# Effects of levodopa on motor sequence learning in Parkinson's disease

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**Abstract—***Background:* Dopaminergic therapy with levodopa improves motor function in PD patients, but the effects of levodopa on cognition in PD remain uncertain. *Objective:* To use $H_2{}^{15}O$ and PET to assess the effect of levodopa infusion on motor sequence learning in PD. *Methods:* Seven right-handed PD patients were scanned "on" and "off" levodopa while performing a sequence learning task. The changes in learning performance and regional brain activation that occurred during this intervention were assessed. *Results:* During PET imaging, levodopa infusion reduced learning performance as measured by subject report ($p < 0.05$). This behavioral change was accompanied by enhanced activation during treatment in the right premotor cortex and a decline in the ipsilateral occipital association area ($p < 0.01$). Levodopa-induced changes in learning-related activation responses in the occipital association cortex correlated with changes in learning indexes ($p < 0.01$). *Conclusions:* Levodopa treatment appears to have subtle detrimental effects on cognitive function in nondemented PD patients. These effects may be mediated through an impairment in brain activation in occipital association cortex.

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Levodopa may cause hallucinations and confusion in patients with PD, and these side effects appear to occur more commonly in patients with dementia.[1,2] Careful neuropsychological testing, however, can detect subtle cognitive abnormalities even in early-stage PD,[3,4] and in these patients, it remains unclear whether levodopa has beneficial or adverse effects on cognition.[5,6]

PET imaging during levodopa infusion provides a means of studying the mechanisms of clinical benefit and side effects afforded by this intervention. Previous PET studies using both fluorodeoxyglucose and $^{15}O$-labeled water ($H_2{}^{15}O$) to assess the respective effects of levodopa on resting state metabolism[7] and on regional brain activation during simple motor execution[8] have demonstrated that medication-induced improvement in parkinsonian symptoms is associated with the suppression of a PD-specific metabolic brain network (PD-related pattern) at rest and with the enhancement of the activity of several nodes of the motor corticostriatopallidothalamic (CSPTC) circuit during movement.[9]

Levodopa may also affect the functioning of neural pathways relating to complex behavior. In early to moderate PD, specific aspects of executive function may be either improved or worsened by levodopa.[5,6,10-20] The mechanism by which levodopa might alter performance on complex neurobehavioral tasks is unknown, although involvement of nonmotor CSPTC circuits is likely.

We have developed a series of motor learning tasks designed to evaluate the functioning of these neural pathways with imaging.[21,22] In a recent study, we used PET to scan unmedicated early-stage PD patients and normal control subjects during motor sequence learning.[22] Although the learning achieved during the PET epoch was lower in the PD patients, performance in both groups correlated significantly with the activity of a common network of brain regions comprising the dorsolateral prefrontal cortex (DLPFC), the premotor cortex (PMC), and the posterior parietal cortex. Whereas internal pallidal deep brain stimulation (GPi DBS) can improve sequence learning in moderately advanced PD,[23] the effects of dopaminergic medication on regional brain activation responses during learning have not been investigated.

In the current study, we used the general imaging approach that we developed to assess the effects of antiparkinsonian interventions on brain function.[8,22-25] These studies were done as part of the levodopa infusion experiments described above.[7,8] We scanned seven PD patients with $H_2{}^{15}O$ PET "on" and "off" levodopa while they performed a motor sequence learning task and a kinematically controlled motor execution reference task. The PET data were used to determine

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***Table 1*** *Subject characteristics*

| Patient no. | Age, y | Sex | Hoehn and Yahr stage | Levodopa infusion dose, mg/h | UPDRS* "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 |

* Unified Parkinson's Disease Rating Scale (UPDRS) motor ratings ("off"/"on" levodopa).
† Clinical improvement, defined as ([levodopa "off" − "on"]/levodopa "off") × 100%.
‡ 1 = levodopa/carbidopa; 2 = dopamine agonist; 3 = anticholinergic; 4 = selegiline.

whether levodopa infusion significantly alters local activation responses during motor sequence learning.

