Effects of levodopa infusion on motor activation responses in Parkinson's disease

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Abstract—*Background:* Clinical improvement with levodopa therapy for PD is associated with specific regional changes in cerebral glucose metabolism. However, it is unknown how these effects of treatment in the resting state relate to alterations in brain function that occur during movement. In this study, the authors used PET to assess the effects of levodopa on motor activation responses and determined how these changes related to on-line recordings of movement speed and accuracy. *Methods:* Seven right-handed PD patients were scanned with $H_2{}^{15}O$/PET while performing a predictable paced sequence of reaching movements and while observing the same screen displays and tones. PET studies were performed during "on" and "off" states with an individually titrated constant rate levodopa infusion; movements were kinematically controlled across treatment conditions. *Results:* Levodopa improved "off" state UPDRS motor ratings (34%; $p < 0.006$) and movement time (18%; $p = 0.001$). Spatial errors worsened during levodopa infusion (24%; $p = 0.02$). Concurrent regional cerebral blood flow (rCBF) recordings revealed significant enhancement of motor activation responses in the posterior putamen bilaterally ($p < 0.001$), left ventral thalamus ($p < 0.002$), and pons ($p < 0.005$). Movement time improvement with treatment correlated with rCBF increases in the left globus pallidus and left ventral thalamus ($p < 0.01$). By contrast, the increase in spatial errors correlated with rCBF increases in the cerebellar vermis ($p < 0.01$). *Conclusion:* These results suggest that levodopa infusion may improve aspects of motor performance while worsening others. Different components of the motor cortico-striato-pallido-thalamo-cortical loop and related pathways may underlie motor improvement and adverse motoric effects of levodopa therapy for PD.

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We recently used PET with [^{18}F]fluorodeoxyglucose (FDG) to measure resting state changes in brain metabolism in response to therapeutic interventions for PD. Specifically, we found that levodopa infusion suppresses an abnormal PD-related pattern (PDRP) of brain metabolism and that the degree of suppression of the PDRP correlates with the extent of clinical improvement afforded by this therapy.[1] Similarly, we found that PDRP expression is suppressed by other therapies for PD, including pallidotomy, deep brain stimulation of the internal globus pallidus (GPi DBS), and subthalamotomy.[2-4] As with levodopa therapy, PDRP suppression by these surgical interventions also correlates with clinical changes as measured by the motor portion of the Unified PD Rating Scale (UPDRS).[5] It remains unclear, however, how these resting state changes in brain metabolism relate to changes in brain function during actual movement.

In recent studies, we used three-dimensional imaging methods to quantify both resting state and movement-related blood flow activation responses in the same PET session.[3,6] With this approach, we assessed brain responses to GPi DBS and demonstrated very specific functional changes in discrete nodes of the motor cortico-striato-pallido-thalamo-cortical (CSPTC) loop[7] and related pathways.[6] Furthermore, on-line recordings of different movement parameters (timing and spatial errors) correlated with changes in different subcircuits of these networks.

Although GPi DBS and levodopa infusion improve motor function in PD and suppress PDRP, the mechanism of action is likely to differ. For example, levodopa may produce dyskinesias, while pallidal DBS suppresses dyskinesias. Additionally, the two interventions appear to have disparate effects on motor learning.[8] Furthermore, PET studies utilizing ^{15}O-labeled water ($H_2{}^{15}O$) revealed disparities between surgical therapies for PD such as GPi DBS and pallidotomy,[6,9-11] suggesting that successful therapies for PD may have different underlying physiologic mechanisms. These different mechanisms may have consequences for the spectrum of benefits of the therapy (motoric, psychiatric, and cognitive) as well as for potential adverse effects of the therapy.

