Does practice of multi-directional stepping with auditory stimulation improve movement performance in patients with Parkinson's disease

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DOES PRACTICE OF MULTI-DIRECTIONAL STEPPING WITH AUDITORY STIMULATION IMPROVE MOVEMENT PERFORMANCE IN PATIENTS WITH PARKINSON’S DISEASE?

A Dissertation

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in

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by
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December 2009
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ADL</td>
<td>Activities of Daily living</td>
</tr>
<tr>
<td>BG</td>
<td>Basal Ganglia</td>
</tr>
<tr>
<td>DSD</td>
<td>Direction Switch Duration</td>
</tr>
<tr>
<td>C</td>
<td>Cue group</td>
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<td>NC</td>
<td>No Cue group</td>
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<td>DGI</td>
<td>Dynamic Gait Index</td>
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<td>FMRI</td>
<td>Functional Magnetic Resonance Imaging</td>
</tr>
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<td>FOGQ</td>
<td>Freezing Of Gait Questionnaire</td>
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<td>MMSE</td>
<td>Mini-Mental State Examination</td>
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<tr>
<td>PD</td>
<td>Parkinson’s Disease</td>
</tr>
<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
</tr>
<tr>
<td>POST</td>
<td>Post test</td>
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<td>Pre test</td>
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<tr>
<td>PT</td>
<td>Physical Therapy</td>
</tr>
<tr>
<td>RAS</td>
<td>Rhythmic Auditory Stimulation</td>
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<tr>
<td>RT</td>
<td>Reaction Time</td>
</tr>
<tr>
<td>RTW</td>
<td>Retention Week</td>
</tr>
<tr>
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<td>Step Number</td>
</tr>
<tr>
<td>SL</td>
<td>Step Length</td>
</tr>
<tr>
<td>SH</td>
<td>Step Height</td>
</tr>
<tr>
<td>TUG</td>
<td>Timed Up and Go TEST</td>
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<tr>
<td>UPDRS</td>
<td>Unified Parkinson’s Disease Rating Scale</td>
</tr>
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<td>VEL</td>
<td>Peak step velocity</td>
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ABSTRACT

Parkinson’s disease (PD) is a debilitating neurodegenerative disorder causing many physical limitations. Rhythmic auditory stimulation (RAS) influences motor complications not alleviated by medicine and has been used to modify straight line walking in this population. However, motor complications are exacerbated during more complex movements including those involving direction changes. Thus immediate RAS effects on direction switch duration (DSD) and other kinematic measures during a multi-directional step task were investigated in PD patients. Long term RAS application was also explored by evaluating functional gait and balance and kinematic step measures before and after 6 weeks of multi-directional stepping either with (Cue, C group) or without (No cue, NC group) RAS use. Evaluations were also administered 1, 4 and 8 weeks after training termination. Kinematic measures were collected during stepping without, then with RAS for the C group and without RAS for the NC group. Step testing/training was performed at slow, normal and fast speeds in forward, back and side directions.

Participants with PD switched step direction during the stepping task faster with RAS use before training. Like straight line walking RAS application influenced the more complex task of direction switching and counteracted the well-known bradykinesia in PD.

After training both groups improved their functional gait and balance measures and maintained balance improvements for at least 8 weeks. Only the C group retained gait improvements for at least 8 weeks after training termination. Adding RAS resulted in functional benefits not observed in training without it.

Kinematic measures compared before and after step training clarified the underlying contributors to functional performances. Both groups reduced the variability of DSD. The C group participants maintained this alteration longer. DSD reduction also occurred after training
and was retained for at least 8 weeks for this group. These outcomes further support the advantages of adding RAS to training regimens for those with PD.

The current results indicate that RAS effects are not limited to simple activities like straight line walking. Moreover, RAS can be used for improving and maintaining improvements longer in activities involving various forms of transition which present most difficulties for those with PD.
CHAPTER 1: INTRODUCTION

Parkinson’s disease (PD) is a neurodegenerative disorder first introduced by James Parkinson in Essay on the Shaking Palsy in 1817 as “Paralysis agitans” [1]. PD is the most common neurodegenerative disease after Alzheimer’s disease with an annual incidence of 13.4 in 10,000 Americans [2]. The main problem in PD is the dopaminergic deficiency of the basal ganglia (BG) [3]. Under normal conditions dopamine release allows the basal ganglia to serve as an internal trigger, enabling movements to occur in a sequential manner. Disruption of dopamine due to PD disrupts the normal functioning of the basal ganglia, thus voluntary movements. Consequently, motor deficits remain a primary complaint of patients from this population.

Despite the arduous efforts of scientists that have increased our knowledge of the disease, there is neither a cure for PD nor a definitive treatment for its symptoms. Current rehabilitation techniques provide a means for reducing some of the motor complications associated with PD [4] that are not relieved with medication or surgical interventions. Use of external stimuli to help trigger movement has received special attention, as PD patients show the ability to improve some of their symptoms under externally triggered conditions that do not occur with other treatments (i.e. movement variability and efficiency).

External Stimulation

“Kinesia paradoxical” refers to the ability of PD patients to produce normal movements under certain conditions. The use of external stimulation is one condition that can enable patients to perform a motor task more like their healthy peers. Such ability has been associated with gaining direct access to other areas of the motor cortex through bypassing the basal ganglia-supplementary motor area (BG-SMA) pathway under external stimulation [4-7]. This was observed directly in a study on regional cerebral flow measures, where authors reported less activity in SMA and putamen cortical areas in PD patients during an internally driven task but
similar activity of the cortical areas of PD patients to that of controls during an externally (auditory) driven task [7].

Visual stimuli [8-10], cutaneous triggers such as vibration [11] and electrical stimulation [12] and auditory stimulation [13, 14] are types of external stimulation used successfully in assisting PD patients alter movement. Although auditory and visual cues are the most common modalities used as external stimuli for treatment of PD symptoms, there is evidence that rhythmic auditory stimulation (RAS) may have benefits over visual cues. The termination of activation of the auditory specific brain areas upon removal of RAS is unlike the continuous activity of visual specific brain areas after removal of visual stimulation. This phenomenon is interpreted as direct transfer of auditory information to a stable motor output [15] and/or inadequacy of the CNS to direct generation of a motor response in response to visual stimuli [16]. Encoding temporal characteristics of rhythmic visual stimulation to the auditory cortex accounts for the prolonged brain activity of the visual modality [17]. Increase in excitability of spinal motor neurons via the reticulo-spinal pathway in response to an unexpected noise [18] and facilitation of the H-reflex in response to a low threshold single auditory sound [19] are evidence for sub-cortical processing of auditory stimuli [20, 21] and add to the potential benefits of its use. Superiority of RAS to visual stimulation is evident with better performance of normal participants in synchronizing and syncopating a movement to the former modality when compared to the latter. Because syncopation is considered more complex due to additional cognitive demands this finding suggests that RAS is easier to follow regardless of the task complexity [15]. Individuals have a higher tendency to match the pattern of their finger tapping to auditory distracters during a visual synchronization task when compared to the opposite condition [22]. In presence of both RAS and visual stimuli the temporal pattern of the inter response interval (IRI) of finger tapping [23] and the benefits of improving gait velocity and
stride length [24] are similar to that of auditory alone. Moreover, reaction time is longest for vision, followed by that of touch, then by audition [25], allowing for faster initiation of motor responses to auditory cues than the other senses.

The advantages of auditory stimulation use for motor responses are numerous. Auditory stimulation offers superior temporal organization of movement and perception, and thus appears to be the most appropriate external stimulation modality for motor control. Moreover, RAS seems to activate neural areas that remain functional in PD patients, thus may offer benefits in rehab for this population that are not offered through other methods.

**Methodological Considerations for Intervention**

The current literature involving use of different therapeutic techniques incorporate several characteristics of a good intervention in a guideline suggested for use with PD patients after a comprehensive Physical Therapy (PT) literature review. This guideline suggests avoiding simultaneous tasks especially at initial stages of therapy for PD patients and advises breaking a sequential task into its components at initial stages of the disease for PD patients [4]. This guideline results in training regimes that follow several motor learning strategies designed to promote better learning and retention of certain skills, including the practice of single simple tasks prior to increasing task difficulty. The following text reveals additional factors that should be considered when designing training regimens for those with PD.

**Measures of Evaluation**

Tests of balance and mobility and kinematic/kinetic measures of movement performance offer insight to movement dysfunction in different populations, including PD. In general PD patients who experience falls perform poorly on the functional reach test [26, 27], as well as various balance and gait measures such as tandem gait, tandem stance and turning around, the dynamic gait index (DGI) and the Tinetti gait and balance tests [28]. PD patients with higher
rates of falls also show a significant amount of increase in the number of steps when required to turn [29] and during the Timed-Up-and-Go (TUG) test [27]. Functional outcomes are important for evaluation of the effectiveness of a program because they offer insight to the potential for individual success in more “natural” settings and have been linked fall risk. In contrast, kinematic/kinetic measures offer insight to specific functional performances that can help explain functional outcomes. Slower movement velocity common in PD patients [8], which does not allow for quick recovery could be from decreases in movement distance, movement frequency or both. Kinematic analyses of performances help determine the movement characteristics and the potential causal factors of functional deficits and training results. Testing of functional outcomes without movement kinematics/kinetics or vice versa may limit the generalization of the findings, hence by testing different measures one can offer greater insight needed to better understand the nature of functional performances, including practice outcomes.

Duration of Practice and Retention

Duration of training or practice of a skill can often influence performance outcomes. Most auditory cued training studies for PD involve single session practices [13, 14, 30, 31]. The number of studies identifying long term outcomes for this population after intervention with only RAS use is limited. Many of the collected measures were recorded immediately after practice termination [32-34]. Studies including a retention analysis are few and reveal conflicting results from methodological differences [35, 36]. Hence, it is very difficult to determine and/or predict the benefits of auditory stimulation as a rehabilitation regimen. Improvements using RAS occurring in a short practice period are impressive, however there is still need to determine the neural plasticity retention sought after practice termination.
Direction of Movement

Direction of movement can influence task difficulty thus movement performance and enhancement with practice. The cause of falls can be specific in PD patients and appears linked to more complex tasks such as changes in movement direction. Unlike healthy older adults, PD patients experience indoor falls more than outdoor falls [28]. PD patients report problems (i.e. freezing, akinesia) while changing directions and crossing over obstacles [37-39]. Freezing due to a direction change is not a major concern for most older adults without neurological disease. The literature on RAS use with PD patients primarily focuses on forward movements such as that used for walking forward in a straight line path (straight line walking). Although these studies offer good insight to gait function, they exclude movements made in different directions used commonly for daily movement such as stepping backwards or to the side after hand washing. Studies for improving more complex movements in PD patients are still needed.

Speed

Changing performance speed often affects performance outcomes. Daily activities are not always performed at the same speeds. Rushing to answer a ringing phone may be performed faster than a movement to go check the mail. PD patients perform movements slower than their aged matched controls [40] and have difficulty controlling relatively fast and slow movements [41]. Incorporating different speeds in training protocol allows the PD patients opportunity to prepare for different tasks, while changing the level of movement difficulty.

Multimodal Training

Several recent studies have used auditory cues within their therapeutic design for PD patients after completion of 3-8 weeks of training. Some report long term retention in functional improvements after training with external cues compared to those PD participants using the same techniques with no external cues [36, 42]. These studies incorporate various training strategies.
For example, in one study auditory cues of a metronome were combined with other forms of external stimuli (visual/tactile) [36]. In another study a combination of mobility and stretch exercises were utilized with various visual cues and “sounds” [42]. Thus while these studies offer some insight regarding the existence of continuation effects after long term practice with external stimulation they make it difficult to determine which strategy/strategies led to the successful outcomes.

Additional Considerations

Motor learning strategies used by scientists are proven effective for normal healthy people and PD patients alike. Adjusting the amount of feedback [43, 44] and the order of practice (blocked/random) [45] can affect and enhance motor learning results in those with PD. These strategies appear to vary according to the task studied, resulting in ambiguities for choosing the correct technique. Thus while more research is required, it is important to carefully design the training protocol and utilize the most appropriate learning techniques.

In summary the outcomes of several studies showed that including external stimuli in rehabilitation are effective in improving various aspects of movement in PD patients. Although studies involving training with RAS showed improved movement, the effectiveness of RAS when used as the only external cue for long term intervention and after practice termination are rare in this population. It appears that the need for an intervention involving training PD patients with RAS is necessary to understand its effects on motor symptoms and functional performance in this population. To enhance the chances for success, the training should be for a relatively long time period (4-6 weeks), should gradually increase task difficulty, use different movement speeds and utilize movements involving different directions and/or obstacle avoidance. Successful results in this type of study would offer behavioral evidence that support previous
work for use of altered neural pathways underlying movements with RAS. A more detailed literature review is included in Appendix A.

Dissertation Outline

**Chapter 1** provided the background information to motivate the experiments to follow. Background information regarding PD and related motor complications offered insight to the population studied. Review of the existing literature allowed us to justify the use of RAS and to identify techniques useful for helping those with PD to improve their existing motor complications. This was especially important for activities that increase risks of falls such as those that involve more complex movements such as direction changes. We chose to determine whether modifications observed for straight line walking in those with PD with the use of RAS would occur for tasks involving the more difficult task of direction transitions during performance of a multi-directional step task, while simultaneously improving functional abilities linked to fall risk. As a result **Chapter 2** was designed to explore the immediate effects of RAS on the multi-directional step task by having individuals with PD perform the task without and with RAS. The primary goal was to determine the immediate effects of RAS on duration of step direction switching abilities or direction switching duration (DSD). Several other kinematic measures were collected and calculated for additional insight to short term effects of RAS on stepping performance. The results allowed us to determine the immediate effects of RAS on multi-directional stepping and to pose assumptions regarding the potential long term application of multi-directional step training with the use of RAS.

A training program can be considered effective if participants can generalize what they learn to similar activities in different contexts of everyday life. Individuals with PD are no exception and should be able to benefit from a training program beyond the borders of a laboratory or clinic. In **Chapter 3** results of the effects of 6 weeks of multi-directional step
training with and without the use of RAS on functional gait and balance activities were determined. We explored the effects of training on various functional activities immediately after and up to 8 weeks after training termination. These results provided us with key information regarding the abilities of those with PD to generalize and maintain step training effects on gait and balance measures depending on whether they practiced stepping with or without RAS.

In Chapter 4 we compared the kinematic results from performance of the multidirectional step task with and without RAS use before and after training to better understand the training alterations to functional performances identified in chapter 3. The primary goal was to determine whether DSD and other kinematics, calculated during performance of the multidirectional step task without RAS use, were influenced by training with and without the use of RAS differently. The results of this chapter allowed us to better understand the underlying factors of the observed functional improvements and to pose speculations regarding the involved central mechanisms.

Figure 1.1 provides an outline of how chapters 2, 3 and 4 were developed as subcomponents of one large study. All participants completed functional tests of gait and balance which were always collected without RAS. Step training and testing differed slightly for the two defined groups so that those who trained with RAS (Cue, C group) were tested without and with cues in the No RAS and RAS conditions, respectively, while those who trained without RAS (No Cue, NC group) were only tested in the No RAS condition. In chapter 2 analyses concentrated on pre-test measures and immediate effects of RAS use. In chapter 3 analyses from training effects on functional measures were presented. Analyses from training effects on kinematic measure were offered in chapter 4 to give insight to functional alterations.

The outcomes of chapters 2, 3 and 4, add to previous literature and provide insight regarding the effects of RAS on activities that have not been explored previously. Chapter 5
brings this manuscript to a close by reviewing the key findings, discussing how certain key findings of each chapter relate, indicating limitations of the current work and offering future investigations for better assisting individuals with Parkinson’s disease.

**Figure 1.1** The general outline of the overall dissertation study. The outline indicates screening, testing and training visits and associated training and testing for each group. Results were separated and presented in three chapters (2, 3 and 4) as shown.

### References


CHAPTER 2: DURATION TO SWITCH STEP DIRECTION DURING A MULTI-DIRECTIONAL STEP TASK IN PARKINSON’S PATIENTS IMPROVES WITH RHYTHMIC AUDITORY STIMULATION

Introduction

Parkinson’s disease (PD) is a progressive neurodegenerative disorder associated with many motor complications. Although deficits in performing voluntary movements are evident in individuals with PD, research suggests that the ability to generate normal movement is not lost [1]. The main problem in this population involves the inability of the basal ganglia (BG) to “switch” an existing motor pattern with a more suitable response according to the environment or task demands [2, 3]. The “switching” problem is evident during unilateral [4] or bilateral [5] multi-limb movements, dual task performance [6, 7], multi-task performance [8] and when required to change movement direction [9, 10].

Bradykinesia accompanies the difficulties in changing movement direction in PD. Individuals with PD experience longer transition in muscle activation during a rise-to-toe task when gastrocnemius activity replaces that of the tibialis anterior [11]. They also experience a longer gap when switching from hip flexion to hip extension during forward and back direction stepping [9] and the sit-to-stand task [10]. Delays in switching movement direction accounts for overall slowness [10] and the augmentation of temporal (longer step durations) and spatial (smaller step lengths) step deficits in turning compared to straight line walking [12].

In PD the deficient BG are incapable of triggering inhibition and releasing relevant motor responses [13, 14]. Replacement of this failing internal trigger is suggested in order to counteract the associated movement deficiencies [15]. Candidates for trigger replacement include visual [16, 17], auditory [16, 18] and tactile [19, 20] external cues. More extensive application of rhythmic auditory stimulation (RAS) compared to other external cues for sequential movements likely occurs because of robust connections between temporal aspects of
RAS and movement generation [21, 22]. Moreover, RAS can result in temporal gait alterations for people with PD that do not occur with visual [23] or tactile [24] stimuli.

Gait difficulties are one of the most noticeable motor deficits in individuals with PD [25], involving spatial [26, 27] and temporal [28-30] aspects of movement. Interestingly, different frequencies of RAS can influence temporal and spatial measures of walking. Observed changes in velocity [18, 22, 31-33], step amplitude [22], step duration variability [22], step length [22, 23, 31-33] and cadence [18, 31, 33] contribute to our understanding of RAS applications for straight line walking. However turning difficulties commonly contribute to gait complications in this population [34], causing higher incidence of falls [35-37] and regular freezing episodes [38, 39]. Research on the effects of RAS use involving direction transitions are still needed. Beneficial effects of RAS use for gait turns performed by individuals with PD exist [38, 40]. In the present work we continue the study of RAS application for its immediate use in step direction transitions performed by those with PD as a precursor to training applications.

The primary goal of the current study was to investigate the effects of RAS on step kinematics obtained when PD patients performed a multi-directional step task. The time required to switch step direction (direction switch duration, DSD) served as the primary measure, due to slowing difficulties in shifting direction in this population. We hypothesized that DSD would decrease with application of RAS compared to without it. As an added value we explored the relationships between DSD, disease severity and functional performance measures in this population. Because of the progressive nature of the disease [41] and associated worsening of motor symptoms [42], we expected longer and/or more variability in DSD with increased disease severity and decreased function.
Methods

Participants

Twenty-seven people with idiopathic PD volunteered for the study. Six people were excluded, thus 21 individuals served as participants in the experiment.

Participants consented to partake in the study approved by the university’s Internal Review Board. The Hoehn and Yahr (H&Y) scale [43] and Unified Parkinson’s Disease Rating Scale (UPDRS) [44] were used for determining severity of the disease and PD motor symptoms, respectively. The participating volunteers were diagnosed with idiopathic PD with disease severity of 2 to 4 according to H&Y. Inclusion criteria were also contingent on stable drug use, the ability to stand and walk with or without an assistive device, the ability to hear and differentiate auditory tones (described below) and a Mini Mental State Examination (MMSE) score > 24 [45]. Participants were also excluded if they had other disorders that could affect their performance, if they experienced unexpected off periods (the time when medication effects wear off and many off medication symptoms return) indicated by items 37 and 39 of UPDRS (scores = 1 and > 2, respectively), and if they reported a change in medication.

Study Design

During an initial screening visit PD participants were evaluated and informed about the study. Preliminary data from 5 volunteers provided insight to the effectiveness of the initial experimental design, thus were placed in a pilot group (group P). Design changes led to limited data from this group (see characteristic list from all participants in Table 2.1). These characteristics and various step kinematics during performance of the multi-directional step task were collected on the remaining 16 volunteers. Eight of these participants performed stepping with no external cues (No cue group or NC), while the remaining 8 performed the task with and without external cues (Cue group or C). The grouping for NC and C participants resulted from
commitments to a step training program with and without RAS use. Overall, we analyzed initial functional measures from 21/21 qualified participants, kinematic measures for stepping with No RAS from 16/21 participants and kinematic measures with and without use of RAS from 8/21 participants.

Comfortable/normal walking and/or stepping cadences were determined for each participant on the screening visit. Participants were asked to walk approximately 6 m at a comfortable walking speed 5 times. Cadence for 4 m was averaged over the 5 trials and used to determine each participant’s normal walking cadence. Calculating cadence for the shorter distance allowed avoidance of large changes expected at the beginning and end of the walkway. Because participants in group P reported difficulties in using the walking cadence as their step cadence, C and NC participants were asked to perform forward stepping (see below) for 10 s 5 times to determine an average comfortable stepping cadence. This cadence was used for RAS frequency determination for individuals in group C. Average step cadence for this group is presented in Table 2.2.

Multi-directional Step Task

Sixteen participants performed the stepping task approximately 1 hour after medication intake. Participants from group C performed the task with and without RAS, while group NC only performed the latter, which is described next.

During the No RAS condition, participants started with legs in anatomical position at a self-selected distance apart. Instructions and/or a demonstration of the stepping protocol preceded testing and were repeated after every break. Participants were instructed to step away and back in three directions (forward—F, side—S and back—B) at a predetermined speed: “normal” or “relatively faster” or “relatively slower” than normal. Stepping started after the verbal trigger of “Ready? Start.” Stepping in one direction was performed for approximately
Table 2.1 Characteristics and test measures from 21 participants

<table>
<thead>
<tr>
<th>Subject details</th>
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<tr>
<td>Age (years)</td>
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<tr>
<td>Gender</td>
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<tr>
<td>Height (cm)</td>
<td>170.1 ± 2.4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76.9 ± 3.8</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>8.9 ± 1.8</td>
</tr>
<tr>
<td>Modified H&amp;Y = number of participants for each stage</td>
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</tr>
<tr>
<td></td>
<td>2.5 = 13</td>
</tr>
<tr>
<td></td>
<td>3 = 3</td>
</tr>
<tr>
<td></td>
<td>4 = 2</td>
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<td>Normal walking cadence (steps/min)</td>
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<td>MMSE</td>
<td>28.1 ± 0.4</td>
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<td>16.3 ± 0.6</td>
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<td>UPDRS-Composite</td>
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<td>Tinetti-total</td>
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<td>Tinetti-gait</td>
<td>7.0 ± 0.5</td>
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<tr>
<td>Tinetti-blance</td>
<td>10.6 ± 0.7</td>
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<td>TUG (s)</td>
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<td>FOGQ</td>
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</tbody>
</table>

Mean ± 1 standard error of the mean for various characteristics and functional measures of the 21 participants. H&Y—Hoehn and Yahr scale; F—female; M—male; Mini Mental State Examination—MMSE; Dynamic Gait Index—DGI; Unified Parkinson’s Disease Rating Scale—UPDRS; Activities of Daily Living—ADL; Timed-Up-and-Go—TUG; Freezing of Gait Questionnaire—FOGQ.
Table 2.2 Characteristics and test measures from C group participants

<table>
<thead>
<tr>
<th>Subject details</th>
<th>Mean ± 1 SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>73.3 ± 2.22</td>
</tr>
<tr>
<td>Gender</td>
<td>F= 3, M = 5</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168.8 ± 3.3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79.5 ± 0.18</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>8.9 ± 1.8</td>
</tr>
<tr>
<td>Modified H &amp;Y = number of participants for each stage</td>
<td>2 = 1</td>
</tr>
<tr>
<td></td>
<td>2.5 = 5</td>
</tr>
<tr>
<td></td>
<td>3 = 1</td>
</tr>
<tr>
<td></td>
<td>4 = 1</td>
</tr>
<tr>
<td>Normal walking cadence (steps/min)</td>
<td>110.5 ± 4.8</td>
</tr>
<tr>
<td>Normal stepping cadence (steps/min)</td>
<td>56.8 ± 6.0</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.3 ± 0.50</td>
</tr>
<tr>
<td>DGI</td>
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</tr>
<tr>
<td>UPDRS-Motor</td>
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</tr>
<tr>
<td>UPDRS-ADL</td>
<td>13.9 ± 1.31</td>
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<tr>
<td>Composite-Score</td>
<td>8.1 ± 1.0</td>
</tr>
<tr>
<td>Tinetti-Total</td>
<td>17.0 ± 1.8</td>
</tr>
<tr>
<td>Tinetti-gait</td>
<td>6.4 ± 0.7</td>
</tr>
<tr>
<td>Tinetti-balance</td>
<td>10.6 ± 1.2</td>
</tr>
<tr>
<td>TUG (s)</td>
<td>15.0 ± 2.0</td>
</tr>
<tr>
<td>FOGQ</td>
<td>12.5 ± 1.9</td>
</tr>
</tbody>
</table>

Mean ± 1 standard error of the mean for various characteristics and functional measures of the Cue group participants (N=8). Normal walking cadence represents the average step frequency of a 4 meter walk. Normal stepping cadence was calculated from 10 seconds of the forward step task. H&Y—Hoehn and Yahr scale; F—female; M—male; Mini Mental State Examination—MMSE; Dynamic Gait Index—DGI; Unified Parkinson’s Disease Rating Scale—UPDRS; Activities of Daily Living—ADL; Timed-Up-and-Go—TUG; Freezing of Gait Questionnaire—FOGQ.
11.25 s before switching to the next direction, resulting in the total trial duration of 33.75 s to complete steps in each direction. Note the relatively short time period (~ 30 s) to avoid fatigue [46]. For each step participants were told that the foot should be lifted completely from the ground then come to complete contact with the underlying surface. Instructions to keep speed constant within each trial and within a speed range were also given. In order to avoid mental overload that could occur with step counting participants were given a “Last step” cue approximately 1 second prior to a direction switch and a “stop” cue at the end of the trial.

Participants in the group C were also asked to perform the multi-directional step task with RAS. Auditory tones, one for each direction, were presented at three stepping speeds: normal step cadence and 10% faster and slower than normal step cadence, +/-10%, respectively. Participants were instructed to step in time with the auditory cues. A verbal preparatory command of “Ready? Here it comes.” was provided prior to the first cue used to signal stepping onset. A tone change signaled a direction change after the 11.25 s and 22.5 s of the preceding directions and participants stopped when the beats stopped.

Three different auditory cues: cluck, ding and soft cork, were recorded at a 22.5 kHz. The cluck, ding and soft cork sounds had frequencies of 1003.3 Hz, 784.93 Hz and 529.38 Hz, durations of 88 ms, 915 ms and 127 ms and corresponded to the forward, side and back step directions, respectively. Cue presentations for RAS were generated by a specially designed LabView program and presented through two speakers at approximately 75 dB, well above the average hearing loss range (25-40 dB) suggested for older population [47]. Prior to testing P and C participants were presented with cues in a random order and were able to raise their hands and describe them when heard.

Several factors were taken into consideration to design the trials for the multi-directional stepping. The original goal was to test participants on their abilities to switch directions to and
from all possible directions and speeds. Six direction combinations (F→S→B, F→B→S, B→S→F, B→F→S, S→F→B and S→B→) at each speed were performed with and without RAS to total 36 trials during pilot tests. Despite taking sufficient breaks P group participants were exhausted after functional evaluations and equipment prep time. To offset fatigue effects during a single session we limited direction combinations to F→S→B, S→F→B, and B→S→F to yield 18 trials (9 with RAS, 9 without RAS) for the C group and 9 trials for the NC group (No RAS only). These direction combinations allowed participants to initiate stepping to each of the three directions and included step changes to each direction. Trials were randomized and repeated if participants did not adhere to primary instructions. Two participants from group C and one participant from group NC repeated 1 to 3 trials for not adhering to instructions in the No RAS condition. Two participants repeated 3 and 4 trials for not adhering to instructions in the RAS condition.

Evaluation

Participants were evaluated for experimental inclusion and functional measures on screening and test visits. Comfortable walking/step cadence determined on the screening visit was used for the stepping task performed on the test day. Visits were at the same time of the day and in the same location. Medication intake was confirmed prior to each session. Collecting functional measures during both visits allowed us to determine the stability of these measurements in participants. RAS frequencies used for step cueing on the test day were determined from comfortable/normal walking cadence (P group) or step cadence (C group) determined at the screening visit. Functional tests were conducted before performance of the multi-directional step task. Order of functional measurements was randomized. The multi-directional stepping with RAS always followed the No RAS condition (for P and C groups) to avoid carry over effects from the auditory stimulation (e.g. [48, 49]). As mentioned previously,
speed and direction combinations were randomized within each condition. Reducing direction combinations along with scheduled and optional breaks for C and NC participants allowed these participants to complete setup and testing within 1.5 hours and without the fatigue concerns observed in the P group.

PD symptom severity scores and tests of physical and mental function were evaluated in all participants. The H&Y and MMSE scores, described previously, offered insight to disease severity and mental function, respectively. The Dynamic Gait Index (DGI) determined the likelihood of falling in older adults by testing eight facets of simple and complex gait. The Timed-Up-and-Go (TUG) offered another measure of fall risk [50]. The Motor and Activities of Daily Living (ADL) sections of the UPDRS determined the level of overall motor and ADL functional disability in participants. Similar to previous work [51], the UPDRS-composite score involving UPDRS gait and balance items (13-15, and 29-30), was also included. The Tinetti gait and balance test was also used as a measure of fall risk. Lastly, the Freezing of Gait Questionnaire (FOGQ) determined perceived gait in daily living skills and the quality and frequency of freezing of gait [52]. See Appendix B for the functional tests’ instructions and score sheets.

Step kinematics were also determined. Three-dimensional motions of passive reflective markers placed on the lateral malleoli of the ankles were monitored during the multi-directional step task using a four camera digital video system (Qualisys Mediaclla AB). The first auditory cue in a trial triggered signal capture at 60 Hz. For the No RAS condition this program was muted during collection. The visual display corresponded to temporal occurrences in a trial and allowed the examiner to signal the participant for step initiation, direction switching and termination in the No RAS condition.
Position data of ankle markers were filtered using a zero-phase lag 10 point averaging process. Tangential velocity profiles were calculated using five-point differentiation of the filtered position data. Position and velocity profiles were plotted across time, visually inspected and marked to determine kinematic measures. Movement end (END) corresponded to the frame just after the movement ended and was determined as the last discernable change in the given movement direction from position profiles. Onset of movement (ON) was determined as the frame prior to the first discernable movement determined in a given direction.

Several movement kinematics were determined to offer insight to the temporal and spatial characteristics of stepping in those with PD. We used the average duration to switch step direction, direction switch duration (DSD), as the primary measure because it offered insight into temporal transitions in movement direction which are disrupted in PD [9, 10]. DSD was defined as the interval in seconds between the time one foot returned to the platform and stopped moving in one direction and the time the opposite foot moved to leave the platform in another direction. For example, the absolute difference between the frame for END of right ankle back and the frame for ON of left ankle side was divided by the 60 Hz sampling frequency. Illustration of vertical bars used to identify frames for END DSD and ON DSD of one trial for one participant are shown in Fig. 2.1A. Average DSD values were calculated for each direction to which the switch was made within a given speed for each participant. Peak tangential velocity, known to decrease in individuals with PD when performing voluntary movements [53], offered insight to the spatiotemporal kinematics of stepping. This was determined by identifying the maximal step velocity (VEL) between ON and END of each step from the tangential velocity profiles of the ankle markers (see ON MOV and END MOV, Fig 2.1B). Step length (SL), step height (SH) and step number (SN) were also calculated due to reductions in step length [32], increased shuffling [54] and changes in cadence [55] commonly observed in this population. SL was calculated as
the displacement of the ankle marker in the lateral (y-) direction for side steps or anterior/posterior (x-) direction for forward or back steps (see SL, Fig. 2.1B). In a back step for example, SL was the difference between the x-values at ON and END of a given step. SH was determined as the z-value difference between the step END and the initial trial z-value during stance and prior to step initiation (see SH, Fig. 2.1B). Velocity profiles were also used to determine SN in whole or half steps for each direction of a trial during the 11.25 s. A half trial was counted if more than half, but less than the whole velocity profile was included in the time frame. Peak of the velocity profile was used as the half way mark. One can count 7.5 steps in the back direction using velocity profiles in Fig. 2.1B (the interval between frame 0 and the line marking 11.25 identify the duration s for this direction). For each participant average SL, VEL, SH and SN values were determined for each direction within a given speed for each leg (R, L). Standard deviations were used for variability of these measures, excluding SN, and are presented with a “var” subscript in the text.

