Neurobiology of Disease

Dopaminergic Suppression of Brain Deactivation Responses during Sequence Learning

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Cognitive processing is associated with deactivation of the default mode network. The presence of dopaminoceptive neurons in proximity to the medial prefrontal node of this network suggests that this neurotransmitter may modulate deactivation in this region. We therefore used positron emission tomography to measure cerebral blood flow in 15 Parkinson's disease (PD) patients while they performed a motor sequence learning task and a simple movement task. Scanning was conducted before and during intravenous levodopa infusion; the pace and extent of movement was controlled across tasks and treatment conditions. In normal and unmedicated PD patients, learning-related deactivation was present in the ventromedial prefrontal cortex ($p < 0.001$). This response was absent in the treated condition. Treatment-mediated changes in deactivation correlated with baseline performance ($p < 0.002$) and with the $val^{158}met$ catechol-O-methyltransferase genotype. Our findings suggest that dopamine can influence prefrontal deactivation during learning, and that these changes are linked to baseline performance and genotype.

Key words: levodopa; Parkinson's disease; sequence learning; deactivation; default mode network; *COMT* genotype

Introduction

Motor sequence learning has been used increasingly to investigate the neural basis of skill acquisition in health and neurological disease. Functional imaging studies have revealed that this cognitive process is associated with a distinct activation pattern involving prefrontal, premotor, and posterior parietal cortical regions, as well as the basal ganglia (Nakamura et al., 2001; Carbon et al., 2003; Doyon, 2008). Like many goal-directed behaviors, motor sequence learning is also associated with deactivation in brain regions with pronounced metabolic activity in the rest state (Tamás Kincses et al., 2008). These areas, which include the medial prefrontal and parietal association regions, as well as the posterior cingulate cortex, comprise the default mode network (Raichle et al., 2001; Greicius et al., 2003). This spatially distributed neural system is thought to facilitate cognitive performance by reallocating neural resources to critical brain regions. Interestingly, the medial prefrontal node of this network receives input from the anterior cingulate area (Bates and Goldman-Rakic, 1993; Picard and Strick, 1996), a major locus of dopaminergic input to the cerebral cortex (Crino et al., 1993). L-Aromatic amino acid decarboxylase (AADC) is normally expressed in this brain area (Brown et al., 1999), and its expression is elevated in

early stage Parkinson's disease (PD) patients (Rakshi et al., 1999; Kaasinen et al., 2000; Brück et al., 2005). Thus, levodopa can be decarboxylated and retained in dopaminergic terminals in this region.

We have found previously that levodopa can alter motor sequence learning performance and concurrent cortical activation responses in PD (Carbon et al., 2003; Feigin et al., 2003). We therefore investigated the possibility that this medication can influence task performance by dopaminergically modulating the medial prefrontal deactivation response. Positron emission tomography (PET) was used to measure cerebral blood flow (CBF) in PD patients while they performed a motor sequence learning task (SEQ) and a kinematically matched motor reference task. Scanning was conducted in an unmedicated baseline condition and repeated during intravenous levodopa infusion. In addition to assessing the effect of drug on learning-related deactivation, we determined how this response varied across subjects with differing baseline performance (Gibbs and D'Esposito, 2005; Cools et al., 2007). We also examined the relationship of intrinsic differences in prefrontal dopamine levels to local deactivation responses in both treatment conditions. This was achieved by correlating learning performance and associated neural responses with genotypic differences in the catechol-O-methyltransferase (*COMT*) $val^{158}met$ polymorphism, which regulates dopamine metabolism in this brain region (Akil et al., 2003; Meyer-Lindenberg et al., 2005).

Materials and Methods

Subjects

We studied 15 right-handed PD patients [12 men and 3 women; age, 58.1 ± 7.5 years (mean ± SD)]. The patients were chronically treated

Table 1. Subject characteristics

	Age (years)	Hoehn-Yahr stage	UPDRS (motor)[a]		Onset time (ms)		Movement time (ms)		Retrieval index	
			OFF	ON	OFF	ON	OFF	ON	OFF	ON
PD	58.1 (±7.5)	2.3 (±0.7)	25.1 (±7.5)	16.3 (±5.2)	−568 (±223)	−595 (±220)	592 (±132)	516 (±109)	11.9 (±7.3)	11.5 (±9.4)
Performance subgroups[b]										
Good	59.9 (±8.6)	2.6 (±0.4)	22.9 (±6.3)	16.4 (±5.9)	−554 (±154)	−630 (±186)	595 (±195)	514 (±113)	20.7 (±3.5)	11.3 (±10.8)
Bad	55.2 (±4.1)	2.0 (±0.6)	25.0 (±5.7)	16.2 (±3.4)	−478 (±323)	−583 (±265)	536 (±87)	517 (±113)	6.3 (±2.3)	14.1 (±9.7)
Genotypic subgroups[c]										
VAL	54.1 (±7.9)	2.1 (±0.8)	20.9 (±3.9)	12.3 (±2.5)	−563 (±343)	−663 (±218)	593 (±87)	548 (±77)	10.9 (±6.5)	15.4 (±12.2)
MET	53.6 (±2.6)	1.9 (±0.6)	23.6 (±6.1)	15.0 (±3.1)	−560 (±196)	−663 (±286)	534 (±84)	505 (±109)	6.9 (±3.1)	11.7 (±11.0)

Data are shown as mean (± SD).

[a]UPDRS items 19 –31.

[b]Defined based on the distribution of baseline retrieval index (RET$_{OFF}$) values (see Materials and Methods).