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Table 1 *Subject characteristics in a study of the effects of levodopa infusion on motor activation responses in PD*

Patient no.	Age, y	Sex	Hoehn and Yahr stage	Levodopa dosage, mg/hour	UPDRS motor ratings "off"/"on" (%)*	Medications†
1	56	M	1	50	14/11 (21.4)	1, 2
2	64	M	2	70	20/13 (35.0)	1, 2
3	55	F	1.5	100	25/12 (52.0)	1, 2
4	66	F	2	100	35/27 (22.9)	1, 2
5	56	M	1	60	15/10 (33.3)	2, 3, 4
6	60	M	3	30	35/23 (34.3)	1, 2
7	59	M	2.5	60	32/27 (15.6)	1, 2

* Clinical improvement defined as ([levodopa "off"–"on"]/levodopa "off") × 100%.
† 1 = levodopa/carbidopa; 2 = dopamine agonist; 3 = anticholinergic; 4 = selegiline.

UPDRS = Unified PD Rating Scale; "off" = no levodopa infusion; "on" = levodopa infusion.

In the current study, we performed $H_2{}^{15}O$/PET during movement to evaluate changes in cerebral blood flow (CBF) that occur with levodopa therapy and to assess their relevance to clinical outcome. These studies were done on the same subjects and during the same scanning sessions as reported earlier for the FDG studies.[1] We sought to determine whether levodopa can significantly enhance motor activation regional CBF (rCBF) responses and whether the changes in brain activation mediated by levodopa correlate with psychophysical measures of motor performance obtained concurrently during the PET experiment.

Methods. *Patients.* Seven levodopa-responsive nondyskinetic PD patients (five men and two women; mean age ± SD, 59.4 ± 4.2 years; mean Hoehn and Yahr stage ± SD, 1.9 ± 0.7) underwent both clinical evaluation and PET on each of two consecutive days. The clinical characteristics of the patients are described in table 1. A diagnosis of PD was made if the patient had "pure" parkinsonism without a history of known causative factors such as encephalitis or neuroleptic treatment and did not have dementia, supranuclear gaze abnormalities, or ataxia. All patients had at least a 20% improvement in the motor portion of the UPDRS[5] during levodopa infusion. Family histories were negative for neurodegenerative illnesses.

Study design. Patients were studied over a 3-day period as described previously.[3,6] All antiparkinsonian medications were withheld for at least 12 hours before each day of testing. The first day was utilized for task training and for selection of experimental task parameters for the PET experiments. On each of the next 2 days, the patients underwent PET with $H_2{}^{15}O$ and FDG. The results of the latter resting state PET experiments have been previously reported.[1] On one of the days of PET, the patients were scanned without the levodopa infusion ("off" state). On the other day, the same patients were scanned during an individually titrated constant rate levodopa infusion ("on" state). The order of the scanning sessions was randomized so that four subjects underwent levodopa infusion on the first day and the three other subjects underwent levodopa infusion on the second day. The details of the levodopa infusion and clinical rating procedures have been previously reported.[1] Subjects underwent "on" state evaluations and scanning after a steady state had been reached, which was determined by serial UPDRS and serum levodopa measurements; the same steady state was utilized for both the $H_2{}^{15}O$ and the FDG scanning sessions.

Behavioral tasks. The experimental paradigm consisted of two tasks during PET: a motor execution task and a sensory reference task. The characteristics of these tasks have been described in detail elsewhere.[6,12,13] Briefly, the motor task (M*pred*) required subjects to move a cursor on a digitizing tablet while hand position and target locations were displayed on a computer screen. Targets were eight circles 45° apart displayed on the screen with a central starting area. Targets appeared in a counterclockwise predictable order and were presented at constant time intervals in synchrony with a 160-ms tone. Subjects were instructed to reach for each target from the starting point and to synchronize the reversal of their movements with the tone so that movements were initiated *before* target appearance as in "timed response" tasks.[6,12-14] If the movement reached the target within 250 ms prior to and after each tone, the target turned gray, signaling a successful hit. The tone interval and extent of movement were held constant across conditions ("on" and "off" states) and were identical for all subjects.

In the sensory reference task (S), subjects remained immobile but experienced the same visual and auditory stimuli as during M*pred*. Screen targets, cursor images, and tones were presented to the subjects asynchronously and irregularly in numbers equal to those used in M*pred*. All trial blocks lasted 90 seconds.