**Patients and methods.** The subjects consisted of seven right-handed PD patients (age 60.1 ± 5.7 years; Hoehn and Yahr stage 2.0 ± 0.9) who underwent PET imaging during levodopa infusion. The details of this procedure, the clinical characteristics of the subjects, and the levodopa infusion rates and plasma concentrations have been reported previously[7,8] and are summarized in table 1. *Study design.* Patients were studied over a 3-day treatment period as described previously.[23,25] 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 the selection of experimental parameters for the PET studies. Imaging was performed over the next 2 days, with treatment condition randomized to being "on" one day and "off" the other. On the "on" day, levodopa infusion rates were adjusted to achieve maximal improvement in the motor portion of the Unified Parkinson's Disease Rating Scale (UPDRS items 19 to 31)[26] without inducing dyskinesia. Imaging in the "on" condition commenced once a clinical steady state was demonstrated by ≤5% variation in UPDRS motor ratings performed every 30 minutes. The presence of a steady state was confirmed by the measurement of plasma levodopa levels at multiple time points during the infusion.[7]

*Behavioral tasks.* Because levodopa can affect the execution of simple movements and potentially also the learning of sequential movements, we assessed the effects of therapy on each behavior separately. In each treatment condition, subjects performed two kinematically matched reaching tasks during PET imaging[1]: a motor sequence learning task (ML) and[2] a motor execution reference task (MR). The characteristics of these tasks have been described in detail previously.[21-23] In both tasks, subjects moved a cursor on a digitizing tablet with their right hand. Movements were out and back from a central starting position to one of eight radial targets displayed on a computer screen. Target extent was 1 cm. Targets appeared in synchrony with a tone at a 1.5-second intertone interval. Subjects were instructed to reach for each target from the starting point and to synchronize the reversal of their movements with the tone. In the ML task, the eight targets appeared in a pseudo-random repeating order without repeating elements.[22] The subjects were instructed to discover and learn the sequence order so as to anticipate the target and reach it as it appeared. At the end of each block trial, subjects were asked to indicate the order of the sequence verbally. During training sessions conducted before imaging, each subject experienced two or three different sequences; during PET scanning, entirely different sequences were employed. In the MR task, targets appeared in a predictable counterclockwise order. To reach the target in synchrony with the tone, subjects had to initiate movement before it appeared. All trial blocks lasted 90 seconds. Experimental task parameters were held constant across treatment conditions.[25] A Macintosh (Apple) computer generated screen displays and acquired kinematic data from the digitizing tablet at 200 Hz as described previously.[21,27]

*Learning performance: behavioral measure.* Because subjects were instructed to identify the sequence explicitly and to reach for the correct target before it appeared, anticipatory movements to the correct target were considered to reflect explicit learning. (Movements were considered anticipatory according to reaction time criteria defined previously.[22,23] Correct responses were defined as movements with directional error of ≤22° at peak velocity.) In each scan, learning performance was quantified by the total number of correctly anticipated movements during the 90 seconds of PET imaging. This psychophysical measure was termed the global learning index. We also obtained a declarative score defined as the number of accurate target locations reported by the patient at the end of each trial block (0 = no awareness of a repeating sequence to 8 = complete correct sequence). Changes in the learning measures with therapy were assessed by comparing "on" and "off" values with paired Student's *t*-tests. Changes were considered significant for $p < 0.05$ (two tailed).

*PET.* Patients were scanned on consecutive days in the "on" and "off" treatment conditions. They fasted overnight prior to both imaging sessions. PET studies were performed in three-dimensional mode using the GE Advance (St. Louis, MO) tomograph at North Shore University Hospital (Manhasset, NY).[28] In each of the two PET sessions ("on" and "off"), subjects were scanned while performing the ML and MR tasks in randomized order. All subjects performed the two tasks twice in each treatment condition. Psychophysical recording of learning performance was acquired with every run. 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 regional cerebral blood