[c]Defined by *COMT val^{158}met* haplotype (see Materials and Methods).

with oral levodopa/carbidopa, either alone or in combination with do-pamine agonists. The demographic features of these patients are summa-rized in Table 1. All subjects were scanned with H$_2$ ^{15}O PET, in an off state (OFF), defined as 12 h after the cessation of medication, and again in a stable on state (ON) during an intravenous levodopa infusion. The de-tails of the experimental design and the infusion protocol have been described previously (Feigin et al., 2003; Hirano et al., 2008). Antipar-kinsonian medications were withheld for at least 12 h before each PET session. The patients were rated according to the motor portion of the Unified Parkinson's Disease Rating Scale (UPDRS; items 19–31) in the baseline OFF state and subsequently every 30 min during the levodopa infusion. Levodopa infusion rates were individually adjusted to achieve maximal improvement in motor ratings in a stable ON state without dyskinesia. The imaging experiments in the ON state were conducted in a steady state defined by ≤5% variation in motor ratings, and plasma levodopa levels recorded every 30 min. In this cohort, levodopa infusion (mean rate, 0.83 ± 0.76 mg/kg/hr; mean ON state plasma levodopa level, 13.94 ± 8.1 μg/ml) resulted in a stable improvement in UPDRS motor ratings (mean, −34 ± 12%; $p < 0.001$). Nine right-handed healthy vol-unteer subjects (five men and four women; age, 55.9 ± 10.8 years) served as controls for the imaging studies.

The participants were nondemented and nondepressed with neuro-psychological testing compatible with early/moderate PD (Asanuma et al., 2006). In the baseline OFF state, their scores were as follows: esti-mated intelligence quotient, 118 ± 13; Beck Depression Inventory, 5 ± 3; Brief Test of Attention, 7 ± 2; Hopkins Verbal Learning Test, 20 ± 5; delayed recall, 5 ± 2; symbol digit, 36 ± 8; word fluency, 44 ± 14. There was no visual evidence of atrophy or other structural brain abnormalities on magnetic resonance imaging (MRI). Ethical permission for all studies was obtained from the Institutional Review Board of North Shore Uni-versity Hospital. Written consent was obtained from each subject after detailed explanation of the procedures.

Behavioral testing
Tasks. In each treatment condition, subjects performed two motor tasks during PET imaging: an SEQ and a kinematically matched motor execu-tion control task (CCW) in which subjects moved to targets in a known counterclockwise order. The characteristics of these tasks have been described in detail previously (Nakamura et al., 2001; Ghilardi et al., 2003). Representative clips of the tasks can be viewed at http://feinsteinneuroscience.org/video/.

In performing both tasks, subjects moved a cursor on a digitizing tablet with the dominant right hand. Movements were out and back from a central starting position to one of eight radial targets displayed on the screen. In SEQ, the eight targets appeared in an unknown, pseudoran-dom order without repeating elements that was repeated over the 90 s trial block. Subjects were informed that a sequence was to be presented. They were instructed to learn the sequence order while reaching for the targets, to anticipate successive targets, and to reach each target in syn-chrony with a tone. Sequences were different in each trial run. For each SEQ run, a reaction time threshold for target anticipation was deter-mined in a random reaction time task performed outside the scanner. In CCW, the eight targets appeared in a predictable counterclockwise order.

To reach the target in synchrony with the tone, subjects had to initiate movement before it appeared.

The pace of the movements in SEQ and CCW, represented by the intertone interval, was adapted to the subject's motor ability in the base-line OFF state, thereby experimentally fixing the rate of movement across tasks (SEQ, CCW) and treatment conditions (ON, OFF) (Feigin et al., 2003). The intertone interval was 1.5 s in 12 of the 15 PD subjects, 2.0 s in two of the subjects and 1.83 s in one subject. Similarly, movement size was also held constant by adjusting the gain to a target extent of 1 cm for all subjects, tasks, and treatment conditions.

Performance measures. For SEQ, we computed the number of correct movements initiated below the reaction time threshold measured in the random reaction time task. These movements reflect anticipation and successful retrieval of previously acquired targets (Nakamura et al., 2001). The sum of all correctly anticipated targets in each trial block was defined as the retrieval index (RET) (Carbon et al., 2003; Ghilardi et al., 2003). This measure was used as the descriptor of the learning achieved in each SEQ trial. Levodopa-mediated changes in learning performance were assessed by comparing RET$_{ON}$ and RET$_{OFF}$ values using paired Student's t tests. These changes were also correlated with baseline values (RET$_{OFF}$) by calculating Pearson's product-moment correlation coefficients.

For CCW, we measured the mean onset time and movement time across cycles for each run (Carbon et al., 2007). The former measure can be considered the lead time before the movement start; the latter mea-surement is a reflection of movement speed. These values were correlated with the corresponding RET measures and were considered significant for $p < 0.05$.

Positron emission tomography
All subjects fasted overnight before imaging. Regional CBF (rCBF) was estimated using H$_2$ ^{15}O PET in three-dimensional mode on the GE ad-vance tomography at North Shore University Hospital (Nakamura et al., 2001). In the OFF and ON scan sessions, the SEQ and CCW tasks were performed in a randomized order with the dominant right arm. In 11 of the patients, the two tasks were performed twice. In the remaining four patients, the tasks were performed only once because of patient fatigue. In total, 24 complete scan sets (defined as paired SEQ and CCW scans acquired in both the ON and OFF states) were generated for additional analysis. The OFF state preceded the ON state in 16 sets; the ON state preceded the OFF state in the remainder.

Data processing was performed using SPM5 software (Wellcome De-partment of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm/software/spm5/). Standard preprocessing (realignment, spatial normalizing, smoothing with 10 × 10 × 10 mm) was applied followed by voxel-by-voxel comparisons using the flexible factorial model. SPM(t) maps were generated to assess the effects of task (SEQ, CCW) and treatment condition (ON, OFF), and the interactions of these factors. In these analyses, RET was entered as a covariate of interest. To control for potential confounds resulting from variability in movement rate, the intertone interval was entered as a nuisance variable.