Motor performance parameters. The details of data acquisition and the analysis of motor performance have been described previously.[6,12] The following performance variables were computed for each movement: movement time (MvT), the time from the onset of the outward motion to the reversal point; onset time, the time from target and tone presentation to movement onset; and spatial error (equivalent to linear error),[12] the shortest distance of the reversal point from the center of the target. For each M*pred* run, we computed means and variances (SD) of these parameters. Mean values across runs were averaged and compared between levodopa conditions with paired Student's *t*-tests. The performance measures that changed significantly ($p < 0.05$) with levodopa infusion were then

utilized in correlational analysis with the activation PET data.

PET. The patients fasted overnight prior to both PET sessions ("on" and "off" states). PET studies were performed in a three-dimensional mode using the GE Advance Scanner (General Electric, Milwaukee, WI) at North Shore University Hospital (Manhasset, NY).[15] This eight-ring bismuth germanate scanner provided 35 two-dimensional image planes with an axial field of view of 14.5 centimeters and transaxial resolution of 4.2 mm (FWHM) in all directions. In each PET session, patients were positioned in the scanner using the Laitinen stereoadapter[16] (Sandstrom Trade and Technology, Welland, Ontario, Canada) with three-dimensional laser alignment with reference to the orbitomeatal line. To minimize repositioning errors, we used identical stereoadapter and laser settings in both imaging sessions. In both PET sessions, each subject was scanned in randomized order while performing each task (M*pred* and S) twice. Motor tasks were performed with the dominant right arm, and an IV catheter was placed in the left arm for administration of $H_2{}^{15}O$. Relative rCBF was estimated using a modification of the slow bolus method.[6,13,17] Ethical permission for these studies was obtained from the Institutional Review Board of North Shore University Hospital. Written consent was obtained from each subject following detailed explanation of the procedures.

Data analysis. Data processing was performed using SPM99 (Department of Cognitive Neurology, Wellcome, London, UK) implemented in MATLAB (Mathworks, Sherborn, MA). The scans of each subject were aligned, nonlinearly warped into Talairach space,[18] and proportionately scaled such that the mean global count was 50. The images were smoothed with an isotropic gaussian kernel (FWHM, 10 mm for all directions) to allow for interindividual gyral variation and to improve the signal-to-noise ratio. To compare our results with prior SPM analyses of rCBF activation studies, we utilized the same fixed effects model for the comparison of the two stimulation conditions.

Effects of levodopa on motor activation. To identify voxels associated with the effect of levodopa on movement, we analyzed all four conditions (M_{ON}, S_{ON}, M_{OFF}, and S_{OFF}) in a two-factor ANOVA. All scans (seven subjects, four conditions, and two scans per condition) were entered simultaneously in the design matrix, and the differences were detected by specifying a contrast of (1, −1, −1, 1). We hypothesized that levodopa alters motor activation responses within a set of voxels with known activation by this task through previous $H_2{}^{15}O$/PET studies. To test this hypothesis, we utilized a mask defined by M*pred* − S activation obtained for an independent population of right-handed subjects (16 unmedicated patients with PD and 20 normal volunteers) as previously described.[6] This mask was compiled with 168 preexisting M*pred* and S scan pairs, and the peak threshold was $p < 0.001$.[6] Levodopa effects on M*pred* − S activation within the population mask were considered to be hypothesis-driven. Effects within these areas were considered part of the distributed network of regions activated by M*pred* and thus not independent of each other. Therefore, we considered these activations significant when the p value was at a peak threshold of <0.01, uncorrected for independent multiple comparisons. Effects of levodopa outside the mask were considered to be hypothesis-generating if they were significant ($p < 0.001$), uncorrected for multiple comparisons; additionally, these effects were considered to be significant if they survived a correction for multiple comparisons at $p < 0.05$. We also sought to examine the effects of levodopa in the absence of movement during the sensory reference condition. To exclude levodopa effects in the S condition confounding these results, we compared rCBF in S_{ON} with S_{OFF} using a relatively liberal threshold of $p < 0.001$, uncorrected for multiple comparisons.