***Table 2*** *Performance indexes*

| Patient no. | Global learning index* "Off" | Global learning index* "On" | Declarative score† "Off" | Declarative score† "On" |
|---|---|---|---|---|
| 1 | 1.81 | 2.38 | 1.5 | 1.5 |
| 2 | 3.38 | 1.50 | 2.5 | 3.5 |
| 3 | 1.94 | 2.31 | 5 | 3 |
| 4 | 1.75 | 1.13 | 1 | 2 |
| 5 | 2.00 | 1.13 | 4 | 1.5 |
| 6 | 2.50 | 1.81 | 6 | 5 |
| 7 | 2.94 | 2.69 | 7.5 | 3 |
| Average (SE) | 2.33 (0.79) | 1.85 (0.79) | 3.93 (1.55) | 2.79 (1.12) |

* Mean number of correctly anticipated movements per cycle (see text).
† Number of correctly reported target locations averaged across trial blocks (see text).

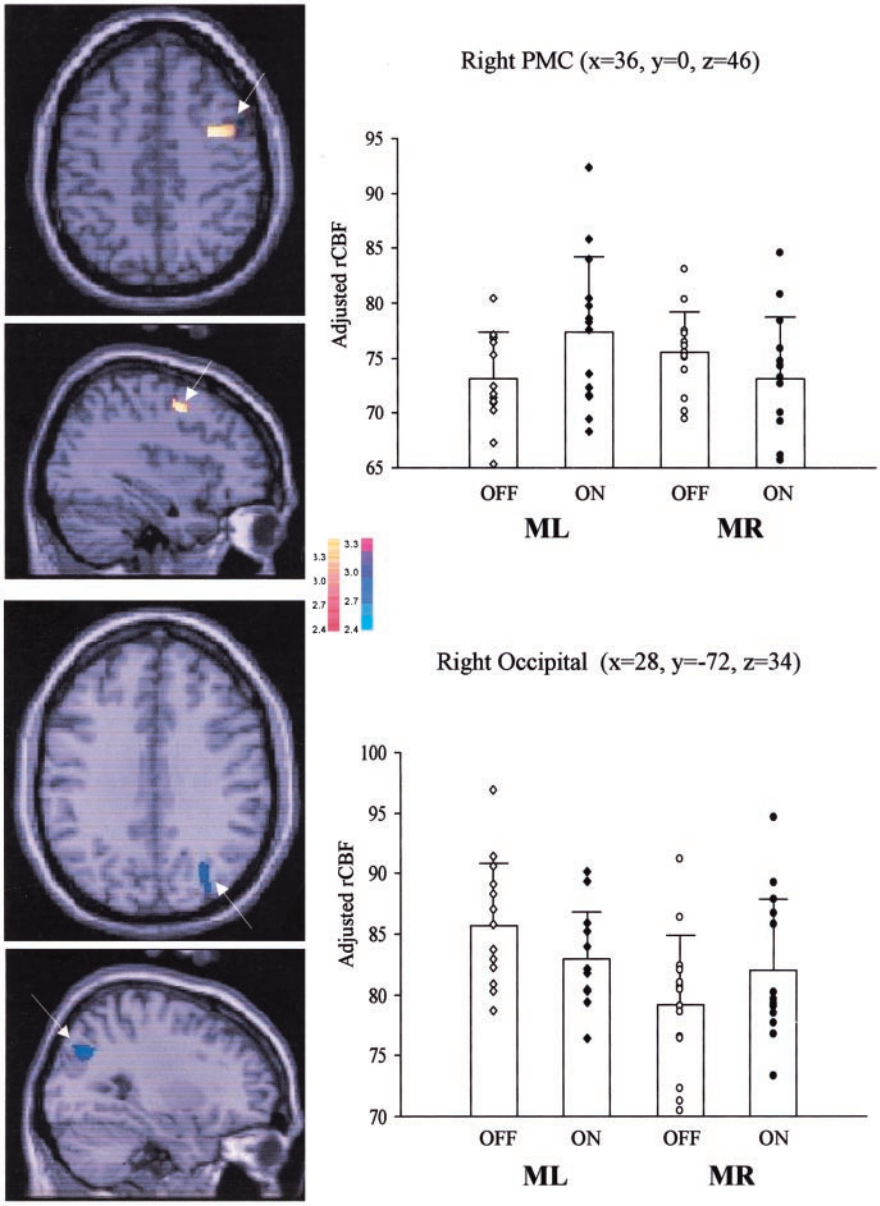


*Figure 1. Brain regions in which levodopa therapy significantly altered regional cerebral blood flow (rCBF) during motor sequence learning. Bar graphs of rCBF measured during the motor learning (ML) task and the motor execution reference (MR) task are presented to the right of each image. Levodopa infusion increased rCBF during learning in the right premotor cortex (PMC) (top) and reduced rCBF in the right occipital association cortex (bottom). In these brain regions, there were no significant effects of either intervention on rCBF measured during the motor execution reference task (see text). The color stripe represents* Z *scores thresholded at 2.56,* $p < 0.01$. *SD are represented by error bars.*

flow (rCBF) was estimated using a modification of the slow bolus method[22,29]; values were corrected for global CBF. 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.

*Treatment effects on brain activation during learning.* We sought to identify brain regions in which levodopa infusion significantly altered rCBF during motor sequence learning. This was achieved with SPM 99 software (Wellcome Department of Cognitive Neurology, London, UK) using a two-factor analysis of variance (ANOVA) that included all four conditions (ML"$_{on}$", MR"$_{on}$", ML"$_{on}$", MR"$_{off}$").