Rhythmic Auditory Cueing of Gait in Parkinson Disease

Adam Patrick Horin

Washington University in St. Louis

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Rhythmic Auditory Cueing of Gait in Parkinson Disease
by
Adam Patrick Horin

A dissertation presented to
The Graduate School
of Washington University in
partial fulfillment of the
requirements for the degree
of Doctor of Philosophy

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Adam P. Horin

Washington University in St. Louis

May 2020
Dedicated to my family.
ABSTRACT OF THE DISSERTATION

Rhythmic Auditory Cueing of Gait in Parkinson Disease

by

Adam Patrick Horin

Doctor of Philosophy in Movement Science

Washington University in St. Louis, 2020

Professor Gammon Earhart, Chair

Parkinson disease (PD) is a neurodegenerative movement disorder characterized by motor complications such as gait deficits and is caused by the depletion of dopamine producing neurons in the basal ganglia (BG). Gait deficits, including decreased velocity and increased variability, are among the most debilitating symptoms of PD and lead to an increased risk of falls. Common pharmacological treatments do not target many gait symptoms. Therefore, gait rehabilitation methods that can improve these deficits in gait are highly important. A common form of gait rehabilitation is known as rhythmic auditory cueing, in which an individual matches their footfalls to the beat an auditory stimulus while walking. This form of gait rehabilitation has shown benefits in older adults and people with neurological disorders such as PD, however it is still not fully understood who responds best or what underlying neural mechanisms are involved. The purpose of the studies of this dissertation is to expand our knowledge of these aspects of gait rehabilitation in people with PD. In Chapter 2, we aimed to investigate the effects of external and self-generated auditory cues on gait in people with PD with and without FOG. We found people with PD with and without FOG responded similarly to both cue types. We also found that those with higher baseline gait variability were more at risk of falls and responded best to both cue
types. In Chapter 3, we aimed to investigate the effects of external and self-generated auditory cues on gait, finger tapping, and foot tapping, in an effort to design a methodology to be used in future neuroimaging studies. A secondary aim was to investigate associations between rhythm skills and auditory imagery abilities on response to rhythmic auditory cues. We found gait and finger tapping responded similarly to both cue types, suggesting finger tapping may serve as an adequate proxy for gait in neuroimaging studies. We found associations between beat perception and finger tapping performance, but not gait performance. In Chapter 4, we used resting state functional connectivity MRI to investigate associations between brain networks with gait characteristics and beat perception in people with PD. We found gait velocity was associated with functional connectivity within the visual network and between motor and cognitive networks; most notably between the BG and thalamus networks. There were no associations between beat perception with gait characteristics or functional connectivity. In Chapter 5, we investigated the usability of a mobile health (mHealth) application administering daily exercises including cued gait training for people with PD. We found no effects on outcome measures after a three-month intervention using the mHealth application, and low adherence indicated the usability of the mHealth application was limited. Overall, the results of this dissertation helped to expand our understanding of gait characteristics and rhythmic auditory cueing, and their clinical implications in people with PD.
Chapter 1: Background and specific aims
1.1 Introduction
Mobility declines with age and this is further exacerbated in people with neurological disorders, such as Parkinson disease (PD). Gait deficits are among the most debilitating in PD, leading to decreased quality of life and increased fall risk, and are indicative of worsening disease severity. With an aging population and an increasing prevalence of PD, it is highly important to study rehabilitation approaches that can alleviate gait impairments and potentially prevent serious injuries caused by falls. One form of gait rehabilitation that has shown promise for improving gait in neurological disease and has been studied over the past several decades is rhythmic auditory cueing. The studies of this dissertation aim to provide insights into the use of this form of gait rehabilitation that will help to improve its efficacy in people with PD.

1.2 Gait Deficits in Parkinson Disease
Common gait deficits in people with PD include decreased velocity and stride length, as well as increased variability measures such as stride length, stride time, and step time variability. These deficits in gait can be attributed in part to stooped posture and biomechanical constraints such as decreased knee and ankle flexion and decreased range of motion. All together, these deficits typically present as walking with short, shuffling steps. Freezing of gait (FOG), a phenomenon that presents as an inability to initiate or continue intended locomotion, is another common gait deficit that will affect more than a third of people with PD, and increases in prevalence with disease duration. It is challenging to address FOG with interventions because the underlying neural mechanisms that cause FOG are not fully understood.
1.1.1 Gait Stability and Falls
Increased gait variability is associated with an increased fall risk in older adults and people with PD.\textsuperscript{10,11} People with PD with FOG have particularly higher gait variability compared to people with PD without FOG.\textsuperscript{10} Due to the association between gait variability and fall risk, gait variability has been widely used as a measure of gait stability in studies investigating the effects of gait rehabilitation in neurological disorders.\textsuperscript{12–14} Computerized walkways used in experimental settings have been well-validated to reliably measure gait measures.\textsuperscript{15} One of the driving factors in gait rehabilitation for people with PD is the lack of response of many gait impairments to common pharmacological interventions, such as dopamine replacement therapies.\textsuperscript{16} This lack of response has been shown especially for gait variability measures.\textsuperscript{17} As higher gait variability is associated with fall risk, it is important to investigate the effects of gait rehabilitation methods on these variability measures.

1.3 Neural Mechanisms of Parkinson Disease
PD is a neurodegenerative movement disorder caused by the depletion of dopamine producing neurons in the basal ganglia.\textsuperscript{18} The typical mechanistic framework is that there are hyperactive inhibitory signals sent from the basal ganglia to the thalamus, leading to underactive excitatory signals sent from the thalamus to cortical motor areas, such as the primary motor cortex and the supplementary motor area. These underlying neural mechanisms cause typical motor symptoms such as resting tremor, bradykinesia, postural instability, and the cardinal gait deficits in PD.\textsuperscript{19–21} Studies have shown not only neural dysfunction among motor pathways in people with PD, but have also demonstrated differences in functional connectivity among brain networks in people with PD compared to controls.\textsuperscript{22} People with PD with FOG show even further deficits in brain network functional connectivity compared to those without FOG.\textsuperscript{23} However, this neural
dysfunction at the network level has not yet been clearly associated with clinically relevant gait characteristics in PD.

1.4 Rhythmic Auditory Cueing and Gait Rehabilitation

1.4.1 Gait Rehabilitation
One method of gait rehabilitation that has been widely studied over the past few decades is rhythmic auditory cueing. This gait rehabilitation technique uses an auditory stimulus with a salient beat for an individual to match their footfalls to while walking. The effects of rhythmic auditory cueing have been shown in older adults with a variety of neurological conditions, and in particular has seen promising effects in people with PD. However, there are inconsistencies in the literature regarding the magnitude of effect sizes and there is a lack of agreement in factors that would help to personalize and optimize this form of gait rehabilitation. For instance, our research group has studied various forms of auditory cueing such as externally generated (e.g. music, metronome, etc.) and self-generated (e.g. singing, mental singing, etc.) cues. While both forms of cues can improve spatiotemporal characteristics of gait such as velocity and stride length, externally generated cues increase variability measures, whereas self-generated cues do not. When considering the necessity of reducing gait variability to stabilize gait and prevent falls, the effects of cue type on gait are important to consider. This is especially important to consider with the heterogeneity of gait dysfunction seen in people with PD, particularly when considering people with and without FOG. Previous studies have shown rhythmic auditory cues affect people with FOG differently and those without FOG and this may be due to the differences in underlying neural mechanisms that cause FOG.
1.4.2 Auditory-Motor Entrainment and Beat Perception
The concept of entrainment, the synchronization of oscillating biological systems, has been used to explain the mechanism of how rhythmic auditory cueing works.\textsuperscript{28} In this context, auditory sensory input and motor output are synchronized, thereby enhancing overall motor performance.

The beat is the even, metric pulse of the auditory stimulus. The perception of the beat may inherently play a role in the effectiveness of rhythmic auditory cueing of gait.\textsuperscript{29} In music, the beat drives the tempo of a song. Using music as an auditory stimulus for rhythmic auditory cueing is beneficial in two ways. First, an auditory stimulus has been shown to be beneficial over other forms of sensory cueing, such as visual cues.\textsuperscript{30,31} Second, music itself has been shown to improve the efficacy of gait rehabilitation, due to its rhythmic structure enhancing synchronization, as well as providing emotional aspects that may reduce fatigue during movement.\textsuperscript{32}

Beat perception is thought to involve processing of the temporal structure of an auditory stimulus in the basal ganglia.\textsuperscript{33} It has also been shown to involve connectivity between the striatum and cortical motor areas, as well as the cerebellum, which may be involved in error detection.\textsuperscript{33,34} While people with PD do experience deficits in temporal processing and rhythm discrimination, beat perception seems to remain intact.\textsuperscript{35,36} It has been proposed that rhythmic auditory cueing involves cerebellar pathways that act as compensatory for the dysfunctional basal ganglia in people with PD.\textsuperscript{37} Rhythm skills may be associated with gait stability in neurological conditions, however this relationship has not been fully understood and more research is needed to understand this relationship.\textsuperscript{38}
1.4.3 Mental Singing and Auditory Imagery
Our research group has investigated the effects of singing and mental singing on gait as forms of self-generated auditory cueing and have shown similar benefits. Singing has been shown to elicit greater sensorimotor synchronization when it is like to movement, has been shown to entrain to cortical activity in the brain and activate the cerebellum. Mental singing, which is a form of auditory imager, activates similar areas of the brain as singing out loud and auditory imagery of a beat has also been shown to elicit cortical entrainment.

1.4.4 Gait Rehabilitation in FOG
FOG presents additional challenges in gait rehabilitation for people with PD. Since there are underlying neural deficits that differentiate people with and without FOG, techniques using rhythmic auditory cueing must be carefully considered as to best optimize the capacity of patients who may benefit. Given the differences in mechanisms that may be involved in different cue types it is important to understand how this may have implications people with FOG. For instance, studies have shown that different cue rates affect stride length differently for people with and without FOG. People with PD with FOG have also been shown to have greater dysrhythmia when internally cueing movement compared to people with PD without FOG. This may suggest people with PD with FOG have poor internal temporal processing and may not be capable of using self-generated cues effectively. However, the use of self-generated cues, such as mental singing, has not been studied in people with PD with FOG. Aim 1 will address this by investigating the effects of rhythmic auditory cues on people with PD with and without FOG.
1.5 Movement and Neuroimaging

There are several neuroimaging methods that can be used in order to better understand the neural mechanisms involved in gait rehabilitation. Among the most commonly used methods of neuroimaging is functional magnetic resonance imaging (fMRI). Task-based fMRI is commonly used to study the effects of auditory cues on movement.\textsuperscript{46-48} A limitation of these fMRI studies is that data acquisition is confined to a small space and participants must remain still in order to reduce motion artifacts. Therefore, small, simple movements must be performed in place of walking. While this provides information about movement in general, this makes it difficult to draw conclusions about the neural mechanisms involved in the effects of auditory cues on gait.

In order to make this connection, the effects of auditory cues on gait and finger tapping outside of the scanner can be compared. In a study by del Olmo et al.\textsuperscript{48} they found similar effects of rhythmic auditory cueing on gait and finger tapping variability measures. This justified their use of finger tapping as a proxy for gait in neuroimaging. They found changes in activation of sensorimotor brain regions for people with PD after taking part in a gait rehabilitation trial using auditory cues. This study provides evidence for observing the effect of rhythmic auditory cueing of gait using a finger tapping paradigm with neuroimaging. However, this study only investigated the use of an externally generated cue, so it is necessary to investigate the effects of self-generated cues on gait and finger tapping in order to design a methodology to be used in neuroimaging. A recent study investigated the differences in neural mechanisms involved in externally-guided vs internally-guided movements, and demonstrated that people with PD recruited the cerebellum more than controls when performing internally-guided movements, further supporting the hypothesis that rhythmic auditory cueing of movement in PD relies on the
cerebellum. Aim 2 will investigate a methodology that can be used to study the neural mechanisms of externally and self-generated cues.

While task-based fMRI can provide insight into the mechanisms involved in cueing of movement, there is still an obvious limitation in results from finger tapping carrying over to gait. Another neuroimaging method known as resting-state functional connectivity MRI, can be used to associate behavioral measures performed outside of the scanner, such as gait, with functional connectivity in the brain. This neuroimaging method measures temporal coherence of the BOLD signal of the brain at rest. It has been demonstrated that regions of the brain that are more associated have greater functional connectivity.

Clinically relevant gait measures have been associated with strength of functional connectivity within and between brain networks in healthy older adults. For instance, gait velocity has been associated with motor, cognitive, and visual networks. Dual task performance, which negatively affects gait variability, has been associated cognitive attention networks. Resting-state functional connectivity has been shown to be impaired in people with PD compared to controls, and there are notable differences in FC between people with and without FOG. However, FC has not been directly associated with clinically relevant gait characteristics in people with PD. Task-based functional connectivity has shown that beat perception involves connections between striatal and motor cortical regions, suggesting it may be processed in similar areas of the brain as gait. This may explain the relationship between gait and beat perception and its implication for the efficacy of rhythmic auditory cueing, however this has
not been observed on the network level. Aim 3 will address the relationship between gait and beat perception with strength of functional connectivity in people with PD.

