance (Mann–Whitney *U*-tests, p's>0.40; although note that these are very small sample sizes). Finally, it may be that response inhibitions, or dopaminergic modulation of response inhibition, are not critical features of TD, at least in neuroleptic-naive adults with normal GNG performance.

Alternative explanations for these results include effects of time or practice, placebo effects, or changes in tic frequency during scanning. Although these factors cannot be entirely excluded, our data suggest that they may not have an important impact in this study. For example, task performance did not change across time, suggesting that subjects did not benefit significantly from practice. In addition, tic frequency did not change substantially or consistently across TD subjects with levodopa, and tic suppression (which might occur preferentially during task blocks) was not reported to affect right cerebellar or right parietal BOLD signal [60]. Both of these observations also argue against an important placebo effect. However, it would be useful to include a saline infusion control condi-

tion and improve tic monitoring during scanning in future studies. Event-related paradigms may also be helpful in decomposing GNG performance to determine if trials that require inhibitory control (no-go) are differentially affected by levodopa challenge or diagnosis.

In summary, this study demonstrates that there is dopaminergic modulation of specific regions involved in response inhibition performance. The precise function of this dopaminergic modulation in shaping response inhibition performance remains to be determined. This study illustrates how the combination of pharmacological and cognitive activation techniques can test hypotheses about the neurotransmitter systems, pathways, or regions mediating cognitive and motor symptoms of TD and other disorders.

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