Dopamine overdose and motor sequence learning

Title: Effect of dopaminergic medications on the time course of explicit motor sequence learning in Parkinson's disease

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Abstract

The capacity to learn new motor sequences is fundamental to adaptive motor behavior. The early phase of motor sequence learning relies on the ventral and anterior striatal circuitry whereas the late phase relies on the dorsal and posterior striatal circuitry (Lehericy et al., 2005). Early Parkinson’s disease (PD) is mainly characterized by dopaminergic denervation of the dorsal and posterior striatum while sparing anterior and ventral regions. Dopaminergic medication improves dorsal and posterior striatum function by compensating for the loss of dopamine. However, previous work has shown that dopaminergic medication interferes with the ventral and anterior striatum function, by overdosing this relatively intact structure in early state PD (Cools, 2006). Here we test whether these effects are also observed over the time course of motor sequence learning. Fourteen PD patients ON and OFF dopaminergic medications and eleven healthy age matched control participants performed an explicit motor sequence learning task. When sequence learning was compared across different learning phases in patients ON and OFF medication, a significant impairment associated with medication was observed in the early relative to later phases of learning. The rate of learning in the early phase measured trial by trial in patients ON was significantly slower than controls and when patients were OFF. No significant impairment was found in the later learning phases. These results demonstrate that dopaminergic medications may selectively impair early phase motor sequence learning. These results extend and generalize the dopamine overdose effects previously reported for (antero)ventral striatum-mediated cognitive tasks to motor sequence learning.
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Introduction

Parkinson’s disease (PD) is a progressive neurodegenerative disorder, characterized primarily by motor symptoms such as tremor, rigidity and bradykinesia. However, cognitive executive deficits also occur, even in the early stages of disease diagnosis (Caballol et al. 2007). The Braak staging system describes PD as a schema of ascending pathology, beginning in the lower brainstem and anterior olfactory structures, progressing to the basal mid- and forebrain nuclei, and then to the cortex (Braak et al. 2006; Braak et al. 2003). In stage 3 of the Braak system, when motor symptoms first begin to appear, the neuropathology of PD is demonstrated by the loss of dopaminergic neurons in the substantia nigra pars compacta and the ventral tegmental area with degeneration of the striatal nerve terminals (Braak et al. 2006). Dopaminergic denervation is not distributed evenly in the striatum in PD. Dopaminergic denervation begins asymmetrically and then becomes bilateral later in the disease (Hornykiewicz 1966). Additionally, there is also a dorsal to ventral and posterior to anterior gradient in dopamine (DA) depletion. Specifically, depletion is greater in the dorsal and posterior striatum as opposed to the ventral and anterior striatum early in the disease, with subsequent involvement of the anteroventral striatum with disease progression (Bernheimer et al. 1973; Frey et al. 1996; Kish et al. 1988; Rakshi et al. 1999). Anti-Parkinsonian dopaminergic medications such as L-DOPA and dopamine agonists ameliorate motor deficits of PD by compensating for the loss of dopamine. However, these medications can have conflicting effects on cognitive performance particularly in the early stages of the disease (Shohamy et al. 2006; Shohamy et al. 2005; Shohamy et al. 2008). One proposed explanation for these conflicting effects is
the so-called “dopamine over-dose hypothesis” (Cools 2006; Cools et al. 2006; Cools et al. 2001; Frank 2005; Frank et al. 2004; Gotham et al. 1988; Swainson et al. 2000). This hypothesis proposes that in early PD, while dopaminergic medications can improve cognitive performance on tasks associated with the depleted dorsal and caudal striatum such as task switching (Brass et al. 2003; Sohn et al. 2000), they can interfere with the normal cognitive performance associated with the ventral and rostral striatum such as reversal learning (Cools et al. 2002) by overdosing this region which is relatively intact in the early stage of the disease (Cools 2006; Cools et al. 2001). These findings that support the “dopamine-overdose hypothesis” are consistent with the ‘inverted U’ relationship between dopamine and cognition identified in experimental animal studies, which demonstrates that both insufficient and excess levels of dopamine impair normal cognitive functions (Arnsten 1998; Williams and Goldman-Rakic 1995; Zahrt et al. 1997).

