# Pink noise in rowing ergometer performance and the role of skill level

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# Does Dopamine Replacement Medication Affect Postural Sequence Learning in Parkinson's Disease?

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Deficits in sequence-specific learning (SSL) may be a product of Parkinson's disease (PD) but this deficit could also be related to dopamine replacement. The purpose of this study was to determine whether dopamine replacement affected acquisition and retention of a standing Continuous Tracking Task in individuals with PD. SSL (difference between random/repeated Root Mean Square Error

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across trials) was calculated over 2 days of practice and 1 day of retention for 4 groups; 10 healthy young (HY), 10 healthy elders, 10 individuals with PD *on*, 9 individuals with PD *off* their usual dosage of dopamine replacement. Improvements in acquisition were observed for all groups; however, only the HY demonstrated retention. Therefore, age appeared to have the largest effect on SSL with no significant effect of medication. Additional research is needed to understand the influence of factors such as practice amount, task difficulty, and dopamine replacement status on SSL deficits during postural tasks.

***Keywords:*** implicit sequence-specific learning, aging, acquisition, retention



Parkinson's disease (PD) is a neurodegenerative disorder associated with observed motor signs such as, muscular rigidity, bradykinesia, and postural instability (Jankovic, 2008). The motor signs are typically minimized through the use of dopamine-replacement medication acting on the sensorimotor striatum. However, recent evidence suggests that this treatment may actually be "overdosing" the associative striatum (Vaillancourt, Schonfeld, Kwak, Bohnen, & Seidler, 2013), a candidate neuroanatomical correlate for motor sequence learning (Cools, Altamirano, & D'Esposito, 2006; Doyon, 2008).

Motor sequence learning refers to the process by which simple or complex serial movements come to be performed as a single unit of movement after practice and can be studied via a continuous tracking task (CTT) in which participants continuously track a visual stimulus through voluntary body movement (Boyd & Winstein, 2006; Doyon, 2008; Gheysen, Van Opstal, Roggeman, Van Waelvelde, & Fias, 2010; Nissen & Bullemer, 1987; Wulf, Schmidt, & Deubel, 1993). In the CTT paradigm, individuals practice a specific sequence without explicit knowledge that a repeating sequence is embedded within random sequences. Thus, the CTT is defined as an implicit motor sequence learning paradigm. Typically, individuals improve their tracking performance of the repeating sequence across practice; however, individuals with PD have been observed to have difficulty with this sequence-specific learning (SSL) compared with age-matched controls (Bischoff-Grethe, Martin, Mao, & Berns, 2001; Siegert, Taylor, Weatherall, & Abernethy, 2006; Smith & McDowall, 2006; van Asselen et al., 2009).

To date, few studies have reported or controlled for medication state (*on* or *off*) during SSL, with little knowledge about how medication state influences the process of SSL (Brown et al., 2003; Muslimovic, Post, Speelman, & Schmand, 2007; Seidler, Noll, & Chintalapati, 2006; van Tilborg & Hulstijn, 2010). Therefore, the documented SSL deficits in individuals with PD may be attributed to either a relative 'under dose' of endogenous dopamine or an overdose of exogenous dopamine. The primary purpose of this study was to examine motor learning of a specific motor sequence in individuals with PD and to determine whether dopamine replacement medication affects implicit learning of this sequence. We hypothesized that regardless of age, disease, or medication state, all participants would improve tracking ability over two days of practice (acquisition), and that these improvements would be retained 48 hr later (retention). We further hypothesized that SSL deficits would be more pronounced *on* medication compared with *off* medication due to the potential dopamine overdose in the associative striatum. Although previous studies have used CTT in which participants track a visual cursor on a screen by moving a joystick

with their arm while seated, we developed a task in which participants tracked the cursor by swaying back and forth while standing. Thus, this study incorporated a potentially salient and relevant motor task for measuring motor sequence learning in conditions that challenge the postural instability associated with PD (Dibble, Addison, & Papa, 2009; Foreman, Addison, Kim, & Dibble, 2011).

# Methods

## Participants

Participants were recruited from within the Department of Neurology at the University of Utah and the community of the greater Salt Lake City area, and provided informed consent in compliance with the University of Utah Institutional Review Board. A priori power analyses based on previous skill acquisition research in individuals with PD (Kwak, Muller, Bohnen, Dayalu, & Seidler, 2010; Muslimovic et al., 2007; Stephan, Meier, Zaugg, & Kaelin-Lang, 2011; Boyd, et al., 2009; Siengsukon & Boyd, 2009) compared with age-matched controls or individuals with PD on and off medication during sequence-specific learning was assessed, based on the interaction effect size from the ANOVA F statistic of 0.20 suggested 7 subjects per group to achieve power of 0.80 with an alpha of 0.05. To account for possible attrition, 10 subjects were recruited for each PD group. Inclusion criteria for PD participants were: a) confirmed idiopathic PD according to the UK Brain Bank Criteria (Jankovic, 2008); b) Hoehn and Yahr stages 1–2.5 when *off* medication (assessed at prescreening); c) 50–90 years of age; and, d) on a stable dosage of dopamine replacement medication for ≥ 6 months. Exclusion criteria were: a) acute medical problems (e.g., unstable heart disease); b) uncorrected vision loss; c) previous surgical management of PD (e.g., deep brain stimulation); d) other conditions that affected mobility and balance abilities (e.g., orthopedic, metabolic, vestibular); and, e) dyskinesias that were disabling for more than 25% of the day. Participants in the PD *on* group were asked to take their prescribed dosage of dopamine replacement medications 1–1.5 hr before each day of testing. Participants in the PD *off* group were asked to withdraw from their usual dosage of levodopa medication 12 hr before each day of practice and retention but were allowed to stay on their usual dosage of dopamine agonists to minimize the potential burden on these participants (Pahwa et al., 2006; Reichmann & Emre, 2012). A group of healthy young (HY, < 40 years of age) and healthy elders (HE) who were age matched with the PD groups were recruited to act as controls.

