

EFFECT OF AGE, PARKINSON DISEASE, AND DOPAMINE
ON ACQUISITION PERFORMANCE AND RETENTION
LEARNING OF A STANDING IMPLICIT MOTOR
SEQUENCE TASK

by

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A dissertation submitted to the faculty of
The University of Utah
in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Department of Exercise and Sport Science

The University of Utah

May 2014

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The University of Utah Graduate School

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ABSTRACT

Parkinson disease (PD) is a progressive neurodegenerative disorder with selective damage of dopaminergic neurons within the Basal Ganglia (BG), leading to the most clearly recognized sequelae of motor deficits observed in PD. The BG have also been shown to be important during implicit motor sequence learning (IMSL), and individuals with BG lesions have demonstrated impairment in IMSL compared to healthy age matched controls. Additionally, individuals with PD are typically prescribed dopamine replacement or agonist medications, which have been found to reduce the observed movement deficits. However, it has been observed that dopamine addition may potentially impair IMSL.

The primary purpose of this paper was to describe impairments in IMSL in individuals with PD, describe a neurobiological model for the observed deficits in IMSL, and to determine the impact of dopamine addition on acquisition performance and retention learning of repeated segments during a standing implicit continuous tracking task in individuals with PD. We hypothesized that IMSL would be impaired in individuals with PD on their usual dosage of dopamine. Secondarily, the impact of age, PD, and dopamine on sequence-specific integration was assessed, and it was hypothesized that there would be a graded deficit related to age, PD, and dopamine on sequence-specific integration. Finally, the relationship of spatial and temporal parameters within sequence learning was assessed as an exploratory aim.

The results of this study supported an IMSL deficit primarily related to age and secondarily related to PD, but not dopamine replacement. Additionally, individuals with PD, regardless of medication, demonstrated impaired spatial integration compared to healthy young and elder participants. The type of task performed in this study was a demanding postural task compared to the traditional IMSL paradigms using the upper extremity and task difficulty could account for the lack of observed difference during acquisition. Longer time to practice the paradigm may be required to observe improved performance. Finally, although IMSL has been observed to be impaired in individuals with PD, a better understanding of the IMSL deficit related to the impact of medication and age during a standing motor task is warranted.

I dedicate this to my father, Harry Hayes, Jr, MD who always taught me to question and learn and to my husband, Larry Coats, for patiently supporting my questioning and learning endeavors.

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CHAPTER 1

INTRODUCTION

Parkinson disease (PD) is a progressive neurodegenerative disorder associated with abnormal protein metabolism in components of the peripheral and ultimately the central nervous system (Halliday, Lees, & Stern, 2011). Initial selective damage of dopaminergic neurons within a portion of the midbrain (substantia nigra, one of four nuclei of the Basal Ganglia [BG]) leads to the most clearly recognized sequelae of motor deficits observed in PD; tremor at rest, muscular rigidity, akinesia (inability to initiate movement) and bradykinesia (slowness of movement), and postural instability (Jankovic, 2008). With disease progression, additional and multiple deficits may be observed besides the common motor symptoms

Multiple studies have demonstrated that implicit motor sequence learning (IMSL) is impaired in individuals with PD, but these limitations seem to be independent of cognitive or motor decline (Bailey & Mair, 2006; Dominey, Ventre-Dominey, Broussolle, & Jeannerod, 1997; Fama & Sullivan, 2002; Smith & McDowall, 2004). These results are not surprising, because it has been shown that the BG are critical players during the consolidation of implicit motor sequences (Doyon, 2008). Individuals with PD often report having difficulty with simple sequential tasks such as getting out of bed or transitioning from sit to stand or turning around. Rehabilitation specialists often

spend many therapy sessions helping their patients relearn to perform these skills; however, current rehabilitation strategies have limited long-term effect on improving implicit motor sequence skills (Brichetto, Pelosin, Marchese, & Abbruzzese, 2006; Nieuwboer, De Weerdt, Dom, & Bogaerts, 2002).

Because of the deficit of the neurotransmitter dopamine, individuals with PD are typically prescribed dopamine replacement or dopamine agonist medications. These medications have been found to reduce the movement deficit, tremor at rest, rigidity, akinesia, and bradykinesia; however, postural instability is typically not mitigated by medication (Jankovic, 2008). The impact of medication on motor sequence learning has only recently begun to be studied (Feigin et al., 2003; Kwak, Muller, Bohnen, Dayalu, & Seidler, 2010; Stephan, Meier, Zaugg, & Kaelin-Lang, 2011). Understanding the effect of medication on individuals with PD during the sequence learning of a postural task could have a profound impact on the role of rehabilitation.

This paper (a) defines IMSL, (b) describes results of IMSL in individuals with BG lesions, (c) describes a neurobiological model of IMSL, (d) describes IMSL impairments in individuals with BG lesions, (e) describes an additional reason IMSL in individuals with BG lesions may be impaired, (f) identifies the postural instability deficits of individuals with BG lesions, (g) describes limitations to current research, (h) describes a research study designed to assess the impact of dopamine on IMSL in individuals with BG lesions during a postural task, and (i) describes methods, results, and discussion of the study.

Implicit Motor Sequence Learning Defined

Implicit versus Explicit Learning

Implicit learning, also termed nondeclarative learning refers to the unconscious awareness of what is learned. Examples of implicit learning include habit and skill learning and operant conditioning (Kandel, Schwartz, & Jessell, 2000). Explicit learning, in contrast, is based on learning of facts or rules with a declarative awareness of what has been learned. Examples of explicit learning include memorizing a phone number or an address.

Implicit and explicit learning have been studied both by imaging and experimental paradigms, and results suggest that these systems are dissociated (Knowlton, Mangels, & Squire, 1996). Explicit learning has been found to be supported by discrete regions within the brain, specifically the hippocampus within the medial temporal lobe (Squire & Zola, 1996), whereas implicit learning appears to be widely distributed throughout multiple brain regions including the BG, cerebellum, amygdala, and the neocortex (Squire & Zola, 1996).

Multiple experimental paradigms on individuals with specific brain lesions further support this dissociation. It has been observed experimentally that individuals with PD in the early course of the disease have difficulty performing implicit movements while the explicit learning system remains intact (Feigin et al., 2003; Smiley-Oyen, Lowry, & Emerson, 2006; Soliveri, Brown, Jahanshahi, & Marsden, 1992). This paper focuses on deficits with implicit motor skill learning observed in individuals with PD.

Learning versus Performance

Motor learning is defined as "a set of processes associated with practice or experience leading to a relatively permanent change in the capability for movement" (Schmidt & Lee, 2005, p. 302). Assessment of learning does not occur directly; rather it is inferred as having occurred through a relatively permanent change in performance after practice. Note that learning in this paper will refer only to implicit motor learning, or learning of a motor skill without conscious awareness. Furthermore, this paper uses performance assessments to infer learning.

Performance assessments can be used to determine change in performance of a motor skill. Three types of assessments are typically used to determine performance change and are differentiated by time course or tasks performed and include acquisition, retention, and transfer. During acquisition, initial changes in performance are typically observed across practice trials; however, the observed performance changes may only be temporary, and further assessment is needed to determine if a relatively permanent change in performance is maintained, indicating that learning has occurred. Acquisition performance implies that during acquisition, only change in performance is being assessed during the initial time of practice.

A repeat of the performance after a period of time with no practice is required to determine if the motor skill has or has not been learned and is termed a retention test (Schmidt & Lee, 2005). If the task performance on the retention test demonstrates the same results or further change in results, either negative or positive compared to the end of the performance during acquisition, then learning is stated to either have or have not

occurred (negative or positive, respectively). Assessment via a retention test refers to retention learning, implying that on a retention test learning is being evaluated.

A final method for determining if information has been learned occurs via a transfer test. A transfer test requires the individual to perform the same skill or sequence that was practiced but under different practice situations or conditions (Magill, 2007). The measurement of skill improvement on a transfer test is based on a percentage transfer (negative or positive) and the relationship of observed performance of Task A compared to Task B (Schmidt & Lee, 2005). Acquisition performance and retention learning as assessments of performance and learning are the focus of this paper.

Motor Sequence Learning

Motor sequence learning refers to the process by which simple or complex serial movements come to be performed effortlessly as a single unit of movement (Doyon, 2008; Gheysen, Van Opstal, Roggeman, Van Waelvelde, & Fias, 2010). Examples of motor sequence learning include driving a car, brushing one's teeth, getting out of bed, or riding a bicycle (Doyon, 2008; Magill, 2007). Paradigms assessing motor sequence learning will embed a repeating sequence within random sequences and seek to differentiate between the ability to learn this repeating motor sequence (sequence-specific skill) compared with general motor learning capability (general skill). General skill learning refers to the general ability to learn the skill, compared to sequence-specific skill learning, which refers to the learning of the embedded repeating sequence of the skill. Assessment of motor sequence learning can refer to both the acquisition performance and

retention learning of the general skill capacity and the acquisition performance and retention learning of sequence-specific skill capacity (Kandel et al., 2000).

Assessment of the general skill (Gsk) capacity acts as a control and thus allows comparison to the learning of the sequence-specific capacity. Individuals often demonstrate a change in their ability to perform the Gsk from initial practice to final practice. This paper focuses on acquisition performance and retention learning of sequence-specific skill (SSsk) rather than acquisition performance and retention learning of Gsk. Varying experimental paradigms have assessed both general skill and sequence-specific skill acquisition performance and retention learning. See Figure 1.1 for a graphical representation of the difference between Gsk and SSsk.

Paradigms of motor sequence learning can be explicit if individuals are informed that a sequence-specific component is embedded. However, if they are not informed of the sequence-specific component, then performance and learning changes observed within the SSsk compared to the Gsk implies performance and learning of a motor sequence has occurred implicitly. Typical experimental paradigms utilize an implicit model to determine the difference between the SSsk learning and the Gsk learning. Both implicit and explicit motor learning paradigms are described in the literature. This study focuses on implicit motor sequence learning, meaning that individuals will not be told there is a sequence-specific component embedded. The primary literature focus described in this paper will be on implicit motor sequence learning; however, if explicit motor learning is described, the reader will be informed.

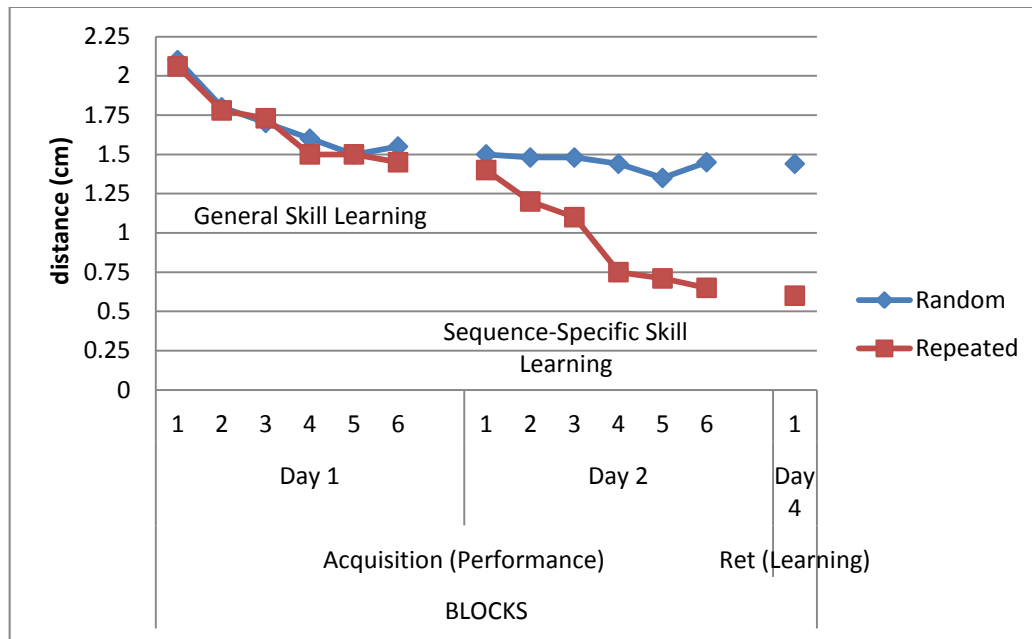


Figure 1.1. A graphical representation of potential performance patterns. Root mean square error (RMSE) on the y-axis, with lower numbers representing a reduction in performance error across time (x-axis). Two days of acquisition (performance) with 12 blocks total practiced, and on Day 4 a retention (learning) test occurred with 1 block performed. During Day 1, general skill learning is observed, as both the repeated and random sequences show a reduction in error. However, after more practice on Day 2 and on the retention test, the repeated pattern continues to demonstrate reduced errors indicating sequence-specific skill learning.

Experimental Paradigms of Motor

Sequence Learning

Motor sequence learning has been studied using a variety of experimental paradigms including but not limited to serial reaction time tasks (Nissen & Bullemer, 1987) and continuous tracking tasks (Boyd & Winstein, 2006; Wulf, Schmidt, & Deubel, 1993).

Performance assessments of motor sequence learning have been studied extensively using the serial reaction time (SRT) task (Figure 1.2; Nissen & Bullemer,

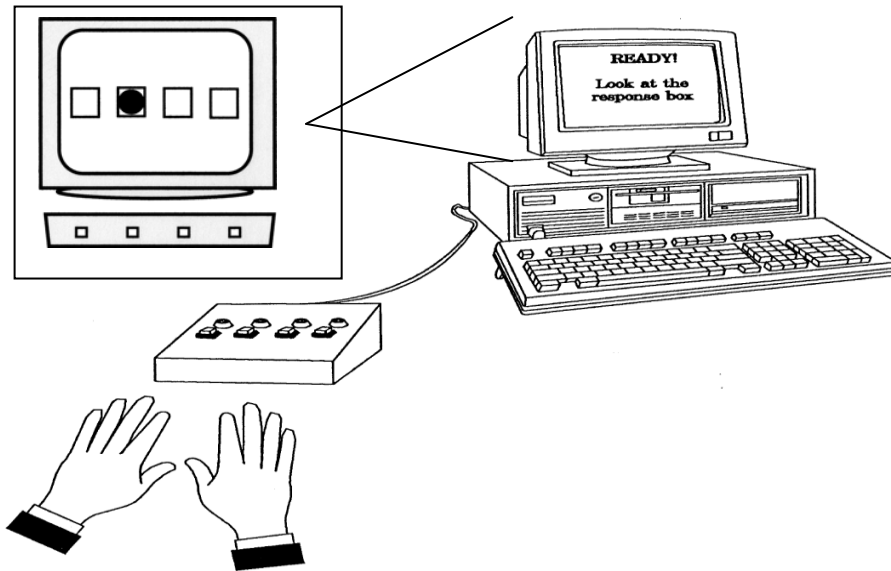


Figure 1.2. Serial reaction time task. The individual views the computer screen and depresses the corresponding key responses. (Adapted from Keisler, Ashe, & Willingham, 2007)

1987). During a SRT task, subjects are instructed to map a visuospatial stimulus (a point on a computer screen) to a corresponding response key. The stimuli are presented in a series of either repeating or random sequences, without (implicit) the subject's knowledge of a repeated pattern being presented. Improvement in sequence-specific performance is observed at the end of acquisition as the individual demonstrates faster reaction times when performing the repeated sequence compared to the random sequence. The difference in performance observed during acquisition between the random and repeated sequences is an indication of sequence-specific acquisition performance (SSAP).

In a continuous tracking task (CTT) participants are required to synchronize the movements of a cursor with a sinusoidal target on the computer screen by manipulating a joystick with their arm, or if they are standing with their body sway. This task is similar to the SRT task in that patterns presented can consist of repeating or random sequences.

Measurement of CTT occurs by assessing the participant's deviations from the target as measured by error (Muslimovic, Post, Speelman, & Schmand, 2007). A decrease in the amount of error means the individual has become more accurate in the performance, which is assessed by using overall accuracy, the root mean square error (RMSE) in degrees or a unit of distance. The RMSE reflects the extent to which the participant matches their movement to the target line (Figure 1.3; Shea, Wulf, Whitacre, & Park, 2001).

In summary, assessment of learning for motor sequence learning can occur by assessing performance on a SRT task or CTT. Within these experimental paradigms both general skill and sequence-specific skill acquisition performance and retention learning can be assessed (Muslimovic et al., 2007).

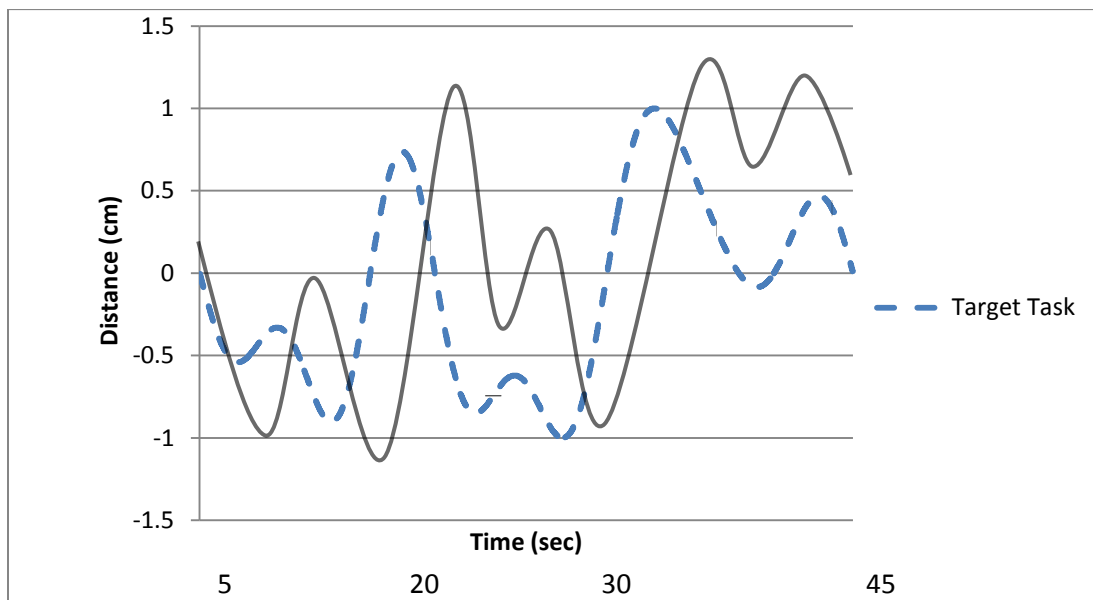


Figure 1.3. Example of a continuous tracking task. Y-axis is the distance (cm) of movement or repeating wave trajectory. X-axis is time (seconds). The average difference between the target pattern (blue) and the subjects' movements (black) is the Root Mean Square Error (RMSE).

Implicit Motor Sequence Learning in Individuals with Basal

Ganglia Lesions

Multiple studies have assessed IMSL in individuals with PD or BG lesions using the SRT task and the CTT (Boyd & Winstein, 2004; Jackson, Jackson, Harrison, Henderson, & Kennard, 1995; Muslimovic, et al., 2007; Stefanova, Kostic, Ziropadja, Markovic, & Ocic, 2000). Within the assessment of IMSL using a SRT task or CTT, both Gsk and SSsk have been assessed separately.

Acquisition Performance of General Skill and Sequence-Specific Skill

Assessment of Gsk using a SRT task or a CTT in individuals with PD or BG lesions, such as stroke, consistently demonstrate that these individuals are able to acquire the general skill; however, during the acquisition phase, the performance of the Gsk is impaired compared with healthy, age matched controls when assessing reaction time (slower) or accuracy (reduced error; Boyd & Winstein, 2006; Boyd et al., 2009; Doyon et al., 1997; Ferraro, Balota, & Connor, 1993; Muslimovic et al., 2007; Siengsukon & Boyd, 2009; Stephan et al., 2011).

This impairment in the capacity to acquire the Gsk has been thought to be due to the movement disorder, bradykinesia (slowness of movement). However, two aspects that refute the idea that the limitation observed in Gsk performance is due to the movement disorder include the following findings. First, the initial performance on SRT task and the CTT between the groups do not show a difference between the groups, indicating that both groups perform the new task at similar rates and accuracy; thus, slowness of

movement is not an initial factor in task performance. Secondly, performance of the random sequences across the acquisition phase shows no difference between groups, indicating that individuals with BG lesions are capable of performing the random tasks at the same speed and accuracy as controls (Boyd et al., 2009). Thus, difficulties observed in CTT or SRT is not thought to be due to poor capacity of performing a Gsk during acquisition. Thus, assessment of the SSsk aspect becomes critical to understanding the deficit observed in implicit learning in individuals with BG lesions.

The assessment of SSsk during acquisition finds that individuals with PD are consistently slower (delayed reaction time), and less accurate than healthy age-matched controls on the sequences. A meta-analysis by Siegert, Taylor, Weatherall, and Abernathy (2006) assessed SSsk using a SRT task (the difference in reaction time between the last block of the repeated sequence and random sequence trial at the end of acquisition). She assessed six studies; 67 people with PD and 87 healthy controls. Her meta-analysis results showed a standardized mean difference of 0.73 (95% confidence interval = 0.38, 1.07) between the two groups on the SRT task. Thus, assessment of SSsk at the end of the acquisition phase of learning demonstrated that individuals with BG lesions were impaired as evidenced by a delayed reaction time compared to healthy controls. In summary, the above results suggest that individuals with BG lesions are able to demonstrate improved performance of a Gsk and SSsk, but not as efficiently as healthy controls. More specifically, the ability to acquire the SSsk appears to be the area of concern in individuals with BG lesions.

Retention Learning

The delays in performance capacity at acquisition observed in both Gsk and SSsk have been found to persist on retention learning testing in individuals with BG lesions. Studies that have assessed Gsk retention learning after the initial acquisition phase on a SRT task or CTT report that those individuals with PD or BG lesions demonstrate an ability to maintain or improve their performance on the task at retention, indicating learning of Gsk. However, the percent difference between controls and individuals with BG lesions observed at the end of acquisition persists into the retention test and thus, overall is still less than healthy controls (Boyd & Winstein, 2006; Siengsukon & Boyd, 2009). Similar results have been shown with SSsk on retention learning. Individuals with BG lesion are able to demonstrate an ability to maintain or improve their performance on SSsk, but the percent difference between the random and repeated blocks observed at the end of acquisition persisted on the retention test, indicating learning but not to the same capacity as controls (Boyd et al., 2009).

Only one study has assessed SSsk using a transfer test on individuals with PD (Seidler, Tuite, & Ashe, 2007). A SRT task was used and involved a switch from right hand to left hand after training to determine the maintained sequence-specific learning by assessing the number of errors performed during the transfer task. Individuals with PD were able to demonstrate transfer of the SSsk using the other hand as indicated by the observed difference in errors between the repeated and random sequences.

Taken together, these results indicate that individuals with PD or BG lesions are able to acquire a SSsk, retain a SSsk, and transfer the SSsk under different conditions as evidenced by decreased reaction times and/or decreased error; however, the improvement

in reaction times and error are consistently less than healthy, similar age-matched controls. This difficulty does not appear to be solely related to a Gsk learning deficit. These results can be understood with an understanding of the neuroanatomical correlates of IMSL and PD.

Neurobiological Model of Implicit

Motor Sequence Learning

Brain imaging techniques, such as functional MRI or PET scans have been used to ascertain neuroanatomically related structures associated with IMSL and have elucidated results involving the cognitive, frontostriatal circuit. It has been suggested that the BG, specifically the striatum, (one of the four nuclei of the BG, composed of the caudate and putamen) is an important player in IMSL (Doyon, 2008; Knowlton et al., 1996). Doyon has proposed a neuroanatomical model of the progression of IMSL based on these imaging findings (Figure 1.4; Doyon, 2008). Learning of implicit information occurs slowly over time and requires many practice repetitions and thus, the process of acquiring and learning implicit information has been described as occurring in phases: encoding, consolidation, and automatization.

As an individual begins to practice a novel skill, the information becomes encoded as the sequence of information of what to perform is being learned. Typically this occurs quickly as one becomes familiar with the skill. Assessment of performance during this early acquisition phase will usually demonstrate a rapid improvement in performance. Over time, as the individual continues to practice and to further refine performance of the skill, a slow encoding phase occurs when subtle performance changes

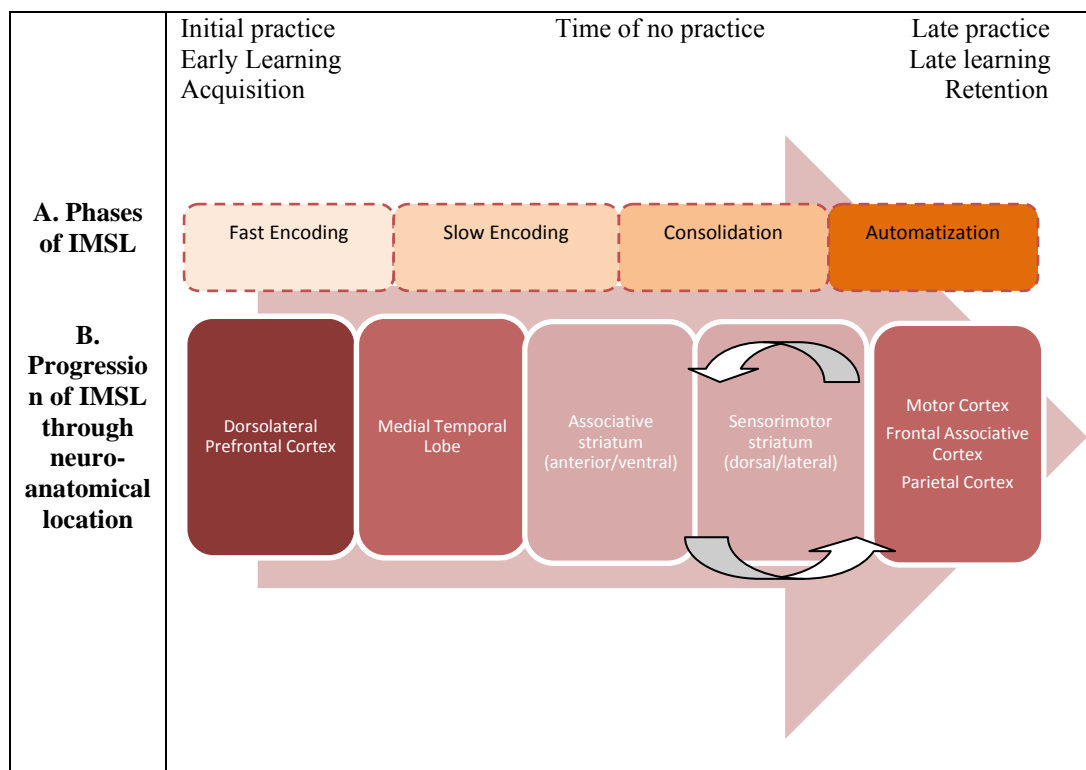


Figure 1.4. Proposed neurobiological pathway for implicit motor sequence learning (IMSL). Depicts the progression of IMSL through the neuroanatomical locations with the phases of IMSL. (Adapted from Doyon, 2008)

are observed. After the individual has practiced sufficiently, a retention test is provided to see if the performance on the skill has been integrated, meaning information is stable in memory and thus indicating that learning has taken place. With further practice over time, the skill becomes automatized, and only subtle changes in performance will be observed. Doyon proposed a neuroanatomical model describing the progression of IMSL through the central nervous system, which can be related to the above phases. Initially, as a skill is introduced and practiced, the dorsolateral prefrontal cortex (DLPFC) is active, an area responsible for planning, organizing, regulating, and complex problem solving (McGeorge & Faull, 1989). During this early learning, cognitive processes are required to understand the demand of the novel skill being performed.

After the initial cognitive processes occur, Doyon proposed that the information is then transferred to the medial temporal lobe (MTL). The MTL has typically been associated with conscious explicit learning rather than implicit learning, and it is thought that these two processes are dissociated (Knowlton et al., 1996). However, Schendan, Searl, Melrose, and Stern (2003) reported that some portions of the implicit learning system may be associated with the MTL. Schendan et al. (2003) proposed that the MTL may be involved in associations of complex multievent processes such as occur during motor sequence learning, where perceptual, cognitive, and motor behaviors are all required to be integrated.

Doyon (2008) then proposed that as information is being encoded, the striatum becomes active. Specifically, information is sent from the DLPFC and MTL to the associative striatum and then to the sensorimotor striatum (Bailey & Mair, 2006; Hikosaka, Nakamura, Sakai, & Nakahara, 2002; Jankowski, Scheef, Huppe, & Boecker, 2009; Yin, 2010). The associative striatum has been shown to be responsible for the learning and planning of sequences, whereas the sensorimotor striatum has been shown to be responsible for higher order organizational processes such as "chunking" prior to the execution phase of sequence-specific learning (Bailey & Mair, 2006). Chunking has been defined as the organization of individual motor elements within a larger sequence allowing for subsequences to be grouped together known as a chunk (Boyd et al., 2009; Miller, 1956). Consolidated information could be thought of as a series of chunks or a group (chunk) of sequences.