Another behavior that could plausibly be affected by dopamine overdose in Parkinson’s patients is motor sequence learning. Motor sequence learning underlies many everyday activities such as typing, driving, or playing a musical instrument. It also constitutes a critical component of physical rehabilitation interventions. In healthy controls motor sequence learning relies on the basal ganglia thalamocortical loops, including the dorsal and posterior striatal pathways involving the supplementary motor area and the premotor cortex, as well as the ventral and anterior striatal pathways involving the anterior cingulate cortex (Berns et al. 1997; Hikosaka et al. 2002; Lehericy et al. 2005; Miyachi et al. 1997; Seidler et al. 2002; 2005). The neural recruitment of these pathways changes across the time course of learning. Specifically in the early phase of learning, when subjects acquire sequences of action in a controlled manner by
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engaging in cognitive processes, the ventral and anterior striatal pathway (i.e. associative striatum) is involved (Doyon et al. 2003; Duff et al. 2007; Hikosaka et al. 2002; Lehericy et al. 2005; Tamas Kincses et al. 2008). In the later phase of learning, when subjects perform acquired sequences in a more automatic fashion, the dorsal and posterior striatal pathway (i.e. sensorimotor striatum) becomes involved (Doyon et al. 2003; Duff et al. 2007; Hikosaka et al. 2002; Lehericy et al. 2005; Tamas Kincses et al. 2008). Due to the participation of basal ganglia thalamocortical circuits in motor sequence learning, this behavior has been frequently studied in PD patients (Carbon et al. 2004; Doyon 2008; Doyon et al. 1997; Feigin et al. 2003; Ghilardi et al. 2003; Ghilardi et al. 2007; Helmuth et al. 2000; Muslimovic et al. 2007; Nakamura et al. 2001; Pascual-Leone et al. 1993; Price and Shin 2008; Roy et al. 1993; Seidler et al. 2007; Smith et al. 2001). These studies show that some aspects of sequence learning are preserved in PD patients whereas others are impaired (Muslimovic et al. 2007; Seidler et al. 2007; Smith et al. 2001). Not many of these studies have looked at the effects of medication status on sequence learning in PD patients, however, which would be required to determine whether a dopamine overdose effect plays a role in this behavior. Furthermore, the studies that have tested whether sequence learning performance changes with medication status in PD patients have found mixed results (Argyelan et al. 2008; Feigin et al. 2003; Ghilardi et al. 2007). Feigin et al. (2003) found that L-dopa administration led to reduced sequence learning in patients with PD, but this was only observed using a subjective measure of self-reported learning (i.e. the number of accurately performed sequence elements self-reported by each participant). When comparing objective measures such as reaction time and accuracy, investigators have
not observed significant differences between performance in the ON versus OFF medication states (Ghilardi et al. 2007). In addition, a recent functional neuroimaging study found that the level of learning-related brain deactivation was reduced with dopamine, but there was no significant behavioral evidence for ON versus OFF performance differences (Argyelan et al. 2008). We believe that such mixed findings are due to the fact that prior studies did not compare patients ON and OFF medication specifically at different phases of sequence learning, while the dopamine overdose hypothesis predicts a different effect of medication across different learning phases.

That is, since early sequence learning relies on the relatively intact ventral and anterior striatum (Lehericy et al., 2005), administration of dopaminergic medication should reduce performance selectively in the early phase of sequence learning for PD patients. In contrast, the late phases of sequence learning rely on the dorsal and posterior striatum (Lehericy et al., 2005), which are impacted by early stage PD. Given this, administration of dopaminergic medication should improve performance in the late phase of sequence learning for PD patients. Thus, a selective deficit in the ON state in early sequence learning may have been missed by previous studies which have evaluated performance averaged across the time course of learning.

In the current study we tested whether there is an interaction between the time course of sequence learning and the presence or absence of dopaminergic medication in early stage PD patients. To test the “over-dose hypothesis”, we compared motor sequence learning performance across different phases of learning in PD patients ON and OFF medication and healthy age-matched control participants. Previous literature has used multiple tasks to assess motor sequence learning, including the serial reaction
time task, trial and error learning, and probabilistic motor sequence learning. All of these have the component of learning a sequential movement either implicitly or by using an explicit strategy. Due to the common nature of learning sequential movements, studies have found similar underlying neural systems including corticostriatal pathways during different sequence learning paradigms. For example, probabilistic motor sequence learning involves the primary motor cortex (Wilkinson et al. 2009) and striatum (Wilkinson and Jahanshahi 2007), and trial and error sequence learning involves prefrontal cortex (Sakai et al. 1998) and the pre-motor and supplementary motor areas (Mentis et al. 2003). Many studies have either just focused on sequence learning itself not taking into consideration the different phases of learning or did not find involvement of different striatal regions across the phases of learning. The motor sequence learning paradigm that has shown a clear striatal involvement in different phases of learning has been an explicitly learned sequence of finger actions (Lehericy et al. 2005). Thus in our study, we used the classic serial reaction time task with explicit instructions. The time course of learning in our task (30 – 40 minutes) was comparable to the period over which a shift in basal ganglia activation was observed by Lehericy et al. (2005; 10 – 50 minutes). Our early phase of learning was approximately 10 – 15 minutes in duration, corresponding with time T2 in Lehericy et al. (10 minute time point).