1.6 Optimizing Rhythmic Auditory Cueing of Gait
While rhythmic auditory cueing has been widely studied, there are clear discrepancies in its efficacy and generalizability to people with PD. A limitation has been the generally small and homogeneous sample populations used for much of the research on rhythmic auditory cueing. It is important to identity factors from both a person with PD (e.g. FOG status, baseline gait performance, etc.) and the auditory stimulus (e.g. tempo, external or self-generated, etc.) that may improve this efficacy. Studies that target investigating subgroups of a disease population and that study the overlapping neural mechanisms related to neurological disorders and rhythmic auditory cueing can help to improve the efficacy of this form of gait rehabilitation. Another limitation in using rhythmic auditory cueing is its overall lack of accessibility, which could be alleviated by the use of self-generated cues or mobile health (mHealth) technologies that would make this form of gait rehabilitation readily available to use at the convenience of an individual who could benefit from it.

Increasing accessibility of cued gait training through new technologies, could help to improve the regularity of treatment and hopefully improve outcomes. Typical gait rehabilitation may be administered through a clinician, such as a physical therapist, however sessions with a clinician may be intermittent. At home cued gait training using mHealth technologies have been shown to improve gait, however the training was still supervised with a trained therapist. Therefore, it is important to begin investigating the usability of mHealth technologies that could be used independently by the patient which will be addressed in Aim 4.
1.7 Specific Aims

1.7.1 Specific Aim 1
To assess the effects of different cue types on people with PD with and without FOG.

Aim 1a: To confirm the relationship between gait variability and fall risk in people with PD.

Hypothesis 1a: Higher gait variability will be associated with an increased risk of falls in people with PD.

Aim 1b: To determine the effect of externally-generated and self-generated cues on people with PD with and without FOG, and controls.

Hypothesis 1b: Externally-generated cues will increase gait variability across groups, and self-generated cues will not increase gait variability for people with PD without FOG and controls.

Aim 1c: To determine whether baseline gait characteristics are associated with response to rhythmic auditory cueing of gait.

Hypothesis 1c: Participant with higher baseline gait variability measures will have the greatest response to rhythmic auditory cues.

1.7.2 Specific Aim 2
To design a methodology to investigate the neural mechanisms of rhythmic auditory cueing of movement.

Aim 2a: To compare the effects of externally-generated and self-generated cues on different movement types, including gait, finger tapping and foot tapping in people with PD and controls.
Hypothesis 2a: Externally-generated cues will increase movement variability and self-generated cues will not, compared to uncued movement, across all movement types and groups.

Aim 2b: To investigate the effects of rhythm skills and auditory imagery abilities on response to rhythmic cues across movement types.

Hypothesis 2b: Greater beat perception will be associated with lower movement variability across all cues, movement types, and groups, and greater auditory imagery abilities will be associated with lower movement variability for self-generated cues across all movement types and groups.

1.7.3 Specific Aim 3
To investigate associations between gait characteristics and beat perception with resting-state functional connectivity of brain networks.

Aim 3a: To determine associations between strength of resting-state functional connectivity within and between brain networks with gait characteristics in people with PD.

Hypothesis 3a: The strength of functional connectivity within and between motor networks will be associated with forward walking gait characteristics, and strength of functional connectivity within and between cognitive networks, including attention, will be associated with dual task walking gait characteristics.

Aim 3b: To determine the association between beat perception and gait characteristics, as well as strength of functional connectivity within and between brain networks.

Hypothesis 3b: Beat perception will be associated with gait variability and strength of functional connectivity within and between motor and cognitive attention networks.
Aim 3c: To determine whether strength of functional connectivity within and between brain networks and established clinical measures are predictive of clinically relevant gait characteristics.

*Hypothesis 3c: Strength of functional connectivity and clinical measures will be predictive of clinically relevant gait measures.*

1.7.4 **Specific Aim 4**

To determine the usability of a mHealth application to administer daily cued gait training.

Aim 4a: To determine the effect of a mHealth application on motor, speech, and dexterity symptoms in people with PD.

*Hypothesis 4a: The intervention group will show greater improvements in mobility, speech, and dexterity measures compared to the control group.*

Aim 4b: To investigate the effect of adherence to the mHealth application exercises on motor, speech, and dexterity exercises in people with PD.

*Hypothesis 4b: Level of adherence to the mHealth application exercise in each treatment domain will be associated with improvements in their respective targeted symptoms.*
1.8 References


Chapter 2: People with Parkinson disease with and without freezing of gait respond similarly to external and self-generated cues

This chapter has been submitted for publication:

2.1 Abstract

Background: Gait deficits in Parkinson disease (PD), including freezing of gait (FOG), can be among the most debilitating symptoms. Rhythmic auditory cueing has been used to alleviate some gait symptoms. However, different cue types, such as externally-generated and self-generated cues, affect gait variability differently. The differential effects of these cue types on people with PD with FOG (PD+FOG), who often have higher gait variability, and those with PD without FOG (PD-FOG) is unknown. Given the relationship of gait variability to fall risk, this is an important area to address.

Research Question: This study aims to 1) confirm the association between falls and gait variability measures in PD-FOG, PD+FOG and age-matched Controls; 2) investigate the effects of different cue types on gait variability in PD-FOG and PD+FOG; and 3) determine whether baseline gait characteristics are associated with response to cues.

Methods: This cross-sectional study investigated PD-FOG (n=24), PD+FOG (n=20), and Controls (n=24). Gait trials were collected during use of externally-generated and self-generated cues for all participants. Gait variability measures were the primary outcomes to assess the effects of rhythmic auditory cues.

Results: Logistic regression models showed increased gait variability was associated with falls across groups. Repeated measures ANOVAs showed externally-generated cues increased gait variability, whereas self-generated cues did not, for all groups. Pearson’s correlations showed participants with higher baseline gait variability had greater reduction in gait variability with rhythmic auditory cueing.

Significance: Higher gait variability is associated with falls. This study demonstrates that PD+FOG are capable of using self-generated cues without increasing gait variability measures,
thereby stabilizing gait. People with higher baseline gait variability are likely to experience the largest reductions in variability with the addition of external cues.

**Keywords:** Parkinson disease, Gait variability, Falls, Freezing
2.2 Background

Parkinson disease (PD) is a neurodegenerative movement disorder with an increasing prevalence, and is expected to affect more than nine million people by the year 2030. Gait deficits are among the most debilitating for people with PD and lead to decreased mobility and increased risk of falls. Freezing of gait (FOG), an inability to initiate or continue intended locomotion, is a disabling gait deficit that will affect more than a third of people with PD. While the neural mechanisms are not fully understood, FOG has been associated with dysfunction in areas of the brain responsible for executive functioning and attention. Common pharmacological interventions do not adequately target gait deficits, particularly gait variability. It is therefore important to investigate novel forms of gait rehabilitation that target gait variability.

Typical parkinsonian gait includes decreased velocity and stride length, as well as increased variability in stride length and in step time. People with PD with FOG (PD+FOG) have higher gait variability than people with PD without FOG (PD-FOG). Targeting gait variability with gait rehabilitation is likely important because higher gait variability measures are associated with an increased risk of falls among older adults and people with PD.

Rhythmic auditory cueing has been widely studied as a method of gait rehabilitation for people with PD. This form of rehabilitation uses an auditory stimulus to which an individual matches their footfalls. Various cue types have previously been investigated, including externally-generated cues (e.g., music) and self-generated cues (e.g., singing and mental singing). Singing is associated with increased sensorimotor synchronization when linked to movement and research has shown singing and mental singing affect gait velocity and stride length similarly. However,
externally-generated cues also increased gait variability measures, whereas self-generated cues did not.\textsuperscript{15} These previous findings were irrespective of FOG status.

Previous research showed people with PD with and without FOG may respond differently to various cue types.\textsuperscript{16} While PD+FOG may benefit from external rhythmic auditory cues to enhance velocity and stride length,\textsuperscript{17} the effects of self-generated cues on FOG have not been studied. A finger tapping study using a synchronization-continuation task demonstrated that PD+FOG had higher dysrhythmia of tapping during the continuation phase than PD-FOG, suggesting FOG may be associated with worse internal beat timing.\textsuperscript{18} This would suggest PD+FOG may not be able to use self-generated cues effectively.

The present study had several aims. The first aim was to confirm that higher gait variability is associated with falls across all groups in our sample, in keeping with prior literature. The second aim was to determine the effect of externally-generated and self-generated cues on PD-FOG, PD+FOG, and Controls. We hypothesized externally-generated cues would increase gait variability for all groups, and that self-generated cues would not increase gait variability for PD-FOG and Controls only. The final aim was to determine which participants responded most to cues based on their baseline, uncued gait characteristics. We hypothesized participants with higher baseline gait variability would have the greatest response to rhythmic auditory cues.
2.3 Methods

2.3.1 Participants
Participants were recruited from the Movement Disorders Clinic at the medical campus of the university and the local chapter of the American Parkinson Disease Association. All participants were diagnosed with idiopathic PD. All participants met the following inclusion criteria: able to stand independently for at least 30 minutes; normal peripheral neurological function; no history of vestibular disease, no evidence of dementia (determined by a Mini Mental State Examination (MMSE) score of $\geq 24$), and at least 50 years of age. Exclusion criteria included: any serious medical problem aside from PD; use of neuroleptic or other dopamine-blocking drug; evidence of abnormality on brain imaging from any previous clinical evaluation; history or evidence of other neurological deficit (e.g., previous stroke or muscle disease); history or evidence of orthopedic, muscular, psychological problem or hearing impairment; or having deep brain stimulation or any other neural implants. All participants were asked to maintain their normal medication dosage, and those taking medication were tested in their self-reported ON state for all assessments. Participants with PD were divided into two groups, people with PD without FOG (PD-FOG) and people with PD with FOG (PD+FOG). FOG status was confirmed with a score $\geq 1$, during the participant’s testing visit, indicating that they answered “yes” to the first question, “Did you experience freezing episodes in the past month?”, on the New Freezing of Gait Questionnaire (N-FOGQ). Participants were asked to retrospectively report how often they had fallen in the last six months to determine fall status. Fall status was defined as non-fallers (no falls in the past six months) and fallers (one or more falls in the past six months). This study was approved by the Institutional Review Board at the university and written informed consent was obtained from all participants prior to starting the study.
2.3.2 Participant Characteristics

Participant characteristics are summarized in Table 2.1. For participants with PD, motor function was assessed using the Movement Disorders Society Unified Parkinson Disease Rating Scale Part 3 (MDS-UPDRS-III) and disease stage was assessed using the modified Hoehn & Yahr score\textsuperscript{19} by a trained research staff member. Freezing status and severity was determined by the New Freezing of Gait Questionnaire (NFOG-Q).\textsuperscript{20} Medication dosage was determined by the levodopa-equivalent daily dose (LEDD).

### Table 2.1 Participant Characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>PD-FOG</th>
<th>PD+FOG</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (female)</td>
<td>24 (19)</td>
<td>24 (14)</td>
<td>20 (7)</td>
<td>-</td>
</tr>
<tr>
<td>Age</td>
<td>66.04±7.30</td>
<td>68.79±6.92</td>
<td>67.10±8.28</td>
<td>0.44</td>
</tr>
<tr>
<td>MMSE, median (range)</td>
<td>29 (25, 30)</td>
<td>28 (26, 30)</td>
<td>29 (26, 30)</td>
<td>0.18</td>
</tr>
<tr>
<td>Fallers</td>
<td>6</td>
<td>9</td>
<td>16</td>
<td>-</td>
</tr>
<tr>
<td>Yrs since dx</td>
<td>-</td>
<td>6.04±3.44</td>
<td>8.65±5.77</td>
<td>0.07</td>
</tr>
<tr>
<td>LEDD</td>
<td>-</td>
<td>777 ± 476 (22)</td>
<td>1,307 ±1,032 (18)</td>
<td>0.06</td>
</tr>
<tr>
<td>UPDRS III</td>
<td>-</td>
<td>24.04±8.68</td>
<td>27.55±15.09</td>
<td>0.34</td>
</tr>
<tr>
<td>H&amp;Y, median (range)</td>
<td>-</td>
<td>2 (2, 2)</td>
<td>2 (2, 3)</td>
<td>0.12</td>
</tr>
<tr>
<td>N-FOGQ</td>
<td>-</td>
<td>0.00±0.00</td>
<td>16.85±8.24</td>
<td>-</td>
</tr>
</tbody>
</table>

Values are mean ± SD unless noted. Fallers defined as participants who experienced one or more falls in the past 6 months. T-tests and ANOVAs used for between group comparisons as appropriate. Abbreviations: Hoehn and Yahr, H&Y; Levodopa-Equivalent Daily Dose, LEDD; Mini Mental State Examination, MMSE; Movement Disorders Society Unified Parkinson Disease Rating Scale Part 3, MDS-UPDRS-III; New Freezing of Gait Questionnaire N-FOGQ.