## Prescreening Assessment of Participants

All participants completed a prescreening assessment to obtain demographic data, cognitive status, and balance status. This included age, gender, Trails Making Test (TMT) Part B (Corrigan & Hinkeldey, 1987); Mini Mental State Exam (MMSE; Folstein, Folstein, & McHugh, 1975); and Berg Balance Scale (BBS; Berg, Maki, Williams, Holliday, & Wood-Dauphinee, 1992). Additional disease-specific data were collected in individuals with PD to further characterize the population of individuals with PD in the study: time since medical diagnosis, the full Unified Parkinson's disease Rating Scale (UPDRS) including the sub scores of the UPDRS

for postural instability/gait disturbance (Lozano et al., 1995) and axial measures (Burn et al., 2003); Hoehn & Yahr disease state (Hoehn & Yahr, 1967); and their levodopa equivalent daily doses (LEDD; mg/day; Esselink et al., 2004). The TMT is a timed cognitive-motor task associated with task shifting and is a reliable and valid measure of distributed and switching attention and working memory (Camicioli, Wieler, de Frias, & Martin, 2008; Corrigan & Hinkeldey, 1987). The MMSE is a clinical assessment tool of cognitive status. The BBS is a reliable (ICC = 0.94) and validated rating of overall balance and fall probability in individuals with neurological disabilities (Tyson & Connell, 2009). Individuals with PD were assessed both *off* and then *on* their levodopa medication to determine if they met the inclusion criteria. Once confirmed, they were then randomized to one of 2 groups for practicing *on* or *off* their usual dosage of levodopa. Non-PD participants were assigned to control groups based on their age, HY and HE.

## Continuous Tracking Task (CTT)

Participants stood on an in-ground force plate (Advanced Medical Technologies Inc., Watertown, MA) 300 cm from a white wall projection screen. Ground reaction force and moment data were collected at 200 Hz (Winter, 2005). All participants' maximal center of pressure (COP) excursion was determined as they shifted their weight forward and backward as far as they could. The experimental setup is shown in Figure 1.

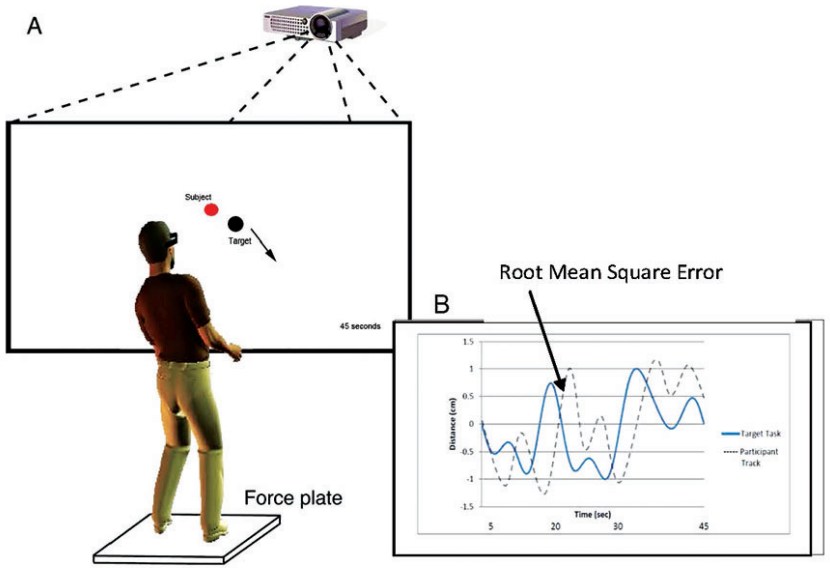


**Figure 1** — (A) Individual standing on force plate with the target projected as it crosses the screen in a sinusoidal fashion. The individual attempts to accurately track they target by anterior and posterior shifts of their center of pressure. (B) The difference between the target wave and the participants' performance was quantified by Root Mean square Error (RMSE).

Two items were projected onto the screen; 1) a red circle ('cursor'; 2.0 cm diameter) corresponding to the location of the participant's COP position, and 2) a moving black dot ('target'; 0.5 cm diameter). The target moved up and down across the screen in a sinusoidal fashion from left to right, as programmed in LabView (National Instruments, Corp, Austin, Texas). The target motion was comprised of repeating and random sequences; both generated using the same polynomial equation as reported in Wulf & Schmidt (1997; Eq. 1). The repeated sequences were constructed using the same coefficients for every trial. The random sequences were created using randomly generated coefficients ranging from 10 to -10. To ensure similarity of difficulty, we implemented several procedures (Chambaron, Ginhac, Ferrel-Chapus & Perruchet, 2006). First, the repeated and random sequence slopes were within 20% of each other at the point of transition, and within 5% of each other on the vertical axis ranges. Secondly, we calculated the repeated wave velocity (0.63 cm/s) and an average velocity for each random wave. We set an average velocity minimum (0.50 cm/s) and maximum (0.65 cm/s ) for the random waves and eliminated random waves with velocities above and below this range. Lastly, the peak amplitude of all sequences was scaled for each participant to equal 25% of this maximum COP excursion. Participants were instructed to continuously track the target, as accurately as possible, with the motion of their cursor by voluntarily shifting their COP forward and backward. A spotter was provided for safety purposes.



## Practice

One block of practice consisted of 10 CTT trials. Each CTT trial was 45-s in duration, and consisted of two sequences of target motion (one random and one repeated sequence presented in random order). During the first 5 s of a trial, the target did not shift in a sinusoidal fashion to allow the participant to orient to the task. COP data during these first 5 s were not included in the analysis of performance. A 25-s standing rest occurred in between every two trials in the block. At the end of each block, a 5-min rest was provided. Participants performed six blocks (i.e., 60 trials) each day for two consecutive days (day 1 and day 2). Thus, the *acquisition phase* of this study was comprised of 120 total trials, meaning that the participants were exposed to 120 repeating sequences and 120 random (nonrepeating) sequences. A one-block *retention test* occurred 48 hr later (on Day 4). No practice occurred on Day 3.