Table 2. Regions with significant correlations between learning-related response and task performance

| Brain region | Coordinates (mm)[a] | | | Z_{max} | Cluster size | p value[b] | Correlations[c] | |
	x	y	z				r	p value
Positive correlations								
PARi, IPS, PARs (BA 40/7)	36	−74	28	3.73	375	0.031**	0.51	0.000
Precuneus (BA 7)	−14	−80	44	5.19	161	0.001***	0.48	0.000
preSMA/cingulate gyrus (BA 6/32)	4	18	46	2.81	44	0.003*	0.39	0.005
DLPFC (BA 9)	36	8	44	3.31	90	0.000*	0.36	0.011
Negative correlations								
vmPFC (BA 10)	0	50	6	3.39	56	0.000*	−0.36	0.009
Inferior and middle temporal area (BA 20/21)	−58	−10	−20	2.88	89	0.002*	−0.38	0.006

PARi, Inferior parietal cortex; PARs, superior parietal cortex; IPS, intraparietal sulcus; DLPFC, dorsolateral prefrontal cortex.

[a]Coordinates are in Montreal Neurological Institute (MNI) space.

[b]Values at peak voxel within the hypothesis-testing mask (see Materials and Methods).

[c]Pearson product moment correlation coefficients (r) and significance levels (p) for correlations between the RET and activation responses (SEQ − CCW) measured in VOIs corresponding to each of the significant clusters.

*Values uncorrected for multiple comparisons; **false discovery rate corrected; ***family-wise error corrected.

Treatment-mediated changes in learning-related neural responses

Regions with significant effects of levodopa on learning-related activation (SEQ > CCW) or deactivation (SEQ < CCW) were then classified based on whether treatment caused a loss, gain, or recovery of the responses seen in healthy subjects. This was done by categorizing the CBF data measured in volumes of interest (VOIs) corresponding to the significant SPM clusters. For an individual VOI, an asterisk indicated a significant local learning-related neural response (i.e., SEQ > CCW or SEQ < CCW; $p < 0.05$, paired t test); a dash indicated the absence of local response (i.e., no significant difference between the SEQ and CCW tasks). For each VOI, the learning-related response was signified by listing an asterisk or dash for the responses observed on each of the three conditions in order: the healthy controls first, followed respectively by the PD patients in the OFF and ON conditions. Thus, a "loss of response" was indicated by (*, *, −), reflecting a significant learning-related response in healthy controls and unmedicated PD patients, but not in levodopa-treated patients. A "gain of response" was indicated by (−, −, *), reflecting a significant learning-related response in levodopa-treated PD patients. Last, a "recovery of response" was indicated by (*, −, *), reflecting a significant learning-related response that was present in normal and treated PD patients, but not in unmedicated PD patients.

Correlation between learning performance and associated neural responses

Regions in which learning-related neural responses (activation, deactivation) correlated with task performance were identified in a voxelwise search. SPM correlational analysis was conducted within a predefined learning-specific brain volume (Feigin et al., 2003). In the present study, this mask (supplemental Fig. 1, available at www.jneurosci.org as supplemental material) was constructed from 104 SEQ and CCW scan pairs acquired in a separate population of 35 PD patients scanned at baseline and 18 healthy volunteers (mean age, 54.1 ± 15.6). Discrete learning-related spaces for activation (SEQ > CCW) and deactivation (SEQ < CCW) were specified at a voxel-level threshold of $p < 0.001$, followed by correction for multiple comparisons at $p < 0.05$. The individual regions comprising these spaces are presented in supplemental Table (available at www.jneurosci.org as supplemental material).

Voxel-wise correlations within the mask were considered significant at the hypothesis-testing threshold of $p < 0.01$, uncorrected. An additional analysis used VOIs corresponding to the significant clusters in which local neural responses correlated with RET scores. Pearson product moment correlation coefficients were computed for each VOI, and were considered significant at $p < 0.05$. In the significant regions, the VOI data were used *post hoc* to confirm that the correlations were not caused by interactions with the CCW motor task (Carbon et al., 2004). These VOIs were also used for hypothesis testing in the following subgroup analyses.

Predictors of levodopa-mediated alterations in learning responses

Effect of baseline performance. The effect of baseline learning performance on levodopa-mediated changes in activation was further explored by contrasting good and bad learners. These patient subgroups were determined based on the distribution of the baseline learning scores (RET_{OFF}), with good learners defined by performance in the upper tierce of values and bad learners by performance in the lower tierce (supplemental Fig. 2, available at www.jneurosci.org as supplemental material). Learning-related neural responses in the two performance subgroups were first contrasted in the VOIs in which learning performance was found to correlate with local task-related activation (SEQ > CCW) or deactivation (SEQ < CCW) responses (Table 2).

In addition, we directly compared the SEQ and CCW scans obtained in the two performance subgroups by entering them into a flexible factorial model SPM to generate maps reflecting the effects of task (SEQ, CCW), treatment condition (OFF, ON), and performance subgroup (good, bad learners). In this exploratory analysis, the results were reported in the hypothesis-testing mask at $p < 0.01$, uncorrected. This voxel-based method was used to compare the effects of levodopa on the activation responses across the two performance subgroups.

Regional interactions between subgroups and treatment condition were assessed in VOIs corresponding to the significant clusters detected in the SPM subgroup comparison, and in those identified in the correlation analysis described above. Learning-related neural responses (SEQ − CCW) were measured in each VOI and entered into a two-way repeated-measures ANOVA (RMANOVA) model with subgroup (good and bad learners) as the between-subject variable and condition (ON and OFF) as within-subject repeated measures. The results were considered significant at $p < 0.05$.