2.3.3 Gait Measures

Spatial and temporal parameters of gait were measured using a five-meter instrumented, computerized walkway (GAITRite, CIR Systems, NJ), which has been well-validated for reliably measuring gait characteristics.\textsuperscript{21} Primary outcome measures included velocity, cadence, stride
length, as well as gait variability measures, including step time coefficient of variation (CV),
stride length CV, and single support time (SST) CV. Velocity and stride length were normalized
to average leg length, measured as the distance from the participant’s greater trochanter to their
lateral malleolus (cm). For all trials, participants walked across the walkway one time, starting
and ending one meter off the walkway, and were asked to wear their own comfortable pair of
shoes. This was repeated three times for every condition. There was an average of 19.9±4.0
(mean±sd) total steps for each condition, which can reliably measure gait variability. CV was
calculated as (standard deviation/mean) x 100 for all gait variability measures.

A baseline measurement of each participant’s uncued walking (UNCUED) was collected first.
Participants were asked to walk across the walkway at their normal, comfortable pace. Three
trials were collected and averaged, and the cadence was measured by the GAITRite system.
After their typical cadence was determined, the tempo of the auditory cue was set to 100% of this
cadence using an open source audio editing software (The Audacity Team,
audacity.sourceforge.net/) to optimize the cue rate for effects on gait variability measures. The
auditory cue used for all conditions was a piano arrangement of a familiar children’s song (‘Row,
Row, Row, Your Boat’). This song was selected for its salient beat. Two cued conditions were
then collected, in a randomized order, using this tempo. The externally-generated cue was the
music condition (MUSIC). For this condition, the music was played continuously and after
listening one time through, participants were asked to walk across the walkway, matching their
footfalls to the beat of the music, as it continued to play. The self-generated cue was the mental
singing condition (MENTAL). In this condition, the song was played through one time and after
the music stopped participants were asked to sing the song in their head while matching their
footfalls to the beat of their mental singing. Variability change scores, calculated as the difference in variability between each cued condition and uncued gait, were used as an indicator of response to cues.

### 2.3.4 Statistical Analysis
All statistical analyses were conducted in the R statistical computing environment. Between group comparisons were performed on participant characteristics using unpaired t-tests or analysis of variance models when appropriate to determine any differences between groups. Univariable and multivariable (adjusted for N-FOGQ, age, gender, LEDD, and MMSE) logistic regression models were performed to assess the association between falls (dependent variable) and gait variability measures (independent variable). Two-way repeated measures (RM) ANOVAs were used to determine main effects of group, condition, and interaction effects of group and condition for each gait outcome measure using the *afex* package in R. Within subject variation was accounted for in the models. Outliers were identified using the median absolute deviation and were winsorized by group and condition, and violations of sphericity were corrected using the Greenhouse Geisser method. Pairwise comparisons between groups and conditions were conducted with alpha = .05 and adjusted for multiple comparisons using the Tukey method. Pearson’s correlations were performed by group to determine associations between baseline gait variability measures and change scores from auditory cueing.

### 2.4 Results
Seventy-six participants were enrolled in the study. After enrollment and consent, two Controls (one due to MMSE < 24 and one due to pre-existing knee pain), one PD-FOG (due to inability to follow instructions), and five PD+FOG (two due to fatigue, one due to high frequency of
freezing that prohibited completion of the gait tasks, and two due to medical history) were excluded. Characteristics for 68 participants who completed the study are summarized in Table 2.1. There were no significant differences in participant characteristics between groups.

Uncued gait characteristics between groups and faller status are summarized in Table 2.2. Higher step time CV, stride length CV, and SST CV were all associated with falling. Results of the univariable and multivariable logistic regression models are summarized in Table 2.3.

**Table 2.2 Uncued Gait Characteristics.**

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>PD-FOG</th>
<th>PD+FOG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-fallers (n=18)</td>
<td>Fallers (n=6)</td>
<td>Non-fallers (n=15)</td>
</tr>
<tr>
<td>Normalized Velocity (m/sec/LL)</td>
<td>1.55±0.22</td>
<td>1.61±0.18</td>
<td>1.47±0.19</td>
</tr>
<tr>
<td>Cadence (steps/min)</td>
<td>110.69±8.75</td>
<td>110.85±0.21</td>
<td>109.16±9.03</td>
</tr>
<tr>
<td>Stride Length (cm)</td>
<td>127.67±12.38</td>
<td>129.65±17.70</td>
<td>128.37±18.53</td>
</tr>
<tr>
<td>Step Time CV (%)</td>
<td>2.36±0.52</td>
<td>2.14±0.24</td>
<td>2.55±0.72</td>
</tr>
<tr>
<td>Stride Length CV (%)</td>
<td>1.79±0.77</td>
<td>1.98±1.01</td>
<td>1.71±0.75</td>
</tr>
<tr>
<td>SST CV (%)</td>
<td>3.02±0.85</td>
<td>2.92±0.18</td>
<td>3.21±0.99</td>
</tr>
</tbody>
</table>

All values are mean ± SD. Abbreviations: Coefficient of Variation, CV; Leg Length, LL; Single Support Time, SST.
Table 2.3 Logistic Regression.

<table>
<thead>
<tr>
<th></th>
<th>Univariable</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>P</td>
<td>OR</td>
<td>95% CI</td>
<td>P</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step Time CV</td>
<td>3.11</td>
<td>1.45-7.45</td>
<td>0.006</td>
<td>6.45</td>
<td>1.87-33.40</td>
<td>0.009</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stride Length CV</td>
<td>2.15</td>
<td>1.19-4.19</td>
<td>0.016</td>
<td>3.61</td>
<td>1.32-12.14</td>
<td>0.020</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SST CV</td>
<td>1.83</td>
<td>1.15-3.13</td>
<td>0.017</td>
<td>2.97</td>
<td>1.37-8.00</td>
<td>0.013</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Univariable and multivariable logistic regression showing an association between falls (dependent variable) and each gait variability measure (independent variable). *Adjusted for N-FOGQ, age, gender, LEDD, and MMSE. Abbreviations: Odds Ratio, OR; Single Support Time, SST.

Cued gait conditions by group are summarized in Table 2.4. For normalized velocity (Figure 2.1A), there was a significant main effect of group (F_{2,65}=3.95, p=.02, \eta^2_p=.11). Pairwise comparisons of group indicated a significantly lower normalized velocity in PD-FOG compared to Controls (p=.04). There was also a significant main effect of condition for normalized velocity (F_{1,55,100.85}=4.56, p=.02, \eta^2_p=.07), with pairwise comparisons indicating MUSIC was significantly higher than MENTAL (p=.0001). The interaction between group and condition for normalized velocity was also significant (F_{3,10,100.85}=4.14, p=.008, \eta^2_p=.11). Pairwise comparisons showed MUSIC was significantly higher than MENTAL for Controls (p=.006) and PD-FOG (p=.01); MUSIC was significantly lower than UNCUED for PD-FOG (p=.02); and UNCUED was significantly higher than MENTAL for PD-FOG (p=.01).
Table 2.4 Summary of gait performance by group and condition.

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>PD-FOG</th>
<th>PD+FOG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UNCUED</td>
<td>MUSIC</td>
<td>MENTAL</td>
</tr>
<tr>
<td>Normalized Velocity</td>
<td>1.55 ± 0.21</td>
<td>1.58 ± 0.19</td>
<td>1.54 ± 0.21</td>
</tr>
<tr>
<td>(m/sec/LL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cadence (steps/min)</td>
<td>110.70 ± 8.36</td>
<td>111.23 ± 8.88</td>
<td>110.03 ± 8.65</td>
</tr>
<tr>
<td>Stride Length (cm)</td>
<td>127.84 ± 12.41</td>
<td>129.46 ± 9.96</td>
<td>127.18 ± 10.98</td>
</tr>
<tr>
<td>Step Time CV (%)</td>
<td>2.34 ± 0.50</td>
<td>2.75 ± 0.74</td>
<td>2.38 ± 0.71</td>
</tr>
<tr>
<td>Stride Length CV (%)</td>
<td>1.80 ± 0.77</td>
<td>2.39 ± 0.96</td>
<td>2.25 ± 1.02</td>
</tr>
<tr>
<td>SST CV (%)</td>
<td>3.01 ± 0.81</td>
<td>3.34 ± 1.03</td>
<td>3.02 ± 0.97</td>
</tr>
</tbody>
</table>

All values are mean ± SD. Abbreviations: Coefficient of Variation, CV; Leg Length, LL; Single Support Time, SST.

For cadence (Figure 2.1B), there was no main effect of group ($F_{2,65}=1.73, p=.18, \eta_p^2=.05$). There was a significant main effect of condition for cadence ($F_{1.64,106.44}=8.19, p=.001, \eta_p^2=.11$), with pairwise comparisons indicating MUSIC was significantly higher than MENTAL ($p=.0004$) and UNCUED ($p=.02$). There was a significant interaction between group and condition for cadence ($F_{3.28,106.44}=3.41, p=.02, \eta_p^2=.09$). Pairwise comparisons showed MUSIC was significantly higher than MENTAL for PD-FOG ($p=.0008$); MUSIC was significantly higher than UNCUED for PD+FOG ($p=.003$); and UNCUED was significantly higher than MENTAL for PD-FOG ($p=.005$).
Figure 2.1 Effect of cues on spatial and temporal gait characteristics (A-C) and gait variability measures (D-F) across groups. Pairwise comparisons between groups (vertical brackets) and conditions (horizontal brackets) are indicated, *p<.05, **p<.01, ***p<.001.

For stride length (Figure 2.1C), there was not a main effect of group (F_{2.65}=1.81, p=.17, \eta_p^2=.05) or condition (F_{1.43,92.88}=1.48, p=.23, \eta_p^2=.02). There was a significant interaction effect of group and condition for stride length (F_{2.86,92.88}=3.52, p=.02, \eta_p^2=.10) with pairwise comparisons indicating significantly higher stride length in MUSIC compared to MENTAL for Controls (p=.04); and UNCUED was significantly higher than MENTAL for PD-FOG (p=.02).

For step time CV (Figure 2.1D), there was no main effect of group (F_{2.65}=2.33, p=.11, \eta_p^2=.07). There was a significant main effect of condition for step time CV (F_{1.87,121.45}=10.47, p<.0001, \eta_p^2=.14), with pairwise comparisons indicating a significantly higher step time CV in MUSIC
compared to MENTAL (\(p=.0007\)) and UNCUED (\(p=.002\)). There was no significant interaction
effect of group and condition for step time CV (\(F_{3.74,121.45}=.36, p=.82, \eta^2=.01\)).

For stride length CV (Figure 2.1E), there was no main effect of group (\(F_{2,65}=98, p=.38, \eta^2=.03\)).
There was a significant main effect of condition for stride length CV (\(F_{1.98,128.67}=3.23, p=.04, \eta^2=.05\)), with pairwise comparisons indicating a significantly higher stride length CV in MUSIC
compared to UNCUED (\(p=.05\)). There was no interaction effect of group and condition for stride
length CV (\(F_{3.96,128.67}=1.62, p=.17, \eta^2=.05\)).

For SST CV (Figure 2.1F), there was no main effect of group (\(F_{2,65}=2.01, p=.14, \eta^2=.06\)) or
condition (\(F_{1.98,128.65}=2.27, p=.11, \eta^2=.03\)). There was no interaction effect of group and
condition for single support time CV (\(F_{3.96,128.65}=.81, p=.52, \eta^2=.02\)).

Pearson’s correlations across groups indicated significant moderate negative correlations
between baseline measures and MUSIC change scores for step time CV (\(R=-0.50, p<.001\)), stride
length CV (\(R=-0.44, p<.001\)), and SST CV (\(R=-0.60, p<.001\)) and for MENTAL change scores
for step time CV (\(R=-0.50, p<.001\)), stride length CV (\(R=-0.40, p<.001\)), and SST CV (\(R=-0.52, p<.001\)). Pearson’s correlations by group are shown in scatter plots in Figure 2.2.
Figure 2.2 Gait variability measure change scores from UNCUED for the MENTAL conditions (A-C) and for the MUSIC conditions (D-F). Trend lines and results of Pearson’s correlations by group are identified on the plots.

2.5 Discussion
The primary aims of the present study were to 1) confirm the association between gait variability and falls in healthy older adults and people with PD; 2) determine the effects of externally-generated and self-generated cues on gait variability in people with PD with and without FOG; and 3) determine who responded most to rhythmic auditory cues in this sample.

The results of this study first established gait variability measures are associated with falls in PD-FOG, PD+FOG, and Controls in this sample. This is consistent with previous findings of gait variability being associated with fall risk, however our sample had lower overall variability than
previous work. These results also established the gait variability measures as an adequate measure of gait stability in this study.

The results regarding effects of cue type on gait indicated externally-generated cues increased gait variability compared to uncued gait for all three groups, whereas self-generated cues did not. This finding is consistent with previous research, however, this is the first study to establish these similar effects of different cue types among PD+FOG. This is contrary to our hypothesis, as PD+FOG have been shown to have greater dysrhythmia than PD-FOG during internally-cued movement. However, this past study focused on upper extremity movements and cued using a metronome, which could explain their different results.