Statistical Analyses

Pair wise t tests were used to determine whether values of patient characteristics and functional measures did not differ for screening and test visits. In order to evaluate participants’ abilities to follow the presented RAS beats t tests were performed to determine if the number of steps taken within each speed and direction were similar to the number of RAS beats presented. A randomized blocked on subject design with a 2 x 3 x 3 treatment analysis and Kenward Rogers adjusted degrees of freedom was used to determine if differences in each kinematic measure existed for group C when performing with and without RAS. Within subject factors included: Condition (RAS, No RAS), Speed (fast, normal, slow) and Direction (forward, side, back). Subject was the only random factor. Tukey’s post-hoc tests were used when significant main effects or interactions were identified. A Pearson Correlation Matrix was performed to assess the
Figure 2.1 Example of position and velocity marking. Examples of position (A and B) and velocity (B) profiles used for identifying different kinematic variables are presented. Data are from two different trials for plots in A and B. Example markings used for direction switch duration (DSD) are plotted in A and those for peak step velocity (VEL), step length (SL), step height (SH), step number (SN) and reaction time (RT) are plotted in B. Position and velocity profiles are separated in B for better clarity. Plots in A show the end of the movement of the right ankle marker in the back direction (x) is indicated by the END DSD solid line and the onset of the movement of the left ankle marker in the side direction (y) is indicated by the ON DSD solid line. Plots in B show corresponding lines determined for a single step and indicate ON MOV and END MOV of the first back step (x) of the right ankle marker. The vertical dashed line represents 11.25 s associated with the timing for a direction change.
relationship between kinematic measures (N = 16; C and NC), functional measures (N = 21) and disease severity (N = 21). Data were analyzed using SAS (V.9.1) with significance level set at $\alpha = 0.05$.

**Results**

Several measurements from the 21 participants and 8 participants in group C are included in Tables 2.1 and 2.2, respectively, to offer insights to the populations used. The majority of participants were males and at a moderate stage of the disease (H&Y = 2.5) with 3 participants at stages 2 and 3, and 2 participants at stage 4 (Table 2.1). Fall risk of participants was high as indicated by scores on the DGI ($\leq$ 22 [56]), TUG (> 8.50 s [50]) and Tinetti gait and balance test (total < 19 [57]). Average normal step cadence for the 16 participants used in kinematic analyses (56.9 ± 4.8 steps/min) was much lower than that for normal walking cadence for all participants listed in Table 2.1. Step cadence included each foot placement during the forward step task (i.e. stepping forward and back) with alternating legs, thus required opposing direction adjustments that account for the slower cadence. According to the t tests walking cadence was similar (p > 0.05) across the 3 groups (C = 110.5 ± 4.8 steps/min NC = 111.3 ± 5.3 steps/min P =110.6 ± 2.4 steps/min) and step cadence was similar for groups C (56.8 ± 6.0 steps/min) and NC (57.0 ± 7.1 steps/min).

**Correlations**

Significant correlations among disease severity, functional measures and certain kinematic measures during multi-directional stepping with No RAS were identified. Correlations between H&Y scores and functional measures from all participants are presented in Table 2.3 and show several significant associations. Higher H&Y scores significantly correlated with lower DGI and Tinetti scores and higher TUG scores indicating greater fall risk for those with greater disease severity. Higher H&Y scores also correlated with higher UPDRS-Motor, UPDRS-ADL,
and UPDRS-Composite scores indicating greater functional motor impairment with greater disease severity. Moreover, higher scores on the FOGQ correlated with higher H&Y scores indicating greater perceived gait deficits with greater disease severity. A significant positive correlation between DSD and H&Y scores was also determined (Table 2.4) so that higher DSD values were associated with greater disease severity. Thus, it was not surprising to find significant correlations of functional measures with DSD in the same direction as those with disease severity (compare signs in Table 2.5 for DSD and Table 2.3 for H&Y), regardless of the lower number of participants used for kinematic comparisons (N = 16 compared to N = 21). Moreover, significant correlations of DSD$_{var}$ with the UPDRS-Motor and FOGQ suggested that the more variable the DSD, the greater overall motor impairment and the greater perceived gait dysfunction, respectively. Slowness during step direction switching, and possibly greater variability in these durations, are associated with greater actual or perceived functional impairments in those with PD.

**RAS vs No RAS**

Kinematic measures were determined with and without RAS for the 8 participants in the C group. Analyses demonstrated no significant difference between the numbers of steps taken with RAS for each speed ($S = 6.0 \pm 1.1$ steps, $N = 9.5 \pm 1.1$ steps, $F = 12.3 \pm 1.1$ steps) and the number of RAS beats for compatible speeds ($S= 8.6$ beats, $N= 10.6$ beats, $F= 12.6$ beats). See Appendix C for average number of steps and RAS beats for each subject. These results provide evidence that participants were able to step to the different auditory cue frequencies. Similar to previous work [20], we identified no significant differences between the right and the left sides for all collected kinematics using pair wise $t$ test comparisons. Therefore data from the two sides were combined and associated analyses performed. Results presented next are from the combined data.
Table 2.3 Correlation analysis of disease severity and functional measures.

<table>
<thead>
<tr>
<th></th>
<th>DGI</th>
<th>TUG</th>
<th>Tinetti balance</th>
<th>Tinetti gait</th>
<th>UPDRS ADL</th>
<th>UPDRS Motor</th>
<th>UPDRS Composite</th>
<th>FOGQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>H&amp;Y</td>
<td>-0.63</td>
<td>0.79</td>
<td>-0.73</td>
<td>-0.58</td>
<td>0.72</td>
<td>0.65</td>
<td>0.54</td>
<td>0.65</td>
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</tbody>
</table>

The r-values from the Pearson correlation between disease severity (Hoehn and Yahr scale—H&Y) and functional measures of the 21 participants. Bold numbers represents significant r-values. Dynamic Gait Index—DGI; Timed-Up-and-Go—TUG; Unified Parkinson’s Disease Rating Scale—UPDRS; Activities of Daily Living = ADL; Freezing of Gait Questionnaire—FOGQ.

Table 2.4 Correlation analysis of disease severity and kinematic measures

<table>
<thead>
<tr>
<th></th>
<th>DSD</th>
<th>DSD_var</th>
<th>VEL</th>
<th>VEL_var</th>
<th>SL</th>
<th>SL_var</th>
<th>SH</th>
<th>SH_var</th>
<th>SN</th>
</tr>
</thead>
<tbody>
<tr>
<td>H&amp;Y</td>
<td>0.60</td>
<td>0.00</td>
<td>-0.22</td>
<td>0.02</td>
<td>0.06</td>
<td>0.02</td>
<td>-0.35</td>
<td>0.39</td>
<td>-0.28</td>
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</tbody>
</table>

The r-values from the Pearson correlation between disease severity (Hoehn and Yahr scale, H&Y) and various kinematic measures obtained from the 16 participants from C and No cue NC groups performing the multi-directional step task in the No RAS condition. Bold numbers represent significant r-values. Direction switch duration—DSD; velocity—VEL; step length—SL; step height—SH; step number—SN. Variability of presented measures is shown with a “var” subscript.

Significant main effects of Direction and Speed were identified for various kinematic variables, however a Condition x Speed interaction was also revealed. Results of the Condition x Speed interactions for DSD ($F_{2,26} = 6.10, p = 0.01$), VEL ($F_{2,25.8} = 9.59, p = 0.04$) and SN ($F_{2,20.9} = 23.66, p < 0.01$) are shown in Fig. 2.2A, B and C, respectively. Plots reveal the main effects of speed (square brackets with asterisks) with or without RAS for DSD ($F_{2,23.91} = 5.81, p = 0.045$), VEL ($F_{2,26.21} = 8.32, p = 0.04$) and SN ($F_{2,24} = 3.62, p = 0.04$), showing that for the faster cadence VEL (0.51 ± 0.03 m/s) and SN (11.3 ± 0.8 steps) increased and DSD (1.04 ± 0.14 s) decreased compared to the normal cadence (VEL = 0.44 ± 0.03 m/s, SN = 8.8 ± 0.8 steps, DSD = 1.23
Table 2.5 Correlation analysis of kinematic and functional measures

<table>
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<tr>
<th></th>
<th>DGI</th>
<th>TUG</th>
<th>Tinetti balance</th>
<th>Tinetti Gait</th>
<th>UPDRS ADL</th>
<th>UPDRS Motor</th>
<th>UPDRS Composite</th>
<th>FOGQ</th>
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<tbody>
<tr>
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<td>0.93</td>
<td>-0.64</td>
<td>-0.67</td>
<td>0.72</td>
<td>0.52</td>
<td>0.70</td>
<td>0.76</td>
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<td>DSD_{var}</td>
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<td>-0.38</td>
<td>-0.41</td>
<td>0.39</td>
<td>0.56</td>
<td>0.40</td>
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<tr>
<td>VEL</td>
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<td>0.01</td>
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<td>-0.11</td>
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<td>-0.09</td>
<td>0.12</td>
<td>0.08</td>
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<td>SH</td>
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<td>SN</td>
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<td>-0.29</td>
<td>-0.38</td>
<td>0.29</td>
<td>0.37</td>
<td>0.41</td>
<td>0.28</td>
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</table>

The r-values from the Pearson correlation analysis of kinematic and functional measures of the 16 participants from the C and NC groups. Bold numbers represent significant r-values. Dynamic Gait Index—DGI; Timed-Up-and-Go—TUG; Unified Parkinson’s Disease Rating Scale—UPDRS; Activities of Daily Living—ADL; Freezing of Gait Questionnaire—FOGQ; Direction switch duration—DSD; velocity—VEL; step length—SL; step height—SH; step number—SN. Variability of presented measures is shown with a “var” subscript.

±0.13 s). In addition VEL (0.31 ± 0.02 m/s) and SN (5.8 ± 0.8 steps) decreased while DSD (1.47 ± 0.14 s) increased at slower cadences compared to normal cadence values. Voluntary speed changes and those induced by RAS had a similar relative influence on VEL, SN and DSD. Plots also reveal shorter DSD (Fig. 2.2A) and faster VEL (Fig. 2.2B) values for the RAS condition compared to the No RAS condition (see asterisks for curly bracket comparisons). SN also increased for some subjects with the use of RAS, however the larger mean SN values with RAS use (Fig. 2.2C) did not achieve significance for slow (p = 0.07), normal (p = 0.07) and fast (p = 0.06) speeds. Overall, stepping with RAS resulted in shorter durations in switching step direction and increased peak step velocity.
Analyses also revealed a significant main effect of Direction for $SL_{\text{var}}$ ($F_{2,29.6} = 3.89$, $p = 0.03$) and $SH_{\text{var}}$ ($F_{2,25.4} = 9.56$, $p < 0.001$) and showed that variability of step length and height were greater during back steps ($SL_{\text{var}} = 0.17 \pm 0.02$ m, $SH_{\text{var}} = 0.035 \pm 0.003$ m) compared to forward ($SL_{\text{var}} = 0.15 \pm 0.02$ m, $SH_{\text{var}} = 0.028 \pm 0.002$ m) and side ($SL_{\text{var}} = 0.16 \pm 0.02$ m, $SH_{\text{var}} = 0.026 \pm 0.003$ m) stepping directions. These results demonstrate that the back stepping direction involved the highest variability of these spatial measures compared to the other directions. In summary individuals with PD were able to modify their stepping movements under various speed requests with or without the use of RAS.

RAS use influenced the movement regardless of the movement direction and speed, but did not affect spatial aspects of the movement, unlike that of movement direction effects on SL and SH variability. Moreover, DSD was significantly correlated with disease severity, both of which were significantly correlated with functional measures. Implications of these results are discussed in the following section.

**Discussion**

Everyday activities require constant changes in movement patterns that present problems for those with PD. We expanded on the limited findings for RAS effects and its use in direction switching in this population for which we also describe associations among disease severity, functional performance and kinematic measures. Those with less severe PD had shorter durations for switching step direction during multi-directional stepping with No RAS and greater functional abilities than those in later stages of the disease. Participants with disease stages 2-4, were able to move faster during stepping and when switching directions, and some participants did this with a greater number of steps with the use of RAS during task performance. These findings add to the evidence on effects of RAS that offset certain deficits in movement kinematics resulting from the disease.
Figure 2.2 Kinematic measures across different speeds with and without RAS. Kinematic measures of (A) direction switch duration (DSD), (B) peak step velocity (VEL) and (C) step number (SN) for slow (triangles), normal (squares) and fast (circles) speeds are shown. Filled shapes represent the No RAS condition while the empty shapes represent the RAS condition. Note, curly brackets are for RAS and No RAS condition comparisons within a given speed, while square brackets are for slow and fast comparisons relative to the normal speed. The asterisks indicate significant differences of the corresponding values at each bracket ends.
Variable Associations

Disease severity was associated with several functional measures. Functional scales such as the DGI [56], TUG [50] and Tinetti [57] are successful tools for identifying PD fallers. Frequencies of falls from self-reports also have a robust linear relationship with disease severity [58, 59]. Together these results explain the significant correlations of DGI, TUG and Tinetti with disease severity as identified on the H&Y scale. Results from significant associations between FOGQ and disease severity here and elsewhere [39] indicated that perceptions of gait deficiencies also increase with severity of the disease in PD. The significant correlations between UPDRS scores and disease severity were expected, as the H&Y scale was used to determine the convergent validity of UPDRS scores [60], which are known to worsen (increase) with advanced stages of the disease [52].

Only one kinematic measure determined during multi-directional stepping with No RAS (i.e. DSD) was significantly correlated with disease severity (Table 2.4) and functional measures (Table 2.5). In addition greater variability in DSD (DSD_{var}) showed a significant correlation with UPDRS-Motor and FOGQ, thus overall motor and perceived gait dysfunction. In other studies step duration variability of PD patients was significantly correlated to disease severity [26], incidence of falls, UPDRS-Motor and UPDRS-ADL [61] during straight line walking, while mean step duration was not [61]. With evidence that transitions during movement is abnormally slow in PD [10], we suggest that transition durations and variability of step durations or step transition durations can be valuable measures that offer insight to motor complications in PD.

Non-significant results of the present work also support previous findings from gait studies in this population. For instance, although the time from toe off to heel contact when walking differs from the time to switch step direction as defined in this study, step length during walking was not significantly associated with disease severity [26]. Moreover, peak step velocity
during walking was not significantly associated with incident of falls, UPDRS-Motor or UPDRS-ADL [61]. Clearly, temporal kinematics differ from spatial and spatiotemporal kinematics by definition. Their relative change may also differ for certain behaviors and populations, suggesting different mechanistic control [26].

Direction Effects

For people with PD backward directional effects for variability of step length and height for multi-directional stepping match those for postural instabilities in the backward direction [62]. Authors identified that smaller stability margins in the backward direction after perturbation in this direction exist in PD patients. Abnormal muscular function [63] as indicated by higher muscular noise and higher variability of generated forces [64] explain the greater instabilities. Such muscular abnormalities could also explain the greater variability in step length and height in the back stepping direction in the present study and the shorter backward walking step lengths elsewhere [65]. One may blame less activity after disease diagnosis for the abnormal muscular behavior, however with no significant correlations between SL$_{\text{var}}$ and SH$_{\text{var}}$ and disease severity, it appears that neural connections associated with temporal movement control are responsible. The disruption of BG-SMA connections in PD, which disrupt the temporal organization of movement [66], support this view. Further testing is required to verify this hypothesis.

Speed Effects

Speed effects in peak step velocity and duration of step direction switching were observed when stepping with and without the use of RAS. Participants in the current study adjusted DSD, VEL and SN from their comfortable self-selected stepping cadence, regardless of RAS use. Previous research also reports adaptation abilities for voluntary speed change in activities like a self-selected [67] or cued [68] sit-to-stand task. Furthermore, individuals with PD
can modify cadence, average gait velocity and step duration at different self-generated walking speeds [55]. Cadence, average velocity and step duration during walking can also be modified at lower [22, 31] and higher [18, 22, 31] RAS frequencies. Despite their ability to modify movement with speed, individuals with PD have a lower peak velocity, a lower amplitude of muscular activity [53] and an abnormal motor firing pattern during speed changes [69] compared to healthy age-matched controls. Thus although participants modified the movement speed relative to their comfortable stepping, it is probable that the underlying muscular pattern was not comparable to that of healthy adults performing the same task.

Spatial measures in the current manuscript including step length and step height were not influenced by speed. This is in line with previous work which reports no changes in step length [55] and step height [70] at different non-cued gait speeds and for step length with RAS set to 7.5% and 15% higher than the comfortable waking speed [18]. Low muscle activation at different speeds of gait apparently does not allow those with PD to alter step amplitude changes while walking [55].

PD patients maintain the ability to increase or decrease their stepping cadence for relatively small changes in RAS frequencies (e.g. ±10% [31] and ±15% [18]). This is not true for frequencies of ±20%, for which those with PD are unable to modify cadence and average gait velocity [22, 31]. In addition both PD and age-matched healthy individuals show irregularities in stride length regulations at these frequencies [18, 22]. Thus, it seems that larger speed alterations lead to spatial gait irregularities for healthy and individuals with PD, alike. Whether PD individuals can become accustomed to more extreme cadence alterations with training is yet to be determined.
RAS and No RAS Comparisons

Despite an overall ability to modify stepping speed regardless of RAS use, additional differences were observed when use of RAS was compared to the No RAS condition within each speed (i.e. fast, normal and slow). Higher peak step velocities were observed with RAS frequencies compared to the compatible No RAS conditions. Higher values of average gait velocity were also reported during gait with a 10% faster RAS frequency compared to a self-generated maximum gait speed for individuals with PD, on and off medication [32]. Another investigation revealed increased average gait velocity with use of a comfortable RAS frequency compared to a self-selected, comfortable walking cadence in PD [22]. Interestingly, a higher average velocity of gait was observed for PD patients walking with a 10% lower RAS frequency in comparison to their comfortable self-generated gait speeds [22]. Clearly use of RAS can and does increase movement velocity. Two possibilities can be used to explain the greater movement velocity with RAS use. It may be that the underlying central mechanism for movement control differs in the presence of RAS [22] and/or that certain central neurons entrain to temporal RAS features [71]. Regardless of the underlying explanation for RAS control, its use in PD patients also results in significant reduction in DSD during the multi-directional step task, a decrease in step duration variability and the overall duration during gait with a turn [38, 40]. Therefore, RAS use is not limited to increases in movement velocity for straight line walking, as it can modify temporally related variables during various tasks, including those that require direction change.

We expected changes in step number with the use of RAS to accompany the decreases in DSD and increases in peak step velocity in this same condition. One can reason that if time between each step decreases and the movement speed during the step increases with no increase in step length, that step number should also increase. It is possible that the duration between each step in the same direction increased or stayed the same instead of a reduction similar to that for
DSD. It is also possible that the average step velocity increased or remained constant while the peak step velocity increased. However, it seems more likely that step number changes with RAS were not deemed significant because the magnitude of the counts (in half steps) was not sensitive enough to detect such a change given the relatively large variability among subjects. This is highly possible, especially when one considers the relatively small p-values reported for SN at each speed (p < 0.10).

Conclusion

The current findings indicate that the effects of RAS on lower limb movements are not limited to temporal features of straight line walking. RAS can also influence temporal features of the multi-directional step task where participants must constantly change directions to oppose the movement (out and back) and intermittently change their radial direction of movement. These abilities are not limited to one stepping speed or direction. Moreover, the short term alterations mirror those of other studies, while offering a task that requires little space and a setup which makes it easy to monitor using a gait belt for safety. Use of the multi-directional step task with RAS for a potential training regime in the PD population is currently underway.

References


CHAPTER 3: PARKINSON’S PATIENTS TRANSFER MULTI-DIRECTIONAL STEP TRAINING EFFECTS TO FUNCTIONAL MEASURES OF GAIT AND BALANCE

Introduction

Neurodegeneration of the basal ganglia (BG) results in Parkinson’s disease (PD) which is a common disorder disrupting gait and balance. These difficulties are not well treated by medication [1] or surgery [2] and can lead to falls [3]. Individuals with PD have a 9 times greater risk than age-matched controls of experiencing falls [4]. Therefore, complications of gait and balance affect patients’ perceptions of their quality of life [5] and are considered key factors of PD disability [5].

When people with PD encounter multiple movement options or require movement changes, the BG do not function properly to release appropriate motor responses, while inhibiting others [6]. These individuals experience problems, especially when adaptations to the environment become necessary (i.e. changing directions, clearing obstacles, etc) [7]. They experience falls while turning [4], and freeze during gait initiation [8], turning [9] and dual tasking [8]. This explains why difficulty in movement transition is a fundamental motor performance issue for PD [10]. Difficulties in timely inhibition and release of movement further explain poor functional performance on the Dynamic Gait Index (DGI), Tinetti gait and balance test [4] and Timed-Up-and-Go (TUG) test [11], tasks which involve several movement transitions.

Medication and surgery limitations on functional performance, and the debilitating consequences of falls on physical and emotional welfare of individuals with PD, highlight the importance of supplementing standard medical treatments with effective rehabilitation. Although successful conjunctive rehabilitation for PD patients exists [12], use of inconsistent strategies and inadequate support for many applied methods do not offer clinicians the most effective training approach for use with this population. One tactic that appears effective for enhancing
motor aspects in PD is the use of external cues. It is assumed that those with PD maintain the ability to generate correct movements [6] and that proper movement can be released by replacing the lost internal trigger with an external cue [13]. Research provides support for its use with PD [14].

External cues vary by sensory modality, however auditory cueing appears the most effective in terms of its translation to motor output. Temporal components of auditory cues can directly transfer into accurate and stable motor output, dismissing the need for continuous activation of modality-specific brain areas after stimulation removal [15]. Auditory stimulation can increase excitability of spinal motor neurons using the reticulospinal pathway [16] and facilitate the H-reflex, thus enhance motor activation [17] without involving the damaged BG. This becomes significant as limitations in temporal movement organization via connections between the BG and Supplementary Motor Area lead to inadequate movement execution in Parkinson’s patients [18].

Rhythmic auditory cues directly alter gait kinematics of individuals with PD [19-21]. Single session application of rhythmic auditory stimulation (RAS) leads to increased gait velocity [20], step length [20] and cadence [22] and decreased double support time [22]. Practice with auditory stimulation can also alter movement. Practice with RAS results in reduced variability of leg muscle activity patterns [23], increased gait velocity [21], stride length [21] and cadence [24], however RAS shows no change in the number of freezing episodes [19].

Research on the ability of individuals with PD to retain practice effects [25] or transfer training effects to non-cued functional performance [21, 25] using RAS are limited. RAS effects for straight, single direction walking are promising, and may or may not transfer to more complex environments like those in the home, where PD gait complications occur most often due to the need for constant adjustments [4]. Use of auditory, visual and sensory external stimuli with
multi-directional gait practice as its primary intervention has produced immediate functional benefits in PD patients [25]. However further research is needed to clarify training effects with RAS alone on skills for which people with Parkinson’s have difficulties performing (i.e. changing direction).

The goal of this study was to test the hypothesis that a RAS based intervention would improve the abilities of PD patients to transfer multi-directional step training effects to gait as measured by the DGI and to retain the functional improvements that occur. Specifically, we wanted to determine: if training with and without RAS for 6 weeks would improve functional gait of people with PD (immediate training effects); if any improvements beyond pre-training values would be maintained for 1, 4 and/or 8 weeks after practice terminated (retention effects); and if differences in functional gait immediately after training and during retention tests existed between the groups trained with and without RAS. We hypothesized that 6 weeks of multi-directional stepping would significantly improve gait function for individuals with PD and that improvements in gait function would still be observed after eight weeks of no practice for those who trained with RAS.

Methods

Participants

Twenty-seven individuals with PD were screened to take part in this study. Six patients did not meet all the inclusion and exclusion criteria and 5 participants were used for pilot tests. As such, 16 volunteers participated in this study. Participants signed informed consent approved by the university’s Internal Review Board. Inclusion criteria was as follows: diagnosed with idiopathic PD; identified as Hoehn and Yahr (H&Y) stage 2 to 4; maintained stable drug use; could stand independently and walk with or without an assistive device; and be able to hear and differentiate auditory cues (described below). Disease severity from the modified H&Y scale
was administered alongside the Unified Parkinson’s Disease Rating Scale (UPDRS) [27] for categorizing PD motor symptoms. Participants were excluded if they presented with: cognitive deficits (Mini Mental State Examination Score (MMSE) < 24); history of disorders other than PD that could potentially influence balance and walking abilities and interfere with successful completion of the program; long lasting unexpected off periods indicated by items 37 (score = 1) and 39 (score > 2) of UPDRS or medication change.

Study Design

PD participants were given study details, consented to participate and were evaluated for participation during a screening visit. Qualified participants were pseudo-randomly assigned to one of two training groups: a group that received auditory cues during training (Cue, C) or one that did not (No cue, NC). Once disease stage was determined, the individual was randomly assigned to a group. The next participant with the same disease stage was assigned to the opposite group to maintain the same distribution of disease severity between groups. Pilot data from 5 people with PD indicated that 6 individuals per group were needed to achieve 80% power on our primary measure, the DGI. Participant and group information are included in Table 3.1.

Comfortable/normal stepping cadence was also determined during the screening visit. Forward stepping cadence of 5 trials each lasting 10 seconds was averaged to establish this cadence and RAS frequencies.

Multi-directional Step Training

Participants trained 3 times per week (45-60 minutes) for 6 weeks. Pre-tests on the screening visit and day 1 of training (PRE), a post-test on the last day of training (POST), and retention tests, 1 week (RTW1), 4 weeks (RTW4) and 8 weeks (RTW8) after training terminated, were conducted in the same location. Collections during the screening and PRE visits allowed us to determine the initial stability of measurements in participants. Participants were
Table 3.1 Characteristics and pre-test measures from the C and NC groups

<table>
<thead>
<tr>
<th>Items</th>
<th>C group</th>
<th>NC group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>73.3 ± 2.2</td>
<td>70.5 ± 2.2</td>
<td>0.59</td>
</tr>
<tr>
<td>Gender</td>
<td>F=3, M=5</td>
<td>F=2, M=6</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168.8 ± 3.3</td>
<td>171.8 ± 4.3</td>
<td>0.52</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79.5 ± 0.2</td>
<td>78.4 ± 0.2</td>
<td>0.80</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>8.9 ± 1.8</td>
<td>7.5 ± 1.2</td>
<td>0.28</td>
</tr>
<tr>
<td>Modified H&amp;Y = number of participants for each stage</td>
<td>2=1, 2.5=5</td>
<td>2=1, 2.5=5</td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>28.3 ± 0.5</td>
<td>27.8 ± 0.8</td>
<td>0.23</td>
</tr>
<tr>
<td>DGI</td>
<td>16.3 ± 1.0</td>
<td>15.4 ± 0.8</td>
<td>0.46</td>
</tr>
<tr>
<td>UPDRS-Motor</td>
<td>27.1 ± 3.6</td>
<td>27.0 ± 3.4</td>
<td>0.98</td>
</tr>
<tr>
<td>UPDRS-ADL</td>
<td>13.9 ± 1.3</td>
<td>14.9 ± 1.2</td>
<td>0.61</td>
</tr>
<tr>
<td>UPDRS-Composite</td>
<td>8.1 ± 1.0</td>
<td>8.1 ± 0.8</td>
<td>0.71</td>
</tr>
<tr>
<td>Tinetti-total</td>
<td>17.0 ± 1.8</td>
<td>16.6 ± 1.5</td>
<td>0.67</td>
</tr>
<tr>
<td>Tinetti-gait</td>
<td>6.4 ± 0.7</td>
<td>6.5 ± 0.8</td>
<td>0.91</td>
</tr>
<tr>
<td>Tinetti-balance</td>
<td>10.6 ± 1.2</td>
<td>10.1 ± 0.8</td>
<td>0.71</td>
</tr>
<tr>
<td>TUG (s)</td>
<td>15.0 ± 2.0</td>
<td>15.4 ± 2.2</td>
<td>0.93</td>
</tr>
<tr>
<td>FOGQ</td>
<td>12.5 ± 1.9</td>
<td>12.8 ± 2.1</td>
<td>0.67</td>
</tr>
</tbody>
</table>

Mean ± 1 standard error for various characteristics and functional measures of the C (cue) and NC (no cue) groups recorded on the first day of practice are provided. The p-value results of t tests used to compare groups on these measures are listed. F—female; M—male; Hoehn and Yahr—H&Y; Mini Mental State Examination—MMSE; Dynamic Gait Index—DGI; Unified Parkinson’s Disease Rating Scale—UPDRS; Activities of Daily Living—ADL; Timed-Up-and-Go—TUG; Freezing of Gait Questionnaire—FOGQ.
encouraged to continue with normal daily activities from screening to RTW8 periods, but received no step training after POST.

A physical therapist, certified in UPDRS collection, evaluated and trained all participants. Each participant attended training and testing sessions 1 hour after medication intake at the same time of day. Medication intake was confirmed before each session. Sessions were postponed and repeated on the earliest available date within the same week 1 time each for 3 participants due to off periods or improper medication intake.

When training with RAS, participants started with feet in anatomical position at a self-selected distance apart. They stepped away and back in time with each beat of RAS presented at one of 3 speeds: normal/comfortable cadence—N and 10% faster (fast) and slower (slow) than normal cadence. Each tone represented one step direction (forward—F, side—S, back—B). Trial step time was 33.75 s close to 30 seconds to avoid fatigue in this population [28]. Participants were instructed to step in time with the beat and that the foot should completely leave the surface, then completely contact the floor with each step. Speed remained constant within trials. Demonstrations and/or instructions were repeated every session before practice/testing, after breaks and when requested. Due to challenges in alternating limbs [29] and changing directions [30] for this population, training increased in complexity based on the following schedule:

Week 1: each direction separately, legs separately (e.g. right leg, forward steps (and back) for 33.75 s);

Week 2: each direction separately, legs alternated;

Week 3: two directions per trial, legs separately (e.g. left leg, backward steps for 11.25 s, then sideward steps for 22.5 s);

Week 4: two directions, legs alternated;
Week 5: three directions per trial, legs separately (e.g. left leg, sideward steps for 11.25 s, then forward steps for 11.25 s, then backward steps for 11.25 s; and

Week 6: three directions, legs alternated.

Thirty-six trials were performed in each training session. During week 1, participants performed each speed/direction combination twice (3 speeds x 3 directions x 2 legs x 2 times). During week 3, 6 direction combinations (B→F, B→S, F→S, F→B, S→F and S→B) were performed (3 speeds x 6 direction combinations x 2 legs). During week 5, 6 different direction combinations (F→S→B, F→B→S, B→S→F, B→F→S, S→F→B and S→B→F) were performed (3 speeds x 6 direction combinations x 2 legs). During even numbered weeks alternating feet replaced performing each side independently. Combinations were randomized within each training day and for each leg separately on odd weeks. One to five trials were repeated for 4 participants for not adhering to instructions.

Auditory cues used for the RAS training included cluck, ding and soft cork sounds recorded at a 22.5 kHz with durations of 88 ms, 915 ms and 127 ms, respectively. Sound volumes were approximately 75 dB, well above average hearing loss range (25-40 dB) reported for older adults [31]. Participants acknowledged cues upon presentation and could describe each.

Step training setup and scheduling for the No RAS condition were the same as that for the RAS condition with the following exceptions. Participants were to keep speed constant within a speed category and to perform the task for each direction at “comfortable”, “relatively faster” or “relatively slower” pace than normal. Participants were given a “last step” verbal cue approximately 1 second before a direction switch and a “stop” cue to end the trial to maintain the desired protocol and lessen the potential cognitive load. Three participants repeated 3-5 trials for not adhering to instructions.
Evaluation

Several functional measures were performed to offer a comprehensive determination of gait and postural difficulties associated with PD [32] and to gain insight to improvements participants experienced after training. The DGI, a fall risk indicator that challenges participants to perform simple to difficult gait patterns, was selected as the primary measure of functional gait. Secondary measures included the UPDRS-Motor and UPDRS-ADL sections to evaluate overall motor symptoms of PD and activities of daily living (ADL), respectively. Similar to previous work [25], the UPDRS-Composite score, involving UPDRS gait and balance items (13-15, and 29-30), was also included. The TUG test evaluated fall risk as the time to stand from a chair, walk 3 meters, turn, walk back and sit down. Evaluations of the Tinetti (gait, balance and total) identified impaired gait and balance and assessed fall risk [33]. The Freezing of Gait Questionnaire (FOGQ) assessed perceived changes in gait and the quality and frequency of freezing of gait [34]. Measurement order was randomized within evaluation sessions.

Statistical Analyses

Pair-wise $t$ tests were performed on functional measurements collected during screening and PRE visits to determine short term stability of these measures within our participants. Pair-wise $t$ tests were also used to compare MMSE scores, disease duration, age, height, weight and PRE functional measures of groups prior to training to determine group similarities. Repeated measures ANOVAs with a random factor for subject, a between subject factor of Group (C, NC) and repeated measures of Test-day (PRE, POST, RTW1, RTW4 and RTW8) were used to compared measurement differences between groups and among test days. A Kenward Rogers adjusted degrees of freedom was used because of the relatively small sample size and some missing test values (Fig. 3.1). Tukey’s post-hoc tests were used when appropriate to answer the experimental questions via PRE/POST comparisons and PRE/retention comparison for each
**Figure 3.1** A schematic of the number of participants (N) at various stages of the study. Pre-test (PRE), post-test (POST) and retention tests 1 week (RTW1), 4 weeks (RTW4) and 8 weeks (RTW8) after training were performed. C—Cue group; NC—No cue group. Reasons for reduced numbers are provided: Med change—change in medication and conflict—scheduling conflict that was not made up.