Effect of the COMT val[158]met *genotype.* Nine of the 15 subjects were retrospectively genotyped for the *COMT val[158]met* polymorphism to analyze the relationship of genotype to learning performance and levodopa-mediated changes in the related neural responses. The correlation between genotype (number of valine alleles) and mean baseline performance (RET_{OFF}) across subjects was determined by computing the Spearman rank order correlation coefficient, which was considered significant for $p < 0.05$. The effect of *COMT* haplotype on treatment-mediated changes in neural responses associated with learning was assessed using the same analytical strategy that was used to contrast the good and bad performance subgroups. The genotyped patients were divided into two subgroups: valine allele carriers (VAL) and methionine homozygotes (MET) (Meyer-Lindenberg et al., 2005). Interactions between subgroup (VAL, MET) and treatment condition (ON, OFF) were assessed as described above in the comparison of the good and bad learner performance subgroups. Data were analyzed in VOIs corresponding to the regions with significant activation/performance correlations as well as those with significant subgroup differences in treatment response. In these VOIs, the data were analyzed using two-way 2 × 2 RMANOVA and were considered significant at $p < 0.05$. All statistical analyses were performed in SPSS.
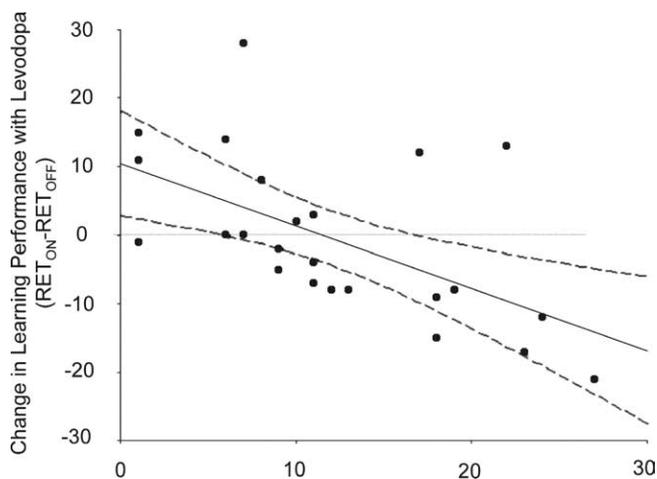
Figure 1. Sequence learning performance: relationship of levodopa-mediated changes to baseline values. Correlation between baseline performance (RET_{OFF}) and the levodopa-mediated changes in learning ($RET_{ON} - RET_{OFF}$). A significant negative correlation ($r = -0.58, p = 0.002$) was observed between these variables. The solid line is the best linear fit; dashed lines represent the 95% confidence interval.

Table 3. Regions with significant effects of levodopa on learning-related neural responses

Brain region	Coordinates (mm)[a]			Z_{max}	Cluster size	p value[b]
	x	y	z			
Levodopa-mediated changes in activation/deactivation response[c]						
Loss of response						
vmPFC (BA10)	−4	52	0	4.14	259	<0.000
Posterior insula	48	−14	4	4.21	839	<0.000
Recovery of response[d]						
PMC (BA 6)	−22	0	60	5.08	516	<0.000
Gain of response[d]						
preSMA (BA 6)	14	6	72	3.57	47	<0.000

[a]Coordinates are in MNI space.

[b]Uncorrected values at peak voxel.

[c]See text for classification of the significant treatment effects.

[d]See supplementary Figure 3 (available at www.jneurosci.org as supplemental material) for illustration of the cerebral blood flow data in these regions.

Results

Effects of levodopa on learning performance

Group mean values ($\pm$SD) for the learning and general movement performance measures in the two treatment conditions are presented in Table 1. There was no change in learning performance with treatment across the patient cohort ($p = 0.85$, paired t test) and no effect of order with two treatment states ($F_{(1,23)} = 0.46, p = 0.50$). Nonetheless, a significant inverse correlation ($r = -0.58, p = 0.002$) was evident between treatment-mediated changes in learning and baseline task performance (Fig. 1). Learning performance did not correlate with UPDRS motor ratings or with onset time and movement time indices measured during CCW in either treatment condition (OFF, $|r| < 0.17, p > 0.42$; ON, $|r| < 0.15; p > 0.46$).

Effects of levodopa on learning-related neural responses

Treatment-mediated changes in regional activation/deactivation
Regions with significant levodopa-mediated changes in learning-related neural responses are presented in Table 3. Levodopa was associated with a loss of learning-related deactivation (SEQ < CCW) responses in the left ventromedial prefrontal cortex (vmPFC) (Fig. 2, top). A similar treatment-mediated loss of the deactivation response was detected in the right posterior insula,

extending into the adjacent temporal cortex (Fig. 2, bottom). In both these areas, significant learning-related deactivation was present in healthy controls and unmedicated PD patients. This response was not present when the patients were scanned on levodopa.

Despite the loss of these deactivation responses with levodopa, no areas were identified in which learning-related activation (SEQ > CCW) was reduced by treatment. Levodopa was, however, associated with increases in learning-related activation in the left dorsal premotor cortex [Brodmann's area (BA) 6] and in the right presupplemental motor area (pre-SMA) (Table 3, supplemental Fig. 3, available at www.jneurosci.org as supplemental material). In the former region, there was recovery of the normal activation response by levodopa. In the latter region, there was a treatment-mediated gain of response in that significant learning-related activation was present only when the patients were scanned on levodopa therapy.

Correlation between learning performance and neural responses
Regions in which learning-related (SEQ − CCW) activation responses correlated with task performance are presented in Table 2. Positive correlations between these measures were observed in the left precuneus (BA 7), and in the right dorsolateral prefrontal cortex (BA 46/9), inferior parietal lobule (BA 40), and the intraparietal sulcus (BA 40/7). Positive correlations were also present in the pre-SMA and anterior cingulate gyrus (BA 32). A significant negative correlation between learning and regional activation was observed in the vmPFC (BA 10), at coordinates similar to those associated with loss of deactivation during treatment (Table 3). A negative correlation was also identified in the inferior temporal gyrus (BA 20/21).