Lastly, this study showed who responded most to rhythmic auditory cues with respect to gait variability. Participants with higher gait variability measures showed the greatest reduction in variability with cueing, during both externally-generated and self-generated cueing conditions. This is important as it demonstrates participants most in need of gait rehabilitation benefited from rhythmic auditory cues. This is also consistent with recent findings that found people with lesser gait deficits in the early stages of PD receive less benefit from auditory cues than people in later stages of PD.

Gait deficits, including increased gait variability, are associated with increased risk of falls in older adults, and particularly people with neurological disorders. Like previous research showing higher step time variability was associated with risk of falls in older adults, the results of the present study also demonstrated that increased gait variability is associated with falls risk in
healthy older adults and people with PD. To reduce fall risk, identifying cues that will not increase gait variability measures is essential. The present study showed externally-generated cues increased gait variability, whereas self-generated cues do not. This finding is important for gait rehabilitation programs that are targeting a similar population.

We did not investigate the effect of these different cue types on number and frequency of freezing episodes and we only used cues set at 100% of baseline cadence. We chose 100% of baseline cadence to optimize the cue for gait variability measures.17,23 However, prior work found auditory cues set at 110% of baseline cadence reduced the number of freezes and duration of freezes in PD+FOG.27 In contrast, another study found that cueing at 110% of baseline cadence was detrimental to stride length for PD+FOG, yet beneficial for PD-FOG.16

2.5.1 Limitations
There are several limitations with this study. Participants with PD had mild to moderate disease severity, evidenced by low MDS-UPDRS-III and H&Y scores. This could contribute to the participants in this study having relatively low uncued gait variability, which could have presented a floor effect with less potential for improvement from the cues. Participants were asked to retrospectively report how often they fell in the last six months, and they were not provided with a formal definition of a fall. This may have introduced bias in the measurement of falls in the present study and may have impacted the reliability of this measure. The present study was also powered a priori for the gait variability outcomes, not the outcome of falls, and therefore may have been underpowered to provide firm conclusions from fall status compared to larger previously reported sample sizes.10,11 Finally, the number of steps measured in the present
study may have been low to reliably measure gait variability measures, so future studies should aim to collect data continuously with more steps.

2.5.2 Future Directions
A recent randomized controlled trial showed rhythmic auditory cueing over several months reduced the incidence of falls in people with PD. The authors, however, did not report on gait variability measures. Another previous study showed externally-generated auditory cues reduced gait variability with training. In the current study, cues were presented as a novel task, so there may be increased attention on the cue evidenced by increased motor variability. With training however, as a cue requires less attention, motor variability may decrease. Future work could investigate the difference in effects of externally-generated and self-generated cues in a randomized controlled trial that includes training in use of cues over a period of months. Future studies should also aim to better optimize rhythmic auditory cues for people with PD with and without FOG, investigating parameters such as cue rate and song familiarity.

2.6 Conclusion
People with PD with and without FOG are capable of using both externally-generated and self-generated cues for gait modification. Across all groups, externally-generated cues increased gait variability, whereas self-generated cues did not. Future studies should investigate these cue types at different rates in order to optimize their benefit on gait, and should investigate the effects of prolonged training with these to determine the role of motor learning on the long-term effects of different cue types on gait.
2.7 References


Chapter 3: Finger tapping as a proxy for gait: Similar effects on movement variability during external and self-generated cueing

This chapter has been submitted for publication:

3.1 Abstract

Introduction: Rhythmic auditory cueing has been widely studied for gait rehabilitation in Parkinson’s disease (PD). Our research group previously showed externally-generated cues (i.e., music) increase gait variability measures from uncued gait, whereas self-generated cues (i.e., mental singing) do not. These different effects may be due to differences in underlying neural mechanisms that could be discerned via neuroimaging, however movement types that can be studied with neuroimaging are limited. As such, the primary aim of the present study was to investigate the effects of these different cue types on gait, finger tapping, and foot tapping, to determine if tapping can be used as a surrogate for gait in future neuroimaging studies. The secondary aim of this study was to investigate whether rhythm skills or auditory imagery abilities were associated with responses to these different cue types.

Methods: Controls (n=24) and PD (n=33) performed gait, finger tapping, and foot tapping at their preferred pace (UNCUED) and to externally-generated (MUSIC) and self-generated (MENTAL) cues. Spatiotemporal parameters of gait and temporal parameters of finger tapping and foot tapping were collected. The Beat Alignment Task (BAT) and Bucknell Auditory Imagery Scale (BAIS) were also administered.

Results: MUSIC elicited higher movement variability than MENTAL across all movements. MUSIC also elicited higher movement variability than UNCUED for gait and finger tapping.

Conclusions: This study shows different cue types affect gait and finger tapping similarly. Therefore, finger tapping may serve as an adequate proxy for gait to study the underlying neural mechanisms of these cue types.

Keywords: Parkinson’s, gait, tapping, auditory cues, rehabilitation
3.2 Introduction
Parkinson’s disease (PD) is a neurodegenerative movement disorder characterized by the loss of dopaminergic neurons in the basal ganglia. Gait impairments are among the most debilitating symptoms, leading to an increased risk of falls and worsening disease severity. Common pharmacological and surgical treatments do not adequately target gait impairments, so novel gait rehabilitation approaches must be investigated.

Rhythmic auditory cueing is a commonly studied method of gait rehabilitation, that uses an auditory stimulus with a salient beat as a template to which an individual matches their footfalls. While effective for people with PD and other neurological disorders, there are inconsistencies regarding how to optimize these cues for people with PD. Our research showed externally-generated cues, such as music, help increase velocity and stride length but also reduce gait stability by increasing gait variability measures. This can have negative impacts such as increasing risk of falls. However, we also found self-generated cues, such as mental singing, can elicit these same positive benefits on gait without increasing gait variability.

Several factors may influence optimizing cues for people with PD. Improved rhythmic skills are linked to greater responses to externally-generated rhythmic auditory cueing in people with PD. Impairments in rhythmic skills, such as beat perception, among people with PD may be due to dysfunction in the basal ganglia. Auditory imagery may also play a role in effectiveness of self-generated cues, as imagined auditory rhythms entrain to cortical oscillations.
Cued movements in PD may involve compensatory cerebellar pathways bypassing the dysfunctional basal ganglia.\textsuperscript{13} Differences in response to cue types may be explained by differences in underlying neural mechanisms. Studying these mechanisms would provide insight for optimizing different cue types.

To study these neural mechanisms, the effects of different cue types must be established using movements suitable for neuroimaging techniques. Previous studies showed similar effects of externally-generated cues on gait and finger tapping performance have been shown,\textsuperscript{14} but this has not been studied with self-generated cues. Therefore, the primary aim of this study compared the effects of externally-generated and self-generated cues on different movement types, including gait, finger tapping, and foot tapping among people with PD and healthy older adults. We hypothesized externally-generated cues would increase movement variability from uncued movement across all movement types and groups while self-generated cues would not. Our secondary aim investigated the effects of rhythm skills and auditory imagery abilities on response to rhythmic cues across movement types. We hypothesized greater beat perception would be associated with lower movement variability across all cues, movement types, and groups, and greater auditory imagery abilities would be associated with lower movement variability for self-generated cues across all movement types and groups.

3.3 Methods

3.3.1 Participants
Participants were recruited through the Movement Disorders Clinic at the medical campus of the university, the local chapter of the American Parkinson Disease Association, and the community.
All participants with PD were diagnosed with idiopathic PD based on established criteria and met the following inclusion criteria: able to stand for at least 30 minutes; normal peripheral neurological function; no history of vestibular disease; no evidence of dementia (mini mental state examination MMSE score of ≥ 24); and at least 50 years of age. Exclusion criteria included: any serious medical problem aside from PD; use of neuroleptic or other dopamine-blocking drug; evidence of prior abnormal brain scan; history or evidence of other neurological deficit (e.g., previous stroke or muscle disease); history or evidence of orthopedic, muscular, psychological problem; hearing impairment; or having deep brain stimulation or any other neural implants. Participants taking PD medications were asked to maintain their normal medication dosage and were tested in their self-reported ON state for all assessments. This study was approved by the Institutional Review Board at the university and written informed consent was obtained from participants prior to starting the study.

3.3.2 Assessments
All measures were administered by a trained research staff member. Assessments for participants with PD included the Movement Disorders Society Unified Parkinson Disease Rating Scale Part 3 (MDS-UPDRS-III), the New Freezing of Gait Questionnaire (NFOG-Q), and the levodopa-equivalent daily dose (LEDD).

The Beat Alignment Test (BAT) measured rhythm skills. In the beat production task, participants tapped to the beat of twelve musical stimuli. Their mean asynchrony to the beat was measured in milliseconds (ms). In the beat perception task, participants determined whether an embedded isochronous tone in musical stimuli was on (aligned) or off (faster, slower, or phase shifted) the beat. The assessment was scored as the proportion of their correct responses. Due to
a technical error with the beat perception task, a majority of participants were only presented with 34 of the 36 randomized stimuli. Multiple imputation using a logistic regression method was used to determine the scores of the missing values using the mice package for R.¹⁹

The Bucknell Auditory Imagery Scale (BAIS) assessed vividness (BAIS-V) and control (BAIS-C) of participants’ auditory imagery.²⁰ Both sections were scored as the participant’s mean rating on a seven-point scale of their auditory image of described sounds.

3.3.3 Movement Trials
Spatial and temporal parameters of gait were measured using a five-meter GAITRite walkway (CIR Systems, NJ, USA). Temporal parameters for finger tapping of the dominant hand (using the space bar on a computer keyboard) and foot tapping of the dominant leg (using a USB footswitch pedal) were collected using a custom-written MATLAB script that recorded tap times. Primary outcome measures included cadence (steps or taps per minute) and movement variability (coefficient of variation (CV) of step time for gait or inter-tap time for finger and foot tapping). CV was calculated as (standard deviation/mean) x 100. Secondary gait performance measures included velocity, stride length, stride length CV, and single support time (SST) CV. Velocity and stride length were normalized to each participant’s leg length (average leg length in cm).

For the movement trials, participants first walked (gait) or tapped (finger tapping and foot tapping) at a comfortable pace (UNCUED). Three trials were collected and averaged to determine the participant’s preferred cadence for each movement type. The auditory cue was set to 100% of the preferred cadence for each movement type using audio editing software (The
Audacity Team, audacity.sourceforge.net). A piano arrangement of ‘Row, Row, Row Your Boat,’ a familiar song with a salient beat, was used for the auditory cue. Two cued conditions were presented in randomized order within movement types. For the externally-generated cue (MUSIC), the auditory stimulus was played and participants stepped or tapped to the beat. For the self-generated cue (MENTAL), participants listened to the same auditory stimulus one time through and then sang the song in their head while stepping or tapping to the beat of their mental singing.

3.3.4 Statistical Analysis
All statistical analyses were performed using the R statistical computing environment. Between group comparisons were run on participant characteristics using unpaired samples t-tests.

Repeated measures (RM) ANOVA models (2x3) included the main effect of group (Controls and PD), the main effect of condition (UNCUED, MUSIC, and MENTAL), and the interaction of group and condition for each gait performance outcome (normalized velocity, stride length, stride length CV, and SST CV). Statistical significance was set to alpha = .013 to correct for multiple comparisons.

RM ANOVA models (2x2x3) included the main effect of group (Controls and PD), condition (UNCUED, MUSIC, and MENTAL), and movement type (gait, finger tapping, and foot tapping) to compare the effects of cues on cadence and movement variability (CV of step time for gait or inter-tap time for finger and foot tapping) for each movement type. The movement variability values for gait CV, finger tapping CV, and foot tapping CV were normalized by movement (scale of 0-1) to compare outcomes between movement types. These RM ANOVA models also
included the interactions of group by condition, group by movement type, condition by movement type, and group by movement type by condition. Statistical significance was set to alpha = .025 to correct for multiple comparisons. Violations of sphericity were corrected using the Greenhouse Geisser method. Pairwise comparisons were adjusted for multiple comparisons using the Tukey method. All RM ANOVA models were run using the afex package for R. Outliers in the data were winsorized when appropriate.

Pearson’s correlations tested for associations between BAT scores with cued movement variability. Pearson’s correlations were also used to test for associations between BAIS outcomes and MENTAL movement variability; correction for multiple comparisons was set to alpha = .003.