Group and C and NC comparisons for each POST and retention test. Significance level was preset at $p < 0.05$ for all analyses (SAS V.9.1).

**Results**

Similarities in functional measures identified between screening and PRE visits suggest that participants were functionally stable before training. Values of various group characteristics and PRE measurements are presented in Table 3.1 and reveal relatively poor scores associated with increased fall risk ($\text{DGI} \leq 22$ [32]; $\text{TUG} > 8.5$ s [35] and Tinetti-total $< 19$ [33]) in participants before training. Groups did not differ in age, height, weight, disease duration or
mental status and had similar functional scores at baseline. A moderate disease stage (2.5 H&Y) was most common. Seven freezers (4 C and 3 NC) were identified as those who experienced freezing at least once per week [25]. Figure 3.1 depicts the number of participants at each stage of the study and shows that all participants completed training, yet not all completed follow-up evaluations due to scheduling conflicts or a medication change.

Figures 3.2 and 3.3 depict the primary training results of the study. It is important to note that the analyses and plots account for the missing participants for RTW4 and RTW8. The number of participants were C = 6 and NC = 7 on RTW4 and C = 7 and NC = 6 on RTW8. A main effect of Test-day (F_{4,35.2} = 55.62, p < 0.0001) and a Group x Test-day interaction (F_{4,35.2} = 16.30, p < 0.0001) were observed for the DGI. Figure 3.2 shows that although higher DGI scores for both groups were identified immediately (POST) and 1 week (RTW1) after training compared to pre-training (PRE), scores for the C group were greater than those for the NC group for 1 week and 4 week follow-up evaluations. Only people in the C group retained higher scores relative to PRE values for 8 weeks. Moreover, 4 participants in the C group recorded scores greater than 22 at POST, thus were identified as non-fallers [32] immediately after training. A main effect of Test-day for Tinetti-balance scores (F_{4,37.9} = 11.67, p < 0.0001) revealed that scores higher than PRE values for combined groups were achieved immediately after training and maintained for 8 weeks (Fig. 3.3). These findings indicated that multi-directional step training results in functional gait and balance improvements in PD patients and that use of RAS can enhance the retention effects on gait function.

Outcomes from secondary measures show several similar results to those reported for the DGI. Significant effects of Test-day were identified for all measurements, UPDRS-ADL (F_{4,32.1} = 14.55, p < 0.0001), UPDRS-Motor (F_{4,39.8} = 18.08, p < 0.0001), UPDRS-Composite (F_{4,33.5} = 14.55, p < 0.0001)
Figure 3.2 Mean scores of the Dynamic Gait Index (DGI) for the C and NC groups. C and NC groups are presented in blue and red colors respectively. The DGI scores are shown for the pre-test (PRE), post-test (POST) and retention tests 1 week (RTW1), 4 weeks (RTW4) and 8 weeks (RTW8) after training. Colored asterisks represent a significant difference from the PRE values for the corresponding group. Curly brackets with black asterisks indicate significant differences between C and NC groups.

Mean scores for Tinetti-total ($F_{4,36.2} = 30.19$, $p < 0.0001$), Tinetti-balance ($F_{4,37.9} = 11.67$, $p < 0.0001$), Tinetti-gait ($F_{4,40.4} = 22.17$, $p < 0.0001$), TUG ($F_{4,18.18} = 23.30$, $p < 0.0001$) and FOGQ ($F_{4,37.6} = 32.76$, $p < 0.0001$), indicating improvements over PRE values. UPDRS-Motor measurements were back to baseline values within 1 week (Table 3.2). Group x Test-day interactions identified for the UPDRS-ADL ($F_{4,32.1} = 2.8$, $p = 0.0425$), UPDRS-Composite ($F_{4,33.5} = 3.33$, $p = 0.024$), Tinetti-total ($F_{4,36.2} = 3.63$, $p = 0.014$), Tinetti-gait ($F_{4,40.4} = 3.91$, $p = 0.009$), TUG ($F_{4,18.18} = 8.16$, $p = 0.0005$) and FOGQ ($F_{4,25.8} = 5.34$, $p = 0.0029$) are also shown in Table 2. People in the C group retained several improvements in the UPDRS-Composite, Tinetti-
Figure 3.3 Mean Tinetti-balance scores for the two groups combined. These values are shown for the pre-test (PRE), post-test (POST) and retention tests 1 week (RTW1), 4 weeks (RTW4) and 8 weeks (RTW8) after training. Asterisks represent a significant difference from PRE values. Error bars represent 1 standard error.

Total, Tinetti-gait, TUG and FOGQ scores relative to PRE values for 8 weeks. UPDRS-ADL improvements were also maintained up to 4 weeks for this group. The NC group only maintained improvements over PRE values in the UPDRS-Composite, Tinetti-total and Tinetti-gait for 1 week and in the UPDRS-ADL and the TUG on the post-test. Clearly, use of RAS resulted in retention of better functional scores over training without it. Furthermore, self-identified freezers in the C group received FOGQ scores of 16-22 before training and 10-14 after training, whereas scores for freezers in the NC group only dropped from 15-20 before training to 13-19 after training. FOGQ scores for the NC group did not change significantly, suggesting this group did not perceive meaningful changes in gait with training like group C. Overall, 6 weeks of multi-directional step training enhanced participant function. Results also revealed important benefits of RAS application discussed next.
Table 3.2 Secondary functional measures of C and NC groups for each test day

<table>
<thead>
<tr>
<th>Test</th>
<th>Group</th>
<th>PRE</th>
<th>POST</th>
<th>RTW1</th>
<th>RTW4</th>
<th>RTW8</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPDRS</td>
<td>C</td>
<td>13.9 ± 1.3</td>
<td>11.0 ± 0.8</td>
<td>11.6 ± 1.0</td>
<td>10.8 ± 0.7</td>
<td>12.7 ± 1.3</td>
</tr>
<tr>
<td>ADL</td>
<td>NC</td>
<td>14.9 ± 1.2</td>
<td>13.5 ± 1.1</td>
<td>14.0 ± 1.1</td>
<td>14.9 ± 1.3</td>
<td>13.2 ± 1.3</td>
</tr>
<tr>
<td>UPDRS</td>
<td>C</td>
<td>27.1 ± 2.7</td>
<td>25.1 ± 3.3</td>
<td>25.6 ± 3.5</td>
<td>22.8 ± 2.3</td>
<td>26.3 ± 3.8</td>
</tr>
<tr>
<td>Motor</td>
<td>NC</td>
<td>27.0 ± 3.4</td>
<td>27.0 ± 3.3</td>
<td>27.0 ± 3.3</td>
<td>24.7 ± 3.2</td>
<td>25.2 ± 3.9</td>
</tr>
<tr>
<td>UPDRS</td>
<td>C</td>
<td>8.1 ± 1.0</td>
<td>6.3 ± 0.9</td>
<td>6.8 ± 1.0</td>
<td>6.3 ± 1.1</td>
<td>8.3 ± 1.2</td>
</tr>
<tr>
<td>Composite</td>
<td>NC</td>
<td>8.1 ± 0.8</td>
<td>6.6 ± 0.9</td>
<td>7.5 ± 0.9</td>
<td>8.3 ± 0.9</td>
<td>6.7 ± 0.7</td>
</tr>
<tr>
<td>Tinetti</td>
<td>C</td>
<td>17.0 ± 1.8</td>
<td>22.9 ± 1.3</td>
<td>22.8 ± 1.4</td>
<td>23.7 ± 1.1</td>
<td>24.0 ± 1.2</td>
</tr>
<tr>
<td>total</td>
<td>NC</td>
<td>16.6 ± 1.5</td>
<td>22.3 ± 1.3</td>
<td>21.0 ± 1.3</td>
<td>18.9 ± 1.4</td>
<td>18.0 ± 1.2</td>
</tr>
<tr>
<td>Tinetti</td>
<td>C</td>
<td>6.4 ± 0.7</td>
<td>9.9 ± 0.6</td>
<td>9.8 ± 0.6</td>
<td>10.3 ± 0.4</td>
<td>9.4 ± 0.7</td>
</tr>
<tr>
<td>gait</td>
<td>NC</td>
<td>6.5 ± 0.8</td>
<td>9.8 ± 0.8</td>
<td>9.0 ± 0.8</td>
<td>8.1 ± 0.7</td>
<td>7.8 ± 0.8</td>
</tr>
<tr>
<td>TUG</td>
<td>C</td>
<td>15.0 ± 2.0</td>
<td>9.4 ± 1.1</td>
<td>9.9 ± 1.1</td>
<td>9.1 ± 0.8</td>
<td>11.1 ± 1.3</td>
</tr>
<tr>
<td></td>
<td>NC</td>
<td>15.4 ± 2.2</td>
<td>12.7 ± 1.8</td>
<td>15.2 ± 2.1</td>
<td>14.6 ± 3.0</td>
<td>14.1 ± 2.3</td>
</tr>
<tr>
<td>FOGQ</td>
<td>C</td>
<td>12.5 ± 1.9</td>
<td>7.5 ± 1.3</td>
<td>8.3 ± 1.2</td>
<td>9.7 ± 1.6</td>
<td>11.4 ± 1.8</td>
</tr>
<tr>
<td></td>
<td>NC</td>
<td>12.8 ± 2.1</td>
<td>11.9 ± 1.9</td>
<td>12.3 ± 2.0</td>
<td>11.6 ± 2.0</td>
<td>10.3 ± 2.2</td>
</tr>
</tbody>
</table>

Mean ± 1 standard error of several secondary functional measures are provided for the C (cue) and NC (no cue) groups on each test day. Values are for the pre-test (PRE), post-test (POST) and retention tests, 1 week (RTW1), 4 weeks (RTW4) and 8 weeks (RTW8) after training. Bold values represent a significant difference from the PRE values. Unified Parkinson’s Disease Rating Scale—UPDRS; Activities of Daily Living—ADL; Timed-Up-and-Go—TUG; Freezing of Gait Questionnaire—FOGQ.

Discussion

Eighteen sessions of multi-directional step training improved the DGI scores and other functional measures for individuals with PD and thereby demonstrate that practicing step training
transfers to a variety of functional gait and balance tasks. Although RAS use did not always provide immediate post-training improvements over step training with No RAS, it was superior to help participants extend the maintained improvements in gait function for 8 weeks after training ended. These findings support other studies that show positive outcomes of PD training programs, and highlight the importance of supplementing regular treatments with rehabilitation for this population.

The present results support evidence that motor learning abilities are preserved in people with PD [36]. Participants generalized multi-directional step training effects to the different contexts of gait and balance, two well-known deficiencies in this population [37]. The abilities of the participants to improve functional gait measures after step training, that unlike others [25, 38, 39] did not involve walking, indicate that the training context for PD patients may be generalized to different tasks. PD patients’ abilities to generalize 8 weeks of pedaling practice to manual dexterity skills [40] support this view. However PD patients were also unable to reach the desired arm movement speed in a blocked or random practice paradigm after training in the opposite paradigm for 2 days [41]. This inability to transfer training outcomes to a different context may be due to short term practice or practice using the upper limb in this population, however further tests are needed to test these possibilities.

Balance in Parkinson’s patients improved with multi-directional step training. Inability of individuals with PD, to properly respond to external (i.e. platform movement [42]), and internal (i.e voluntary movements such as rising-to-toes [43]) demands account for balance difficulties in these individuals. Some researchers blame immobility for these problems [44], explaining why balance improvements occur after 10 weeks of tai chi [45] and 8 weeks of gait training [39] and are maintained after 10 weeks of balance and strength training exercises [46]. Increased activity partially explains the improved balance observed in the present study as 9/16 participants
reported no commitments to regular physical activity before training. We reasoned that switching
between different movement components and standing between trials during training also helped
participants improve Tinetti-balance items for standing balance and turning.

Different abilities of groups to maintain improvements after training adds to the limited
research on effects of external cues on retention abilities in PD patients [21, 25, 38]. Longer
training duration [47], providing augmented [48] and positive feedback [49], higher intensity of
practice [40] and modifying levels of contextual interference [50] can result in longer retention.
Adherence to one or more of these strategies resulted in longer retention of accurate/better
performance of sequential whole body positioning and shirt buttoning [47], balancing (Jessop et
al., 2006; Jobges et al., 2004) and grasping [40] in this population. Longer retention abilities for
the C group compared to the NC group indicates that use of RAS is effective for acquiring longer
retention of certain motor skills. These results comply with reported retention of UPDRS-ADL
scores 6 weeks after 6 weeks of physical therapy with auditory cues compared to those without
them [38]. With reduced improvements in TUG and UPDRS-Composite scores 6 weeks after a
3-week cued gait training protocol [25], it is clear that training duration and external cues can
influence retention abilities, thus should be considered when enhancing retention in PD patients
is desired.

Using RAS during multi-directional step training may alter fall risk in people with PD.
The greater improvement in POST scores on the DGI for the C group and individual differences
exemplify such benefits. Remember that 4 participants in the C group scored greater than 22 on
the DGI, while all NC participants scored less than 22 immediately after training. Thus, half the
C participants at low disease stage (H&Y ≤ 2.5) changed from faller to non-faller status (i.e. DGI
> 22 [32]) after training. Although possible, the idea that longer training with RAS may result in
better scores for those at higher disease stages requires verification. Regardless, the use of RAS clearly enhanced performance to a more meaningful extent from a fall risk perspective.

C group participants also identified perceptible differences in their gait and/or number of freezing episodes. Self-identified freezers in the C group dropped 5-8 points in their FOGQ after training, revealing an obvious dichotomy and significant change for PRE/POST score comparisons (Table 3.3). The 1-2 point FOGQ score drop for freezers in the NC group did not produce significant changes in this measure. With freezing episodes associated with temporal gait deficits [51] and rhythmic auditory cues targeting temporal aspects of the movement [52], we associate C group FOGQ improvements with temporal improvements in movement. The current freezing results also follow those where PD patients revealed less freezing after 3 weeks of cued gait training [25]. Since freezing episodes remained unchanged after 1 week of home cue training [19], the observed freezing improvements were attributed to longer cue training duration, further emphasizing the necessity of relatively long training periods for individuals with PD.

Group similarities in UPDRS-Motor scores were identified so that improvements observed immediately after training were not maintained on follow-up evaluations. This seems to contradict the effectiveness of long term rehabilitation protocols in improving UPDRS-Motor scores, thus overall motor deficits in Parkinson’s patients [40, 53, 54]. Note this measure was unsuccessful in presenting an accurate portrayal of mobility in this population based on its low correlation with functional measures (TUG, Berg Balance scores and Functional Reach tests [55]), while gait and posture items of the UPDRS showed high correlations with functional measures of the Tinetti [33]. These associations explain the different outcomes for UPDRS-Composite and UPDRS-Motor scores observed in this study. Further investigations are required
to determine the sensitivity of the UPDRS-Motor in detecting more specific motor changes in PD patients.

Current results are indicative of central changes as research indicates that practicing sequential movements with [56] or without RAS [57, 58] results in changes in activity of various brain areas. Activation of additional cortical and sub-cortical regions despite continuous activity of the deficient BG in those with PD allows these individuals to achieve motor improvements after practice without RAS [57, 58]. RAS use also enhances motor performance by recruiting similar brain regions [56]. However, unlike self-generated movements, activity of the BG is not required because the movement is externally paced [59]. This pattern of activity is sustained after withdrawal of auditory tones [56]. Apparently, individuals with PD can benefit from practice alone however application of RAS holds additional benefits. Although not tested directly, the current results add to the evidence that rhythmic auditory cues facilitate a compensatory pathway in people with PD that offers at least a temporary substitute for the defective internal clock, the BG. How long such improvements are maintained in people with PD is likely linked to disease severity, but requires further testing for verification.

References


CHAPTER 4: PEOPLE WITH PARKINSON’S DISEASE CHANGE STEPPING DIRECTION FASTER AFTER MULTI-DIRECTIONAL STEP TRAINING WITH RHYTHMIC AUDITORY STIMULATION

Introduction

Movement difficulties [1], including those with walking [2], are prominent in individuals with Parkinson’s disease (PD). Walking deficits also contribute greatly to the perception of quality of life and disability for these individuals [3]. Their gait manifests decreased stride length and gait speed [4, 5], hypokinesia, increased cadence [6], freezing of gait and stride-to-stride variability [7]. Longer step duration and reduced step length observed in people with PD during straight line walking [8] worsen during a turn [9]. Some of these gait abnormalities are observed in other populations and do not limit daily function. For example, decreases in stride length and gait speed commonly exist in normal older persons [10], but do not limit these people’s abilities to grocery shop or perform other daily tasks. However other difficulties such as those associated with turning can play a significant role in loss of stability and balance [11]. Additional complications such as freezing of gait are also experienced during turning [12] and further contribute to increased fall risk in this population [13].

In PD central problems with the basal ganglia (BG) inadequately inhibit and release movement responses to the task demands [14, 15], thus are most observable during tasks involving transitions. The transition problem is evident in several activities. For example, difficulties are experienced during unilateral [16] or bilateral [17] multi-limb movements, dual task performance [18, 19], multi-task performance [20], when performing a sit-to-stand task [21] and when required to change movement directions during gait [22]. Orderly inhibition and excitation of associated muscles are necessary for transitions in each of these tasks.

Scientists suggest that training with rhythmic auditory stimulation (RAS) is an effective method for improving gait and balance in PD [23, 24]. It is thought that RAS serves as an
external trigger to replace the deficient internal trigger, the BG [25]. Training of this type involves the use of repetitive auditory cueing to which individuals attempt to synchronize a sequential and repetitive task. Finger tapping [10, 26], repetitive reaching [27] and stepping [28-31] to a rhythmic input are common tasks for investigation, although stepping is more common when gait is of interest. Music and metronomes offer different sources of rhythmic input [32]. Use of a metronome seems to offer advantages over music [33]. Other forms of external modalities such as visual [34] and tactile [35, 36] cues are also used for those with PD. However the inherent temporal connections between RAS and movement generation appear to surpass the effects of the other modalities [37, 38].

Immediate effects of RAS on gait have been investigated to a great extent and reveal changes according to that of RAS frequency. For example, frequencies of RAS higher than the normal/comfortable walking cadence result in increased velocity [30, 37, 39, 40, 41, 57], step amplitude [37], step length [28, 42] and cadence [30, 39, 41]. Frequencies of RAS lower than normal cadence usually cause the opposite response. Use of RAS commonly decreases step duration variability [37], regardless of frequency, as long as the frequency is not too extreme relative to the comfortable cadence (e.g. [43]). Few immediate RAS effects for turning exist for those with PD. These studies reveal turning alterations in response to RAS similar to those of walking [44, 45]. These findings provide useful information for applications of RAS but do not offer insights regarding the potential long term use of RAS.

Unlike the short term investigations, effects of RAS on movement after its long term use are rare for PD. Those that do exist have offered several insights to RAS use for straight line walking. These studies report changes in the pattern of leg muscle activation [46, 47], velocity [47, 29], stride length [47] and cadence [29] more similar to those of healthy age-matched controls after weeks of RAS gait training. Some retention abilities after weeks of training with
RAS use also exist. Improved activities of daily living were maintained 6 weeks after 6 weeks of physical therapy with auditory cues imbedded in the training [49]. In contrast gait, balance and physical function measures were not maintained 6 weeks after a 3 week cued gait training protocol [50]. Further investigations are warranted to uncover whether the retention effects of using RAS are limited to the duration of training and to establish RAS effects on more difficult movement patterns.

The primary goal of the current study was to explore the abilities of individuals with PD to alter their stepping performance with no cues after 6 weeks of multi-directional step training with RAS. Since switching from one task to another is a major function of the BG and this ability is impaired in PD, the duration of switching step direction (direction switch duration, DSD) served as the primary kinematic measure of step performance. The ability of PD patients to retain changes over baseline values for a relatively long period of time was also investigated. We hypothesized that DSD during step performance without RAS would decrease after training with RAS and that changes would remain at least for several weeks after training. Other kinematic measures were determined to offer comparisons between the present step task and the more commonly used task of walking. Step performance with RAS before and after training offered additional insight to training effects on the trained task (task specificity).

Methods

Participants

Twenty-seven individuals diagnosed with PD volunteered to participate in the study. Of the 21 who qualified for participation 5 were used for pilot tests (group P), leaving 16 to participate using the final protocol. All participants provided consent approved by the university’s Internal Review Board. Disease severity was identified according to the Hoehn and Yahr (H&Y) scale [51] and the intensity of the motor symptoms was determined according to
Unified Parkinson’s Disease Rating Scale (UPDRS) [52]. Qualified participants: 1) were diagnosed with idiopathic PD; 2) presented with disease severity stages 2 to 4 (H&Y); 3) had stable drug usage; 4) were capable of standing and walking independently with or without an assistive device; 5) were able to identify auditory cues and 6) had no signs of cognitive deficits as determined by the Mini Mental State Examination Score (MMSE > 24, [53]). Participants were also disqualified if they reported a history of other disorders or acute injuries that could influence their ability to complete the program. Unstable drug use was determined according to individual reports of medication change and according to items 37 (score = 1) and 39 (score > 2) of the UPDRS.

Study Design

Participants visited the training site during a screening visit where they became familiar with the study design, were evaluated for qualification and agreed to participate. Once qualified, participants were assigned to a Cue (C) or a No cue (NC) training group in a pseudo-random fashion. This design allowed homogeneity across groups by randomly assigning the first qualified volunteer to one group and allocating the next participant with the same disease level to the opposite group, yielding 8 participants per group. Those in the C group participated in a multi-directional step training protocol with and without RAS while those in the NC group performed the step training with No RAS only. In addition to several individual characteristics an average forward stepping cadence from five 10 second trials was calculated to obtain a comfortable/normal step cadence (Table 4.1). Screening, training and evaluations were conducted in the same location by a physical therapist, certified in UPDRS collection.

Multi-directional Step Training

Step training took place 3 times per week for 6 weeks in sessions approximately 1 hour in length. Participants took medication about 1 hour prior to each session, which was confirmed
upon arrival. Three participants had to postpone 1 session each for not adhering to their medication schedule.

During RAS step training participants received instructions and demonstrations for the corresponding step training task at the beginning of each session, after given breaks and upon request. Participants started with their feet in anatomical position at a self-selected distance apart. They were asked to step away and back in time with the RAS beats and told that the foot should completely leave the ground and foot sole completely contact the floor with each step. Trial duration was kept relatively short (33.75 s) in order to avoid fatigue [54]. This duration resulted from the specially designed software. The training schedule followed previous suggestions for PD training regiments, which suggest breaking down complex movements at initial training sessions [23]. Accordingly, the following weekly schedule was implemented:

Week 1: each direction separately, legs separately (e.g. right leg, forward steps (and back) for 33.75 s);
Week 2: each direction separately, legs alternated;
Week 3: two directions per trial, legs separately (e.g. left leg, back steps for 11.25 s, then side steps for 22.5 s);
Week 4: two directions, legs alternated;
Week 5: three directions per trial, legs separately (e.g. left leg, side steps for 11.25 s, then forward steps for 11.25 s, then back steps for 11.25 s; and
Week 6: three directions, legs alternated.

Thirty-six trials were performed in each training session. During week 1 participants performed each speed/direction combination twice (3 speeds x 3 directions x 2 legs x 2 times). Participants performed 6 direction combinations (B→F, B→S, F→S, F→B, S→F and S→B) for week 3 (3 speeds x 6 direction combinations x 2 legs). They performed 6 different direction
combinations (F→S→B, F→B→S, B→S→F, B→F→S, S→F→B and S→B→F) for week 5 (3 speeds x 6 direction combinations x 2 legs). During even numbered weeks the number of trials was equal to that of the two legs combined of the odd weeks, as alternating feet replaced performing each side independently. Combinations were randomized within each training day and for each leg separately on odd weeks. One to five trials were repeated for 4 participants for not adhering to instructions.

Three different auditory cues, cluck, ding and soft cork, were recorded at a 22.5 kHz. The cluck, ding and soft cork sounds had frequencies of 1003.3 Hz, 784.93 Hz and 529.38 Hz and durations of 88 ms, 915 ms and 127 ms, respectively. Cue presentation for RAS was generated by a specially designed LabView program and presented through two speakers at approximately 75 dB, well above the average hearing loss range (25-40 dB) for older adults [55]. Prior to testing participants in P and C groups were presented with cues in a random order and were asked and able to raise their hands and describe them when heard.

RAS was absent during the No RAS condition, thus individuals were instructed to step at a “comfortable” cadence or “relatively faster” or “relatively slower” than their normal step cadence. In order to avoid mental fatigue and allow accurate performance within a specified direction, participants were given a “last step” verbal cue approximately 1 second before a direction switch. Initiation of trials was prompted by “Ready?”, pause, “Start” command and a “Stop” command was used for trial termination. Other details of the training protocol were similar to the RAS condition. Three to 5 trials were repeated for 3 participants for not adhering to instructions.

Evaluation

Testing sessions involved the multi-directional step task performed on week 6 to gain insight to kinematic alterations that were expected with training. Three direction combinations,
F→S→B, S→F→B, and B→S→F, were performed at the 3 speeds to yield 9 trials without RAS for the NC group and 18 trials (9 RAS and 9 No RAS) for group C. These direction combinations allowed participants to initiate stepping in each of the three directions and to change step direction to and from each direction. The reduction from the 6 possible combinations to 3 resulted from fatigue effects noted with group P. Since group C was tested with and without RAS, the No RAS condition was always tested first. This allowed comparison of the No RAS condition after similar warm up to the NC group and eliminated immediate short term effects of RAS. The order of direction combinations was randomized within each condition on each test day.

Stepping performance of participants was recorded on the first day of training for a pre-test (PRE), on the last day of training for a post-test (POST), and for retention tests, 1 week (RTW1), 4 weeks (RTW4) and 8 weeks (RTW8) after training. Three-dimensional motion of reflective markers placed on the lateral malleoli of the two ankles, were recorded with a four camera digital video system (Qualisys Mediacla AB). The first auditory cue of RAS triggered initiation of the camera capture and simultaneous 60 Hz data collection of markers. The RAS cues in a direction change occurred after the 11.25 s and 22.5 s according to the given cadence for a given speed. For the No RAS conditions this program was silenced and the visual display of the programs allowed the examiner to signal the participant for movement initiation, direction switching and termination as described previously. Participants did not receive step training between POST and RTW8 and were asked to continue with normal activities during the program.

Data from the ankle markers were analyzed through customized Matlab and LabView programs. Position data were filtered through a zero phase lag 10 point averaging design. Tangential velocity profiles were calculated by five-point differentiation of the filtered position
data. Position and tangential velocity profiles were plotted across time, visually scanned and marked to help determine kinematic measures. Figures 4.1A and 4.1B show plots from these profiles and example markings used for calculating kinematic measures described below.

Movement onset (ON) and end (END) corresponded to the frame prior to the first discernable movement in the given direction and the frame after the last discernable change in the given movement direction, respectively, from position profiles.

Several spatial and temporal kinematic measures affected by PD were calculated to offer insight regarding movement changes before and after training. Selected measures were based on reductions in gait velocity [56] and step length [57] in addition to shuffling of the feet during gait[6] and changes in cadence [58] for those with PD. Direction switch duration (DSD) was selected as the primary measure because temporal movement transition is a well-known disruption in PD [21, 22]. DSD was defined as the duration between the time the foot returning to the platform stopped moving in one direction and the time when the opposite foot moved to leave the platform to the next direction according to ankle markers. For example, the frame for ON of the left ankle side was subtracted from the frame for END of the right foot back divided by the 60 Hz sampling frequency (see ON-DSD and END-DSD, Fig. 4.1A). Peak tangential step velocity (VEL) was identified as the maximal step velocity between ON and END of each step from the tangential velocity profile of the ankle marker of interest (see ON-MOV and END-MOV, Fig. 4.1B). Kinematic variables of step length (SL), step height (SH) and step number (SN) were also calculated. SL was calculated as the displacement of the ankle marker in the lateral (y-) direction for side steps or anterior/posterior (x-) direction for forward or back steps. In a back step, for example, SL was the difference between the x-values at END and ON of a given step (see END-MOV and ON-MOV, Fig. 4.1B). SH was determined as the maximal z-value during this same time minus the average of the first five z-value frames during stance at
Figure 4.1 Example of position and velocity marking. Examples of position (A and B) and velocity (B) profiles used for identifying different kinematic variables are indicated. Data are from two different trials for plots in A and B. Example markings used for direction switch duration (DSD) are plotted in A and those for peak step velocity (VEL), step length (SL), step height (SH), step number (SN) and reaction time (RT) are plotted in B. Position and velocity profiles are separated in B for better clarity. Plots in A show the end of the movement of the right ankle marker in the back direction (x) is indicated by the END DSD solid line and the onset of the movement of the left ankle marker in the side direction (y) is indicated by the ON DSD solid line. Plots in B show corresponding lines determined for a single step and indicate ON MOV and END MOV of the first back step (x) of the right ankle marker. The vertical dashed line represents 11.25 s associated with the timing for a direction change.
the beginning of a trial. SN in whole or half steps for each direction of a trial during the 11.25 s
was also determined. A half trial was counted if the peak of the profile was included in the time
frame while the END was not (7.5 steps were identified for Fig. 4.1B). For SL, VEL, SH and SN
average values for each participant were determined for each direction within a given speed. For
DSD trials were separated based on the direction to which switching occurred. For example, a
B→S→F trial included switching to S and to F directions, thus DSD was determined for these
directions, before average values were calculated for each direction within a given speed for each
participant. Standard deviations were used to determine variability of these measures (see “var”
subscripts), except for step number. Including initial reaction time (RT) in the RAS condition for
the C group allowed us to determine effects of RAS use on RT, if any. RTs to the first cue of
each trial were calculated. These measures were determined as the time interval between the first
cue and the ON frame of the ankle marker of interest (see RT between frame 0 and ON-MOV,
Fig. 4.1B). Final RT values were averaged for each direction, speed and participant.

Statistical Analyses
Pair-wise t tests were performed to compare group characteristics obtained before training (see
characteristics under subject details, Table 4.1). Repeated measures ANOVAs with a random
factor for subject, between subject factor of Group (C, NC), within subject factors of Direction
(F, S, B) and Speed (F, N, S) and repeated measures on Test-day (PRE, POST, RTW1, RTW4,
and RTW8) were used to compared differences between groups and among test days for the No
RAS condition while accounting for direction and speed effects. A similar design with a within
subject factor of Direction and Speed and repeated measures on Test-day was used to compared
the RAS condition across test days. A Kenward Rogers adjusted degrees of freedom was used
because of the relatively small sample size and missing participants on certain test days. Tukey’s
post-hoc tests were used when appropriate to compare selected measures across test days.
Table 4.1 Characteristics and pre-test measures from C and NC groups.

<table>
<thead>
<tr>
<th>Subject details</th>
<th>C group</th>
<th>NC group</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>73.3 ± 2.2</td>
<td>70.5 ± 2.2</td>
<td>0.59</td>
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<tr>
<td>Gender</td>
<td>F = 3, M = 5</td>
<td>F = 2, M = 6</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168.8 ± 3.3</td>
<td>171.8 ± 4.3</td>
<td>0.52</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79.5 ± 0.18</td>
<td>78.4 ± 0.2</td>
<td>0.80</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>8.9 ± 1.8</td>
<td>7.5 ± 1.2</td>
<td>0.28</td>
</tr>
<tr>
<td>Modified H&amp;Y = number of participants for each stage</td>
<td>2 = 1</td>
<td>2 = 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.5 = 5</td>
<td>2.5 = 5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 = 1</td>
<td>3 = 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 = 1</td>
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</tr>
<tr>
<td>Normal step cadence (steps/min)</td>
<td>56.8 ± 6.0</td>
<td>57.0 ± 7.1</td>
<td>0.63</td>
</tr>
<tr>
<td>DSD (s)</td>
<td>1.34 ± 0.19</td>
<td>1.36 ± 0.25</td>
<td>0.59</td>
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<tr>
<td>DSD\textsubscript{var} (s)</td>
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<td>0.45 ± 0.09</td>
<td>0.41</td>
</tr>
<tr>
<td>VEL (m/s)</td>
<td>0.37 ± 0.04</td>
<td>0.31 ± 0.05</td>
<td>0.56</td>
</tr>
<tr>
<td>VEL\textsubscript{var} (m/s)</td>
<td>0.47 ± 0.08</td>
<td>0.33 ± 0.08</td>
<td>0.53</td>
</tr>
<tr>
<td>SN (steps/11.25 s)</td>
<td>8.0 ± 0.9</td>
<td>8.3 ± 0.8</td>
<td>0.27</td>
</tr>
<tr>
<td>SL (m)</td>
<td>0.28 ± 0.02</td>
<td>0.26 ± 0.02</td>
<td>0.40</td>
</tr>
<tr>
<td>SL\textsubscript{var} (m)</td>
<td>0.15 ± 0.02</td>
<td>0.14 ± 0.02</td>
<td>0.09</td>
</tr>
<tr>
<td>SH (m)</td>
<td>0.06 ± 0.04</td>
<td>0.06 ± 0.03</td>
<td>0.23</td>
</tr>
<tr>
<td>SH\textsubscript{var} (m)</td>
<td>0.027 ± 0.032</td>
<td>0.024 ± 0.037</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Mean ± 1 standard error for subject characteristics and kinematic measures of the C (cue) and NC (no cue) groups recorded on the first day of practice are provided. The p-value results of t tests used to compare groups on these measures are listed. F—female; M—male; H&Y—Hoehn and Yahr score; DSD—direction switch duration; VEL—peak step velocity; SN—step number; SL—step length and SH—step height. The “var” subscript stands for variability of associated measures.