Materials and Methods

Participants

14 PD patients (65 ± 10 yrs, 2 females) in the mild to moderate stages of disease (Hoehn and Yahr stages 1 – 2.5, (Hoehn and Yahr 1967) and 11 healthy
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participants (64 ± 9 yrs, 3 females) in the same age range participated in this study. Patients were excluded for any neurological or psychiatric disease other than PD. Patients were included as long as they were on a stable dosage of dopaminergic medications for the previous 6 months, and were evaluated using the motor section of the Unified Parkinson’s Disease Rating Scale (UPDRS, Fahn et al. 1987) by a neurologist. All study participants underwent the Mini-Mental State Exam (MMSE, Folstein et al. 1975) and the Mattis Dementia rating scale (MDRS, Mattis 1988). The demographic and clinical characteristics of the patients are listed in Table 1. Participants were compensated for their participation, which included two testing days for PD patients. All participants signed a consent form approved by the Institutional Review Board of the University of Michigan.

[Insert Table 1. here]

Procedure

PD patients underwent two testing days corresponding to the ON and OFF medication states, separated by no more than two weeks. Seven patients were tested ON first and seven OFF first. Patients withdrew from their regular dose of anti-parkinsonian dopaminergic medication 12 - 18 hours prior to testing for the OFF state. Control participants (NC) underwent one testing session. On each testing session, participants performed the explicit motor sequence learning task. Additionally, the Purdue Pegboard Test (Tiffin and Asher 1948) and the Grooved Pegboard Test (Lafayette Instruments, Lafayette, IN) were used to measure motor abilities.
Explicit Motor Sequence Learning

Participants were instructed to press a key-press device with their fingers in response to stimuli presented on a computer screen. The index and middle finger from each hand were assigned to the four response buttons in the following fashion: left middle – first button, left index – second button, right index – third button, and right middle – fourth button. There were four visual stimulus boxes corresponding to each of the four response buttons. Participants were instructed to press the appropriate button as fast as possible when an “X” appeared in one of the stimulus boxes. The trial blocks were either a “sequence” block, in which stimuli were presented in a sequential order, or a “random” block, in which stimuli were presented in a pseudorandom fashion.

Participants were presented with a 6-element sequence (i.e. 1, 3, 2, 3, 4, 2) repeatedly in the sequence block. Participants were explicitly told that there was a sequential pattern to the stimuli presentation, and they were shown the 6 element sequence prior to the test session. They were instructed to learn the sequence. They were informed of which of the two blocks (i.e. random or sequence) they would be performing at the beginning of each block. If participants failed to respond by pushing the correct button, the same stimulus location was presented again on the next trial. Each block consisted of 96 trials spaced by a constant response-to-stimulus interval (RSI) of 500 ms, and there were 11 blocks in total including both sequence and random blocks. The order of sequence and random blocks were as follows: R1-R2-S3-S4-R5-S6-S7-R8-S9-S10-R11 (S: sequence, R: random). The first two sequence blocks (S3 and S4) were referred to as the early phase and the last two sequence blocks (S9 and S10) as the late phase of learning. Patients were presented with different sequences on the two testing days.
Data Analysis

Sequence learning performance was measured by reaction time and number of errors. The random blocks in the sequence learning paradigm were positioned in between sequence blocks across the duration of the task to account for a baseline motor function and the possible learning of general visuomotor behavior across the sequence learning paradigm in each group (NC, PD_ON and PD_OFF). The first trial in each block, error trials, and trials immediately following an error were excluded from RT analysis. We computed the median RT and total number of errors in each block for analysis. Repeated measures ANOVA and paired or independent sample t-tests were performed. The Huynh-Feldt epsilon (Huynh and Feldt 1970) was used to determine whether the repeated measures data met the assumption of sphericity (\( \Sigma > 0.75 \)). In cases where the sphericity assumption was not met, the F statistic was evaluated for significance using the Huynh-Feldt adjusted degrees of freedom.