3.4 Results
Data from fifty-seven participants are included in these analyses. Seventy-six participants initially consented, but two controls were excluded (one due to MMSE < 24 and one due to pre-existing knee pain that interfered with foot tapping) and seventeen PD were excluded (one due to fatigue, one due to not following instructions, three due to medical exclusions determined after consent, and twelve due to tester error during tapping data collection). Participant characteristics are reported in Table 3.1. Unpaired sample t-tests showed no significant differences between controls and PD in participant characteristics.
Table 3.1 Participant Characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>PD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (female)</td>
<td>24 (19)</td>
<td>33 (15)</td>
<td>-</td>
</tr>
<tr>
<td>Age</td>
<td>66.04±7.30</td>
<td>67.70±8.39</td>
<td>.441</td>
</tr>
<tr>
<td>MMSE, median (range)</td>
<td>29 (25, 30)</td>
<td>29 (26, 30)</td>
<td>.885</td>
</tr>
<tr>
<td>Education (years)</td>
<td>16.25±2.38</td>
<td>15.33±2.58</td>
<td>.177</td>
</tr>
<tr>
<td>Years since diagnosis</td>
<td>-</td>
<td>8.18±5.02</td>
<td>-</td>
</tr>
<tr>
<td>LEDD</td>
<td>-</td>
<td>1,025±899</td>
<td>-</td>
</tr>
<tr>
<td>MDS-UPDRS-III</td>
<td>-</td>
<td>24.61±11.08</td>
<td>-</td>
</tr>
<tr>
<td>H&amp;Y, median (range)</td>
<td>-</td>
<td>2 (2, 3)</td>
<td>-</td>
</tr>
<tr>
<td>N-FOGQ</td>
<td>-</td>
<td>8.09±10.46</td>
<td>-</td>
</tr>
</tbody>
</table>

All values are mean ± SD unless otherwise noted. P-values are from unpaired samples t-tests comparing groups. Abbreviations: Hoehn and Yahr, H&Y; Levodopa-Equivalent Daily Dose, LEDD; Mini Mental State Examination, MMSE; Movement Disorders Society Unified Parkinson Disease Rating Scale Part 3, MDS-UPDRS-III; New Freezing of Gait Questionnaire, N-FOGQ.

3.4.1 Gait Performance

Results of the 2x3 RM ANOVAs comparing gait performance outcomes are reported in Table 3.2. There was a main effect of group for normalized velocity (F_{1,55}=6.88, p=.01, η_p²=.11), as pairwise comparison showed normalized velocity was significantly higher for Controls than PD across conditions (p=.011). There was no main effect of condition (F_{1,55,85,43}=3.83, p=.04, η_p²=.07), or interaction of group and condition (F_{1,55,85,43}=.15, p=.81, η_p²=.003).
### Table 3.2 Gait performance outcomes.

<table>
<thead>
<tr>
<th></th>
<th>Control (n=24)</th>
<th>PD (n=33)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Normalized velocity (m/s/LL)</td>
<td>Uncued: 1.55±0.21</td>
<td>Uncued: 1.41±0.22</td>
<td>Music: 1.58±0.19</td>
<td>24</td>
<td>33</td>
<td>.01</td>
<td></td>
</tr>
<tr>
<td>Stance phase duration (s)</td>
<td>Uncued: 127.8±12.4</td>
<td>Uncued: 123.0±19.9</td>
<td>Music: 129.5±10.0</td>
<td>24</td>
<td>33</td>
<td>.16</td>
<td></td>
</tr>
<tr>
<td>Stride length CV (%)*</td>
<td>Uncued: 3.01±0.81</td>
<td>Uncued: 3.62±1.49</td>
<td>Music: 3.34±1.03</td>
<td>24</td>
<td>33</td>
<td>.10</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SD. P-values represent main effects of group. *Significant difference between UNCUED and MUSIC across groups (p<.001). Abbreviations: Leg length, LL; Single support time, SST.

For stride length there was no main effect of group (F\textsubscript{1,55}=2.01, p=.16, η\textsuperscript{p}²=.04), condition (F\textsubscript{1,36,75.07}=.87, p=.39, η\textsuperscript{p}²=.02), or interaction of group and condition (F\textsubscript{1,36,75.07}=1.16, p=.30, η\textsuperscript{p}²=.02).

For stride length CV there was no main effect of group (F\textsubscript{1,55}=.4, p=.84, η\textsuperscript{p}²<.001) or interaction of group and condition (F\textsubscript{1,98,109.06}=3.85, p=.23, η\textsuperscript{p}²=.03). There was a main effect of condition (F\textsubscript{1,98,109.06}=7.09, p=.001, η\textsuperscript{p}²=.11); pairwise comparisons showed MUSIC was significantly higher than UNCUED across groups (p<.001).

For SST CV there was no main effect of group (F\textsubscript{1,55}=2.88, p=.10, η\textsuperscript{p}²=.05), condition (F\textsubscript{1,99,109.63}=3.85, p=.02, η\textsuperscript{p}²=.07), or interaction of group and condition (F\textsubscript{1,99,109.63}=.73, p=.48, η\textsuperscript{p}²=.01).
3.4.2 Movement Types
Results of the effect of cues types on cadence and movement variability across movement types are shown in Figure 3.1. For cadence there was a main effect of group (F_{1,55}=7.51, p=.008, \eta_p^2=.12); pairwise comparisons indicated Controls had lower cadence than PD across movement types and conditions (p=.008). There was no main effect of condition (F_{1.32,72.52}=2.71, p=.09, \eta_p^2=.05). There was a significant main effect of movement type (F_{1.87,102.73}=16.06, p<.0001, \eta_p^2=.23); pairwise comparisons indicated significantly higher cadence in finger tapping compared to gait (p<.0001), and foot tapping compared to gait (p=.007). There was no interaction of group and condition (F_{1.32,72.52}=1.58, p=.22, \eta_p^2=.03). There was an interaction of group and movement type (F_{1.87,102.73}=6.06, p=.004, \eta_p^2=.10); pairwise comparisons indicated Controls had significantly lower cadence in foot tapping than PD (p=.003). There was no interaction of condition and movement type (F_{2.99,164.54}=2.65, p=.05, \eta_p^2=.05), and no interaction of group, condition, and movement type for cadence (F_{2.99,164.54}=1.37, p=.25, \eta_p^2=.02).
Figure 3.1 Plots representing cadence and movement variability measures (gait CV, finger tapping CV, and footing CV) by condition, movement, and group. Pairwise comparisons between conditions by movement type across groups are shown (* p<.025, ** p<.001, *** p < .0001).

For movement variability there was no main effect of group (F_{1,55}=2.97, p=.09, \eta^2_p=.05). There was a main effect of condition (F_{1.80,99.17}=19.49, p<.0001, \eta^2_p=.26); pairwise comparisons indicated significantly higher movement variability in MUSIC compared to UNCUED (p=.004) and MENTAL (p<.0001) across groups and movement types. There was a main effect of movement type (F_{1.70,93.33}=4.25, p=.02, \eta^2_p=.07), however pairwise comparisons were not significant between movement types. There was no interaction of group and condition (F_{1.80,99.17}=1.22, p=.30, \eta^2_p=.02). There was no interaction of group and movement type (F_{1.70,93.33}=1.29, p=.28, \eta^2_p=.02). There was an interaction effect of condition and movement type (F_{3.46,190.16}=8.06, p<.0001, \eta^2_p=.13); pairwise comparisons indicated higher movement variability
for MUSIC compared to UNCUED for gait (p=.001) and finger tapping (p<.0001), and MUSIC compared to MENTAL for gait (p=.004), finger tapping (p=.0004), and foot tapping (p<.0001); and for UNCUED compared to MENTAL for foot tapping (p=.0001). Lastly, there was no interaction of group, condition, and movement type (F_{3.46,190.16}=.77, p=.53, \eta^2_p=.01).

### 3.4.3 BAT and BAIS Outcomes

BAT and BAIS scores are summarized in Figure 3.2. Results of the unpaired samples t-tests indicated there were no group differences for BAT perception scores (p=.993), BAT production scores (p=.323), BAIS-V scores (p=.456), or BAIS-C scores (p=.092). Given the lack of group differences, Pearson’s correlations of BAT and BAIS outcomes to cued movement performance were run with groups combined.

![Figure 3.2](image.png)

**Figure 3.2** Graphs representing the scores from the BAT and BAIS by group. Values are mean ± SEM. Unpaired samples t-tests were performed between groups. There were no significant differences. Abbreviations: Beat Alignment Task, BAT; Bucknell Auditory Imagery Scale, BAIS.
There was a significant negative correlation between BAT perception scores and MUSIC finger tapping CV (R=-.42, p=.001); and MENTAL finger tapping CV (R=-.41, p=.002), indicating higher BAT perception scores were associated with lower movement variability of finger tapping for these cue types. There were no strong correlations between BAT perception scores and MUSIC gait step time CV (R=.08, p=.53); MENTAL gait step time CV (R=.05, p=.72); MUSIC foot tapping CV (R=-.31, p=.02); or MENTAL foot tapping CV (R=-.24, p=.07).

There were no significant correlations between BAT production scores and MUSIC gait step time CV (R=-.14, p=.31); MENTAL gait step time CV (R=-.18, p=.17); MUSIC finger tapping CV (R=-.01, p=.92); MENTAL finger tapping CV (R=-.11, p=.40); MUSIC foot tapping CV (R=-.13, p=.34); or MENTAL foot tapping CV (R=-.25, p=.07).

There were no significant correlations between BAIS-V scores and MENTAL gait step time CV (R=-.01, p=.93); MENTAL finger tapping CV (R=.11, p=.41); or MENTAL foot tapping CV (R=.10, p=.48). There were no significant correlations between BAIS-C scores and MENTAL gait step time CV (R=-.09, p=.53); MENTAL finger tapping CV (R=.11, p=.42); or MENTAL foot tapping CV (R=.08, p=.56).

3.5 Discussion
This study investigated the effects of externally-generated and self-generated cues on gait, finger tapping, and foot tapping performance. Based on the results, movement variability of gait and finger tapping were similarly affected by these cues. This study also sought to investigate the association of rhythm skills and auditory imagery abilities on different cue types. Only beat perception was associated with performance with externally-generated cues for finger tapping
and foot tapping, and auditory imagery abilities were not associated with performance on self-generated cues for any movement types.

There were no significant differences in gait performance outcomes between conditions. This was expected as the cue rate was set at 100% of preferred cadence, chosen to optimize the effects of the cues on gait variability.\textsuperscript{23} The similar effects of the cues across movement types, particularly gait and finger tapping, were expected. While all movements had lower variability in response to self-generated cues than externally-generated cues, foot tapping exhibited higher uncued variability compared to both externally and self-generated cues, and compared to uncued variability of gait and finger tapping. Higher foot tapping variability could be due to high biomechanical constraints from ankle dorsiflexion for this movement, compared to gait and finger tapping.

The similar response of movement variability of gait and finger tapping to cues aligns with previous research. In a clinical trial studying the effect of external rhythmic auditory cueing training in PD, gait CV and finger tapping CV changed similarly in response to cues.\textsuperscript{14} The present study is the first to demonstrate this similar effect of self-generated cues on gait and finger tapping variability. Differences in cadence between groups for finger tapping and foot tapping were worth noting and may be due to a reduction in movement amplitude, which has been demonstrated in people with PD,\textsuperscript{24} but was not measured in the present study.

In regard to rhythm skills, there was no difference in performance on the BAT between groups. This is consistent with results from Cameron et al.,\textsuperscript{25} showing no significant differences between
controls and PD on the BAT perception task. However, this is surprising considering Grahn and Brett\textsuperscript{11} showed people with PD had no beat-based advantage in a rhythm discrimination task compared to controls. In the present study, BAT performance was associated with finger and foot tapping performance to externally-generated cues, but not gait performance. This was unexpected as previous studies showed a link between rhythm skills and response to rhythmic auditory cues on gait.\textsuperscript{10,26} Beat perception may inherently play a role in the efficacy of rhythmic auditory cueing, as the beat is the metered structure of music used for synchronization. However, for the present study we did not measure synchronization to the beat, which could explain the lack of association.

For auditory imagery (or something), there was no difference in performance between groups and the BAIS did not relate to response to rhythmic auditory cues, specifically self-generated cues, on movement variability. We hypothesized performance on the BAIS would be related to response to rhythmic cues since Lima et al.\textsuperscript{27} demonstrated higher BAIS-V scores were associated with greater grey matter volume in the supplementary motor area (SMA), a region also involved in beat perception.\textsuperscript{28} However, while the BAIS has some items relevant to music, other item domains include environment, voice, and mixed domains. Therefore, the BAIS may not be sensitive to the cue types in the present study.

3.5.1 Limitations
This study has additional limitations besides the ones noted above. The PD participants exhibited mild to moderate disease severity, based on a median H&Y score of 2, and non-significant gait deficits compared to controls, so the results are not generalizable to a broader population of people with PD. Also, investigating mental singing presents a limitation in assessing cue
performance, however, our previous research has shown similarities in performance between singing aloud and mental singing.  

3.5.2 Future Directions
Future studies should optimize cues for multiple characteristics of gait to better individualize cues for people with PD. Neuroimaging studies may also help increase our knowledge of the effects of different cue types. A recent study demonstrated people with PD showed greater connectivity between motor and cerebellar networks during an external auditory cued motor task.  