Predictors of levodopa-mediated changes in learning responses

Effect of baseline performance
We defined the top and bottom tierces of the distribution of RET scores at baseline as representing the good and bad performance subgroups (supplemental Fig. 2, shaded areas, available at www.jneurosci.org as supplemental material). The good learner subgroup (RET_{OFF}, 17–27) was comprised of eight scan sets (SEQ − CCW pairs in the OFF and ON conditions) from six patients. The bad learner subgroup (RET_{OFF}, 1–8) was comprised of nine scan sets from seven patients. The clinical features of these subgroups are presented in Table 1. The good and bad learners did not differ with respect to age, baseline disease severity, or change in motor UPDRS ratings with levodopa treatment ($p > 0.19$). The two performance subgroups also did not differ in the movement parameters (onset time and movement time) recorded during CCW performance ($p > 0.22$) or in neuropsychological performance at baseline ($p > 0.17$). The good and bad performers did however differ in the effect of levodopa on sequence learning ($F_{(1,15)} = 7.92, p = 0.01, 2 \times 2$ RMANOVA). *Post hoc* testing revealed that levodopa improved performance in the bad learners ($p = 0.04$, paired t test), and was associated with a trend toward worsening performance in the good learners ($p = 0.09$).

We next identified subgroup differences in the brain regions in which learning-related activity correlated with performance (see Materials and Methods). We found that the effect of levodopa on learning-related deactivation in the vmPFC differed for good and bad learners (Fig. 3A). For the good learners scanned in the unmedicated state, the deactivation response in this region resembled that of healthy subjects. Nonetheless, a significant reduction in this response occurred with levodopa treatment ($p =$
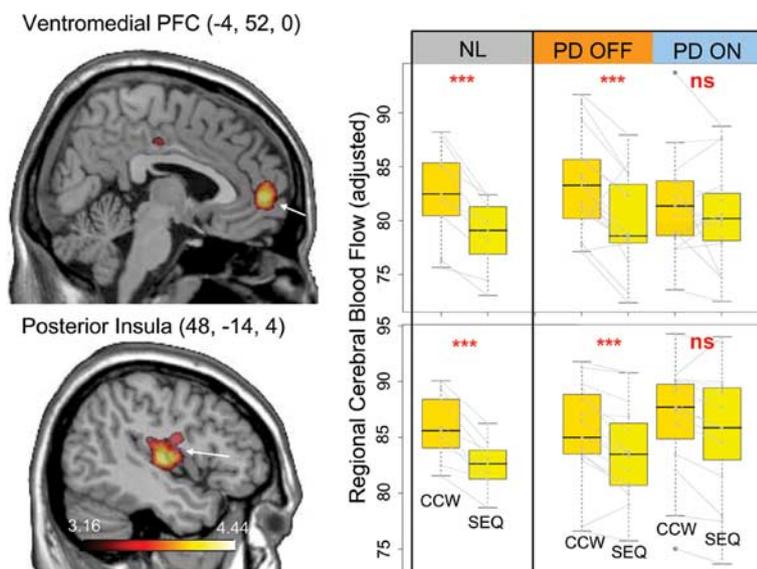
Figure 2. Changes in learning-related rCBF with levodopa infusion. Treatment was associated with loss of learning-related deactivation responses (SEQ < CCW) in the ventromedial prefrontal cortex (top) and the posterior insula (bottom). In both regions (arrows), significant deactivation during learning was present in healthy volunteers (NL) and unmedicated patients (PD OFF). These responses were not present in the same patients when they performed the sequence learning task during levodopa infusion (PD ON). Left, Voxel-based display of significant task (SEQ, CCW) by condition (OFF, ON) interaction effects on rCBF (SPM slices depict significant clusters at a threshold of $p < 0.001$, uncorrected). Right, *Post hoc* analysis of rCBF data from VOIs corresponding to the clusters with significant interaction effects. Values for each task and condition are presented by box-and-whisker plots. ***$p < 0.001$, paired t test. Paired rCBF data across tasks for each subject are connected by lines.

0.04, paired t test). In contrast, baseline learning-related deactivation was minimal in the bad learners and was not altered by levodopa treatment ($p = 0.97$). Treatment-mediated changes in the other regions with significant correlations between performance and activation response did not differ across the two subgroups.

Direct voxel-based comparison of levodopa-mediated changes in activation across the performance subgroups disclosed a significant subgroup by treatment condition interaction effect in the precuneus (8, −84, −26; $Z_{max} = 4.22$, $p < 0.001$, uncorrected), which was confirmed on *post hoc* VOI analysis ($F_{(1,15)} = 13.8$, $p = 0.002$; 2 × 2 RMANOVA). In this region (Fig. 3B), levodopa enhanced learning-related activation in bad learners ($p < 0.05$) while reducing this response ($p < 0.01$) in the good learners.

Effect of COMT val^{158}met *genotype*
Of the nine subjects who were genotyped for the *COMT val^{158}met* polymorphism (supplemental Fig. 2, color-coded data, available at www.jneurosci.org as supplemental material), four (seven scan sets) were *met/met*, four (seven scan sets) were *val/met*, and one (one scan set) was *val/val*. The clinical features of the *val* allele carriers (VAL) and the *met* homozygotes (MET) are presented in Table 1. These genotypic subgroups did not differ with respect to age, baseline disease severity, or the motor response to levodopa treatment ($p > 0.27$). They also did not differ in the CCW movement parameters ($p > 0.21$) or in baseline neuropsychological testing ($p > 0.14$). A trend toward positive correlation was present between baseline learning performance (RET $_{OFF}$) and the number of valine alleles (Spearman's $r = 0.475$, $p = 0.09$), with relatively worse performance associated with met homozygosity.

Of the VOIs with significant correlations between learning-related activation responses and performance, a significant inter-

action between genotype and treatment condition was present only in the vmPFC (Fig. 4A). This effect was significant with or without including the *val* homozygote (all *val* allele carriers: $F_{(1,13)} = 10.9$, $p < 0.01$; *val/met* only: $F_{(1,12)} = 9.3$, $p < 0.01$, 2 × 2 RMANOVA). In this region, levodopa reduced the magnitude of learning-related deactivation in VAL ($p < 0.05$), although tended to enhance this response in MET ($p = 0.059$).