[23] In this way, we assessed treatment effects on activation during learning as well as potential interaction effects with motor execution. All scans were entered simultaneously in the design matrix, and the differences were detected by specifying a contrast of (1, −1, −1, 1). We hypothesized that during learning, treatment would alter rCBF within the set of voxels known through previous $H_2{}^{15}O$ PET studies to be specifically activated by the ML task. To confine statistical analysis to this known set of voxels, we created a mask defined by (ML − MR) rCBF differences obtained in an independent population comprising 22 unmedicated PD patients and 18 normal volunteers who performed both tasks.[23] This mask was compiled with 73 pre-existing learning and reference scan pairs and was thresholded at $p < 0.001$. The mask included bilateral learning-related rCBF increases in the DLPFC, PMC, pre-SMA, precuneus, and posterior parietal cortical regions. Treatment effects on learning activation within the population mask were considered to be hypothesis driven and significant for $p < 0.01$ (uncorrected for independent multiple comparisons). Treatment effects outside this mask were considered to be hypothesis generating for $p < 0.001$ (uncorrected for multiple comparisons) and significant if they survived a correction for multiple comparisons at $p = 0.05$.

Additionally, we determined whether the effects of treatment at each significant voxel were specific for learning or whether they were confounded by the effect of treatment on motor execution. This was achieved by post hoc testing to assess changes in MR activation in the voxels that exhibited significant effects of intervention during ML task performance. RCBF changes at these voxels were considered to relate to motor execution if the "on"–"off" differences in rCBF during MR performance were significant for $p < 0.05$ (paired Student's *t*-test, two tailed). We also performed a separate SPM correlational analysis between "on"–"off" scans and the change in the global learning index. Correlations were considered significant for $p < 0.01$ (uncorrected).

**Results.** *Treatment effects on learning performance.* Measures of learning performance in the "off" and "on" states are presented