3.5.3 Conclusions
These results demonstrate gait and finger tapping are similarly affected by externally-generated and self-generated cues. Therefore, finger tapping may serve as an adequate surrogate for gait to study the differences in neural mechanisms involved in these different cue types in future neuroimaging studies.
3.6 References


Chapter 4: Resting state functional connectivity associated with gait characteristics and beat perception in people with Parkinson disease
4.1 Abstract
Parkinson disease (PD) is a movement disorder caused by dysfunction in the basal ganglia (BG). Gait deficits, such as decreased velocity and increased variability, are among the most debilitating symptoms in PD and are indicative of increased risk of falls, which may be due to underlying neural dysfunction. Reductions in functional connectivity (FC) between resting state networks have been identified in PD compared to controls. The association between gait characteristics and FC of brain networks has not been studied in PD. This could provide insights into the neural mechanisms of gait relevant to rehabilitation methods, such as rhythmic auditory cueing, a form of gait rehabilitation that uses the beat of an auditory stimulus to guide steps while walking. The primary aim of this study investigated associations between gait characteristics and FC of brain networks. A secondary aim was to investigate associations of beat perception, a skill related to rhythmic auditory cueing, with gait characteristics and FC of brain networks. Resting-state FC MRI analysis was conducted on scans of participants with PD (N=50). Normalized velocity was associated with FC within the visual network and between motor and cognitive, including attention networks; most notably between the BG and thalamus networks. Beat perception was not associated with gait characteristics or FC within or between networks. A stepwise regression analysis showed strength of FC between BG and thalamus networks and motor exam scores were predictive of normalized gait velocity. The results of the present study demonstrate gait characteristics are associated with functional organization of the brain at the network level. This provides insight into the neural mechanisms of gait, which could help to better optimize gait rehabilitation for people with neurological conditions.

Keywords: functional connectivity, networks, gait, Parkinson disease
4.2 Introduction
Parkinson disease (PD) is a movement disorder characterized by dysfunction in the basal ganglia (BG).\textsuperscript{1} Many of the motor deficits in PD, including tremor, bradykinesia, postural instability, and rigidity are attributed to this underlying neural dysfunction. Gait deficits, including decreased velocity and increased spatial and temporal variability, are among the most debilitating symptoms in PD and are indicative of increased risk of falls and worsening disease severity.\textsuperscript{2,3} Common dopamine replacement medications do not adequately target these gait symptoms.\textsuperscript{4,5} It is therefore of clinical importance to better understand the neural mechanisms of gait characteristics in PD to optimize gait rehabilitation.

An emerging method of studying neural mechanisms associated with behavior is resting-state functional connectivity (FC) MRI. This method measures the temporal coherence of low-frequency blood-oxygen-level-dependent (BOLD) signals throughout the whole brain while participants lay still and alert.\textsuperscript{6} Signals from different brain regions with greater temporal correlations with one another indicate areas of the brain that are functionally connected and can be associated with behavioral measures collected outside of the scanner. This is an ideal method for studying neural correlates of gait, as walking cannot be performed during an MRI scan.

Recent studies have found associations between the strength of FC with clinically relevant gait characteristics in older adults. For example, gait velocity has been associated with strength of FC within sensorimotor, frontoparietal, and visual networks.\textsuperscript{7-9} Decreased walking performance while doing a dual task (DT) can be an indicator of gait impairment and has been shown to affect gait velocity and variability. Recent studies found decreased FC was associated with declines in
walking performance in people with PD. DT walking performance has been associated with strength of FC in attention networks in healthy older adults, and impaired DT performance in PD has been associated with reduced striatal activity. FC has been studied in people with PD, showing differences within and between sensorimotor, thalamic, and cerebellar networks compared to controls. However, the strength of FC in people with PD has not been associated with clinically relevant gait characteristics.

Rhythmic auditory cueing is a gait rehabilitation method where an individual matches their footfalls to the beat of an auditory stimulus and has been shown to have positive effects on spatial and temporal characteristics of gait and gait variability measures. This form of gait rehabilitation is thought to work through neural mechanisms that bypass the dysfunctional BG-thalamo-cortical pathways, such as cerebellar-thalamo-cortical pathways that remain relatively intact. People with PD have shown increased FC between motor-related and auditory networks during auditorily cued movement tasks.

Rhythmic auditory cueing may rely on one’s ability to perceive the beat; the even, metric structure of the auditory stimulus. A study using cued gait training for people with PD showed improvements in both gait characteristics and beat perception after the training, supporting potentially shared neural mechanisms. Beat perception is thought to be processed in the BG and is associated with FC between the striatum and cortical motor areas, which may cause impairments in beat perception in people with PD. There is also evidence the cerebellum is involved in beat perception, and may act as a compensatory pathway necessary for effective rhythmic auditory cueing of gait for people with PD.
A limitation of previous resting-state FC studies is their networks for analysis were mostly represented by cortical structures. However, recent methodological advances allow for the inclusion of subcortical structures vital in motor performance, such as the BG, thalamus, and cerebellum.\(^\text{20}\) Taking advantage of these methodological advances, the primary aim of this study was to determine associations between strength of resting state FC within and between brain networks with gait characteristics in people with PD. We hypothesized stronger FC within and between cortical, subcortical, and cerebellar motor-related networks would be associated with better forward walking gait characteristics, and stronger FC within and between attention-related networks would be associated with better dual task walking gait characteristics. A secondary aim of the study was to determine whether beat perception was associated with gait characteristics and strength of FC within and between brain networks. We hypothesized beat perception would be associated with gait variability and stronger FC within and between motor and attention related networks. Finally, we also aimed to investigate whether strength of brain network FC could be as adequate as clinical measures at predicting clinically relevant gait characteristics.

### 4.3 Methods

#### 4.3.1 Participants
Participants were recruited as part of a longitudinal exercise intervention study. Data from the baseline evaluation were used for the present study. All participants had a diagnosis of idiopathic PD. All participants were tested in the OFF state of their medication (withdrawn for at least 12 hours) and met the following inclusion criteria: at least 50 years of age, at least a high school education, and no dementia (evidenced by an MMSE score \(\geq 27\)). Motor performance was
assessed by trained research staff using the Movement Disorders Society Unified Parkinson Disease Rating Scale Part 3 (MDS-UPDRS-III). This study was approved by the university’s Institutional Review Board and all participants gave written informed consent.

4.3.2 Gait Measures
Spatiotemporal gait parameters were measured using a five-meter GAITRite walkway (CIR Systems, NJ, USA). Primary gait outcome measures included velocity and the coefficient of variation (CV) of step time. Velocity was normalized to each participant’s average leg length in cm. Coefficient of variation was calculated as (standard deviation/mean) x 100.

For the gait assessments two conditions were collected: comfortable, normal paced walking (FWD) and dual task walking (DT). For the DT, participants performed a verbal fluency task in which participants were asked to list words starting with a given letter of the alphabet while walking across the GAITRite. Five trials were collected and averaged for each condition. DT cost (DTC) was calculated for normalized velocity and step time CV as (DT-FWD) / FWD to quantify the effect of the DT on gait characteristics. For normalized velocity, a negative DTC indicates worse performance, and for step time CV, a positive DTC indicates worse performance.

4.3.3 Beat Perception
The Beat Alignment Task (BAT) from the Goldsmiths Musical Sophistication Index was used to assess beat perception. Participants determine whether an isochronous tone embedded in a series of musical stimuli is on (aligned) or off (faster, slower, or phase shifted) the beat, and are scored by their proportion of correct responses. The BAT was administered to a subgroup of the cohort (N=20).
4.3.4 MRI Data Acquisition
MRI data were collected using a Siemens Trio 3.0T scanner and a standard 12-channel head coil.

First, two structural scans were collected: a T1-weighted (T1W) sagittal, magnetization prepared rapid acquisition with gradient echo (MP-RAGE, TR=2400 ms, TI=1000 ms, TE=3.16 ms, FA=15°, 0.9 mm³ voxels, 8:09 min) and a T2-weighted (T2W) fast spin echo (TR=3200 ms, TE=455 ms, 1.0 mm³ voxels, 4:43 min). Two resting state scans were acquired from BOLD sensitized fMRI (TR=2200 ms, TE=61 ms, 4.0 mm³ voxels, two 7:26-minute runs of 200 frames each) while participants remained alert but relaxed with their eyes closed. Participants with sustained tremor observed during scans were removed prior to further analysis.

4.3.5 Preprocessing
For anatomical preprocessing Freesurfer 5.0 was used to segment the T1-weighted images and create grey matter, white matter, and cerebrospinal fluid masks for each participant. For functional preprocessing, the first 14 frames were removed from each scan to account for magnetization equilibrium. Functional data were aligned using the following steps: 1) slice time correction to temporally align each slice to the start of each volume, 2) rigid body transformation to correct for head motion within and across runs, and 3) whole-brain mode 1000 normalization to normalize the data within each run. Data were resampled to 3x3x3 mm voxels and functional data were aligned to the T1-weighted structural image and then to a Talairach atlas using affine registration in a single step. Frame-wise displacement was measured and frames with an FD greater than 0.2 mm were removed. Segments with fewer than 3 contiguous frames were also removed (mean±sd frames retained = 276.8±75.2). Participants without at least five minutes of BOLD data were removed from further analysis.24
4.3.6 Functional Connectivity Processing
Steps were followed according to Power et al. The data were demeaned and detrended to take away any temporal trends or drifts in the data caused by the scanner during data acquisition. This zeroed the mean of the data, removing potential measurement bias. Nuisance masks were used to regress out the BOLD activity related to the global signal, white matter, CSF, six motion parameters, their derivatives. This step treated these variables essentially as covariates and removed their effects on the signal. A bandpass filter (0.009-0.08 Hz) was applied because low frequencies are most prevalent in the resting state. Spatial smoothing was used to average the intensities of neighboring signals to remove additional noise in the signal. A gaussian method using a full width at half maximum (FWHM) of 6 mm was used for the smoothing.

4.3.7 Functional Connectivity Calculations
A set of 250 8-10 mm spherical seeds covering the cortex, subcortex, and cerebellum were used to define functional networks. FC values were calculated as Fisher z-transformed temporal correlations between pairs of averaged BOLD signals from each seed. Using previously defined network assignments for each seed, a correlation matrix was created for each participant. Within network correlation composite scores were calculated as the average correlation between seeds within the network, excluding the on diagonal correlations. Between network correlations composite scores were calculated as the average correlation scores between seeds from two different networks (e.g. basal ganglia network seeds and thalamus network seeds).
4.3.8 Networks of Interest
Networks including cortical and subcortical seeds were chosen based on previously defined associations. Networks were identified as motor networks (somatomotor dorsal (SMd), basal ganglia (BG), cerebellum, thalamus), cognitive networks including default mode network (DMN), attention (ventral attention (VAN) and dorsal attention (DAN)), and executive control (cinguloopercular (CO) and frontoparietal (FP)), and sensory networks (visual and auditory) (Figure 4.1). Correlation matrices of the network blocks were visually inspected to confirm blocked structure of correlations similar to what has been observed previously in PD (Figure 4.2).

**Figure 4.1** Networks of Interest. A set of cortical and subcortical regions were used representing 11 distinct networks. Seeds are shown in the axial (A), coronal (B), and sagittal (C) views and color coded by their functional networks.
Figure 4.2 Large-scale networks in people with PD, represented in an averaged correlation matrix of all participants. Strong network organization is shown, with high correlations within networks, represented in the diagonal, and lower correlations between networks, represented in the off-diagonals. Abbreviations: Cinguloopercular, CO; Dorsal attention network, DAN; Default mode network, DMN; Frontoparietal, FP; Ventral attention network, VAN.

4.3.9 Statistical Analysis
All statistical analyses were conducted in the R statistical computing environment. Paired samples t-tests were performed to determine differences between FWD and DT gait characteristics. Pearson’s correlations were run to determine associations between gait characteristics and beat perception scores. Pearson’s correlations were run to determine
associations between the strength of FC scores and behavioral measures. A stepwise regression was performed using the MASS package in R,\textsuperscript{28} for DT normalized velocity, including the significant FC scores and MDS-UPDRS-III scores as predictors, covarying for age and sex. Data were winsorized when appropriate to account for outliers.\textsuperscript{29} Statistical significance was set to $\alpha = .05$.

\section*{4.4 Results}

\subsection*{4.4.1 Participant Characteristics}

Initially, 83 participants were identified from a previously collected dataset from a longitudinal exercise intervention study. After study exclusions (two excluded for age under 50 years old, four excluded for MMSE score $\leq 26$, and two for less than 12 years of education) and MRI processing (20 excluded for not enough usable frames, and seven excluded for errors in FreeSurfer segmentation), data from 50 participants were retained for further analysis. Participant characteristics are summarized in Table 4.1.
Table 4.1 Participant Characteristics.