Correlations between task performance and brain activation. Using paired t-tests, we identified the specific performance parameters that changed significantly with levodopa. We used SPM to correlate "on" − "off" state differences in each of these behavioral measures with "on" − "off" state differences in M*pred*. The changes in the significantly improved behavioral parameters (see above) were correlated with the difference scan of each patient. Correlations were performed on a voxel-by-voxel basis within the areas previously demonstrated to be activated by the motor task (i.e., within the M*pred* − S mask) and considered significant for a peak threshold of $p < 0.01$, uncorrected for multiple comparisons.

Results. *Effects of levodopa on motor performance.* UPDRS motor ratings improved significantly with levodopa (mean ± SD: from 25.7 ± 9.9 to 16.6 ± 6.7 [34.3%]; $p < 0.006$). Significant improvements were also evident in the kinematic measurements recorded during the motor task. MvT improved (declined) by 18% ($p = 0.001$), and spatial errors worsened (increased) by 24% ($p = 0.02$) during levodopa infusion. There was a trend toward improvement in onset time (14.7% improvement; $p = 0.08$), and the change in onset time correlated with the change in MvT ($r = -0.75$; $p < 0.002$). There was a significant correlation between the decline in MvT and the increase in spatial errors ($r = -0.75$; $p = 0.002$). Change in MvT did not correlate with change in UPDRS.

Effect of levodopa on brain activation. Areas in which levodopa significantly enhanced motor rCBF responses ($[M_{pred} - S]_{ON} > [M_{pred} - S]_{OFF}$) are presented in figure 1 and table 2. Hypothesis-driven searches within the population mask revealed highly significant levodopa-induced augmentation of activation responses in the left posterior putamen ($p < 0.001$, corrected) and in the posterolateral pons in the vicinity of the pedunculopontine nucleus ($p < 0.005$, corrected). Significant increases were also present in the right posterior putamen and in the left ventral thalamus ($p < 0.002$, uncorrected). Scatter plots of adjusted rCBF responses in these regions are presented for each run in the two levodopa conditions in figure 2. Significant decreases in rCBF activation responses were not evident with levodopa, and there were no areas of significant change outside the mask. Comparison of rCBF without movement ($S_{ON} - S_{OFF}$) did not reveal significant changes between levodopa conditions.

Correlation between brain activation and performance measures. MvT and spatial error were correlated with "on" − "off" state rCBF differences in M*pred*. Talairach coordinates and z scores for the local maxima of significant correlations are presented in figure 3 and table 3. Improvements (i.e., reductions) in MvT correlated with rCBF increases in the left globus pallidus ($p < 0.01$) and left ventral thalamus ($p < 0.01$). By contrast, worsening (i.e.,