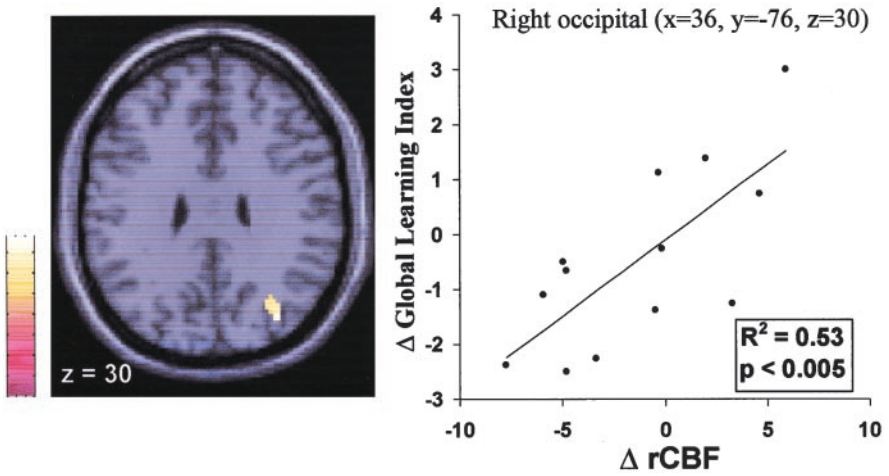


*Figure 2. Brain regions in which levodopa-induced changes in regional cerebral blood flow (rCBF) during motor sequence learning correlate with changes in an on-line measurement of global learning (see text). The global learning index correlated with levodopa-mediated changes in rCBF in right occipital association cortex (left). At the $Z_{max}$ for the correlation, $R^2 = 0.53$, $p < 0.005$ (right).*

for each patient in table 2. UPDRS motor ratings improved on levodopa from 25.7 ± 9.9 to 16.6 ± 6.7 (34.3%; $p < 0.01$). Levodopa infusion did not significantly alter the global learning index ($p = 0.3$), but there was a reduction in the declarative score ($p < 0.05$) (see table 2). Changes in learning measures with therapy did not correlate ($R^2 < 0.15$) with reductions in UPDRS motor ratings.

*Treatment effects on brain activation during learning.* Areas in which levodopa significantly enhanced learning-specific activation responses ($[ML - MR]_{"on"} > [ML - MR]_{"off"}$) are presented in figure 1. Hypothesis-driven searches within the ML − MR population mask revealed enhanced activation in the right PMC (Brodmann area [BA] 6) but not in other brain regions. In addition, levodopa infusion gave rise to significant declines in learning-related activation that were localized to the right occipital association cortex (BA 19). SPM correlational mapping revealed that the levodopa-induced decline in the latter region ($Z_{max} = 3.25$; $x = 36$, $y = -76$, $z = 30$; $p < 0.005$, uncorrected) was related to "on"–"off" changes in the global learning index (figure 2).

All significant effects of intervention on ML activation were localized to brain regions lying within the mask. In these regions, treatment did not have a significant effect on blood flow during MR task performance (see figure 1, bar graphs; table 3).

**Discussion.** We found that levodopa impaired aspects of sequence learning performance in nondemented PD patients. Specifically, the worsening in declarative score during our motor sequence learning task suggests that levodopa may have negative effects on aspects of cognitive processing linked to target retrieval.[22] The PET results indicate that this behavioral change may be related to defective activation of cortical association pathways, most notably in the parieto-occipital region. These findings contrast dramatically with those of a prior study demonstrating improved motor sequence learning following GPi DBS.[23] In that study, we found that motor improvement comparable with that achieved with levodopa was accompanied by enhanced, rather than reduced, sequence learning. These cognitive effects were mediated by activation of prefrontal–parietal association pathways that normally mediate learning performance. These observations suggest that comparably effective therapies for PD may have quite different effects on nonmotoric features of the disease because of differences in the modulation of higher-order CSPTC and related transcortical circuits.[9] It should be noted, however, that our findings are limited to the specific cognitive domains required for our motor sequence learning task, and prior reports have found worsening in some cognitive domains with subthalamic nucleus DBS as well.[30,31]

Brain regions known to be involved in the normal learning of new movement sequences include DLPFC, PMC, posterior parietal cortex, and the occipital association area.[22,32] As mentioned above, we have found that GPi DBS can enhance activation in these areas during motor sequence learning, resulting in improved performance.[23] By contrast, the current study demonstrates a worsening in motor sequence learning with levodopa infusion despite increases in brain activation in PMC. The notable absence of DLPFC activation on levodopa suggests that this region may be critical in the performance of our