Significance level was preset at p < 0.05 for all analyses (SAS V.9.1).
Results

Sixteen participants completed 6 weeks of training and PRE, POST and RTW1 tests. Three participants were unable to complete RTW4 and RTW8 tests either because of medication change or a scheduling conflict. Two participants from the C group and 1 participant from the NC group missed testing on RTW4, while 1 participant from the C group and 2 participants from the NC group missed testing on RTW8. Analyses and plots in Figs. 4.2 and 4.3 and Table 4.2 account for the change in participant numbers during tests conducted 4 and 8 weeks after training ended.

Subject characteristics and pre-training kinematic measures for stepping with No RAS are presented in Table 4.1 to offer insight to the C and NC participants. These data verify the disease matching between groups and show that most participants were at the moderate stage of the disease (H&Y = 2.5). Results from $t$ tests show that age, weight, height, disease duration, MMSE scores, normal stepping cadence and kinematic measures did not differ between groups.

Training Effects for the No RAS Condition

Certain step kinematics were influenced by training type, but only when accounting for Test-day. Significant Group x Test-day interactions existed for DSD ($F_{4,99.2} = 7.74, p < 0.0001$), DSD$_{var}$ ($F_{4,66.1} = 7.03, p < 0.0001$), SN ($F_{4,58.9} = 21.03, p < 0.0001$) and VEL ($F_{4,65.9} = 10.03, p < 0.0001$) and reveal the major results of this study. For the C group DSD values decreased (Fig. 4.2A), while those of VEL (Fig. 4.2B) and SN (Fig. 4.2C) increased after training and alterations compared to pre-training values were maintained for at least 8 weeks (see blue asterisks, Fig. 4.2). DSD, VEL and SN were significantly different for the C group compared to the NC group on POST, RTW1 and RTW4 (see black asterisks on brackets in corresponding plots identifying group differences). DSD$_{var}$ also remained lower than PRE values up to RTW4 for both groups and was maintained up to RTW8 for the C group (Table 4.2). Differences between groups were
Figure 4.2 Mean kinematic values during the No RAS condition for C and NC groups. Values of (A) direction switch duration (DSD), (B) peak step velocity (VEL) and (C) step number (SN) for C (blue diamonds) and NC (red squares) groups are shown for pre-test (PRE), post-test (POST) and retention tests 1 week (RTW1), 4 weeks (RTW4) and 8 weeks (RTW8) after training for the No RAS condition. Blue asterisks represent a significant difference from the PRE values for the C group. Curly brackets with black asterisks represent a significant difference between groups on the given test day. Error bars represent 1 standard error.
Table 4.2 Mean direction switch duration variability for test day

<table>
<thead>
<tr>
<th>Group</th>
<th>PRE</th>
<th>POST</th>
<th>RTW1</th>
<th>RTW4</th>
<th>RTW8</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>0.413 (8)</td>
<td>0.247 (8)</td>
<td>0.259 (8)</td>
<td>0.189 (6)</td>
<td>0.231 (7)</td>
</tr>
<tr>
<td>NC</td>
<td>0.449 (8)</td>
<td>0.264 (8)</td>
<td>0.244 (8)</td>
<td>0.324 (7)</td>
<td>0.331 (6)</td>
</tr>
</tbody>
</table>

Mean variability of direction switch duration (DSD$_{var}$) during the No RAS condition of the C (cue) and NC (no cue) groups for each test day are shown for the pre-test (PRE), post-test (POST) and follow-up retention tests 1 week (RTW1), 4 weeks (RTW4) and 8 weeks (RTW8) after training. The values in parenthesis represent the number of participants for that test day. Bold values represent significant differences from the PRE values. Asterisks on curly brackets represent a significant difference between groups for the given day.

Figure 4.3 Mean variability values during the RAS condition. Variability measures of (A) direction switch duration (DSD$_{var}$), (B) peak step velocity (VEL$_{var}$), (C) step length (SL$_{var}$) and (D) step height (SH$_{var}$) for the C (cue) group are shown for the pre-test (PRE), post-test (POST) and retention tests 1 week (RTW1), 4 weeks (RTW4) and 8 weeks (RTW8) after training. Asterisks indicate significant differences from the PRE test. Error bars represent 1 standard error.

identified for RTW4 and RTW8 (see asterisks on brackets, Table 4.2), showing that training with RAS helped maintain decreased DSD variability for at least 8 weeks and longer than training.
without it. Overall these findings indicate that certain step kinematics changed more or lasted longer for those training with RAS compared to those without it for the No RAS condition.

Training Effects for the RAS Condition

Training effects on kinematic variables during step performance with RAS for group C showed that variability of the different kinematics during multi-directional stepping was influenced by training with RAS use. A significant effect of Test-day existed for DSD_{var} (F_{4,117} = 3.00, p = 0.0214), VEL_{var} (F_{4,91.9} = 3.40, p = 0.0122), SL_{var} (F_{4,74.1} = 6.54, p = 0.0001) and SH_{var} (F_{4,70.5} = 6.56, p = 0.0002). Plots in Figs 4.3A-D, show that these values decreased after training termination, and remained below PRE values on all retention tests. Other spatial and temporal measures, including RT, did not change significantly after training. Thus 6 weeks of multi-directional step training with RAS decreased the variability of spatial and temporal measures during task performance that were maintained at least 8 weeks after training termination.

Speed and Direction Effects

A main effect of Speed was identified for different kinematic variables obtained during step task regardless of RAS condition. Main effects of Speed were determined for DSD (No RAS: F_{2,222} = 18.73, p = 0.002; RAS: F_{2,115} = 7.35, p = 0.001), VEL (No RAS: F_{2,110} = 10.51, p = 0.006; RAS: F_{2,117} = 13.42, p < 0.0001) and SN (No RAS: F_{2,78.2} = 14.19, p < 0.0001; RAS: F_{2,115} = 9.13, p = 0.002). Figure 4.4 shows that VEL (A) and SN (B) increased for the fast speed and decreased for the slow speed relative to the normal stepping speed for No RAS (left panels) and RAS (right panels) conditions. Participants also decreased DSD for the fast speed and increased it for the slow speed in comparison to the normal stepping speed (Fig 4.4C). These results suggest that participants were able to adjust peak step velocity, duration of step direction switching and number of steps to either follow task instructions related to speed change in the No RAS condition or follow auditory cues in the RAS condition. Direction effects were also
Figure 4.4 Mean kinematic values across speeds without and with RAS. Mean values of the (A) peak step velocity (VEL), (B) step number (SN) and (C) direction switch duration (DSD) are shown for slow, normal and fast speeds for the No RAS (black plots, left panel) and RAS (blue plots, right panel) conditions. N = 16 (C and NC participants) for the No RAS plots and N = 8 (C participants) for the RAS plots. Asterisks between slow and normal and normal and fast speeds indicate a significant difference between the corresponding values. Error bars represent ±1 standard error. Note, some bars are too small to see in plots.

identified for most kinematic variables during the step task whether RAS was used or not.

Significant main effects of Direction were determined for SL (No RAS: $F_{2,88.2} = 13.69$, $p < 0.0001$; RAS: $F_{2,116} = 7.75$, $p < 0.0001$), SL$_{var}$ (No RAS: $F_{2,109} = 16.57$, $p < 0.0001$; RAS: $F_{2,115} =$
SH (No RAS: $F_{2,229}=17.21$, $p < 0.0001$; RAS: $F_{2,116}=5.03$, $p < 0.0001$), SH$_{var}$ (No RAS: $F_{2,141}=21.82$, $p < 0.0001$; RAS: $F_{2,116}=3.84$, $p = 0.001$), VEL (No RAS: $F_{2,118}=24.31$, $p < 0.0001$; RAS: $F_{2,118}=18.01$, $p < 0.0001$) and VEL$_{var}$ (No RAS: $F_{2,171}=3.48$, $p = 0.03$; RAS: $F_{2,115}=268.65$, $p < 0.0001$). Figure 4.5 shows that SL (A), SH (B) and VEL (C) were always smallest for the back stepping direction for the No RAS (left panels) and RAS (right panels) conditions. In contrast the variability of these measures were largest for back steps (No RAS: SL$_{var}=0.17 \pm 0.09$ m, SH$_{var}=0.028 \pm 0.002$ m, VEL$_{var}=0.44 \pm 0.05$ m/s; RAS: SL$_{var}=0.15 \pm 0.09$ m, SH$_{var}=0.027 \pm 0.002$ m, VEL$_{var}=0.41 \pm 0.02$ m/s) and significantly different from forward (No RAS: SL$_{var}=0.13 \pm 0.09$ m, SH$_{var}=0.025 \pm 0.009$ m, VEL$_{var}=0.40 \pm 0.05$ m/s; RAS: SL$_{var}=0.12 \pm 0.09$ m, SH$_{var}=0.020 \pm 0.002$ m, VEL$_{var}=0.29 \pm 0.03$ m/s) and side (No RAS: SL$_{var}=0.13 \pm 0.94$ m, SH$_{var}=0.023 \pm 0.002$ m, VEL$_{var}=0.39 \pm 0.05$ m/s; RAS: SL$_{var}=0.12 \pm 0.89$ m, SH$_{var}=0.021 \pm 0.002$ m, VEL$_{var}=0.31 \pm 0.02$ m/s) step directions. Step length, step height and peak step velocity clearly differed for back steps compared to the forward and side steps in this task. Overall, 6 weeks of multi-directional step training with and without RAS resulted in alterations that were maintained at least 4 weeks after training termination. These alterations are discussed further in the following section.

**Discussion**

This study was conducted in order to add to the limited research on long term training effects of RAS use on transitional movements for those with PD. The multi-directional step protocol was designed to focus on step direction changes in a supervised environment. Such changes in movement are known to cause difficulties for people with PD [22]. C group participants decreased their absolute duration of step direction switching, increased their peak step velocity and the number of steps in a given time period and maintained these improvements above baseline values at least 8 weeks after practice terminated. Step practice resulted in decreased variability of the duration of step direction switching during the No RAS task regardless of RAS use in training. Participants who trained with RAS were able to maintain these
Figure 4.5 Mean kinematic values across directions without and with RAS. Mean values of the (A) step length (SL), (B) step height (SH) and (C) peak step velocity (VEL) are shown for forward, side and back directions for the No RAS (black plots, left panel) and RAS (blue plots, right panel) conditions. N = 16 (C and NC participants) for the No RAS plots and N = 8 (C participants) for the RAS plots. Horizontal bars indicate significant differences at the bars’ ends. Error bars represent ±1 standard error. Note, most bars are too small to see in plots.

Improvements longer. Supplementing multi-directional step training with RAS offered several kinematic alterations when performing the step task without RAS use that were not observed in those training without it. These alterations appear beneficial as the changes that occurred mimic those of walking in healthy adults.
Training Effects

The severe slowness during transitions observed previously for PD patients [22, 69] led to expected slowing of step direction switch durations in this population prior to training. The present study did not, nor was it designed to observe this slowing prior to training. Rather, it revealed a significant reduction in DSD accompanied by increase in peak step velocity and step number for the No RAS condition after training for the C group participants. No such changes were detected for those in the NC group. These findings follow those of straight line walking where reduced durations of Vastus Lateralis activity accompanied increased step cadence and average gait velocity only for PD participants who received 3 weeks of gait training with RAS [47]. Minimal, non-significant changes were detected for individuals with PD receiving the same type and amount of training with no external cues [47]. Together these studies provide evidence that RAS training results in movement modifications when performing tasks involving directional adjustments without cues that do not occur without use of RAS in training. Moreover, results from the current study showed that PD patients were able to retain such improvements in the stepping task for at least 8 weeks.

Unlike the aforesaid measures DSD\text{var} obtained during stepping in the No RAS condition decreased similarly for both groups immediately after training termination and was maintained for at least 1 week. Higher temporal variability without cues reported for finger tapping [59], repetitive wrist flexion [60] and stepping [4] in this population is observed, thus it is not surprising that temporal variability can decrease with certain applications. Remember that verbal commands were given at the end of each direction time period for participants during the No RAS condition. Results from the No RAS condition mimic those for reduced variability of movement duration after presentation of a single auditory tone provided shortly before initiation of a multi-segmented reaching task compared to reaching without a tone [61]. It is possible that
the attention control offered by a verbal start cue [21] for the direction change in the No RAS condition for both groups was adequate to result in the immediate decrease in $DSD_{\text{var}}$. However, this does not explain why participants in the C group were able to maintain these improvements longer. Alterations in neural pathways may help explain the greater retention capabilities observed for this group as reductions in step to step variability during non-cued walking after RAS gait training are directly linked to changes in central pathways according to Positron Emission Topography (PET) records [62]. These activated pathways were similar to those reported during RAS paced finger tapping and different from those of internally generated finger tapping [63]. Further studies are warranted to verify such direct effects of RAS on attention and neural pathway alterations in this population.

Retention abilities in No RAS conditions were not exclusive to $DSD_{\text{var}}$ as changes in DSD, VEL and SN, were also maintained 8 weeks after training termination for the C group participants. Using RAS during training appears to help people with PD maintain alterations in step kinematics for a period of time longer than the training period, exceeding that of equal retention reported previously; 6-week retention of UPDRS-ADL scores were observed after 6 weeks of physical therapy with auditory cues compared to that with no cues [49]. The present results suggest that longer retention of these scores would be observed if tested, however maintaining movement alterations for a period of time twice as long as the training period seems unlikely for walking or stepping, as loss of improvements in average gait velocity and stride length were observed when walking without RAS, 6 weeks after a 3-week RAS gait training protocol [50]. Future studies could determine whether longer training regimes such as 6 weeks can produce longer relative training retention over shorter training regimes such as 3 weeks. Regardless of such findings, it seems clear that supplementing training with RAS results in
certain kinematic changes that carry over to the No RAS condition and can be maintained over a relatively long period of time.

Training effects with RAS use on spatial kinematic measures during the No RAS condition are not as consistent as the kinematic measures just discussed. No changes in spatial values of SL, SH and their associated variability measures were detected for the No RAS condition of the multi-directional step task. Increase in step length with and after application of RAS was reported in some cases of straight line walking (e.g. [41]), however not in others [30, 40]. It is thought that RAS use may not influence muscular amplitude to an extent to cause absolute step length changes [40], as its primary influence is on temporal aspects of movement [30, 40]. Thus although effects of RAS on spatial measures do exist, these different outcomes may result from indirect rather than direct links to RAS use. Direct effects of RAS use on spatial variability help explain the different study findings in absolute length changes and offer further insight on this issue.

Kinematic outcomes from multi-directional step training with RAS for the C group often differed from those in the No RAS condition. Kinematic alterations after training were limited to the variability measures for RAS condition. These variability reductions remained at least 8 weeks post training. Thus, although temporal variability reductions were detected for both RAS and No RAS conditions for DSD_{var}, changes in spatial variability were limited to the RAS condition. Different neural mechanisms suggested for temporal and spatial variability measures are blamed for this disparity. While temporal variability appears under the control of central time keepers, possibly located in BG and cerebellum [62], spatial variability has been linked to the noisy muscle output [64]. Specifically, the abnormal activity of sub-cortical structures such as the reticular formation is linked to the abnormal muscle activity in PD [65]. Thus, it is possible
that changes in spatial variability represent the influence of RAS on the proposed reticulo-spinal pathway [66, 67] because it does not carry over to the No RAS condition.

Results on reaction time (RT) support previous findings for people with PD. Step RT to initial cues did not change for C participants after training. Previous work indicated no changes in simple and choice RT after hundreds of practice trials for a discrete reaching task for those with PD [68]. It appears that, whether using the upper or lower limbs or simple or choice RT, training does not affect RT in certain subgroups of this population. These findings are not verified for PD patients with more or less disease severities or severe freezers with the disease.

Several alterations in kinematics determined during performance of the multi-directional step task after practice with RAS use were observed. On the other hand only one measure, the variability of step direction switch duration, changed after training without RAS use. Training with RAS resulted in significant reductions in spatial and temporal variability measures. In this case the temporal variability of step measures reduced in the No RAS condition after training, no such alterations occurred for spatial variability measures. Thus, not all RAS training effects transferred to the No RAS condition.

**Speed and Direction Effects**

Certain kinematic alterations were identified during multi-directional step performances in RAS and No RAS conditions. Most effects of speed and direction on these variables occurred regardless of training.

Individuals with PD are capable of adjusting muscular force internally [69] and to external demands [21]) when movement speed requires adjustments. However, the peak movement velocity and muscle amplitude remain abnormally low [69] due to deficient muscle activation [70]. Thus, individuals with PD can also modify cadence, average step velocity and step duration for different non-cued [58] and cued [39] walking speeds even though the overall
speed remains slower than healthy controls [39, 58]. In the current study participants showed similar capabilities by adjusting DSD, VEL and SN to slow and fast stepping speeds regardless of the RAS condition. They also showed no alterations in step length like other PD individuals walking at different speeds [58] or with different RAS frequencies [30]. Therefore, PD participants in the current study were able to adjust certain step kinematics to alter their speed for the selected stepping task even with expected low muscle activation levels and overall slowness.

It is important to note that although individuals with PD can modulate movement speed, adding RAS can enforce further alterations for a given speed. For example, gait velocity increased with use of a comfortable RAS frequency compared to a self-selected walking speed in PD [37]. Higher values of velocity detected during gait with +10% RAS compared to a self-generated maximum gait for individuals with PD, on and off medication also exist [57]. Furthermore previous findings indicated higher VEL and lower DSD values for all RAS speeds compared to their corresponding No RAS stepping speed prior to training (see chapter 2). According to these findings it is evident that speed regulation occurs regardless of RAS, but adding this modality may lead to faster movements in response to a given speed (e.g. peak step velocity for the normal speed with RAS was higher than peak velocity for the normal speed without RAS, Chapter 2). Moreover, the speed adaptations occurred, regardless of the movement direction and despite higher instabilities reported for the back direction [71].

Moving in the back direction clearly differs from side and forward movements for those with PD. In the current study stepping back resulted in lower VEL and higher VEL variability. These findings agree with a previous report which indicated that back direction stepping is significantly slower than forward stepping for those with PD [72]. However no known reports on greater peak step velocity variability for this direction and population exist until now. The lower SL, SH and associated variability measures for back stepping in the present work is likely
indicative of greater imbalance in this direction. This is because higher stride length variability [73], reduced step height [74] and stride length [72] are associated with gait initiation instabilities.

Conclusion

Results from the current study indicate that movement kinematics for multi-directional stepping are modified after RAS training. This was indicated by a faster step direction transition (DSD), greater step frequency and velocity and lower variability for DSD. These changes were maintained at least 8 weeks after training terminated and indicate the effectiveness of this modality for modifying activities that require direction transition, a difficult movement for those with PD.

References


CHAPTER 5: GENERAL DISCUSSION

Key Results

The debilitating effects of PD on motor performances have led to many investigations for alleviating motor symptoms for this population. Medical and surgical treatments relieve several motor symptoms but some complications such as temporal movement parameters are resistant to these treatments. Rehabilitation methods such as RAS application hold many benefits as noninvasive strategies for improving motor performance for repetitive movements such as straight line walking in those with PD. In this document studies on the effects of RAS use during performance of the multi-directional step task extend the knowledge of RAS use to a more complex activity which presents difficulties for those with PD.

In chapter 2 we explored the effects of RAS on multi-directional stepping kinematics in PD participants where they performed the stepping task with and without RAS. Results showed that direction switch duration (DSD) of stepping, peak step velocity (VEL) and step number (SN) differed across speeds for performances with and without the use of RAS. An increase in VEL and decrease in DSD was observed for participants stepping with the use of RAS. Various functional gait and balance measures were also collected to evaluate associations of kinematic and functional measures with one another and disease severity. Results showed that DSD was the only kinematic measure with significant links to disease severity and various functional measures of gait and balance including the primary measure of interest, the dynamic gait index (DGI). These results offered short term effects of RAS use on the multi-directional step task.

Investigation of the long term effects of RAS use with multi-directional step training were explored in chapters 3 and 4. Step training and RAS influence on functional gait and balance measures were presented in chapter 3. The multi-directional step task was performed by two groups of PD patients, those who received RAS/auditory cues (Cue, C) and those who did
not (No cue, NC). Both groups underwent 3 days/week of multi-directional step training for 6 weeks with increasing difficulty each week. Performance of PD participants during non-cued gait and balance functional testing was investigated before training, immediately after training and up to 8 weeks after training termination. Immediately after practice both C and NC groups showed improvements in the primary gait measure of interest (DGI), as well as other gait measures. Although both groups were able to maintain balance improvements for at least 8 weeks, only the participants from the C group maintained gait improvements during this time.

Chapter 4 was used to explore the underlying cause of such functional improvements. Kinematics obtained from C and NC groups during performance of the multi-directional step task without RAS use was studied along with functional tests before training, immediately after training and up to 8 weeks post training. The variability of DSD (DSD\text{var}) during step performance without RAS use reduced immediately after practice and remained lower than pre-test measures at least 4 weeks post training for both groups. The C group maintained this change for at least 8 weeks. Participants in this group were also able to decrease DSD and increase VEL and SN after training and maintain these changes relative to pre-test measures on all retention tests. After training the C group was also able to reduce the variability of SL, SH, VEL and DSD, retaining these changes on all post training visits in the RAS condition.

The following sections will focus on discussion of the relationship among the major results from chapters 2-4. Limitations of the current work and suggestions for future research directions complete this chapter.

**Discussion of the Key Results**

*Linking Immediate and Long Term RAS Effects*

Several investigators have evaluated the use of RAS on gait related activities for various populations to offer insight to either its short term (immediate) or long term (training) effects.
The following section will focus on RAS effects for such immediate and training comparisons for the PD population.

Studies to examine RAS effects after its short term [1-7] and long term [8-11] use exist. While in the short term studies investigators evaluate activities with and without RAS, those for the long term investigations emphasize assessment of non-cued performances only. This latter assessment offers excellent insight into generalization of activities to a more common, non-cued environment but does not clarify the specific cue influence on movement after practicing with RAS. The current design allowed us to compare some short term and long term training effects with use of RAS on multi-directional step performance with and without cueing.

Figure 5.1 shows the major outcomes for the RAS/No RAS comparisons of different kinematic measures for the C group. Immediate RAS effects were identified for DSD and VEL during the pre-test (Fig. 2.2A, B) and did not change significantly with training (chapter 4). The values for each of these variables after training for post and retention tests were very similar to pre-test values and similar to values for the No RAS condition (see Fig. 5.1A, B). The non-significant trend identified for immediate RAS effects for SN (Fig. 2.2) also did not change significantly with training (chapter 4), however post-test and retention test values were similar for the RAS and No RAS condition regardless of the training improvements observed for the latter (see Fig. 5.1C). Thus, it is evident that for the specified measures any immediate RAS effects do not improve with training. Furthermore, training with auditory cues resulted in alterations in the No RAS condition to achieve similar changes to those immediate effects of RAS use. These results indicate no additional improvements in these measures with the use of RAS during step performance after training (i.e. observe similar POST-RTW8 values for RAS alterations in the No RAS condition to achieve similar changes to those immediate effects of RAS use. These results indicate no additional improvements in these measures with the use of
Figure 5.1 Mean kinematic values with and without RAS for the C group across test-days. Mean values of (A) direction switch duration (DSD), (B) peak step velocity (VEL), (C) step number (SN), (D) direction switch duration variability (DSD_var), (E) peak step velocity variability (VEL_var), (F) step length variability (SL_var) and (G) step height variability (SH_var) are shown for the pre-test (PRE), post-test (POST) and retention tests 1 week (RTW1), 4 weeks (RTW4) and 8 weeks (RTW8) after training. All data are from the C (cue) group participants for No RAS (blue) and RAS (black) conditions. Blue and black asterisks represent a significant difference from the PRE values for the No RAS and RAS conditions respectively. Error bars represent 1 standard error. Note, some bars are too small to see in plots.
RAS during step performance after training (i.e. observe similar POST-RTW8 values for RAS and No RAS, Fig. 5.1A-C). In contrast, no immediate changes for DSD\textsubscript{var} were found with RAS application, but DSD\textsubscript{var} decreased after training completion and remained that way during all No RAS (see group C, Table 4.2) and RAS (Fig. 4.3A) post-training tests. Figure 5.1D shows these results plotted together, emphasizing a greater variability reduction for DSD with the use of RAS during post training evaluations. The reductions in DSD\textsubscript{var} observed after training with RAS results in DSD\textsubscript{var} reductions for stepping with and without cues, however stepping with cues will offer additional reductions in this variable for those with PD. Like DSD\textsubscript{var}, variability of step length, (SL\textsubscript{var}), step height (SH\textsubscript{var}) and peak step velocity (VEL\textsubscript{var}) did not change significantly with RAS use on pre-tests (chapter 2) but did change significantly after training completion for the RAS condition (Fig. 4.3B-D and Fig. 5.1E-G). No alterations in these variables were observed for the No RAS condition across different test days (Fig. 5.1E-G). It appears that for these variables RAS training effects are context specific. Together, these results provide evidence for immediate RAS effects on absolute temporal variables and training RAS effects on spatial and temporal variability measures for the multi-directional step task. Previous work on RAS effects for either its immediate or long term use support the findings just listed, and were discussed in chapters 2 (immediate) and 4 (long term).

The Underlying Mechanisms

By including C and NC groups and testing functional and kinematic parameters we are able to make several speculations regarding the underlying mechanisms involved for the observed changes. As specified earlier RAS use with training for participants with PD resulted in several kinematic measurement alterations in the No RAS condition that were maintained on follow-up evaluations (see DSD, VEL and SN plots, Fig. 4.2). Alteration in one functional measure was also determined for post- and follow up tests exclusively for the C group (see
FOGQ values in Table 3.2). In other cases training resulted in kinematic and function measurement alterations regardless of RAS use, however the measurement changes retained for a longer period of time in PD participants that trained with RAS (see DSD\textsubscript{var} values, Table 4.3; DGI plots, Fig. 3.2 and UPDRS-ADL, UPDRS-composite, Tinetti-gait and TUG values, Table 3.2). These observations indicate that the underlying factors for the observed alterations differed between groups. Thus different mechanisms can be suggested for practice with and without RAS.

Two suggestions have been posed to explain the carry over effects of RAS use to a no RAS condition for people with PD. One suggestion is that RAS resets the central time keepers which allow the movement to be entrained to temporal features of RAS [8]. This assumption is based on the ability of PD participants to regenerate a given movement with high levels of accuracy and low levels of temporal variability during a no RAS walking condition performed immediately after a RAS walking condition [8]. This explanation leaves one to wonder how the central time keepers reset in PD with a deficient component. Thus, a second suggestion to explain the carry over effects of RAS use in PD is the activation of a compensatory pathway which bypasses the defective BG. Projections from the cerebellum to the SMA and higher cortical areas offer a suitable compensatory pathway for explaining kinematic and functional findings in general [11]. Activation of such a pathway was proposed when associated activities were observed during a PET scan of finger tapping without RAS immediately after RAS gait training in the same participants with PD. Not only was there a transfer to an environment with no external cueing, the movement task changed from the lower to upper limbs. A similar pathway has also been suggested to take over auditory paced finger tapping compared to internally generated tapping [12]. Outcomes of the current and other RAS studies offer behavioral evidence for insights to the neural compensation abilities using external cueing.
Practice without RAS also results in central changes which can explain some of the improvements observed for the NC participants. PET scans [13] and functional magnetic resonance imaging (FMRI) [14] results after practice reflect the patient’s ability to overcome certain deficiencies by recruiting greater neural areas. After learning sequential aiming tasks, PD patients revealed additional brain activation in pre-frontal and parietal cortices compared to healthy individuals [13]. Patients who presented with abnormal activity in the BG recruited additional areas including parts of the cerebellum, pre-motor, pre-frontal and parietal cortices after learning a sequential finger movement sequence while counting letters [14]. Similar increased activation exists following learning of sequential arm movements [15] and aiming tasks [16]. Evidently, patients recruit multiple cortical and sub-cortical regions to override the inappropriate output of the BG and to overcome certain motor deficits during motor learning.

While practice without the use of RAS helps individuals with PD activate additional brain areas, the primary neural pathway involving the deficient BG does not change. Alternatively, externally paced movements using RAS are better performed because they are controlled through a pathway that circumvents the BG. Thus while similar compensatory brain areas are involved with or without RAS practice the abnormal signals from the deficient BG do not interfere when RAS is applied. This can be a possible advantage for adding RAS to a regular practice regiment and might be the primary source of the observed differences between C and NC participants.

It is possible that the aforementioned central mechanisms are not the only factors behind the observed changes. The improvements that occurred only during the RAS testing for the C group (SL\textsubscript{var} and SH\textsubscript{var}) which did not transfer to the No RAS condition is an indication of this issue. In addition lack of correlation between DSD\textsubscript{var} and functional tests that improved in the NC group indicates that other factors might be involved. Reports indicate changes in muscle activation symmetry in lower extremities during gait after RAS gait training [8] and increases in
muscle strength after No RAS balance training [17]. It is possible that similar muscular related changes occurred but we cannot verify this as they were not collected in this study. Furthermore, it is difficult to make assumptions regarding the underlying muscle changes based on the current findings because several gait related kinetic and kinematic measures appear to be independent of one another. For example, the generated power in the lower extremity appears to have no connections to gait velocity [18]. Elsewhere, the generated forces during walking are independent of walking speed, gait symmetry and gait swing durations [19]. More research is required to clarify muscular mechanisms involved with training in PD and RAS use. Such findings would allow us to better understand the underlying causes of behavioral improvements post-training and to better identify the effectiveness of various training programs.

**Limitations**

Limitations that may affect generalization of findings exist in every study. Those linked to participant characteristics are listed first. This is followed by those linked to study methodology.

One of the primary limitations is that associated with the participants’ disease characteristics. Participants in the current study were primarily at the moderate stage of the disease. While those with more severe disease within this group revealed observed improvements, the overall lack of distribution in terms of disease severity poses limitations to generalizing the current results to individuals at more and less severe stages of the disease.

Other participant characteristics present potential limitations in the present study. Since most of the participants were recruited from a local support group, it is likely that participants were seeking strategies to deal with their disease and were highly motivated, thus represent a limited group of individuals with PD. The participating individuals also lacked obvious cognitive disorders. Lack of cognitive deficits is used as the primary inclusion criterion for many of the
rehabilitation studies [8, 20-22]. Yet research indicates that the annual MMSE decline for those with PD is 1 point per year [23]. One in 5 individuals with Parkinson’s disease has dementia [24] and declines 2 points per year in the MMSE scores [23]. These observations make one wonder whether the training protocol could be generalized to people with PD with less motivation or greater cognitive deficits.

Other limitations of the study were not dependent on participant characteristics. Although numbers of participants needed to achieve 80% power on the main functional measure of the DGI were only 6 in each group, this number did not ensure appropriate power on all variables of interest. Having a design with a tester not blind to the study is another limitation. It is clear that double blind placebo controlled studies can produce more credible results. Lastly, including a healthy age-matched control group would have provided more insight to the pre-test deficits and nature of improvements in those with PD.

Regardless of study limitations, several positive outcomes were identified. Overall, use of auditory cues for multi-directional step training altered certain movement abilities to mimic those of controls and/or helped with maintenance of abilities in people with Parkinson’s.

**Future Directions**

Rehabilitation is considered a useful non-pharmacological approach to accompany regular medication in controlling motor complications in PD (Morris, 2000). Reviews of the previous rehabilitation literature [25-27] indicate beneficial effects of practice for PD [28]. Training through rehabilitation appears to be a valuable means for improving motor abilities of PD, including those identified by the UPDRS-Motor and ADL scores and the PD disability scale [29]. With numerous techniques and no unified rehabilitation approach it is difficult to specifically determine a single beneficial rehab regime for those with PD [28]. Rehabilitation effects on motor deficits in PD should continue to add to the evidence-based practices to devise
such a regime or a series of specific well-accepted guidelines to better assist individuals from this population. Studies addressing the limitations listed for the current study are suggested in addition to the following.