## Testing of Explicit Knowledge

At the end of the final assessment, participants were interviewed to determine whether any repetitions had been detected during the course of the experiment. They were presented with a 10-trial recognition test of the sinusoidal waves to assess for explicit knowledge of the repeating sequence. Seven of the patterns were random and three of the patterns were the same repeated pattern that had been consistently presented in each trial. After each pattern had been presented, participants were asked if they recognized the pattern as one that they had been practicing during the training days. A participant's explicit knowledge of the sequence was defined as correct if they demonstrated greater than 50% (better than chance) awareness

of sequence recognition. This criteria was determined if individuals were able to recognize two of the three repeating sequences AND four of the seven random sequences.

## Primary Dependent Variables for Acquisition and Retention

Performance on the CTT was measured as the root mean square error (RMSE; $cm^2$): the difference between the target motion and the COP cursor motion. The median RMSE of each repeated and random sequence was computed then averaged for each block. To determine whether participants learned the sequence, the mean random RMSE was subtracted from the mean repeated RMSE. This difference quantified the amount of sequence-specific learning (SSL), and was compared over the course of practice. Thus, evidence of SSL was documented as a decrease (less negative) mean repeated RMSE *and* less change in mean random RMSE.

The 2 days of acquisition with 12 blocks were divided into four assessments across time, such that an average SSL value was calculated for blocks 1–3 (early day 1); blocks 4–6 (late day 1); blocks 7–9 (early day 2); and blocks 10–12 (late day 2). Retention was measured as a retention score (Siengsukon & Boyd, 2008), calculated as the difference in mean SSL values between late day 2 (block 10–12) and day 4; and also as a percentage score (Schmidt & Lee, 2005), calculated as change from the end of acquisition to the retention test divided by the amount of skill gained from early day 1 to the end of acquisition multiplied by 100. The percentage score reflects the relative amount of SSL retained between acquisition and retention expressed as a percentage of the skill gained during acquisition.

## Statistical Analyses

Data were analyzed with SPSS version 17.0 (SPSS Inc, Chicago, Illinois). Baseline demographic, cognitive, balance and disease-specific data were summarized using point and interval estimators (Blackwelder, 1982). Separate one-way ANOVA's determined if there were differences between the groups on performance of the task, including assessment of their maximal COP excursion and early day 1 performance as measured by their performance on repeated, random and sequence-specific RMSE values. The assumptions for parametric statistics were tested (Munro, 2005).

To test the hypothesis of whether dopamine replacement medication affected the learning of a specific motor sequence in individuals with PD, we compared SSL values during acquisition and retention phases between all groups with an omnibus $4 \times 5$ repeated-measures ANOVA. Group (HY vs. HE vs. PD *on* vs. PD *off*) was the between-subject factor and time (early day 1 vs. late day 1 vs. early day 2 vs. late day 2 vs. day 4) was the within-subject factor ($\alpha = .05$). Post hoc pairwise comparisons were assessed when warranted by significance and a Bonferroni adjustment for multiple comparisons was performed. The magnitude of within-group effect sizes for time was estimated using omega squared ($w^2$) calculations (Lakens, 2013). The retention scores were analyzed with a one-way ANOVA (HY vs. HE vs. PD *on* vs. PD *off*) based on the retention score. Relative retention was calculated as a percentage score.

# Results

## Participant and Task Characteristics

Thirty-nine adults participated in this study: 10 Healthy Young (HY), 10 Healthy Elder (HE); 10 participants with PD *on* their physician-prescribed dosage of levodopa medication (PD *on*); and nine participants with PD *off* their physician-prescribed dosage of levodopa medication (PD *off*). One individual in the PD *off* group was unable to complete the study due to an intolerance of the off-medication state. As shown in Table 1, the HE and the PD groups were comparable in age and balance. A significant difference was noted in the MMSE ($p < .03$) but not for the TMT ($p = .67$). The PD groups demonstrated a significant in time since diagnosis ($p = .02$) with the PD *off* group having a longer diagnosis; however, there was no difference in disease-specific data; UPDRS and Hoehn and Yahr. In addition, there were no significant differences for maximal COP excursion or on initial performance of sequence-specific early day 1 RMSE ($p = .05$), but there was a difference between early day 1 performance on the repeated and random RMSE values ($p < .01$) between the groups (Figure 2). The majority of participants did not demonstrate explicit knowledge of the repeating sequence with none of the individuals stating with certainty that a single repeating sequence was present.

## Analysis of Acquisition

The initial statistical analysis of acquisition using a repeated-measures ANOVA did not meet the assumption of compound symmetry; thus, results were based on Greenhouse-Geisser epsilon correction for the within-subject main and interaction effects. Overall, no significant interaction was observed between group and time ($F = 0.76$, $df = 8.8$, $p = .65$) on SSL values. Main effects of group ($F = 14.03$, $df = 3$, $p < .01$) and time ($F = 5.19$, $df = 2.9$, $p = .01$) on SSL values were observed. However, post hoc analyses showed that 1) only the HY group was significantly different from the other groups ($p < .05$) and 2) only early day 1 vs. late day 2 and late day 2 vs. day 4 were significantly different ($p < .05$). Figure 3 provides a graphical representation of the overall trend in SSL values between groups and over the acquisition and retention time periods. Interestingly, the trend from early day 1 to late day 2 resulted from a decrease in error across acquisition, but the significant results observed for late day 2 to retention are because of an increase in error (see retention results below). The effect sizes (Omega squared, with percent variance explained) for each group's acquisition from early day 1 to late day 2 were the following: HY = 31%; HE = 13%; PD *on* = 32%; and PD *off* = 53%.

## Analysis of Retention

Retention scores (i.e., SSL late day 2 minus SSL day 4) were not significantly different between groups ($F = 2.19$, $df = 3$, $p = .11$). Relative retention, (i.e., amount of SSL retained from acquisition vs. lost) based on the percentage score finds only the HY group retained ~50% of what they learned over acquisition. In fact, the HE group lost 430%, the PD *on* group lost 184% and the PD *off* group lost 95%. Overall these results suggest that all groups improved their continuous tracking task performance during acquisition, but only the HY retained their acquired skill.

