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Performance of a motor task learned ON levodopa deteriorates when subsequently practiced OFF

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Abstract

Background—Studies in animals and in people with Parkinson's Disease (PD) demonstrate complex effects of dopamine on learning motor tasks; its effect on retention of motor learning has received little attention. Recent animal studies demonstrate that practicing a task in the OFF state, when initially learned in the ON state, leads to progressive deterioration in performance.

Methods—We measured the acquisition and retention of 3 different motor tasks in the presence and absence of levodopa. Twenty individuals with Hoehn and Yahr Stage 1.5–3 PD practiced the tasks for two, 4-day weeks, half practicing ON levodopa the first week and OFF the second week. The other half practiced OFF levodopa both weeks. The tasks were: 1. alternate tapping of two keys, 2. moving the body toward two targets on a posturography device and 3. mirror drawing of a star.

Results—For the finger tapping and body movement tests, those who practiced ON the first week had a progressive decline in performance with practice during Week 2, while subjects OFF during Week 1 maintained or improved. In contrast, for the mirror task, subjects ON levodopa initially had much more difficulty completing the task compared to subjects who practiced OFF.

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Authors' Roles

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Fay Horak: protocol design, manuscript review and critique

Michael Lasarev: statistical analysis design and execution

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Both groups improved with practice during the first week and had flat performance the second week.

Conclusions—These data suggest that performance of speed-accuracy tasks learned in the ON state may progressively worsen if practiced in the OFF state. In addition, performance, but not learning, of some tasks may be impeded by levodopa.

Keywords

levodopa; learning; Parkinson's

Introduction/Background

Levodopa and, presumably, elevations of brain dopamine from levodopa, have complex effects on learning new motor tasks in animals with dopamine deficiency and in humans with PD. In this study we sought to examine the effect of levodopa on the acquisition and retention of three different motor tasks in individuals with Parkinson's disease (PD).

Most studies demonstrate that implicit motor sequence learning becomes impaired as PD progresses.^{1,2} The effects of levodopa on motor learning are mixed, in part due to the heterogeneity of motor learning tasks studied and severity of disease. Levodopa has had little effect on implicit motor learning on such exercises as serial reaction time^{3,4} and probabilistic learning.⁵ Levodopa impairs explicit motor sequence learning in early PD⁶ but restores learning on a different explicit motor learning sequencing task.⁷ Levodopa has also had a negative impact on feedback-based learning requiring error-correction⁸ and on tasks requiring “reversal learning,” or unlearning of previously learned responses.⁹⁻¹² Levodopa also has differential effects on feedback-based learning, with impaired learning seen with levodopa when negative reinforcement is used.¹³

The bulk of studies on learning in humans have evaluated the effect of levodopa over one day of testing, thereby focusing on the acquisition phase of learning. Little is known regarding how practice in the OFF state affects performance of new tasks initially learned in the ON state. Parkinsonian rodents have demonstrated retention of motor learning acquired in the ON state which was subsequently lost with practice in the OFF state,¹⁴ but this has not been demonstrated in humans. In this study we examined motor learning over the course of two 4-day weeks, to determine whether practice effects after learning ON levodopa may be progressively reversed by subsequent practice OFF levodopa. In addition, we asked whether performance of a new task is improved or impaired by levodopa, in two types of tasks: a hand and a postural movement task requiring speed-accuracy tradeoffs for achieving the target and a visual-motor transformation task requiring inhibition or reversal of previously learned behavior.

Methods

a. Participants

Twenty subjects were recruited from patients associated with a university Movement Disorders program (see Table One, Subject Demographics). Inclusion criteria included mild to moderate idiopathic Parkinson's disease consistent with established guidelines.¹⁵ All participants had been treated with levodopa for at least one year, reported a good response to the medication and had been on a stable dose for at least a month. Levodopa response was established by clear history upon screening, and confirmed via chart review and additional investigator phone interview if indicated. Exclusion criteria included cognitive impairment, atypical parkinsonism, psychosis, or other musculoskeletal or systemic illness which could

affect participation in the study. All received informed consent via procedures approved by the OHSU Institutional Review Board.

b. Tasks

Finger tapping (upper extremity speed-accuracy task)—Subjects alternately tapped between two manual counters for one minute, repeated for 5 sets, with one-minute breaks between sets. They were asked to tap as quickly and accurately as possible. Outcome measured was number of taps per minute. The finger tapping task has been used in prior studies of individuals with PD as a measure of bradykinesia and levodopa response.¹⁶