Results

Neuropsychological Assessments

Paired t-test showed no significant difference between PD_ON and PD_OFF for the MDRS (\( t (13) = 0.096, p = 0.925 \), PD ON: 142 ± 3, PD OFF: 141 ± 3) or MMSE (\( t(13) = -0.836, p = 0.418 \), PD ON: 27 ± 2, PD OFF: 28 ± 2). Independent sample t-tests showed no significant difference between NC and PD_ON for MDRS (\( t (23) = 1.269, p = 0.217 \), NC: 143 ± 2) or MMSE (\( t (23) = 1.257, p = 0.221 \), NC: 28 ± 1). There was also no significant difference between control and PD_OFF for MDRS (\( t (23) = 1.661, p = 0.11 \))
or MMSE (t (23) = 0.455, p = 0.645). These results demonstrate that patients' general
cognitive abilities (MMSE, MDRS) were not significantly different ON and OFF
medication or compared to NC. In patients, performance on the Purdue pegboard and
the Grooved pegboard was analyzed separately for the more affected and less affected
sides. Paired t-tests showed no significant performance differences in the Purdue
pegboard test across medication states in both the more affected (t (13) = 1.57, p =
0.142) and less affected (t (13) = 0.74, p = 0.472) side. Similarly in the Grooved
pegboard test, no significant difference was found for either the more affected (t (13) =
1.31, p = 0.212) or less affected (t (13) = -0.14, p = 0.891) sides. When compared to NC,
both PD_ON (right: t (23) = 2.265, p = 0.033, left: t (23) = 2.158, p = 0.042) and
PD_OFF (right: t (23) = 2.485, p = 0.021, left: t (23) = 2.277, p = 0.032) performed
worse in Purdue pegboard in both left and right hand. Performance in Grooved
pegboard was marginally different between NC and PD_ON in right hand (t (23) = -2.01,
p = 0.056) and between NC and PD_OFF in right (t (23) = -1.899, p =0.07) and left (t
(23) = -2.004, p = 0.057) hand. The UPDRS motor component showed a significant
difference between ON and OFF medication (t (13) = -5.2, p < 0.00001), reflecting that
motor symptoms were more severe in OFF (mean ± S.D: 20 ± 7.6) than ON (15 ± 7.7)
medication. These results demonstrate that patients' manual motor performances
(Purdue pegboard, grooved pegboard) were worse compared to controls in either ON or
OFF. However they were not significantly different ON and OFF medication, whereas
patient's motor symptoms (UPDRS) were more severe in OFF medication state.
Explicit Motor Sequence Learning

We hypothesized that medication status would affect sequence learning in a phase-dependent fashion. To test this hypothesis we first performed a medication status (PD_ON, PD_OFF) by learning phase (early, intermediate, late) by block series (first, second, third block) repeated measures ANOVA in RT with medication status, learning phase and block series as within subject factors. R2, S3, S4 were considered as the first, second, and third block series of the early phase whereas R5, S6, S7 and R8, S9, S10 were considered as the intermediate and late phases, respectively. We considered sequence learning as the change in RT across the three block series starting from a random block within each phase. We found a significant main effect of phase ($F(1.397, 18.164) = 11.033, p = 0.002$) and a main effect of block series ($F(2, 26) = 24.334, p < .00001$) (Fig. 1.). This indicates that RT was different across the three learning phases and that sequence specific learning, represented as change in RT across block series within each phase, was present throughout the task. Importantly, we also found a significant medication status by phase by block series interaction ($F(2.971, 38.619) = 3.052, p = 0.04$). This indicates that medication status affected sequence specific learning in a phase-dependent fashion. We also found a marginally significant medication status by block series interaction ($F(2, 26) = 3.2, p = 0.057$). No significant medication status main effect or other two way interactions were found. In light of the significant medication status by phase by block series interaction, we followed up with a medication status by block series repeated measures ANOVA with medication status and block series as repeated measures in each learning phase separately. A significant medication status by block series interaction was found selectively in the early phase ($F$
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(1.489, 19.352) = 7.7, p = 0.006) and not in the intermediate (F (1.464, 19.029) = 0.047, p = 0.909) or late phases (F (2, 26) = 2.151, p = 0.137). This indicates that medication status affected sequence learning specifically in the early phase. In order to test whether performance on the last sequence block was significantly changed from random, we proceeded with paired t-tests to test for RT difference between the first random block (R2) and the last sequence block (S4) in the early phase in PD_ON and PD_OFF separately. There was a significant RT decrease across the two blocks in PD_OFF (t (13) = 5.676, p < .00001). However no significant RT difference was found in patients ON medication (t (13) = 0.738, p = 0.474). This indicates that sequence learning in the early phase was impaired in patients ON medication. We also compared the last sequence block (S4) of the early phase to the following random block (R5) using paired t-tests in order to confirm that the medication-associated impairment was specific to sequence learning and not merely representing changes in stimulus-response (S-R) mapping over time. RT was significantly different between S4 and R5 (t (13) = -6.235, p < 0.00001) in PD_OFF, but not significantly different in PD_ON (t (13) = -1.343, p = 0.202). This confirms that RT improvements exhibited by PD_OFF represent sequence-specific learning.