Weeks of motor training are reported to cause improvements when certain strategies are followed. These strategies offer evidence based procedures for future rehab studies and may contribute to the final “specific guidelines” for therapists to assist individuals with PD. PD patients learned to correct their own body position errors and retain these abilities for a relatively long period of time when given more practice time than healthy individuals [30]. Providing these people with constant augmented feedback (observing their body sway via their center of pressure measurement on a computer screen) also resulted in improvements and maintenance in balance 1 week post training [31]. Positive reinforcement allowed people with PD to learn and maintain compensatory stepping strategies up to 1 month after 7 weeks of gait training [32]. Practice schedules that began with easy skills and progressed to more difficult skills likely contributed to the improvements observed for stepping [32] and body positioning [30] just reported, as breaking down a sequential movement at initial training period is also suggested for this population [33]. We observed several successful outcomes in the present study by following several of these strategies. While C and NC groups followed similar training techniques, RAS use resulted in longer retention and better improvements for the C group participants. Our knowledge of the neural mechanisms involved with externally paced movements, the behavioral evidence regarding RAS use and more importantly the simplicity of RAS application makes this modality a suitable candidate for further use in other training programs for those with PD. Future research should incorporate this modality with effective learning strategies in order to enhance the training outcomes in individuals with PD with mild and severe levels of disability.
Physical activity is an essential factor for preventing many motor complication associated with sedentary life and alleviating emotional problems associated with PD [34]. Recent investigations also indicate neuro-protective benefits of exercise in a PD animal model [35]. However research indicates low rates of participation in physical activity and sports in those with PD [23]. Similar to these findings over half the participants (9/16) in the current study were not involved in a regular activity or a rehabilitation program. These participants expressed many reasons for activity limitations including transportation limitations (11/16), financial issues (9/16) and insurance restrictions (14/16). These concerns are not limited to the current participants as the average health care costs for an individual with PD is twice and much as a healthy age matched individual [36], while the amount of rehabilitation covered by insurance for these individuals is limited [37]. Therefore it is clear that designing a safe yet effective exercise protocols that can be performed by individuals with PD at home is essential. In fact, research indicates that 8 weeks of self-supervised home exercise can be as effective as a physical therapist supervised design in reducing UPDRS-Motor and TUG scores[21]. However, safety should be a major concern. Use of the multi-directional step protocol from the current study may be a home-based training possibility for these people. Stepping from a stationary position where one can use a walker for assistance should be easier and safer for those at later stages of the disease with severe difficulties in balance and walking. Other techniques, such as mental imagery [38], have been successful to combat motor complications in this population and may offer greater safety in the home. However, evidence regarding its effects on retention abilities are not currently identified. Thus, future investigations are needed to explore and design safe, simple and effective activities specific for individuals with PD at various disease stage that can be performed in the convenience of their home. Based on results from the present work, we suggest that the multi-direction step task with RAS may be such an activity.
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APPENDIX A: LITERATURE REVIEW

Effectiveness of auditory stimulation on movement control in Parkinson’s:
A Literature Review

General Examination
Literature Review

Submitted to the Graduate Faculty of the
Louisiana State University and Agricultural and Mechanical College
in partial fulfillment of the requirements of the general examination
for the degree of Doctor of Philosophy

in

The Department of Kinesiology

by
Zahra Kadivar
B.S. University of Shiraz Medical Center 2003
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<td>BG</td>
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<td>bmp</td>
<td>beats per minute</td>
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<td>BOS</td>
<td>Base Of Support</td>
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1. INTRODUCTION

1.1. Aims of Review

Ever since James Parkinson described the clinical features of Parkinson’s disease (PD) in 1817, scientists became curious to know more about this disease. Despite the arduous efforts of scientists that have increased our knowledge of the disease, there is neither a cure for PD nor a definitive treatment for its symptoms. Consequently, motor deficits remain a primary complaint of patients from this population.

Current rehabilitation techniques provide a means for reducing some of the motor complications associated with PD. Use of external stimuli to help trigger movement has received special attention, as PD patients show the ability to improve some of their symptoms under externally triggered conditions that do not occur with other treatments. Emphasis will be on auditory stimulation because of the greater temporal benefits identified with its use.

The first aim of this review is to introduce major motor complications of people with PD. The second aim of this document is to review the rehabilitation techniques applied to Parkinson’s patients, incorporating the benefits of using auditory stimulation as the external stimulation for improved motor outcomes for those with PD.

1.2. Scope of Review

Because PD reflects the dysfunctional basal ganglia, these complicated nuclei and their cortical and sub-cortical connections are introduced first. These findings will lead to the description of the disease and its pathophysiology with emphasis on motor complications. The role of the basal ganglia in motor control is then addressed in theoretical links. A complete review on the medical and surgical interventions is beyond the scope of this review; therefore a brief discussion on these interventions is provided and followed by a more detailed review of different rehabilitation techniques and motor learning outcomes in PD patients. Presentation of movement alterations in PD patients from rehabilitation using auditory stimulation complete the
topics reviewed. Finally, a summary of the findings, which lead to questions for future research and the associated hypotheses, are offered.

2. OVERVIEW OF PARKINSON’S DISEASE

Parkinson’s Disease (PD) is a neurodegenerative disease which was first introduced by James Parkinson in *Essay on the Shaking Palsy* in 1817 as “Paralysis agitans” [1]. PD is the most common neurodegenerative disease after Alzheimer’s disease. The incidence of PD is 13.4 in 10,000 Americans per year [2]. The main problem in PD is mainly the dopaminergic deficiency of the basal ganglia [3]. Under normal conditions dopamine release allows the basal ganglia to serve as an internal trigger, enabling movements to occur in a sequential manner. Disruption of dopamine due to PD disrupts the normal functioning of the basal ganglia, thus voluntary movements. Clearly, to better understand PD and its associated deficiencies, one should first understand the normal functioning of associated neural structures and pathways. The focus of this chapter is to examine the major neural structures and pathways associated with PD, including the major nuclei of the basal ganglia and its connections, and to review the pathophysiology of the disease.

2.1. Neural Structure Overview

2.1.1. Major Nuclei and Pathways of the Basal Ganglia

The basal ganglia (BG) are a group of sub-cortical nuclei that have been grouped and sub-grouped various ways in the literature. For this manuscript BG composition will include: the striatum (STR), which includes the caudate, putamen and nucleus accumbens (NAC); the subthalamic nucleus (STN); the two sections of the substantia nigra (substantia nigra pars reticulata-SNr and substantia nigra pars compacta-SNc), the globus pallidus (GP) divisions of the internal segment (GPi), external segment (GPe) and the ventral pallidum (VP) [4]. The internal and external connections of the BG described below are represented schematically in

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Figure 1. A schematic diagram of the major connections of the Basal Ganglia (BG). Arrow ends connect the structure(s) releasing neurotransmitters and points connect to the targeted structure(s). Excitatory connections are represented by filled arrows and inhibitory connections are represented by empty arrows. Bold arrows represent connections of the BG to external cortical and sub-cortical structures (see key). The orange, blue and red lines represent direct, hyperdirect and indirect pathways, respectively. D1 and D2 are the dopamine receptors located on most striatum neurons. (SNC—substantia nigra pars compacta; SNR—substantia nigra pars reticulata; STN—sub-thalamic nucleus; Gpe—globus pallidus pars externa; Gpi—globus pallidus pars interna; PPN—pedunculopontine nucleus; BS—brain stem; VP—ventral pallidum)

Many BG nuclei are involved in inhibition or dis-inhibition of their associated targets.

The STR [5] and STN [6] serve as the input nuclei. While GPi and SNr are considered the major output nuclei of BG [7], VP is also known as an output nucleus [8]. The striatum receives input from different areas of the cerebral cortex [6], the hippocampus and the amygdala [9]. The
structures of the striatum contain several receptors for different types of neurotransmitters. Of our interest are the dopamine receptors, D1 and D2, which receive their dopamine from the SNc. D1 receptors project to output nuclei, while D2 receptors project to GPe. Upon receiving the dopamine, D1 receptors facilitate the neural transmission of cortically received information in striatum while D2 receptors inhibit such transmission. The output nuclei GPi, VP and SNr receive projections from STN, STR and GPe prior to sending the signals to the ventro-lateral (VL), ventro-anterior (VA), mediodorsal (MD) and intralaminar (IL) nuclei of thalamus, which further target different areas of the cortex (for further details, see [10]). Figure 1 shows a schematic representation of these connections.

Research on BG has led to the proposal of a classic view including two parallel cerebro-basal ganglia loops which start in cerebral cortex, pass through the BG and end back in the cerebral cortex [11-13]. The loop involves direct and indirect pathways which are responsible for excitation and inhibition of voluntary movements, respectively. In the direct pathway the STR inhibit the major output nuclei (yellow arrow, Fig. 1), removing their inhibitory effect on the thalamus, resulting in excitation of the cortex and facilitation of voluntary movements [13]. However in the indirect pathway the STR first inhibit the GPe, which removes the inhibition over the STN (red arrows, Fig. 1), thus facilitating the inhibitory effect of the output nuclei on the thalamus [13].

Although projections of cortex to STN were identified long ago [6] only recently a third pathway was added to the cerebro-basal ganglia model [14, 15]. The relatively new hyperdirect pathway (blue arrow, Fig. 1) involves direct activation of STN from frontal lobe projections [14] leading to movement inhibition similar to the indirect pathway, but faster [15]. It is suggested that during the voluntary movement the three pathways work together to withhold (hyperdirect), release (direct pathway) and terminate (indirect) the desired motor commands [15].
these three external pathways several other external and internal circuits exist (Fig. 1), which contribute a great deal to the normal functioning of the BG [16]. For example besides the aforementioned indirect influence, GPe receives feedback from the STN and has direct projections to the output nuclei [17], and the thalamus [18]. The dopaminergic connection of the SNC to the STR [19] is another example of an internal circuit essential for normal functioning of the input nuclei.

2.1.2. Other Connections of the Basal Ganglia

Just listing the structures associated with basal ganglia pathways allows one to appreciate the intricate nature of BG function. However, knowledge of the cortical and subcortical connections will assist in understanding complications following disruption of BG. Anatomical techniques such as anterograde and retrograde viral injections [20] and electrical stimulation [21] have made it possible to reveal projections among the BG and cortical or subcortical structures. Activities in some of the cortical areas have been noted through single neuron recordings to identify the specific functions of different regions [22].

2.1.2.1. Cortical Connections

The input and output nuclei of the BG have well organized topographic areas for several cortical regions [23]. For example, through retrograde viral transportation a certain location within GPi directly linked to the distinct arm area of primary motor cortex (M1) [24]. Support for this finding includes evidence that stimulation of M1 led to the inhibition of GPi [25] and that trans-neuronal transport of herpes simplex virus (HSV1) revealed that the mid-rostrocaudal level of the GPi nucleus had direct connections to M1 [20]. Similar results exist for the input nuclei where anterograde transmissions show the connection of BG to the motor cortex, as injection of anterograde traces in forelimb and hind limb areas of rats label dorsolateral quarters of the caudate and putamen [26].
Similar examples are available for areas other than M1 and non-motor regions. Research indicates links between supplementary motor area (SMA) neurons and dorsal regions of GPi as well as pre-motor cortex/ventral section (PMv) and the ventrolateral portion of GPi [20]. Frontal eye fields (FEF) connect to the lateral region of posterior two third of SNr [20] and dorsomedial regions of striatum [26]. Gpi and SNr projections also target areas in prefrontal cortex [20], suggesting that areas in GPi and SNr are not only limited to motor areas.

The evidence regarding cortical area connections with the BG are numerous. These studies converge on the fact that cortico-basal ganglia connections via input or output nuclei are related to motor and non-motor areas, are topographically separated and the separation allows for parallel processing of sensory and motor information [27]. Organization of BG could be thought of as reentering loops that start from a specific region in cortical area, pass through functionally related BG region by entering input nuclei and returning to the cortical areas once again. Therefore basal ganglia cortical circuits could be referred to as cortico-basal ganglia-thalamo-cortical circuits.

General functions of different cortical areas are fairly well-known. Through connections with the BG, knowing the major functions of each cortical area will assist with understanding the function of the BG. For example, knowing that SMA is involved in internal guidance of sequential movements [20] will allow us to make sense of how the BG could be involved in such guidance. Moreover, understanding that a patient with damage to dorsal regions of GPi will likely have difficulty with sequential guided movements will help with their rehabilitation.

2.1.2.2. Sub-cortical Connections

The basal ganglia have direct and indirect connections to sub-cortical structures. Direct outputs of BG target the brainstem or more specifically the midbrain [28, 29]. Projections of BG connect to the mesencephalic locomotor region (MLR) [30, 31] and the pedunculopontine
nucleus (PPN) [32] of the mesopontine tegmentum (the junction of midbrain and pons) [33]. Some connections of midbrain and BG are reciprocal but indirect, as the midbrain is the major recipient of BG output [34-37]. Other examples include STN connection to PPN [38], and unidirectional projections from the PPN to SNc [39]. Topographical organization observed in the cortical region is also reported for BG-tegmental projections [36, 40].

The connections of the BG nuclei to midbrain are of importance because the medial reticulo-spinal tract, which passes through the ventromedial medulla and therefore spinal cord, stems from the midbrain region [41]. There is evidence that projection of MLR to the spinal cord through medial reticulospinal tract activates central pattern generators (CPG) in cats [42], therefore it is also linked to locomotion control [28]. The involvement of MLR in locomotion is further supported as stimulation of areas (e.g. PPN and SNr) with major associations to MLR evoke locomotion in rats [43] and cats [40, 44].

More specifically, descending projections of PPN can reduce inhibition of muscular tone [21] and increase muscle tone inhibition via reticulo-spinal tract connections [40, 44-46]. If the MLR through its connection to PPN controls muscular activity and contributes to initiation of locomotion and its maintenance [21], it is reasonable to assume that projections of BG to MLR control locomotion by projecting to PPN and controlling muscular activation.

Although neurological structures of cats or rats are not identical to that of human, some scientists regard the PPN as a BG nucleus (Webster, 1990), while others regard it as a close family member [47]. In humans it seems that the efferent projections of the brainstem (PPN) to the BG may be more important to movement compared to afferent stimuli [48], however its exact role is yet to be discovered.
2.1.2.3. Functions of the Basal Ganglia Based on Connections

Regardless of whether through the cortical or sub-cortical connections, functions of the BG involve contributions to movement. Review of the major functions of the corresponding connections with these nuclei will precede the associated pathophysiology in the following text.

As mentioned previously, the input nuclei of the BG receive numerous projections from different cortical areas in a topographic manner [49]. However, indications of several overlapping areas result in common functions of separate regions [50]. For example, because of prefrontal cortical projections to the caudate and pre-commissural putamen and somatosensory cortical projections to the putamen with few to the caudate, it should not be surprising that the caudate appears to be mostly involved in preparation of the movement (prefrontal) and that parts of caudate and the anterior putamen are involved in preparation (prefrontal), response and generation (somatosensory) of movement [51]. Due to the nature of connections malfunction of the caudate cause behavioral disorders [52], cognitive disorders [53], spatial neglect [54], language difficulty (aphasia) [55] and other major prefrontal syndromes such as dysfunctions in planning, abstracting rules and working memory function [56]. The putamen on the other hand has a significant roles in control of movement and is rarely involved in emotional or cognitive control [57-59].

Because of the nature of these connections the projections of the STR and STN could be regarded as the sensori-motor, associative or limbic [60]. The function of other nuclei such as GPi/SNr, GPe and SNr cannot be evaluated in isolation. These nuclei complete the loop originally started from the cortex and the input nuclei and similar to the input nuclei these areas are topographically and functionally distinct [48, 61]. Therefore, the function of each specific region within these nuclei depends on their anatomical connection to the STR and STN. For example, the area of GPe associated with caudate will regulate emotion and cognition [62]. The
section of SNr receiving input from head and body of caudate contributes to saccadic eye movement [63]. Therefore the functions of different areas of GPi/SNr in internal generation of sequential movements, or control of cognition and executive function depend on the origin within the BG or the cortex [20, 58]). Specifically, inputs to the BG specify what type of information these nuclei can process, while outputs from the BG reflect their function [64]. Connectional organization of the BG shown in Fig. 2 should help with understanding these functions.

The numerous individual roles of the BG nuclei act collectively, so that they function as a whole. Thus, a BG lesion in one nucleus will affect whole system function [65]. During the review of the pathophysiology of PD the focus is on the function of BG once again, but only relative to the associated pathology.

2.2. Pathophysiology

PD results from a dopaminergic deficiency within the nigrostriatal pathway of the BG [3]. Loss of neurons within the SNc, faster turnover of dopamine and reduction in the enzyme that converts the amino acid, L-Dopa, to dopamine cause dopamine depletion within the STR [1, 66]. Reduction of dopamine levels, which vary from individual to individual, is more apparent in the putamen than the caudate, both of which contain major receptors for dopamine [58] discussed previously (i.e. D1 and D2). In the classic model upon reception of dopamine, D1 receptors facilitate the direct pathway, while D2 receptors inhibit (suppress) the indirect pathway, thus lack of dopamine reduces the activity of the direct pathway and over activating that of the indirect [67]. This excessive inhibition of the output nuclei suppress thalamic and corresponding cortical activity, leading to akinesia or other hypokinetic symptoms observed in PD. However, findings from more recent experiments oppose the classical model as they show
that dopamine does not affect the direct and indirect pathway as previously assumed [68]. In a newer dynamic perspective (discussed in detail in chapter III) researchers suggest

**Figure 2.** A schematic representation of functional organization of the Basal Ganglia (BG) based on cortical connections. The input and output BG nuclei are usually segregated based on three major functions: limbic function (behavior, emotion, attention, memory, learning), associative function (planning, oculo-motor, perception, speech) and sensori-motor function (planning and execution of motor actions). Each function is not limited to one pathway (note multiple pathways for each function). From top to bottom each schema includes: the cortical areas that project to the BG, the input BG nuclei (1st bold box), the thalamic nuclei and the cortical efferent target(s). Bold font represents structures that receive or send more prominent projections than normal font structures. Efferent cortical areas and thalamic nuclei vary depending on the cortical source. (Association areas—the dorsolateral and ventrolateral pre-frontal cortices, areas 8, 9, 10, 46, portions of the intraparietal sulcus and the border of the superior temporal sulcus; Gpi—Globus Pallidus pars interna; Gpe—Globus Pallidus pars externa; MD—Medio-Dorsal thalamic nucleus; M1—primary motor area; SMA—Supplementary Motor Area; SNr—Substantia Nigra pars reticulate; VA—Ventral-Anterior thalamic nucleus; VAL—Ventral Antero-Lateral thalamic nucleus; VAp—Ventral-Anterior parvo cellularis thalamic nucleus; VAmc—Ventral-Anterior pars magnocellularis thalamic nucleus; VL—Ventral-Lateral thalamus nucleus; VLa—Ventral-Lateral thalamic nucleus anterior part; VLD—Ventral-Lateral thalamic nucleus dorsal part; VLP—Ventral-Lateral thalamic nucleus principal part; VM—Ventral-Medial thalamic nucleus; VP—Ventral Pallidus).
that the depletion of dopamine changes the synchronized activity of the direct, indirect and hyperdirect pathways [16]. After depletion of dopamine, the weak direct pathway can no longer oppose the stronger hyperdirect pathway [16] and therefore fails to release the selected motor command(s) withheld by the hyperdirect pathway [69]. As a result the hyperdirect pathway expands its target areas in the thalamus and cortex and remains active for a longer period of time [15]. Even in cases where the selected motor command is released, it is present for a shorter duration of time [15]. How the indirect pathway is affected is not clear, however it is assumed that the initiation of a movement is associated with a sharp activity of the adjacent areas, therefore the striatal region related to the direct pathway [70]. This sudden activity is conducted to the region of the striatum designated for the indirect pathway to trigger the termination of the movement [70]. In PD the weak signals of the direct pathway are not sufficient to trigger the neighboring indirect pathway, thus terminating the motor command [70].

The complete pathophysiology of PD remains unclear. Although a general consensus in dopamine deficiency and nigrostriatal pathway involvement in PD exists, the role of dopamine involvement is still under debate. No matter what the role of dopamine, its contribution to the motor dysfunction cannot be denied. In the next section research on motor dysfunctions associated with PD are presented.

3. TEMPORAL CONTROL AND HUMAN MOVEMENT

When it comes to temporal control of movement there are discrepancies regarding the role of BG and cerebellum in timing sequential movements [71-74]. The focus of this section is to review the literature on temporal control and human movement, differentiating the role of the BG from other regions, which will help associated its use with Parkinson’s patients.
3.1. Central Representation of Time

Internal generation of a rhythmic movement requires accurate perception of the temporal sequence, preparation of the motor plan and production of the rhythm which is sometimes based on the perceived temporal characteristics [75]. An accurate temporal perception and a temporally organized motor output necessitate a central representation of time through which a neural control could occur (Ivry 2001). This representation serves as an internal clock that characterizes the time point, duration or interval and will therefore determine the temporal characteristics of an event [76].

The internal representation is viewed as a system of oscillatory pacemakers with flexible and reproducible frequencies [77] or as a battery of hour glasses [78], each corresponding to a specific frequency or duration. In humans several oscillatory units might interact and form various temporal patterns, which then serve as a reference for estimating a specific duration or performing a rhythmic action [77, 79]. Rhythm is defined here as “a patterned sequence of events, which can be completely characterized by the number of events in the sequence and the time interval between those event” [75].

Use of the “multiple time model,” an expansion of the hour glass model, may help explain the internal representation of time [80]. According to the authors the representation of time, whether perceptual or motor, is composed of elements with specific connections and duration. These elements can be considered a group of neurons, which habituate to a specific temporal range as one starts to learn a specific rhythm, produce a rhythmic movement or perceive a rhythmic modality. For a rhythmic action to occur distinct temporal representations are set for each effector system. Several motor commands compete and the first motor plan to reach the specified temporal threshold will be selected. If a novel rhythm is introduced, the set
effectors are inhibited to allow for development of a new element, temporal range and associated motor responses.

Temporal elements can be located in any cortical or sub-cortical area. Cortical regions which are active during performance of rhythmic motor tasks may involve motor, premotor, parietal and prefrontal, cortices [75, 81-83]. Certain areas within each region make specific contributions. For example, SMA and Pre-SMA regulate movement initiation and its internal guidance, while pre-motor cortex (PM) and M1 contribute to preparation and execution of the movement [75]. The controversial issue revolves around the role of sub-cortical areas, such as the roles of the BG and cerebellum in temporal perception and performance.

3.2. Comparison of BG and Cerebellum in their Temporal Role

The BG are associated with different aspects of temporal control including perception, learning and execution. Unfortunately, some of these functions are also related to the cerebellum and therefore complicate the exact role of the BG. The focus of this section is to review the literature on the temporal roles of the BG and cerebellum.

Numerous investigators that recognize the cerebellum as the major sub-cortical structure for temporal processing, perception [84], learning [85, 86] and execution [84-86]. These functions are attributed to cerebellum as patients with cerebellar atrophy are incapable of detecting time interval changes in rhythmic auditory stimulation, show a significant amount of inter-response interval (IRI) variability when tapping to a rhythmic pattern [84] and severing different areas of cerebellum interferes with learning and executing a new temporal sequences [85]. The role of the BG in temporal control is less clear.

The BG play a role in temporal perception [87, 88]. This assumption is based on activity of the BG during temporal discrimination tasks [88], increase in the minimal threshold of the temporal discrimination in PD [87] and deficiency of these patients in estimating time intervals.
of presented rhythmic stimuli [89]. Such deficiency in perception of temporal intervals is not modality specific and is present with tactile, visual and auditory rhythmic sequences [87]. On the other hand because of the pattern of activation of the STR and cerebellum during temporal sequence learning, the BG are associated with encoding time intervals, while the cerebellum is associated with temporal perception [74]. In this case the BG contribute to learning temporal sequences, while the cerebellum functions to optimize sensory input upon receiving it from the associated areas.

The role of BG in movement timing is implied from various experiments involving PD patients. It is suggested that the increase in variability of the IRI during generation of a self-paced rhythmic movements in PD patients reflects involvement of the BG in temporal control of internally generated movements [89-91]. Because the ability to synchronize finger tapping to external stimulation is also impaired, the BG may contribute to externally guided rhythmic movements as well [92]. EEG recordings of the PD patients during cued and uncued rhythmic movements reveal reduced BG and SMA activity prior, during and after the uncued rhythmic movement compared to the cued movement [93]. Such pattern of an activity and its sensitivity to the temporal component, bring further evidence for the role of BG in internal temporal control of movement via connections to SMA.

The role of the BG in temporal control of movement has been viewed yet another way. It is suggested that the BG play a functional role in integration of spatial and temporal components of a sequence, as PD patients are capable of performing [72] and learning [94] spatial and temporal sequences in isolation, but they fail to do so when the two are combined. In contrast, because of the inability of cerebellar patients to perform temporal or sequential tasks in isolation, the cerebellum is associated with forming temporal or spatial sequences. [72].
The temporal role of the BG is rejected by other investigators who report activation of cerebellum only during changes of temporal intervals of a rhythm [95, 96] and those who show insensitivity of the BG to temporal sequencing of the movement [97]. The latter study makes a comparison between temporal and ordinal sequencing. Their ordinal sequence involved performing a rhythm in different tone orders (fixed intervals) with several key pads (one for each tone), while the temporal sequence involved producing a rhythm with one key pad by changing the stroke interval. FMRI recordings of the BG and cerebellum under these conditions suggested that the BG have no role in temporal control of movement, but contribute significantly to ordinal organization. They further propose that the cerebellum is important for temporal control, spatiotemporal organization and ordinal control of the movement. However, in a case where primates were trained to reach to a sequence of fixed number illuminated targets but in various orders of presentations (ordinal task), the BG became active only if a target was presented in a specific order and formed a temporal relationship with the other targets [98]. The temporal control of movement viewed in a different context may help explain these differences.

Rhythmic movements can be categorized into those that need event-based timing (discrete rhythmic movements) or emergent timing (continuous rhythmic movements) [99]. Comparison of PD patients with those of cerebellar lesion and healthy controls reveals a similar performance in PD patients and healthy individuals for event-based timing task [99]. It is also reported that patients with unilateral striatum damage show no evidence of motor timing problem during finger tapping to auditory rhythmic stimulation in ipsilesional and contralesional hands [100]. These findings suggest: 1) event-based timing deficits are dissociated from the emergent timing; 2) tasks that require precise timing are more vulnerable to cerebellar damage; 3) the BG are involved in emergent-based timing task; and 4) PD is not a good model for studying temporal movement dysfunction. Unlike the studies mentioned previously [91, 101], these experiments
reject the role of BG in precise timing of rhythmic sequential movement (event-based timing), however may help explain discrepancies regarding the role of the BG in temporal control.

Some investigators relate the controversy regarding temporal role of BG and cerebellum to the complexity of the rhythmic tasks [75, 102]. Both the cerebellum and BG are involved in temporal organization of sequential movements, however considerable reduction in BG activity and escalation in cerebellum activity with the increased complexity of the rhythmic motor task (defined as number of different time intervals implanted within the rhythm) occur [75]. An opposite pattern of BG activation is suggested for temporal perception [102]. In this case temporal duration estimation of simple rhythms relate to activation of the cerebellum, however as the duration estimation task becomes more difficult other brain areas such as the BG, dorsolateral prefrontal cortex (DLPFC), PM and SMA are recruited, suggesting a context dependent activity of BG but a constant control of cerebellum in temporal perception.

Some authors suggest that some tasks are inadequate in bringing out the contribution of the BG [78, 103]. The following roles are reported for the cerebellum (Penhune, Zattore, & Evans, 1998): 1) Extracting temporal aspects of the perceived sensory information; 2) Extracting temporal aspects of motor output; and 3) “leaning novel temporally precise motor responses” [103] and temporal characteristics of the sequence in response to the environment (Dreher & Grafman 2000). These authors further describe the “non-significant” role of the BG as detectors of the unpredictable temporal errors in a task including ordinal information alone (anterior STR) or a combination of timing and task order (posterior putamen, head of the caudate). It is possible that those who deny the role of the BG in temporal control probably did not design a task that could tap the BG.

In a comprehensive literature review Ivry and Spencer, 2004 propose that the cerebellum is the major structure for rhythmic perception, learning and execution and the BG are the
threshold regulators to determine the amount of required sensory input (perception) and to regulate the threshold for the desired response (motor execution). Therefore, if the BG lower the threshold for a specific response, it has a better chance to be selected and executed. Considering that a dysfunctional BG may cause a rise in the threshold \[104\], may explain why PD patients recognize two distinct temporal stimuli at a higher interval and threshold \[87\]. Reflecting back to the “multiple time model” the function of the BG would select the first movement plan to reach the minimum threshold set.

One should be aware that the debate over the distinct function of cerebellum and BG continues to this date. Investigations are successful in clarifying some of the overlap, but not all. The presented models have their limitations as they fail to explain the behavior of the BG during ordinal and temporal tasks and across sequential movements with different complexities. It seems that the BG are important in emergent-timing, but their control over event-based timing and therefore temporal organization of sequential movements is negligible. In this case gaining temporal control over rhythmic movements for PD by recruiting the intact cortical and sub-cortical areas does not appear to be an impossible task.

4. MOTOR COMPLICATIONS AND PARKINSON’S DISEASE

People with PD can possess several motor and non-motor symptoms classified as Parkinsonism or non-Parkinsonism syndromes, respectively. Parkinsonism syndrome includes tremor, bradykinesia, postural instability and rigidity, while non-Parkinsonism syndrome involves depression, cognitive disorders, sleep disorders or autonomic dysfunction. According to UK Parkinson’s Disease Society Brain Bank a patient is diagnosed with PD if they show signs of bradykinesia and one other symptom within the Parkinsonism syndrome category \[105\]. Because other diseases, such as multisystem atrophy or vascular pseudo-parkinsonism also share Parkinsonism signs \[105, 106\], there are exclusion and supportive criteria that help with the
diagnosis of PD (For details see Appendix A). Due to the overlap and lack of a standard measure, errors do occur and PD is not always accurately differentiated at the initial stages of the disease [106]. Note, that PD patients do not always present with non-Parkinsonism symptoms. Therefore, the focus of this chapter is to elaborate on Parkinsonism syndrome and other motor complications that exist in the Parkinson’s population, to review how these complications affect control of upper and lower extremities and to introduce a theoretical link to such control.

Motor complications usually appear on one side of the body and gradually become symmetric through progression of PD [1]. For completeness each major basic motor complication associated with PD is defined and in Appendix B. These include those categorized as Parkinsonism syndrome as well as other common motor complication. Motor complications, as they apply to the upper and lower extremities, are presented in the corresponding sections that follow.

4.1. Motor Complications and Control of Upper Extremities

Upper extremity movements are an integral part of activities of daily living. It is of no surprise that complications in performing such tasks can limit an individual at a functional level. Functional abilities of upper extremity control in those with PD become worse with the severity of the disease [107]. Simple tasks such as grasping a cup to drink may require more time and effort for people from this population [108, 109]. The focus of this section is to review the motor complications for people with PD identified for unilateral reaching and grasping tasks and tasks involving bimanual coordination. These actions will provide insight to upper extremity movements performed concurrently in those with PD.

4.1.1. Reaching and Grasping

Aiming, reaching and grasping tasks, the most common tasks used to evaluate control of the upper extremities in PD [110-113], offer a good action for evaluating upper extremity
control. As common tasks they are well-practiced relatively easy movements for various populations to perform. Moreover, they represent goal-directed sequential movements, which demand coordination of transportation and grasp phases [114] to not only provide insight to movement coordination, but also movement precision similar to that of a single aiming movement [115].

Patients with PD perform the reaching aspect of a reach and grasp task different than people with no known movement disorders. They underestimate target distance [116] and move towards an object in an irregular and jerky matter [117, 118]. Movement time (MT) of reaching increases significantly in PD patients [110, 117] usually due to a prolonged initial segment of movement execution [110, 119, 120], which can increase up to 30% compared to that of healthy population [117].

Investigations on the two components of the reach and grasp reveal temporal and spatial deficiencies in those with PD. A temporal link between the maximum grasp aperture and the hand transport phase in healthy individuals exist [115, 121] such that maximum aperture occurs at the time of maximum deceleration of the transport phase [115]. Consistency of the relative distance of peak aperture to the targets across varying target distances [121, 122] and sizes [121] while reaching toward the target, further reveal “normal” spatial coordination in healthy controls. During reach and grasp tasks patients with PD generally vary the time and distance of the grip aperture regulation relative to the reaching action, unlike that of controls [122-125]. PD patients produce smaller maximum apertures (hypokinesia) [123] and generate grip forces at a slower rate [126]. They also generate the maximum grip aperture with a significant delay [117, 123], possibly explaining why they close the aperture close to the target [115, 124].

The delays in movement control could be considered secondary to bradykinesia and muscle force production (discussed later), as hand velocity is highly correlated to the grip
aperture closure time, distance as well as rate of muscular force production [124, 127]. As a strategy to overcome the constant oscillation of a pathological action tremor, individuals with PD perform the task slower than usual, a sign of secondary bradykinesia [128]. A direct correlation between tremor in agonist muscles and peak acceleration and velocity profiles during arm extension [129] further support the role of tremor in slowing movements.

In tasks where accuracy is not an issue PD coordination and synergy between the acceleration and deceleration transport phases are closer to that of the normal population. The movement organization becomes more irregular as task performance becomes more complex [130, 131], like tasks demanding precise contact to small targets [130], fast accurate reaching [122] or simultaneous prehension of two limbs [131]. Deficits such as these indicate a central shortcoming in regards to coordination [122, 132]. Because many movement difficulties disappear during externally guided reaching tasks, some suggest this phenomenon could represent dysfunction of the BG in triggering internally generated movement [133, 134]. However, given the example above, it seems that task or type of internally generated movement must also be considered. It is unclear what makes the task “too complex” for a Parkinson’s patient. However, central control involving additional demands of attention, sensorimotor integration or a combination of the two seem to be viable possibilities.