Center of Mass (CoM) Movement velocity (whole body speed-accuracy task)—Subjects moved their body center of mass to targets indicated on the Neurocom Equitest® posturography device. This system is comprised of two force plates connected to a computer with a monitor visible to the subject. The force plate records shifts in the center of pressure under the feet as the subject leans towards one of two predetermined, square targets in space, using a computer generated stick figure image as visual guidance. The two targets require the subject to alternately lean forward to the left and forward to the right for 15 repetitions daily. The outcome was movement velocity, or average speed of center of gravity movement toward the target, in degrees per second. Other studies in individuals with Parkinson's disease have demonstrated that practice of this task results in motor learning in the form of improved movement velocity.¹⁷ Movement velocity results were calculated as summed scores for speed of movement (degrees per second) towards each of the two targets each trial, based on previous studies demonstrating no significant difference in laterality of performance on this task in individuals with PD.¹⁷

Mirror drawing (visual-motor transformation task)—Subjects used a computer mouse to draw a star-shaped figure on a computer screen. The star figure was comprised of a series of dots on the screen; each dot appeared in fixed sequence after the subject clicked on a dot with the mouse to make the next dot appear. The mouse was programmed “backwards” requiring the subject to move his or her hand in the opposite direction of the cursor on the screen to successfully complete the figure. Thus, the subject had to inhibit the normal manner in which to draw a line to each succeeding dot and institute the opposite movement in response to the visual cue. The outcome measured was the average time, in seconds, to complete the task. The task was repeated nine times each day. PD patients have demonstrated motor learning on mirror-reversed vision tasks in some previous studies^{18,19} but not in another when participants practiced for one or three days.²⁰

c. Protocol

Subjects were randomized into 2 groups: 1) ON-OFF: learn the tasks for a week in the ON levodopa state after taking their usual morning dose of medication one hour before testing or 2) OFF-OFF: learn the tasks for a week in the practical OFF levodopa state, defined as taking their last levodopa dose before midnight the night before testing. Randomization was assigned via irregular group assignments in a pattern established at the beginning of the study; eg, the first 3 subjects were in the ON-OFF Group, the second 2 subjects in the OFF-OFF Group, etc. Both groups practiced the motor tasks for a second week in the OFF levodopa state. Thus, subjects in the OFF-OFF Group practiced OFF levodopa both weeks. The subjects participated in two sequential weeks of testing consisting of four days each week. Most subjects had a three day break over the weekend between Week One and Week Two, but there were exceptions due to scheduling issues and holidays. One subject in the ON-OFF Group had a one day break, one subject in the ON-OFF Group and two subjects in the OFF-OFF Group had a two day break, and two subjects in each group had a four day break. Most subject visits occurred at 8 am in the morning. Subjects resumed their usual

medication regimen following testing each morning. A UPDRS motor score was taken each day of testing, and a Montreal Cognitive Assessment (MOCA) was obtained the final day of testing.

d. Analysis

On any given testing day, each measured response consisted of multiple trials on the tasks: 9 trials of mirror drawing, 5 trials of finger tapping, or 15 trials on the CoM movement velocity task. The analysis proceeded by first computing the median response among the trials of one task and then analyzing these medians for changes over time, changes between groups and for whether the changes over time differed between groups. Generalized estimating equations^{21,22} (GEE) were used for all analyses to account for the correlated nature of the measurements across time. All models utilized an autoregressive lag-1 (AR1) correlation structure and employed a robust sandwich estimator of the variance for all hypothesis tests and confidence intervals. Different probability distributions were used depending upon the type of response: Finger Tapping (counts per minute) was modeled as Poisson; Body Movement (CoM velocity) was modeled as normal and mirror drawing (a latency time) was modeled according to a gamma distribution. Secondary questions regarding retention of learning from Week One to Week Two were considered by applying the above methods to responses from only the last day's testing (of Week One) and the first day of testing during Week Two. Statistical significance was held to 0.05 and all tests are two-sided.