**Table 1 Demographic, Cognitive, Functional, Disease-Specific, and Task-Specific Data for Each Group**

| Variable | Mean (SD) (95% CI) | | | | |
|---|---|---|---|---|---|
| **Group** | **HY (N = 10)** | **HE (N = 10)** | **PD on (N = 10)** | **PD off (N = 9)** | **p-value** |
| Age | 28.4 (6.5) (23.8–33.0) | 71.0 (8.7) (64.8–77.2) | 68.0 (9.1) (61.5–74.5) | 71.1 (7.1) (65.7–76.6) | .00 between HY and HE, PD on, PD off |
| Gender (M:F) | 2:8 | 3:7 | 9:1 | 8:1 | |
| Trail Making Test Part B* (seconds) | | 66.8 (22.7) (50.6–83.0) | 87.1 (82.5) (28.1–146.1) | 72.8 (22.4) (55.6–90.0) | .67 |
| Mini Mental State Exam (Max 30) | 30 | 29.8 (0.4) (29.5–30.1) | 28.7 (1.3) (27.7–29.7) | 28.6 (1.4) (27.5–29.7) | .03[1] |
| Berg Balance Scale (Max 56)* | 56 | 55.6 (1.3) (54.7–56.5) | 55.3 (1.3) (54.3–56.3) | 54.6 (1.9) (53.1–56) | .12 |
| Time since diagnosis (months) | | | 50.5 (26.3) (31.7–69.3) | 90.2 (38.3) (60.8–119.6) | .02 |
| UPDRS total* | | | 27.5 (11.8) (19.0–36.0) | 35.7 (10.6) (27.5–43.8) | .13 |
| UPDRS axial*[2] | | | 1.0 (0.7) (0.5–1.5) | 1.1 (0.8) (0.5–1.7) | .74 |
| UPDRS PIGD*[3] | | | 2.6 (1.3) (1.7–3.5) | 2.4 (1.4) (1.3–3.5) | .81 |

*(continued)*

**Table 1 *(continued)***

| Variable | Mean (SD) (95% CI) | | | | |
|---|---|---|---|---|---|
| **Group** | **HY (N = 10)** | **HE (N = 10)** | **PD on (N = 10)** | **PD off (N = 9)** | **p-value** |
| Hoehn and Yahr* | | | Median 2.0 (0.6) (Range 1–2.5) | Median 2.0 (0.6) (Range 1–2.5) | .22 |
| Levodopa Equivalent Daily Dose* | | | 1021.6 (791.6) (455.3–1587.8) | 444.4 (490.2) (67.6–821.2) | .08 |
| Maximum Center of Pressure Excursion (cm) Front | 8.9 (2.5) (7.1–10.7) | 8.6 (2.8) (6.6–10.7) | 8.4 (2.1) (6.7–10.0) | 9.6 (1.7) (8.4–10.9) | .67 |
| Maximum Center of Pressure Excursion (cm) Back | -6.7 (1.6) (-7.9—-5.6) | -8.2 (2.2) (-9.8—-6.6) | -7.2 (2.4) (-9.0—-5.3) | -8.4 (1.9) (-9.8—-7.1) | .21 |
| Early Day 1 Repeating Sequence RMSE ($cm^2$) | 0.8 (0.1) (0.8–0.9) | 1.2 (0.3) (1.0–1.4) | 1.2 (0.3) (1.1–1.4) | 1.2 (0.2) (1.1–1.4) | < .01 between HY and HE, PD on, PD off |
| Early Day 1 Random Sequence RMSE ($cm^2$) | 0.9 (0.1) (0.8–0.9) | 1.1 (0.3) (1.0–1.3) | 1.2 (0.2) (1.0–1.3) | 1.1 (0.2) (1.0–1.3) | <.01 between HY and HE, PD on, PD off |
| Early Day 1 Sequence Specific RMSE ($cm^2$) | 0.01 (0.06) (-0.03–0.05) | -0.03 (0.04) (-0.06—-0.00) | -0.08 (0.12) (-0.17—-0.00) | -0.08 (0.09) (-0.15—-0.01) | 0.05 |

*Note*. Cell values are mean, standard deviation, and 95% confidence intervals.

*Values for the PDOFF group are based on their off medication state.

[1]HY and HE, $p = .65$; HY and PD *on*, PD *off*, $p = <.01$; HE and PD *on*, PD *off*, $p = .01$; PD *on* and PD *off*, $p = .75$

[2]The UPDRS axial sub score is comprised of 4 items from the UPDRS total, items 27–30 (arise from chair, posture, gait and postural stability).

[3]The UPDRS, PIGD (postural instability/gait disturbance is comprised of 6 items from the UPDRS total, items 13–15 (falling, freezing, walking) and 28–30 (posture, gait and postural stability).

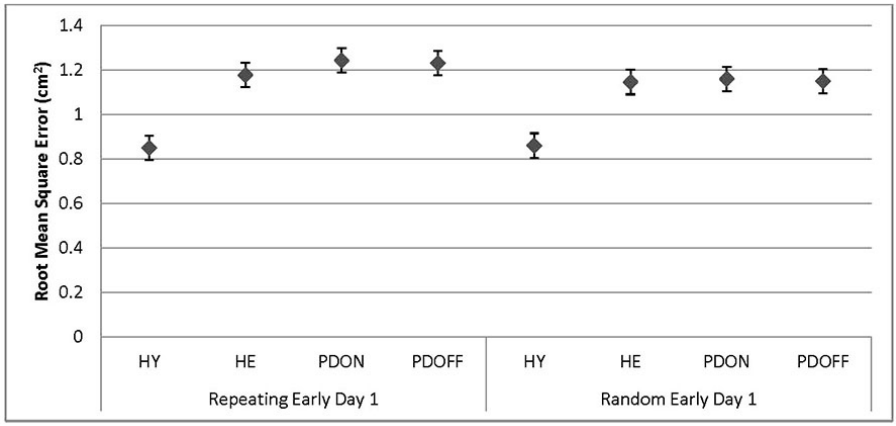


**Figure 2** — Baseline performance on Early Day 1 for each group on the repeating and random sequences based on Root Mean Squared Error ($cm^2$). The Healthy Young (HY) performed significantly different from the other three groups, Healthy Elder (HE), Parkinson *on* and *off* medications (PDON, PDOFF, respectively). Error bars are standard error.