The final process requires the motor cortex, parietal cortex, and frontal associative regions all to be active and recruited while the sequence is being performed. The motor

cortex, parietal cortex, and frontal associative regions become more highly and precisely activated as more practice occurs. After practice, the motor sequence skills are thought to become more automatic, and the performance assessments demonstrate that minimal cognitive resources are required and performance is resistant to both interference and the effects of time. Performance assessment of the automaticity of a task can be obtained during a transfer test. If the task has been successfully consolidated, then automaticity is stated to have occurred when further improved performance is observed even under the altered (transferred) conditions.

Because of the role of the striatum in motor sequence learning, individuals with dopamine loss, such as PD have aided our understanding of motor sequence learning. In PD, the initial loss of dopaminergic neurons occurs in the substantia nigra, resulting in the observed initial movement disorder. With time, further dopamine loss is observed in the striatum because the dopaminergic neurons project from the substantia nigra to the sensorimotor (dorsal/lateral) striatum and then to the associative (anterior/ventral) striatum (Rakshi et al., 1999). The progression of PD through the striatum (sensorimotor to associative) is the opposite of progression of IMSL through the striatum (associative to sensorimotor; Figure 1.5). Thus, loss of dopamine within the striatum seen in individuals with PD may account for the observed deficit in IMSL. An individual with greater PD severity (more loss of dopamine) where both the associative and sensorimotor striatum may be involved have been shown to be impaired in IMSL, and this extra loss of dopamine supports the role of dopamine impairment impacting IMSL (Carbon & Eidelberg, 2006; Feigin et al., 2003; Levesque et al., 2007; Tremblay et al., 2009). Furthermore, in individuals with early PD (where potentially only the sensorimotor

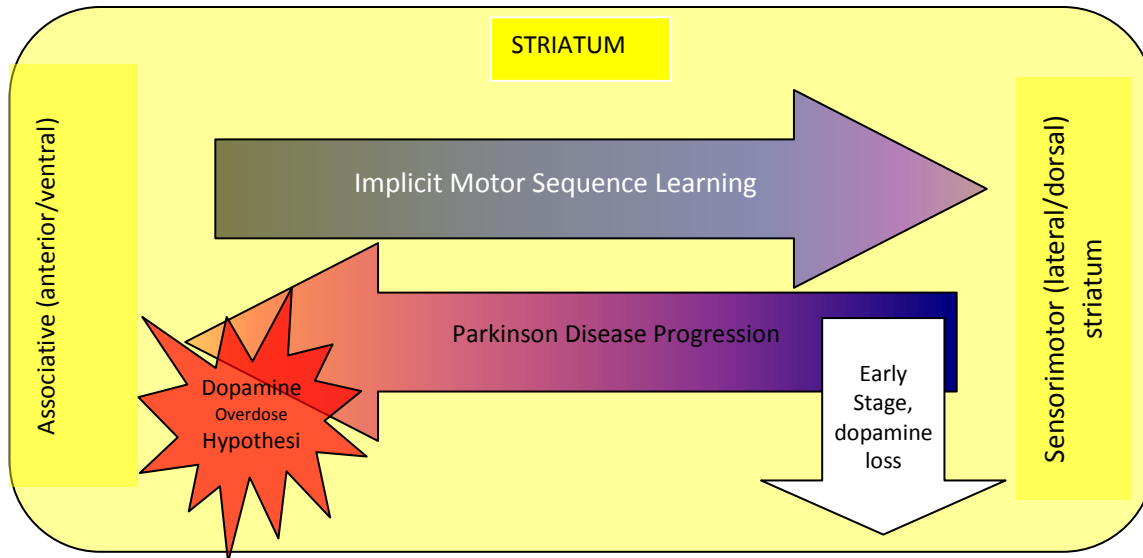


Figure 1.5. Depiction of the progression of implicit motor sequence learning and Parkinson disease (PD) through the striatum. Implicit motor sequence learning progresses from the associative striatum to the sensorimotor striatum, whereas loss of dopamine in individuals with PD begins with the sensorimotor striatum. Individuals with early PD provided dopamine may aid the dopamine loss in the sensorimotor striatum, but may provide too much dopamine in the associative striatum providing the “overdose” hypothesis and negatively impact IMSL.

striatum has been impacted), prescription of exogenous dopamine may improve function in the sensorimotor striatum but may "overdose" the associative striatum, potentially creating difficulties for effective implicit motor sequence learning.

Implicit Motor Sequence Learning and Basal Ganglia Lesions

As stated above, individuals with PD or BG lesions have been shown to be impaired in IMSL including both Gsk and SSsk learning. However, based on the neurobiological model described above, an understanding of the influence of the role of dopamine and severity of disease may aid in understanding the relative contributions of

Gsk or SSsk learning impairments. If disease progression affects both the associative and sensorimotor striatum, then it is anticipated that IMSL (both Gsk and SSsk), requiring both associative and sensorimotor striatum, will be impacted because of the overall loss of dopamine in individuals with more advanced disease.

Literature supports this neurobiological model because Gsk learning has not been found to be related to disease severity; rather SSsk learning is impaired (Stephan et al., 2011). Specifically, individuals with a higher axial rating score (indicating more advanced disease) on the Unified Parkinsons Disease Rating Scale (UPDRS; Fahn, Elton & UPDRS Program members, 1987) subsection III (Appendix A) and with a more severe Hoehn and Yahr score (stages 2–3 compared to stage 1; Appendix B) are more impaired in SSsk learning (Deroost, Kerckhofs, Coene, Wijnants, & Soetens, 2006; Doyon et al., 1997; Muslimovic et al., 2007; Stephan et al., 2011). Furthermore, PD duration and severity of tremor, bradykinesia, and rigidity have not been found to be associated with impairments in SSsk learning (Muslimovic et al., 2007; Stephan et al., 2011). In summary, individuals who present with a higher axial rating scale and Hoehn and Yahr score are more impaired in IMSL, specifically SSsk learning. These results suggest that the influence of dopamine (loss) is a critical component to SSsk learning because with progression of disease an increase in dopamine loss is thought to occur. Thus, for individuals with PD, both the influence of dopamine loss and dopamine addition via medication on IMSL needs to be considered.

Dopamine can influence individuals with early PD in two ways: via reduction and addition. A reduction of dopamine, as may occur in early PD may result in an IMSL deficit, as individuals with early sensorimotor dopamine loss may have difficulty

consolidating information. As well, an addition of dopamine (with medication, such as dopamine replacement) in someone with early PD may also result in an IMSL deficit. It has been hypothesized that the dopamine replacement may be sufficient to replace the dopamine loss in the sensorimotor striatum, but may “overdose” the associative striatum, which may not be depleted in early PD. Thus, the influence of dopamine within the striatum results in a potential dopamine mismatch, impacting IMSL. The influence of dopamine as a result of both severity of the disease (loss of dopamine) and the use of medications (addition of dopamine) needs to be considered when assessing performance outcome measures of IMSL.

The assessment of early nonmedicated patients with PD and the role of medication on IMSL have only recently begun to be studied. Most studies of IMSL assessing Gsk and SSsk learning have not controlled for medication and thus, most subjects have been assessed on their usual dosage of dopamine medication. This has made it difficult to understand the true impact of medication on the role of Gsk and SSsk.

Dopaminergic therapy with carbidopa/levodopa and levodopa agonists results in improved symptomatic management of movement deficits in PD including, bradykinesia, rigidity, and tremor (Fedorova & Chigir, 2006; Hauser, 2009) and is typically provided at the onset of these symptoms to ameliorate them. However, as stated above, the associative striatum is not typically affected during early PD, and use of dopaminergic therapy may result in excess in the associative striatum, leading to an overdose effect (Kwak et al., 2010).

Conflicting results on the impact of medication on Gsk and SSsk learning have been reported. A study by Stephan et al. (2011) reported a moderate, significant

correlation between SSsk learning and dopamine ($\rho = -0.45$, $p = 0.03$), such that individuals with higher amounts of dopamine were less accurate. They reported no significant relationship between Gsk learning and medication. A study by Muslimovic et al. (2007) reported a weak, nonsignificant relationship between SSsk learning and dopamine dosage amount ($\rho = -0.13$, $p = 0.22$). However, Muslimovic et al. (2007) had a large group of individuals who had never been medicated and who were found to have no impairment in Gsk or SSsk learning compared to healthy individuals (Muslimovic et al., 2007).

One study assessed individuals with early PD ($N = 14$; Hoehn and Yahr range, 1–2.5) on and off medication using an explicit SRT task (Kwak et al., 2010). Individuals with PD acted as their own controls with half assessed on medication first and then within two days, they were assessed off medication, whereas the other half underwent testing off, then on medication. SSsk learning was assessed across an early phase (block 3–4) and late phase (block 9–10) over 1 day of acquisition. There was no significant difference between individuals off medication and healthy controls throughout any of the phases of acquisition. When the individuals were on their medication, they exhibited a significant impairment in SSsk learning during the early phase of acquisition compared with when the same individuals were off their medication and compared to healthy controls. There was no significant difference at the late phase of learning between healthy controls and the individuals when they were on or off their medication; however, upon visual inspection, when the individuals were on their medication they still presented with a delay compared to the healthy controls and when the same individuals were off their medication. This study suggested that medication may be impairing SSsk learning in mild

to moderate PD and supports the overdose hypothesis during early acquisition of SSsk learning.

Thus far, the impact of the overdose hypothesis has only been studied during the acquisition phase of learning using an explicit SRT task. A confounding variable impacting the results is that explicit instructions have been found to affect IMSL in individuals with BG lesions regardless of the type of task, SRT or CTT (Boyd & Winstein, 2006). The effect of medication on IMSL on retention and transfer of learning has not been studied; it is possible that the influence of medication status during acquisition practice may impact consolidation of information.

Overall, SSsk learning appears to be impaired in individuals with BG lesions. Because of the role of the BG in IMSL and specifically SSK, the severity of the disease is an important factor to consider in the capacity of individuals to acquire SSsk learning. However, severity of the disease alone may not account for the observed deficits. Addition of medication may also be a factor in limiting IMSL in individuals in the early stage of PD, possibly due to an overdose effect of the associative striatum. Although IMSL appears to be impaired in individuals with BG lesions, an additional factor may be influencing this impairment, including the amount of practice.

Influence of Quantity of Practice on IMSL

It has been suggested that the deficit in IMSL for individuals with PD or BG lesions may be due to limited amount of practice (Korman, Raz, Flash, & Karni, 2003). The quantity of practice allowed during acquisition in studies discussed thus far using SRT task or CTT have varied. Table 1.1 provides details of the quantity of practice

provided during multiple studies of IMSL using a SRT task or a CTT. Most often, practice during acquisition using the SRT task has taken place over 1 day only (Ferraro et al., 1993; Muslimovic et al., 2007; Seidler et al., 2007; Stephan et al., 2011). However, even if training is allowed to take place over more days (max of 3 days) regardless of the type of task (CTT or SRT), individuals with BG lesions still show a persistent deficit in SSsk performance (Boyd & Winstein, 2006). Table 1.1 provides details of the amount of practice provided during multiple studies of IMSL using a SRT task or a CTT. In summary, individuals with BG lesions are impaired in IMSL and more specifically with SSsk learning. The amount of practice provided has not been shown to overcome this deficit. It is possible that even more practice may be required for individuals with BG lesions to overcome impaired IMSL. Extensive amounts of practice have not been studied to determine if individuals with BG lesions can achieve a similar capacity of SSsk learning as healthy controls.

The focus of this paper thus far has been on the description of current studies on IMSL in individuals with BG lesions; however, these studies have only focused on relatively simple tasks, such as the use of only the upper extremity with the SRT task and the CTT. Many sequential tasks in real-world settings such as walking can often require fast reactions to environmental stimuli. Additionally, during walking and standing the postural control system demands more degrees of freedom to be controlled to effectively respond to various controlled or unknown stimuli. Thus, it is important to understand the role of IMSL during higher demand tasks where the postural control system will be challenged.

Table 1.1. Summary of the amount of practice repetitions provided by authors during an implicit motor sequence task.

1. Serial Reaction Time task							
<i>Author</i>	<i>A. Number presses^a</i>	<i>B. Items in sequence^b</i>	<i>C. Number of blocks^c</i>	<i>D. Order repeating^d</i>	<i>E. Order random</i>	<i>F. Days of practice</i>	<i>G. Total practice trials repeating sequence (BxCxF)^e</i>
Ferraro et al., 1993	100	10	5	1-4	5	1	40
Muslimovic et al., 2007	100	Not stated	7	2-6	1,7	1	
Seidler et al., 2007	94	12	12	2-5, 8, 11	1,6-7,9,10,12	1	144
Stephan et al., 2011	100	10	8	4,5,6,7	1,2,3,8	1	80
Doyon et al., 1997	100	10	4	1-4	none	6	240
Boyd et al., 2009	120	12	6	2-6	1	2	144
Boyd & Winstein, 2006	100	10	6	2-5, 7	1,6	3	180
Kwak et al., 2010	96	6	11	3,4,6,7,9,10	1,2,5,8,11	1	66
2. Continuous Tracking Task							
<i>Author</i>	<i>A. Segments^f</i>	<i>B. Trials^g</i>	<i>C. Blocks^h</i>	<i>D. Order repeating</i>	<i>E. Order random</i>	<i>F. Days of practice</i>	<i>Number of repeating sequences (BxCxF)ⁱ</i>
Shea et al., 2001	3	7	2	2	1,3	4	56
Boyd & Winstein, 2006	3	10	5	2	1,3	3	150
Siengsukon & Boyd, 2009	2	10	10	1	2	1	100
Vidoni & Boyd, 2009	2	10	5	1	2	2	100
Hayes (study)	2	10	6	1	2	2	120

^anumber of presses is the number of times the participants pressed a key; ^b items in sequence refers to the number of items in a trill of items displayed, whether it be random or repeated; ^c a block is the total presses; ^dthe order of repeating refers to when the repeating compared with random sequences are presented. ^ethe total practice trials column is the sum of the repeating sequences presented, and indicates the total number of presses of the repeating sequence that were performed. ^fa segment refers to the trill of items presented. ^ga trial is comprised of the number of segments (e.g., 7 means the participant performed 3 segments 7 times). ^ha block is the total of the trials performed (e.g., 2 blocks of 7 trials of 3 segments each). ⁱNumber of repeating sequences refers to the number of times the repeating sequence was presented during the study.

Postural Instability of Individuals with PD

Postural instability is one of the four cardinal movement features of PD. It refers to an impairment of postural reflexes resulting in reduced limits of stability. The pathophysiology of postural instability remains unknown; however, the observed deficit is associated with difficulty in executing and timing responses to external challenges or when performing voluntary movements (Bloem, 1992; Marinelli et al., 2007). This impaired response to external challenges often results in individuals reporting difficulties with balance and falling (Hirsch, Toole, Maitland, & Rider, 2003). Although medications have been found to reduce movement deficits associated with PD, such as tremor at rest, rigidity, akinesia, and bradykinesia, postural instability is typically not mitigated by medication (Grimbergen, Langston, Roos, & Bloem, 2009; Jankovic, 2008). Rehabilitation specialists spend a great deal of time assisting individuals with PD on the impairment of postural instability; however, current rehabilitation techniques, although successful initially, are typically not successful in the longer term management of this deficit (Smania et al., 2010).

Many of the tasks that we perform on a daily basis require a combination of sequences during a postural task, such as sit to stand, or standing to reach overhead in a cabinet. Individuals with BG lesions are impaired in both sequence learning and postural instability. The addition of dopamine does not appear to improve postural instability and may even inhibit sequence learning. Understanding the influence of medication on sequence learning and postural instability may allow for an improvement in rehabilitation strategies and impact how rehabilitation specialists approach retraining for postural instability.

Numerous studies of healthy individuals have used a standing sequential motor task paradigm, which requires the learner to coordinate their movements in accordance with an external stimulus via either an anticipatory or reactive postural response (Shea et al., 2001; Van Ooteghem et al., 2008; Van Ooteghem, Frank, Allard, & Horak, 2010; Van Ooteghem, Frank, & Horak, 2009). These studies have assessed IMSL by providing random and repeated sequences to the individuals across the training under an anticipatory tracking paradigm and a reactive paradigm. Under the anticipatory tracking paradigm, the participants are standing on a stabilometer, a moving platform, and the participant is required to adjust their center of mass to maintain stability while matching the pattern observed on a screen similar to a CTT (Shea et al., 2001). The studies, utilizing a reactive task, require the participant to adapt their center of mass to the perturbations being produced that are either repeating perturbation sequences or random perturbation sequences.

These studies on healthy individuals have shown that during the tracking task an improvement in Gsk and SSsk learning on acquisition and retention were observed as evidenced by improved accuracy (Shea et al., 2001). Interestingly, the reactive paradigm demonstrated GsK learning during acquisition and retention, but not SSsk learning (Van Ooteghem et al., 2008). The authors assessing the reactive paradigm suggested that the lack of observed SSsk learning may be because the postural control system adapts to a generalized postural control strategy rather than a specific postural control strategy.

Other postural control studies on individuals with BG lesions have assessed Gsk learning during a posturally demanding condition. Individuals with PD have been shown to improve their limits of stability and are capable of demonstrating Gsk learning (Ioffe et

al., 2004; Jessop, Horowicz, & Dibble, 2006). Additionally, individuals with PD showed less improvement during the acquisition phase compared to controls; however, they did retain the information on a retention test, but not to the same capacity as controls (Ioffe et al., 2004). No studies have assessed IMSL during a sequential postural task on individuals with BG lesions.

Spatial and Temporal Integration of a Motor Sequence

Successful performance of motor sequence tasks requires integration of both spatial and temporal parameters. Limited assessment of spatial and temporal parameters utilizing a CTT and the SRT task has occurred, and results have been mixed related to the deficits in spatial parameters during sequential tasks such as a SRTT in individuals with PD (Helmuth, Mayr, & Daum, 2000; Postle, Jonides, Smith, Corkin, & Growdon, 1997; Schwarb & Schumacher, 2009; Shin & Ivry, 2003). However, a spatial response selection deficit was not observed in individuals with BG stroke during a CTT of the upper extremity (Boyd & Winstein, 2004). It has been proposed that there is neuroanatomical overlap within the Basal Ganglia of spatial selection and sequence learning and thus, successful sequence learning requires successful spatial response selection (Koch & Hoffmann, 2000; Schwarb & Schumacher, 2009; Werheid, Ziessler, Nattkemper, & Yves von Cramon, 2003). Perhaps, the management of spatial response selection is an impairment dependent on the influence of dopamine within the BG, rather than a general BG deficit. The influence of dopamine has been suggested to impact spatial parameters during walking by mitigating a decreased amplitude (Morris, Iansek, McGinley, Matyas, & Huxam, 2005). No studies have assessed the impact of the

medication dopamine on spatial and temporal parameters during a standing implicit motor sequence task.

Limitations in Current Research

Based on the literature covered in the previous section, there are still many areas of study that need to be explored within both specific and broad contexts related to IMSL in individuals with PD. Previous research studies have been compromised by methodological shortcomings, including the following:

1. Kwak et al. (2010) assessed individuals with PD on and off medication; however, they used an explicit task and thus informed the individuals with PD about the presence of a repeated sequence. The need to explore IMSL on and off medication is warranted.
2. Most studies to date have only assessed the acquisition phase of SSsk learning in individuals with PD; therefore, the capacity of retention learning is warranted.
3. The lack of control for disease severity may have impacted results. It is not possible to know how much of the striatum may be impacted in individuals with PD; however, controlling for individuals described as less severe (Hoehn and Yahr, stage 1–2.5) and without overt postural instability is warranted.
4. Studies utilizing a posturally demanding task on individuals with PD have only assessed Gsk learning. Thus, understanding SSsk learning during a posturally demanding task in individuals with PD is warranted.
5. Furthermore, because medications have not been found to mitigate deficits of postural instability, it is important to determine the influence of the medication

dopamine during learning of a posturally demanding task.

6. To our knowledge no studies have assessed sequence learning related to spatial and temporal parameters utilizing a CTT while standing in individuals with PD.

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CHAPTER 2

OVERVIEW OF STUDY

The overall objective of this study was to determine the impact of dopamine addition on sequence-specific acquisition performance and retention learning during a posturally demanding (standing) implicit continuous tracking task in individuals with early Parkinson disease (PD).

The primary question of interest related to the primary aim is the potential impact of dopamine medication on the performance and learning of implicit motor sequences in individuals with early PD. Only one study (Kwak et al., 2010) has assessed acquisition performance using an explicit motor sequence task of individuals with PD on and off medication. Kwak et al. (2010) found that individuals with PD on dopaminergic medication demonstrated impaired performance during the early phase of acquisition compared with individuals with PD off dopaminergic medication, suggesting support for a negative influence of dopamine during performance of a SSsk. No studies have assessed the learning capacity of individuals with PD on and off dopaminergic medication based on retention testing.

The secondary aim of this study was to explore the components comprising a motor sequence, specifically spatial and temporal components in individuals with PD on and off their dopaminergic medication. This secondary aim sought to determine if

medication differentially influenced amplitude (spatial) and/or timing components during the acquisition phase of this CTT being performed in a standing position. Assessment of the spatial and temporal components within sequence learning has been studied in individuals with PD during a serial reaction time task (Shin, Aparicio, & Ivry, 2005; Shin & Ivry, 2003), but the impact of medication on these variables has not been studied.

Definition of Terms

Acquisition Performance

Acquisition performance refers to the observed behavioral act of executing the continuous tracking task in the laboratory during the acquisition phase (See Table 2.1 for summary of terms). Assessment of acquisition performance occurs by assessing performance on the repeated segments (see definition) during the acquisition phase between groups, termed the "acquisition performance." Assessment of acquisition performance occurs by assessing "sequence-specific acquisition performance" (see definition).

Acquisition Phase

Acquisition phase refers to the time during which the continuous tracking task is being practiced. The acquisition phase in this study will take place over 2 days.

Block

A block refers to 10 trials (see definition). Individuals will be asked to perform a 45-second trial, followed by a 25-second standing or seated rest. After 10 trials have been

Table 2.1. Overview of the definition of terms as related to the aims, hypotheses, and dependent variables.

Groups	ACQUISITION PERFORMANCE			RETENTION LEARNING
	<i>Acquisition phase</i>			<i>Retention test</i>
	<i>Day 1</i>	<i>Day 2</i>		<i>Day 4</i>
	<i>12 blocks (10, 45 second trials)</i>			<i>1 block</i>
PDON PDOFF	1. Dependent variable	Sequence-specific acquisition performance (Primary aim 1 Hypothesis 1)		Sequence-specific learning score (implicit learning) (Primary aim 1 Hypothesis 2)
	1. Measurement	Difference between repeated RMSE and random RMSE		
HY HE PDON PDOFF	1. Dependent variable	Sequence-specific acquisition performance (Primary aim 1 Hypothesis 1)		Sequence-specific learning score (implicit learning) (Primary aim 1 Hypothesis 2)
	1. Measurement	Difference between repeated RMSE and random RMSE		
HY HE PDON PDOFF	3. Dependent variable	Spatial lag (Secondary aim Hypothesis 1)	Temporal lag (Secondary aim Hypothesis 2)	
	3. Measurement	Adjusted repeated segment RMSE		

performed, a block has been completed. An individual is allowed to rest 5 minutes between blocks. Six blocks/day will occur. See Appendix D for a schematic of the training paradigm.

Implicit Learning

Implicit learning refers to an observed, improved performance without awareness that this improvement has occurred. In this study, individuals are told that a repeating

sequence is embedded in the continuous tracking task. They will practice the same embedded repeating sequence throughout the study. Implicit learning in this study is inferred based on the difference in performance observed between the repeated and random segments via a "sequence-specific learning score" (see definition).

Implicit Motor Sequence Learning

Implicit motor sequence learning (IMSL) refers to the process by which simple or complex serial movements come to be performed effortlessly as a single unit of movement without the intention to learn the repeated performance of the serial pattern (Doyon, 2008; Gheysen et al., 2010). This term is used in a global sense in this study to describe the overall objective of the study to determine the ability of individuals with early PD to demonstrate learning of an implicit motor sequence during a posturally demanding task.

Learning

The term learning refers to a "change in the capability of a person to perform a task. It is inferred from a relatively permanent improvement observed in the performance of the task as a result of practice" (Magill, 2007, p. 438). Learning in this study is inferred based on the change in performance on the repeated segments during a continuous postural tracking task via a "learning score" (see definition).

Learning Score

The learning score (Siengsukon & Boyd, 2008) is a dependent variable and is the difference between the repeated segment RMSE for block 12 (final block of acquisition) and the repeated segment RMSE on the single block at the retention test. The learning score is a reflection of the learning that has been achieved. A retention test assesses the degree of persistence of the performance improvement observed during acquisition after a period with no practice. If learning has occurred, then the learning score will reflect a positive difference (learning savings) as a continued improvement in performance is observed. If no learning has occurred, then the learning score will reflect zero; thus, no change in performance at the retention test is observed. If learning has not occurred, then the learning score will reflect a negative value (learning cost) or worse performance on the retention test compared to the changes observed during the acquisition phase.

Performance

The term performance in this study refers to the behavioral act of executing the continuous postural tracking task in the laboratory. Performance capacity of this task was assessed across the acquisition phase (12 blocks over 2 days) and on the retention testing day (1 block performed 1 day). The root mean square error (RMSE) is a measurement of performance capacity.

Retention Learning

Retention learning refers to the change in performance observed on retention testing (see definition; See Table 2.1). Assessment of retention learning will occur by

assessing the learning score (see definition). Assessment of retention learning also occurs by assessing the "sequence-specific learning score" (see definition).

Retention Performance

Retention performance refers to the behavioral act of executing the continuous postural tracking task in the laboratory during the retention test.

Retention Test

A retention test will occur on the fourth day. Individuals will have a period of time with no practice on Day 3. The individual was asked to perform only 1 block on the day of the retention test.

Root Mean Square Error (RMSE)

RMSE is the primary measure of tracking accuracy during the continuous tracking task. This value reflects tracking errors in the kinematic pattern and is the average difference between the target pattern and the participants' movements, reflecting the extent to which the participant can match their movement to the target line. An overall RMSE represents the distance in centimeters² that an individual did not match the target based on the shifting of the center of pressure. A median value of RMSE (distance in centimeters²) will be calculated for each repeated and each random segment per trial (each a 45 second time frame across the screen). The median value will be utilized because of the highly variable capacity in performance as the median is less influenced by extremes in scores but rather provides the middle of the distribution. The median

value will be calculated for each trial for each random and repeated segment, and an average of these median values will be computed for each block to provide the mean RMSE for each block. In summary, a mean RMSE for the repeated segments (which will be termed *repeated segment RMSE*) will be provided as well as a mean RMSE for the random segments (*random segment RMSE*), which are based off the median values recorded per trial per segment.

Segment

The term segment refers to either a random or repeated continuous sinusoidal wave pattern presented on the screen during the tracking task. During a trial (see definition), two segments will be presented randomly, one random, and one repeated. The repeated sinusoidal wave will always be the same throughout the study. The random segments will never be the same throughout the study.

Sequence-specific Acquisition

Performance (SSAP)

Sequence-specific acquisition performance is a dependent variable and is the difference between the performance of random and repeated segment RMSE during the acquisition phase between groups at the final acquisition block, block 12.

Sequence-specific Learning

Score (SSLS)

The SSLS is a dependent variable and refers to the difference between the random and repeated segment RMSE within a block performed at retention. This difference between the random and repeated segment RMSE represents the capacity of the individual to learn the embedded repeating sequence implicitly.

Spatial Tracking Accuracy

Spatial tracking accuracy is measured by assessing the remaining lag error that persists after the correction for temporal tracking accuracy based on the RMSE in centimeters² that remains. Figure 2.1 depicts a schematic of the shifting of a participants tracking along the x-axis.

Task

The task to be performed in this study is a standing continuous tracking task that is performed in standing, on a force plate while the individual visualizes a target track on a screen.