5. Results

Twenty-one subjects passed telephone screening and were enrolled in the study. One subject withdrew during the first week due to scheduling conflicts, leaving a total of ten subjects per group. The two groups were comparable with regard to age, average levodopa dose, Hoehn & Yahr stage, MOCA score, and UPDRS off medication (Table One). Subjects in the ON-OFF group had a significantly lower average UPDRS score for Week One when they were tested ON levodopa compared to Week Two, OFF levodopa, suggesting a clinically significant response to levodopa. Subjects in both groups had minimal dyskinesia, reflecting relatively mild to moderate PD in both groups.

a. Finger Tapping

Week 1: The two groups had the same average tapping speed on Day One. Both the ON-OFF group and the OFF-OFF group improved their performance on the finger tapping task during Week One, with no significant difference ($p=0.96$) between the two groups at any point during the four testing sessions (Figure 1 and Suppl. Table 1, Finger Tapping). The rate of improvement did not differ between the two groups ($p=0.23$) with both groups experiencing a 3.9% (95% CI: 2.7—5.0%; $p<0.001$) increase in the mean number of taps per minute per day.

Week 2: Both groups started Week Two with an average of 135 (95% CI: 122-150) taps per minute during their first session, a value comparable to the performance of both groups at the conclusion of the first week's testing. However, the performance of the ON-OFF Group declined as they practiced OFF levodopa during Week Two, with a decrease in tapping speed of 2% per day (95% CI: 0.1—3.3%; $p=0.039$). In contrast, the OFF-OFF Group continued to show an increase of 4.4% per day (95% CI: 2.4—6.3%; $p<0.001$) in mean number of taps per minute during the first two days of Week Two, then leveled off during days 3 and 4 [Figure 1].

b. CoM Movement Velocity

Week 1. The two groups started Week One with no difference in movement velocity ($p=.221$). During Week One, both ON-OFF and OFF-OFF groups demonstrated a significant increase in movement velocity that did not differ between groups ($p=0.60$) (Fig. 1 and Suppl. Table 2, CoM Movement). For both groups, each additional day of testing was associated with a .35 degrees per second increase in the mean combined response (95% CI: 0.11–0.60 degree/sec. increase; $p=0.004$). The two groups did not differ significantly on any given testing day ($p=.221$), averaging only 1.35 degrees per second lower in the OFF group than the ON group.

Week 2. On the first day of the second week, when both groups practiced without levodopa overnight, average performance was comparable between groups ($p=.82$). Over the following three days, the two groups demonstrated a pattern of performance similar to that observed on the finger tapping task. The ON-OFF Group, who trained when ON levodopa, had a significant worsening of performance, with each day of practice associated with a decrease of .47 degrees per second (95% CI: 0.15–0.78 degree/sec. decrease; $p=0.004$). The OFF-OFF Group, who practiced the task when OFF levodopa during Week One, had an insignificant ($p=0.87$) decrease of 0.02 degrees per second for each additional day of practice. Although the two groups were not significantly different at any of the four specific testing days during this second week, changes in performance over time did differ between the groups ($p=0.017$; test of group:day interaction).

c. Mirror Drawing

Week 1. At the beginning of Week One, subjects ON levodopa took almost three times as long to complete the mirror drawing of the star than those OFF levodopa (2.86 [95% CI: 1.35–6.25 times as long], $p=0.006$) (Suppl. Table 3, Mirror Drawing). From this point, both groups demonstrated significant improvements in performance, although the two rates of improvement significantly differed between groups ($p=0.004$; test of group:day interaction). The ON-OFF Group decreased their time to complete the mirror drawing by 24% each additional day of testing (95% CI: 14–33%; $p<0.001$) while the OFF-OFF Group decreased their time by 8.6% (95% CI: 5–12%; $p<0.001$) each additional day of testing. The rate of improvement was significantly different between groups ($p=0.004$). These trends are displayed in Figure 1.

Week 2. At the beginning of Week Two, both groups had mirror drawing times comparable to their performance at the end of Week One ($p=.73$) and did not improve further with practice. In this second week, the pattern of performance over time was essentially the same for both groups ($p=0.95$; test of group:day interaction), implying parallel profiles of performance over time for the two groups. On any given day, the ON-OFF Group, who had practiced ON levodopa the week prior, had average latencies that were 1.5 (95% CI: 0.98–2.29) times as great as those for the OFF-OFF group ($p=0.059$).

Discussion

We have examined the effects of levodopa on motor learning for three tasks, a fine motor task involving limb muscles, a postural adjustment task involving axial muscles and a mirror drawing task requiring reversing normal limb movements. A unique aspect of our study is that we examined the retention of motor learning during continued practice.