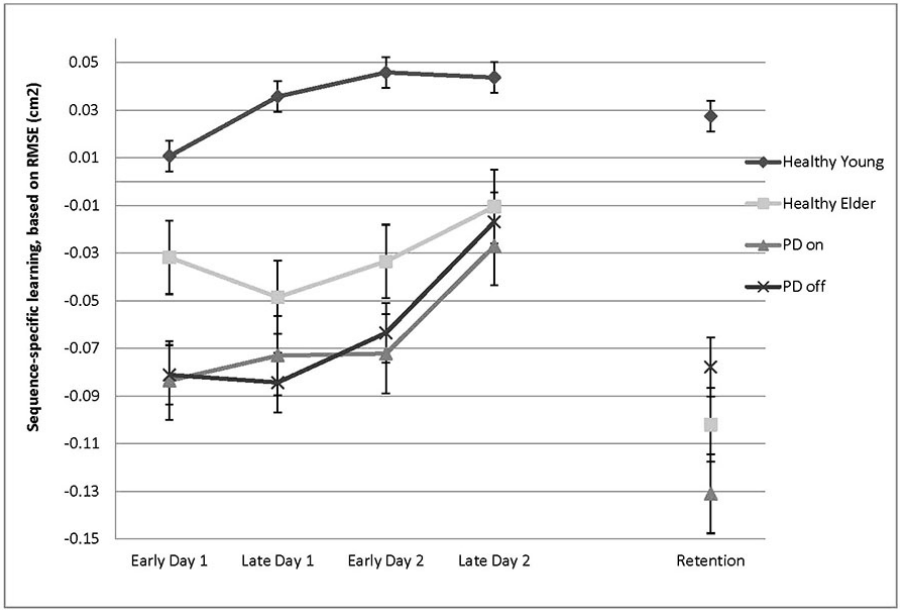


**Figure 3** — Performance curve of acquisition and retention trials, with sequence-specific learning as the dependent variable, assessed with Root Mean Square Error (RMSE, $cm^2$) of 4 groups, Healthy Young, Healthy Elder, Parkinson's disease on (PD *on*) their usual dosage of levodopa and PD off (PD *off*) their usual dosage of levodopa. The postural continuous tracking task was practiced for 2 days, with the average of 3 blocks accounting for early and late times. The difference between the random and repeated values accounts for sequence specific learning and values less than zero indicate that sequence specific learning occurred. Increasing values indicates improved performance across time. Error bars are standard error.

## Discussion

The purpose of this study was to examine implicit learning of a postural motor sequence in individuals with PD and to determine whether dopamine replacement medication affected the learning of this motor sequence. As hypothesized, all participants improved tracking performance over two days of acquisition, regardless of age, disease, or medication state (Muslimovic et al., 2007; Stephan et al., 2011; Tyson & Connell, 2009). Contrary to our hypothesis, however, participants with PD *on* or *off* their medication and their age-matched controls showed substantial retention loss. We had also hypothesized that we would observe less motor sequence learning, as measured by acquisition and retention, in participants with PD *on* medication compared with *off* medication, due to the potential dopamine "overdose", yet no significant differences due to disease or medication state were observed.

Because of the lack of sustained change observed at retention, the results of this study are different from prior sequence-learning studies in PD where individuals with PD demonstrate continued performance improvement at retention; even though, their performance generally lags behind controls (Stefanova, Kostic, Ziropadja, Markovic, & Ocic, 2000; Shin & Ivry, 2003; Jackson, Jackson, Harrison, Henderson, & Kennard, 1995). The delay in sequence-specific learning (SSL) in this study may be attributed to two factors: the type of task used and the amount of practice provided.

The type of task used in this study is unique relative to prior studies because of its postural demands. To our knowledge, this is the first SSL study in individuals with PD in which the sequence to be learned was posturally demanding. Because of the known postural declines associated with aging (Bosek, Grzegorzewski, Kowalczyk, & Lubinski, 2005) and PD (Blaszczyk & Orawiec, 2011), the postural demands of the task used in this study may have substantially increased the level of task difficulty for the HE and PD groups. Although we did not directly measure or probe for task difficulty, the clear differences in early day 1 performance (Figure 2) between the HY and all other groups suggest, given their level of postural skill, variations in functional task difficulty were present. When considered in the context of the Challenge Point Framework model (Guadagnoli & Lee, 2004) these results suggest that while the functional task difficulty was appropriate for the HY group, this level of difficulty may have disrupted learning and retention in individuals with PD (Onla-or & Winstein, 2008). The use of learning tasks with varied effectors (e.g., postural, upper extremity) in future studies may provide a more thorough probe of the effects of task difficulty on skill acquisition.

The second yet related factor that may have contributed to our findings is the amount of practice provided. The dose of CTT practice in this study (120 trials over 2 days) was based on previous studies showing significant acquisition and retention using 56–150 trials of the repeating sequence (Boyd & Winstein, 2006; Shea, Wulf, Whitacre, & Park, 2001). However, only the healthy young participants' in this study demonstrated a plateau in their performance curve (see Day 2, Figure 3) that reflected consistency in the coordination of the task and stable performance. This consistency was then partially retained following a period of no practice. In contrast, none of the PD and HE groups demonstrated a plateau in their learning curves. This suggests that this practice dosage and duration was insufficient to

achieve a consistent motor output and stable performance that could be retained. An alternative approach to studying sequence learning in clinical populations may be to use practice dose (i.e., number of repetitions or trials, Lang et al. 2009) as the dependent measure and retention as a probe for determining how many practice sessions are needed to demonstrate performance stability.