Temporal Tracking Accuracy

Temporal tracking accuracy refers to another dependent variable and is a subcomponent of RMSE. It will be assessed using a time series analysis. Temporal tracking accuracy of the movement sequence will be measured by serially correlating the

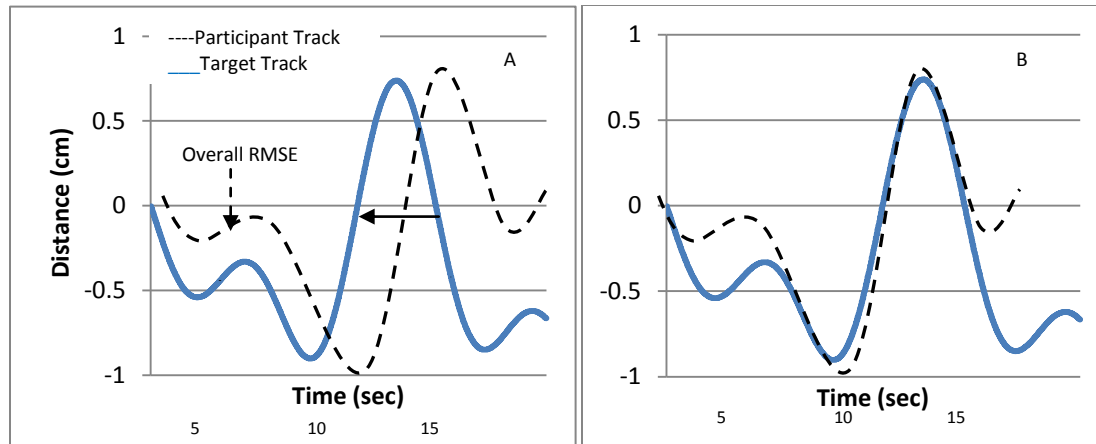


Figure 2.1. Sample of tracking pattern versus target pattern. Participants tracking pattern (dashed lines) with the target pattern (solid blue). The x-axis is time in seconds and depicts only a portion (20 seconds) of a participants' performance. The y-axis is RMSE in distance of cm. (A) Uncorrected data and an overall RMSE is calculated (dotted arrow). (B) Corrected data after serial correlation allows for separation of spatial and temporal tracking accuracy. The participants' tracking pattern is shifted along the target pattern (black arrow) until a maximum correlation coefficient is achieved. The final position allows calculation of the temporal accuracy based on the shift along the x-axis in seconds and is a single value. The remaining difference in distance is the spatial accuracy and a single value.

data points from the participant's tracking pattern with the target pattern until a maximum correlation coefficient is achieved (Figure 2.1). The maximum correlation coefficient will be determined off the maximum number of data points (Boyd & Winstein, 2004). When the correlation coefficient reaches the maximum within a 1-second time frame, the two waveforms will be considered a best fit. The time lag of tracking is calculated by determining the distance that the data points were moved along the target data to achieve the maximum correlation coefficient. The distance the time lag is moved is converted into milliseconds and represents the shift of the data across time. In summary, temporal tracking accuracy is calculated in milliseconds to determine the average time difference between the target marker and the participant's tracking time.

Trial

A trial refers to a single 45-second pass of the target to be tracked on the continuous task that occurs across the computer screen. The trial consists of a 5-second flat target at the start to allow the person to orient to the screen, followed by either the repeated segment or a random segment (each 40 seconds in length).

Aims

Primary Aim 1

The primary aim 1 is to determine sequence-specific acquisition performance and retention learning of overall RMSE of individuals with early PD (on and off dopaminergic medication) during a continuous sequential task under posturally demanding conditions.

Hypothesis 1

Individuals with early PD on dopamine replacement medication will demonstrate impaired sequence-specific acquisition performance during the initial 2 days of practice of a continuous sequential postural task compared to individuals with early PD off dopamine replacement medication.

Hypothesis 2

Individuals with early PD on dopamine replacement medication will demonstrate impaired sequence-specific retention learning during the retention testing of a continuous

sequential postural task compared to individuals with early PD off dopamine replacement medication.

Primary Aim 2

The primary aim 2 is to determine sequence-specific acquisition performance and retention learning for individuals with early PD (1 group on dopaminergic medication and 1 group off dopaminergic medication), healthy elders, and healthy young during a continuous sequential task under posturally demanding conditions.

Hypothesis 3

A difference between 4 groups, individuals with early PD on and off medication, healthy elders, and healthy young will be observed in sequence-specific acquisition performance during the acquisition phase of a continuous sequential postural task.

Hypothesis 4

A difference between 4 groups, individuals with early PD on and off medication, healthy elders, and healthy young will be observed in the sequence-specific learning score during the retention test of a continuous sequential postural task.

Secondary Aim

The secondary aim is to determine spatial tracking accuracy and temporal tracking accuracy of repeated segment RMSE during the acquisition phase of individuals with early PD (on and off dopaminergic medication) during a continuous sequential task under posturally demanding conditions.

Hypothesis 5

There will be a difference in performance of temporal tracking accuracy between individuals with early PD (on and off dopaminergic medication) during the acquisition phase.

Hypothesis 6

There will be a difference in spatial tracking accuracy between individuals with early PD (on and off dopaminergic medication) during the acquisition phase.

A retention test will occur on Day 4, consisting of 1 block only (See Appendix D for a visual depiction of the practice paradigm).

Research Design

Design and Analysis

This study is a randomized controlled trial with a primary focus of assessing sequence-specific acquisition performance and retention learning capacity for IMSL in individuals with early PD on and off dopamine replacement medication. Two additional groups are participating in the trial as comparison groups, including healthy young and healthy elders. Alpha was set at the 0.05 level.

The assumptions of parametric statistical tests will be tested for each analysis and will include the following: (a) data will be normally distributed, and for data that does not meet the normal distribution, alternative solutions will be explored (i.e., transformation of the data); (b) mutually exclusive groups will be utilized; different individuals in each group (PD on and off medication) are being utilized; (c) test for homogeneity of variance

for the dependent variables will be met to allow analysis of between subjects' effect; (d) compound symmetry and variance for the dependent variables will be met for within subject effect, and if compound symmetry is not met, then the univariate analysis Huynh-Feldt epsilon will be reported for the within subject effect.

Statistical Analysis

The first primary aim was to determine sequence-specific acquisition performance and retention learning of repeated segment RMSE of individuals with early PD (on and off dopaminergic medication) during a continuous sequential task under posturally demanding conditions.

It was hypothesized that individuals with early PD on dopamine replacement medication will demonstrate impaired sequence-specific acquisition performance during the initial 2 days of practice of a continuous sequential postural task compared to individuals with early PD off dopamine replacement medication.

To analyze the primary aim 1, hypothesis 1, the following analysis is performed: A repeated measure ANOVA with the dependent variable, sequence-specific acquisition performance (difference between the random and repeated segments across the acquisition blocks) of the overall RMSE is performed on the blocks during the acquisition phase. The between group variable has two levels of group (PD on and off medication) and the within subject variable has 12 levels of blocks (6 blocks/day). The median values for each repeated and random segments is calculated, and an average of the median RMSE is calculated for the random and repeated sequences for each block (See Appendix D for a visual depiction of median calculations). The statistical

significance was reported for the interaction effect of group x block and for the main effect of group. The use of within subject repeated contrasts on block allows for determination if there is a difference across the blocks. See Figure 2.2 for a visual depiction of analysis.

We also hypothesized that individuals with early PD on dopamine replacement medication will demonstrate impaired sequence-specific retention learning (as measured by a smaller learning score) during the retention testing of a continuous sequential postural task compared to individuals with early PD off dopamine replacement medication.

To address primary aim 1, hypothesis 2, the following analysis will be performed: An independent samples t test on two groups (individuals with early PD who trained on dopaminergic medication versus individuals who trained off dopaminergic medication) with one-tail analysis will be performed on the dependent variable, sequence-specific learning score. The sequence-specific learning score is the difference between the random and repeated segment RMSE noted for block 12 (final block of acquisition) and the random and repeated segment RMSE on the single block at retention test. A difference is expected to be observed between the groups because the delay observed in acquisition performance of sequence-specific acquisition will persist on retention testing. See Figure 2.2 for a graphical representation of analyses for primary aim 1, hypotheses 1 and 2.

The second primary aim was to determine sequence-specific acquisition performance and retention learning for individuals with early PD (1 group on dopaminergic medication and 1 group off dopaminergic medication), healthy elders, and

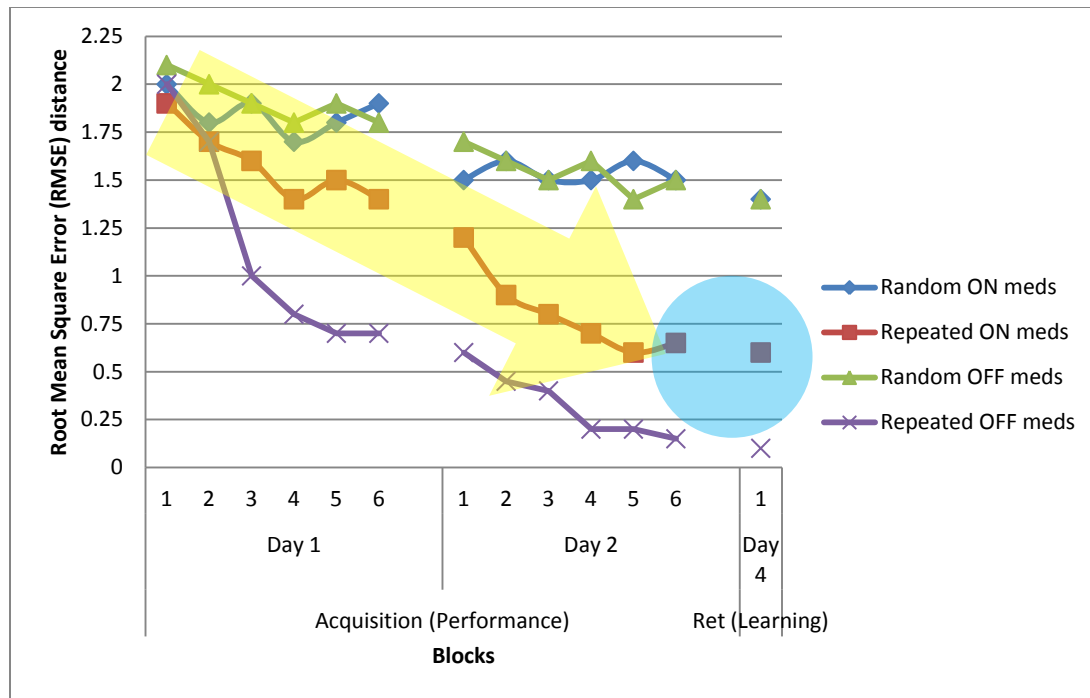


Figure 2.2. Sample graphical representation of acquisition performance and retention learning for primary aim 1. RMSE reported on the y-axis (cm). Two groups are depicted: individuals with PD on (ON) and off (OFF) dopaminergic medication. The performance on random and repeated segment RMSE for each block are presented across practice trials. Sequence-specific acquisition performance and retention learning are calculated as the difference between the random and repeated segments. On Day 1 and Day 2 (acquisition performance), 6 blocks are performed each day. A retention test is performed on Day 4 with 1 block. The highlighted yellow arrow is the analysis for primary aim 1, hypothesis 1, for repeated segment RMSE across the acquisition phase (acquisition performance). The blue circle depicts the area of analysis for primary aim 1, hypothesis 2, the learning score.

healthy young during a continuous sequential task under posturally demanding conditions.

We first hypothesized that a difference between 4 groups; individuals with early PD on and off medication, healthy elders and healthy young) will be observed in sequence-specific acquisition performance during the acquisition phase of a continuous sequential postural task.

To analyze primary aim 2, hypothesis 3 the following analysis will be performed: The dependent variable, sequence-specific acquisition performance, will be determined for each of the 12 blocks performed during the acquisition phase. SSAP refers to the difference between the random and repeated segment scores within a block. A repeated measures ANOVA with 4 groups by 12 blocks with a Bonferroni correction and repeated contrasts on SSAP will be conducted. A difference between the groups is expected to be observed.

We also hypothesized that a difference between 4 groups; individuals with early PD on and off medication, healthy elders, and healthy young will be observed in the sequence-specific learning score during the retention test of a continuous sequential postural task.

To analyze primary aim 2, hypothesis 4 the following analysis will be performed: The dependent variable, sequence-specific learning score, will be determined for the final block of acquisition and the block performed at retention test. A one-way ANOVA with 4 groups by 2 blocks on the SSLS will be conducted. A difference between the groups is expected to be observed. See Figure 2.3 for a graphical representation of analyses for primary aim 1, hypotheses 1 and 2.

Our secondary aim was to determine spatial tracking accuracy and temporal tracking accuracy of repeated segment RMSE during the acquisition phase of individuals with early PD (on and off dopaminergic medication) during a continuous sequential task under posturally demanding conditions.

Due to the exploratory nature of this aim, a directional hypothesis is not stated based on the effect of medication; thus, there will be a difference in performance of

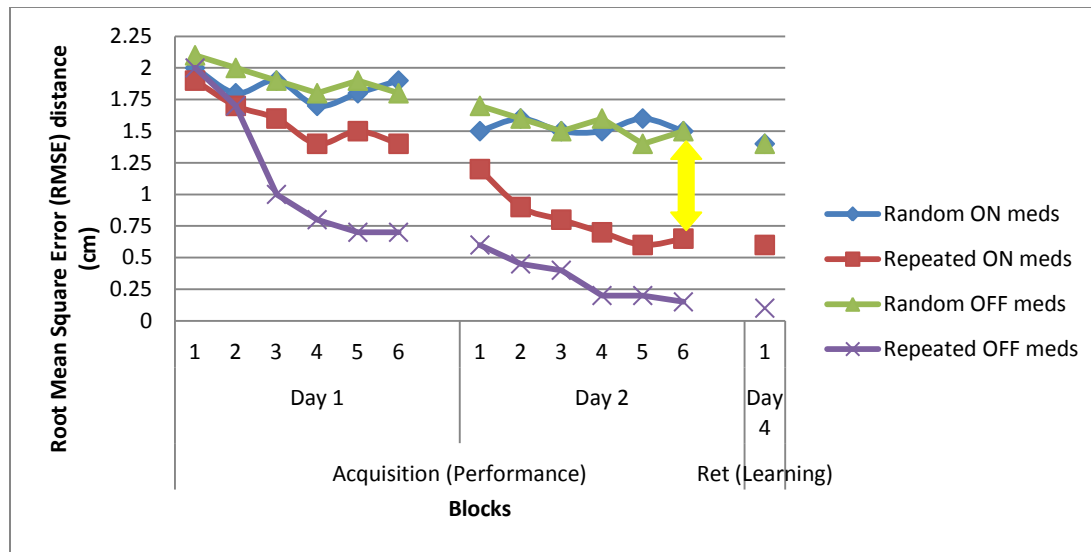


Figure 2.3. Sample graphical representation of acquisition performance and retention learning for primary aim 2. RMSE reported on the y-axis (cm). Two groups are depicted: individuals with PD on (ON) and off (OFF) dopaminergic medication. The performance on random and repeated segment RMSE for each block are presented across practice trials. On Day 1 and Day 2 (acquisition performance), 6 blocks are performed each day. A retention test is performed on Day 4 with 1 block. The yellow arrow depicts the difference score that will be calculated between the random and repeated segments for each group (PD ON or OFF) for each block. This calculation allows the analysis of the sequence-specific acquisition performance based on 12 blocks during acquisition performance and the sequence-specific learning score based on the final block of acquisition performance and the single block of retention learning.

temporal tracking accuracy (as measured by temporal lag) between individuals with early PD (on and off dopaminergic medication) during the acquisition phase.

Our second hypothesis was that there will be a difference in spatial tracking accuracy (as measured by spatial lag) between individuals with early PD (on and off dopaminergic medication) during the acquisition phase.

To analyze the secondary aim, hypotheses 5 and 6 the following analyses were performed: A repeated measures ANOVA with a Bonferroni correction will be performed on the dependent variable, temporal lag. The between-subject variable is the group with 2 levels (PD on and PD off medication) and the within subject variable is the adjusted

repeated segment RMSE for temporal tracking accuracy for blocks 1–12 during the acquisition phase. The same analysis will be used to examine hypothesis 6, spatial tracking accuracy, with spatial lag as the dependent variable. The same analysis will be performed on the dependent variable, spatial lag. A difference between the groups is expected to be observed for spatial tracking accuracy, but not temporal tracking accuracy for individuals with PD on and off medication since it has been suggested that a spatial integration deficit may be present in individuals with PD (Werheid et al., 2003).

Sample Size

A priori calculation of sample size was performed based on effect size (ES; Cohen's *d*) reported in the literature. A summary of the effect sizes reported for multiple studies can be found in Appendix E. The primary aim of this study is acquisition performance and retention learning in individuals with early PD on and off dopaminergic medication to determine if there is an overdose effect impacting learning of repeated segments. In general, prior studies have demonstrated that individuals with PD (not related to impact of dopamine) are capable of learning a repeated motor task but not to the same capacity as healthy controls (Stephan et al., 2011). It has been proposed that the delay observed in learning a repeated motor task is related to a deficit in sequence-specific learning (large effect size observed of 0.73) rather than an inability to learn a general task (Siegert et al., 2006). Furthermore dopaminergic medication has been proposed as a component contributing to a delay in sequence-specific learning as well (Kwak et al., 2010). Individuals who have never been medicated demonstrate no difference in sequence-specific learning when compared to healthy controls (Muslimovic

et al., 2007), further supporting that dopamine may be interfering with sequence-specific learning. Only one study has reported the effect of dopamine medication in individuals with PD (Kwak et al., 2010) during the acquisition phase. They reported a large interaction effect size ($d = 1.03$) for seven individuals with PD who trained on and then off medication during acquisition performance of repeating segments. As the acquisition trials continued, the individuals off medication were able to demonstrate improved performance on the repeated segments at a similar rate to individuals on medication, but the difference between the groups persisted across the final acquisition trials.

These large effect sizes on few subjects suggest that an interaction will be observed in this study during acquisition performance. An a priori sample size calculation was performed to reflect the primary aim, hypothesis 1, interaction effect using repeated measures with a 2-group by 8-repetitions. An average of the interaction effect sizes presented in Appendix E for acquisition performance on repeated segments finds an effect size of 0.50 or a medium effect according to Cohen's classification (Cohen, 1992). The ANOVA effect size value (f) indicates that Cohen's d conversion would equate to 0.25. This (f) 0.25, a preset alpha level of 0.05, and a desired power of 0.80 suggest a sample size of 14 participants, 7 per group is required. With an expected attrition of 25%, 10 participants per group will be recruited (10 on medication, 10 off medication). Additional controls will include 10 healthy elders and 10 healthy young.

Limitations and Concerns

Little is known about the impact of medication on IMSL and the potential for an “overdose” effect on individuals in early stages of the disease. Additionally, no studies

have assessed IMSL during a posturally demanding task, and sequential postural tasks are an essential component to our daily activities.

This study seeks to control for severity of the disease by assessing individuals with “early” PD as characterized by movement deficits on the Hoehn and Yahr (stages 1–2 and 1–2.5); however, the relationship of sequence learning and severity of disease is not clearly understood (Carbon, Reetz, Ghilardi, Dhawan, & Eidelberg, 2010; Stephan et al., 2011). Although it is generally accepted that sequence learning is more impaired in more advanced stages of disease, it is not known if this relationship can be characterized as a deficit in the early stage of the disease.

This study does not specifically address potential mechanical restrictions, such as muscle rigidity or increased stiffness, which may relate to decreased amplitude in individuals with PD, therefore impacting our accuracy results on this continuous tracking task. This variable will not be controlled for during the “off” medication state and may impact the amplitude accuracy on RMSE and/or spatial/temporal accuracy. However, attempts will be made to reduce the amplitude of the target to meet the individuals’ maximum amplitude as needed for the individual as 25% of their maximum excursion will be the value used in assessment (Van Ooteghem et al., 2009). Additionally, determination of the spatial lag and temporal lag may allow more insight into this problem.

Individuals with severe dyskinesias as a side effect of medications will be excluded to be able to analyze the data effectively. Furthermore, a filter on the data will allow a smoothing out of the data should a lower extremity tremor or dyskinesia be present. The removal of dopamine only and not the withdrawal of dopamine agonists may

impact the results. However, because L-DOPA has a shorter half-life than the dopamine agonists, it is thought that the impact of L-DOPA removal and addition will be sufficient to determine a differential effect. Additionally, individuals will be asked to be off their medications for 12 hours for 3 (assessment and training days) of the 4 days. Because of the potential burden on these participants to not take their medication for 12 hours the minimal removal of drugs is recommended (Reichmann & Emre, 2012).

The primary aim of this study is to determine if an interaction effect exists during acquisition performance on the repeated segments and has been powered off this aim. This power analysis was based on large effect sizes observed in 14 individuals with early PD who were assessed on and off medication. Primarily, large effect sizes have been observed for a within group effect, which makes sense as during acquisition performance individuals have demonstrated improved performance, indicating general skill learning. Sequence-specific learning also demonstrates a significant difference, but the effect sizes have been small (0.26 to 0.52) with an average effect size of (Cohen's *d*) 0.41. This sequence-specific learning was typically performed on healthy elders and individuals with PD, not individuals with PD on and off medication. This study has not been powered to detect this interaction. The number of subjects needed to achieve a power of 0.80, alpha of 0.05, and an ANOVA effect size value (f) of 0.20 is 24 subjects total, or 12 subjects per group. However, sequence-specific learning is primary aim 2 and not the primary focus of this study.

The methodology for determining sample size was based on the F statistic for a repeated measure ANOVA. This is not as conservative a measure as the t test; however, efforts to create a more conservative F-statistic effect size (0.25) were taken.

The amount of practice provided in this proposed study is relatively equivalent to the practice performed on a continuous tracking task compared to other studies assessing sequence learning using a continuous tracking task (See Appendix E for a comparison). The amount of practice needed to show change is not known in this novel task; an estimate to provide more practice is being used because of the potentially more complicated task being demanded in this study. Secondly, studies have not sought to determine how much practice may be needed before a change in the acquisition of a repeated segment is observed in individuals with PD. This study may provide insight into that because of the greater amount of practice. Finally, additional practice may be warranted because the individuals will be off their medication by the end of the acquisition periods for up to 16 hours. The impact of the ability to learn and perform the task secondary to fatigue is not known with the continued residual effects of the medication.

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CHAPTER 3

DO INDIVIDUALS WITH BASAL GANGLIA LESIONS HAVE DIFFICULTY WITH IMPLICIT MOTOR SEQUENCE LEARNING? A META-ANALYSIS

Abstract

Assessment of implicit motor sequence learning (IMSL) in individuals with Parkinson disease or subcortical stroke because of a basal ganglia (BG) lesion finds mixed results on the impairment of IMSL compared to age matched healthy controls (HC). The purpose of this paper is to present results of a meta-analysis examining the hypothesis that IMSL is impaired in individuals with BG lesions when compared to HC. Seventeen articles met our final criteria and assessed 308 individuals with BG lesion and 253 HC. Overall, the results found a moderate effect size, 0.61, suggesting that individuals with BG lesions were impaired in IMSL. The secondary analysis assessed studies that performed only 1 day of practice, and a large effect size was observed, 1.08. This was contrasted to studies that provided multiple days of practice that showed a negative and moderate–large effect size, -0.83 , suggesting that, with sufficient practice, individuals with BG lesion improved to a greater degree than HC. Further research is warranted to understand the impact of increased practice, influence of medication, role of cognition, influence of type of lesion, and influence of type of task in this learning deficit in individuals with BG lesions.

Introduction

Implicit learning refers to the unconscious awareness of what is learned. Examples of implicit learning include skill and habit learning, such as juggling and riding a bicycle (Kandel, Schwartz, & Jessell, 2000). Explicit learning, in contrast, is based on learning of facts or rules with a declarative awareness of what has been learned. Examples of explicit learning include memorizing a phone number or an address.

Implicit and explicit learning have been studied by imaging and experimental paradigms, and results suggest that these systems are dissociated (Knowlton et al., 1996). Explicit learning is supported by discrete regions within the brain, specifically the hippocampus within the medial temporal lobe (Squire & Zola, 1996), whereas implicit learning appears to be widely distributed throughout multiple brain regions including the basal ganglia (BG), cerebellum, amygdala, and the neocortex (Squire & Zola, 1996). This dissociation of implicit and explicit learning has also been supported when studying individuals with specific brain lesions, such as individuals with Parkinson disease (PD) or stroke.

Implicit motor sequence learning (IMSL) is a specific type of implicit learning and refers to the process by which simple or complex isolated serial movements come to be performed effortlessly as single unit of movement without awareness of the serial pattern that has been learned (Doyon, 2008; Gheysen et al., 2010). Examples of IMSL include driving a car or brushing one's teeth (Doyon, 2008; Magill, 2007).

IMSL has been studied experimentally by the serial reaction time task (SRTT) (Nissen & Bullemer, 1987) and the continuous tracking task (CTT; Boyd & Winstein, 2006; Gheysen et al., 2010; Wulf et al., 1993). These experiments embed a repeating

motor sequence within random sequences during practice and do not inform about the presence of the embedded repeating sequence. At the end of practice, evidence of sequence-specific learning (SSL) occurs if there is greater improvement (as measured by a decrease in reaction time or error) on the repeating sequence compared to the random sequence. Because the participant has no explicit knowledge about the presence of the repeating sequence, researchers infer that any improvement occurs via implicit processes. Experimental studies have suggested that IMSL may be impaired in individuals with these BG lesions, and this impairment is not related to motor deficits (Seidler et al., 2007; Werheid et al., 2003a). Furthermore, imaging studies have led to a proposed neurobiological model for IMSL (Doyon, 2008). Within this model the BG and the striatum in particular are stated to be two of the critical neural structures for the consolidation of implicit motor sequences. Therefore, studying individuals with a BG deficit, such as PD, a disease characterized by a degeneration of dopamine-producing neurons in the BG, or a subcortical stroke impacting the BG, may elucidate a deficit in IMSL relative to those without BG damage. Experimental studies assessing IMSL using either the SRTT or CTT paradigms on individuals with these BG lesions, PD, or BG stroke have reported mixed results on the impairment of IMSL compared to age matched healthy controls (Deroost et al., 2006; Jackson et al., 1995; Smith & McDowall, 2004). Because of variability in these studies related to practice amount, type of task, and sample studied, it is difficult to soundly conclude that individuals with BG lesions are impaired in IMSL. A meta-analysis is a useful tool for combining research results and establishing a pooled overall effect size. Combined research results allow assessment of increased sample sizes in order to better determine the magnitude of observed changes.

A prior meta-analysis performed by Siegert et al. (2006) reviewed articles from 1987 to 2005 and reported a standardized mean difference effect size of 0.73 suggesting that implicit sequence learning was impaired in individuals with PD. The study performed by Siegert et al. assessed implicit sequence learning using only studies that administered the SRTT in individuals with confirmed PD and included motor sequences as well as verbal sequences in the analysis.

This study seeks to expand the prior review and broaden the understanding of the role of the BG in IMSL by (a) assessing articles published from 1995 to 2013; (b) assessing individuals with BG lesions, such as confirmed PD or individuals with confirmed BG stroke; (c) utilizing either the SRTT or a CTT; and (d) assessing only motor sequences. Thus, the purpose of this paper was to present results of a systematic review with a meta-analysis to examine the hypothesis that IMSL, specifically SSL, is impaired in individuals with BG lesions when compared to healthy, age-matched controls (HC). An additional secondary analysis will create subgroups analyzing the impact that the amount of practice may have on IMSL in these same groups.

Methods

A meta-analysis was performed by starting with a systematic review of the existing literature. Specific criteria were utilized to ensure that the review was comprehensive and that there was no bias in the decision to include or exclude studies. This was followed by a quantitative analysis of the data from the resultant research articles using Cochrane Review Manager (Centre, 2008) for determination of the standardized mean difference.

Literature Search

The following electronic databases were searched: Medline, CINAHL, Biomedical Reference Collection, Sport Discus, The Cochrane Library, PsycArticles, Psychology and Behavioral Health Collection, Psycinfo, and Google Scholar. The search was limited to studies in English with human subjects, published between January 1995 to the end of March 2013. The author read titles and abstracts in separate databases to identify potential studies. This initial search assessed published studies containing the following keywords and their variants for pathology: Parkinson disease and Basal Ganglia Stroke. The search also included the following keywords and their variants for intervention: CTT or SRTT. The final keywords and their variants included implicit motor task, skill or learning.

The second step of the search required further screening of the identified articles to ensure that the initial criteria were met. Articles that met our criteria were read to identify if (a) a motor task was performed (verbal tasks were excluded), (b) a CTT or SRTT was performed, (c) individuals were not informed of a repeating sequence, thus an implicit task was performed, and (d) SSL could be determined from the articles by providing performance data for repeated and random segments at the end of the experiment.

Level of Evidence and Quality of Study

The final step was to determine the level of evidence and quality of each study using a scale described by the American Academy of Cerebral Palsy and Developmental Medicine (AACPDM; Darrah, Hickman, O'Donnell, Vogtle, Wiart, 2008). Level of

evidence is rated on a five-category scale. Level I designs are defined as well-controlled experiments requiring random allocation and manipulation of the intervention.