Direct voxel-based comparison of scans from the VAL and MET subgroups revealed only one additional region with a significant genotype by treatment condition interaction effect. This cluster was localized to the cerebellar declive (lobule VI: 8, −84, −26; $Z_{max} = 4.22$, $p < 0.001$, uncorrected). This effect (Fig. 4B) was significant with or without including the *val* homozygote (all *val* allele carriers: $F_{(1,13)} = 22.0$, $p < 0.0001$; *val/met* only: $F_{(1,12)} = 21.0$, $p < 0.001$, 2 × 2 RMANOVA). In this region, levodopa reduced learning-related activation in VAL ($p < 0.0001$) while increasing this response in MET ($p < 0.05$). *Post hoc* testing also revealed that at baseline, learning-related activation in this area was significantly lower in the MET subgroup ($p < 0.02$).

Discussion
In this study, we show that levodopa can influence sequence learning performance through a loss of the cortical deactivation responses that are present in the unmedicated baseline state. The current findings revealed that levodopa specifically suppressed the normal deactivation response that occurs in the vmPFC during motor sequence learning (Tamás Kincses et al., 2008) (Fig. 2, top). The mechanism by which dopamine modulates the deactivation response is not known. We note that this region is closely associated with the ventral striatum (West and Grace, 2002; Grace et al., 2007). Dopaminergic input to this area is relatively preserved in PD, perhaps rendering it more susceptible to local overdose effects (Cools, 2006). Alternatively, the effect of levodopa on learning-related vmPFC deactivation may be a consequence of increases in dopaminergic activity in the anterior cingulate cortex. Significant elevations in AADC activity have been noted in this region in PD patients undergoing ^{18}F-fluorodopa PET imaging (Rakshi et al., 1999; Kaasinen et al., 2001; Brück et al., 2005). Thus, systemically administered levodopa can be decarboxylated to dopamine in this region, resulting in potential overdose effects locally and in the adjacent medial prefrontal cortex.

These data suggest that learning-related deactivation in medial prefrontal cortex can be modulated by dopaminergic neurotransmission via the anterior cingulate cortex. Moreover, the observed treatment-mediated loss of deactivation responses in the insula, which is also closely connected with the anterior cingulate (Van Hoesen et al., 1993), may have occurred through a similar mechanism. These findings raise the possibility that, by analogy with the indirect striatopallidal pathway in the basal ganglia (Gerfen, 2000), D$_2$-like receptors on anterior cingulate neurons modulate output to projection targets in the neighboring medial pre-
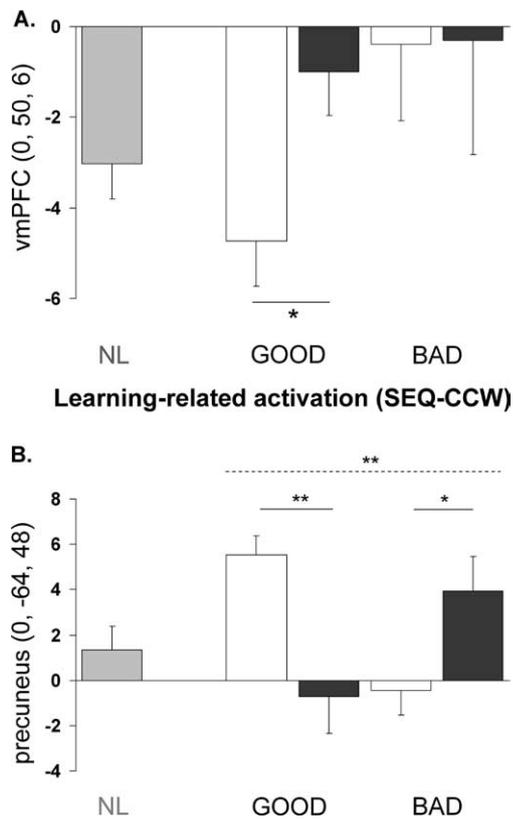
Figure 3. Effect of baseline performance on changes in learning-related neural responses with levodopa treatment. **A**, Bar graph of learning-related deactivation (SEQ < CCW) in the vmPFC for the patient subgroups with good and bad baseline performance (see Materials and Methods). In the unmedicated state (open bars), the good learners achieved a degree of deactivation that was comparable with healthy controls (shaded bar). In contrast, these responses were minimal in bad learners scanned at baseline. Neither of the two subgroups exhibited significant vmPFC deactivation in the treated state (filled bars). **B**, Bar graph of learning-related activation (SEQ > CCW) in the precuneus for the good and bad performance subgroups. In this region, levodopa enhanced activation in bad learners, but attenuated this response in good learners. Parallel treatment-mediated behavioral effects were observed in the concurrently recorded learning performance data for the two subgroups (see Results). The dashed lines represent significant interaction effects (2 × 2 RMANOVA). The solid lines represent significant pairwise differences (paired Student's t tests). $*p < 0.05$, $**p < 0.01$. Error bars indicate SEM.