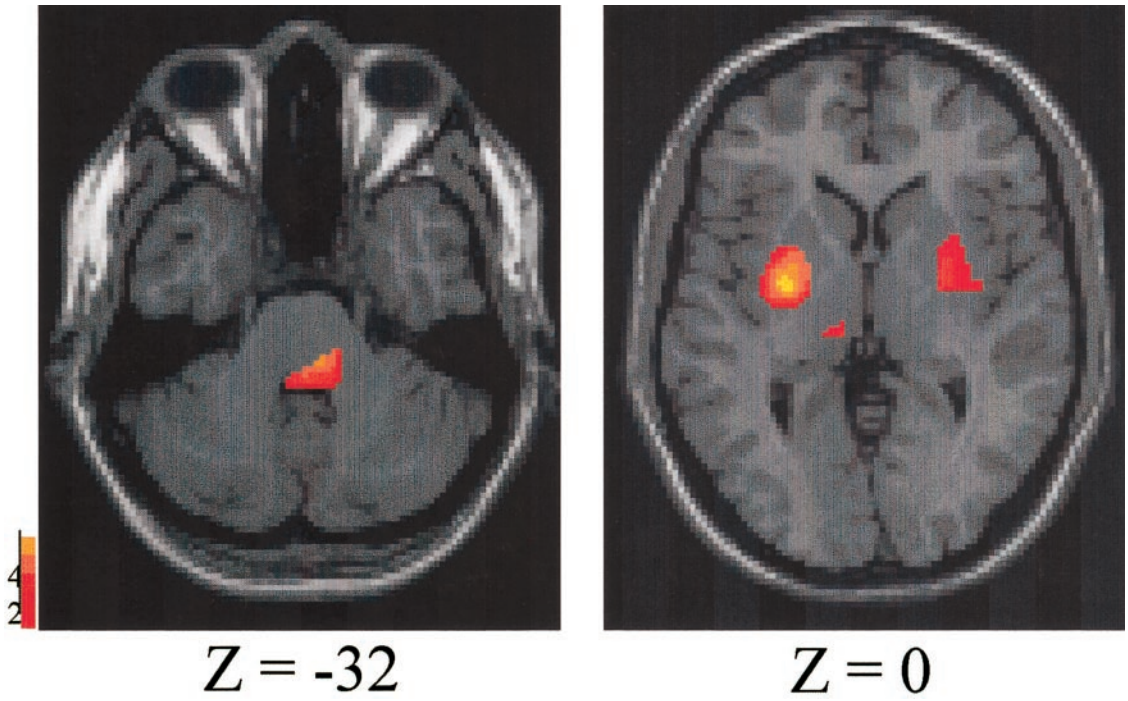

Figure 1. Brain regions associated with significant increases in regional cerebral blood flow motor activation responses with levodopa infusion (see table 1). Brain regions activated by the task included the posterior putamen bilaterally, left ventral thalamus, and pons. (The color stripe represents z scores at a threshold of 2.56 [p < 0.01].)

increased) spatial error during levodopa infusion correlated with rCBF increases in the cerebellar vermis ($p < 0.01$).

Discussion. In this study combining $H_2{}^{15}O$/PET and movement analysis, we found that rCBF activation responses were significantly enhanced by levodopa infusion. With this intervention, increases in activation were present bilaterally in the posterior putamen, left ventral thalamus, and dorsal pons, regions demonstrated to be activated by our motor task in prior PET studies.[6,12] Aspects of motor performance during PET were improved by levodopa infusion, especially with regard to MvT and, perhaps to a lesser degree, movement initiation. Improvements in bradykinesia correlated with augmented activation in the left pallidum and ventral thalamus. By contrast, we observed worsening in spatial accuracy during levodopa infusion, and this clinical change correlated with increased activation in the cerebellar vermis. Thus, levodopa can enhance activation responses within the motor CSPTC loop.[7] However, enhanced activation of functional circuits relating to spatial accuracy, as has been described in the cerebellum,[6] may promote an increase in errors during therapy.

Table 2 *Brain regions with significant levodopa-induced increases in activation responses in PD*

Brain region	Coordinate (mm)			z_{max}	Peak p value
	x	y	z		
L putamen (posterior)	−28	−6	2	5.4	<0.001*
R putamen (posterior)	28	−2	0	3.2	<0.001†
L thalamus (ventral)	−8	−24	2	3.0	<0.002†
Pons (PPN)	8	−32	−32	4.5	<0.005*

* Corrected for multiple independent comparisons.
† Uncorrected.

PPN = pedunculopontine nucleus.

In addition to improving UPDRS motor ratings, levodopa infusion also had a discernible effect on physiologic descriptors of motor performance. Specifically, this intervention ameliorated parkinsonian bradykinesia as manifested by a reduction in MvT and a trend toward improvement in timing error.[6,12] We note that there may have been residual effects of dopaminergic therapy even in the "off" state due to dopamine agonists or long-duration effects of levodopa. Nonetheless, these effects were likely to be small in magnitude compared with the acute effects of levodopa and would be expected only to have diminished the difference between "off" and "on" states, rather than alter the nature of the results. Furthermore, residual dopaminergic effects should have been equal between the "off" state and the "on" state, given the same duration of drug withholding. Although a longer period of withholding medications would be ideal, this would not have been practical.