Lastly, the implicit nature of this CTT task may have influenced our results. Prior research showing a significant effect of medication status on sequence learning in PD has used a task where participants' had explicit knowledge of the task (Kwak et al., 2010). The differences in our data raise the possibility that the type of memory or cues (implicit vs. explicit) used to drive learning may be differentially affected by an over-dose of exogenous dopamine within the associative striatum. When considered with recent research (Vaillancourt et al., 2013; Kwak et al., 2010), the divergence of the PD *on* and PD *off* groups at initial practice and at retention implies that the dopamine overdose hypothesis requires additional examination with consideration of the type of memory and how learning is defined (e.g., immediate postpractice performance, retention, generalization).



## Limitations and Implications for Future Research

Although these results suggest that the amount of practice differentially influenced learning and that dopamine replacement medications may not have a large effect on postural motor learning in this task, they should be interpreted with caution. While we characterized the cognitive status of the groups using the MMSE and the trail making test, these tests provide global measures of cognition and may not adequately reflect the elements of cognition critical for motor learning. Factors such as fatigue during task practice and sleep quality between practice days may have also influenced the results and should be considered in future studies (Al-Sharman & Siengsukon, 2014; Siengsukon & Boyd, 2008; Verneau, van der Kamp, Savelsbergh, & de Looze, 2014).

In addition, participant related factors may have contributed to the variability in our results. First, although the method of dopamine replacement medication withdrawal used in this study (12 hr withdrawal of levodopa only) was similar to other studies (Seidler, Tuite, & Ashe, 2007; Tremblay et al., 2010), the withdrawal duration may have been insufficient. Our use of levodopa equivalent doses for each participant provides a basis for subsequent comparisons of dopamine dosage effects on motor learning. Secondly, the inherent variability of PD and the potential that the varied motor or cognitive phenotypes influenced our results cannot be eliminated (Vandenbossche, Deroost, Soetens, & Kerckhofs, 2009; Vandenbossche et al., 2013). Future research of larger samples with more detailed characterization of cognition, motor phenotype, and postural status is warranted.

# Conclusions

All groups in this study, regardless of age, Parkinson's disease, or medication status, acquired a postural skill as a result of practice; however, only healthy young participants demonstrated some retention of this skill. The posturally-demanding implicit task combined with an insufficient practice dosage for the PD and healthy older groups may account for observed results. Future research is needed to gain

insight into the influence of factors such as practice dosage and task type and difficulty on sequence specific learning.

## References


Al-Sharman, A., & Siengsukon, C.F. (2014). Performance on a functional motor task is enhanced by sleep in middle-aged and older adults. *Journal of Neurologic Physical Therapy; JNPT, 38*(3), 161–169. PubMed doi:10.1097/NPT.0000000000000048

Berg, K.O., Maki, B.E., Williams, J.I., Holliday, P.J., & Wood-Dauphinee, S.L. (1992). Clinical and laboratory measures of postural balance in an elderly population. *Archives of Physical Medicine and Rehabilitation, 73*(11), 1073–1080. PubMed

Bischoff-Grethe, A., Martin, M., Mao, H., & Berns, G.S. (2001). The context of uncertainty modulates the subcortical response to predictability. *Journal of Cognitive Neuroscience, 13*(7), 986–993. PubMed doi:10.1162/089892901753165881

Blackwelder, W.C. (1982). "Proving the null hypothesis" in clinical trials. *Controlled Clinical Trials, 3*(4), 345–353. PubMed doi:10.1016/0197-2456(82)90024-1

Blaszczyk, J.W., & Orawiec, R. (2011). Assessment of postural control in patients with Parkinson's disease: Sway ratio analysis. *Human Movement Science, 30*(2), 396–404. PubMed doi:10.1016/j.humov.2010.07.017

Bosek, M., Grzegorzewski, B., Kowalczyk, A., & Lubinski, I. (2005). Degradation of postural control system as a consequence of Parkinson's disease and ageing. *Neuroscience Letters, 376*(3), 215–220. PubMed doi:10.1016/j.neulet.2004.11.056

Boyd, L., & Winstein, C. (2006). Explicit information interferes with implicit motor learning of both continuous and discrete movement tasks after stroke. *Journal of Neurologic Physical Therapy, 30*(2), 46-57; discussion 58-49.

Boyd, L., Edwards, J.D., Siengsukon, C.S., Vidoni, E.D., Wessel, B.D., & Linsdell, M.A. (2009). Motor sequence chunking is impaired by basal ganglia stroke. *Neurobiology of Learning and Memory, 92*(1), 35–44. PubMed doi:10.1016/j.nlm.2009.02.009

Brown, R.G., Jahanshahi, M., Limousin-Dowsey, P., Thomas, D., Quinn, N.P., & Rothwell, J.C. (2003). Pallidotomy and incidental sequence learning in Parkinson's disease. *Neuroreport, 14*(1), 21–24. PubMed doi:10.1097/00001756-200301200-00004

Burn, D.J., Rowan, E.N., Minett, T., Sanders, J., Myint, P., Richardson, J., . . . McKeith, I.G. (2003). Extrapyramidal features in Parkinson's disease with and without dementia and dementia with Lewy bodies: A cross-sectional comparative study. *Movement Disorders, 18*(8), 884–889. PubMed doi:10.1002/mds.10455

Camicioli, R.M., Wieler, M., de Frias, C.M., & Martin, W.R. (2008). Early, untreated Parkinson's disease patients show reaction time variability. *Neuroscience Letters, 441*(1), 77–80. PubMed doi:10.1016/j.neulet.2008.06.004

Chambaron, S., Ginhac, D., Ferrel-Chapus, C., & Perruchet, P. (2006). Implicit learning of a repeated segment in continuous tracking: A reappraisal. *The Quaterly Journal of Experimental Psychology, 59*(5), 845–854. PubMed doi:10.1080/17470210500198585