Level II designs do not include randomization but are well-controlled experiments or prospective comparison studies. Level III designs are retrospective comparison studies.

Level IV designs have no comparison group or condition. Level V designs are

nonempirical evidence. For each study, a quality score based on AACPD

guidelines was calculated with a point provided for positive responses on each of the

following questions: (a) Were inclusion and exclusion criteria of the study population

well described and followed?; (b) Was the intervention well described and was there

adherence to the intervention assignment?; (c) Were the measures used clearly

described?; (d) Was the outcome assessor unaware of the intervention status of the

participants?; (e) Did the authors conduct and report appropriate statistical evaluation

including power calculations?; (f) Were dropout/loss to follow-up reported and less than

20%?; (g) Considering the study design, were appropriate methods for controlling

confounding variables and limiting potential biases used? Quality scores were

categorized as follows: strong (score of 7 or 6), moderate (score of 5) and weak (score of

4 or less).

Study Inclusion Criteria

Studies were included in this review if (a) they were level I or II studies based on the AACPD level of evidence criteria; (b) they met a quality rating score of at least 4 according to the AACPD scale; (c) data were reported or could be extracted to

determine a SSL, such that a random sequence was provided and a repeated sequence was provided; and (d) the comparison group were healthy, age-matched controls.

Data Extraction Methods

Raw mean and standard deviation data for the final block of repeated and the final block of the random practice trials were obtained for each study according to the following methods: (1) full data were presented in the article; (2) for missing data, such as the standard deviation in the text, then the authors of the studies were contacted to obtain missing data; (3) for missing data when the authors did not respond, the raw data was obtained by reading the data from the plots/figures provided. This graphical analysis required extracting the raw values (means and standard error or standard deviation) from the plots, and the mean extraction values obtained were utilized. If the article had been included in Siegert et al. (2006), then their mean was combined to obtain the value of SSL. When standard error was provided, the standard deviation was calculated by multiplying the standard error by the square root of the sample size.

Analysis

The mean between-group difference and the standard deviation of SSL were calculated for individuals with BG lesions and healthy controls. Forest plots were used to depict the comparison of the groups by assessing the standardized mean difference (Portney & Watkins, 2009). Statistical analysis utilized random effect sizes with 95% confidence intervals (CI) and I^2 value for overall heterogeneity. If heterogeneity was less

than 74%, then fixed effect sizes were reported. Alpha of less than 0.05 was considered statistically significant.

All articles meeting the primary criteria were initially placed in the Forest plot to determine the overall effect of IMSL as described by the authors. The initial analyses included the values reported by authors related to SSL and did not account for practice effects. A secondary analysis was performed in which studies were separated based on the amount of practice provided; thus, one Forest plot was created for studies that reported IMSL at the end of 1 day of practice, and a separate Forest plot was created for studies that reported a retention test on a later day.

Results

PRISMA and Demographic Information

The initial literature search performed by the author and identified 41 articles. After duplicates were removed, 35 articles were screened again to ensure they met initial criteria. Ten articles were excluded upon the second screening because they did not include a motor task or individuals did not have a BG lesion. Thus, 25 articles met the original criteria and were assessed via full-text review. Of the 25 articles, 17 met the a priori inclusion criteria and were reviewed for meeting the AACPD level of evidence and quality rating scale criteria. All 17 articles met the AACPD criteria established (See Table 3.1). See Figure 3.1 for an illustration of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

The number of individuals with a confirmed BG stroke was 52 and with confirmed PD was 254, for a total assessment of 306 individuals with BG lesions

Table 3.1. Level of evidence and methodological quality of studies according to the AACPD guidelines.

Author	Level of evidence	Quality rating
Boyd & Winstein, 2004	I	5
Boyd & Winstein, 2006	I	5
Boyd et al., 2009	II	5
Brown et al., 2003	II	4
DeRoost et al., 2006	II	5
Exner et al., 2002	II	4
Helmuth et al., 2000	II	5
Jackson et al., 1995	I	5
Meehan et al., 2011	II	6
Muslimovic et al., 2007	II	5
Seidler et al., 2007	II	4
Shin & Ivry, 2003	II	4
Somme et al., 1999	II	5
Stefanova et al., 2000	II	5
VanTilborg & Hulstijn, 2010	II	5
Werheid et al., 2003a	II	5
Werheid et al., 2003b	II	5

compared to 253 age matched healthy controls. Summary of demographic variables age, sex, cognition, severity, duration of disease, and medication status are provided in Table 3.2 The mean age of the subjects, BG: M = 59.8 years (range 49.3–67.5) and HC: M = 60.0 years (range 48.3–71.0), were similar across groups and number of subjects; males (N = 278) and females (N = 218) were equally distributed. Eleven of the 17 studies utilized the Mini Mental State Exam (MMSE; max score of 30) as an assessment of cognitive function. On average, individuals with BG lesions scored 28.3 compared to the HC scoring 29.1. In five studies, individuals with BG stroke were examined; thus, Hoehn and Yahr (H&Y) was not assessed. In five studies of individuals with PD, H&Y scores were not reported. The remaining seven studies reported PD severity from H&Y scores and yielded an overall mean of 2.0 (range 1–3), and this includes values on and off

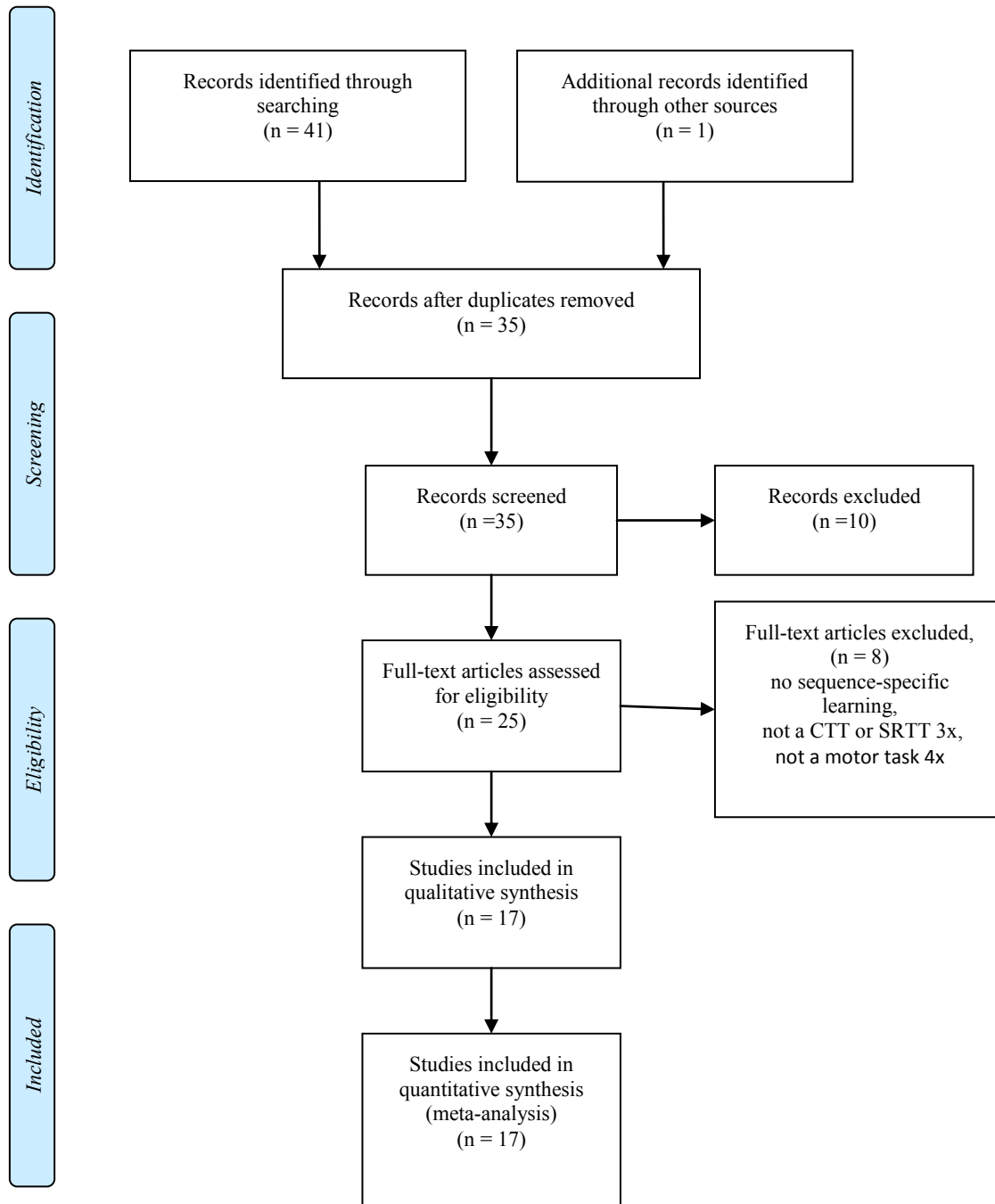


Figure 3.1. PRISMA 2009 Flow Diagram (Adapted from Moher et al., 2009).

Table 3.2. Summary data of demographic characteristics and assessment of sequence-specific learning for each article and subgroup analyses included in the meta-analysis.

Reference	BG lesion/ Control, (N) (gender, M:F)	Mean Age, years (SD)	Hoehn & Yahr, Mean (SD) /UPDRS, Mean (SD)	Duration of symptoms, Months (SD)	Cognitive status	Training ON/OFF dopamine meds	Type of task	Practice trials total	Sequence- specific assessment
Boyd & Winstein, 2004	BG Stroke, No Explicit (5)(3:2) HC, No Explicit (5)(2:3)	BG Stroke No Explicit 58.2(14.6) HC, No Explicit 57.4(16.1)	H&Y NA/ UPDRS NA	10.4 (5.6)	MMSE BG Stroke, No Explicit 28.4(1.1) HC, No Explicit 29.6(0.5)	NA	CTT (RMSE)	CTT 4 days total, 3 days practice (50 trials/day, 10 trials/blocks), 1 day retention 1 trial, Middle 1/3 of every trial was repeated with the beginning and last 1/3 of the segment random	Retention test, mean difference of average random/repeated
Boyd & Winstein, 2006	BG Stroke, No Explicit (5)(3:2) HC, No Explicit (5)(2:3)	BG Stroke, No Explicit 58.2(14.6) HC, No Explicit 57.4(16.1)	H&Y NA/ UPDRS NA	10.4 (5.6)	MMSE BG Stroke No Explicit 28.4(1.1) HC, No Explicit 29.6(0.5)	NA	CTT (RMSE)	CTT 4 days, 3 days practice (50 trials/day, 10 trials/blocks), 1 day retention 1 trial, Middle 1/3 of every trial was repeated with the beginning and last 1/3 of the segment random	Retention test, mean difference of average random/repeated
Boyd et al., 2009	BG Stroke (13)(8:5) HC (13)(5:8)	BG Stroke 59.6(15.5) HC 59.4(15.9)	NA	59.6(52.9)	MMSE BG Stroke 28.3(2) HC 29.8(0.6)	NA	SRTT (ms)	3 days 2 days practice (6 blocks), block 1 random, blocks 2-6 repeated, 1 day retention, 1 block random, 1 repeated	Retention test, difference between random, repeated

Table 3.2. Continued.

Reference	BG lesion/ Control, (N) (gender, M:F)	Mean Age, years(SD)	Hoehn & Yahr, Mean (SD) /UPDRS, Mean (SD)	Duration of symptoms, Months (SD)	Cognitive status	Training ON/OFF dopamine meds	Type of task	Practice trials total	Sequence- specific assessment
Brown et al., 2003	Pre-op PD (10)(9:1) HC (10)(6:4)	Pre-op PD 54.9(8.9) HC 7.2(14.8)	H&Y not stated / UPDRS not stated	Pre-op 192(32.4)	Not stated	OFF	SRTT (ms)	1 day (10 blocks) blocks 3– 8, 10 repeated; blocks 1,2,9 random	Mean of 8, 10 repeated compared to 9 random
DeRoost et al., 2006	PD (16)(6:10) HC (16)(6:10)	PD 66.6(5.7) HC 65.9(6)	H&Y 3 UPDRS not stated	138(61.6)	MMSE PD 27.3(1.5) HC 28.8(1.2)	ON	SRTT (ms)	1 day FOC (first order conditional association, the upcoming target can be predicted, 11 blocks All repeated, except block 10 (random)	FOC Between blocks 10 (random) and 9,11 (repeated)
Exner et al., 2002	BG Stroke (20)(17:3) HC(20)(15:5)	BG Stroke 53(11) HC 52(9)	H&Y NA/ UPDRS NA	24(14)	WAIS-R BG Stroke 100(18) HC 111(18)	NA	SRTT(ms)	1 day, 8 blocks	Compared block 5 repeated to block 6 random
Helmuth et al., 2000	PD (24)(not stated) HC (24)(not stated)	PD 58.8(10.9) HC 64.6(9.1)	H&Y range 1–3/ UPDRS not stated	Not stated	Not stated	ON	SRTT(ms)	1 day Phase 2: 15 blocks Random far spatial blocks 24,25. Repeated 26	24/25 to 26 far spatial
Jackson et al., 1995	PD (11)(7:4) HC (10)(not stated)	PD 65.6(7.5) HC 67.5(not stated)	H&Y not stated/ UPDRS not stated	57.6(27.6)	MMSE PD 28.5(1.1) HC (not stated)	Not stated	SRTT (ms)	1 day, 8 blocks 1–6 repeated, 7 random, 8 repeated	Compared block 6 repeated to block 7 random

Table 3.2. Continued.

Reference	BG lesion/ Control, (N) (gender, M:F)	Mean Age, years(SD)	Hoehn & Yahr, Mean (SD) /UPDRS, Mean (SD)	Duration of symptoms, Months (SD)	Cognitive status	Training ON/OFF dopamine meds	Type of task	Practice trials total	Sequence- specific assessment
Meehan et al., 2011	BG Stroke (9)(6:3) HC (9)(4:5)	BG Stroke 63.9(6.2) HC 63.1(7.0)	NA	53.2(49.8)	MMSE BG Stroke 29.3(.78) HC 29.7(.50)	NA	CTT (RMSE)	7 Days, 6 days of practice; 5 blocks/10 trials/day. each block 1/2 random and 1/2 repeated, 1 day retention, 1 block	Retention test, mean difference random/repeated
Muslimovic et al., 2007	PD (95)(58:37) HC (44)(23:21)	PD 64.9(8.9) HC 64.1(8.3)	PD H&Y 2.0(0.7) UPDRS 18.2(9.2)	PD 37.2(31.2)	MMSE PD 27.9(1.7)	71 ON 24 OFF	SRTT (ms)	1 day, 7 blocks (6 repeating, 7 random)	Difference between block 6 repeating and block 7 random
Seidler et al., 2007	PD (8)(3:5) HC (6)(2:4)	PD 57.4(8.0) HC 59.2(7.4)	H&Y not stated UPDRS total 48.6(14.5)	Not stated	MMSE PD 28 (not stated) HC 29.6 (not stated)	OFF	SRTT (ms)	1 day 12 blocks Distracted during training, block 1 random 2-5 repeated, block 6 random Training R hand Assess R hand, block 7 random, 8 repeated, 9 random	Difference between average of random blocks 7,9 and repeated block 8
Shin & Ivry, 2003	PD (10)(7:3) HC (10)(4:6)	PD 64(not stated) HC 71(not stated)	H&Y not stated / UPDRS not stated	168(79.2)	MMSE All scored normally (28-30)	ON	SRTT (ms)	1 day, 27 blocks of 56 trials Spatial blocks 13-16	Mean of the outer sequenced blocks from the altered (random) blocks in the middle

Table 3.2. Continued.

Reference	BG lesion/ Control, (N) (gender, M:F)	Mean Age, years(SD)	Hoehn & Yahr, Mean (SD) /UPDRS, Mean (SD)	Duration of symptoms, Months (SD)	Cognitive status	Training ON/OFF dopamine meds	Type of task	Practice trials total	Sequence- specific assessment
Sommer et al., 1999	PD (11)(9:2) HC (15)(10:5)	PD 55.9(9.6) HC 51.7(10)	H&Y, not stated UPDRS Motor 33.6(10.3)	68.76(25.2)	Mattis PD 139.4(3.5) HC 141.8(2.7)	ON	SRTT (ms)	1 day, 7 blocks, 6 repeated, block 7 random	Compared block 6 repeated to block 7 random
Stefanova et al., 2000	PD (39)(24:15) HC (31)(11:20)	PD 49.3(5.7) HC 48.3(9.6)	H&Y 2.0(0.5) UPDRS not stated	57.6(19.9)	26-30 for all	ON	SRTT (ms)	1 day, 8 blocks; blocks 1-4 repeated, block 5 random, blocks 6-8 repeated	Compared block 4 repeated to block 5 random block 5 random
Van Tilborg & Hulstijn, 2010	PD (12)(7:5) HC (12)(6:6)	PD 67.5(9.7) HC 69.6(13.9)	H&Y 2.0(0.67) UPDRS not stated	Not stated	MMSE PD 28.3(2.3) HC 27.5(1.8)	6 ON 6 OFF	SRTT (ms)	1 day, 6 blocks, blocks 1 and 6 random; 2-5 repeated	Compared block 5 repeated to block 6 random
Werheid et al., 2003a	PD (7)(5:2) HC (7)(2:5)	PD 58.7(7.8) HC 52.9(5.5)	H&Y 2.0(0.3) UPDRS 32.2(12.5)	32.4(19.7)	Not stated	ON	SRTT (ms)	1 day, 13 blocks, repeated 1-10, random 11, 12-13 repeated	Compared block 11 random to average of block 9, 10 repeated
Werheid et al., 2003b	Spatial stimulus PD (11)(4:7) HC (11)(4:7)	Spatial PD 60.3(4.5) HC 59.3(4.1)	Spatial H&Y 2.0 (0.69) UPDRS 26.3(16)	Spatial 52.8(45.6)	MMSE no lower than 24	ON	SRTT (ms)	Participants came in 2 days. 1 day experiment 1 and 1 day experiment 2. 18 blocks of 64 trials 1,5,9, 13, 17 random.	Difference was mean of random blocks 5, 9, 13, 17 compared to the preceding repeating blocks (4, 8, 12, 16)

Table 3.2. Continued.

Reference	BG lesion/ Control, (N) (gender, M:F)	Mean Age, years(SD)	Hoehn & Yahr, Mean (SD) /UPDRS, Mean (SD)	Duration of symptoms, Months (SD)	Cognitive status	Training ON/OFF dopamine meds	Type of task	Practice trials total	Sequence- specific assessment
SUMMARY	Overall BG lesion N = 306 (BG Stroke N = 52, PD N = 254) HCN = 253 Males 278 Females 218	BG: M = 59.8 (range 49.3– 67.5) (BG Stroke M = 58.6, PD M = 61.1) HC: M = 60.0 (range 48.3– 71.0)	H&Y range overall 1–3 (median 2.0) UPDRS motor (range 18.2–30.6) (mean 31.8)	68.7 months post diagnosis (range 10.4– 192) (BG Stroke M = 31.5, PD M = 89.4)	11 studies: BG: 28.3 HC: 29.2 /30 max (BG Stroke M = 28.6, PD M = 28)	5 NA, 1 not stated, 4 OFF, 7 ON	3 CTT, 14SRTT		

medications. Five studies reported the Unified Parkinson Disease Rating Scale (UPDRS) motor score, which averaged 31.8 (range 18.2–30.6), and this includes values on and off medications. One study reported a UPDRS total of 48.6. Assessment of the H&Y and UPDRS scores based on medication status was unable to be determined because of variability in reporting. Fifteen of the studies reported duration of symptoms (mean 68.7 months [range 10.4 to 192.0]). Medication status for the individuals with PD was reported in 11 of 12 studies. Four of the studies had some or all of the individuals off their usual dosage of dopamine.

Meta-analysis

An initial overall assessment of SSL for all 17 studies was performed and standardized mean differences, using a random effect size and 95% confidence intervals (CI) are summarized in Table 3.3 and Figure 3.2. Because one study (Boyd & Winstein, 2006) included data on retention testing for both a SRTT and a CTT group, 18 studies are reported in the Forest plot (Figure 3.2). The total number of subjects reported for BG lesion was 308 and for HC was 253. An I^2 value of 88% was observed, indicating high heterogeneity. The overall effect size was moderate, 0.61 (0.02, 1.20), ($p = 0.04$), indicating that individuals with BG lesions appeared to be impaired in SSL compared to healthy controls.

The secondary analysis separated studies based on the amount of practice to determine if increased practice affected deficits of IMSL in individuals with BG lesions. Figure 3.3 depicts the Forest plot of 17 studies ($N = 308$ for BG and $N = 253$ for HC)

Table 3.3. Means and standard deviation and number of subjects for sequence-specific learning for each study and subgroup for both individuals with Basal Ganglia lesions and healthy age-matched controls.

Reference	SSL Task	BG lesion N	BG Mean	BG SD	Control N	Control Mean	Control SD	Favors (better SSL)
Boyd & Winstein, 2004 ^{a,d}	Continuous Tracking Task, (CTT)*	5	143	60.4	5	165.5	76.0	HC
	Day one CTT ^{d,e,f}	5	218	71.6	5	188	162.8	BG
Boyd & Winstein, 2006 ^{d,e,f}	CTT*	5	-57.5	4.5	5	-76	8.9	BG
	Serial Reaction Time Task (SRTT)*	5	-63.5	1.1	5	-79	4.5	BG
Boyd et al., 2009 ^{e,f,g}	Day one, CTT and SRT combined ^{d,e,f}	10	-96	5.6	10	-91	2.2	HC
	SRTT*	13	87	39.7	13	176	43.3	HC
Brown et al., 2003 ^{c,j}	Day one and Day two practice ^{d,e,f}	13	25.3	15.14	13	136	7.2	HC
	SRTT, Pre-op	10	35	71.0	10	54.1	46.9	HC
Deroost et al., 2006 ^b	SRTT, First Order Condition	16	24	83	16	74	34	HC
Exner et al., 2002 ^{g,h,i}	SRTT	20	29	24	20	48	5	HC
Helmuth et al., 2000 ^{a,i}	SRTT for spatial	24	38	54.75	24	21	37.52	BG
Jackson et al., 1995 ^b	SRTT	11	9.3	33.9	10	74	41.9	HC
Meehan et al., 2011 ^{d,e,f}	CTT*	9	1.3	0.9	9	0.6	0.2	BG
Muslimovic et al., 2007 ^b	Day one, CTT	9	5	24	9	-0.1	9	BG
	SRTT	95	24	27	44	36	36	HC
Seidler et al., 2007 ^{d,e,f}	SRTT	8	1.5	45.3	6	26.5	4.9	HC
Shin & Ivry, 2003 ^{c,d}	SRTT, Spatial	10	15	22.1	10	44	28.5	HC
Sommer, et al., 1999 ^b	SRTT	11	78.3	218.1	15	103.8	86.6	HC
Stefanova et al., 2000 ^g	SRTT	39	16.7	21.7	31	188.4	41.0	HC
van Tilborg, & Hulstijn, 2010 ^{g,h}	SRTT	9	55	40	12	105	78	HC
Werheid et al., 2003a ^{d,i}	SRTT	7	46	71.8	7	65	71.8	HC
Werheid et al., 2003b ^b	SRTT, SR Compatibility	11	47	37	11	87	39	HC

^aMeans from text, ^bMeans and SD from text or table, ^cMeans and SE in text, ^dSE calculated from equation: SD = SEVn, ^eMeans extracted from Figure (using average of author's values and values from Siebert et al., 2006 if in the review), ^fSE extracted from Figure, ^gMean SD calculated by SD1 minus SD2, ^hData received from author, SD converted from t statistic: $t = (X_1 - X_2) - \text{Null} (0)/SE$, ⁱUnable to obtain full data from table or text or author, * studies that provided more than one day of practice, HC (healthy controls), BG (Basal ganglia), SR (stimulus response), SSL (sequence-specific learning)

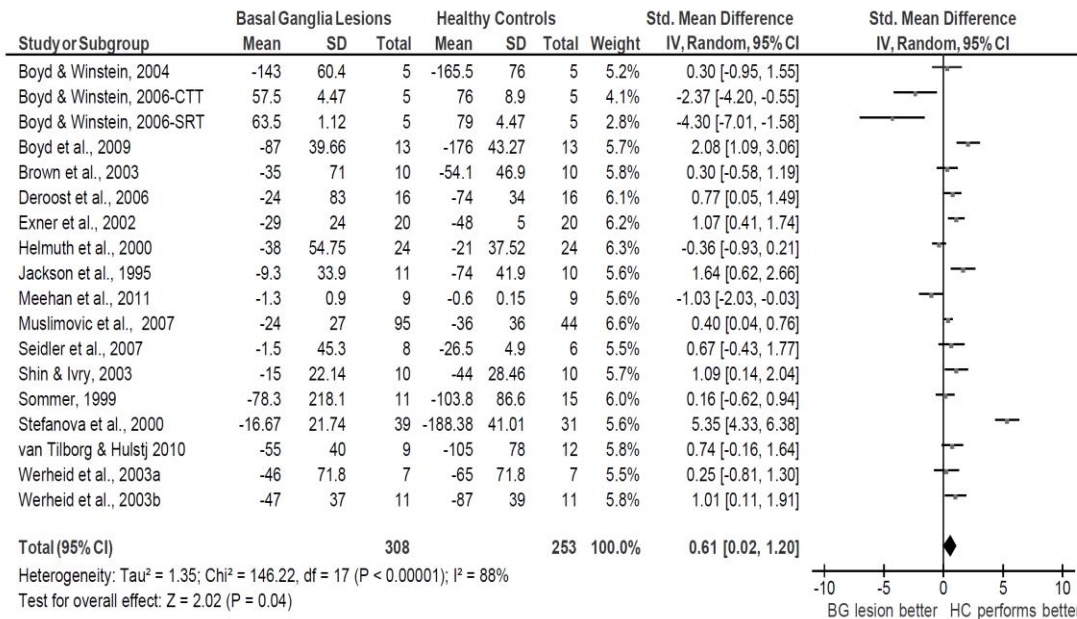


Figure 3.2. Forest plot of comparison of all 17 studies in the meta-analysis describing sequence-specific learning in individuals with Basal Ganglia (BG) lesions and Healthy Controls (HC). Random effect size of standardized mean difference and 95% confidence intervals are shown. Results suggest a moderate effect and that HC were better at sequence-specific learning compared to BG lesion.

after only one day of practice. The I^2 value was 89%, and a large effect size was observed 1.08 (0.47, 1.68), ($p < 0.001$). These results suggest that when assessing IMSL following only one day of practice, SSL is even more impaired in individuals with BG lesions compared to healthy controls.

This is contrasted to the studies that provided multiple days of practice (Figure 3.4), with 37 subjects, an I^2 value of 89%, and a moderate–large effect size -0.83 (-2.69 , 1.03), ($p = 0.38$). These results indicate that, when provided more practice, SSL in individuals with BG lesions exceeded that demonstrated by HC. However, the results were not statistically significant and consisted of only five studies, all of which were the

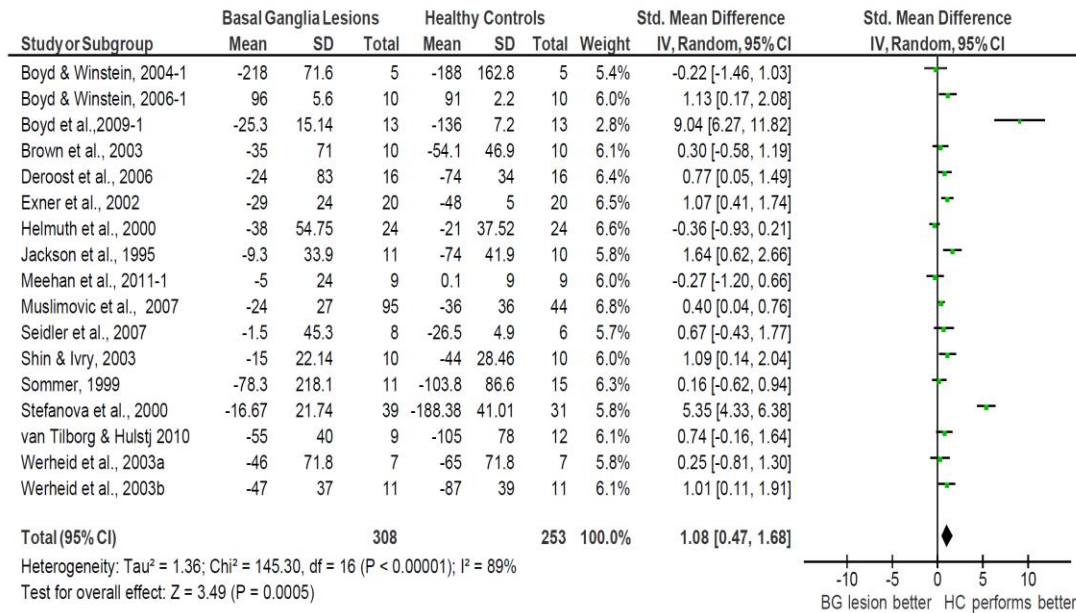


Figure 3.3. Forest plot of comparison of studies included in the meta-analysis, which provided only 1 day of practice describing sequence-specific learning in individuals with Basal Ganglia (BG) lesions and Healthy Controls (HC). Random effect size of standardized mean difference and 95% confidence intervals are shown. Results suggest a large effect and that HC were better at sequence-specific learning compared to BG lesion.