Interestingly, we found that levodopa infusion worsened spatial error of the movements—i.e., deviation of the maximal excursion of the trajectory from the center of the target. Although the subjects in this study did not have visible levodopa-induced dyskinesias, we hypothesize that the worsening in spatial

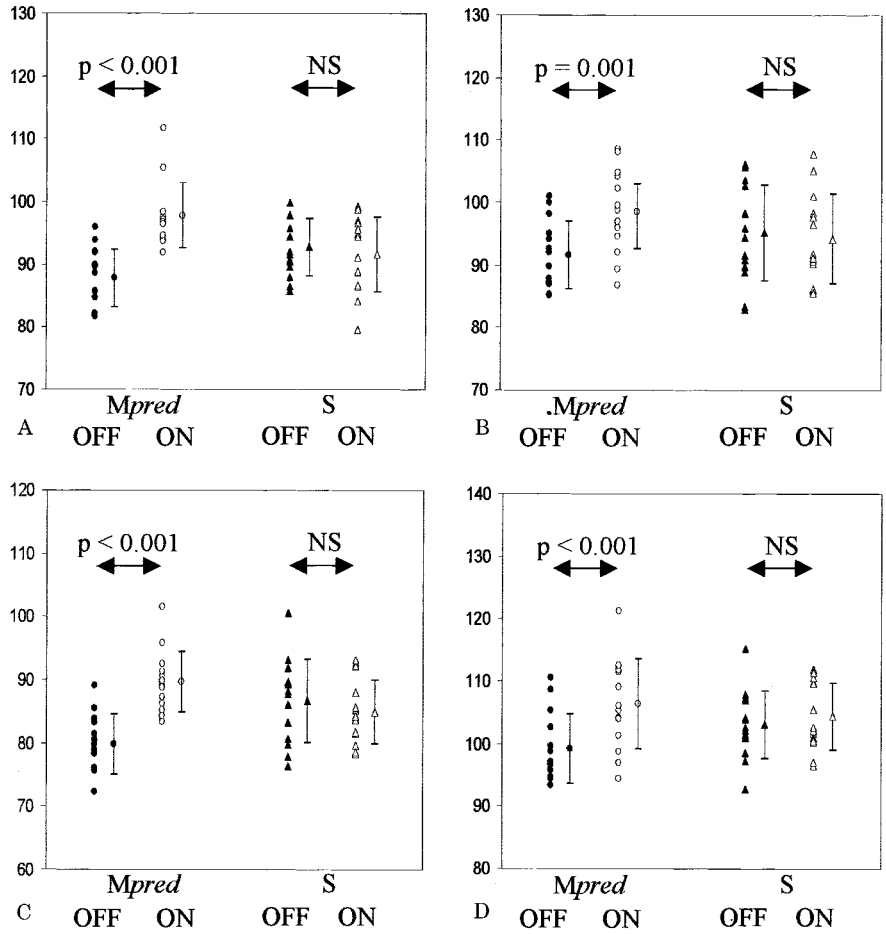

*Figure 2. Scatter diagrams of adjusted regional cerebral blood flow responses for the regions displayed in the (A) left posterior putamen (−28, −6, 2), (B) right posterior putamen (28, −2, 0), (C) pons (PPN; 8, −32, −32), and (D) left ventral thalamus (−8, −24, 2). Data are presented for each pair of movement (M*pred *= motor execution task) and rest (S = sensory reference task) both during (ON) and without (OFF) levodopa infusion (SD are represented by error bars). The values represent those from the voxels demonstrating the largest activation response. NS = not significant.*

error may represent a very early subclinical manifestation of this side effect of medication. Supporting this contention is the observation from earlier studies that GPi DBS improves spatial error in our motor task;[6] both GPi DBS and pallidotomy are known to suppress dyskinesias as well.[19] Furthermore, our correlational analyses demonstrated that the worsening in spatial error correlated with changes in the cerebellum, a region that would be expected to be hyperactive in patients with dyskinesias. However, given that GPi DBS also produces cerebellar activation while suppressing dyskinesias,[6] the role of the cerebellum in generating dyskinesias remains uncertain. Perhaps increased cerebellar activation during motor execution is a feature common to symptomatic therapies for PD.