Cools, R., Altamirano, L., & D'Esposito, M. (2006). Reversal learning in Parkinson's disease depends on medication status and outcome valence. *Neuropsychologia, 44*(10), 1663–1673. PubMed doi:10.1016/j.neuropsychologia.2006.03.030

Corrigan, J.D., & Hinkeldey, N.S. (1987). Relationships between parts A and B of the Trail Making Test. *Journal of Clinical Psychology, 43*(4), 402–409. PubMed doi:10.1002/1097-4679(198707)43:4<402::AID-JCLP2270430411>3.0.CO;2-E

Dibble, L.E., Addison, O., & Papa, E. (2009). The effects of exercise on balance in persons with Parkinson's disease:A systematic review across the disability spectrum. *Journal of Neurologic Physical Therapy; JNPT, 33*(1), 14–26. PubMed doi:10.1097/NPT.0b013e3181990fcc

Doyon, J. (2008). Motor sequence learning and movement disorders. *Current Opinion in Neurology, 21*(4), 478–483. PubMed doi:10.1097/WCO.0b013e328304b6a3

Esselink, R.A., de Bie, R.M., de Haan, R.J., Lenders, M.W., Nijssen, P.C., Staal, M.J., . . . Speelman, J.D. (2004). Unilateral pallidotomy versus bilateral subthalamic nucleus stimulation in PD: A randomized trial. *Neurology, 62*(2), 201–207. PubMed doi:10.1212/01.WNL.0000103235.12621.C3

Foreman, K.B., Addison, O., Kim, H.S., & Dibble, L.E. (2011). Testing balance and fall risk in persons with Parkinson disease, an argument for ecologically valid testing. *Parkinsonism & Related Disorders, 17*(3), 166–171. PubMed doi:10.1016/j.parkreldis.2010.12.007

Folstein, M.F., Folstein, S.E., & McHugh, P.R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12*(3), 189–198. PubMed doi:10.1016/0022-3956(75)90026-6

Fritz, C.O., Morris, P.E., & Richler, J.J. (2012). Effect size estimates: Current use, calculations, and interpretation. *Journal of Experimental Psychology. General, 141*(1), 2–18. PubMed doi:10.1037/a0024338

Gheysen, F., Van Opstal, F., Roggeman, C., Van Waelvelde, H., & Fias, W. (2010). Hippocampal contribution to early and later stages of implicit motor sequence learning. *Experimental Brain Research, 202*(4), 795–807. PubMed doi:10.1007/s00221-010-2186-6

Guadagnoli, M.A., & Lee, T.D. (2004). Challenge point: A framework for conceptualizing the effects of various practice conditions in motor learning. *Journal of Motor Behavior, 36*(2), 212–224. PubMed doi:10.3200/JMBR.36.2.212-224

Hoehn, M.M., & Yahr, M.D. (1967). Parkinsonism: Onset, progression and mortality. *Neurology, 17*(5), 427–442. PubMed doi:10.1212/WNL.17.5.427

Jackson, G.M., Jackson, S.R., Harrison, J., Henderson, L., & Kennard, C. (1995). Serial reaction time learning and Parkinson's disease: Evidence for a procedural learning deficit. *Neuropsychologia, 33*(5), 577–593. PubMed doi:10.1016/0028-3932(95)00010-Z

Jankovic, J. (2008). Parkinson's disease: Clinical features and diagnosis. *Journal of Neurology, Neurosurgery, and Psychiatry, 79*(4), 368–376. PubMed doi:10.1136/jnnp.2007.131045

Kwak, Y., Muller, M.L., Bohnen, N.I., Dayalu, P., & Seidler, R.D. (2010). Effect of dopaminergic medications on the time course of explicit motor sequence learning in Parkinson's disease. *Journal of Neurophysiology, 103*(2), 942–949. PubMed doi:10.1152/jn.00197.2009

Lakens, D. (2013). Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs. *Frontiers in Psychology, 4,* 863. PubMed doi:10.3389/fpsyg.2013.00863

Lang, C.E., Macdonald, J.R., Reisman, D.S., Boyd, L., Jacobson Kimberley, T., Schindler-Ivens, S.M., . . . Scheets, P.L. (2009). Observation of amounts of movement practice provided during stroke rehabilitation. *Archives of Physical Medicine and Rehabilitation, 90*(10), 1692–1698. PubMed doi:10.1016/j.apmr.2009.04.005

Lozano, A.M., Lang, A.E., Galvez-Jimenez, N., Miyasaki, J., Duff, J., Hutchinson, W.D., & Dostrovsky, J.O. (1995). Effect of GPi pallidotomy on motor function in Parkinson's disease. *Lancet, 346*(8987), 1383–1387. PubMed doi:10.1016/S0140-6736(95)92404-3

Munro, B.H. (2005). *Statistical Methods for Health Care Research* (5th ed.). Philadelphia: Lippincott Williams & Wilkins.

Muslimovic, D., Post, B., Speelman, J.D., & Schmand, B. (2007). Motor procedural learning in Parkinson's disease. *Brain, 130*(Pt 11), 2887–2897. PubMed doi:10.1093/brain/awm211

Nissen, M.J., & Bullemer, P. (1987). Attentional requirements of learning; evidence from performance measures. *Cognitive Psychology, 19,* 1–32. doi:10.1016/0010-0285(87)90002-8

Onla-or, S., & Winstein, C.J. (2008). Determining the optimal challenge point for motor skill learning in adults with moderately severe Parkinson's disease. *Neurorehabilitation and Neural Repair, 22*(4), 385–395. PubMed doi:10.1177/1545968307313508

Pahwa, R., Factor, S.A., Lyons, K.E., Ondo, W.G., Gronseth, G., Bronte-Stewart, H., . . . Weiner, W.J. (2006). Practice Parameter: Treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology, 66*(7), 983–995. PubMed doi:10.1212/01.wnl.0000215250.82576.87

Reichmann, H., & Emre, M. (2012). Optimizing levodopa therapy to treat wearing-off symptoms in Parkinson's disease: Focus on levodopa/carbidopa/entacapone. *Expert Review of Neurotherapeutics, 12*(2), 119–131. PubMed doi:10.1586/ern.11.203

Schmidt, R.A., & Lee, T.D. (2005). *Motor Control and Learning: A behavioral emphasis* (4th ed.). Champaign, IL: Human Kinetics.