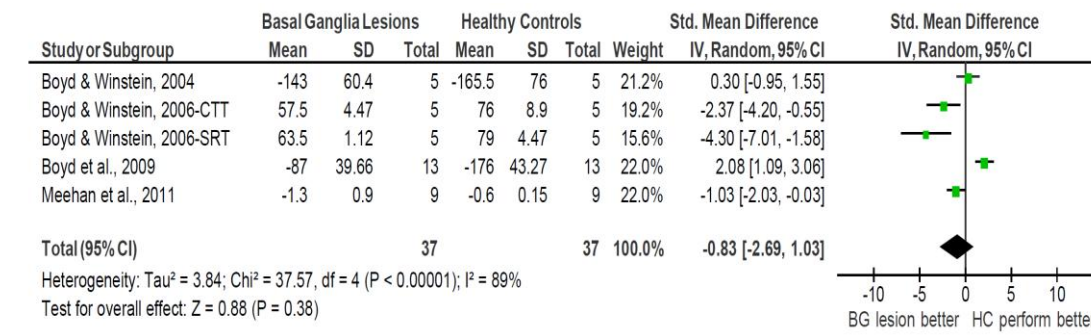


Figure 3.4. Forest plot of comparison of studies included in the meta-analysis, which provided a retention test after 2–7 days of practice describing sequence-specific learning in individuals with Basal Ganglia (BG) lesions and Healthy Controls (HC). Random effect size of standardized mean difference and 95% confidence intervals are shown. Results suggest a moderate–large effect and that BG lesions were better at sequence-specific learning on retention testing compared to HC.

assessment of individuals with BG stroke; therefore, results should be cautiously interpreted.

Discussion

Previous research examining IMSL in individuals with BG lesions has reported mixed results on the impairment of IMSL compared to age matched healthy controls (Deroost et al., 2006; Jackson et al., 1995; Smith & McDowall, 2004). This study sought to utilize meta-analytic techniques to clarify the role of the BG in IMSL and to examine the influence of varying amounts of practice delivered in each of the studies. When considering the final results of all studies, without accounting for the days of practice, individuals with BG lesions, regardless of origin, appeared to be moderately impaired in SSL compared to healthy controls. However, when studies that utilized just one day of practice were segregated from studies that utilized multiple days of practice, different results became apparent. When limited to one day of practice, the standardized effect size suggested that individuals with BG lesions were even more impaired in the acquisition of SSL compared to healthy controls than the general analysis suggested. Conversely, when studies that included multiple days of practice were examined, the standardized effect size indicated that individuals with BG lesions were able to improve their performance to a greater degree than healthy controls. Interestingly, the majority of studies that examined multiple practice days utilized persons with BG stroke as opposed to persons with PD. These results reinforced the presence of IMSL deficits in persons with BG lesions and emphasized the importance of practice in influencing learning outcomes, raising a question about the effects of lesion type of IMSL.

Persistent Deficits in Motor Skill After Practice

The results of this meta-analysis indicate that individuals with BG lesions have impaired performance after only 1 day of practice compared to HC. Thus, the question arises, "was this motor skill deficit still present in individuals with BG lesions after more days of practice?" All of the five articles that assessed motor skill over multiple days documented poorer performance in the BG lesion groups compared to HC even after multiple days of practice. Thus, it appears that individuals with BG lesion can improve performance with additional practice, but never achieve equivalent performance to the HC.

Practice Effects

It has been suggested that the deficit in IMSL for individuals with BG lesions may be due to insufficient practice (Korman et al., 2003). The quantities of practice provided by the studies in this meta-analysis have varied extensively. Thus, for individuals with BG lesions, although more practice may result in larger performance improvements, there is certainly more to understand about the amount of practice that needs to be provided to obtain equivalent learning as HC. Still, the studies presented here that provided more practice did not provide a simple answer. For example, the study by Meehan, Randhawa, Wessel & Boyd (2011) provided 7 days of practice, but did not demonstrate the largest improvement in IMSL relative to the other multiple days of practice. Boyd and Winstein (2004) showed the opposite trend, demonstrating better performance improvements in individuals with BG lesions after 1 day of practice and showing better performance in HC

after more practice. More research is warranted to assess the impact that more practice may have on this deficit in individuals with BG lesions.

Type of Lesion

The types of lesion described in this study included individuals with a confirmed BG lesion, such as PD or a BG stroke. We recognize the mechanism of the lesion is different for these deficits, one related to a progressive loss of dopamine and one related to a vascular event. Based on the neurobiological model of Doyon (2008), the striatum, one of the four nuclei of the BG, is important for motor sequence learning. All of the studies in this meta-analysis, which utilized individuals with a BG stroke, identified the stroke lesions within the putamen, a part of the striatum. For the studies assessing PD, there is no clear clinical correlate for progression of disease through the BG; however, Lim, Fox, and Lang (2009) proposed that progression of the disease is from the substantia nigra through the sensorimotor striatum. Our individuals with PD did not present with postural control or cognitive deficits, which are typically associated with further progression of the disease and thus, although a clear demarcation of the nuclei impacted in the individuals with PD cannot be established, we feel they potentially represent individuals with a substantia nigra deficit and progression of the disease.

Additional Confounding Variables and Limitations

This meta-analysis provided an overview of motor sequence learning and was able to assess the influence of practice on learning in this population; however, there are other variables that could have influenced the results, including type of task, cognition,

and medication status. It was not possible to individually assess the impact of these variables in this meta-analysis.

The types of tasks that have been used for IMSL include both the CTT and SRTT; however, of the 17 articles assessed, only three administered a CTT, and these all utilized longer practice periods. Thus, it is possible that the nature of the task (CTT compared to SRTT) accounted for the improvement observed with more practice because SRTT was not evaluated in conjunction with longer practice periods. The CTT is a more complex and longer duration task and thus may require more time to master. One study in this meta-analysis utilized both the CTT and SRTT tasks to compare the influence of task on IMSL (Boyd & Winstein, 2006). Results showed that individuals improved on both the CTT and SRTT with more practice. Although improvement was greater for SRTT, the authors concluded that the CTT task was not too difficult a motor task to ascertain if IMSL is impaired. Larger sample sizes need to be assessed to conclusively determine the influence of task type in learning.

In the studies analyzed, evaluation of cognitive status was limited and inconsistent. To evaluate how cognitive status impacts IMSL, more consistent and specific cognitive assessments need to occur. Because measurable cognitive decline occurs in 20–80% of patients with Parkinson disease, a more thorough determination of cognitive status is warranted in all future studies (Zadikoff et al., 2008). Even though multiple studies assessing IMSL have suggested that limitations in IMSL are independent of cognitive decline, future research is warranted to more clearly determine potential deficits within the facets of cognition, such as attention, executive function and

psychomotor speed (Bailey & Mair, 2006; Dominey et al., 1997; Exner et al., 2002; Fama & Sullivan, 2002; Smith & McDowall, 2004;).

Medication plays an important role in IMSL. Specifically, the "overdose hypothesis" (Kwak et al., 2010; Seidler et al., 2005) suggests that individuals "on" their usual dosage of dopamine may be more impaired in IMSL than individuals "off" their usual dosage of dopamine. Although the studies presented in this meta-analysis provided data on medication status, it was not possible to extract the data to determine the influence of the role of dopamine. More consistent methods and data collection on severity of disease, cognitive deficits, and medication effect are warranted to ensure consistency of results.

The meta-analysis attempts to integrate as much information as possible from the multiple studies that met the criteria. Data were obtained via author, text, or extraction. Although attempts were made to directly obtain raw data from study authors, responses were limited. The extraction method required estimation of data means and standard deviations.

Overall, the I^2 values in the meta-analysis were high and indicate the high variability observed in these studies. In an attempt to minimize these effects, a random effect size was utilized to account for the lack of homogeneity of the studies; however, the calculation of fixed effects found no difference in effect sizes or I^2 values. Although this was not a perfect solution, this study provides data from 17 articles with a large sample size, and the maximum weight observed in any one study was 6.6%.

Conclusion

This meta-analysis assessed if IMSL, specifically SSL, was impaired in individuals with BG lesions, including individuals with PD and BG stroke. Experimental studies assessing IMSL using either the SRTT or CTT paradigms on individuals with BG lesions have reported mixed results on the impairment of IMSL compared to age matched healthy controls. The results suggest that during early practice individuals with BG lesions are impaired in IMSL compared to HC; however, with more practice across days, this deficit is diminished and individuals with BG lesions improved their performance. More research is warranted to assess varying practice paradigms needed to accommodate this deficit in individuals with BG lesions. Additionally, further assessment of the influence of the type of lesion, type of task, cognitive deficits, and medication status is warranted to ensure consistency of results and to determine the influence of these variables on learning in individuals with BG lesions.

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CHAPTER 4

THE EFFECT OF AGE, PARKINSON DISEASE, AND DOPAMINE MEDICATION REPLACEMENT DURING A STANDING MOTOR SEQUENCE LEARNING TASK

Abstract

Parkinson disease (PD) is a progressive disorder impacting dopaminergic neurons in the Basal Ganglia. Besides the common motor deficits, a deficit in motor sequence-specific learning (SSL) has been observed. Although this SSL deficit may be a product of PD, alternatively it could be related to dopamine replacement treatment. The purpose of this study was (a) to determine the impact of age and PD during acquisition and at a retention test on SSL and (b) to determine the impact of dopamine medication replacement during acquisition in individuals with PD. To examine these hypotheses, an implicit, standing, continuous tracking task (CTT) was performed using Root Mean Square Error (RMSE) as the dependent variable. SSL (difference between the random and repeated RMSE tracks across trials) was calculated. Four groups were tested: 10 healthy young (HY), 10 healthy elders (HE), 10 individuals with PD on (PDON) their usual dosage, and 9 individuals with PD off (PDOFF) their usual dosage of dopamine replacement. All participated in 2 days of acquisition and 1 day of retention testing. All groups improved in performance across the acquisition period. A significant difference

between all 4 groups during acquisition was observed, with HY improving on SSL compared to the other groups. No significant difference between individuals with PDON or PDOFF during acquisition was observed. At retention, all of the groups demonstrated worse performance of the sequence. Analysis of learning cost/savings was performed and results suggested that only the HY demonstrated SSL, whereas only the PDOFF group demonstrated general skill learning. The results of this study did not support dopamine replacement related deficits on SSL during acquisition. However, assessment of the overall improvement in performance across time suggests that age and medication status affect skill acquisition performance and may warrant consideration in the design of practice paradigms during rehabilitation.

Introduction

Parkinson disease (PD) is a progressive neurodegenerative disorder associated with selective damage of dopaminergic neurons within the basal ganglia (BG) and other regions of the central and peripheral nervous system (Jellinger, 2012). The most clearly recognized sequelae are the motor deficits observed in PD: tremor at rest, muscular rigidity, akinesia (inability to initiate movement) and bradykinesia (slowness of movement), and postural instability (Jankovic, 2008). With disease progression, additional deficits may be observed beyond the common motor symptoms, including a deficit in motor sequence learning (MSL; Bailey & Mair, 2006; Dominey et al., 1997; Fama & Sullivan, 2002; Smith & McDowall, 2004).

MSL refers to the process by which simple or complex serial movements come to be performed effortlessly as a single unit of movement and has been studied

experimentally by the serial reaction time task (SRTT) and the continuous tracking task (CTT; Boyd & Winstein, 2006; Gheysen et al., 2010; Nissen & Bullemer, 1987; Wulf et al., 1993). Within MSL, the integration of the sequence has been identified as a deficit. These results are not surprising because it has been shown that the BG are important for the consolidation of implicit motor sequences (Doyon, 2008). Assessment of SSL during early learning trials finds that individuals with PD are consistently slower (delayed reaction time) and less accurate than healthy age-matched controls on the integration of the sequences (Bischoff-Grethe, Martin, Mao, & Berns, 2001; Siegert et al., 2006; van Asselen et al., 2009).

Dopamine can influence individuals with PD in two ways: via reduction and addition. A reduction of dopamine within the BG, as may occur during early stages of PD, may result in an SSL deficit. Specifically, individuals with early sensorimotor striatum dopamine loss may have difficulty consolidating information. Paradoxically, an addition of dopamine (with medication, such as dopamine replacement) in someone with early PD may also result in an SSL deficit. It has been hypothesized that the replacement of dopamine may be sufficient to replace the dopamine loss in the sensorimotor striatum, but may “overdose” the associative striatum, which may not be depleted in early PD (Cools, Altamirano, & D'Esposito, 2006). Thus, the influence of dopamine within the striatum results in a potential dopamine mismatch, impacting SSL. The influence of dopamine needs to be considered when assessing performance outcome measures of SSL. Few studies have reported medication state during SSL, and even fewer of these have reported the impact of dopamine on SSL (Brown et al., 2003; Muslimovic et al., 2007; Seidler, Noll, & Chintalapati, 2006; van Tilborg & Hulstijn, 2010). Furthermore, only 1

study has assessed the potential for "overdose hypothesis" in individuals with PD during a SSL task assessing only 1 day of practice using an explicit SRTT.

The primary purpose of this study was to determine the impact of age and disease state on the acquisition and retention of a standing implicit motor sequence task. We hypothesized that all individuals would demonstrate improved skill during acquisition and with further practice (after retention testing); however, individuals with PD would still be delayed compared to the healthy young (HY) and healthy elder (HE) subjects. Our secondary purpose was to assess the impact of dopamine replacement on individuals with PD during acquisition and hypothesized that individuals with PD on their medication would be delayed compared to individuals off their usual dopaminergic medication, due to the excess dopamine in the associative striatum. Finally, we sought to characterize the overall learning trend to determine a learning cost or savings.

Methods

Study Design

A randomized intervention trial was performed. Four groups, Healthy Young (HY), Healthy Elders (HE), individuals with PD on (PDON), and off (PDOFF) their usual dosage of dopamine, participated in two sequential days of training on a motor sequence task followed by a delayed retention test. An a priori power analyses for a repeated measures ANOVA was determined from the average of the small–large interaction effect sizes (Mean, Cohen's $d = 0.58$) observed for individuals on and off their medication based on the change reported for the repeated sequences during acquisition (Kwak et al., 2010; Muslimovic et al., 2007; Stephan et al., 2011). An a priori power

analysis to determine the number of subjects needed to achieve: a power of 0.80, alpha of 0.05, a conservative ANOVA effect size value (f) of 0.25, and 4 groups (HY, HE, PDON, PDOFF) was calculated to be 7 subjects per groups. With an expected attrition rate of 30%, 10 subjects were recruited for each group.

Participants

Participants were recruited from medical providers within the Department of Neurology at the University of Utah and community neurologists in the greater Salt Lake City area over 24 months (June 2011– July 2013). The flow diagram of enrollment based on the Consolidated Standards of Reporting Trials (CONSORT) statement is illustrated in Figure 4.1 (Moher et al., 2012). The purpose and procedures of the study were explained to the participants, and a consent statement approved by the University of Utah institutional review board was signed. Individuals with PD were included if they had (a) confirmed idiopathic PD according to the UK Brain Bank Criteria (Jankovic, 2008), (b) Hoehn and Yahr (Table 4.1) stages 1 to 2.5 when OFF medications, (c) 50–90 years of age, and (d) a stable dosage of dopaminergic medications for the previous 6 months. Individuals were excluded if they (a) had acute medical problems, (b) had uncorrected vision loss, (c) had previous surgical management of PD, (d) had other conditions that affected mobility and balance abilities (arthritis, orthopedic complications, metabolic, vestibular), (e) had moderately disabling dyskinesias defined as impacting them greater than 25% of day, and (f) were fluent in speaking English. Individuals with PD were randomized by blinded drawing by the participants for training either on or off their usual dosage of dopamine. They were asked to withdraw from their usual dosage of dopamine

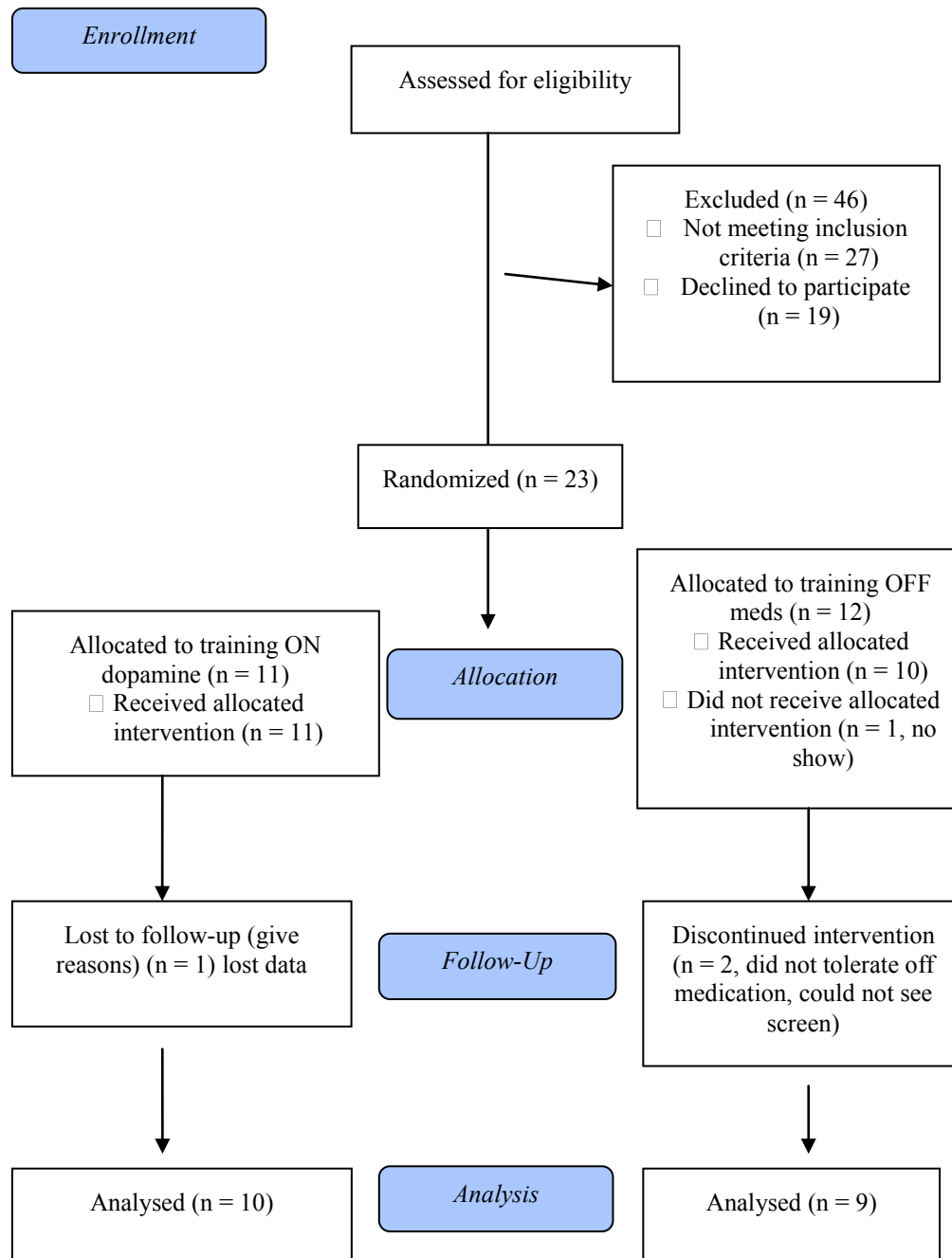


Figure 4.1. The flow diagram of enrollment based on the Consolidated Standards of Reporting Trials (CONSORT; Adapted from Moher et al., 2012).

Table 4.1. Modified Hoehn and Yahr staging system (Hoehn & Yahr, 1967).

Stage	Presentation of disease
Stage 0	No signs of disease
Stage 1	Unilateral disease
Stage 1.5	Unilateral disease plus axial involvement
Stage 2	Bilateral disease, without impairment of balance
Stage 2.5	Mild bilateral disease, with recovery on pull test
Stage 3*	Mild to moderate bilateral disease, some postural instability; physically independent
Stage 4*	Severe disability; still able to walk or stand unassisted
Stage 5*	Wheelchair bound or bedridden unless aided

*Excluded in this study if greater than Stage 2.5 when individuals with PD were off their usual dosage of dopamine.

replacement medication for 12 hours prior to participation for pre-assessment, for each training day and for the retention test. They were allowed to take their usual dosage of dopamine agonists. The removal of dopamine replacement medications only and not the withdrawal of dopamine agonists was decided upon because L-DOPA has a shorter half-life than the dopamine agonists, and it is thought that the impact of L-DOPA removal is sufficient to determine a differential effect (Pahwa et al., 2006). Additionally, individuals were asked to be off their medications for 12 hours for 4 (assessment and training days) days; thus, because of the potential burden on these participants, the minimal removal of drugs was desired (Reichmann & Emre, 2012).

Data Collection

Collection of demographic, health, cognitive, functional, and disease-specific data took place in the morning for consistency of participants' medication states. Participants presented on the first screening day off their usual dosage of dopamine medication to ensure they met the criteria of H&Y, less than 2.5 off their medication, for increased

safety during the training. All participants' demographic and health data included the following: (a) height (needed for accurate assessment of center of pressure), (b) gender, (c) date of birth (age), and (d) blood pressure and heart rate at rest.

Cognitive data was collected on HE, and individuals with PD and included the following: (a) Mini Mental State Exam (MMSE; Folstein, Folstein, & McHugh, 1975) and (b) Trails Making Test (TMT) Part A, B (Corrigan & Hinkeldey, 1987). The MMSE is a clinical assessment tool of cognitive status. The Trails Making test is a reliable and valid measure of distributed attention and working memory (Corrigan & Hinkeldey, 1987). It is a timed cognitive-motor task associated with set shifting (Camicioli, Wieler, de Frias, & Martin, 2008). For individuals with PD, the TMT was performed in both on and off medication state.

Functional data were assessed for HY, HE, and individuals with PD. These measures included the following assessments of balance and mobility: (a) Berg Balance Scale (BBS) and (b) Functional Gait Assessment (FGA). The BBS is a reliable and validated measure of overall balance and fall probability in individuals with neurological disabilities (ICC = 0.94; Tyson & Connell, 2009). The individual is asked to perform multiple tasks (14) performed while standing, such as picking up an object and standing with eyes closed. The FGA is a reliable and validated measure of dynamic balance in individuals with neurological disabilities (reliability = 0.91, 0.93; validity = 0.78; (Leddy et al., 2011). It includes 10 items like walking down the hall while turning their head. The BBS and FGA were used to characterize the sample in terms of potential postural instability deficits (Dibble & Lange, 2006). For individuals with PD, balance and mobility measures were performed in both on and off medication status.

Disease specific data were performed on individuals with PD: (a) the full Unified Parkinson Disease Rating Scale (UPDRS) with disease subtype and motor section score calculated, (b) stage of disease by H&Y (Hoehn & Yahr, 1967), (c) duration of disease, defined as the time from medical diagnosis to the assessment for this study, and (d) the levodopa equivalent daily dose (LEDD) based on the individuals usual dosage of medication. The LEDD (mg/day) was calculated according to the conversion formula reported by Esselink et al., (2004). Disease specific data were assessed in both on and off medication status.

Apparatus

Participants stood on one in-ground force plate (Advanced Medical Technologies Inc., Watertown, MA) capturing force and moment data with sampling set at 1000 Hz to assess kinetic data. Analog data from the force plate allowed calculation of the mean position of the center of pressure (COP), defined as the net reactive forces as determined by the assessing surface, in this case, foot pressure as assessed during standing on a force plate (Horak, Dimitrova, & Nutt, 2005). The location of the participant's center of pressure (COP) position was denoted as a red circle on a white background computer screen located in front of each participant. The experimental task was to move the COP via anterior posterior weight shifts in order track a vertical path denoted by a black dot of a target, which crossed from left to right across the screen in a sinusoidal fashion (22.5 seconds total; LabView software; National Instruments, Corp, Austin, Texas; Figure 4.2). Unknown to the participants, a repeating pattern of target cursor motion was presented interspersed with random patterns. The waves were generated using the polynomial

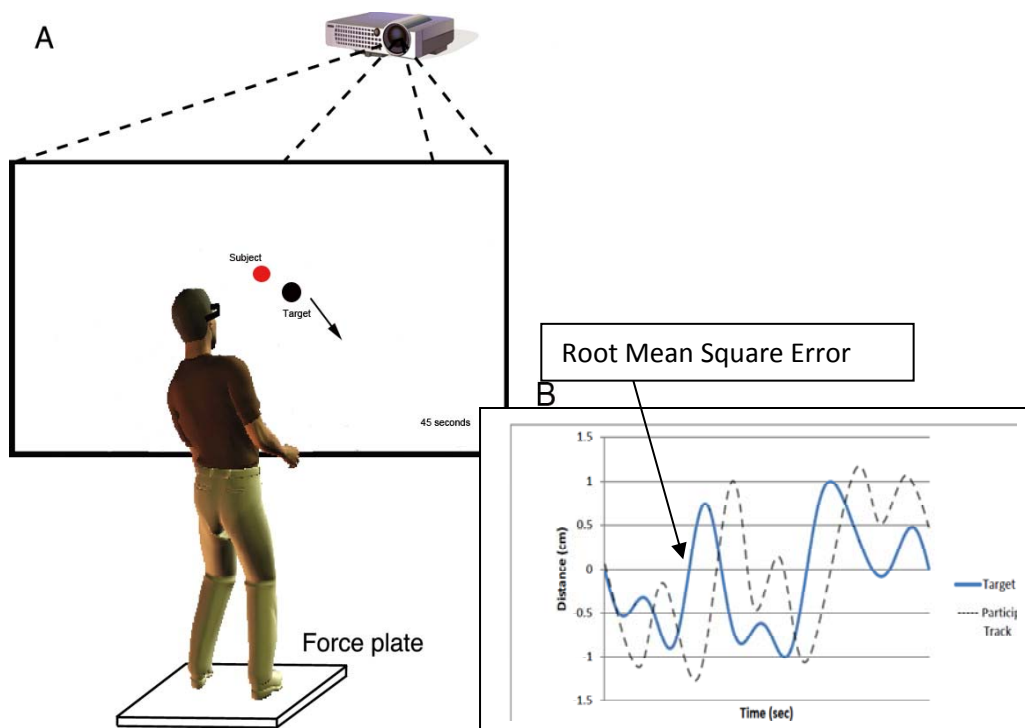


Figure 4.2. Individual standing on force plate shifting their center of pressure anterior and posterior to match the target sinusoidal wave as accurately possible; the difference in the target and actual performance constitutes the Root Mean Square Error. (A) Individual standing on force plate with the target projected as it crosses the screen in a sinusoidal fashion. The individual attempts to accurately track the target by anterior and posterior shifts of their center of pressure. (B) The difference between the target task wave and the participants track performance was quantified by Root Mean square Error (RMSE).

equation described by Wulf and Schmidt, (1997). The repeated segment was constructed by using the same coefficients for every trial. The random segment of the tracking pattern was generated randomly using coefficients ranging from 10 to -10 , and the slope of the random segment was required to be within 20% of the repeated segment at the point of transition.

Attempts were used to equate the difficulty of the random and repeated segments

by first calculating the range of motion of the random segment and rejecting the random if its range of motion was not within 5% of the range of motion of the repeated segment. Secondly, an average velocity criterion was developed using performance data from 12 subjects on 60 different random patterns. Based on a root mean square error (RMSE) analysis, which reflected the overall accuracy of tracking, the random patterns were ranked (1–60) for each participant, and then the ranking averaged across all subjects and identification of waveforms which subjects performed well or poorly on were eliminated. The average velocity for each random wave was calculated. There was a strong pattern showing waves with the lowest RMSE rankings (ranked as “easy”) also had low average velocity. Finally, the average velocity for the repeated cycle was calculated and compared with the values of the random waves. Based on this analysis, an average velocity minimum was determined and waves with an average velocity lower than this value were eliminated from consideration.