PD patients also produce grasp forces that do not match object properties, again reflecting some degree of abnormality [126, 135]. The link to abnormal force production appears to be associated with object unfamiliarity. Force regulation appears to be normal for PD patients when manipulating familiar objects [136] or using self-regulated speeds [137, 138]. Abnormal force production occurred in cases involving objects lighter and smaller than expected [126] or having to move faster than normal [137, 138]. In the latter cases the demands of temporal and/or spatial accuracy elevate, possibly explaining why during tasks that involve manipulation of fine objects
the regulation becomes impaired [122]. In these cases evidence supports that force production problems result from the patient’s inability to generate regular and sufficient forces [139] for the novel sensory inputs, possibly resulting from inadequate sensorimotor integration [126]).

During voluntary movements the pathological tremor can impose on the task and appear as an abnormality in force regulation [140]. There is evidence that when performing an action in the presence of tremor, the frequency of muscle bursts become entrained to that of the tremor, making it difficult to accumulate bursts to create the appropriate force [141]. These constant force oscillations are usually present during all phases of the movement and can eventually lead to reduction of the total grip force [142].

PD patients produce insufficient and irregular forces [139, 143] that can affect movement accuracy [126], which necessitates intact proprioception and sensorimotor integration [144]. PD patients demonstrate proprioceptive deficits, as they show deficiencies in detecting passive upper extremity movements [145]. Intact proprioceptive-related evoked potentials in the brain reveal normal afferent information and provide evidence that suggest impairment in cortical processing of kinesthesia in PD [146]. Evidence for underestimation of target location in reaching to a visual target compared to that with a kinesthetic target [147] and for difficulty in matching a visually cued hand posture to that of a kinesthetic posture in individuals with PD, offer support for the hypothesis that proprioceptive and sensorimotor integration deficits are to blame for irregular force production in those with PD [148].

Although some unilateral movement deficits are viewed as secondary to bradykinesia [127] and tremor [140], most PD deficits appear to result from the inability of BG to integrate [126]) and coordinate [132] various aspects of the movement. Thus, production of the desired movement [134] or force [143] and inhibition of unnecessary movement is impaired.
4.1.2. Bimanual Coordination

Bimanual tasks present good examples for evaluating concurrent upper extremity control used for movement coordination. The BG through connections to SMA contribute to coordination of bimanual movements [149], thus providing a good action to study those with damage to the BG.

In individuals with and without PD the ability to perform anti-phase or asymmetric bimanual coordination tasks becomes unstable as a function of speed, causing the anti-phase movements to relapse into the in-phase or symmetric movement at fast performance rates [150]. Not only do PD patients perform worse than controls at higher rates, but they tend to switch to the in-phase state at lower frequencies [151, 152]. Also, when PD patients are asked to reach for objects of different sizes with both upper limbs simultaneously, they tend to synchronize their grip patterns (unlike controls) reflecting the inability to independently adjust each limb to properties of the objects [153]. Not surprisingly, PD patients also perform the bimanual tasks at slower speed and amplitudes [151]. Bradykinesia especially occurs during conditions where processing of several sensory inputs is required (e.g. full vision vs. no vision), which might reflect an adopted strategy to allocate enough time for processing and integrating all the available sensory information in order to achieve maximum accuracy [154, 155]. However, sometimes even allocation of more time does not guarantee precision [155], possibly reflecting bradykinesia associated with the disease rather than that of a control strategy.

Variability in movement amplitude, movement duration and variability of the relative phase between the limbs increases in PD patients performing bimanual tasks [155-157]. The increase in variability for in-phase coupling of the two limbs in PD patients with great asymmetric symptoms is less frequent than that of anti-phase bimanual tasks [155-157]. During anti-phase movements such behavior might be secondary to additional sub-movements during
deceleration, a phenomenon that does not occur in the healthy population and that represents efforts to avoid switching to the more stable in-phase condition [149]. The patients’ inability to resist the underlying force towards synchronization more often than controls provides additional evidence that PD patients have greater difficulty independently controlling each limb during complex skills [153, 158].

Limb dominance is another factor that can affect bimanual task performance in PD patients. Similar to healthy individuals, patients reveal greater movement variability and errors in the non-dominant hand during metronome-paced bimanual tasks, however, the difference between the two limbs is significantly exaggerated in the patients [131, 152]. Unlike controls, PD patients do not synchronize the non-dominant hand to a shift in frequency ([151]. The reason is unclear, but by increasing use of the limb that entails more proficiency the patient exaggerates the movement differences of the limbs [131, 152].

Some scientists explain the added deficiencies in PD patients performing familiar bimanual skills as manifestations of the compensation of other CNS structures for the dysfunctional BG [131, 159]. Since the PD population is more accurate in making transitions to in- or anti-phase bimanual movements and maintaining the correct relative phase performing these tasks in the presence of external cues, the greater deficits without the cues may be explained by the basal ganglia’s role in internal guidance of a movement [151, 154], like that associated with SMA function [160]. Transcranial magnetic stimulation (TMS) of SMA affects anti-phase coordination tasks in such a way that it forces the anti-phase movement into the stable in-phase pattern [149]. Combined with the information that monkeys with SMA lesions have difficulty with independent limb control [161], these findings support that greater movement deficits in PD are linked to the altered BG connections to the SMA.
In summary, not only do deficits for PD patients undermine the ability to coordinate different segments of a movement within a limb in a reach and grasp task [132], they also undermine these abilities across limbs in a bimanual coordination task [153, 158]. Most evidence for the cause of such deficits is contributed to dysfunction in the BG-SMA connections, known to contribute to coordination of bimanual movements [149]. A generalization of these findings would suggest similar bilateral movement deficits for the lower limbs.

4.2. Motor Complications and Control of Posture

Postural instabilities are one of many motor complications present in patients with PD [162]. These complications are of special interest as they are resistant to medication and even some surgical procedures [162] and they increase risk of falling. A fall in an older adult, like many with PD, normally leads to injury and further motor complications. Insight to posture and its underlying control factors in this population may lead to therapies that help reduce this downward spiral.

Abnormalities of postural responses in PD patients manifest in muscle reactions to sudden perturbations and postural transitions. PD patients show impaired muscular timing and amplitude for changing and coordinating motor actions [163-165]. Experiments reveal changes in latencies in the stabilizing and the destabilizing muscle responses to a sudden dorsiflexion for PD patients [166]. Reduced and impaired [167] stretch reflexes of leg muscles also exist. When required to make a transition from backward displacement to toe up rotation, the amplitude of muscle activation does not respond accordingly [165]. These deficits contribute to the abnormal postural responses in PD [168] through abnormal force production.

PD patients commonly provide inadequate force to meet the sudden changes in external (i.e. platform movement) and internal (i.e. voluntary movements, heel rises) perturbations [163, 169, 170]. The latter of which explains the abnormal anticipatory postural adjustment (APA) in
PD patients present with difficulties in modifying the magnitude of muscle force and manifest unnecessary muscle activation, affecting the regulation of force production. The inability to produce sufficient muscle force also explains the reduced center of pressure (COP) and the increased center of mass (COM) displacements in response to perturbations in PD. Insufficient muscle activation in the lower limbs leads to a small COP displacement, inadequate to control the COM, therefore increasing its displacement. Compensatory efforts to reduce the COM-COP distance (safety or stability margin) in PD involve a limited body movement, narrow base of support (BOS) and stiff posture.

The size of the stability margin is a good indicator of the level of stability for different directions in PD patients. Unlike the constant stability margin of healthy individuals, stability margin changes for perturbations in different directions in people with PD. The smallest margin appears to be for the backward displacement, explaining why PD patients are more susceptible to backward falls. The stooped posture, which is common in PD patients, might be a functional compensatory strategy used to diminish backward displacement of the COM for preventing backward falls. The mediolateral displacement is the second most unstable condition for posture control, but unlike the backward displacement the condition improves with a wider BOS.

In summary, PD patients present with major deficits in stability, linked to muscle activation, thus force production. These deficiencies also stem from insufficient postural reflexes in response to external forces and internal muscular noise and stiffness. Some link the abnormality of postural reflexes to modulations in spinal and supra-spinal reflexes as a result of a defective BG.
4.3. Motor Complications and Control of Lower Extremities

Normal function of the lower extremities is essential for performing certain daily activities. Loss of balance and difficulty with walking (gait) are two noticeable motor complications in patients with PD involving the lower limbs. Common contributors to these deficits for these patients are a forward posture and muscular rigidity [178]. The focus of this section is to offer insight to the motor complications associated with postural and gait control for PD patients.

4.3.1. Gait Control

Difficulty with walking is one of the most noticeable motor complications in patients with Parkinson’s. Higher cadences occur as a compensation to the shorter stride length [179], resulting in increased step numbers. The typical stooped posture, shuffling of feet, reduction of arm swing and joint range of motion (ROM) apparent during gait [10, 180] cause PD patients to walk with flexed knees, hips and ankles and therefore on their toes [10, 58, 181]. Additional characteristics of PD gait include decreased movement amplitude [182, 183] and gait speed [184, 185], increased freezing of gait and asymmetric stride time (increased stride to stride variability) [182] and difficulties in gait initiation (akinesia) [186, 187] and termination [188]. Some of these characteristics are indicative of performance of other populations and do not limit daily function. Decreases in stride length and gait speed commonly exist in the normal older person (e.g., Nagasaki et al., 1996), but do not limit these people’s abilities to grocery shop or perform other daily tasks. Other characteristics such as freezing of gait and shuffling of feet may limit functional performance and/or increase fall risk, thus are of most concern within this population.

Since approximately 80% of PD patients on medication show symptoms of freezing and akinesia [189] and because the risk of experiencing recurrent falls is nine times higher in PD than that of age-matched controls [175], gait deficits are of a major concern to this population.
Discussing the motor deficits in various divisions of the gait cycle (gait initiation, progression and termination) should help explain the major motor complications of PD gait.

4.3.2. Gait Initiation

Gait initiation is a motor task that involves a transition from a stationary double support position, to a dynamic gait cycle [190]. The initiation of the step is tightly connected to equilibrium [191], vertical height above the ground (posture) [192] and activation of the major lower limb muscles [59, 176, 190]. “Start hesitation,” one landmark of Parkinson’s gait [187], especially occurs after long periods of immobility [186] where PD patients take several short steps before they can generate a large enough propulsion that can lead to a normal step length [186].

In PD velocity and amplitude of forward COM displacement reduces significantly for the preparatory (postural) and stepping phases of gait initiation [192]. Hesitation in starting the movement is partly attributed to prolongation of the postural phase because attaining a stable condition for initiating gait demands more effort and time [193]. Slower stepping phases can result from improper force production in the plantar and dorsi flexors due to a stooped posture [194], in the antigravity muscles of the leg due to impairment in the sensory detection of body load [195] and in other homologous muscles due to central mechanisms [193]. In a healthy individual activation of SMA is observed prior to gait initiation, reflecting its role in planning different components of gait [194]. Activity of SMA is terminated by signals from the BG, which is followed by activity in M1 and preparation for planning of the next sub movement [196, 197]. Therefore, the BG fail to trigger SMA on time, where the activation of M1, the execution of the current movement and the preparation of the subsequent movement do not occur [196, 197].
To summarize, the dysfunction of the BG causes slowness of gait initiation in PD due to insufficient force production and inabilities in detecting the amount of force produced. Patients who are unable to accurately detect gravitation forces have difficulty adjusting their posture to prepare for the initial step [195]. Insufficient force production leads to reduction in COP displacement and a smaller and slower COM displacement, causing a delay and a smaller and less effective propulsive force, thus a slower and smaller step [193]. The BG delay in activating SMA leads to a delay in recruiting the motor units [194] needed to produce greater force.

4.3.3. Gait Progression

Gait patterns within gait progression commonly adhere to a rhythmic and cyclic pattern in the normal functioning adult. Although this activity is much different than gait initiation, similar deficits can occur in PD patients. The following sections will correspond to major motor complications associated with the gait progression including freezing of gait, muscular activity and gait variability.

4.3.3.1. Freezing of Gait

Freezing of gait (FOG) is a complicated motor symptom in PD with unclear pathophysiology [198] that represents the lack of movement during repetitive and sequential tasks [199]. As with start hesitation, freezing is another important subcategory of akinesia [199]. It is characterized by sudden, involuntary, transient and paroxysmal episodes where the individual becomes incapable of maintaining gait and re-starting it, despite arduous efforts [58, 200, 201]; instead several tiny steps are produced [58, 178]. This complication especially occurs when patients approach a narrow space like a doorway (25% of patients), need to make a turn (45% of patients), cross over an obstacle, shift their attention or are under stress [58, 192, 198]. This phenomenon is highly debilitating, increasing the risk of falls and jeopardizing patients’ independence [202].
The prevalence of FOG is 7% in mild cases and 45% or more in severe cases of PD (severity determined by the stage of the disease according to Hoehn and Yahr scale, Appendix C) [198, 203, 204]. Longer disease duration (>5 years) and longer medication treatment (i.e. levodopa) contribute to prevalence of FOG [198, 204, 205]. Only 16% of patients under no medication experience this phenomenon [58, 204] which, if present, will be mild and of short duration [203]. FOG is more prevalent in PD patients who demonstrate signs of dementia, dyskinesia, speech disorder, dystonia, postural instabilities and longer double support time during gait [200, 205], however for unknown reasons it is experienced less in those whose disease involves major signs of tremor [204, 205].

FOG is often accompanied by the hastening phenomenon of festination, where the cadence increases just prior to the freezing [178, 206]. During this time shifting the weight between legs takes place more rapidly and appears to be incomplete, as the amplitude of medial-lateral transfer of the COP decreases [178] and accompanies a decrease in stride length [206], signifying decreased force production and loss of control over cadence [206]. The loss of temporal control is also evident when one considers that stride-to-stride duration variability is correlated to the severity of FOG [207]. In terms of muscular activity, FOG is viewed as the co-activation and dys-synchronization of leg muscles [178, 208]. Unlike the consistent reciprocal pattern of activation in flexor and extensor muscles of the thigh and legs in a healthy individual, the reciprocal activation is interrupted by co-contraction of flexors and extensors in PD patients just prior to freezing [178]. The co-contraction of muscles describes a dystonia specific to gait [205]. Prominent EMG signals in the lower leg muscles are premature and prolonged [208], emphasizing major irregularities in the temporal domain, which influence spatial irregularity.

According to the current literature, freezing stems from spatial and temporal dysfunctions in PD muscle activation. The greater muscular dys-synchronization highlight the
temporal deficits such as co-contraction possibly leading to inadequate force production and the associated reduction in movement amplitude, as that in the shorter stride length. Limited research in this area makes it difficult to determine causality. However, evidence from other research on motor complications in PD would place emphasis on the BG-SMA connection deficits.

4.3.3.2. Muscular Activity

In the previous sections changes of muscular activity and their contribution to gait initiation and pattern complications were presented. To avoid redundancy changes that were not discussed previously are presented below.

Abnormalities in muscular synergies and loss of functional symmetry of muscle activation complicate the gait of PD patients when performed at comfortable speeds [184, 209]. Some scientists suggest the general pattern of muscle activation is unsmooth, “noisy” and variable with a significant disruption in the “rate of force production” [139], while others show similar timing activation to healthy older adults [210] or report impairments only when excessive adaptation to external situations is required [211], thus for complex tasks. Some researchers believe that changes in muscle activity during gait in those with PD include [210][209][209] less amplitude in distal muscle activity, a delay in reaching the maximum force and over-activity of proximal muscles [139, 210].

Problems with force production during gait are always present [211] and since the abnormalities become more significant in patients at later stages of the disease [210], a role of the BG may be in regulation of force. This would explain how the low amplitude in dorsiflexion and premature, prolonged and ineffective activity of plantar flexors delay the development of forward momentum preceding the first step in start hesitation [193]. The reduction in activity of the plantar flexors [195, 210-212] along with insufficient activity of the hip extensor muscles, cause a very weak push off [210, 211], reducing the stride length [181, 210]. Moreover,
significant weakness in dorsiflexors [210] further affect the swing phase resulting in shuffling of
gait [210].

Production of adequate force and accurate timing of force production are essential
contributors for accurate movement control. Deficits in the BG resulting in inadequate timing,
through inadequate and abnormal muscle stimulation, likely contribute to dysfunctional control
of gait initiation and patterns.

4.3.3.3. Gait Variability

Rhythmicity is an important feature reflected in stride-to-stride variability [184].
Arrhythmia describes increase in stride-to-stride variability [213], where rather than a continuous
sequential movement the individual performs a series of disconnected strides [184]. Temporal
and spatial variability are features that remain constant (coefficient of variation for stride length
and stride time are 3-6% and < 3% respectively) [214] as one ages, unless some type of
complication occurs [215, 216]. Therefore, alterations in variability of gait are important in
reflecting a pathological dysfunction [215].

Patients with PD show increase in variability of spatial and temporal components of gait
[182, 184, 217]. Increases in variability of force amplitude of the leg muscles [209], stride length
[182, 217, 218] and gait cycle duration [184, 217, 219] are present at very early stages of the
disease [213], preceding changes in step velocity and length [219]. Variability in stride length
and duration significantly correlate with frequency of falls and episodes of freezing in PD [207,
213, 220, 221] and support the pathological nature of these findings. However, some
investigators reject the connection of stride length variability to disease severity [181], report an
increase only in stride time variability at early stages [219] or do not regard the stride length
variability a distinct feature of PD [222], resulting in more attention towards variability of stride
duration. Stride time and length variability are independent of other factors that can vary across
PD patients such as velocity [209], average gait cycle duration [184, 213], bradykinesia, rigidity and tremor [213], making measures of variability good candidates for evaluating motor complications in PD.

Several investigators have searched for a theory to explain the increased variability in PD. Because pattern of spatial variability in mice differ according to the region of BG disrupted by neurotoxins, some researchers blame spatial variability on a specific neural pathway involving the BG for specifying step length and width [223]. Two causative explanations for temporal variability in Parkinson’s exist; central malfunction and motor fluctuations. Based on the two components of variability (central and motor) introduced by Wing & Kristofferson 1973, temporal variability is related to the central time keeping systems, due to the strong correlation between the variability of the central command and the IRI variability of finger tapping in PD [224]. This finding is in line with more recent studies that also show an increase only in the central component of variability during finger tapping [90] and others who report that temporal gait variability occurs without detection of any changes in force amplitude [219, 225] or lacks the correlation with amplitude of muscle force [226]. Comparison of finger tapping to gait is reasonable as there is evidence for significant correlation between IRI variability of finger tapping to that of stride duration [213]. Opposing views consider the motor component (muscular noise representing random variability during the execution) an additional factor to that of the central for explaining the increase in temporal variability in sequential movements in PD [91, 227]. This opposition is based on the significant correlation found between the motor component of the variability and the variability of IRI of finger tapping in PD.

No matter what underlies the increase in variability in PD, the presence of increased variability at early stages of the disease, before consumption of any medication exists. The close relationship between measures of variability and freezing or falls reflects the significance of
these measures in predicting motor complications and possibly in establishing an appropriate evaluation measure for the effectiveness of a treatment.

### 4.3.4. Gait Termination

Termination involves transition from a dynamic state to a static one leading to a more stable condition [228]. Gait termination demands control of a person’s COM, whether it is a transition that is planned or a response to a sudden perturbation [229]. The lower limbs must increase the decelerating (braking) forces in the swing limb and decrease the accelerating forces in the stance limb [230, 231] to keep the COM within the BOS at movement end [232].

Complications with gait termination are relevant to the PD patient’s general inability to control changes of the displacement of COP and COM [163]. To compensate for a failure to generate sufficient braking forces in a planned gait termination, PD patients reduce gait velocity earlier in the course of walking, reaching the final step with a slower velocity than that of the control (84% vs 90%) [188]. Unlike healthy individuals PD patients also produce muscle activation patterns opposite to that of controls, leading to inadequate force generation and corresponding to use of the compensatory “extra step strategy” not only during sudden stops [188], but also when sudden changes in direction are required [233].

Clearly, defective force production associated with stopping difficulties in PD must result from ineffective muscle contraction. The limited studies on gait termination in this population make it difficult to offer any conclusions on muscular control. However, one can hypothesize similarities to our previous discussions regarding muscle activation (i.e. inadequate and abnormal muscle stimulation due to BG deficits) exist for gait termination.

### 4.4. Theoretical Links

Different theories and/or models have been proposed to describe the functional connections of the BG nuclei and to predict the pathologies related to the motor dysfunction of
these nuclei in PD. In the literature two theories stand out for their ability to explain functional pathways within the BG nuclei (internal loops) and predict results of motor malfunctions in the pathways among the nuclei and other neural structures used in motor control (external loops). The dynamic theory of the BG proposes a model to describe internal loop function and the motor set theory targets the external loop function.

The dynamic theory describes the BG as a network of non linear dynamic pathways which work in symmetry to produce a normal behavior [15, 16, 69, 234]. The internal circuits of the BG are considered self stabilizers of the system whose function is necessary for “modulating the excitability” of the BG (Obeso et al. 2000). The output is viewed as gains for the direct, indirect and hyperdirect pathways and the projections of the BG output nuclei, representing information necessary for feed-forward (projections to cortical areas not involved with input, e.g. second column, Fig. 2) and feedback (projections to cortical areas of input, e.g. fifth column, Fig. 2) control of each limb (Suir, Albani, & Glattfelder, 1997). Therefore the internal self-stabilizing circuits regulate the net gain of the system and provide a state in which the desired motor plans affecting the trajectories, velocities and forces are released. Examples of such stabilizing routes are the connections of the GPe to the STR, the SNc to the STR and the thalamus to the STN and STR (Fig. 3), which work together to regulate properties of the functional units of the input nuclei by affecting their net membrane potential [235] or oscillation frequency [236].

With PD some of the internal circuits become affected and the symmetry among the external BG pathways is lost. For instance, the dopamine deficiency does not allow for the normal interaction of all projections received by the STR, affecting the cell membrane potential. Therefore, repetitive movements during which the minimum cell potential is held constant and the discrete movements during which the cell potential is temporarily depolarized both become affected [235]. In other terms harmony between the projections to the STR is lost and changes
the oscillatory patterns of cells affecting their output [236]. Such changes in properties of the input nuclei not only cause the overall gains of direct, indirect and hyperdirect pathways to become abnormally small or large (spatial) (Suir, Albani, & Glattfelder, 1997), but also cause disequilibrium among the three pathways (temporal) and therefore a shift in the net output (Obeso et al. 2000). As a result, cortical areas and desired action become inhibited and abnormal behaviors occur [15, 237]. This theoretical description efficiently introduces a system of internal BG networks where normal functioning is essential for a normal and context appropriate output, but ignores its external connections.

Figure 3. A schematic diagram of the inter-neurons and afferent projections to the striatum that regulate its excitability. Two inter-neurons and two striatum neurons are depicted. Only two dopamine receptors (D1 and D2) located on a striatum neuron are highlighted. Excitatory connections are represented by filled arrows with external connections in bold and inhibitory connections are represented by empty arrows. (Ach—acetylcholine; GABA—gamma amino butyric acid, SNC—substantia nigra pars compacta; STN—sub-thalamic nucleus; Gpe—globus pallidus pars externa)
The “motor set” model describes the motor functions of the BG (external connections) while disregarding specific internal circuits. The term set was introduced sometime before 1911. The idea of a set has been used in various ways including a response to a stimulus—motor set [238]. The idea of a motor set, was developed through experiments involving dichotic listening [239] and reaction times (RT) [240]. Flower and Robertson, 1985 provide us with the most comprehensive description of a motor set. Motor sets are “the characteristics of an action plan which determine the kind of movement or sequence of movements to be executed in order to fulfill the goal or intention contained in the plan” [241]. A motor plan refers to designating one or more predetermined movement characteristics (motor program) for an action. In more specific terms motor sets execute the following actions: they 1) impede execution of alternative motor plans and activate the desired one(s); 2) maintain the activated motor plan(s); and 3) respond to changes in the environment or goals of action by changing the plan, terminating or replacing it. Specifically, the motor set has the function of maintenance or regulation of the motor plan which already harbors the appropriate motor program(s).

The BG via their numerous cortical and sub-cortical connections function as motor sets in humans. Such an assumption mounts from investigations on RT and choice RT of PD patients, which report no evidence for delayed formulation of central motor programs [242], only a significant increase in MT and therefore impairment in implementing the motor program [64]. The ability of PD patients to learn and generate two sequences of button pressing, each tested in isolation but not in sequence, and to learn and generate an action that required transformation of two different sequences into a new combination, suggest that the inability is not in integration or learning of information but rather involves the maintenance of an action plan or its modification in response to environmental needs [243].
Various motor symptoms in PD patients relate to a dysfunctional motor set. The patients’ inability to perform more than one movement sequence simultaneously [101, 243], their difficulty in executing relatively long sequences [219, 226, 244], their failure to maintain the global goal during a sequence of actions [245-247], their impairment in execution of tasks that demand aiming to unexpected target locations [111] and their generation of movements and postures irrelevant to the environment [172, 248] are examples that would not occur with a normal motor set function. Akinesia, freezing and bradykinesia also relate to a motor set that cannot release or maintain a motor plan. Therefore, the ability of PD patients to gain normal movement magnitude [249] and initiation [250] or to decrease abnormal movement characteristics (i.e. variability) [219, 226] in presence of external cues suggest a compensatory strategy for accessing the motor plan [248, 249] via bypassing the dysfunctional motor set.

Two theories were presented to help explain the internal and external connections of the BG. In order to impede alternative motor plans and activate the desired one(s), the normal hyperdirect and direct pathways are required. The dynamic theory explained how PD can affect the internal direct, hyperdirect and possibly indirect pathway connections to alter the BG output and produce erratic movement results. The motor set theory suggests that the external connections to the BG are involved in selecting, maintaining or terminating the appropriate plans for desired movement. Whether it is possible for the internal pathways to respond to changes in the environment by allowing for an alternative motor plan to replace the original (motor set theory) in PD is still unclear. However, since no model currently explains all aspects of the complex BG and a disease with unclear pathophysiology, this combination develops a framework for the possibility of effective treatment.
5. TREATMENT OF PARKINSON’S DISEASE

Various treatment strategies are used to manage motor complications associated with PD. Medications and surgical interventions relieve some symptoms with fewer side effects in the latter. Insufficient medicinal and surgical interventions in alleviating all motor symptoms in PD emphasize the need for careful review of successful rehabilitation strategies in this population. Physical therapy approaches, which are considered useful non-pharmacological treatments to improve motor complications in Parkinson’s patients [183] vary so greatly, that at present, it is impossible to suggest a universal protocol for this population. Review of the treatment approaches will offer insight to current treatment strategies for PD and identify gaps and limitation in evidence-based studies. Thus, the focus of this chapter is to briefly describe the current medications and surgical treatments used for this population, but to offer more detailed review of the therapeutic treatments to guide future study design in this area.

5.1. Medication

Pharmacological interventions are based on pathophysiology of PD. Administration of medication aims to alleviate motor and cognitive symptoms of PD [251]. Although medication is successful in relieving motor symptoms such as bradykinesia, tremor and rigidity in early stages, its long term application leads to secondary complications which debilitate PD patients, causing cognitive problems such as hallucinations [10, 252] and motor dysfunction such as dyskinesia [58, 252, 253]. Motor complications such as akinesia, freezing, postural instabilities [252] and changes in stride duration variability [254] are not alleviated by most medications targeting the dopamine system, are linked to unclear causes and require a different form of treatment. Several drugs are available for targeting the dopamine related symptoms of PD. At the initial stages drugs that cause less side effects and motor fluctuations may be prescribed (MAO-B inhibitors or Amantadine). With progression of the disease stronger medication (i.e. L-dopa or
dopamine agonists) are administered as an adjunct to earlier medication or in isolation [251]. Unfortunately, each medication comes with several limitations. For example, dopamine agonists cannot control PD symptoms for more than 3 to 5 years, obligating addition of a stronger medication. The stronger medication of L-dopa causes major secondary symptoms such as dyskinesia calling for changes in dose and frequency of the medication and/or regulation of the adjunct drugs. Table 1 summarizes the common drugs administered for relieving motor symptoms of PD. Readers are referred elsewhere [253, 255] for further information regarding medication for PD. As just reviewed, medications are somewhat effective in alleviating PD symptoms at initial stages of the disease. They lose their efficiency and cause secondary motor and cognitive complications, not to mention they only affect some PD symptoms. Such limitations call for other treatment options such as surgery and therapy.

5.2. Surgical Intervention

Surgical interventions that do not prevent the neuro-degeneration process of PD, are used for symptomatic treatments. More importantly, this method does not lead to the debilitating side effects present with medication [256]. Surgical interventions for PD may involve severing certain parts of the basal ganglia as with pallidotomy, thalamotomy and subthalamotomy [257] or less abrasive methods such as deep brain stimulation (DBS) [257-260]. The latter is preferred because similar benefits with fewer side effects are achieved. Advantages of DBS over neural removal are numerous and include decreased demand for re-operation, lower morbidity rates, reversibility, larger improvements in motor and non-motor symptoms [259, 260] and decreased dose demand for medication [261, 262]. DBS can target different nuclei within the BG and its connections. Targeting the thalamus eliminates signs of tremor [263] without affecting other motor symptoms [264]. Stimulation of GPi reduces signs of drug induced dyskinesia and major PD motor symptoms such as bradykinesia, akinesia and rigidity [265], but the effectiveness
declines after the first year of the surgery [266]. The most common procedure is stimulation of the STN, where benefits involve general improvement in motor function (58%) and reductions in

Table 1. Summary of major drugs prescribed for alleviating motor complication in PD. The characteristics of each drug and its cardinal advantages and disadvantages are included. Adopted from [255]b

<table>
<thead>
<tr>
<th>Drug</th>
<th>Characteristics</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tr>
<td>L-dopa</td>
<td>Precursor of dopamine, usually administered in conjunction with catechol-O-methyltransferase (COMT) inhibitors (entacapone, tolcapone) to prolong half life of L-dopa. It is metabolized to dopamine &amp; 3-o-methyl dopa.</td>
<td>-relieves major motor symptoms&lt;br&gt;-increases life expectancy&lt;br&gt;-improves quality of life&lt;br&gt;-most effective for symptomatic treatment of PD&lt;br&gt;-the most effective &amp; gold standard drug</td>
<td>-causes motor fluctuations&lt;br&gt;-causes dyskinesia&lt;br&gt;-does not affect non-dopaminergic symptoms (freezing, dysautonomia, dysarthria)&lt;br&gt;-non-motor side effects; nausea, hallucination, sleepiness, autonomic problems</td>
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<tr>
<td>Dopamine agonists</td>
<td>Stimulate dopamine receptors&lt;br&gt;bromocriptines, cabergoline, dihydroergocryptine, lisuride, pergolide, pramipexole, ropinirole</td>
<td>-reduced incidence of motor fluctuations &amp; complications compared to L-dopa&lt;br&gt;-antioxidant effect&lt;br&gt;-provide neuron protection</td>
<td>-nausea, vomiting, bradycardia, postural hypotension, dizziness&lt;br&gt;-high risks of daytime sleepiness, hallucination, psychosis, insomnia&lt;br&gt;-dyskinesia with L-dopa&lt;br&gt;-less motor improvement</td>
</tr>
<tr>
<td>MAO-B inhibitors:</td>
<td>Increases half life of dopamine in the brain by inhibiting oxidative deamination of dopamine</td>
<td>-reduces symptom severity&lt;br&gt;-delays start of L-dopa&lt;br&gt;-reduces motor fluctuations</td>
<td>-insomnia&lt;br&gt;-with L-dopa increases nausea, dyskinesia, confusion, hallucination, autonomic side effects (orthostatic hypotension)</td>
</tr>
<tr>
<td>Amantadine</td>
<td>Exact mechanism unknown. Enhances release of dopamine from dopamine terminals. Increases affinity of dopamine receptors</td>
<td>-delays start of L-dopa&lt;br&gt;-reduces akinesia, tremor, rigidity&lt;br&gt;-reduces cardinal symptoms some&lt;br&gt;-compared to L-dopa mild side effects with appropriate dosage</td>
<td>-efficacy reduces after months of continuous use&lt;br&gt;-side effects include livedo reticularis, ankle edema, dryness of the mouth, blurred vision, difficulty focusing, confusion, depression, nightmares, hallucination</td>
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tremor (82%), akinesia (57%), rigidity (52%), postural instability (49%) and drug-induced dyskinesia (83%) [262]. The exact mechanism of DBS is not known. There is evidence for inhibitory and excitatory effects of stimulation on neuronal activity of the targeted nuclei [267]. Investigators suggest that DBS works by regulating the neural oscillation of the targeted nuclei [268]. Stimulation appears to terminate the dysfunctional activity of neurons and shifts the temporal pattern of their discharge to a more optimal and synchronized frequency [269]. This pattern of activity replaces the random deleterious pattern of BG network with a regular pattern of neural bursts causing a stabilized and symmetric activity across different regions within BG [267].