We found that levodopa infusion enhanced activation responses during the performance of the M*pred* task. This was accomplished using an experimental design in which task parameters were kinematically controlled across levodopa conditions. Thus, the levodopa-related increases in activation responses were not confounded by potential changes in movement rate and extent that could have occurred with this intervention. Additionally, we employed a rigorous method to specify discrete sets of voxels for hypothesis testing and generation.[1,3,4,6] The hypothesis that levodopa affects activation in areas comprising the motor CSPTC loop was tested by restricting the search for rCBF changes to a fixed set of voxels in which significant motor activation responses had been previously documented in a large independently studied cohort. Preexisting $H_2{}^{15}O$/PET scans of normal subjects and untreated PD patients were used to create a population M*pred* − S mask for testing this notion.[6] Within this hypothesis-testing voxel space, we detected significant effects of levodopa on motor activation in the putamen bilaterally, left thalamus, and pons. The fact that these regional changes were localized to voxels situated in the hypothesis-testing mask, and were also significant at the relatively conservative threshold of $p < 0.005$ that was corrected for multiple comparisons, supports the contention that levodopa modulates rCBF during movement at specific nodes of the motor CSPTC pathways.

Surprisingly, we did not observe increases in activation in motor or supplementary motor (SMA) cortices. Prior studies have found increases in SMA and sensorimotor cortex activation with the performance of sequential motor tasks.[20,21] One possible explanation for these differences is that by using a rigorous method of kinematically controlling the extent of movement, we were able to more effectively mitigate the potential confounder of increased motor activity during the "on" state. Furthermore, all our subjects performed the task at a rate of one movement per 1.5 seconds, and this was controlled across subjects and