Figure 4. Effect of *COMT* genotype on changes in learning-related neural responses with levodopa treatment. **A**, Bar graph of learning-related deactivation (SEQ < CCW) in the vmPFC for patient subgroups with different *COMT val158met* genotypes (see Materials and Methods). In this region, levodopa reduced the magnitude of deactivation in valine allele carriers, but enhanced this response in methionine homozygotes. **B**, Bar graph of learning-related activation (SEQ > CCW) in the cerebellum (lobule VI) for the two genotypic subgroups. In this region, levodopa reduced the magnitude of learning-related activation in valine allele carriers and enhanced in the methionine homozygotes. The baseline and treated conditions are represented by open and filled bars, respectively. The shaded bar represents reference values from healthy subjects. The dashed lines represent significant interaction effects (2 × 2 RMANOVA). The solid lines represent significant pairwise differences (paired Student's t tests). $*p < 0.05$; $**p < 0.01$; $***p < 0.001$; $****p < 0.0001$. Error bars indicate SEM.

frontal cortex (Bates and Goldman-Rakic, 1993). D_2 receptors are also present presynaptically on medial prefrontal cortex neurons that project to the ventral striatum (Okubo et al., 1999; Kaasinen et al., 2000; Grace et al., 2007; cf. Nikoshkov et al., 2008). Indeed, stimulation of these receptors has been found to reduce functional input to the latter region (West and Grace, 2002; Goto and Grace, 2005). Therefore, a predominantly D_2-mediated pathway involving the anterior cingulate, medial prefrontal cortex, and ventral striatum potentially influence the default mode network by facilitating deactivation at its prefrontal node.

The relationship between levodopa-mediated changes in learning and baseline capability was further examined by comparing matched patient subgroups with good and bad performance levels in the untreated state. Using this approach, we found that in the good learners, vmPFC deactivation and concurrent task performance were normal at baseline, but declined with levodopa treatment. In contrast, the deactivation response was minimal in the bad learners, whether scanned at baseline or in the treated state. Dopaminergic therapy also affected activation responses in several parietal association regions. These areas corre-
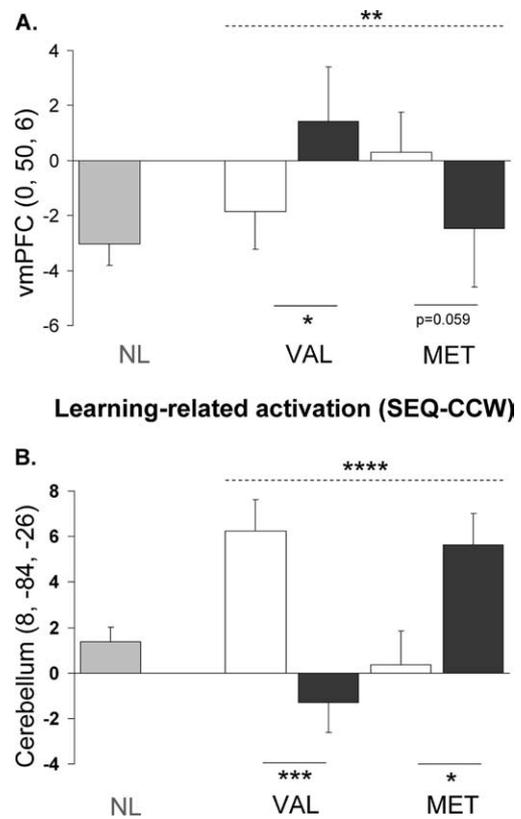
sponded topographically to the posterior cortical nodes of the normal learning-related activation network (Carbon et al., 2003). Indeed, in these regions, the activation responses paralleled the behavioral changes that were observed in the two performance subgroups. The findings suggest that the reduced levels of vmPFC deactivation seen in the bad learners can be compensated to some degree by the enhancement of learning-related activation responses in downstream network regions.

In addition to the influence of baseline phenotype on the cognitive response to dopaminergic therapy, we also found a significant influence of genotype. The observation that the effect of treatment on the vmPFC deactivation response varied according to the *COMT val158met* genotype suggests that this physiologic effect is linked to intrinsic differences in prefrontal dopamine pools. Although only nine of the patients were available for DNA analysis, the results indicated a significant effect of genotype on the treatment-mediated changes in vmPFC deactivation. Specifically, in carriers of valine alleles, levodopa served to suppress learning-related deactivation in this region. In contrast, recovery of this response tended to occur in individuals without this allele (i.e., the methionine homozygotes). Interestingly, the individual data were found to conform to an inverted-U function (Fig. 5). This
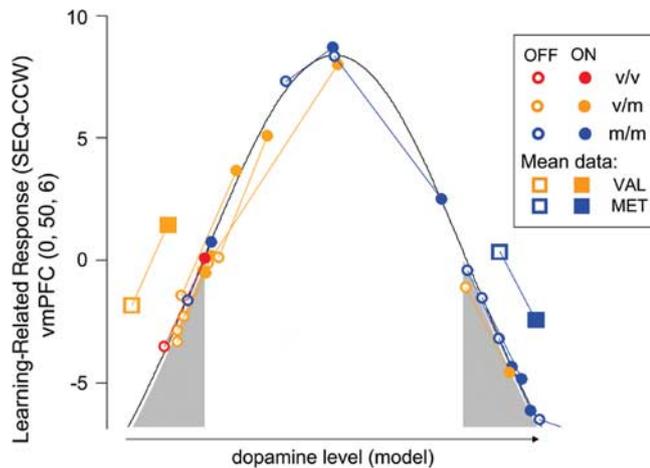
Figure 5. Learning-related deactivation responses in the vmPFC displayed as an inverted-U function. Bands of low and high dopamine at the edges of the curve (shaded areas) represent zones of optimal function in which local deactivation responses (SEQ − CCW < 0) occur during task performance. The data were modeled using a simplex search method (Lagarias et al., 1998) to fit the measured learning-related responses to a Gaussian curve, $f(v) = p_1 \times \exp(-(v)^2/p_2) + p_3$, where v is the hypothetical regional dopamine level and $f(v)$ is the corresponding activation response. The model was based on two major assumptions: (1) for all subjects, the local dopamine level was assumed to be higher in ON relative to OFF ($v_{s,ON} > v_{s,OFF}$, where $v_{i,j}$ is the dopamine level for subject i in condition j); and (2) because the valine allele is associated with greater activity of the enzyme in the brain (Chen et al., 2004), carriers of this allele were assumed to have relatively lower dopamine levels at baseline [mean ($v_{val/val,OFF}$) < mean ($v_{val/met,OFF}$) < mean ($v_{met/met,OFF}$)]. The model included two minor constraints: (1) the increment in dopamine level with treatment was of similar magnitude across genotypes [SD($v_{i,ON} - v_{i,OFF}$)$_{ie\{all\ subjects\}}$ is minimal]; and (2) the amplitude of $f(v)$ was determined by the range of the measured regional data. This fitting procedure was implemented in Matlab 6.5 (MathWorks).