***Table 3*** *Brain regions in which levodopa infusion significantly altered regional activation during motor sequence learning*

| | Coordinates, mm | | | | | | Mean adjusted cerebral blood flow, mL/min/100 g | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Brain region | *x* | *y* | *z* | *Z* score | *p* voxel | *p* cluster | $ML_{"off"}$ | $ML_{"on"}$ | $MR_{"off"}$ | $MR_{"on"}$ |
| Increases | | | | | | | | | | |
| Right PMC (BA 6) | 36 | 0 | 46 | 3.30 | <0.001 | <0.05 | 73.1 ± 4.2 | 77.4 ± 6.8 | 75.5 ± 3.7 | 73.2 ± 5.6 |
| Decreases | | | | | | | | | | |
| Right occipital (BA 19) | 28 | −72 | 34 | 3.15 | <0.001 | NS | 85.7 ± 5.1 | 83.0 ± 3.9 | 79.2 ± 5.7 | 82.0 ± 5.9 |

*p* values are uncorrected for multiple comparisons.

ML = motor sequence learning task; MR = motor execution reference task; PMC = premotor cortex; BA = Brodmann area.

task. In fact, the role of the DLPFC in the early phases of motor sequence learning is widely accepted.[22,33-35] We hypothesize that the failure to improve activation responses in DLPFC on levodopa may stem from the diminution in $D_2/D_3$-receptor binding in this region that has been reported with PET in PD patients.[36] The resulting inability to enhance activation of DLPFC with levodopa may be the primary reason for the lack of improved motor learning with levodopa therapy, but this is unlikely to fully explain the actual decrement in motor learning with levodopa that we observed.

It is noteworthy that levodopa decreases activation of occipital association cortex (BA 19) during motor sequence learning. By contrast, we found that GPi DBS enhanced activation in this region.[23] The reason for the decline in learning-related activation in this cortical region during levodopa administration is not obvious, but this change may underlie the decline in motor learning performance, as this brain region has been linked to the implicit learning of visual elements in a sequence and their relationship to motor responses[37] and to explicit aspects of sequence learning.[21] It is possible that levodopa can affect the activity of learning pathways with varying behavioral impact depending upon dose. In an extreme case, perhaps reductions in the functional activity of the occipital association cortex may be the basis for the visual hallucinosis that can be produced by dopaminergic therapy. This may be a direct effect of dopamine, as dopamine receptors have been identified in occipital association cortex,[38,39] and changes in occipital glucose metabolism have been described in patients with Lewy body dementia.[40,41] Alternatively, reduced posterior cortical activation may represent an epiphenomenon of levodopa treatment in which impaired DLPFC function results in decrements in downstream nodes of transcortical learning pathways. Last, it is conceivable that levodopa might have a general negative effect on visual attention. We note that there may have been residual effects of dopaminergic therapy even in the "off" condition 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" conditions, rather than alter the nature of the results. Although a longer period of withholding medications would be ideal, this would not have been practical.

Comparable therapeutic interventions for the motor features of PD may have disparate effects on cognitive function. Despite the likely similar effects of treatment on motor CSPTC pathways,[7,42,43] different therapies may affect other pathways related to cognition and behavior in varying ways. For example, focal stereotaxic interventions in the pallidum or subthalamic nucleus do not inherently interfere with the functioning of corticocortical pathways. Therefore, assuming that the individual cortical nodes of these functional networks remain structurally intact, a surgical intervention at a remote site in the basal ganglia may facilitate brain activation and sequence learning, perhaps by reducing noisy pallidal output. By contrast, less specific treatments such as levodopa infusion can improve motor signs but may also affect the functioning of dopaminoceptive fields in the cerebral cortex.[39] Indeed, direct pharmacologic alteration of the function of the DLPFC and its efferent projections may interfere with the normal rostrocaudal transfer of information that is fundamental to the explicit learning process.[33] Whether this is a feature of all dopaminergic therapy for PD or just levodopa is a topic of further investigation.


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