<table>
<thead>
<tr>
<th></th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (female)</td>
<td>50 (23)</td>
</tr>
<tr>
<td>Age</td>
<td>66.1 ± 7.4</td>
</tr>
<tr>
<td>MMSE, median (range)</td>
<td>29 (27,30)</td>
</tr>
<tr>
<td>Years of Education</td>
<td>15.7 ± 2.0</td>
</tr>
<tr>
<td>MDS-UPDRS-III (OFF)</td>
<td>36.9 ± 10.9</td>
</tr>
<tr>
<td>H&amp;Y (OFF), median (range)</td>
<td>2 (1,3)</td>
</tr>
<tr>
<td>Years since diagnosis</td>
<td>5.5 ± 4.6</td>
</tr>
</tbody>
</table>

Values are mean ± SD, unless otherwise specified. Abbreviations: Hoehn and Yahr, H&Y; Mini Mental State Examination, MMSE; Movement Disorders Society Unified Parkinson Disease Rating Scale Part 3, MDS-UPDRS-III.

4.4.2 Gait Characteristics and Beat Perception
Normalized velocity was significantly higher in the FWD (mean±sd = 1.36±0.24) compared to the DT (mean±sd = 1.08±0.28) condition (p<.001). Step time CV was significantly lower in the FWD (mean±sd = 3.92±1.06) compared to the DT (mean±sd = 6.30±2.80) condition (p<.001) (Figure 4.3). The mean±sd for normalized velocity DTC was -0.21±0.14 and step time CV DTC was 0.58±0.61.

The BAT was administered to a subset of the participants in this data set. From the retained MRI data after processing, 20 participants had BAT scores. Six participants were excluded for scores under chance (50%), leaving data from 14 participants for further analysis with the BAT (mean±sd = 0.643 ± 0.106). There was no significant association between BAT scores and velocity FWD (r=0.15, p=.61), DT (r=0.01, p=.97), or DTC (r=-0.11, p=.70), or step time CV FWD (r=-0.065, p=.82), DT (r=0.02, p=.95), or DTC (r=0.01, p=.97) (Figure 4.3).
Figure 4.3 Gait characteristics and BAT score associations. Gait characteristics of normalized velocity and step time CV for FWD and DT conditions (A, B) are represented. There was a significant difference between FWD and DT conditions for normalized velocity (p<.001) and step time CV (p<.001). There were no significant correlations between gait characteristics for FWD, DT, or DTC and BAT scores (C, D, E, F, G, H).
4.4.3 Within-Network Functional Connectivity
There was a significant positive correlation between the strength of FC within the visual network and normalized velocity for FWD ($r=0.32$, $p=.024$), DT ($r=0.41$, $p=.003$), and DTC ($r=0.31$, $p=.027$). There were no other significant correlations between gait characteristics and strength of FC within the other networks of interest.

4.4.4 Between-Network Functional Connectivity
There was a significant positive correlation between strength of FC between BG-thalamus networks and higher normalized velocity for DT ($r=0.45$, $p=.001$) and DTC ($r=0.41$, $p=.003$), with a similar trend for FWD ($r=0.27$, $p=.061$). There was a significant negative correlation between strength of FC between BG-thalamus networks and lower step time CV for DT ($r=-0.33$, $p=.019$), with similar trends for FWD ($r=-0.27$, $p=.054$) and DTC ($r=-0.21$, $p=0.138$). There was also a significant correlation between strength of FC between BG-DAN networks and higher normalized velocity for DT ($r=-0.30$, $p=.032$), and between strength of FC between DAN-visual networks and higher normalized velocity for DT ($r=0.32$, $p=.024$). There was a significant correlation between strength of FC between DMN-visual networks and higher normalized velocity for FWD ($r=-.30$, $p=.034$) (Figure 4.4). There were no other significant associations between normalized velocity and step time CV with strength of FC between networks.

There were no significant correlations between BAT scores and strength of FC within or between any networks of interest (Figure 4.5).
Figure 4.4 Significant within and between network correlations with gait characteristics. Normalized velocity for FWD, DT, and DT Cost had positive correlations with strength of functional connectivity within the visual network (A, B, C). Normalized velocity for DT and DT Cost were correlated with positive functional connectivity between BG-thalamus, and step time CV for DT Cost was negatively correlated with positive functional connectivity between BG-thalamus (D, E, F). Other correlations between normalized velocity and functional connectivity between cognitive, attention, sensory, and motor networks are also represented (G, H, I).
Figure 4.5 BAT score associations with functional connectivity within and between networks are represented in a correlation matrix representing R-values (A). There were no significant correlations between BAT score and strength of FC within and between networks of interest (B).
4.4.5 Stepwise Regression Analysis

We ran a stepwise regression model for DT normalized velocity, which had the greatest number of significant associations with FC scores. The full model included MDS-UPDRS-III, within visual FC, between BG and thalamus FC, visual and DAN FC, and DAN and BG FC as predictors for DT normalized velocity. The model was optimized using a stepwise regression method that determined the model based on AIC scores of the models. Then age and gender were added as covariates to the model. MDS-UPDRS-III and strength of FC between BG and thalamus networks remained significant predictors of DT normalized velocity (Table 4.2).

Table 4.2 Summary of stepwise regression analysis predicting DT normalized velocity.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1</th>
<th></th>
<th></th>
<th></th>
<th>Model 2</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>Std. Error</td>
<td>t</td>
<td>p</td>
<td></td>
<td>Estimate</td>
<td>Std. Error</td>
<td>t</td>
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<tr>
<td>(Constant)</td>
<td>1.298</td>
<td>0.399</td>
<td>3.255</td>
<td>.002</td>
<td></td>
<td>1.327</td>
<td>0.340</td>
<td>3.909</td>
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<tr>
<td>MDS-UPDRS-III</td>
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<td>0.004</td>
<td>-2.029</td>
<td>.049</td>
<td></td>
<td>-0.007</td>
<td>0.003</td>
<td>-2.231</td>
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<tr>
<td>BG-Thalamus</td>
<td>1.144</td>
<td>0.616</td>
<td>1.858</td>
<td>.070</td>
<td></td>
<td>1.159</td>
<td>0.542</td>
<td>2.141</td>
</tr>
<tr>
<td>Visual-DAN</td>
<td>0.837</td>
<td>0.817</td>
<td>1.025</td>
<td>.311</td>
<td></td>
<td>0.849</td>
<td>0.519</td>
<td>1.637</td>
</tr>
<tr>
<td>BG-DAN</td>
<td>0.512</td>
<td>1.052</td>
<td>0.487</td>
<td>.629</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Visual</td>
<td>0.283</td>
<td>0.484</td>
<td>0.586</td>
<td>.561</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Adjusted R²</td>
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<td></td>
<td></td>
<td></td>
<td>0.252</td>
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<tr>
<td>F-statistic</td>
<td>3.072</td>
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<td></td>
<td></td>
<td>4.305</td>
<td></td>
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</tr>
<tr>
<td>Model p</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>.003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIC</td>
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<td></td>
<td></td>
<td>7.464</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

After stepwise regression was performed, age and gender were included as covariates in the models. Model 1 is the full model with all variables and Model 2 is the optimized model based on AIC score. Abbreviations: Basal ganglia, BG; Dorsal attention network, DAN; Movement Disorders Society Unified Parkinson Disease Rating Scale Part 3, MDS-UPDRS-III.
4.5 **Discussion**

This study aimed to determine associations between gait characteristics and strength of FC within and between brain networks in people with PD. The results of the study showed normalized velocity was associated with strength of FC within the visual network, and between motor and attention networks, most notably between the BG and thalamus networks.

Previous research has shown better DT ability is associated with greater strength of FC within the DMN network. The effect of a DT on normalized velocity and step time CV was as expected based on previous research. DT conditions have been shown to decrease gait speed and increase gait variability in people with PD, due to the cognitive demand of performing a DT while walking.

There were no associations between BAT scores and gait characteristics in the present study. Previous studies have shown rhythm skills, such as beat perception, have been associated with gait characteristics in people with PD and people with stroke, however this relationship has not been consistently reported in the literature. The results of the present study do not help alleviate these conflicts in the literature and the lack of association in this study may have been due to the small sample size.

Regarding within network FC, in the present study normalized velocity was only associated with strength of FC within the visual network. This relationship between gait characteristics and the visual network is comparable to previous findings. This may be due to the visual network’s involvement in visuospatial processing, which has previously been associated with visual-
cerebellum connectivity. Visuospatial performance has also been linked to gait performance in people with PD. Studies have also shown FC within the visual network to be altered in people with PD who experience freezing of gait, further implicating the visual network in gait performance in people with PD.

Most notably, there were associations between gait and FC between BG-thalamus, BG-DAN, visual-DMN, and visual-DAN networks. Considering the involvement of both the BG and thalamus in communicating with cortical areas for motor control, these results are not surprising. The associations between visual-DAN and BG-DAN were with normalized velocity in the DT condition, implicating the involvement of attention networks in gait performance during a DT. This is consistent with previous research showing DT walking is associated with attention and motor networks. We also found associations between DTC normalized velocity and strength of FC within the visual network and between the BG and thalamus networks. This further implicates these networks being involved in not just the motor component, but also the cognitive component of the DT performance. Overall, these between network associations are important because they provide insight into the functional organization of the brain related to clinically relevant gait characteristics.

Lower step time CV was associated with greater BG-thalamus FC in the DT condition only. Again, this result is not surprising, considering the involvement of the BG and thalamus in motor performance. However, the lack of associations between DT and DTC gait variability measures with attention or other cognitive networks was surprising. Previous research in older adults showed gait variability to be associated with DAN-DMN FC. Considering the importance of
gait variability as an indicator of fall risk in older adults, it is important to further investigate the neural mechanisms of gait variability in neurological conditions.

We did not find associations between gait characteristics and FC within and between networks involving the cerebellum network. The cerebellum is important in motor processing, including DT performance, and previous research has implicated its hyperactivity as a potential mechanism to compensate for striatal dysfunction in people with PD. However, in the present study participants were tested in the OFF state of their medication, and were therefore in a depleted dopamine state, which has been shown to reduce FC in the cerebellum in people with PD. Dopamine administration has been shown to relatively normalize FC in people with PD compared to controls, suggesting levodopa does not exclusively mediate striatal function, so future studies should consider the effects of medication on FC across the brain. Another explanation for the lack of associations between gait characteristics and the cerebellum network could be that the cerebellum is a complex structure in the brain that involves more than just motor processing. Therefore, the composite score of all of the cerebellar seed correlations in the present study could have included irrelevant seeds that washed out cerebellar associations with motor characteristics. Future studies should consider investigating subdivisions of the cerebellum network that may be more associated with motor characteristics.

In the present study there were no significant correlations between BAT scores and FC within or between networks. Previous research has shown that dopamine administration can improve beat perception by modulating temporal processing. Therefore, future studies investigating FC related to beat perception in people with PD should consider testing in the ON state to account
for these effects. The lack of associations seen in the present study could also suggest beat perception is a complex task that involves the interaction of more than one or two brain networks.

From the stepwise regression, we found that MDS-UPDRS-III scores and strength of FC between the BG and thalamus networks significantly predicted DT normalized velocity. This suggests resting state FC could potentially be used as a biomarker for deficits in clinically relevant gait characteristics. In a study investigating the effects of rehabilitation in stroke, they found improved resting-state FC between motor and executive networks in response to rehabilitation. This suggests resting-state FC has potential to be a useful biomarker in clinical trials to help with diagnosis, prognosis, and patient selection for who may respond best to various rehabilitation approaches. The small sample size of the present study limits the generalizability of these results, so future studies with larger sample sizes should investigate the robustness of resting-state FC as a potential biomarker for gait dysfunction in people with PD.

4.6 Conclusions
Overall, this study demonstrates that gait characteristics are associated with strength of FC within and between brain networks in people with PD. The results of this study suggest networks related to motor control, visuospatial performance, and attention are associated with gait characteristics in people with PD. This has important clinical implications to better understand the functional organization of the brain related to common gait deficits in people with PD. These insights can be applied to better optimizing gait rehabilitation for people with neurological
disorders by improving selection of participants who may respond best to different rehabilitation approaches.
4.7 References


Chapter 5: Usability of a daily mHealth application designed to address mobility, speech, and dexterity in Parkinson’s disease

This chapter has been published:

5.1 Abstract

Aim: This study investigated the usability of a mobile health (mHealth) smartphone application to treat gait, speech, and dexterity in people with Parkinson’s disease (PD).

Methods: Participants either used an mHealth application (intervention) or maintained their normal routine (control) for 12 weeks and were evaluated at baseline and post-test time points for primary outcome measures of adherence, gait, speech, and dexterity. mHealth application adherence was compared to percent change scores on gait, speech, and dexterity measures.

Results: Adherence was moderate and there were no significant group, time, or interaction effects for any outcome measures. Correlations between adherence and outcomes were weak and negative.

Conclusion: These data suggest that usability of this mHealth application was limited as indicated by low adherence. The application alone in its present form was not adequate to treat symptoms of gait, speech, or dexterity in people with PD.