Within each individual's practice and retention trials, none of the random segments were repeated during any phase of the experiment. However, to ensure uniformity the same repeated-random tracking patterns were practiced by all of the participants. The trajectories of the target and participants' movements did not leave a trail on the screen and thus, participants were not able to visualize the entire target pattern. Instructions were provided once daily to track the target as accurately as possible on each trial. Participants were not told of the repeated segment.

Task

Participants began each trial standing without shoes quietly on the force plate in a relaxed position with their COP on the force plate at the midpoint of their anterior to posterior limits of their base of support. Initial positioning of the feet was self-selected, and a traced drawing of the feet was used for each subsequent analysis to ensure consistent foot placements. Participants were asked to shift their COP as far as they could, without requiring to step, in a forward and backward weight shift to determine their maximum COP excursion. The excursion of the red target circle during the task was based off 25% of the person's maximum excursion during the calibration trial. This excursion parameter remained throughout the practice and retention training days. Training took place at the same time daily for each individual. A spotter was provided if needed to insure the safety of all participants. Participants were provided a verbal cue of “start” when the tracking was to begin. During the first 5 seconds, the target red circle did not shift in a sinusoidal fashion to allow the individual to orient to the task. This first 5 seconds of tracking was not included in the analysis.

Practice

Two days of training took place, considered the acquisition phase. Two segments (1 random, 1 repeated) were presented to the participant over a 45 second time period, considered a trial. The order of the presentation of the segments in each trial was randomly presented. Subjects rested 25 seconds between every 2 trials. Subjects practiced 6 blocks (1 block = 10 trials) each day for 2 days for a total of 60 trials each day and a total of 120 trials during the acquisition phase. During each day, a 5-minute rest occurred

between each block. Training time per day was 40 minutes with a total time of 80 minutes (with rests). A 1-block retention test occurred on Day 4 (Day 3 was a day of no practice).

Testing of Explicit Knowledge

At the end of the final assessment, participants were interviewed in order to determine whether any repetitions had been detected during the course of the experiment. They were presented with a 10-trial recognition test to assess for explicit knowledge of the repeating sequence. Each individual was shown 10 patterns (sinusoidal waves) on the projected screen. 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 the wave had been presented they were asked if they recognized the pattern as one they had been practicing during the training days. This information was collected as a control variable to determine if participants were aware of the embedded sequence. If individuals were able to recognize two of the three repeating sequences as correct and four of the seven random sequences as incorrect then they were considered to have obtained explicit knowledge of the sequence, as they would be demonstrating better than chance awareness of sequence recognition.

Outcomes, Design and Analysis

The primary dependent variable, sequence-specific learning (SSL) in cm^2 was calculated from the RMSE and reflected the extent to which the participant showed greater improvement on repeated sequences as compared to random ones. A decrease in

RMSE indicated less difference between the participant's trajectory and the target trajectory. Median RMSE was assessed for each segment and the mean of each median was calculated for each block. Thus, over 1 day of practice, 6 blocks were performed containing a value for RMSE on the repeated block and the random blocks. SSL was defined as the difference in RMSE between each random and repeated segment. A negative SSL value meant the individual did not learn the repeated sequence relative to the random sequence (e.g., a random value of 0.6 [not as good a performance] and a repeated value of 0.8 [SSL value equals -0.2] implied that the individual demonstrated better performance on the random sequence compared to the repeated sequence). However, across time, the negative values may be decreasing suggesting that the participants are improving on their performance, but it is not sequence-specific and will be considered improvement in general skill.

To assess changes in acquisition during practice, the mean of blocks 1, 2, 3 and 4, 5, and 6 were calculated each day to provide early and late learning for each day. Thus 4 time points were created, Early Day 1, Late Day 1, Early Day 2, and Late Day 2. SSL values were calculated across time and groups during the first 2 days, defined in this paper as acquisition, when the participants were practicing the motor skill. Secondly, SSL values were also used for assessment of learning at retention by comparing the late day 2 values compared to the single block performed on the retention test. This was used to assess learning and to determine if participants retained the repeating sequence that was embedded.

An additional value was calculated to determine if individuals demonstrated improvement across time by calculating an overall cost or savings in learning. The

cost/savings value was calculated as the difference between early acquisition (Early Day 1 trials) less the one retention block to determine overall trend in performance. Using this difference score, a one way ANOVA was performed for each group to determine if there was a significant cost or savings achieved. A savings was represented by a positive value, indicating the group performed better at retention compared to Early Day 1 trials. If savings did not occur but an improvement in performance was observed that is not SSL, then general skill learning was considered to have occurred.

Data analysis was performed with SPSS version 17.0 (SPSS Inc, Chicago, Illinois) for Windows. The assumptions of parametric statistics were assessed via tests of normality and homogeneity of variance. In all cases, the assumptions were met; therefore, parametric tests were performed. Outliers noted during the assessment trials were assessed for each segment and handled by Winsorization method (Munro, 2005). We compared baseline demographic, health, cognitive, functional, and disease-specific data utilizing a one way ANOVA to determine if there were differences between the groups prior to their participation. An independent samples t test was also performed to determine if there was a difference between groups in SSL on the initial performance on Day 1, block 1.

To address the primary question of the impact of age and disease state, a repeated measures ANOVA was performed on all 4 groups (HY, HE, PDON, PDOFF) across the combined blocks (Early Day 1, Late Day 1, Early Day 2, Late Day 2) of time during acquisition. To assess retention, a repeated measures ANOVA was performed on the 4 groups (HY, HE, PDON, PDOFF) compared at 2 time points (late day 2 practice and retention day, block 1). For each analysis, the time main effect and the group x time

interaction were tested using the within subject criterion of Greenhouse–Geisser. The level of significance was set at $\alpha < 0.05$. Post hoc analysis on the main effects was performed using a Bonferroni correction. Post hoc analyses was performed to determine interaction effect if warranted, using an m-matrix subcommand. To address the secondary aim, the impact of dopamine replacement on acquisition of an implicit motor sequence task in individuals with PD, a repeated measures ANOVA was performed on the 2 groups of individuals with PD (PDON, PDOFF) across the 4 combined blocks (Early Day 1, Late Day 1, Early Day 2, Late Day 2) of time during acquisition (early and late learning across 2 days of practice). Assessment of explicit knowledge was performed based on number of correct answers.

Results

Forty-two individuals were recruited that met the initial criteria (10 HY, 10 HE, 23 individuals with PD). All the HY and HE completed the initial assessment and training. Twenty-three individuals with PD completed the initial assessment and were randomized to either PDON or PDOFF medications. In the PDON group, 11 individuals received the allocated intervention, but one person's data could not be used because of data collection error. Thus, data were complete on 10 individuals in PDON. The 12 individuals randomized to PDOFF ended with 9 individuals completing the training, one was lost to lack of attendance, one was lost to not tolerating being off the medication after starting training, and one was lost to having difficulty seeing the screen.

There were no differences between the HE and PD groups related to age (see Table 4.2). Furthermore, there was no difference between HE and PD groups related to

Table 4.2. Demographic, health, cognitive, functional, and disease-specific data for each group, including mean, standard deviation, range and *p*-value for one-way ANOVA to determine if groups were different at baseline.

Variable	Mean (SD) (Range)				<i>p</i> -value
	HY (N = 10)	HE (N = 10)	PDON (N = 10)	PDOFF (N = 9)	
Age	28.4(6.5) (23–45)	71.0(8.7) (57–87)	68.0(9.1) (52–80)	71.1(7.1) (58–81)	Overall 0.00 Difference between HY and HE, PDON, PDOFF
Gender (M:F)	2:8	3:7	9:1	8:1	
Time since diagnosis (months)			50.5(26.3) (11–84)	90.2(38.3) (35–144)	0.02
Mini Mental State exam	30	29.8(0.4) (29–30)	28.7(1.3) (26–30)	28.6(1.4) (26–30)	Overall 0.00 Difference between HY and PDON, PDOFF; HE and PDON, PDOFF
Berg Balance Scale (Max 56)*	56	55.6(1.3) (52–56)	55.3(1.3) (52–56)	54.6(1.9) (50–56)	0.12
Functional Gait Assessment (Max 30)*	30	28.9(1.0) (27–30)	27.6(1.6) (24–29)	25.9(3.1) (21–30)	Overall 0.00 Difference between HY and PDON, PDOFF; HE and PDOFF; PDOFF and PDON
Trail Making Test Part A*		28.0(11.1) (15.2–48.6)	22.6(6.4) (17.0–38.4)	35.1(13.0) (18.4–64.3)	0.05
Trail Making Test Part B*		66.8(22.7) (36.2–115.1)	87.1(82.5) (27.6–278.3)	72.8(22.4) (41.4–118.3)	0.67
Hoehn and Yahr*			Median 2.0(0.58) (1–2.5)	Median 2.0(0.61) (1–2.5)	0.22
Levodopa Equivalent Daily Dose*			1021.6(791.6) (375–3000)	444.4(490.2) (00–1300)	0.08
UPDRS total*			27.45(11.8) (7–45.0)	35.7(10.6) (20–49.5)	0.13
UPDRS Motor*			13.3(6.7) (2–20.0)	17.8(5.9) (12–25.5)	0.14
RMSE, Sequence- specific learning, Day 1, block 1	–0.03(0.09) –0.10 to 0.04	–0.06(0.10) –0.13 to 0.01	–0.15(0.11) –0.23 to –0.06	–0.12(0.15) –0.24(–0.01)	0.10

*Value reported reflects the score that reflects the dopamine medication state in which the individuals with PD were randomized to.

the BBS and the TMT. The MMSE and the FGA demonstrated a significant difference between the HE and PD groups; however, the values do not suggest either cognitive or balance deficits for our individuals with PD based on clinical guidelines (Bravo & Hebert, 1997; Walker et al., 2007). There was no significant difference noted in SSL during the initial training block (Day 1, block 1) indicating groups were comparable in initial performance capacity.

The primary question addressed the question of age and disease state related to the difference in SSL between all 4 groups during acquisition. When all 4 groups were compared a significant time effect ($F_{2,2,76.8} = 3.25, p = 0.04, \text{power} = 0.63$) and group effect, ($F_{3,35} = 14.68, p < 0.001$) were revealed, but there was not a significant interaction ($p = 0.91$). Post hoc analyses of the main effects found a significant between group difference for only the HY compared to the other three groups and a significant time difference was noted from time 1 to time 4. Overall, individuals improved in performance across time; however, only the HY demonstrated improvement that was sequence-specific while the other groups demonstrated improvement in performance of the general skill. Visual depiction of the performance curves are found in Figure 4.3 with raw values presented in Table 4.3.

Analysis of retention data revealed a significant time ($F_{1,35} = 26.00, p < 0.01$) and group ($F_{3,35} = 6.04, p < 0.01$) main effects, but no interaction effect ($p = 0.11$). Post hoc analyses of the main effects revealed a significant between group difference for only the HY compared to the other three groups, and a significant time difference was noted from time 1 to time 2. However, overall, all individuals showed a decline in their performance on the retention test. Visual depiction of the performance curves are found in Figure 4.4

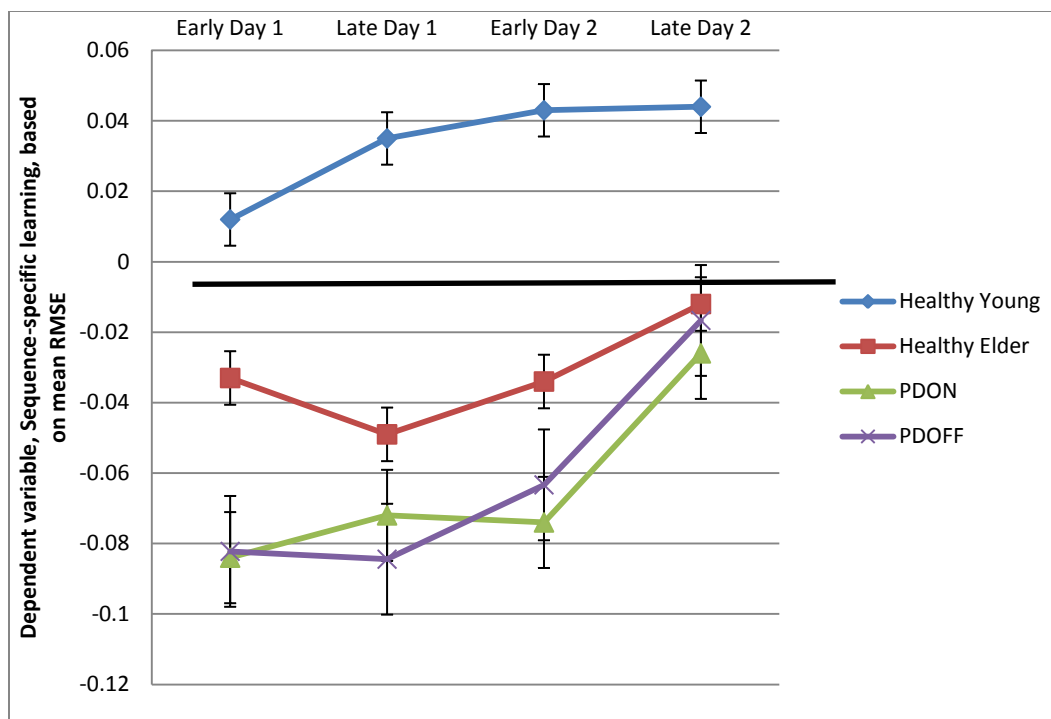


Figure 4.3. Performance curve of acquisition trials, with sequence-specific learning as the dependent variable, assessed with Root Mean Square Error (RMSE) of 4 groups, Healthy Young, Healthy Elder, Parkinson's disease on (PDON) their usual dosage of dopamine and PD off (PDOFF) their usual dosage of dopamine. 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. Decreasing values indicates improved performance across time. Error bars are standard error.

with raw values presented in Table 4.4.

The secondary question was to determine the difference in SSL between individuals who trained on their dopamine replacement (PDON) versus those who trained off their dopamine medication (PDOFF). During acquisition no significant differences were noted for the main effects of time ($F_{1.8, 31.8} = 1.89, p = 0.17, d = 0.61$), or group ($F_{1,17} = 0.01, p = 0.91, d = 0.05$) and interaction ($F_{1.8, 31.8} = 0.06, p = 0.93, d = 0.11$) effects. Visual depiction of the performance curves are found in Figure 4.3 with raw

Table 4.3. Raw mean and standard error values with 95% confidence intervals for sequence-specific learning (SSL) values over 2 days of acquisition. SSL was calculated as the difference between the random and repeated values (random minus repeated); thus, a negative value means the individual did not learn the repeated sequence relative to the random sequence. For example, a repeated value of 0.6 and a random value of 0.8 (indicating not as good a performance on random) would lead to a positive value and sequence-specific learning. A negative value implies **non**-sequence-specific learning or general skill learning if the negative values are decreasing.

Group	RMSE SSL Early Day 1 Mean (SE) 95% CI	RMSE SSL Late Day 1 Mean (SE) 95% CI	RMSE SSL Early Day 2 Mean (SE) 95% CI	RMSE SSL Late Day 2 Mean (SE) 95% CI
Healthy Young	0.01(0.03) -.04 to 0.06	0.04(0.03) -0.01 to 0.09	0.05 (0.02) 0.01 to 0.08	0.04(0.02) 0.00 to 0.09
Healthy Elder	-0.03(0.03) -0.09 to 0.02	-0.05(0.03) -0.10 to 0.00	-0.03(0.02) -0.07 to -0.00	-0.01(0.02) -0.05 to 0.03
PDON	-0.08(0.03) -0.14 to -0.03	-0.07(0.03) -0.12 to -0.02	-0.07(0.02) -0.10 to -0.04	-0.03(0.02) -0.07 to 0.02
PDOFF	-0.08(0.03) -0.14 to -0.03	-0.08(0.03) -0.14 to -0.03	-0.06(0.02) -0.10 to -0.03	-0.02(0.02) -0.06 to 0.03

values presented in Table 4.3.

Determination of the overall performance trends was calculated using a cost/savings variable. The ANOVA results revealed no significant difference between the groups in cost/savings ($p = 0.30$); however, two groups demonstrated a positive value, HY (change score of 0.02) and PDOFF (change score of 0.003), indicating that these 2 groups performed better at retention compared to performance during Early Day 1 (a learning savings). PDON and HE performed worse on retention compared to Early Day 1 (Table 4.4). These results suggest that the HY throughout the paradigm demonstrated better than chance awareness of sequence recognition. The PDOFF group had 4/9 participants acquire explicit knowledge; PDON and HY had 4/10 participants acquire explicit knowledge, and HE participants had 6/10 participants acquire explicit knowledge. Many individuals reported that at times they felt their performance was better, but none of the individuals could state conclusively that a single repeating

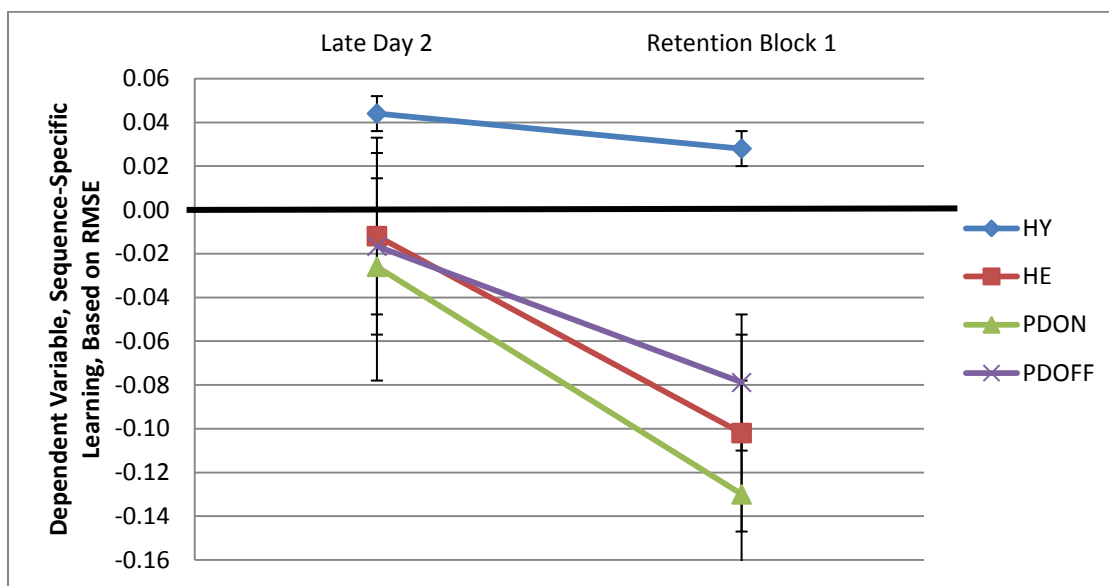


Figure 4.4. Performance curve of end of acquisition trials (Late Day 2) and the final retention trial, with sequence-specific learning as the dependent variable, assessed with Root Mean Square Error (RMSE) of 4 groups: Healthy Young, Healthy Elder, Parkinson's disease on (PDON) their usual dosage of dopamine and PD off (PDOFF) their usual dosage of dopamine. 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 a decline in performance at retention. Error bars are standard error.

sequence was present.

Discussion

The purpose of this study was to assess effects of age, disease state, and dopamine replacement on SSL during acquisition and retention. We hypothesized that all individuals would demonstrate improved SSL during acquisition and with further practice (after retention testing); however, individuals with PD would be less accurate compared to the healthy young (HY) and healthy elder (HE) subjects. We further hypothesized that there would be a difference in SSL during acquisition in individuals with PD based on medication status, such that individuals with PD on their usual dopaminergic medication

Table 4.4. Raw mean and standard error values with 95% confidence intervals for sequence-specific learning (SSL) values for end of acquisition (Late Day 2 trials) and retention for 4 groups. The cost/savings was calculated to describe the trend in performance from the start of the training through the retention test.

Group	RMSE SSL , Late Day 2 Mean (SE) 95% CI	Retention, Block 1 Mean (SE) 95% CI	Cost/Savings Early Day 1 less Retention block 1 Mean (SE), 95% CI	Interpretation of values of cost/ savings from Early Day 1 to Retention block 1
Healthy Young	0.04(0.02) 0.00 to 0.09	0.03(0.03) -0.03 to 0.08	0.02(0.03) -0.04 to 0.08	Savings Sequence-specific learning
Healthy Elder	-0.01(0.02) -0.05 to 0.03	-0.10(0.03) -0.16 to -0.05	-0.07(0.04) -0.16 to 0.02	Cost No learning
PDON	-0.03(0.02) -0.07 to 0.02	-0.13(0.03) -0.19 to -0.08	-0.05 (0.04) -0.15 to 0.05	Cost No learning
PDOFF	-0.02(0.02) -0.06 to 0.03	-0.08(0.03) -0.14 to -0.02	0.003(0.03) -0.06 to 0.07	Savings General skill learning

would be more impaired in SSL than individuals with PD off their dopaminergic medication. Age appeared to account for the primary difference observed on SSL, with only the HY demonstrating a significant improvement in SSL during acquisition. No adverse effect of medication was noted as the individuals with PD did not demonstrate a significant difference in performance on or off their usual dopamine medication during acquisition. Overall, all groups declined in skill at retention relative to the end of acquisition. When accounting for the overall cost/savings both the HY and PDOFF group demonstrated a savings compared to the other groups.

Learning or relearning a skill in a real life setting may involve complex continuous tasks. Individuals with PD in this study did not demonstrate SSL, but individuals with PD off their dopamine did demonstrate general skill learning. Thus, it is important to clarify that individuals with PD are capable of learning a complex, continuous task, and it is not known if with more practice they may demonstrate additional behavioral change.

SSL has been described in the literature as impaired in individuals with PD compared to healthy age-matched controls, and an adverse effect of dopamine replacement has been described; however, our results do not support these prior conclusions (Kwak et al., 2010; Seidler et al., 2006). Importantly, performance on balance, mobility, and working memory do not account for the lack of low rates of SSL shown here. It is possible that other factors mitigate SSL in individuals with PD, such as the type of task utilized and/or the type of memory utilized (i.e., explicit or implicit).

Task type may have contributed to our data failing to support past work that considered age and dopamine replacement. The type of task utilized in this study was a posturally demanding task compared to the traditional MSL task that uses the upper extremity. To our knowledge, this is the first study to address SSL during a posturally demanding sequence in individuals with PD. Because postural instability, an impairment of postural reflexes resulting in reduced limits of stability, is one of the four cardinal movement features of PD, its role in SSL is salient. The pathophysiology of postural instability remains unknown; however, the observed deficit is associated with difficulty in executing and timing responses to external challenges (Matinolli et al., 2007).

Although medications have been found to reduce movement deficits associated with PD, such as tremor at rest, rigidity, akinesia, and bradykinesia, postural instability is typically not mitigated by medication (Grimbergen et al., 2009; Jankovic, 2008). Thus, although the task varies greatly from traditional SSL paradigms, the impact of medication on this task should not have influenced the postural instability of our individuals and be the reason for the limited SSL observed. Furthermore, our individuals with PD did not present with impaired postural stability deficits as measured by functional assessments of

balance and mobility. It should be considered that this type of task may have been more difficult compared to the typical upper extremity paradigms utilized during previous SSL research. Thus, further research is warranted to determine the influence of task difficulty because of additional postural demands on SSL and the impact of medication and age as most SSL occurring in real life situations, such as sit to stand, requires postural demands.

The type of memory utilized in this study may have also contributed to our results differing from the previous reports related to dopamine replacement. This study utilized an implicit task, such that the participant had no explicit knowledge of the repeating sequence. This is in contrast to the one study assessing SSL and the impact of medication replacement, which utilized a task where participants' had explicit knowledge of the task (Kwak et al., 2010). Implicit and explicit learning have been studied both by imaging and experimental paradigms, and results suggest that these systems are dissociated (Knowlton et al., 1996). Explicit learning has been found to be supported by discrete regions within the brain, specifically the hippocampus within the medial temporal lobe, whereas implicit learning appears to be widely distributed throughout multiple brain regions including the BG, cerebellum, amygdala, and the neocortex (Squire & Zola, 1996). Experimental paradigms on individuals with specific brain lesions further support this dissociation as individuals with PD in the early course of the disease have demonstrated difficulty performing implicit tasks while the explicit learning system remains intact (Feigin et al., 2003; Smiley-Oyen et al., 2006; Soliveri et al., 1992). A study by Boyd and Winstein (2006) suggested that providing explicit information to individuals with BG stroke disrupted implicit learning. Because medication would not have been a factor in her sample of individuals with BG stroke,

then the nature of the deficit appears related to the addition of explicit information. It is possible that the impact of explicit information accounted for the deficit in Kwak et al. (2010) rather than dopamine. However, most studies have utilized an implicit SSL paradigm and have not accounted for the influence of dopamine; more information is needed to understand the impact of dopamine replacement on SSL.

Finally, SSL as defined in this study cannot be described as a simple impairment of age, balance, mobility or working memory in this population of individuals with PD. However, a deficit in SSL was present and while they demonstrated improved accuracy during acquisition, they were not as accurate as HY and appeared less accurate compared to HE. The deficit of SSL related to PD, therefore, requires additional analysis to attempt to understand the reason for the deficit. Studies which have assessed SSL related to PD have suggested that the deficit in SSL may be related to the "translation of sequence knowledge into rapid performance" (Seidler et al., 2006, p. 1). This translation into rapid performance has not been associated with impaired motor execution or bradykinesia, and these components were not found to be limited in this study (Boyd et al., 2009; Ghilardi, Eidelberg, Silvestri, & Ghez, 2003). Thus, a further suggestion accounting for the SSL deficit has been that the BG may be responsible for consolidation of information and more specifically with chunking of information (Doyon, 2008; Graybiel, 1998). Chunking has been described as recoding bits of information to form packages or chunks (Miller, 1956). Studies have observed a chunking deficit in individuals with basal ganglia stroke (Boyd et al., 2009), and other studies have suggested that impaired dopamine receptors have been associated with a chunking deficit (Tremblay, Bedard, Levesque et al., 2009; Tremblay, Bedard, Langlois et al., 2010). In this study, we were not able to

determine if a chunking deficit was present; however, the potential influence of dopamine on chunking needs to be considered in future studies. Thus, while overall this study observed primarily an age related deficit in accuracy, more research is warranted to more clearly understand how disease and medication status may impact SSL or not in the task utilized in this study.

It is not known if further practice would have allowed for improved performance by both HE and individuals with PD similar to HY. This study provided equivalent amounts of practice of the repeating sequence as other studies, using a continuous tracking task (Boyd & Winstein, 2006; Shea et al., 2001; Siengsukon & Boyd, 2008; Vidoni & Boyd, 2009). However, as suggested, the difficulty in this task may warrant further practice, and future research is needed to understand the deficit of SSL during this more demanding task. This concept of more practice may be further supported by assessment of the savings and cost of learning. The only group to demonstrate sequence-specific learning was the HY; however, the only group that demonstrated general skill learning across time was the individuals in the PDOFF group, and these results may suggest that these individuals when off their medication were overall learning better. However, this does not account for why the HE did not demonstrate general skill learning.

Limitations and Future Research

Although the results of this study suggest that age, disease state, and dopamine replacement status may influence SSL, they should be interpreted cautiously. Limitations in this study include the method of dopamine removal. However, the method of

withdrawal used in this study is the same methods reported in other studies. We have reported LEDD values, and other studies have not, so a comparison of dosages between studies is not possible. Future work needs to account for the amount of dopamine that individuals with PD are training with in order to better understand the impact of dopamine on learning. An additional limitation is the nature and size of the sample. All participants were recruited as samples of convenience, and the groups were generally small. The HY and HE were primarily females, whereas the PD patients were primarily males. However, there is no evidence that sequence learning is affected by gender in normal populations or in individuals with PD (Deroost et al., 2006). Finally, the lack of observed retention may have been related to a limited amount of observed practice trials performed on the final retention day. While 1 block should suffice, the combined block (Late Day 2) on the final day of acquisition should also be paired with combined blocks on retention. Future work will accommodate the observed performance curves related to the practice trials reported in this study.

Conclusions

The results of this study found that age appeared to have the largest effect on SSL while no adverse effect of medication was noted. However, assessment of the overall improvement in performance across time suggests that only PDOFF and HY demonstrated improved performance: general skill learning and SSL learning, respectively. The type of task performed in this study was a demanding postural task compared to the traditional SSL paradigms using the upper extremity, and task difficulty could account for the lack of observed difference during acquisition. SSL has been

observed to be impaired in individuals with PD. A better understanding of the SSL deficit related to age, disease state, and dopamine replacement is warranted, and a better understanding of the SSL deficit during a complex continuous motor task is warranted.