Benefits of DBS, although promising, are most effective when used in conjunction with patients’ regular medication [253]. Unfortunately, not all PD patients can undergo such surgery. The suitable surgery candidate is responsive to medication, less than 75 years of age with relatively normal cognitive status and disease onset greater than 5 years [270-272]. Therefore, research continues for discovering more effective medical and surgical techniques, including less invasive techniques such as rehabilitation.

5.3. Rehabilitation

The goal of rehabilitation in PD is to overcome the associated motor symptoms for improved functioning. It is assumed that the ability to generate the correct movement is not lost in PD [243], rather that major motor complications rise from the loss of internal ability to activate the appropriate motor plan or suppress the unwanted plans [237, 243]. Incidentally, different rehabilitation techniques such as physical therapy (PT) should focus on activating the correct motor plan.

The beneficial effects of rehabilitation are reported in previous investigations ([273, 274], some almost three decades old [275]), yet the numerous techniques have no unified therapeutic
approach. The focus of the next sections is to review the major therapeutic techniques and the motor learning studies in the literature as they apply to rehab in PD patients to offer insight to successful learning strategies and outcomes that lay the framework for future and/or other interventions.

5.3.1. Physical Therapy

Some scientists report benefits of combining training techniques. Training PD patients with Proprioceptive Neuromuscular Facilitation (PNF), water resistance exercises and coordination exercises of upper and lower extremities [276] for twenty weeks (60 sessions), revealed improvements in the Unified Parkinson’s Disease Rating Scale (UPDRS) scores, walking time and the Self Assessment Parkinson’s Disease Disability Scale (SAPDDS) scores. Franklyn & Stern also report a “modest” improvement in PD patients who attended a four week physical therapy program 2 times per week based on PNF and Bobath and Peto methods which aim at improving balance, posture and gait complications. Similar to Pellachia et al., they believe that the results are successful in improving patients’ quality of life and further report long term beneficial effects even five weeks after cessation of the PT program. Others state advantages of long term PT programs involving passive and active mobilization exercises and walking for four months [277], six weeks (12 sessions) of training with a combination of cardiovascular activities, stretching, strengthening, gait with auditory stimulation, balance training and relaxation exercises [274], or 16 session of stretching, strengthening and balance training over 8 weeks [278]. PT techniques involving repetitive exercises targeting ROM, endurance, balance, walking and motor dexterity for four weeks are also reported to be beneficial [279]. These studies state that such techniques improve functional status of the quality of life regarding physical mobility based on mobility portion of Sickness Impact Profile (SIP-68) [274, 277]. Improvements in the activities of daily living section of the UPDRS [274, 279], the motor section of the UPDRS [278,
and total UPDRS score [274, 278] also exist in this population. Improvements in balance after a ten week program (30 Sessions) composed of strength and balance training where PD patients undergo several conditions challenging the somato-sensory and/or visual systems while predisposed to unstable positions are also reported [280, 281].

More common exercise training regimes may also result in effective rehabilitation for PD. Twelve weeks of karate training, revealed improved coordination of fine movements, gait, tremor and grip strength [282]. Improved aerobic capacity in terms of VO2 max scores and better movement initiation were identified after sixteen weeks of cycling and/or walking [283]. A combination of various training exercises such as flexibility training and resistance exercises in water led to improvements in UPDRS scores and improved range of joint motion, strength and flexibility after 14 weeks of training [284]. High intensity resistance exercise lasting for 12 weeks resulted in increased walking endurance and greater muscular force production and mobility during ascending and descending stair stepping [285, 286]. Focused exercises that target spinal flexibility improve functional reach performance in just ten weeks [287] and eight weeks of exercises concentrating on lower extremity resistance training reveal increases in strength, gait velocity and stride length [286]. The benefits PD patients take from these training types are successful in targeting a specific physical limitation, thus strength, flexibility and endurance training provide similar results to that of the normal population [286].

Another recent intriguing rehab technique involves the practice of motor imagery [288]. This technique shows promising results when used in combination with PT techniques including sitting without support while using upper extremities, standing up, walking, stopping and changing direction. The motor imagery task required PD patients to imagine themselves performing the same tasks as trained. The benefits were more significant for patients who underwent the PT techniques in combination with motor imagery than performing the physical
therapy alone. Most improvements involved performance in sequential movements; walking, standing up, lying down and standing up again and turning in bed, but improvements were also found in the UPDRS motor score and cognitive tasks including clock drawing and stroop tests [288]. The fact that PD patients can practice motor imagery at their convenience makes this method attractive to some patients.

The therapeutic strategies applied in the literature are numerous and results in several improved outcomes in PD patients. The improved functioning resulting from these techniques is of great importance and cannot be denied, however, the combination of techniques does not isolate exercise effectiveness and in some cases lacks a scientific explanation for their effectiveness (i.e. cannot explain how they bypass the dysfunctional BG), making it unclear whether all the exercises are beneficial. Several guidelines have been introduced to overcome some variability in techniques applied in rehabilitation settings (Table 2). Readers are referred elsewhere [289-291] for further information regarding rehabilitation strategies for PD.

<table>
<thead>
<tr>
<th>Table 2. Guidelines for physical therapists in developing rehabilitation strategies.</th>
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<tbody>
<tr>
<td>1 Be knowledgeable of the disease, individual characteristics of the patient, medications and peak effect time (on/off periods), cognitive impairments and presence of other pathologies</td>
</tr>
<tr>
<td>2 Normal movements are not lost, though it is important to find a way to activate them</td>
</tr>
<tr>
<td>3 In order to avoid complexity within a sequence break the movement into components</td>
</tr>
<tr>
<td>4 Allow for attention to take control and compensate for the loss of normal automaticity of a movement and take advantage of the cortically controlled movement</td>
</tr>
<tr>
<td>5 Use external cues, this will allow the patients to start the movement with normal velocity and amplitude</td>
</tr>
<tr>
<td>6 Avoid simultaneous tasks especially at initial stages of therapy</td>
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Adapted from Iansek 1999; Morris, 2000

5.3.2. Motor Learning

Learning is an imperative component for a successful rehabilitation. Motor learning abilities appear to differ according to learning conditions and tasks, making the specific aspects of motor learning in PD not easy to determine. The following paragraphs provide some insight to these aspects.
PD patients are able to learn motor skills with different levels of difficulty and benefit from practice [292]. Patients can improve their performance in pursuit rotor tasks in one day [292, 293] and sequential reaching movements such as pointing to a sequence of targets in two days [292]. Authors suggest that the improved RT (pre-motor and motor components) and MT with practice reflect the ability of this population to improve central (pre-motor time) and peripheral (motor time) components of the movement [292].

Some researchers suggest that PD patients are not able to learn tasks that involve simultaneous learning of different components of a skill (i.e. spatial and temporal components) [72, 294]. They further suggest that PD patients are only able to learn [295] and retain [296] simple to moderate sequences, as those that involve less than seven sequences of upper extremity movements [295]. These concerns for learning abilities in PD are supported by investigators who recognize the BG as the major structures responsible for motor learning in humans [297].

Interestingly, experimental findings suggest that PD patients can learn more complex tasks. Bimanual drawing of triangles is a perfect example. The improvements in cycle duration variability, speed accuracy, synchrony between the limbs and consistency of the size of the three sides of the triangle occur in greater extent in PD subjects compared to age-matched controls after two days of practice [298]. Patients also showed improvements in buttoning a vest, and once re-learned after only ten trials of practice, performed the task concurrently while tapping the foot [299]. In other experiments PD patients learned a complex Tai Kwan Do movement involving twelve postural sequences and coordination of upper and lower extremities within three weeks and retained this performance ability for three weeks after termination of practice [300]. Moreover, after only one day of practice these patients improved balance skills [301] and postural stability [302] in various aspects such as increasing the speed and the level of end point exertion while shifting their center of gravity (COG) and further improved speed of reaction to
perturbation and the length of the compensatory step a week (former) or months (latter) after termination of practice.

Success in learning of more complex skills is possibly attributed to the methodology used. PD patients who were given more time than healthy individuals, were allowed to correct their own errors in learning a Tai Kwan Do movement [300]. Those who were provided with constant augmented visual feedback of their COG to improve their balance in one study [301] and given positive reinforcement after production of the appropriate postural response in the another [302] may have contributed to their improvements. For the studies on improved balance [300, 302] and Tai Kwan Do [300, 302] the practice schedule started with blocked practice and ended with a random practice order. Since blocked practice provides greater opportunity for early success and random practice results in better retention and transfer skill performance [303, 304], this schedule likely aiding with learning and retention of movement.

As indicated by positron emission tomography (PET) scan [295] and functional magnetic resonance imaging (FMRI) [305] studies, motor improvements reflect the PD patients’ ability to overcome their deficiency by recruiting greater areas within the cortical and sub-cortical regions. Unlike the PET scan experiment that reported compensation for simple to moderate tasks, the FMRI study revealed the ability of PD patients to reach automaticity for a sequence of twelve different movements (indicated by performing the skill accurately in presence of a secondary task) by recruiting additional areas such as the cerebellum, pre-motor, pre-frontal and parietal cortices. It appears that with sufficient time and appropriate training strategies learning is limited to mild or moderate skills in PD.

Clearly, PD patients can learn tasks of various difficulties under the appropriate conditions. Providing the additional time, training and or feedback are likely the keys to success of learning more complex tasks in this population. However, whether the PD patients can
maintain the skills for the long term and generalize the learned motor skills to their daily routine is less clear. Studies in these areas should offer insight to rehab in this population.

5.3.3. External Stimulation

“Kinesia paradoxical” refers to the ability of PD patients to produce normal movements under certain conditions [306]. The use of external stimulation is one condition that can enable patients to perform the correct motor task. A strategy to enable motor plan activation in PD involves recruiting neurons from other areas of the brain and bypassing the BG [183, 288]. This was observed in a study on regional cerebral flow measures, where authors report less activity in SMA in PD patients during self-determined tasks but similar activity of the motor cortex of PD patients to that of controls during an externally driven tasks [307], revealing direct access to other areas of the motor cortex and bypass of BG-SMA pathway under external stimulation [308]. These findings highlight the importance of external stimulation in generating normal movements in PD.

Visual feedback is a type of external stimulation used successfully in assisting PD patients in a single session. Providing patients with visual cues (i.e. providing dots on the paper as cues) can aid in controlling hypokinesia (small hand writing) and therefore enlarging the amplitude and size of their strokes [309]. In reaching tasks PD patients behave similar to controls in providing appropriate force and velocity possibly because of the visual feedback provided by the moving target of interest [133]. Aiming tasks with visual feedback of the movement can improve the accuracy of speed and duration of the movement [310]. Stride length and velocity increase with visual feedback of “appropriate” step placement [249, 311, 312]. Balance control with visual feedback of the COP can decrease postural instabilities [313].

PD patients also benefit from practice of visually enhanced gait (walking on the marked floor) [314, 315] and balance (moving the trunk to colored targets) [315]. After four weeks of
practice they improved functionality by increasing independence in activities of daily living measured by performance in walking, dressing, eating and hygiene based on Northwestern University Disability Scale [315] and increased step length and gait speed [314]. These improvements were retained three months (former) and one month (latter) after termination of practice.

Other types of external stimuli were also investigated. An example is an insole vibration device that improved the gait complications of PD patients [316]. Stimulating the feet with vibrating insoles as they contact the ground increased the stride length, speed and cadence and decreased the stride duration variability [316]. The effect of somato-sensory cues in form of vibration for improving stride length was noted elsewhere [317] and appears to be a novel effective strategy. Cutaneous triggers in forms of electrical stimulation of the feet used as a go signal were advantageous in increasing the produced force and anticipatory postural adjustments during gait initiation [170]. During gait presence of cutaneous cues decreased COP displacement, velocity and the abnormally prolonged double support time were evident [318]. Unfortunately, these studies are performed in a single session and long term effects of these stimuli still require further study.

Clearly, the use of external stimuli can improve some of the motor complications in PD. The most valuable stimuli, effectiveness of external stimuli and strategies for their incorporation into patients’ daily routines require further investigation. The next chapter will concentrate on a detailed review of the use of auditory stimulation and how it applies to the PD population.

5.4. Summary

Studies on the use of medications, surgery and rehabilitation can result in improved motor performance for those with PD. It seems that understanding the purpose and limitation of each strategy is imperative to effectively treat PD. Moreover, with greater improvements
identified for the use of combined strategies compared to that of a single strategy (i.e. benefits of PT in improving certain motor symptoms were greatest when used in conjunction with patients medication [276, 289], it is probable that the most successful treatments will involve multiple techniques.

6. AUDITORY STIMULATION, MOTOR CONTROL AND PARKINSON’S DISEASE

Auditory stimulation (AS) is only one type of external stimuli used to manage motor complications associated with PD by replacing the lost internal trigger for movement modulation. Outcomes with visual and tactile cues discussed in the previous chapter gave insight to the successful use of these stimuli, primarily in short sessions with relatively long term effects. Clearly, the review of literature on outcomes of using auditory cues for motor control in this population is warranted, as are the limitations in this research. However, these findings are not as meaningful without motivation for using this technique. Therefore, the first focus of this section is to show why auditory stimulation may have benefits over other sensory modalities.

6.1. Why Use Auditory Stimulation?

Auditory and visual cues are the most common modalities used as external stimuli for treatment of PD symptoms. Researchers consider many outcomes associated with their use successful, explaining why these cues are commonly used and why the following discussion concentrates on outcome studies using these modalities.

Based on measures of variability of the IRI of finger tapping to external stimuli and the ability to coordinate each tap to the stimulus, normal subjects produce less stable and less accurate synchronized and syncopated movements in response to visual stimuli compared to auditory while pacing the finger tapping [319, 320], and continuing it upon removal of the stimuli [319, 320]. In these experiments the subject is asked to synchronize (pace movements with each stimulus presentation) or syncopate (pace movements between each stimulus
presentation) the motor response to a rhythmic external stimulation, and is required to continue the pattern after removal of the stimulus. The outcomes suggest that auditory cues are easier for the healthy subject to follow no matter the task complexity; syncopation, which requires more cognitive effort than synchronization, is considered to be more complex [321].

Investigators also report an “auditory dominance in temporal processing” [322] compared to visual and tactile counterparts. In a bimodal condition, where rhythmic auditory and visual stimuli are both present, the temporal pattern of inter response duration of finger tapping is similar to that of auditory alone [322]. Individuals have a higher tendency to match the pattern of their finger tapping to auditory distracters during a visual synchronization task than to visual distracters during an auditory synchronization task [320]. Use of auditory stimulation in combination with visual cues during gait have no benefits in improving gait velocity and stride length over using the auditory stimulation alone [323]. In addition, perceiving duration of visual intervals are more variable than those of auditory [321, 324] and RT is longest for vision, followed by that of touch, then by audition [325]. Together, these results support the auditory dominance hypothesis.

CNS recordings, which provide evidence for modality dependent mechanisms, compliment the previous findings [319, 321]. The continuous activity of visual specific brain areas after removal of the visual stimulation [321] is unlike that for auditory stimulation, where the auditory specific brain areas become inactive during this time [319, 321]. Interpretation by these researchers include that auditory information directly transfers into an accurate and stable motor output, dismissing the need for continuous activation after stimulus removal [321] and/or that visual information is “too demanding” for directly generating a motor response [319]. Evidence regarding encoding of temporal characteristics of rhythmic visual stimulation to the
auditory cortex accounts for the prolonged brain activity of the visual modality [326] and likely accounts for the auditory dominance previously reported.

The evidence for sub-cortical processing of auditory stimuli [327, 328] adds to the potential benefits of its use. Results that auditory stimulation can increase the excitability of spinal motor neurons via the reticulo-spinal pathway in response to an unexpected loud noise [329] and that listening to a low threshold single tone can facilitate the H-reflex [330] exist. The latter findings manifest the enhanced motor response with auditory stimulation [330] without use of the startle reflex, suggesting support for the auditory signal rather than just an autonomic response.

In summary, advantages of auditory stimulation are numerous. Auditory stimulation offers superior temporal organization of movement and perception thus appears to be the most appropriate external stimulation modality for motor control.

6.2. Outcomes of Auditory Stimulation

Playing music or generating beats with a metronome or computer enable researchers to study the effects of auditory stimulation on movement control. Most scientists that study effects of auditory stimulation use rhythmic beats of a metronome instead of that from music to eliminate the emotional and motivational effect of music (e.g. Pacchetti, Mancini, Aglieri, Fundaro, Martignoni, & Nappi, 2000). Moreover, dance students synchronize their steps better with the rhythm of a metronome compared to music [331], suggesting another advantage for metronome use for movement control.

Several studies use finger tapping to an external rhythm as a common task for investigating sequential movement disorders in PD. However, the aims of these studies involve the role of the BG in control of sequential movements rather than its effects on movement control [90-93]. Therefore, the focus of this section is to review investigations on the study of
short term effects and practice effects of auditory stimulation for enhancing the motor performance in PD and not the roles of the BG.

6.2.1. Short Term Effects

Investigations on the short term benefits of auditory stimulation evaluate the movement during externally driven tasks or during and immediately after removal of the auditory stimuli. Although beneficial effects of AS on different gait parameters are commonly proposed, scientists do not always agree on the training method(s) and the nature of the benefits. Such discrepancies partially rise from the inconsistent methodology across studies. Table 3 offers a brief synopsis of short term training effects of AS on movement control (single session studies), highlighting the methodological differences, while the following text summarizes the major findings and lists the corresponding conclusions.

A fixed AS frequency set to that of a preferred cadence appears to be beneficial for improving control of cadence during the externally driven gait [332, 333]. A 100 beats per minute (bmp) metronome frequency caused changes in PD muscular activity patterns when walking 8.5 meters, revealing increased EMG slope, decreased time to reach maximum force as well as reduced variability of selected EMG time patterns in the lower leg muscles to levels similar to age-matched controls [334]. Patients were also able to walk 40 meters in a shorter duration, with fewer steps and less freezing episodes to a metronome set at 96 bpm compared to a self-selected walk [335]. These findings suggest that the temporal control offered by fixed AS frequencies faster than preferred walking speed alter temporal organization of muscle activity and the ensuing force production and minimize certain undesirable symptoms of PD.

Relative frequencies of AS also reveal mixed findings for short term alterations in people with PD. Decreased double support time [333] and increased step length (Freedland et al., 2002; McIntosh, Brown, Rice, & Thaut, 1997), gait velocity [336] and cadence [332]; [336] are
reported in this population for metronome frequencies set above baselines set at either comfortable or maximum cadence. In contrast there are reports of no change in step length [332, 337, 338, 340] and double support time [332] and speed [338] for rhythmic auditory frequencies 15% higher than the preferred cadence or less. The double support time was reported to improve when compared to comfortable self-paced gait [333] but showed no changes when compared to gait synchronized with metronome set at preferred gait cadence[332]. Gait speed showed no changes in one experiment where subjects practiced to five different frequencies set above that of the preferred cadence[338]. Recanzone, 2003 suggests that spatial changes are not expected with auditory stimulation, as this type of modality is more beneficial in terms of temporal organization of movement. However, opposing outcomes regarding the double support time, step length and speed may result from methodological differences.

Interestingly, significant effects when walking to AS frequencies above preferred and maximum cadence did transfer to free walking conditions. Cadence, step length [336]; Freedland et al. 2002), step velocity [336] and cycle time (Freedland et al. 2002) are reported for walking without stimuli after the application of frequencies at preferred cadence and 10% above. At a more functional level benefits of auditory stimulation also appear to be promising [339]. For example, training PD patients to walk to an auditory rhythm set at the preferred speed while carrying a tray of cups from the kitchen helps increase gait velocity without influencing cadence [339].

A frequency set at -7.5% of preferred cadence bears no effect on gait velocity, stride length, cadence and double support time [332, 340], while that of a -10% does not affect MT or gait velocity [110]. Yet a metronome set at -10% of the preferred cadence increases the stride length and double support time, while decreasing the gait velocity [332]. A frequency of -15% only decreases gait velocity and cadence without affecting the stride length [340], but imposing a
rhythm as low as -20% appears not to affect gait velocity, stride length and cadence beyond that of the -15% [332]. In addition, the -20% frequency increases the step to step variability of the step length and duration and is considered detrimental [222].

A single auditory signal is shown to alter muscular activity affecting the initiation of a task in PD subjects. A single cue can enhance the initiation of the movement by facilitating the suppression of the plantar flexor muscles before the PD individual takes the first step to walk [341]. MT and variability decrease and peak velocity increase during a task where patients reach for a pen and begin to write, if the task is triggered by an initial auditory signal compared to a self-selected start [250]. A single audiovisual signal can increase the peak hip flexion and knee extension torque as the individual with PD starts to rise from a chair, reducing the time to complete the sit to stand task when compared to a self-regulatory condition [342]. Although not performed in isolation, auditory stimulation alone is likely to have a significant effect in the findings of this experiment similar to previous findings [341]. Whether the single auditory stimulus is superior to a visual cue is still unclear, as an increased COP velocity for the single AS condition was associated with a smaller step length than the condition in response to a single visual stimulus [318].

There is also evidence that short term practice with AS contributes to the neural plasticity [343]. TMS of M1 evoked thumb flexion changes in movement amplitude and direction after practice of thumb extension movements under rhythmic AS with a 1 Hz metronome beat for 15 minutes. Post practice, TMS that evoked thumb flexion initially, resulted in more regular (symmetrical) extension movements. These findings were significantly stronger when subjects practiced thumb extension with auditory cue compared to self-paced practice.

Some of the abovementioned improvements such as increase in efficiency of reaching for a pen, peak reaching velocity [250] and suppression of plantar flexors of the step initiation
occur only for PD patients. These observations not only reveal the ability of PD patients to improve but also suggest that unlike the healthy individuals, PD patients possess some movement deficits which open the space for improvements [250].

Review of the short term effects of auditory stimulation are appealing for some aspects of movement control. The use of different methodologies, resulting in varying results, offers some insight to successful protocols. For example, it is probable that the changes that occur during gait practice with AS generalize to normal walking, at least for the short term. However, when the use of similar methodology result in varying results, one must wonder if other factors such as motivation or fatigue during the session are to blame. Results from longer term practice may offer greater insight to the role of AS on movement control.

6.2.2. Practice Effects

The effects of short term training are only successful as a rehabilitation technique if they bear long term benefits. Therefore, the initial focus of this section was to not only determine any additional benefits observed with long term use of auditory stimulation, but also to determine whether the benefits of its use will remain for the long term after termination of practice and upon removal of the external stimulation. However, since no studies involving movement benefits for the long term after the use of AS were identified, the focus of this section is limited to long term use. A brief synopsis of relatively long term training effects of AS on movement control are presented (Table 4), while the following text summarizes the major findings and lists the corresponding conclusions.

Initial studies for relatively long term use of AS in PD patients reveal benefits at the muscular and functional levels. Three weeks of walking to AS of beats imbedded in music at a preferred cadence for 25 minutes per day resulted a significant reduction in variability of the pattern of the activity of lower leg muscles, increase in the symmetry of bilateral leg muscles and
increase in gait velocity and stride length [209]. Over a similar training time for 30 minutes per day using a similar rhythmic auditory stimulation but with frequency ranging from preferred cadence to 10% and 20% faster resulted in increased gait velocity, stride length, symmetry of bilateral leg muscles and a more rapid termination muscle pattern; like that of controls [344]. Training in the latter study was altered such that performances were on flat and inclined surfaces with possible “stop and go” cues or while stair stepping. Together, these findings suggest that the effects of auditory stimulation are important in regulating the motor unit recruitment patterns [209] that result in certain functional alterations.

Movement alterations in PD subjects were also found for practice sessions lasting 60 min for five days a week for four weeks. Training required PD patients to walk to the rhythmic AS of a metronome with frequencies ranging from 30 to 150 bpm while performing manual tasks that became more complex along the course of a four week practice [345]. Gait velocity, step length and cadence increased for preferred walking pace with and without upper limb movement and at maximum speed for 7.62 meters. The variability of the step duration decreased to baseline control level for preferred pace walking with no upper limb movement. Since the variability measures for PD patients were originally similar to that of controls for the maximum speed, no change was expected in this case. However, because walking with upper limb movements offers a higher level of complexity and greater deficits in patients, they had more room for improvement, thus could benefit from a longer practice.

There is no evidence that one week of AS training at the preferred walking speed can reduce the number or duration of freezing episodes in PD subjects [346]. In fact, authors found an increase in their gait duration on a 60 foot track with 2 U-turns and one doorway. Whether alterations in their methodology would result in reduction in the freezing episode number or duration remains to be tested.
Experiments regarding the effect of auditory stimulation on cortical and sub-cortical regions after practice are few in number, especially when considering PD patients. One recent study has addressed this issue. After four weeks of performing manual tasks and walking to auditory cues ranging from 30 to 150 bpm, PD patients reduced the amount of variability of IRI for gait and finger tapping [347]. Although there were no significant changes in other parameters such as movement velocity, stride length and gait or tapping cadence, a significant increase in activation of parietal and temporal lobes as well as right cerebellum hemisphere and dentate nucleus after therapy were identified during finger tapping. According to investigators AS therapy resulted in activation of a pathway used for temporal control of movement [347]. Whether these findings are long lasting and can circumvent the damaged BG over the long term remain to be tested, however the initial results are promising.

6.3. Limitations of Previous Research

The aforementioned studies showed various effects of short and long term practice with AS on different aspects of movement in those with Parkinson’s. Although several alterations were considered beneficial for improving the function in this population, acknowledging the limitations of previous studies will not only highlight the areas that need more research but also guide future investigation improvements.

The first apparent limitation is on the number of studies involving AS effects on movement outcomes in PD. For example, brain imaging studies are numerous when it comes to evaluating brain areas activated during auditory stimulation application [319, 321] or during assessment of general learning abilities [305, 348] in the normal and PD population. However, only a few of the published studies were identified using PD subjects. Moreover, the number of studies identifying long term outcomes for this population is limited. Since the longest reported alterations were recorded only one day after termination of practice [336, 344, 345, 347] it is
very difficult to determine and/or predict the benefits of auditory stimulation as a rehabilitation regimen. Rehabilitation methods should focus on the individuals’ ability to apply what they learn beyond the doors of clinics or research labs.

Understanding the optimal training or practice methodology is not clear because of the presence of different or combined methodologies used and conflicting results. Varied [332, 338, 339, 344, 345, 347] and constant [335] frequencies of AS have resulted in movement alterations in PD, leaving one to wonder which is better. The most difficult training methodology to follow are those studies lacking the clear description of the training condition [344 345, 346], especially when it changes across time and conditions. Although few studies have incorporated different levels of complexities within their auditory stimulation intervention [209, 345] and such changes may be beneficial for the subjects, none used an objective measure to present the new level of complexity. The researchers that set a baseline cadence for practice comparisons have used a maximal [323, 336] or preferred [337, 339, 344, 346] cadence, thus producing varied outcomes due to comparison difference. Auditory stimulation has not been used exclusively in all experiments; it has been used in combination with visual cues for gait [323] or gait initiation [342]. Using multiple stimuli and embedding metronome-like beats in music [336, 349] could offer different results than pure metronome training.

Further limitations are noted with precise inspection of the methodologies. Without a control group [333] it is difficult to determine if PD patients improve to the level of their peers without neurological deficits. It becomes very difficult to make conclusions in some cases because authors do not report the effects of AS on some of the recorded depended variables [333] or lack information regarding the patient population such as duration of the disease [340] or whether patients were tested on or off their medication [333].
Auditory stimulation superiority previously reported for temporal organization of movement and perception is not necessarily true for spatial measures. It has been suggested that vision is of more importance for spatial organization [350]. The fact that AS use does alter spatial measures such as step/stride length [337, 344] is an added benefit, however the extent of such improvement may be incomplete.

The limitations listed above are not inclusive, nor do they deny the movement alterations that have occurred with AS practice in Parkinson’s patients. Rather, they are a reminder that there is still much to learn about the use of AS for movement improvements in this population. Greater insights to the particular use of AS in PD subjects are offered below in the “Future Directions” section.

7. SUMMARY

As a disease of unknown etiology, the pathology of Parkinson’s disease is difficult to understand. The major motor symptoms of tremor, bradykinesia, postural instability and rigidity, used for diagnosis, result from a defective BG with well-mapped connections, however the exact motor role(s) and functional organization of the BG remain a mystery. Although controversies exist in regards to the exact role of the BG and cerebellum in temporal movement control, it is obvious that PD patients are less capable of releasing and inhibiting the appropriate movement at the appropriate time for proper control.

Motor complications resulting from damage to the BG in PD lead to control deficits in this population. Complications of posture and gait that ensue from these deficits are of great importance as they affect independent functioning of the individual, making the person prone to falls and the associated consequences. Although new surgical interventions are promising and lack debilitating side effects present with medication, the outcomes are limited and not all patients qualify for its use.
Because PD patients show preserved motor learning abilities, rehabilitation can play an important role in keeping the individuals active and in overcoming some of their motor complications. Of the various rehabilitation techniques external stimuli are of great interest as they may replace the malfunctioned BG, the lost internal trigger for movement modulation. As the dominating stimulus for temporal processing, auditory stimulation can significantly assist individuals with PD to regain temporal control over their actions with the hope of improving their motor performance.

There is ample evidence that treatment for motor complications associated with PD is multidimensional. For example, Parkinson’s patients on medication commonly receive greater benefits from rehabilitation and surgical techniques than when not medicated. Understanding the literature in regards to successful treatment outcomes is imperative to offering insight to more effective rehabilitation techniques. Summary of the major gaps in the rehabilitation literature and major limitations of previous studies is presented next to offer insight to future directions of treatment for this population.

8. FUTURE DIRECTIONS

8.1. Need for Future Investigations

Reaching, grasping and walking, motor abilities simply and sub-consciously performed by people with no neurological problems, become strenuous activities for patients with PD. No current treatments exist to help these people overcome all their motor deficits. In fact, some treatments cause detrimental secondary side effects.

A century has passed since PD was discovered based on its significant motor symptoms, however no consensus on effective rehabilitation techniques for PD symptoms exists. It is possible that early scientists failed to recognize the plastic nature of the central nervous system and the roles rehabilitation can play, as training use for therapeutic regimes using specialists is
relatively new (PT inception, world war I [351]) and the use of evidence-based research in this field is lacking [352, 353]. Clearly, there is need for additional research on rehabilitation of motor symptoms in people with PD.

8.2. Rehabilitation in Future Investigations

Auditory stimulation has been used to successfully alter temporal control in PD patients. (See the Why use auditory stimulation? section in chapter six for the rationale of using auditory stimulation for rehabilitation for people with PD). Even though researchers report the positive effects of auditory stimulation on movement control, there is still much to be learned about its short and long term effects and how it should be used in rehabilitation efforts. It is clear that with the different stimulus frequencies, durations and methods used previously (see Tables 3 and 4), there is a need for more research on the application of rhythmic auditory stimulation for movement control.

As a preliminary to studying the effect of auditory stimulation on movement of individuals with PD, some initial questions posed to fill gaps regarding stimulus frequency were included in a pilot study. Does training with different frequencies of auditory stimulation affect the temporal outcomes of gait? Does the order of application of different frequencies of auditory stimulation affect the temporal outcomes of gait? Does training in one specific sequence help individuals apply the results to a different sequence? Although order of frequency application did not affect the temporal outcomes of gait in normal young subjects, training in different sequences did. Although similar training outcomes are probable for people with PD, the training effects for using multiple frequencies remain to be tested.

Three major limitations of most, if not all previous experiments on AS, used in PD include: the effects of treatment over a longer time period, its long term effects and the determination of whether it generalizes to daily activity. Although one time training sessions are
easy to arrange and provide insight to AS effectiveness, they provide little time for changes in neural plasticity. Furthermore, in previous AS studies re-evaluation of PD patients’ control long term after practice do not exist, while testing control with stimulus removal in a different context is limited. Thus, how long the benefits last and how well they serve this population in the context of everyday life is unclear. To improve the use of auditory stimulation in a rehab setting, several questions still need to be answered. Accordingly, the following aims and hypotheses are proposed.

8.3. Developed Aims and Hypotheses

**Aim 1:** To investigate the effect of using multiple frequencies and tones of auditory stimuli within a single trial for PD patients. As mentioned previously, the BG are important in selecting, releasing and switching a motor plan which allows for sub-cortical or more automated performance of a sequence of actions. To bypass the BG one should take advantage of performing the tasks at a cortical level. Using one frequency within each session or trial allows one to predict the following beat, habituates the patient and does not challenge the CNS in withholding the competing plans required for daily living. Assigning different tones to different actions will demand constant monitoring of the presented beats to modulate the movement, likely encouraging facilitation of compensatory pathways. It is hypothesized that using different tones or frequencies within a trial will result in improved movement control for PD patients.

**Aim 2:** To investigate how PD patients benefit from longer practice duration that is organized with feedback. There is evidence that PD patients struggle to execute certain movements, especially activities that are more complex in nature and require several sequential movements. However, significant learning and retention of complex sequential movements has occurred in this population often when practice time was extended and feedback was provided. Taking advantage of longer practice schedules and other successful motor learning principals
such as providing feedback and beginning with a simple blocked practice design and moving towards more random design with improvement should foster a good learning environment. It is hypothesized that using different tones or frequencies within trials in an unpredictable random manner after some blocked practice will initially be more difficult for PD patients to perform, but ultimately result in improved movement control abilities.