To further evaluate whether PD_ON and PD_OFF differed in the late phase of learning, we performed an additional medication status by block analysis including data for the patients tested ON and OFF medication for the final sequence and subsequent random block (S10 and R11). This comparison is the standard assessment of the amount of learning that has occurred for studies employing the serial reaction time paradigm. As suggested by the parallel slopes of the lines connecting these two blocks
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for the two medication status groups in Figure 1, this ANOVA resulted in a medication status by block effect of $F(1,13) = 0.000, P = .999$, indicating a lack of medication status effects on sequence learning magnitude in the late phase of learning.

We also compared patients’ performance to controls separately for the two medication states. We performed a group (NC, PD) by learning phase (early, intermediate, late) by block series (first, second, third block) repeated measures ANOVA with learning phase and block series as within subject factors and group as between subject factor including only PD_ON or PD_OFF separately. When PD_ON was compared to NC, a significant main effect of phase ($F (2, 46) = 8.824, p = 0.001$) and block series ($F (2, 46) = 46.049, p < 0.00001$) and significant block series by group ($F (2, 46) = 6.585, p = 0.003$) and phase by block series ($F (2, 46) = 4.348, p = 0.003$) interactions were found. However no significant group by phase by block series interaction was found ($F (4, 92) = 1.472, p = 0.217$). When PD_OFF was compared to NC, a significant main effect of phase ($F (1.473, 18.736) = 18.726, p < 0.00001$) and block series ($F (1.473, 33.058) = 84.387, p < 0.00001$) and a significant phase by series interaction ($F (4, 92) = 5.038, p = 0.001$) were found. No significant group by phase by block series interaction was found ($F (4, 92) = 1.174, p = 0.327$).

We performed the same set of data analyses on the number of errors (Fig. 2). Error data were analyzed in order to confirm that the RT results were not due to differences in speed-accuracy trade-off. As in the RT data, we first performed a medication status (PD_ON, PD_OFF) by learning phase (early, intermediate, late) by block series (first, second, third block) repeated measures ANOVA with medication status, learning phase and block series as within subject factors using number of errors
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in each block. We only found a significant main effect of block series ($F (2, 26) = 8.881,$ $p = 0.001$). No other main effects, two–way or three–way interactions were found to be significant. This confirms that our results with the RT data were not due to speed-
accuracy trade-off differences across the groups. The same set of analyses was
performed comparing NC to PD_ON or PD_OFF. When PD_ON was compared to NC,
we only found a significant main effect of block series ($F (1.285, 29.548) = 6.825, p =$ $0.009$). The same was true for PD_OFF ($F (1.214, 27.926) = 5.422, p = 0.022$).
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less steep compared to PD_OFF or NC. To test our hypothesis, we performed a
medication status (PD_ON, PD_OFF) by trial bins repeated measures ANOVAs using
medication status and trial bin as within subject factors and looked at the within subject
linear contrast across trial bins. The interaction for group by linear contrast was
marginally significant (F (1, 13) = 4.334, p = 0.058). This indicates that there was a
linear decrease in RT across the trial bins in the early phase and the slope of RT
decrease or the learning rate was steeper for PD_OFF than PD_ON. We performed the
same analysis comparing PD_ON and NC using group as a between subject factor. The
group by trial bin linear fit interaction was significant (F (1, 23) = 6.256, p = 0.02), which
demonstrates that the RT across trial bins changed linearly and the slope differed in the
two groups. However, when comparing PD_OFF and NC, the linear contrast for the
interaction effect was not significant (F (1, 23) = 2.754, p = 0.111). These results
demonstrate that compared to controls, patients ON medication were impaired in
sequence learning as characterized by the evolution of RT change trial by trial in the
early phase, whereas patients OFF medication were not impaired compared to controls.