Tapping speed and the CoM speed improved with practice over four days whether practicing ON levodopa or OFF levodopa. These two tasks are similar in that they require pointing to a target with different parts of the body, and represent an implicit motor learning process in which subjects improve spatial accuracy with repetition.²³ Levodopa had no significant

effect on the rate of improvement with practice for either task. The improvements persisted for 3 to 4 days after the first four days of practice ended, indicating that the practiced motor skills were retained and represent motor learning.²⁴ The baseline performances of finger tapping and moving CoM to a target were similar in the subjects ON and OFF levodopa. We attribute the lack of difference in baseline performance in the two groups to the relatively mild parkinsonism in our subjects.

The lack of effect of levodopa on learning these motor tasks is consistent with some but not all studies of levodopa on learning motor tasks. As in our study, levodopa has had little effect on implicit motor learning on such exercises as serial reaction time^{3,4} and probabilistic learning.⁵ The phase and duration of learning involved may also play a role: in explicit learning using a motor sequence task, levodopa inhibited early learning and had little effect on later or consolidation phase learning, as we believe occurred with several days of practice in our study.^{25,26} Levodopa has also been observed to have differential effects depending on whether positive or negative rewards are used with impaired learning in presence of levodopa observed when negative reinforcement is utilized.¹³ Since our subjects were given feedback on their performance, we might have expected enhanced learning in the presence of levodopa; however this feedback was not specifically reward-based. Finally, in tasks involving incremental, feedback based learning that requires error-correction, levodopa has had a negative impact⁸ that was not seen in our study.

The mirror drawing task differed from the other two tasks; it required an inhibition of the normal visual-motor program and the execution of a reverse movement. At baseline, performance of the mirror drawing task was much slower in the subjects ON levodopa than the subjects OFF levodopa. Despite their initial poor performance ON levodopa, the ON levodopa group improved their performance with practice over the four days of the first week, just barely achieving the performance of the subjects who practiced while OFF. Because the subjects learning mirror drawing on levodopa started with a much worse baseline, their rate of learning was faster than the subjects starting OFF levodopa. We do not believe that dyskinesia explains the poor performance of this task on the ON state because dyskinesia scores were low, dyskinesia effects were not observed on the other two tasks and the mirror drawing improved with practice in the ON state.

The pattern we observed with mirror drawing is consistent with other studies in which levodopa has been shown to interfere with acquisition of new motor skills requiring inhibition of previously learned behavior.⁹⁻¹² This demand for inhibition of an established motor program suggests that mirror drawing is a more demanding task in terms of executive function. Levodopa interferes with acquisition and performance of tasks requiring executive function, such as ignoring distractors that were previously relevant.²⁷ One explanation for this observation is the “dopamine overdose” hypothesis, suggesting that the dorsal to ventral progression of striatal dopaminergic denervation in PD results in a gradient of denervation early in disease. This results in worsened performance on learning tasks when exogenous dopamine is introduced in the form of levodopa, due to an excess of dopamine in ventral circuits.^{22,23,28-30} This can result in impaired motor learning on tasks that require greater executive function such as reversal learning¹⁰ or the Iowa gambling task.³¹

Retention of learning was examined the second week when the subjects continued to practice the same tasks on four consecutive days, but now all subjects had levodopa withheld overnight before each practice session. Both the subjects learning ON levodopa and those learning OFF levodopa demonstrated retention of the previous week's learning by tapping and moving the CoM at the same speed on day one of Week Two as they had on the last day of Week One, consistent with motor learning having taken place over the previous week's practice session. The surprising finding was a decay in performance of the tasks

requiring a speed-accuracy tradeoff in pointing to predetermined targets, the finger tapping and body movement tasks, when these tasks were practiced OFF levodopa during the second week, after initially practicing the tasks ON levodopa the first week. In contrast, the subjects who had learned the tasks OFF levodopa either continued to slowly improve or to plateau in their performance on finger tapping and CoM movement.

The decline in performance of tasks learned ON when practiced OFF is a novel observation in parkinsonian humans. However, a similar phenomenon has been observed in parkinsonian rodents. In one study, dopamine deficient mice learned to run on a rotarod with daily practice for five days when treated with levodopa whereas untreated mice did not.¹⁴ The improvement in rotarod performance progressively deteriorated when the levodopa-treated mice subsequently practiced without levodopa treatment.¹⁴ Similar to our subjects, the levodopa-treated mice retained their rotarod performance for up to ten days if they did not practice the task without levodopa treatment. This decline in performance during practice OFF levodopa has been interpreted as representing an active unlearning process, and the investigators suggest this that levodopa is required for motor learning.