Aim3. To investigate the ability of PD patients to generalize what they practice to similar conditions but in different contexts. Many studies test patients after training in a very similar environment of practice. Thus, improvements with training are evident in this environment. However, whether these results transfer to different tasks or environments remains unanswered. It is hypothesized that using different tones or frequencies within trials in an unpredictable random manner will result in improved movement control abilities in similar tasks of different contexts.
REFERENCES


Step1. Diagnosis of Parkinsonian syndrome
Bradykinesia with at least one of the following:
  Muscular rigidity
  4-6 Hz resting tremor
  Postural instability not caused by primary visual, vestibular, cerebellar, or
  Proprioceptive dysfunction

Step2. Exclusion criteria for Parkinson’s disease
  History of repeated strokes with stepwise progression of Parkinsonian features
  History of repeated head injury
  History of definite encephalitis
  Oculogyric crises
  Neuroleptic treatment at onset of symptoms
  More than one affected relative
  Sustained remission
  Strictly unilateral features after 3 years
  Supranuclear gaze palsy
  Cerebellar signs
  Early severe autonomic involvement
  Early Severe dementia with disturbances of memory, language and praxis
  Babinski sign
  Presence of cerebral tumor or communicating hydrocephalus on computed tomography
  Negative response to large doses of levodopa if (if malabsorption excluded)
  1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine exposure

Step3. Supportive prospective positive criteria for Parkinson’s disease
  (Three or more required for diagnosis of definite Parkinson’s disease)
  Unilateral onset
  Rest tremor present
  Progressive disorder
  Persistent asymmetry affecting the side of onset
  Excellent response (70-100%) to levodopa
  Severe levodopa-induced chorea
  Levodopa response for 5 years or more
  Clinical course of 10 years or more

A-APPENDIX B. Modified Hoehn and Yahr Scale for identifying stage of Parkinson’s disease

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.

APPENDIX C. Descriptions of Major PD Motor Complications

Rigidity: a state of muscular stiffness; the abnormal increase in muscular resistance opposing the passive movement of the limb. Lead-pipe rigidity is consistent through the whole movement and cog-wheel rigidity is intermittent. It increases with stress and effort in performing an action and may contribute to reduction of deep tendon reflexes and lead to postural deformities [58, 59].

Dystonia: abnormal co-contraction of antagonist muscles of upper/lower extremities. Dystonia involves abnormal muscle tone and appears secondary to medication. If not controlled, dystonia can lead to limb deformities and abnormal posture. Dystonia can characterize juvenile PD or advanced PD and the change in muscular tone can hardly be distinguished from that of rigidity [354, 355].

Hypokinesia*: reduction of movement size. It is usually the major and initial symptom of PD as its incident is even more common than rigidity and tremor. [356].

Bradykinesia*: Slowness of the voluntary movement [356].

Akinesia*: difficulty in initiation of the movement. [357].

*Unfortunately, hypokinesia, bradykinesia and akinesia are motor symptoms that are sometimes used interchangeably; however each term represents a different complication [356]. Akinesia, hypokinesia and bradykinesia interfere with activities of daily living such as buttoning a shirt, turning over in bed or starting a simple movement. These symptoms worsen with fatigue and severity of the disease but can be prevailed with cognitive effort, external stimulation or emergency at least for short periods of time, a phenomenon referred to as ‘kinesia paradoxical’ [357].

Dyskinesia: Involuntary choreic movements which usually occurs secondary to medication (i.e. levodopa) (prevalence of 40-90%), and it can appear in upper and lower extremities as well as trunk and head [58, 358].

Tremor: Rhythmic oscillation of at least one functional body region [359]. This symptom is more prominent in upper extremities [1]. It usually starts intermittently in one finger. Tremor spreads to other fingers, the wrist and elbows with disease progression and possibly the head, face feet and other regions of the lower extremities in late stage [189]. Resting tremor is tremor at rest. Action tremor could be observed as postural, kinetic and isometric tremors. PD tremors can be categorized into 3 types: Type I (classical parkinsonian tremor)–action (kinetic and postural) and resting tremors with similar frequencies; Type II--similar to type I except that the frequency of action tremor is higher than that of the resting tremor; Type III--postural action tremor observed in isolation, i.e. not accompanied by resting tremor (see (Deuschl, Volkmann, & Raethjen, 2007).
**A-APPENDIX D**

**Table 3:** This table summarizes the major findings of the short term effects of auditory stimulation on movement characteristics in Parkinson’s disease.

<table>
<thead>
<tr>
<th>Rehab</th>
<th>Subjects, Age, PD duration</th>
<th>No Improvements</th>
<th>Major changes</th>
<th>Source</th>
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<tbody>
<tr>
<td>Walking inside and outside on a 4m x 10m walkway with 3 Uturns to march music (type I &amp; II), a metronome or tactile stimulation</td>
<td>23 PD, H&amp;Y: 3-4, Patients experienced freezing</td>
<td>March: Gait duration, Number of freezing episodes, (Type II: Step number)</td>
<td>Tactile: ↑Gait duration, ↑Number of freezing episodes (Inside: ↑Step number; Outside: ↓Step number) <strong>March:</strong> ↓Step number (type I) <strong>Metronome:</strong> ↓Gait duration, ↓Step number, ↓Number of freezing episodes</td>
<td>Enzensberger et al. 1997</td>
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<tr>
<td>Walking 30m a click tone embedded in music at maximum cadence 10% above</td>
<td>21 PDon, 71 yrs, 7.5 yrs, H&amp;Y: 2-4 10 PDoff24 (24h), 73 yrs, 7.5 yrs, H&amp;Y: 2-3 1 PDoff48 (48h), 73 yrs, 8.5 yrs, H&amp;Y: 3 10 Cont, 71 yrs</td>
<td>PDon: Symmetry (time ratio between two successive steps) PDoff24,48: Symmetry Cont: Stride length, Symmetry</td>
<td>PDon, PDoff: ↑Cadence, ↑Velocity, ↑Stride length <strong>Control:</strong> ↑Cadence, ↑Velocity</td>
<td>McIntosh et al. 1997</td>
</tr>
<tr>
<td>Aiming Task: moving a stylus to a target at the distance of 200mm as accurate and fast as possible with rhythmic beats set at 10% below the fastest reaching speed [2]</td>
<td>8 PDoff, 62 yrs, 7.6 yrs, H&amp;Y : 2 8 Cont, 60.8 yrs</td>
<td>Retention PD &amp; Cont: MT, Deceleration duration, Corrective phase duration</td>
<td>Immediate effect PD &amp; Cont: ↑Max acceleration, ↓MT, ↓Deceleration duration, ↓Corrective phase duration Retention PD &amp; Cont: ↓Maximum acceleration</td>
<td>Platz et al. 1998</td>
</tr>
<tr>
<td>Walking 6m with 6 metronome frequencies (comfortable cadence to 125</td>
<td>7 PDon, 44-74 yrs, H&amp;Y: 1-3 5 Cont, 55-60 yrs</td>
<td>PD: Step length, Speed</td>
<td>PD: ↑Step frequency</td>
<td>Zijlstra et al. 1998</td>
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<tr>
<td>Activity Description</td>
<td>Participants</td>
<td>Results</td>
<td>Study Reference</td>
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<td>Walking 10m with metronome set at 20% below preferred cadence</td>
<td><strong>11 PDont</strong>, 60.8 yrs; 20 months; <strong>11 PDoff</strong>, 63.1 yrs; 16 months; <strong>22 Cont</strong>, 61.8 yrs</td>
<td><strong>Cont</strong>: Variability of step duration; <strong>PD (ON &amp; OFF)</strong>: ↑Variability of step length, ↑Variability of step duration, ↓Step length</td>
<td><strong>Ebersbach et al. 1999</strong></td>
<td></td>
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<tr>
<td>Reaching for a pen (R), bringing the pen to the paper (B), and writing down a phrase with a single auditory stimulation present</td>
<td><strong>16 PDont</strong>, 64.6 yrs; 6.6 yrs; H&amp;Y: 2.65; <strong>16 Cont</strong>, 65.6 yrs</td>
<td><strong>PD</strong>: Number of movement units [3] (R), Efficiency [4] (B), Inter-trial variability (B); <strong>Cont</strong>: MT, Peak velocity, Number of movement units, Inter-trial variability, Efficiency (B); <strong>PD</strong>: ↑Efficiency (R); ↑Peak velocity, ↑Number of movement units (B), ↓MT, ↓Inter-trial variability (Ronly); <strong>Cont</strong>: ↓Efficiency (R)</td>
<td><strong>Ma et al. 2001</strong></td>
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<td>Walking 1.5m with a metronome set at preferred cadence and 10% above</td>
<td><strong>16 PD</strong>, 74 yrs</td>
<td><strong>PD</strong>: Size of base of support</td>
<td><strong>Freedland et al. 2002</strong></td>
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<td>Sit to stand from a chair with arm folded in front of the body as fast as possible after: Simultaneous presentation of a flash light and a verbal cue (1 trial).</td>
<td><strong>15 PDont</strong>, 65.5 yrs; 5.5 yrs; H&amp;Y: 2.6; Patients experienced freezing; <strong>15 Cont</strong>, 69.5 yrs</td>
<td><strong>PD</strong>: Peak hip extension torque, Time to peak hip flexion torque; <strong>Cont</strong>: Peak hip flexion, hip extension &amp; ankle torque; Time to peak hip flexion, hip extension, knee extension, ankle torque, Peak COM velocity, MT; <strong>PD</strong>: ↑Peak hip flexion, knee extension torque, ↑Peak COM velocity, ↓Time to peak hip extension, knee extension &amp; ankle torque, ↓MT; <strong>Cont</strong>: ↑Peak knee &amp; ankle torque</td>
<td><strong>Mak et al. 2002</strong></td>
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<td>Walking 20m with a metronome set at comfortable cadence (baseline) and 15% above on right and left sides</td>
<td><strong>7 PDont (PDoff)</strong>, 75.2 yrs; H&amp;Y: 1-3; Patients experienced freezing</td>
<td><strong>Baseline, Right side (ON &amp; OFF)</strong>: ↓Velocity, ↓Cadence; <strong>Left side (OFF)</strong>: ↑Stride length, ↓Velocity, ↓Cadence; <strong>Left side (ON)</strong>: ↑Velocity, ↓Stride length</td>
<td><strong>McCoy et al. 2002</strong></td>
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| Walking 9m with a metronome set at small (7.5%) and large (15%) frequencies above (high) and below (low) preferred cadence. | 11 PD, 54 yrs, H&Y: 1-2 | Higher frequencies: Stride length  
Lower frequencies: small: Gait speed, Cadence, small & large: Stride length | Higher frequencies:  
↑Cadence, ↑Speed  
Lower frequencies: large: ↓Cadence, ↓Gait speed | Howe et al. 2003 |
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<td>Walking 8.5 m, turned 180 degrees, returned to the starting position with metronome set at 100 bmp</td>
<td>6 PD, 58 yrs, H&amp;Y: 3-4 5 Cont, age-matched</td>
<td>Cont: no change</td>
<td>PD: TA &amp; GM: ↑Time to peak amplitude, ↓Time between activation, ↓Activation duration, ↓Variability of Time between activation, Time to peak amplitude, Activation duration</td>
<td>Fernandez del Olmo &amp; Cudeiro, 2003</td>
</tr>
<tr>
<td>Walked 5m as fast as possible after a single metronome signal (SA), the metronome at 96 bmp (RA), feeling electrical stimulus at 96 bpm (RE)</td>
<td>7 PD, 69 yrs, 6.7 yrs H&amp;Y: 2-3 Experienced freezing &amp; akinesia 7 Cont, age-matched</td>
<td>PD RE, RA &amp; SA: RT, Single support time, Sacral velocity</td>
<td>PD RE, RA: ↑Lateral &amp; Posterior COP [7] displacement, ↑COP velocity, ↓Double support time, ↓Sacral displacement, ↓Step length</td>
<td>Dibble et al. 2004</td>
</tr>
</tbody>
</table>
| Walking 7.62 m with Visual cues, metronome 25% above maximum cadence, both | 24 PD, 68.9 yrs, 6.9 yrs, H&Y: 2.75 Experienced instabilities & freezing | Visual cue: Speed  
Metonome cue: Stride length  
Both: Cadence, Stride length | Visual cue: ↑Stride length, ↓Cadence  
Metonome cue: ↑Speed, ↑Cadence  
Both: ↑Speed | Suteerawatananaon et al. 2004 |
| Stand up, walk to the kitchen, grab a tray with two cups & walk, set tray down & sit down with auditory tone and flash light at preferred cadence | 18 PD, 64.6 yrs, 10 yrs, H&Y: 1.5-4, Experienced freezing 10 Cont, age matched | PD [1]: Step length, Cadence  
Cont: Velocity, Step length | PD: ↑Velocity  
Cont: ↑Cadence | Rochester et al., 2005 |
| Thumb extension with metronome, 1 Hz [8] | 7 PDon1, 68.1 yrs, H&Y: 2-3 Experienced freezing 5 PDon2, 61 yrs, H&Y: 2-3 Did not experience freezing 9 Cont, 64.3 yrs | PDon1 & PDon2: ↑Amplitude of TMS induced movement, ↑regularity of thumb movement trace, TMS induced movement changed toward extension (5 PDon1, 4 PDon2) Cont: ↑Amplitude of TMS induced movement, Direction of TMS induced movement changed toward extension [9] (5 people) | Chuma et al. 2006 |
| Moved two steps forward hearing a single auditory warning cue then seeing a single flash light (go cue) | 9 PDon, 66.1 yrs, H&Y: 2-4 7 Cont, 64.6 yrs | PD (trailing leg): SOL amplitude Cont (trailing leg): SOL amplitude, Mean H-reflex amplitude of SOL | Hiraoka et al. 2006 |
| Walking 80 m with metronome at preferred cadence and 10% or 20% above and below | 10 PDon, 60.6 yrs, 6.2 yrs, H&Y: 2.7, Experienced freezing 10 PDon, 68.4yrs, 11.8 yrs H&Y 2.8 Did not experience freezing 10 Cont, 63.6 yrs | PD & Cont preferred speed: Gait speed, Stride length, Double support time Synchronization error [10] PD & Cont higher frequencies: Double support time, Synchronization error Cont lower frequencies: Stride length, Double support time, Synchronization error | Willems et al. 2006 |
| | | PD & Cont preferred speed: ↑Step frequency PD & Cont higher frequencies: ↑Step frequency, ↑Gait speed (non-freezers), ↑Step frequency, ↑Stride length (freezers) PD lower frequencies: ↑Stride length (non-freezers), ↑Double support time, ↑Synchronization error, ↓Gait speed, ↓Step frequency Cont lower frequencies: ↓Speed ↓Step frequency | |

Gastrocnemius (GM); Hoehn and Yahr scale (H&Y); healthy control subjects (Cont); Parkinson’s Disease (PD); on medication (PDon); off medication (PDoff); Soleus muscle (SOL); Tibialis Anterior (TA); Transcranial Magnetic Stimulation (TMS); Range Of Motion (ROM); Center Of Pressure (COP); Center Of Mass (COM); Movement Time (MT); Reaction time (RT)

1- Data were recorded after both trials were completed
2- After every five practice trial the frequency was adjusted to 90% of mean movement time of those five training trials.
3- Movement unit includes 1 acceleration and 1 deceleration phase
4- Efficiency reflects peak velocity/average velocity
5- FAP score: functional ambulation performance calculated by GaitRite system based on spatial and temporal gait parameters
6- The dominant side and the affected side were not identified
7- The amount of COP displacement were smaller for PD in all directions compared to controls
8- TMS evoked thumb flexion was used for testing the effect of practice
9- All changes were significantly higher for those who practiced with metronome, compared to those who practiced thumb extension with no cues.
10- Synchronization error is defined as the absolute time difference between metronome beat and foot contact
### A-APPENDIX E

**Table 4.** This table summarizes the major findings of the practice effect of auditory stimulation on movement characteristics for Parkinson’s disease.

<table>
<thead>
<tr>
<th>Rehab</th>
<th>Subjects, Age, PD duration</th>
<th>Duration</th>
<th>No Improvements</th>
<th>Major changes</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walking an 8m walkway with metronome beats embedded in rhythmically accented music</td>
<td>19 PDon, 71 yrs, 7.2 yrs, H&amp;Y: 2-3 18 Cont, 68 yrs</td>
<td>3 weeks 25 minutes a day</td>
<td>PD: EMG pattern variability (VL), Temporal variability (GM, TA &amp; VL), EMG pattern symmetry (GM, VL), Temporal symmetry (GM, TA &amp;VL)</td>
<td>PD: ↑ Gait speed, ↑Stride length, ↑ EMG pattern symmetry (TA), ↓ EMG pattern variability (GM &amp; TA)</td>
<td>Miller et al. 1996</td>
</tr>
<tr>
<td>1-Walking on a 6m flat surface and a 3m inclined surface with metronome beats embedded in music: a) set at a comfortable cadence b) set at 5-10% above comfortable cadence c) set at 10-15% above the comfortable cadence [1] 2-Stair stepping to a-c 3-Stop and go to a-c</td>
<td>Experimental (EX): 15 PDon, 69 yrs, 7.2 yrs, H&amp;Y: 2.3 Training, similar to EX but no cues (T): 11 PDon, 74 yrs, 5.4 yrs, H&amp;Y: 2.5 Non-training (NT): 11 PDon, 71 yrs, 8.5 yrs, H&amp;Y: 2.6</td>
<td>3 weeks 7 days/week 30 minutes</td>
<td>(EX, T, NT) Flat walkway: Temporal variability (TA, GM, VL), Activation symmetry (TA, GM, VL), Timing [2] (TA, GM) (EX) Flat walkway: Onset duration (GM, TA, VL), Termination duration (GM) (T, NT) Flat walkway: Cadence, Timing (VL) (NT) Flat walkway: Stride length</td>
<td>(EX) Flat walkway: ↑Velocity, ↑Cadence ↑Timing (VL), ↑Stride length (EX, T) inclined walkway: ↑Velocity (T) Flat walkway: ↑Velocity, ↑Stride length (NT) Flat &amp; Inclined walkway: ↓Velocity</td>
<td>Thaut et al. 1996</td>
</tr>
<tr>
<td>Walking with a metronome at preferred cadence. Testing: walked 60ft with 1 doorway &amp; 2 turns.</td>
<td>12 PDon, 65.8 yrs, 12.4 yrs, H&amp;Y: 2-4 freezes</td>
<td>1 week</td>
<td>Freeze duration, Number of freezes, Average duration of all freezes</td>
<td>↑Gait duration,</td>
<td>Cubo et al. 2004</td>
</tr>
<tr>
<td>Walking 30m with a metronome</td>
<td>15 PDon, 61.7 yrs, 7.26</td>
<td>4 weeks 5</td>
<td>PD: ↑Velocity, ↑Step</td>
<td>del Olmo et al. 2005</td>
<td></td>
</tr>
<tr>
<td>Set at 30 to 150 bpm with and without upper limb movements</td>
<td>yrs, H&amp;Y: 2 15 Cont, 63 yrs</td>
<td>days/week 60 minutes</td>
<td>length, ↑Cadence, ↓Variability of step duration</td>
<td></td>
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<tr>
<td>Walking 30m and/or performing uni- or bi-lateral arm movements with and without the use of a metronome set at 30-150 bpm. Testing: movement and PET scan</td>
<td>9 PDon, 61 yrs, 5.7 yrs, H&amp;Y: 1-2 5 Cont, 63 yrs</td>
<td>5 times a week, 4 weeks 60 minutes</td>
<td>PD (movement): Cadence, Gait speed, Stride length</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD (PET scan): ↑Metabolism—temporo-parietal conjunction, cerebellum, dentate</td>
<td>PD, (PET scan): ↓Step duration variability, ↓Finger tapping variability</td>
<td></td>
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</tbody>
</table>

Gastrocnemius (GM); Hoehn and Yahr scale (H&Y); healthy control subjects (Cont); Parkinson’s Disease (PD); on medication (PDon); off medication (PDoff); Positron Emission Tomography (PET); Soleus muscle (SOL); Tibialis Anterior (TA); Vastus Lateralis (VL)

1- After each week of training the frequency of the metronome beats increased by 5%
2- Timing of a muscle represents the temporal focus of EMG activity where higher values reflect “EMG activity focused in a small percentage of the gait cycle”

del Olmo et al. 2006
APPENDIX B --- APPLIED FUNCTIONAL MEASURES

UPDRS II (ADLs) & III (Motor) & Composite (13-15, 29-30)

II. Activities of daily living

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.

Unified Parkinson’s Disease Rating Scale
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 nasogastric tube or gastrotomy 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
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 0.25 in. or more.

20. Tremor at rest
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, with widest amplitude possible, each hand separately)
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 hand in rapid succession with widest amplitude possible, each hand separately)
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 or 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. Foot agility (patient taps heel on ground in rapid succession, picking up entire foot; amplitude should be approximately 3 in.)
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 arise from a straight-back wood or metal 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 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 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.
**Timed-Up-and-Go Test**

The timed "Up & Go" test measures, in seconds, the time taken by an individual to stand up from a standard arm chair (approximate seat height of 46 cm, arm height 65 cm), walk a distance of 3 meters (approximately 10 feet), turn, walk back to the chair, and sit down again. The subject wears his/her regular footwear. If participant’s usually use assistive devices such as canes or walkers, they should use them during the test, but this should be indicated on the data collection form. No physical assistance is given.

**Setting Up the test area**
- Determine a path free from obstruction
- Place a chair with arms at one end of the path.
- Mark off a 3 m (10 ft.) distance using tape or a cone or other clear marking.

**Start the test**
- Speak clearly and slowly.
- Inform participant of sequence and outcome: "When I say go, you will stand up from the chair, walk to the mark(cone) on the floor, turn around, walk back to the chair and sit down." "I will be timing you using the stopwatch."
- Ask participants to repeat the instructions to make sure they understand.

Participant starts with their back against the chair, their arms resting on the arm rests, and their walking aid at hand.
- Using a cue like “Ready, set, go” might be useful.
- Either a wrist-watch with a second hand or a stop-watch can be used to time the performance.

Dynamic Gait Index

1. Gait level surface _____
Instructions: Walk at your normal speed from here to the next mark (20’)
Grading: Mark the lowest category that applies.
(3) Normal: Walks 20’, no assistive devices, good speed, no evidence for imbalance, normal gait pattern
(1) Moderate Impairment: Walks 20’, slow speed, abnormal gait pattern, evidence for imbalance.
(0) Severe Impairment: Cannot walk 20’ without assistance, severe gait deviations or imbalance.

2. Change in gait speed _____
Instructions: Begin walking at your normal pace (for 5’), when I tell you “go,” walk as fast as you can (for 5’). When I tell you “slow,” walk as slowly as you can (for 5’).
Grading: Mark the lowest category that applies.
(3) Normal: Able to smoothly change walking speed without loss of balance or gait deviation. Shows a significant difference in walking speeds between normal, fast and slow speeds.
(2) Mild Impairment: Is able to change speed but demonstrates mild gait deviations, or not gait deviations but unable to achieve a significant change in velocity, or uses an assistive device.
(1) Moderate Impairment: Makes only minor adjustments to walking speed, or accomplishes a change in speed with significant gait deviations, or changes speed but has significant gait deviations, or changes speed but loses balance but is able to recover and continue walking.
(0) Severe Impairment: Cannot change speeds, or loses balance and has to reach for wall or be caught.

3. Gait with horizontal head turns _____
Instructions: Begin walking at your normal pace. When I tell you to “look right,” keep walking straight, but turn your head to the right. Keep looking to the right until I tell you, “look left,” then keep walking straight and turn your head to the left. Keep your head to the left until I tell you “look straight,” then keep walking straight, but return your head to the center.
Grading: Mark the lowest category that applies.
(3) Normal: Performs head turns smoothly with no change in gait.
(2) Mild Impairment: Performs head turns smoothly with slight change in gait velocity, i.e., minor disruption to smooth gait path or uses walking aid.
(1) Moderate Impairment: Performs head turns with moderate change in gait velocity, slows down, stagers but recovers, can continue to walk.
(0) Severe Impairment: Performs task with severe disruption of gait, i.e., stagers outside 15” path, loses balance, stops, reaches for wall.

4. Gait with vertical head turns _____
Instructions: Begin walking at your normal pace. When I tell you to “look up,” keep walking straight, but tip your head up. Keep looking up until I tell you, “look down,” then keep walking straight and tip your
head down. Keep your head down until I tell you “look straight,” then keep walking straight, but return your head to the center.

Grading: Mark the lowest category that applies.

(3) Normal: Performs head turns smoothly with no change in gait.
(2) Mild Impairment: Performs head turns smoothly with slight change in gait velocity, i.e., minor disruption to smooth gait path or uses walking aid.
(1) Moderate Impairment: Performs head turns with moderate change in gait velocity, slows down, staggers but recovers, can continue to walk.
(0) Severe Impairment: Performs task with severe disruption of gait, i.e., staggers outside 15” path, loses balance, stops, reaches for wall.

5. Gait and pivot turn _____
Instructions: Begin walking at your normal pace. When I tell you, “turn and stop,” turn as quickly as you can to face the opposite direction and stop.

Grading: Mark the lowest category that applies.

(3) Normal: Pivot turns safely within 3 seconds and stops quickly with no loss of balance.
(2) Mild Impairment: Pivot turns safely in > 3 seconds and stops with no loss of balance.
(1) Moderate Impairment: Turns slowly, requires verbal cueing, requires several small steps to catch balance following turn and stop.
(0) Severe Impairment: Cannot turn safely, requires assistance to turn and stop.

6. Step over obstacle _____
Instructions: Begin walking at your normal speed. When you come to the shoebox, step over it, not around it, and keep walking.

Grading: Mark the lowest category that applies.

(3) Normal: Is able to step over the box without changing gait speed, no evidence of imbalance.
(2) Mild Impairment: Is able to step over box, but must slow down and adjust steps to clear box safely.
(1) Moderate Impairment: Is able to step over box but must stop, then step over. May require verbal cueing.
(0) Severe Impairment: Cannot perform without assistance.

7. Step around obstacles _____
Instructions: Begin walking at normal speed. When you come to the first cone (about 6’ away), walk around the right side of it. When you come to the second cone (6’ past first cone), walk around it to the left.

Grading: Mark the lowest category that applies.

(3) Normal: Is able to walk around cones safely without changing gait speed; no evidence of imbalance.
(2) Mild Impairment: Is able to step around both cones, but must slow down and adjust steps to clear cones.
(1) Moderate Impairment: Is able to clear cones but must significantly slow, speed to accomplish task, or requires verbal cueing.
(0) Severe Impairment: Unable to clear cones, walks into one or both cones, or requires physical assistance.

8. Steps _____
Instructions: Walk up these stairs as you would at home, i.e., using the railing if necessary. At the top, turn around and walk down.

Grading: Mark the lowest category that applies.

(3) Normal: Alternating feet, no rail.
(2) Mild Impairment: Alternating feet, must use rail.
(1) Moderate Impairment: Two feet to a stair, must use rail.
(0) Severe Impairment: Cannot do safely.

Tinetti Mobility Test

Tinetti Assessment Tool: Balance

Initial Instructions: Subject is seated in a hard, armless chair. The following maneuvers are tested.

1. Sitting balance: Leans or slides in chair =0
   Steady, safe =1

2. Arises: Unable without help =0
   Able, uses arms to help =1
   Able without using arms =2

3. Attempts to arise: Unable without help =0
   Able, requires > 1 attempt =1
   Able to arise, 1 attempt =2

4. Immediate standing balance (first five seconds):
   Unsteady (swaggers, moves feet, trunk sway =0
   Steady but uses walker or other support =1
   Steady without walker or other support =2

5. Standing balance Unsteady =0
   Steady but wide stance (medial heels >4 in. apart) and uses cane or other support =1
   Narrow stance without support =2

6. Nudged (subject at maximum position with feet as close together as possible, examiner pushes lightly on subject’s sternum with palm of hand 3 times):
   Begins to fall =0
   Stagger, grabs, catches self =1
   Steady =2

7. Eyes Closed (at maximum position No. 6)
   Unsteady =0
   Steady =1

8. Turning 360 degrees Discontinuous Steps =0
   Continuous =1
   Unsteady (grabs, staggers) =0
   Steady =1

9. Sitting down Unsafe (misjudges distance, falls into chair) =0
   Uses arms or not a smooth motion =1
   Safe, smooth motion =2
Tinetti Assessment Tool: Gait

Initial instructions: Subject stands with examiner, walks down hallway or across room, first at “usual” pace, then back at “rapid, but safe” pace (using usual walking aids).

10. Initiation of gait (immediately after told to “go”)
   Any hesitancy or multiple attempts to start = 0
   No hesitancy = 1

11. Step length and height
   a. Right swing foot: does not pass left stance foot with step = 0
      passes left stance foot = 1
      right foot does not clear floor completely with step = 0
      right foot completely clears floor = 1
   b. Left swing foot: does not pass right stance foot with step = 0
      passes right stance foot = 1
      left foot does not clear floor completely with step = 0
      left foot completely clears floor = 1

12. Step Symmetry
   Right and left step length not equal (estimate) = 0
   Right and left step appear equal = 1

13. Step Continuity
   Stopping or discontinuity between steps = 0
   Steps appear continuous = 1

14. Path (estimated in relation to floor tiles, 12-inch diameter; observe excursion of 1 foot over about 10 ft. of the course.)
   Marked deviation = 0
   Mild/moderate deviator or uses walking aid = 1
   Straight without walking aid = 2

15. Trunk
   Marked sway or uses walking aid = 0
   No sway but flexion of knees or back or spreads arms out while walking = 1
   No sway, no flexion, no use of arms, and not use of walking aid = 2
16. Walking Time Heels apart =0
Heels almost touching while walking =1

Freezing of Gait Questionnaire

Freezing of Gait Questionnaire (FOGQ)

1. During your worst state—do you walk:
   0 Normally
   1 Almost normally—somewhat slow
   2 Slow but fully independent
   3 Need assistance or walking aid
   4 Unable to walk

2. Are your gait difficulties affecting your daily activities and independence?
   0 Not at all
   1 Mildly
   2 Moderately
   3 Severely
   4 Unable to walk

3. Do you feel that your feet get glued to the floor while walking, making a turn or when trying to initiate walking (freezing)?
   0 Never
   1 Very rarely—about once a month
   2 Rarely—about once a week
   3 Often—about once a day
   4 Always—whenever walking

4. How long is your longest freezing episode?
   0 Never happened
   1 1 – 2 s
   2 3 – 10 s
   3 11 – 30 s
   4 Unable to walk for more than 30 s

5. How long is your typical start hesitation episode (freezing when initiating the first step)?
   0 None
   1 Takes longer than 1 s to start walking
   2 Takes longer than 3 s to start walking
   3 Takes longer than 10 s to start walking
   4 Takes longer than 30 s to start walking
6. How long is your typical turning hesitation (freezing when turning)?
   0 None
   1 Resume turning in 1 – 2 s
   2 Resume turning in 3 – 10 s
   3 Resume turning in 11 – 30 s
   4 Unable to resume turning for more than 30 s

APPENDIX C—AVERAGE STEP NUMBER AND AVERAGE RAS BEATS

Average step number from participants in the C (Cue) group and the average number of rhythmic auditory stimulation (RAS) beats for different speeds are presented below.

<table>
<thead>
<tr>
<th>Participant</th>
<th>Slow steps</th>
<th>Slow RAS-beat</th>
<th>Normal steps</th>
<th>Normal RAS-beat</th>
<th>Fast RAS-beat</th>
<th>Fast RAS-beat</th>
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</thead>
<tbody>
<tr>
<td>C1</td>
<td>11.31</td>
<td>13</td>
<td>15.52</td>
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<td>16.32</td>
<td>18</td>
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<tr>
<td>C2</td>
<td>9.02</td>
<td>11</td>
<td>13.36</td>
<td>13</td>
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<td>C3</td>
<td>6.11</td>
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<td>9.35</td>
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<td>12.51</td>
<td>13</td>
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<td>C4</td>
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<td>7.28</td>
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<td>C5</td>
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<td>8.38</td>
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<td>11.12</td>
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</table>
VITA

Zahra Kadivar was born in August 1980, in Chicago, Illinois. Her parents were Iranian so soon after they moved back to Iran. She graduated from Bentolhoda High school in Shiraz, Iran, in 1998. In 2003, she graduated from Shiraz University Medical Center with a Bachelor of Science degree in physical therapy. After that she moved to United States to continue her education. She started a doctoral program in rehabilitation sciences at University of Kansas Medical Center. She then transferred to Louisiana State University in August 2005 to pursue her doctoral degree at Louisiana State University (LSU) under the direction of Dr. Jan Hondzinski. During this time she served as the Instructor on Record on an upper-level undergraduate course in motor learning. Zahra was a two time recipient of LSU’s Lilian Olson scholarship given by College of Education. She also received the Dissertation Fellowship from LSU. Zahra has accepted an NIH-driven post-doctoral fellowship within the Baylor College of Medicine in Houston, Texas.