[Insert Figure 3]

To provide further support for the claim that the difference in learning rate
between PD_ON and PD_OFF was specific to the early phase of learning, we evaluated
whether there were significant group x linear fit interactions in the middle and late phase
of learning. In addition, because the two groups might be at different stages in the
learning process such that more advanced phases in PD ON will be equivalent to the
early phase in PD OFF (due to the early phase advantage for PD_OFF), we also
evaluated whether rate of learning differed between PD ON from the intermediate phase
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or the late phase of learning with PD OFF from the early phase of learning. There were no significant effects for any of these analyses (P>.05 for all comparisons).

Discussion

Effect of Dopaminergic Medications over the Time Course of Motor Sequence Learning

We found a significant sequence learning impairment associated with dopaminergic medication that was dependent on the phase of learning. Compared to patients OFF medication, patients ON medication showed a significantly reduced drop in RT across the early learning phase. This was also confirmed by the steeper trial by trial RT decrease during the first two sequence blocks for patients OFF medication compared to when they were ON medication. The rate of trial by trial RT decrease for PD_OFF was similar to that of healthy controls. There was no significant medication effect on the number of errors, providing support that the medication effect for RT change was not due to differences in speed-accuracy trade off. In addition, the ON medication deficit was restricted to sequence learning behavior. That is, performance was equivalent ON and OFF medication for the Purdue Pegboard and the Grooved Pegboard tests. Moreover, participants performed more poorly on the UPDRS when OFF than ON medication. This demonstrates that the baseline motor abilities were matched across medication states and patients’ motor symptoms were worse in the OFF state. These behavioral data collectively provide evidence for the dopamine overdose effect in early motor sequence learning, implicating a detrimental effect of dopaminergic medication confined to the phase of learning that is known to be dependent on the ventral and anterior striatal circuitries (Berns et al. 1997; Hikosaka et
Our data showed equivalent learning ON and OFF medication for the intermediate and late phase. One possible cause of this may be the fact that the task has now moved away from the early phase of learning where the medication shows the most deleterious effect. Another possibility is that medication benefitted sequence learning behavior in the later phase which is known to rely on the posterior and dorsal striatal circuitry (Hikosaka et al. 2002; Lehericy et al. 2005; Miyachi et al. 1997; Seidler et al. 2002; 2005). We likely do not have a sufficient number of practice trials in the current study to fully evaluate this, however. In order to reach the late phase during which automatized sequential movements rely purely on dorsal and posterior striatum (i.e. sensorimotor striatum), previous studies have used multiple days of practice (Lehericy et al. 2005). In our task subjects were exposed to only a limited number of trials across 11 blocks, which might not have been enough for them to completely reach the late automatic phase of learning, purely supported by the sensorimotor striatum. In other words, subjects might be in the interim phase relying on both the associative and sensorimotor striatum.

It is of note that our designation of early, intermediate and late phases was in respect to our task design. That is we arbitrarily defined the three learning phases respective to the time course of the task in our study. Since we did not acquire neuroimaging data, we were not able to determine whether there was indeed a shift of neural recruitment across the three arbitrarily defined learning phases in our task. However, in the Lehericy et al. (2005) study, the extent of area activated in the anterior putamen decreased even after 50 mins of motor sequence training. There was also a
significant decrease in anterior putamen activation from 10 mins of training to 50 mins of training. By contrast they found an increase in the extent of posterior putamen recruitment even after 10 min of practice. This shows that the shift from anterior to posterior putaminal recruitment happened within 10 min to 50 min of practice. The sequence learning task used in our study spanned a comparable period (30-40 min in total depending on the individual). Thus we think that the arbitrary designation of the early, intermediate and late phase in our task was capable of capturing the shift in neural recruitment of basal ganglia sub-regions.