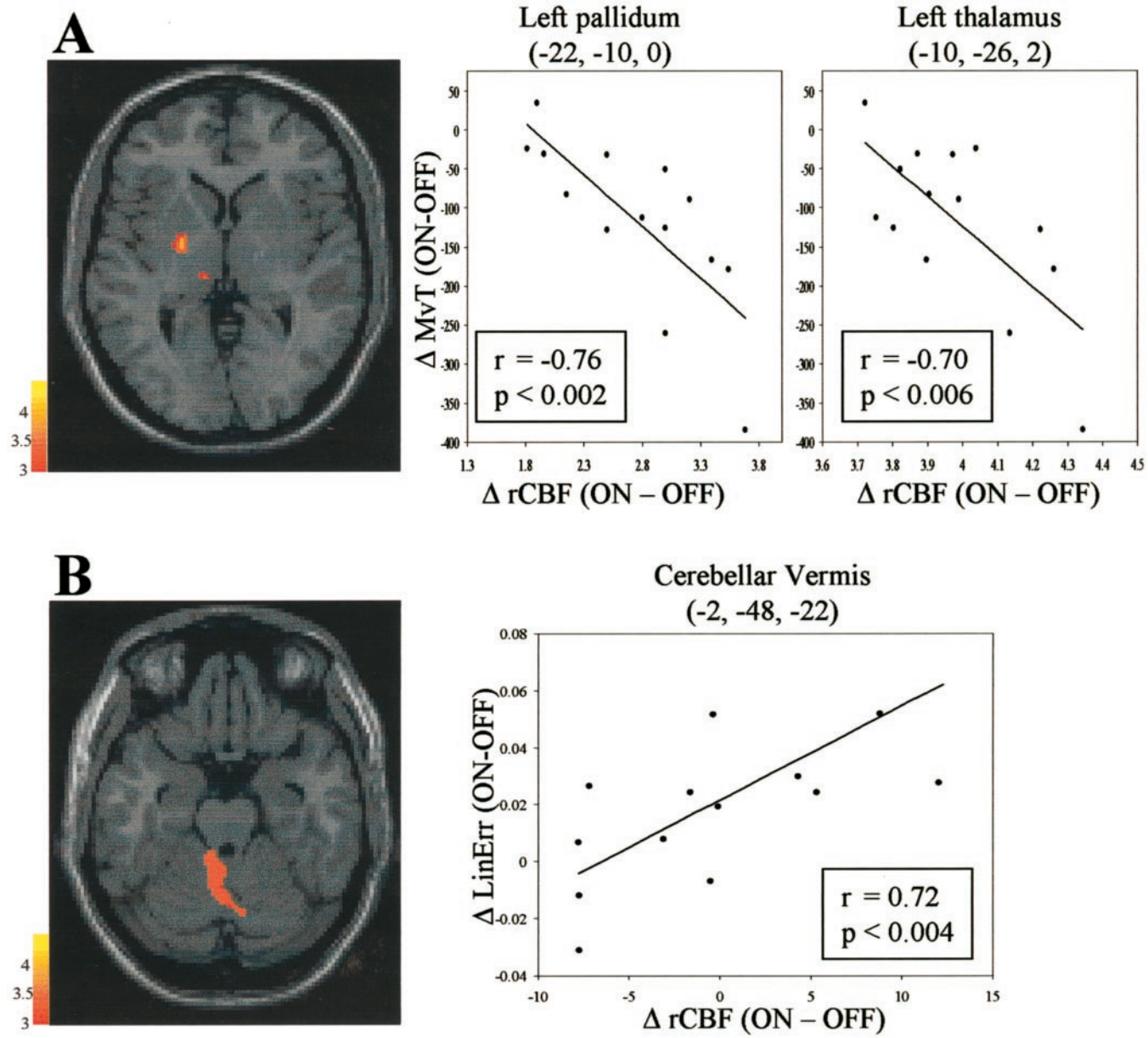

Figure 3. Brain region associated with significant correlations between levodopa-mediated changes in motor performance parameters and regional cerebral blood flow (rCBF) during movement. With levodopa infusion, improvement in movement time (MvT) (A) correlated with increases in rCBF in the left globus pallidus and left ventral thalamus. Worsening in spatial error (B) correlated with rCBF increases in the cerebellar vermis. ON = levodopa infusion; OFF = no levodopa infusion. (The color stripe represents z scores at a threshold of at 2.56 [p < 0.01].)

Table 3 *Brain regions with significant correlations between changes in motor performance and rCBF with levodopa infusion in PD*

	Movement time				Spatial error			
	Coordinate (mm)				Coordinate (mm)			
Brain region	*x*	*y*	*z*	*z* score	*x*	*y*	*z*	*z* score
Left globus pallidus	−22	−10	0	3.5				
Left thalamus (ventral)	−10	−26	2	2.8				
Cerebellar vermis					−2	−48	−22	3.0

rCBF = regional cerebral blood flow.

conditions. SMA activation may be more relevant for slower movements, as was the case in the earlier PET study conducted at a rate of one movement per 2.5 seconds.[20] Finally, M*pred* may be a more externally driven task; it is rhythmic, driven by a tone, and performed in a timed response mode. By contrast, the prior joystick studies may have required comparatively more internal generation of movement and SMA activation. Our finding of no change in rCBF in the resting state (S task) during levodopa infusion in patients chronically exposed to levodopa conforms with findings of prior studies[20,22] and validates its use as a baseline reference task.

We previously found that PDRP is a reproducible pathologic resting network that is reduced by surgical and medical therapies for PD.[1,2,4,6] PDRP activity is directly related to abnormal pallidal output,[23] which is acutely suppressed by dopaminergic pharmacotherapy.[24] Motor improvement in PD therefore appears to require the suppression of pallidal output, which can be quantified by measuring PDRP expression. This metabolic effect in the resting condition results in rCBF activation within the motor CSPTC loop and cerebellocortical system both with dopaminergic therapy and with surgical therapies. Nonetheless, despite the common mechanism of PDRP suppression, the specific nodes modulated by therapy may differ. For example, levodopa appears to exert its effects predominantly subcortically within the striatopallidothalamic system, whereas GPi DBS appears to functionally target the thalamocortical system.[6]

An important strength of this study is that the motor activation paradigm was performed by the same subjects who had participated in the study of the effect of levodopa infusion on resting state brain metabolism.[1] Therefore, the differences between the effects of levodopa on resting state function (suppression of abnormal pallidal output) and during motor activity (increase in the function of components of the normal motor CSPTC loop) cannot be accounted for by differences in patient population, disease severity, duration of exposure to levodopa, or other factors. We propose that levodopa facilitates the activity of brain motor circuits during movement by dampening the noise associated with these functional pathways at rest. In addition, levodopa may also concurrently affect the activity of cerebellocortical pathways, leading to the development of motor complications such as dyskinesias.

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