Seidler, R.D., Noll, D.C., & Chintalapati, P. (2006). Bilateral basal ganglia activation associated with sensorimotor adaptation. *Experimental Brain Research, 175*(3), 544–555. PubMed doi:10.1007/s00221-006-0571-y

Seidler, R.D., Tuite, P., & Ashe, J. (2007). Selective impairments in implicit learning in Parkinson's disease. *Brain Research, 1137*(1), 104–110. PubMed doi:10.1016/j.brainres.2006.12.057

Shea, C.H., Wulf, G., Whitacre, C.A., & Park, J-H. (2001). Surfing the implicit wave. *Quarterly Journal of Experimental Psychology: Section A:UK, 54A*(3), 841–862. PubMed doi:10.1080/713755993

Shin, J.C., & Ivry, R.B. (2003). Spatial and temporal sequence learning in patients with Parkinson's disease or cerebellar lesions. *Journal of Cognitive Neuroscience, 15*(8), 1232–1243. PubMed doi:10.1162/089892903322598175

Siegert, R.J., Taylor, K.D., Weatherall, M., & Abernethy, D.A. (2006). Is implicit sequence learning impaired in Parkinson's disease? A meta-analysis. *Neuropsychology, 20*(4), 490–495. PubMed doi:10.1037/0894-4105.20.4.490

Siengsukon, C.F., & Boyd, L.A. (2008). Sleep enhances implicit motor skill learning in individuals poststroke. *Topics in Stroke Rehabilitation, 15*(1), 1–12. PubMed doi:10.1310/tsr1501-1

Siengsukon, C.F., & Boyd, L. (2009). Sleep to learn after stroke: implicit and explicit off-line motor learning. *Neuroscience Letters, 451*(1), 1–5. PubMed doi:10.1016/j.neulet.2008.12.040

Smith, J.G., & McDowall, J. (2006). The implicit sequence learning deficit in patients with Parkinson's disease: A matter of impaired sequence integration? *Neuropsychologia, 44*(2), 275–288. PubMed doi:10.1016/j.neuropsychologia.2005.05.001

Stefanova, E.D., Kostic, V.S., Ziropadja, L., Markovic, M., & Ocic, G.G. (2000). Visuomotor skill learning on serial reaction time task in patients with early Parkinson's disease. *Movement Disorders, 15*(6), 1095–1103. PubMed doi:10.1002/1531-8257(200011)15:6<1095::AID-MDS1006>3.0.CO;2-R

Stephan, M.A., Meier, B., Zaugg, S.W., & Kaelin-Lang, A. (2011). Motor sequence learning performance in Parkinson's disease patients depends on the stage of disease. *Brain and Cognition, 75*(2), 135–140. PubMed doi:10.1016/j.bandc.2010.10.015

Tremblay, P.L., Bedard, M.A., Langlois, D., Blanchet, P.J., Lemay, M., & Parent, M. (2010). Movement chunking during sequence learning is a dopamine-dependant process: A study conducted in Parkinson's disease. *Experimental Brain Research, 205*(3), 375–385. PubMed doi:10.1007/s00221-010-2372-6

Tyson, S.F., & Connell, L.A. (2009). How to measure balance in clinical practice. A systematic review of the psychometrics and clinical utility of measures of balance activity for neurological conditions. *Clinical Rehabilitation, 23*(9), 824–840. PubMed doi:10.1177/0269215509335018

Vaillancourt, D.E., Schonfeld, D., Kwak, Y., Bohnen, N.I., & Seidler, R. (2013). Dopamine overdose hypothesis: Evidence and clinical implications. *Movement Disorders, 28*(14), 1920–1929. PubMed doi:10.1002/mds.25687

van Asselen, M., Almeida, I., Andre, R., Januario, C., Goncalves, A.F., & Castelo-Branco, M. (2009). The role of the basal ganglia in implicit contextual learning: A study of Parkinson's disease. *Neuropsychologia, 47*(5), 1269–1273. PubMed doi:10.1016/j.neuropsychologia.2009.01.008

van Tilborg, I., & Hulstijn, W. (2010). Implicit motor learning in patients with Parkinson's and Alzheimer's disease: Differences in learning abilities? *Motor Control, 14*(3), 344–361. PubMed

Vandenbossche, J., Deroost, N., Soetens, E., & Kerckhofs, E. (2009). Does implicit learning in non-demented Parkinson's disease depend on the level of cognitive functioning? *Brain and Cognition, 69*(1), 194–199. PubMed doi:10.1016/j.bandc.2008.07.005

Vandenbossche, J., Deroost, N., Soetens, E., Coomans, D., Spildooren, J., Vercruysse, S., . . . Kerckhofs, E. (2013). Impaired implicit sequence learning in Parkinson's disease patients with freezing of gait. *Neuropsychology, 27*(1), 28–36. PubMed doi:10.1037/a0031278

Verneau, M., van der Kamp, J., Savelsbergh, G.J., & de Looze, M.P. (2014). Age and time effects on implicit and explicit learning. *Experimental Aging Research, 40*(4), 477–511. PubMed doi:10.1080/0361073X.2014.926778

Winter, D.A. (2005). *Biomechanics and motor control of human movement*. Hoboken, N.J.: John Wiley & Sons.

Wulf, G., & Schmidt, R.A. (1997). Variability of practice and implicit motor learning. *Journal of Experimental Psychology. Learning, Memory, and Cognition, 23*(4), 987–1006. doi:10.1037/0278-7393.23.4.987

Wulf, G., Schmidt, R.A., & Deubel, H. (1993). Reduced feedback frequency enhances generalized motor program learning but not parameterization learning. *Journal of Experimental Psychology. Learning, Memory, and Cognition, 19*(5), 1134–1150. PubMed doi:10.1037/0278-7393.19.5.1134