In a similar rodent study, rats learned a conditioned or stimulus-response behavior and then received a medial forebrain lesion with 6-hydroxydopamine to induce dopamine deficiency. After 6-hydroxydopamine treatment, the mice initially performed the conditioned task as well as immediately before the surgery, but with subsequent repetition of the conditioned task in the absence of endogenous dopamine, the mice became progressively slower in performance of the task. The investigators proposed that striatal dopamine was required to maintain but not to perform learned actions, and suggested that decay in performance occurs because the reward signal mediated by dopamine had been eliminated.³² Although this decay in performance in our two tasks is similar to these two rodent studies, it is not compatible with the explanations of these two groups because our subjects could learn in the absence of levodopa, and this learning was maintained with continued practice. The difference may be due to the degree of dopaminergic denervation, which was relatively mild in our subjects.

The clinical consequences of this decay in performance of tasks learned ON and subsequently performed OFF is unknown at present. However, our observations raise questions about what treatment conditions are optimal for physical therapy and other learning to take place to have the largest impact on patients' performance in daily life when they are ON and OFF. Our results with mirror drawing also suggest that certain types of learning, especially that requiring executive function, may be learned more easily in the OFF condition, another consideration for the clinician.

Limitations of this study include its relatively small sample size, which in part reflects the substantial time commitment required of our subjects who were willing to delay taking their morning dose of levodopa for 8 days in two weeks. We note, however, that the study was sufficiently powered to find differences between the learning conditions. Our results may be difficult to generalize across the population of individuals with PD as our subjects primarily had mild-moderate disease.

In conclusion, we have studied the effect of levodopa on acquisition and retention of two simple speed-accuracy tradeoff motor tasks and mirror drawing task. We have found that continued practice OFF levodopa produced worsening performance of a simple motor task learned when ON levodopa. In contrast, we have found that in a more complex motor task requiring inhibition of a learned motor behavior, mirror drawing, levodopa may impair performance but does not inhibit learning.

Stock Ownership in medically-related fields; APDM	Intellectual Property Rights: Patents and Patents pending: "Movement Monitoring System" (US 2011/0213278 A1); European Patent No. 04736776.8 "A device for conditioning balance and motor co-ordination"; Quantification of turning with body worn inertial sensors (US 2008)
Consultancies: none	Expert Testimony: none
Advisory Boards: NCMRR of NIH	Employment: OHSU, APDM
Partnerships: none	Contracts: none
Honoraria: Singapore Health Ministry, Reliance Hospital in Mumbai India, U of Sao Paulo, Alaska Physical Therapy Association	Royalties: BESTest Educational DVD from OHSU
Grants: NIH, VA, PD alliance	Other: none

Stock Ownership in medically-related fields - none	Intellectual Property Rights: none
Consultancies:	Expert Testimony: none
1.Elan Pharmaceuticals 2.Lundbeck Inc. 3.ONO Pharma 4.SynAgile Corp 5.Prexa Inc. 6.US World Med. 7.Ceregene	
Advisory Boards: none	Employment: OHSU, VA
Partnerships: none	Contracts: none
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Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIG. 1.

Estimated mean response derived from fitted models relating taps per minute (**A**), CoM velocity (**B**), and star drawing latency (**C**) to testing session (days 1–4) during each week for the two groups of interest (ON/OFF, black dotted line, solid black triangle; OFF/OFF, gray solid line, solid gray square). Plotting symbol denotes mean response; 95% confidence interval for mean is shown by error bars. Note reverse direction of vertical axis in **C**. Slight horizontal offset has been included to minimize overstriking of points.

Table 1

Subject Demographics

	Group One (ON Wk 1, OFF Wk 2)	Group Two (OFF both wks)	T-test*
N, gender (M,F)	10 (7 M, 3 F)	10 (9 M, 1 F)	
Average age (SD)	67.2 (5.3)	65.5 (8.3)	0.47
Average Hoehn & Yahr (SD)	2.2 (.4)	2 (0)	0.17
Average LED (SD)	871 (441)	826 (270)	0.80
Average MOCA (SD)	27 (2.3)	28 (1.4)	0.54
Average UPDRS (SD)	Week 1: 24 (9.8)	Week 1: 30 (8.7)	0.08
	Week 2: 31 (10)	Week 2: 31 (7.6)	0.42
T-test Week 1 vs. 2**	<0.01	0.175809	

*
2 tail T-test, heteroskedastic errors

**
1 tail T-test, homoskedastic errors