type of nonlinear relationship between local neural activity and dopamine level has been documented consistently for task-related activation responses in dorsolateral PFC (Mattay et al., 2000; Goldberg and Weinberger, 2004). This, however, is the first demonstration of this inverted-U relationship involving a localized deactivation response. We note that, unlike the function observed with lateral PFC activation (Vijayraghavan et al., 2007), the peak of the current vmPFC curve corresponded to loss of the deactivation response (i.e., positive SEQ − CCW values). Indeed, a similar relationship has been recently reported in a functional MRI (fMRI) study of interactions between D_2 receptor stimulation and genotype on activation responses during reversal learning (Cohen et al., 2007). This observation lends support to the hypothesis that vmPFC deactivation responses are modulated through D_2 receptors in this cortical region, the ventral striatum, or both (Grace et al., 2007). Moreover, the difference between these inverted-U relationships, with enhancement or attenuation of neural activity at the peak, is consistent with opposing D_1- and D_2-mediated effects on prefrontal functioning (Bilder et al., 2004; Seamans and Yang, 2004).

It is also of interest that, at baseline, better learning performance was associated with valine rather than methionine alleles. In healthy subjects, low-activity *COMT* genotypes like *met/met* involve increases in prefrontal dopamine levels and superior task performance (Malhotra et al., 2002). Nonetheless, this relationship may not apply to early stage PD patients in whom compensatory increases in dopaminergic input have been noted in lateral and medial PFC regions (Rakshi et al., 1999; Kaasinen et al., 2001; Brück et al., 2005). It has therefore been suggested that early stage PD patients are positioned on the descending limb of the classical inverted-U function, with high activity *COMT* alleles (lower prefrontal dopamine) situated nearer to the peak (Foltynie et al., 2004). Indeed, this notion has been

supported by recent fMRI studies in medicated patients in which valine homozygotes were found to have superior performance and prefrontoparietal activation than their methionine counterparts (Williams-Gray et al., 2007, 2008).

The current study revealed similarities and differences with these results. In agreement with the previous findings, methionine homozygotes were situated on the descending limb of the inverted-U curve. Likewise, the valine allele carriers fell to the left of the methionine homozygotes, although now they were on the ascending limb of the curve. As discussed above, individual measures of vmPFC deactivation conformed to a "nonclassical" inverted-U function, in which task-related neural responses were attenuated, rather than enhanced, in the neighborhood of the peak. Thus, optimal functioning was associated with discrete "bands" of dopamine activity (Fig. 5, shaded regions) situated on either side of the central region. This nonlinear relationship allowed for a deterioration of local deactivation responses in valine allele carriers during dopaminergic therapy, despite their positioning at baseline along the ascending portion of the curve.

We acknowledge that in valine allele carriers, the behavioral effects of treatment could also be explained by positioning along the descending limb of the classical inverted-U function, with a concomitant decline in learning-related activation responses (Williams-Gray et al., 2008). Nonetheless, this arrangement does not account for the treatment-mediated recovery of vmPFC deactivation seen in the methionine homozygotes, who presumably lie to the right of the valine allele carriers on this portion of the curve. This observation can, however, be explained by levodopa shifting these individuals further to the right into the band of optimal function on the extreme end of the curve.

We recognize that the behavioral data are not fully correlated with the neuroimaging findings in the vmPFC. Usually, more than one brain region accounts for the majority of individual differences in the performance of a complex task such as this (Nakamura et al., 2001; Carbon et al., 2003, 2004). As shown above (Fig. 3B), the parietal association cortex plays a major role in sequence learning performance. Thus, the vmPFC deactivations in themselves are unlikely to predict all or even most of the behavioral findings. That said, knowledge of the COMT genotype enhanced the understanding of the effects of levodopa on vmPFC function. Indeed, the data suggest that changes in deactivation in this region relate mainly to genotype, whereas parietal activation was determined mainly by baseline performance. Nonetheless, these measures are all interrelated to varying degrees.

We note that when present, vmPFC deactivation responses were associated with concurrent activation of the posterior-medial cerebellum. Thus, abnormally elevated cerebellar activation responses were evident in valine allele carriers scanned at baseline and in methionine homozygotes scanned in the treated condition. It is unlikely that these activations relate directly to levodopa treatment given the scarcity of AADC-positive terminals in this region. Moreover, enhanced cerebellar activation was also seen in valine allele carriers scanned in the unmedicated state. We speculate that the cerebellar response is associated with effective deactivation of the default mode network, as we suggest, occurs in the bands of optimal function situated at the edges of the inverted-U curve (see above). Suppression of activity within one or more nodes of this network would allow for a reallocation of neural resources to other learning-related regions, including the cerebellum.

The results of this study are limited by the relatively small

sample size, especially with regard to inferences based on genotype. Nonetheless, we found that ~30% of subject variation in the effect of levodopa on the vmPFC deactivation response could be predicted by combined knowledge of the *COMT val*[158]*met* genotype and the baseline level of learning performance. It is additionally likely that predictive models of the cognitive levodopa response will become increasingly accurate as additional relevant polymorphisms are considered (Bertolino et al., 2006, 2008; Cohen et al., 2007). Likewise, it is possible that different dopamine genes selectively regulate the activity of the D_1- and D_2-mediated prefrontal-striatal pathways. Additional functional imaging studies using agonists for these receptors will help clarify the specific roles of these pathways in modulating cortical deactivation responses in health and disease.

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