A potential limitation to our study is the large variation seen in the patients’ performance, as evidenced by the relatively large error bars in the plots. This may be due to a small sample size and large variability in the patients’ performance. Despite these limitations, we found a significant medication effect supporting our hypothesis. That is, we found a medication-associated impairment selectively in the early phase and not in the later two phases of learning. We believe this is not due to learning being saturated in the later two phases since there was a main effect of block series showing that sequence learning was present throughout the task. While it is more difficult to detect group differences later in learning when the learning curve starts to plateau, our analyses clearly demonstrated a lack of medication status on sequence learning magnitude in the late phase of learning. It is also noteworthy that large variability in patients’ performance is more apparent in ON medication state. This supports our hypothesis of the medication effect as medication effects can be quite significant but variable at the same time depending on the type and dosage of medication. The variability may also depend on the individual degree of striatal denervation in patients.
Motor Sequence Learning in Parkinson's Patients & Dopaminergic Medications

Previous studies of motor sequence learning in Parkinson's patients have found conflicting results with some showing impaired learning (Helmuth et al. 2000; Muslimovic et al. 2007; Nakamura et al. 2001; Stefanova et al. 2000) and others showing intact learning (Seidler et al. 2007; Smith et al. 2001; Werheid et al. 2003). Our data suggest that relatively intact basal ganglia subregions in the mild to moderate stage of PD, such as the ventral and anterior striatum, can function properly as shown by comparable sequence learning for patients OFF medication and controls.

The effect of dopaminergic medication on motor sequence learning of PD patients has not been clearly identified in previous studies (Argyelan et al. 2008; Feigin et al. 2003; Ghilardi et al. 2007). These studies have either found no significant difference in performance between the two medication states (Argyelan et al. 2008; Ghilardi et al. 2007) or only found a difference for a subjective measure of self-reported learning (Feigin et al. 2003). Our results show a clear detrimental effect of dopaminergic medication that is confined specifically to the early phase of motor sequence learning for PD patients. Whether the nature of this negative medication effect on early motor sequence learning is similar to that of other demonstrations of dopamine overdose such as reversal learning is not clear at this point. In probabilistic reversal learning, there is explicit positive or negative feedback that will invoke reward and error processing by the nucleus accumbens (Cools 2006; Cools et al. 2001). In contrast, our sequence learning paradigm does not include explicit feedback, with the exception of repeated trials in the
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Case of incorrect responses. It is plausible that this indirect feedback might have partially driven learning. For example, the repeating trial might have acted as negative feedback. A previous study has shown that PD patients OFF medication are more sensitive to negative than positive feedback whereas patients ON medication become more sensitive to positive feedback (Frank et al. 2004). Our data corresponds to this finding showing better performance in the OFF state in a task that potentially involves negative feedback. However the specific brain regions involved in early sequence learning that may be sensitive to dopaminergic medication are not clear at this point. Areas including the medial prefrontal cortex and ventral putamen, which receive dopaminergic projections from the ventral tegmental area similar to the nucleus accumbens (Hu et al. 2004) may be involved.

Collectively our data showed that the dopamine overdose effect impacts motor sequence learning in a time varying fashion for PD patients. Specifically, we found that early learning relative to late learning was impaired by dopaminergic medication. These findings underscore the importance of taking into account the time varying nature of the contributions of different striatal loops to motor sequence learning when investigating the effect of dopaminergic medication on sequence learning in PD patients. These data also provide further evidence that ventral and anterior striatal loops play a greater role in early sequence learning.

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Table and Figure Legend

Table 1. Demographic and clinical variables. H&Y: Hoehn and Yahr ratings (Hoehn and Yahr, 1967). * p < 0.05 difference ON and OFF medications. ¹ L-Dopa, ² Dopamine agonist

Figure 1. Group mean of the median response time across 11 blocks in controls, patients ON and OFF medication. Error bars indicate standard error.

Figure 2. Group mean of the number of errors across 11 blocks in controls, patients ON and OFF medication. Error bars indicate standard error.

Figure 3. Group mean of the median response time for each trial bin across the early phase of learning. Trials 1 through 16 and 49 through 64 were from the two bounding random blocks. Trial 17 through 32 and 33 through 48 were from the first two sequence blocks (S3 and S4). Error bars indicate standard error.
Figure 1.
Figure 2.
Figure 3.
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<th>Disease duration (yrs)</th>
<th>H&amp;Y</th>
<th>UPDRS*</th>
<th>DRS</th>
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| Mean ± S.D. | 65±10 | 6±6 | 2 | 15±8 | 20±8 | 142±3 | 141±3 | 27±2 | 28±2 |

Table 1.