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CHAPTER 5

PERFORMANCE ACQUISITION OF SPATIAL, TEMPORAL, AND COMBINED ERROR IN INDIVIDUALS WITH PARKINSON DISEASE DURING A STANDING MOTOR SEQUENCE TASK

Abstract

Parkinson disease (PD) is a progressive neurodegenerative disorder that presents with deficits beyond the commonly recognized motor signs, including a deficit in motor sequence learning (MSL). MSL refers to the process by which simple or complex isolated serial movements come to be performed effortlessly as a single unit of movement. Successful performance of sequential tasks requires integration of both spatial and temporal parameters. Results have been mixed related to the deficits in spatial parameters during sequential tasks in individuals with PD. The purpose of this study was to determine which component of a sequential task may be impaired: spatial or temporal parameters. Ten healthy young (HY), 10 healthy elder (HE), and 19 individuals with PD participated in 2 days of practice of a standing continuous tracking task. Overall root mean square error was assessed and decomposed into spatial and temporal parameters across 4 time periods during acquisition. Individuals with PD demonstrated significantly impaired performance on spatial parameters, but not temporal parameters compared to

HY and HE. These results suggest that the learning deficit may not be general but may be related to integration of specific parameters within the sequence, namely regulation of spatial relationships. Further research is warranted to understand if task difficulty and amount of practice influence these deficits in individuals with PD.

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder associated with selective damage of dopaminergic neurons within the basal ganglia (BG) and other regions of the central and peripheral nervous system (Jellinger, 2012). The most clearly recognized sequelae are the motor deficits observed in PD: tremor at rest, muscular rigidity, akinesia (inability to initiate movement) and bradykinesia (slowness of movement), and postural instability (Jankovic, 2008). Additionally, nonmotor deficits may be observed beyond the common motor signs, including a deficit in motor sequence learning (Bailey & Mair, 2006; Dominey et al., 1997; Fama & Sullivan, 2002; Smith & McDowall, 2004).

Motor sequence learning (MSL) refers to the process by which simple or complex isolated serial movements come to be performed effortlessly as single unit of movement (Doyon, 2008; Gheysen et al., 2010) and has been studied experimentally by the serial reaction time task (SRTT) and the continuous tracking task (CTT; Boyd & Winstein, 2006; Nissen & Bullemer, 1987; Wulf et al., 1993). Assessment of MSL during early learning trials finds that individuals with PD are consistently slower overall (delayed reaction time) and less accurate overall than healthy age-matched controls during the performance of repeated sequences of movement (Bischoff-Grethe et al., 2001; Siegert et

al., 2006; van Asselen et al., 2009). These results are not surprising because it has been suggested that the BG are important for sequence learning, including but not limited to consolidation of information and more specifically with chunking of information (Doyon, 2008; Graybiel, 1998). Chunking has been described as recoding bits of information to form packages or chunks (Miller, 1956).

Successful performance of sequential tasks requires integration of both spatial and temporal parameters. Results have been mixed related to the deficits in spatial parameters during sequential tasks such as a SRTT in individuals with PD (Helmuth et al., 2000; Postle et al., 1997; Schwarb & Schumacher, 2009; Shin & Ivry, 2003). To our knowledge no studies have assessed sequence learning related to spatial and temporal parameters utilizing a CTT while standing in individuals with PD. Because a standing CTT may provide higher demands on motor coordination than one performed while sitting, it may allow for better insight into real-life demands, such as sit to stand or balance activities (Pew, 1974; Schmidt & Lee, 2005).

The purpose of this study was to determine which component (spatial or temporal) may be most impaired during a posturally demanding CTT in individuals with PD compared to healthy controls. Additionally, we sought to determine the difference in performance capacity in individuals with PD compared to healthy controls across time. We hypothesized that individuals with PD would present with impaired performance on spatial parameters (a measure of amplitude) compared to healthy controls (Morris et al., 2005).

Methods

Study Design

An experimental study was performed consisting of three groups: Healthy Young (HY), Healthy Elders (HE), and individuals with PD who participated in 2 sequential days of training on a standing continuous tracking task.

Participants

Participants were recruited from medical providers within the Department of Neurology at the University of Utah and community neurologists in the greater Salt Lake City area. Rolling admission occurred over 24 months (June 2011–July 2013). The purpose and procedures of the study were explained to the participants and a consent statement approved by the University of Utah Institutional Review Board was signed. Individuals with PD were included if they had (a) confirmed idiopathic PD according to the UK Brain Bank Criteria (Jankovic, 2008), (b) Hoehn and Yahr stages 1 to 2.5 when OFF medications, (c) 50–90 years of age, and (d) on a stable dosage of dopaminergic medications for the previous 6 months. Individuals were excluded if they (a) had acute medical problems, (b) had uncorrected vision loss, (c) had previous surgical management of PD, (d) had other conditions that affected mobility and balance abilities (arthritis, orthopedic complications, metabolic, vestibular), (e) had moderately disabling dyskinesias defined as impacting them greater than 25% of day, and (f) were non-English speaking. Based on the change reported for the repeated sequences during acquisition for individuals on and off their medication, an a priori power analysis for a repeated measures ANOVA was determined from the average of the small–large interaction effect

sizes (mean, Cohen's $d = 0.58$) observed (Kwak et al., 2010; Muslimovic et al., 2007; Stephan et al., 2011). Seven subjects per group would be needed to achieve a power of 0.80, alpha of 0.05, and a more conservative ANOVA effect size value (f) of 0.25. With an expected attrition rate of 30%, 10 subjects were recruited for each group.

Data Collection

Collection of demographic, health, cognitive, functional, and disease-specific data took place in the morning for consistency of participants' medication states. All individuals' demographic and health data (pre-assessment only) included the following: (a) height, (b) gender, (c) date of birth (age), (d) blood pressure, and (e) heart rate at rest.

Cognitive, functional, and disease-specific data were collected. Cognitive data were assessed for HE and individuals with PD and included (a) Mini Mental State exam (MMSE; Folstein et al., 1975) and (b) Trails Making Test (TMT) Parts A and B (Corrigan & Hinkeldey, 1987). The MMSE is a quick clinical assessment tool of cognitive status. TMT is a reliable and valid measure of distributed attention and working memory (Corrigan & Hinkeldey, 1987). Functional data were assessed for HY, HE, and individuals with PD and included (a) Berg Balance Scale (BBS) and (b) Functional Gait Assessment (FGA). The BBS is a reliable and validated measure of static standing balance, overall balance, and fall probability in individuals with neurological disabilities (ICC = 0.94; Tyson & Connell, 2009). The individual is asked to perform multiple tasks (14) performed while standing, such as picking up an object or standing with eyes closed. The FGA is a reliable and validated measure of dynamic balance in individuals with neurological disabilities (reliability = 0.91, 0.93; validity = 0.78; Leddy et al., 2011). It

includes 10 items like walking down the hall while turning their head. Disease-specific data were assessed on individuals with PD and included (a) the full Unified Parkinson Disease Rating Scale (UPDRS) with disease subtype and motor section score calculated, (b) stage of disease by H&Y (Hoehn & Yahr, 1967), and (c) duration of disease, defined as the time from medical diagnosis to the assessment for this study.

Apparatus

Participants stood on one in-ground force plate (Advanced Medical Technologies Inc., Watertown, MA) capturing force and moment data with sampling set at 1000 Hz to assess kinetic data. Analog data from the force plate allowed calculation of the mean position of the center of pressure (COP), defined as the net reactive forces as determined by the assessing surface, in this case, foot pressure as assessed during standing on a force plate (Horak et al., 2005). Participants adjusted their center of pressure (COP) position by viewing a red circle on a computer screen located in front of them. Initial positioning of the COP was self-selected and a traced drawing of the feet was used for each subsequent analysis to ensure consistent foot placements. The waves were generated using the polynomial equation described by Wulf and Schmidt (1997). The repeated segment was constructed by using the same coefficients for every trial. The random segment of the tracking pattern was generated randomly using coefficients ranging from 10 to -10 . In addition, the slope of the random segment was required to be within 20% of the repeated segment.

Two screening methods were used in an attempt to equate the difficulty of the random and repeated segments. First, the range of motion of the random segment was

calculated and the random wave was rejected if the range of motion was not within 5% of the range of motion of the repeated segment. Second, an average velocity criterion was developed using performance data from 12 subjects on 60 different random patterns. Based on the overall root mean squared error (RMSE) analysis, which reflects the overall accuracy of tracking, the random patterns were ranked (1–60) for each participant and then the ranking was averaged across all subjects. This measure clearly identified waveforms that subjects consistently performed well or poorly on. The average velocity for each random wave was calculated. There was a strong pattern showing waves with the lowest RMSE rankings (ranked as “easy”) also had low average velocity. Finally, the average velocity for the repeated cycle was calculated and compared with the values of the random waves. The value of the repeated wave average velocity was well above that of the “easy” random waves. Based on this analysis, an average velocity minimum was determined, and waves with an average velocity lower than this value were eliminated from consideration.

Within each individual's practice and retention trials, none of the random segments were repeated during any phase of the experiment. However, to ensure uniformity the same repeated-random tracking patterns were practiced by all of the participants. The trajectories of the target and participants' movements did not leave a trail on the screen and thus, participants were not able to visualize the entire target pattern. Instructions were provided once daily to track the target with movement as accurately as possible on each trial. Participants were not told of the repeated segment.

Task

Participants began each trial standing without shoes quietly on the force plate in a relaxed position with their COP on the force plate at the midpoint of their anterior to posterior limits of their base of support. Participants were asked to shift their COP as far as they could without taking a step, in a forward/backward/weight shift to determine their maximum COP excursion. Excursion of the red target circle during the task was based off 25% of the person's actual excursion during this calibration trial. These parameters remained throughout the practice and retention training days. Training took place at the same time daily for each individual. Individuals were required to change their COP in the sagittal plane in a forward/backward motion to follow the sinusoidal wave. A spotter was provided if needed to insure the safety of all participants. The experimental task was to move the COP via anterior posterior weight shifts in order track the sinusoidal path of the target (goal of aligning their red dot with a target black dot; 45 seconds total; LabView software; National Instruments, Corp, Austin, Texas; [Figure 5.1]). Individuals were provided a verbal cue of “start” when the tracking was to begin. During the first 5 seconds, the target red circle did not shift in a sinusoidal fashion to allow the individual to orient to the task. This first 5 seconds of tracking was not included in the analysis.

Practice

Two days of practice took place, considered the acquisition phase. Two segments (1 random, 1 repeated) were presented to the participant over a 45 second time period, considered a trial. The order of the presentation of the segments in each trial was randomly presented.

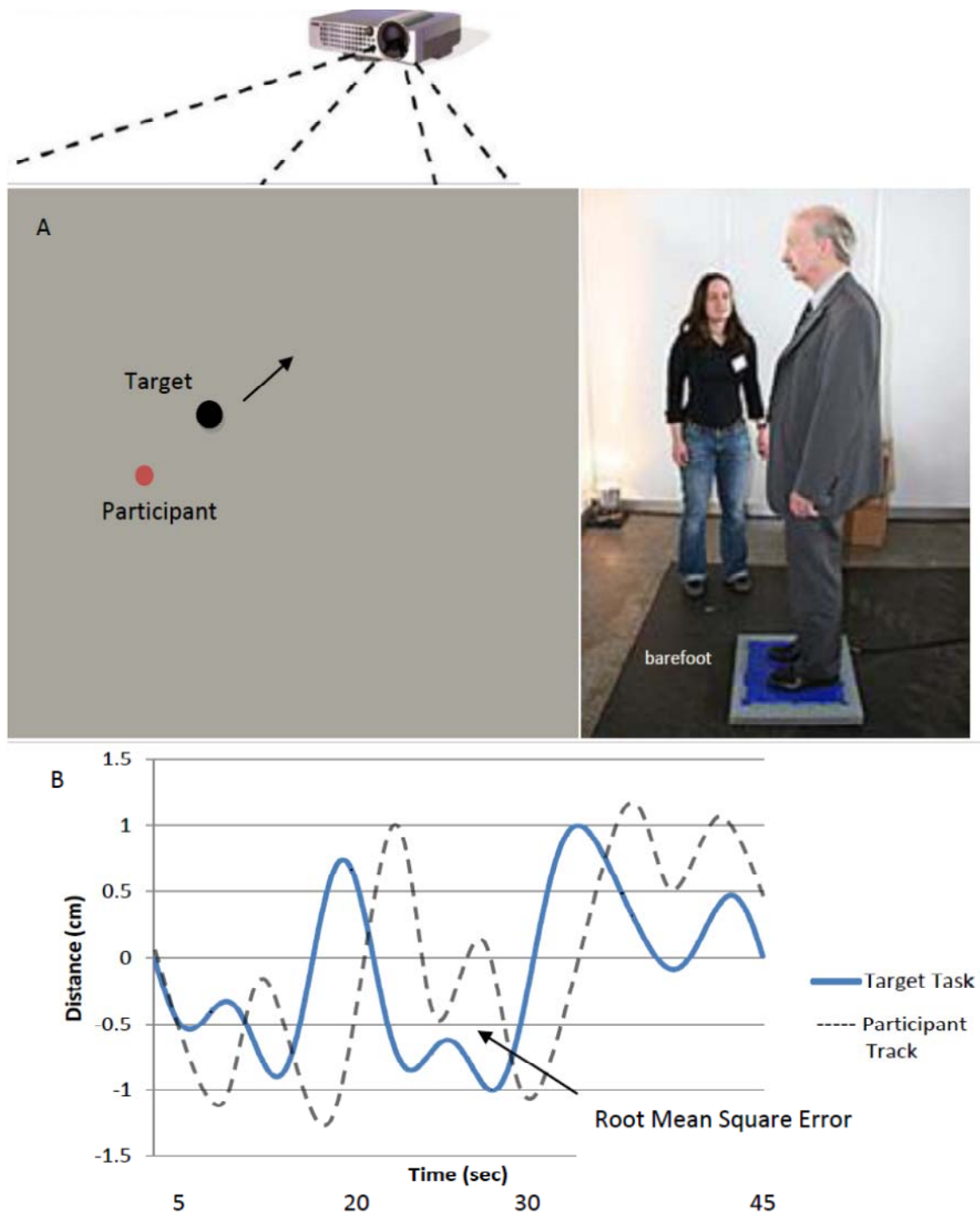


Figure 5.1. Individual stands on a force plate and attempts to track the sinusoidal target as accurately as possible and the difference between the target and actual track comprises the Root Mean Square Error. (A) Individual standing on force plate with the target projected as it crosses the screen in a sinusoidal fashion. The individual attempts to accurately track the target by anterior and posterior shifts of his center of pressure. (B) The difference between the target wave and the participant's performance was quantified by Root Mean Square Error (RMSE).

Subjects rested 25 seconds between every 2 trials. Subjects practiced 6 blocks (1 block = 10 trials) each day for 2 days for a total of 60 trials each day and a total of 120 trials during the acquisition phase. During each day, a 5-minute rest occurred between each block. Training time per day was 40 minutes with a total time of 80 minutes (with rests).

Design and Analysis

Data analysis was performed with SPSS version 17.0 (SPSS Inc, Chicago, Illinois) for Windows. The assumptions of parametric statistics was assessed via tests of normality and homogeneity of variance. In all cases, the assumptions were met; therefore, parametric tests were performed. Outliers noted during the assessment trials were assessed for each segment and handled by the Winsorization method (Munro, 2005). The demographic, cognitive, functional, and disease-specific data are presented in Table 5.1 for each group.

The primary dependent variables were overall tracking accuracy, Root Mean Square Error (RMSE), and spatial and temporal tracking accuracy, decomposed from the Root Mean Square Error (RMSE), which reflected the extent to which the participant matched their movement to the target. A decrease in RMSE indicated a decrease in error and, if decreasing across time, implied that the individual had performed better. The median of the RMSE was assessed for each segment, and the mean of each median was calculated for each block. Thus, over 1 day of practice 6 blocks were performed containing a value for RMSE on the repeated block and the random blocks. To assess early and late learning during acquisition, the mean of blocks 1, 2, 3 and 4, 5, and 6 were

Table 5.1. Demographic characteristics of participants.

Variable	Mean(SD) (95CI)		
	HY (N = 10)	HE (N = 10)	PD (N = 19)**
Age	28.4(6.5) (24–33)	71.0(8.7) (65–77)	69.5(8.2) (66–73)
Gender (M:F)	2:8	3:7	17:2
Mini-Mental State exam (Max 30)	30	29.8(0.4) (29–30)	28.6(1.3)* (28–29)
Berg Balance Scale (Max 56)	56	55.6(1.3) (55–56)	55.4(1.2) (55–56)
Functional Gait Assessment (Max 30)	30	28.9(1.0) (28–30)	26.9(2.6)* (26–28)
Trail Making Test Part A		28.0(11.1) (20–36)	26.3(8.4) (22–30)
Trail Making Test Part B		66.8(22.7) (51–83)	78.8(61.8) (49–109)
Time since diagnosis (months)			69.3(37.6) (51–87)
Hoehn and Yahr			Median, 2.0(0.54) Range (1–2.5)
UPDRS total			28.4(10.6) (23–34)
UPDRS Motor			18.0(14.9) (11–25)
UPDRS Axial			0.84(0.7) (0.5–1.2)
UPDRS PIGD			2.2(1.2) (1.6–2.8)

*p < 0.05 indicating a statistically significant difference between the HE and PD group
**values reflect status of individuals with PD on their usual dosage of dopamine.

calculated each day to provide early and late learning for each day; thus, 4 time points were created, Early Day 1, Late Day 1, Early Day 2, and Late Day 2. For assessment of spatial, temporal parameters and overall RMSE only the repeating segments are reported.

The temporal and spatial subcomponents of tracking accuracy were decomposed from the overall RMSE. This was assessed by using a time series analysis. Temporal tracking accuracy of the movement sequence was measured by serially correlating the data points from the participant's tracking pattern with the target pattern until a maximum

correlation coefficient was achieved (Siengsukon & Boyd, 2009). The maximum correlation coefficient was determined off the maximum number of data points (Boyd & Winstein, 2004). Temporal tracking accuracy was calculated in milliseconds to determine the average time difference between the target marker and the participant's tracking time. Spatial tracking accuracy was measured by determining the amount of RMSE that persisted after the correction for temporal tracking accuracy.

Overall RMSE and spatial and temporal tracking accuracy were calculated for each of the 4 time points. A separate repeated measures ANOVA was performed for each dependent variable (overall RMSE, spatial, and temporal tracking accuracy) with 3 groups (PD, HY, HE) and 4 time points (Early Day 1, Late Day 1, Early Day 2, and Late Day 2). For each analysis, the main effects of group and time, and the group by time interaction were tested using the within subject criterion of Greenhouse-Geisser (Munro, 2005). For the spatial and overall RMSE analysis, a covariate of the initial block (Day 1, block 1) repeating segment was used as there was a significant difference observed between groups at the start of practice for the spatial components and overall RMSE. The level of significance was set at $\alpha < 0.05$. Post hoc analysis was performed using the Least Significant Difference, the main effects of group and time, and l-matrix subcommands to determine the interaction effects. A final analysis was performed using a multiple regression analysis conducted to evaluate how well the spatial and temporal measures predicted overall RMSE in individuals with PD. The predictors were the average spatial and temporal parameters across Day 1 and Day 2 of acquisition, and the criterion variable was the average overall RMSE across acquisition.

Results

Forty-three individuals were recruited that met the initial criteria (10 HY, 10 HE, 23 individuals with PD). All the HY and HE completed the initial assessment and training. Twenty-three individuals with PD completed the initial assessment. Twenty-three individuals with PD were allocated to receive the intervention; however, only 19 individuals are reported on here. One person completed the training, but data was not able to be used because of a data collection error; one person was lost to lack of attendance; one person was lost to having difficulty seeing the screen; and one person was lost to not tolerating being off the medication after starting training. Ten individuals were training on their usual dosage of dopamine, and nine individuals were training off their usual dosage of dopamine (excluding agonists). The training state of our individuals related to medication found no significant difference between these two groups on performance of the repeating sequence at the end of acquisition ($p = 0.81$) and substantial overlap of the 95% confidence intervals for overall RMSE; thus, these groups were combined as individuals with PD (Blackwelder, 1982).

Table 5.1 provides the demographic, balance, mobility, and disease-specific values for the three groups. There was no difference between HE and PD groups related to age, BBS, and TMT. The MMSE and the FGA demonstrated a significant difference between the HE and PD groups; however, the values do not suggest either cognitive or balance deficits for our individuals with PD based on clinical guidelines (Bravo & Hebert, 1997; Walker et al., 2007).

The primary purpose of this study was to examine overall RMSE and the spatial and temporal components of tracking error during a posturally demanding CTT in

individuals with PD compared to healthy controls. For overall RMSE, there was a significant interaction ($F_{4.2,73.7} = 4.67, p < 0.001, \eta^2 = 0.21$) and group effect ($F_{1,35} = 9.96, p < 0.001, \eta^2 = 0.36$), but not a significant time effect ($F_{2.1, 73.7} = 1.27, p = 0.29, \eta^2 = 0.04$; Figure 5.2A). Post hoc analysis for the group effect found a difference between the PD group and the HY and HE ($p < 0.001$) but not the HY and HE ($p = 0.13$). Assessment of the interaction effect finds a significant interaction between both times Early Day 1 and Late Day 1 and times Early Day 1 and Early Day 2 between the PD group and the HE and HY. These results suggest that individuals with PD performed inconsistently and overall made less change in RMSE compared to the other two groups.

For the analysis of spatial error, there were significant group ($F_{2,35} = 13.42, p = 0.00, \eta^2 = 0.43$) and interaction effects ($F_{4.3,75.4} = 2.90, p = 0.02, \eta^2 = 0.14$) but no significant main effect for time ($F_{2.2,75.4} = 0.69, p = 0.52, \eta^2 = 0.02$). Post hoc testing revealed that the group difference was between HY and PD ($p = 0.00$) and HE and PD ($p = 0.00$), but not HE and HY ($p = 0.07$; Figure 5.2B). Post hoc analyses of the observed interaction effect during the spatial error found the difference between the individuals with PD compared to HY and HE from Early Day 1 to Late Day 1 and between individuals with PD compared to HE from Early Day 1 to Early Day 2. These results also suggest that individuals with PD were less consistent and made less change in spatial error across practice as compared to the other two groups.

For the analysis of temporal error, there was a significant effect for time ($F_{2.6,94.3} = 6.56, p < 0.001, \eta^2 = 0.15$) but no significant interaction ($F_{5.2,94.3} = 0.29, p = 0.92, \eta^2 = 0.02$), and no significant group effect ($F_{2,36} = 1.13, p = 0.34, \eta^2 = 0.06$; Figure 5.2C). These results suggest that all groups improved in accuracy of temporal performance

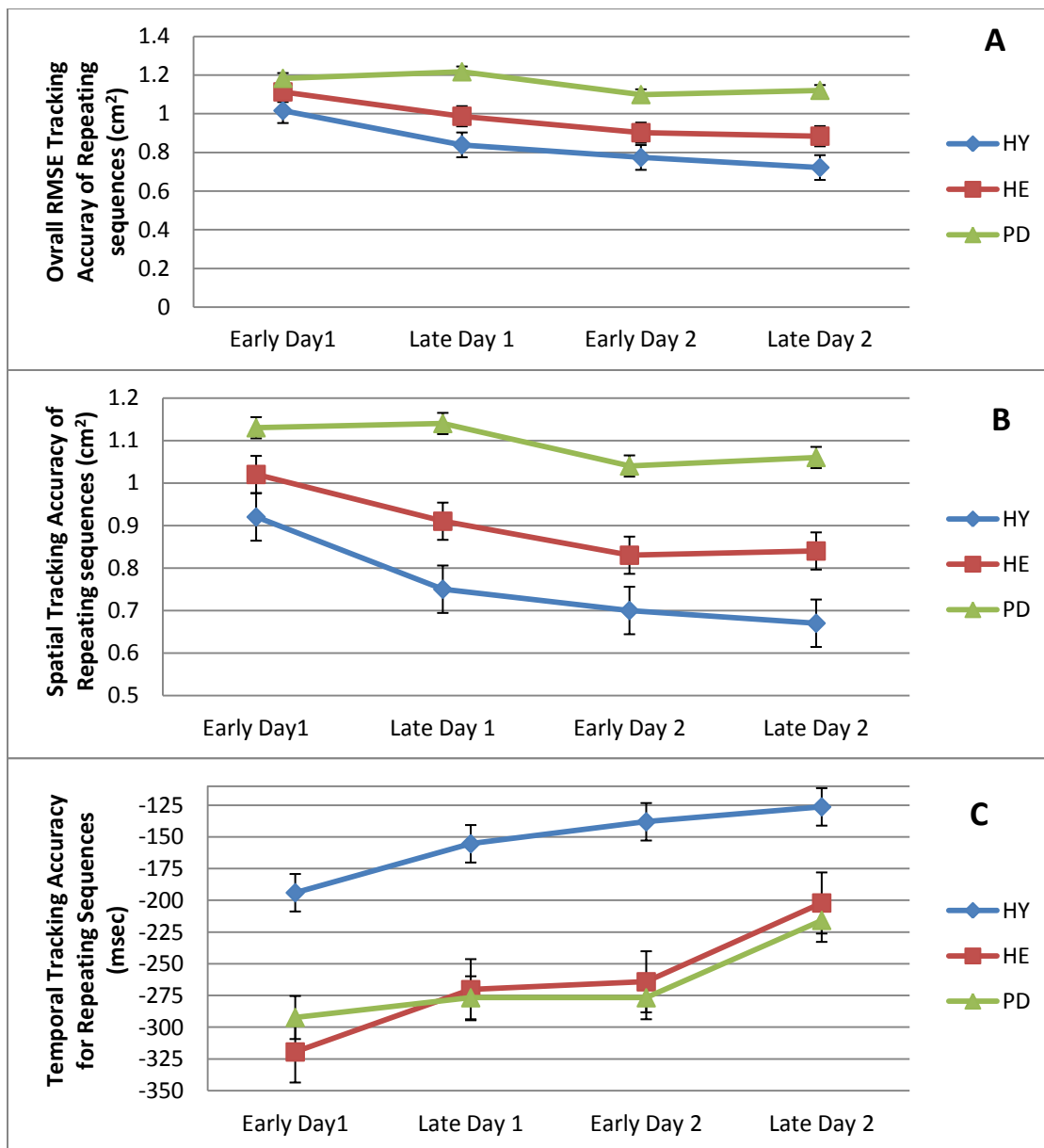


Figure 5.2. Tracking accuracy for the repeating sequences across 4 time points; Early Day 1 (comprised of blocks 1, 2, 3), Late Day 1 (blocks 4, 5, 6), Early Day 2 (blocks 1, 2, 3) and Late Day 2 (blocks 4, 5, 6) for three groups: healthy young (HY), healthy elders (HE), and individuals with Parkinson disease (PD). (A) Overall RMSE (cm²) tracking accuracy, (B) Spatial tracking accuracy (cm²) is remaining error after temporal tracking accuracy was adjusted, and (C) Temporal tracking accuracy (ms) measured by serially correlating the data points from the participant's tracking pattern with the target pattern until a maximum correlation coefficient was achieved.

across time relatively similarly. The relative strength of the individual predictors find the temporal parameters was significant and negatively correlated with overall RMSE on Day 2 only ($\beta = -0.18$, $t(-0.41) = -4.65$, $p < .001$), not Day 1 ($\beta = 0.002$, $t(-0.41) = 0.04$, $p = 0.97$). The spatial parameters were significantly and positively correlated with overall RMSE Day 1 ($\beta = 0.42$, $t(-0.41) = 11.58$, $p < .001$; Day 2 $\beta = 0.53$, $t(-0.41) = 14.17$, $p < .001$). The spatial parameters have a larger contribution to overall RMSE compared to temporal parameters (zero-order correlations, temporal Day 1 = -0.61 , temporal Day 2 = -0.51 , spatial Day 1 = 0.95 , and spatial Day 2 = 0.97).

Discussion

The purpose of this paper was to determine which component(s) of a sequential motor task may be impaired: spatial or temporal parameters of change associated with practicing a standing continuous sequence task. We noted an impairment in overall RMSE, and this was accounted for by a larger influence of change in spatial parameters compared to temporal parameters in the individuals with PD. Furthermore, an interaction effect was observed in individuals with PD at the end of Day 1 compared to the other groups.

Prior research studies have suggested that individuals with PD are consistently impaired in sequence learning compared to healthy age-matched controls, a finding which these results also support (Bischoff-Grethe et al., 2001; Siegert et al., 2006; van Asselen et al., 2009). However, results assessing the influence of a spatial deficit have varied in the literature (Boyd & Winstein, 2004; Helmuth, et al., 2000; Werheid et al., 2003). These differences may be accounted for because of the type of lesion that was

studied, cognitive or motor deficits, or the type of task that was assessed. Additionally, a clear understanding of why an impaired sequence learning deficit persists is not understood, and it has been hypothesized that spatial compatibility may account for the deficit, which these results may suggest.

It has been proposed that there is neuroanatomical overlap, within the Basal Ganglia, of spatial selection and sequence learning and thus successful sequence learning requires successful spatial response selection (Koch & Hoffmann, 2000; Schwarb & Schumacher, 2009; Werheid et al., 2003). However, this type of sequence learning and spatial response selection deficit was not observed in individuals with BG stroke during a CTT of the upper extremity (Boyd & Winstein, 2004). Boyd and Winstein (2004) noted a spatial and temporal deficit was not observed in individuals with a BG stroke. These results do not support our findings, and this may be due to the type of lesion that was assessed. Perhaps, the management of spatial response selection is an impairment dependent on the influence of dopamine within the BG, rather than a general BG deficit. Future studies are warranted to determine the relationship of sequence integration and spatial response selection within the BG.

Additionally, it could be suggested that individuals with PD present with balance or cognitive deficits, which may have impaired spatial and overall accuracy in this study. However, regardless of medication status, we did not observe a difference between our HE and individuals with PD in standing balance as measured by the Berg Balance scale and thus, the individuals with PD were not having difficulty with this standing task because of a balance impairment. The Functional Gait assessment value did differ significantly from the HE; however, the value observed for individuals with PD (26.8) is

not considered a clinically significant value for individuals with gait instability (Leddy et al., 2011). For cognitive measures, we assessed the TMT to determine an impairment in working memory, which has been associated with the dorsolateral prefrontal cortex. The individuals with PD in this study were not impaired on this measure compared to HE. Finally, the MMSE was also utilized to assess a gross cognitive deficit and while a significant difference was observed from HE, the value observed in individuals with PD (28.6) is not considered to be a value indicative of cognitive decline (Athey, Porter, & Walker, 2005). We recognize the limitation of the MMSE and suggest that future research utilize more detailed cognitive assessments when performing MSL tasks due to the role working memory and cognitive factors play in early learning. Regardless of our clinical relationship of cognitive and motor difficulties, an area that was not accounted for in this study was fatigue. The observed interaction effect in individuals with PD may suggest either a motor or cognitive fatigue, which was not assessed during the training. Future research needs to determine the nature of the decline observed at the end of the training on both days.

Additionally, it is possible that our posturally demanding task more closely approximates a more real-life scenario for the challenges that persons with PD will face when learning or relearning new skills. The added postural demand may have inhibited improved spatial compatibility in this paradigm at the expense of sequence integration and future research needs to determine the influence of the relationship of spatial and sequence integration prioritization.

Interestingly, these results suggest a decline in overall RMSE and spatial compatibility in individuals with PD compared to HE and HY from Early Day 1 to Late

Day 1 of practice. This decline may be related to a component of fatigue. While this study provided a similar amount of practice as other studies assessing motor learning utilizing a continuous tracking task, these other studies have assessed the upper extremity rather than a standing task. This comparable amount of practice during a standing task may have been fatiguing for individuals with PD, and future research is warranted to determine the influence of fatigue during this posturally demanding task.

Finally, the deficit of sequence learning in individuals with a BG lesion has been hypothesized to be impaired because of two different reasons. First, it has been suggested that the deficit relates to difficulty in putting the sequences together and has been termed a chunking deficit and secondly, it has been suggested that the deficit arises because of difficulty performing fluent stimulus-to-motor response effectively (Boyd et al., 2009; Helmuth et al., 2000; Shin & Ivry, 2003; Tremblay et al., 2010; Werheid et al., 2003). The results of this study are not able to differentiate the nature of the spatial deficit based on a chunking deficit or a stimulus-to-motor response deficit, and future research is warranted to understand this relationship during a standing implicit motor task.

Conclusions

This study assessed performance of spatial and temporal parameters and overall RMSE accuracy of a standing continuous tracking task in individuals with PD compared to healthy controls. The results suggest that individuals with PD were impaired in overall RMSE as well as spatial parameters but not temporal parameters. These results suggest that the sequence learning deficit may not be general but may be related to learning of specific parameters within the sequence, namely the regulation of spatial components of

the movement. Further research is warranted to understand how task demand and more practice may decrease these deficits in individuals with PD when learning a novel task.

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CHAPTER 6

GENERAL DISCUSSION

The primary aim of this dissertation was to determine sequence-specific acquisition performance and retention learning in individuals with PD (on and off dopaminergic medication) during a continuous sequential task under posturally demanding conditions. We hypothesized that individuals with PD on dopamine replacement medication would demonstrate impaired sequence-specific acquisition performance during the initial 2 days of practice of a continuous sequential postural task compared to individuals with early PD off dopamine replacement medication. Further, we hypothesized the deficit would be sustained at retention learning. The results presented in this study did not support a difference in sequence-specific acquisition performance or retention learning in individuals with PD based on medication status. Both groups demonstrated a trend of improvement during acquisition and inability to retain the information regardless of medication status.

Our secondary aim expanded this concept to determine sequence-specific acquisition performance and retention learning for individuals with PD (one group on dopaminergic medication and one group off dopaminergic medication), healthy elders, and healthy young during a standing continuous sequential task. We hypothesized a difference between the four groups (individuals with early PD on [PDON] and off

[PDOFF] medication, healthy elders [HE], and healthy young [HY]) would be observed in sequence-specific acquisition performance during and at retention of a continuous sequential postural task. The results presented in this study suggested that only the HY were able to demonstrate sequence-specific acquisition. However, there was a trend toward improvement during acquisition with the PDON, PDOFF, and HE, suggesting improvement in acquisition of the general skill. At retention testing, the only group to demonstrate a cost savings related to sequence-specific retention was the HY, and the PDOFF group demonstrated a cost savings related to general skill retention. The HE and PDON group did not demonstrate a cost savings.

Our final hypothesis was exploratory in nature and sought to determine the impact of medication on spatial and temporal tracking accuracy of the repeated segments. Based on the results of the initial study suggesting the lack of a medication effect, the spatial and temporal tracking accuracy was assessed on the individuals with PD combined as one group compared to the HY and HE. The results presented in this study suggested a difference between individuals with PD during overall RMSE and spatial tracking accuracy compared to HY and HE but not during temporal tracking accuracy. These results further suggested an inconsistent performance in individuals with PD during Day 1 of practice compared to HY and HE because of the significant interaction.

Overall, these results are different from expected. We suggest several reasons why this study may have not supported the primary hypotheses related to the impact of dopamine on sequence-specific acquisition and retention and the secondary hypotheses related to age, including 1) the type of task being performed, 2) the type of memory being

utilized, 3) the lack of a dopamine influence, and 4) the influence of dopamine on differing frontostriatal systems.

Limitations and Future Research

This study sought to expand the literature in IMSL by assessing the influence of dopamine during a posturally demanding task. Previous studies had methodological shortcomings, and we sought to account for some of these differences, including the following areas:

1. Kwak et al. (2010) assessed individuals with PD on and off medication; however, they used an explicit task and thus informed the individuals with PD about the presence of a repeated sequence. This study did not see a medication effect in individuals with PD on and off medication utilizing an implicit MSL task. The relationship of dopamine during implicit and explicit paradigms in individuals with PD related to impact of medication needs further exploration.
2. Most studies to date have only assessed the acquisition phase of SSsk learning in individuals with PD; therefore, the capacity of retention learning is warranted. This study assessed SSsk learning through a retention phase, but while we observed a trend in improvement across the days of acquisition practice, we did not observe a sustained retention effect. The meta-analysis performed in this study suggests that individuals with a BG lesion can improve with practice, and it may be that the individuals in this study need even more practice. The amount of practice to retain a skill needs further exploration in individuals with PD.

3. This study sought to control for disease severity, as many studies have not, as we were interested in the influence of dopamine addition and loss. We selected individuals described as less severe (Hoehn and Yahr, stage 1–2.5) and without overt postural instability. However, it is difficult to quantify disease severity related to dopamine loss in individuals with PD related to current clinical measures. Future studies may need to seek a more homogenous group to understand the impact of dopamine addition and loss.
4. Studies utilizing a posturally demanding task on individuals with PD have only assessed Gsk learning. This study sought to determine the ability to integrate SSsk learning during a posturally demanding task. While we observed improvement in Gsk learning during the acquisition phase in our HE and PD groups, we did not see SSsk learning. The relationship of postural control to SSsk learning needs to be further explored as typical daily activities require performance of standing motor sequences, such as sit to stand.
5. Medication has not been found to mitigate deficits of postural instability, and this study sought to determine the influence of the medication dopamine during learning of a posturally demanding sequence task in order to understand the influence of dopamine on learning compared to postural control. This study did not find a medication deficit related to sequence learning, and the influence of the excess demand of the postural control system during sequence learning needs to be further investigated.
6. To our knowledge no studies have assessed sequence learning related to spatial and temporal parameters utilizing a CTT while standing in individuals with PD

and our results suggested a spatial tracking error deficit not related to dopamine response that requires further investigation.

7. Finally, the model that was utilized in this study leading to the hypothesis that dopamine addition and loss would lead to impaired implicit MSL needs to be reconsidered. The neurobiological models that originally supported the influence of dopamine addition and loss were related to different frontostriatal pathways and therefore different learning processes, including probabilistic reversal learning and task set switching, which have differing frontostriatal pathways compared to the proposed MSL frontostriatal circuit (Cools, Barker, Sahakian, & Robbins, 2001; Cools, et al. 2006). A better understanding of the influence of dopamine on these frontostriatal circuits during multiple tasks is warranted.

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APPENDIX A

UNIFIED PARKINSON DISEASE RATING SCALE (UPDRS)

UPDRS Total scale. UPDRS subsection III for axial rating scale (in italics). UPDRS subsection of PIGD (in bold; Adapted from Fahn, Jenner, Marsden, & Teychenne, 1987).

I. MENTATION, BEHAVIOR AND MOOD

1. Intellectual Impairment

0 = None.

1 = Mild. Consistent forgetfulness with partial recollection of events and no other difficulties.

2 = Moderate memory loss, with disorientation and moderate difficulty handling complex problems.

Mild but definite impairment of function at home with need of occasional prompting.

3 = Severe memory loss with disorientation for time and often to place.

Severe impairment in handling problems.

4 = Severe memory loss with orientation preserved to person only. Unable to make judgments

or solve problems. Requires much help with personal care. Cannot be left alone at all.

2. Thought Disorder (Due to dementia or drug intoxication)

0 = None.

1 = Vivid dreaming.

2 = "Benign" hallucinations with insight retained.

3 = Occasional to frequent hallucinations or delusions; without insight; could interfere with daily activities.

4 = Persistent hallucinations, delusions, or florid psychosis. Not able to care for self.

3. Depression

0 = None.

1 = Periods of sadness or guilt greater than normal, never sustained for days or weeks.

2 = Sustained depression (1 week or more).

3 = Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest).

4 = Sustained depression with vegetative symptoms and suicidal thoughts or intent.

4. Motivation/Initiative

0 = Normal.

1 = Less assertive than usual; more passive.

2 = Loss of initiative or disinterest in elective (nonroutine) activities.

3 = Loss of initiative or disinterest in day to day (routine) activities.

4 = Withdrawn, complete loss of motivation.

II. ACTIVITIES OF DAILY LIVING (for both "on" and "off")

5. Speech

0 = Normal.

1 = mildly affected. No difficulty being understood.

2 = moderately affected. Sometimes asked to repeat statements.

3 = Severely affected. Frequently asked to repeat statements.

4 = Unintelligible most of the time.

6. Salivation

0 = Normal.

1 = Slight but definite excess of saliva in mouth; may have nighttime drooling.

2 = Moderately excessive saliva; may have minimal drooling.

3 = Marked excess of saliva with some drooling.

4 = Marked drooling, requires constant tissue or handkerchief.

7. Swallowing

0 = Normal.

1 = Rare choking.

2 = Occasional choking.

3 = Requires soft food.

4 = Requires NG tube or gastrostomy feeding.

8. Handwriting

0 = Normal.

1 = Slightly slow or small.

2 = Moderately slow or small; all words are legible.

3 = Severely affected; not all words are legible.

4 = The majority of words are not legible.

9. Cutting food and handling utensils

0 = Normal.

1 = Somewhat slow and clumsy, but no help needed.

2 = Can cut most foods, although clumsy and slow; some help needed.

3 = Food must be cut by someone, but can still feed slowly.

4 = Needs to be fed.

10. Dressing

0 = Normal.

1 = Somewhat slow, but no help needed.

2 = Occasional assistance with buttoning, getting arms in sleeves.

3 = Considerable help required, but can do some things alone.

4 = Helpless.

11. Hygiene

0 = Normal.

1 = Somewhat slow, but no help needed.

2 = Needs help to shower or bathe; or very slow in hygienic care.

3 = Requires assistance for washing, brushing teeth, combing hair, going to bathroom.

4 = Foley catheter or other mechanical aids.

12. Turning in bed and adjusting bed clothes

0 = Normal.

- 1 = Somewhat slow and clumsy, but no help needed.
- 2 = Can turn alone or adjust sheets, but with great difficulty.
- 3 = Can initiate, but not turn or adjust sheets alone.
- 4 = Helpless.

13. Falling (unrelated to freezing)

- 0 = None.**
- 1 = Rare falling.**
- 2 = Occasionally falls, less than once per day.**
- 3 = Falls an average of once daily.**
- 4 = Falls more than once daily.**

14. Freezing when walking

- 0 = None.**
- 1 = Rare freezing when walking; may have start hesitation.**
- 2 = Occasional freezing when walking.**
- 3 = Frequent freezing. Occasionally falls from freezing.**
- 4 = Frequent falls from freezing.**

15. Walking

- 0 = Normal.**
- 1 = Mild difficulty. May not swing arms or may tend to drag leg.**
- 2 = Moderate difficulty, but requires little or no assistance.**
- 3 = Severe disturbance of walking, requiring assistance.**
- 4 = Cannot walk at all, even with assistance.**

16. Tremor (Symptomatic complaint of tremor in any part of body.)

- 0 = Absent.
- 1 = Slight and infrequently present.
- 2 = Moderate; bothersome to patient.
- 3 = Severe; interferes with many activities.
- 4 = Marked; interferes with most activities.

17. Sensory complaints related to Parkinsonism

- 0 = None.
- 1 = Occasionally has numbness, tingling, or mild aching.
- 2 = Frequently has numbness, tingling, or aching; not distressing.
- 3 = Frequent painful sensations.
- 4 = Excruciating pain.

III. MOTOR EXAMINATION

18. Speech

- 0 = Normal.
- 1 = Slight loss of expression, diction and/or volume.
- 2 = Monotone, slurred but understandable; moderately impaired.
- 3 = Marked impairment, difficult to understand.

4 = Unintelligible.

19. Facial Expression

0 = Normal.

1 = Minimal hypomimia, could be normal "Poker Face".

2 = Slight but definitely abnormal diminution of facial expression.

3 = Moderate hypomimia; lips parted some of the time.

4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more.

20. Tremor at rest (head, upper and lower extremities)

0 = Absent.

1 = Slight and infrequently present.

2 = Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.

3 = Moderate in amplitude and present most of the time.

4 = Marked in amplitude and present most of the time.

21. Action or Postural Tremor of hands

0 = Absent.

1 = Slight; present with action.

2 = Moderate in amplitude, present with action.

3 = Moderate in amplitude with posture holding as well as action.

4 = Marked in amplitude; interferes with feeding.

22. Rigidity (Judged on passive movement of major joints with patient relaxed in sitting position.

Cogwheeling to be ignored.)

0 = Absent.

1 = Slight or detectable only when activated by mirror or other movements.

2 = Mild to moderate.

3 = Marked, but full range of motion easily achieved.

4 = Severe, range of motion achieved with difficulty.

23. Finger Taps (Patient taps thumb with index finger in rapid succession.)

0 = Normal.

1 = Mild slowing and/or reduction in amplitude.

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.

3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.

4 = Can barely perform the task.

24. Hand Movements (Patient opens and closes hands in rapid succession.)

0 = Normal.

1 = Mild slowing and/or reduction in amplitude.

- 2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
- 3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
- 4 = Can barely perform the task.

25. Rapid Alternating Movements of Hands (Pronation-supination movements of hands, vertically and horizontally, with as large an amplitude as possible, both hands simultaneously.)

- 0 = Normal.
- 1 = Mild slowing and/or reduction in amplitude.
- 2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
- 3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
- 4 = Can barely perform the task.

26. Leg Agility (Patient taps heel on the ground in rapid succession picking up entire leg. Amplitude should be at least 3 inches.)

- 0 = Normal.
- 1 = Mild slowing and/or reduction in amplitude.
- 2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
- 3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
- 4 = Can barely perform the task.

27. *Arising from Chair*

(Patient attempts to rise from a straight-backed chair, with arms folded across chest.)

- 0 = Normal.
- 1 = *Slow; or may need more than one attempt.*
- 2 = *Pushes self up from arms of seat.*
- 3 = *Tends to fall back and may have to try more than one time, but can get up without help.*
- 4 = *Unable to arise without help.*

28. ***Posture***

- 0 = ***Normal erect.***
- 1 = ***Not quite erect, slightly stooped posture; could be normal for older person.***
- 2 = ***Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.***
- 3 = ***Severely stooped posture with kyphosis; can be moderately leaning to one side.***
- 4 = ***Marked flexion with extreme abnormality of posture.***

29. ***Gait***

0 = Normal.

1 = Walks slowly, may shuffle with short steps, but no festination (hastening steps) or propulsion.

2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.

3 = Severe disturbance of gait, requiring assistance.

4 = Cannot walk at all, even with assistance.

30. Postural Stability (Response to sudden, strong posterior displacement produced by pull on shoulders

while patient erect with eyes open and feet slightly apart. Patient is prepared.)

0 = Normal.

1 = Retropulsion, but recovers unaided.

2 = Absence of postural response; would fall if not caught by examiner.

3 = Very unstable, tends to lose balance spontaneously.

4 = Unable to stand without assistance.

31. Body Bradykinesia and Hypokinesia (Combining slowness, hesitancy, decreased arm swing, small amplitude, and poverty of movement in general.)

0 = None.

1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.

2 = Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.

3 = Moderate slowness, poverty or small amplitude of movement.

4 = Marked slowness, poverty or small amplitude of movement.

IV. COMPLICATIONS OF THERAPY (In the past week)

A. DYSKINESIAS

32. Duration: What proportion of the waking day are dyskinesias present? (Historical information.)

0 = None

1 = 1–25% of day.

2 = 26–50% of day.

3 = 51–75% of day.

4 = 76–100% of day.

33. Disability: How disabling are the dyskinesias?

(Historical information; may be modified by office examination.)

0 = Not disabling.

1 = Mildly disabling.

2 = Moderately disabling.

3 = Severely disabling.

4 = Completely disabled.

34. Painful Dyskinesias: How painful are the dyskinesias?

0 = No painful dyskinesias.

1 = Slight.

2 = Moderate.

3 = Severe.

4 = Marked.

35. Presence of Early Morning Dystonia (Historical information.)

0 = No

1 = Yes

B. CLINICAL FLUCTUATIONS

36. Are "off" periods predictable?

0 = No

1 = Yes

37. Are "off" periods unpredictable?

0 = No

1 = Yes

38. Do "off" periods come on suddenly, within a few seconds?

0 = No

1 = Yes

39. What proportion of the waking day is the patient "off" on average?

0 = None

1 = 1–25% of day.

2 = 26–50% of day.

3 = 51–75% of day.

4 = 76–100% of day.

C. OTHER COMPLICATIONS

40. Does the patient have anorexia, nausea, or vomiting?

0 = No

1 = Yes

41. Any sleep disturbances, such as insomnia or hypersomnolence?

0 = No

1 = Yes

42. Does the patient have symptomatic orthostasis?

(Record the patient's blood pressure, height and weight on the scoring form)

0 = No

1 = Yes

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APPENDIX B

MODIFIED HOEHN AND YAHR STAGING

Modified Hoehn and Yahr Staging of disease progression (Adpated from Hoehn & Yahr, 1967).

STAGE 0 = No signs of disease.

STAGE 1 = Unilateral disease.

STAGE 1.5 = Unilateral plus axial involvement.

STAGE 2 = Bilateral disease, without impairment of balance.

STAGE 2.5 = Mild bilateral disease, with recovery on pull test.

STAGE 3 = Mild to moderate bilateral disease; some postural instability; physically independent.

STAGE 4 = Severe disability; still able to walk or stand unassisted.

STAGE 5 = Wheelchair bound or bedridden unless aided.

References

Hoehn, M. M., & Yahr, M. D. (1967). Parkinsonism: onset, progression and mortality. *Neurology*, *17*(5), 427–442.

APPENDIX C

UK BRAIN BANK CLINICAL DIAGNOSTIC CRITERIA

Table C1. UK Parkinson Disease Society Brain Bank Clinical Diagnostic Criteria
(Adapted from Hughes, Daniel, Kilford, & Lees, 1992)

Inclusion Criteria	Exclusion Criteria	Supportive Criteria
Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions)	History of repeated strokes with stepwise progression of parkinsonian features	(Three or more required for diagnosis of definite PD)
	History of repeated head injury	Unilateral onset
	History of definite encephalitis	Rest tremor present
And at least one of the following:	Oculogyric crises	Progressive disorder
Muscular rigidity	Neuroleptic treatment at onset of symptoms	Persistent asymmetry affecting side of onset most
4-6 Hz rest tremor	More than one affected relative	Excellent response (70–100%) to levodopa
Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction	Sustained remission	Severe levodopa-induced chorea
	Strictly unilateral features after 3 yr	Levodopa response for 5 yr or more
	Supranuclear gaze palsy	Clinical course of 10 yr or more
	Cerebellar signs	
	Early severe dementia with disturbances of memory, language, and praxis	
	Early severe autonomic involvement	
	Babinski sign	
	Presence of cerebral tumour (sic) or communicating hydrocephalus on CT scan	
	Negative response to large doses of L-dopa if malabsorption excluded)	
	MPTP exposure	

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- Hughes, A. J., Daniel, S. E., Kilford, L., & Lees, A. J. (1992). Accuracy of clinical diagnosis of idiopathic Parkinson's disease: A clinic-pathological study of 100 cases. *Journal of Neurology, Neurosurgery and Psychiatry*, 55(3), 181–184.

APPENDIX D

VISUAL OF PRACTICE PARADIGM

Acquisition Phase: Total time/block: 9.2 minutes
 Time/block →
 Day 1 (Block 1)

T1	T2	T3	T4	T5	T6	T7	T8	T9	T10
R	R	R	P	R	R	R	R	P	R
P	P	P	R	P	P	P	P	R	P
45s	45s	45s	45s	45s	45s	45s	45s	45s	45s
xR, xP	xR, xP	xR, xP	xR, xP	xR, xP	xR, xP	xR, xP	xR, xP	xR, xP	xR, xP
r	r	r	r	r	r	r	r	r	r
25s	25s	25s	25s	25s	25s	25s	25s	25s	25s
5 minute rest									

Day 1 (Block 2)

T1	T2	T3	T4	T5	T6	T7	T8	T9	T10
R	R	R	P	R	R	R	R	P	R
P	P	P	R	P	P	P	P	R	P
45s	45s	45s	45s	45s	45s	45s	45s	45s	45s
xR, xP	xR, xP	xR, xP	xR, xP	xR, xP	xR, xP	xR, xP	xR, xP	xR, xP	xR, xP
r	r	r	r	r	r	r	r	r	r
25s	25s	25s	25s	25s	25s	25s	25s	25s	25s
5 minute rest									

The above paradigm is repeated for 6 blocks.
DAY 2 IS THE NEXT CONSECUTIVE DAY AND IS THE SAME PRACTICE PARADIGM AS ON DAY 1.

Retention Phase: 1 day off, retention is on Day 4
 Retention 1 block only

T1	T2	T3	T4	T5	T6	T7	T8	T9	T10
R	R	R	P	R	R	R	R	P	R
P	P	P	R	P	P	P	P	R	P
45s	45s	45s	45s	45s	45s	45s	45s	45s	45s
xR, xP	xR, xP	xR, xP	xR, xP	xR, xP	xR, xP	xR, xP	xR, xP	xR, xP	xR, xP
r	r	r	r	r	r	r	r	r	r
25s	25s	25s	25s	25s	25s	25s	25s	25s	25s

T = Trial (45 seconds), includes 3 segments: R (Yellow) = Repeated sequence (hypothetical depiction of random presentation of the random/repeated sequences)
 Set of 10 trials equals a block
 r=Rest (25 seconds)
 Analysis:
 xR = median of each random segment per trial, then the mean (\bar{x}) of each block is assessed
 xP = median of each repeated segment per trial, then the mean (\bar{x}) of each block is assessed

APPENDIX E

EFFECT SIZE CALCULATIONS FOR A VARIETY
OF RELATED STUDIES

Table E.1. Effect size (Cohen's *d*) calculations for a variety of studies with similar assessment to the proposed study by Hayes for within group, between group and interaction effect sizes. Note that the studies having varying aspects of similarity to this research study.

<i>Author</i>	<i>Groups and sample size</i>	<i>Task</i>	<i>Performance outcome</i>	<i>Within group effect size</i>	<i>Between group effect size</i>	<i>Interaction effect size (d)</i>
Acquisition performance (Primary aim 1)						
<i>Muslimovic et al., 2007</i>	<i>NMPD: 24 HC: 44</i>	<i>SRTT</i>	<i>Acquisition (1 day)</i>	<i>1.32</i>	<i>0.26 No diff</i>	<i>0.33 No diff</i>
<i>Muslimovic et al., 2007</i>	<i>Total PD: 95 mixed on/off meds HC: 44</i>	<i>SRTT</i>	<i>Acquisition (1 day)</i>	<i>1.18</i>	<i>0.43 No diff</i>	<i>0.28 No diff</i>
<i>Boyd et al., 2009</i>	<i>BG stroke: 13, HC: 13</i>	<i>SRTT</i>	<i>Acquisition (2 days)</i>	<i>1.71</i>	<i>NR</i>	<i>0.56 Diff</i>
<i>Siengsukon & Boyd, 2009</i>	<i>BG stroke: 41, HC: 40</i>	<i>CTT</i>	<i>Acquisition (1 day)</i>	<i>0.69</i>	<i>0.44 Diff</i>	<i>0.21 No diff</i>
<i>Seidler et al., 2007</i>	<i>PD: 8 on meds, HC: 8</i>	<i>SRTT</i>	<i>Acquisition (1 day)</i>	<i>2.38 Diff</i>	<i>NR</i>	<i>NR</i>
<i>Kwak et al., 2010</i>	<i>PD 7 on meds, PD 7 off meds</i>	<i>SRTT</i>	<i>Acquisition (1 day, early phase)</i>	<i>2.85</i>	<i>1.60</i>	<i>1.03</i>
Sequence-specific acquisition performance, (difference between random and repeated sequences during acquisition) (Primary aim 2)						
<i>Siegert et al., 2006</i>	<i>PD: 67 on meds, HC: 87</i>	<i>SRTT</i>	<i>Meta-analysis</i>	<i>NR</i>	<i>0.73</i>	<i>NR</i>
<i>Seidler et al., 2007</i>	<i>PD: 8 on meds, HC: 8</i>	<i>SRTT</i>	<i>Acquisition (1 day)</i>	<i>NR</i>	<i>Stated as not significant</i>	<i>NR</i>
<i>Kwak et al., 2010</i>	<i>PD 7 on meds, PD 7 off meds</i>	<i>SRTT</i>	<i>Acquisition (1 day, early phase)</i>	<i>3.03 off medication .39 on medication No diff</i>	<i>NR</i>	<i>NR</i>
<i>Muslimovic et al., 2007</i>	<i>NMPD: 24 HC: 44</i>	<i>SRTT</i>	<i>Acquisition (1 day)</i>	<i>2.00</i>	<i>0.26 No diff</i>	<i>0.26 No diff</i>
<i>Muslimovic et al., 2007</i>	<i>Total PD: 95 mixed on/off meds HC: 44</i>	<i>SRTT</i>	<i>Acquisition (1 day)</i>	<i>2.05</i>	<i>0.46 Diff</i>	<i>0.46 Diff</i>
<i>Stephan et al., 2011</i>	<i>PD: 39 on meds, HC: 39</i>	<i>SRTT</i>	<i>Acquisition (1 day, early phase)</i>	<i>NR</i>	<i>0.41 No diff</i>	<i>0.52 Diff</i>
Sequence-specific learning scores have not been assessed (difference between random and repeated during a retention test)						

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