Keywords: Parkinson’s disease, Rehabilitation, Gait
5.2 Introduction
Parkinson’s disease (PD) is a neurodegenerative movement disorder which is expected to impact nine million people by the year 2030.\textsuperscript{1} PD is characterized by resting tremor, rigidity, bradykinesia, and postural instability.\textsuperscript{2} These symptoms commonly affect gait, speech, and dexterity. PD is a progressive disorder, so disease severity increases over time and is associated with detrimental effects on daily living.\textsuperscript{3} Common pharmacological treatments often do not alleviate all symptoms and other treatment options are needed.\textsuperscript{4} For instance, physical therapy may be useful for gait impairments,\textsuperscript{5} speech therapy for speech decrements,\textsuperscript{6} and occupational therapy for changes associated with dexterity.\textsuperscript{7} However, the cost of additional treatments can be burdensome, and treatment sessions are often intermittent due to limitations in treatment availability.\textsuperscript{8} With the increasing prevalence of PD, there is a need to study affordable and accessible treatment options for gait, speech, and dexterity impairments.

Impairments in gait are associated with increased fall risk and decreased mobility and indicate worsening disability and disease severity.\textsuperscript{9,10} Gait treatments are often administered through physical therapy. One method of treatment commonly used to address gait deficits in PD is rhythmic auditory cueing, which involves playing an auditory cue with a salient beat to which an individual matches their gait pattern.\textsuperscript{11} This treatment can increase gait velocity and stride length during cueing,\textsuperscript{12,13} however improvements are not retained after training is discontinued.\textsuperscript{14} In-home gait training that could be used on a continuous basis has the potential to facilitate retention of improvements from rhythmic auditory cueing.\textsuperscript{15}
In addition to gait impairments, alternative treatments are also needed for speech and dexterity deficits in PD. Speech deficits affect up to 90% of patients with PD and can include reduced vocal loudness and reduced speaking prosody, hindering communication abilities.\(^6\) Speech and language therapists have targeted these symptoms through several rehabilitative approaches. One approach is the Lee Silverman Voice Treatment (LSVT®LOUD), which improved vocal loudness, prosody, and sustained phonation duration in people with PD, with improvements retained up to 24 months after intensive training concluded.\(^{16,17}\) The LSVT®LOUD treatment has been successfully adapted as a computer program for at-home use in concurrence with in-person therapy to treat speech deficits in PD.\(^{18}\) However, administration of speech treatment exclusively from a mobile health (mHealth) platform has not been investigated.

Affordable and accessible treatments for deficits in dexterity should also be investigated, as dexterity is important for activities of daily living such as dressing and handwriting.\(^{19}\) Dexterity-related issues are typically targeted through treatments provided by occupational therapists. Occupational therapy improved handwriting and fine motor skills in people with PD,\(^{5,20}\) and at-home dexterity training resulted in greater improvements on nine-hole peg test (9HPT) performance than traditional dexterity treatments.\(^{19}\)

In the present study we investigated the usability and effects of an mHealth smartphone application employed over 12 weeks to improve gait, speech, and dexterity in people with PD. The application incorporates evidence-based treatments designed for daily use, improving access and affordability of a continuous treatment. Patients must be able to use the technology\(^{21}\) and adhere to the treatment\(^{22,23}\) in order to effectively receive benefit. As such, ease of use is an
important aspect of successful mHealth treatment, especially in aging populations. Thus, in addition to objective tests measuring the effectiveness of the mHealth application on gait, speech, and dexterity, we also examined the effect of adherence on these outcomes and assessed usability of the mHealth application.

5.3 Materials & measures

5.3.1 Participants
Participants were recruited through the Movement Disorders Clinic at the university and from the local chapter of the American Parkinson Disease Association. All participants were diagnosed with idiopathic PD, with mild-moderate disease severity, Hoehn & Yahr (H&Y) score 2-3, and met the following inclusion criteria: able to stand independently for at least 30 minutes, normal peripheral neurological function, no history of vestibular disease, at least 30 years of age, access to an Apple iPhone (Apple, CA), and no evidence of dementia (determined by a score of 24 or greater on the Mini Mental State Examination (MMSE)). Exclusion criteria included: any serious medical problem other than PD, using neuroleptic or dopamine-blocking drugs, previous abnormal brain scan, history of other neurological deficits such as stroke or muscle disease, or deep brain stimulation. All participants who were taking medication for PD were tested in their self-reported ON state for all assessments. Participants were part of a larger intervention study that included randomization into three groups (mHealth intervention, group exercise intervention, and control); in the present study we will compare the mHealth intervention and control groups only. Baseline and post-test assessments were conducted one week prior to and directly after the intervention or control period by research staff who were not blinded to group
assignment. The study was approved by the Institutional Review Board at the university and written informed consent was obtained from all participants prior to starting the study.

5.3.2 Participant characteristics
Descriptive characteristics included age, gender, years since diagnosis, levodopa-equivalent daily dose (LEDD), and H&Y scores. The Movement Disorders Society Unified Parkinson Disease Rating Scale Part 3 (MDS-UPDRS-III) was used to assess motor function\textsuperscript{25} and was administered by a trained research staff member.

5.3.3 Gait measures
Participants performed three trials of walking at a normal, comfortable pace and at a fast pace which were averaged within each condition. Spatiotemporal gait parameters were measured using a 5-meter instrumented, computerized walkway (GAITRite, CIR Systems, NJ), a well-validated method for measuring gait characteristics\textsuperscript{26}. Velocity, cadence (steps/min) and stride length were measured for each condition. Velocity and stride length were normalized to leg length by dividing velocity (cm/sec) and stride length (cm) by the participant’s average leg length (cm).

We also recorded average steps per day using wearable sensors (wGT3X-BT Activity Monitor, Actigraph, Pensacola, FL) with a three-axis accelerometer measuring at 30 Hz and analyzed at 1 epoch. Participants wore the sensor on their dominant ankle for seven days prior to and seven days after the intervention or control period. Oral and written instructions were provided to the participants on use and care of the sensors. Steps per day has been validated as a reliable measure of daily activity levels for people with PD\textsuperscript{27}. The number of steps per day was averaged over
seven days. One participant in the intervention group only had six days averaged for their post-test assessment due to missing data.

5.3.4 Speech measures
All speech measures were recorded using a head-mounted condenser microphone (ShenZhen Huacam Intelligent Technology Co., Hong Kong, China) and recorded through a digital recorder (Voice Tracer 3500, Philips, Amsterdam, Netherlands) as 44.1 kHz .WAV files. The distance of the microphone to the center of the participant’s lips was measured and kept consistent for the baseline and post-test assessments, to ensure vocal intensity could be compared within participants. Frequency and intensity measures from all audio files were processed using Praat software. Frequency for the reading passage was processed with a pitch setting window of 75 to 300 Hz for male voices and 100 to 500 Hz for female voices. Custom-written MATLAB (MathWorks, Natick, MA) scripts were used to calculate the outcome measures.

Sustained vowel phonation and reading a passage were used to assess speech parameters. For the sustained vowel phonation participants were asked to take a deep breath and say “ah” for as long as they could. Maximum duration (sec) and mean frequency (Hz) were measured using a custom MATLAB script which determined the onset and offset of the vocal phonation. To ensure vocal intensity did not influence the participants’ maximum sustained duration, a paired samples t-test was used to compare baseline and post-test vocal intensity; no significant difference was noted (t=−0.759, p=.453).

For the passage reading task, participants were asked to read The Rainbow Passage at a comfortable pace. In order to assess speaking prosody, the primary variables of interest were
the total time to read (sec) and the semitone standard deviations (STSD) of the fundamental frequency from The Rainbow Passage. Semitones of the fundamental frequency were calculated in reference to 1 Hz.

5.3.5 Dexterity measure
The nine-hole peg test (9HPT) has been validated for use in PD and was used to assess dexterity. Participants performed two blocked trials of the 9HPT starting with their dominant hand followed by their non-dominant hand.

5.3.6 Feasibility measures
Adherence in the intervention group was checked regularly and participants were contacted via telephone if they had not used the application for two or more consecutive days, for up to three times during the study. The percent adherence was calculated based on the total number of exercises a participant completed throughout the study.

An exit survey was administered to the intervention group after their post-test assessment to reflect on their experience using the mHealth application. General comments were collected to qualitatively assess the participants experience with the mHealth application.

5.3.7 Intervention
Participants in the intervention group were instructed to independently complete exercises once a day for approximately 90 days (median + range: 89 + 7 days) using the Beats Medical Parkinsons Treatment App (Beats Medical Ltd, UK) provided to them on their personal smartphone. Exercises were divided into three domains – mobility, speech, and dexterity – and
took approximately thirty minutes in total to complete each day. The mobility exercise consisted of a two-minute calibration walk to assess gait cadence, and a ten-minute walk where participants matched their foot falls to the beat of a metronome playing at their prescribed cadence. The speech exercises included sustained vowel phonations, reading words and sentences aloud, and playing a game involving modulations in volume of sustained phonation. The dexterity exercises included a digitally-adapted version of the 9HPT, pinching exercises, and writing in circles using a provided stylus.

5.3.8 Statistical analysis
All statistical analyses were conducted in the R statistical computing environment. All outcome measures were assessed for normality by examining the residual outliers using the Median Absolute Deviation method. When appropriate, data were winsorized to the next value within the normal distribution and non-normal distributions are identified in the tables. Two-way repeated measures ANOVAs were used to determine group, time, and interaction effects on the outcome measures. Within subject variation was accounted for in the models. Significance was set at $\alpha = 0.004$ to correct for multiple comparisons.

Pearson correlations were used to determine relationships between outcome measure change scores and adherence to their respective exercises in the mHealth application. Primary outcomes measures from each domain were: normalized gait velocity percent change, maximum sustained vowel phonation duration percent change, and 9HPT percent change for mobility, speech, and dexterity outcomes, respectively.
A qualitative analysis of the exit survey was performed by looking for themes based on repetition of keywords in the participants’ comments.34

5.4 Results
Thirty-seven people with PD, 17 intervention and 20 control, completed the study. Participant characteristics are summarized in Table 5.1. Initially, 23 participants were enrolled in the intervention group and 24 participants were enrolled in the control group. In the intervention group, two participants did not complete a baseline evaluation (one lacked physician clearance to participate and one decided not to participate) and four participants discontinued participation (one due to family situation, one due to unrelated injury, one due to unrelated health concerns, and one simply decided not to participate). In the control group, three participants did not complete a baseline evaluation (one due to being unable to contact and two due to family situations) and one participant discontinued participation due to an exclusionary diagnosis.

Adherence to the mHealth application exercises by domain were as follows (mean±SD): mobility was 67.4±26.0%, speech was 66.8±26.5%, and dexterity was 64.6±25.3%.
Table 5.1 Participant Characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Baseline (n = 20)</th>
<th>Control Post (n = 20)</th>
<th>Intervention Baseline (n = 20)</th>
<th>Intervention Post (n = 17)</th>
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<tbody>
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<td>30%</td>
<td>30%</td>
<td>40%</td>
<td>41%</td>
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<tr>
<td>Age</td>
<td>64.9 (8.4)</td>
<td>-</td>
<td>63.4 (8.6)</td>
<td>63.2 (9.3)</td>
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<td>31.9 (13.2)</td>
<td>28.3 (8.7)</td>
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<td>2 (2, 3)</td>
<td>2 (2, 3)</td>
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</tr>
<tr>
<td>Years since dx</td>
<td>6.0 (4.3)</td>
<td>-</td>
<td>6.7 (5.6)</td>
<td>-</td>
</tr>
<tr>
<td>LEDD, mg</td>
<td>937.2 (395.5)</td>
<td>934.7 (442.6)</td>
<td>1,087.0 (730.6)</td>
<td>1,128.7 (753.5)</td>
</tr>
<tr>
<td>MMSE, median (range)</td>
<td>29 (25, 30)</td>
<td>-</td>
<td>29 (27, 30)</td>
<td>-</td>
</tr>
</tbody>
</table>

Values are mean (SD) or n, unless otherwise noted. Abbreviations: Abbreviations: Hoehn and Yahr, H&Y; levodopa-equivalent daily dose, LEDD; Mini Mental State Examination, MMSE; Movement Disorders Society Unified Parkinson Disease Rating Scale Part 3, MDS-UPDRS-III.

There were no significant correlations between outcome percent change scores and adherence for their respective domains: normalized gait velocity percent change and mobility adherence, $r(17)=-.16, p=.53$; maximum sustained vowel phonation percent change and speech adherence, $r(17)=-.17, p=.52$; and 9HPT percent change score and dexterity adherence, $r(17)=-.20, p=.44$.

Outcome measures are summarized in Table 5.1 and Table 5.2. There were no significant main effects of group for MDS-UPDRS-III scores ($F_{1,35}=0.01, p=.94, \eta_p^2<.001$); forward gait normalized velocity ($F_{1,35}=0.01, p=.94, \eta_p^2<.01$), cadence ($F_{1,35}=1.44, p=.24, \eta_p^2=.04$), or normalized stride length ($F_{1,35}=0.38, p=.54, \eta_p^2=.01$); fast gait normalized velocity ($F_{1,35}=0.00, p=.96, \eta_p^2<.001$), fast cadence ($F_{1,35}=1.78, p=.19, \eta_p^2=.05$), or fast normalized stride length...
(F_{1.35}=0.80, p=.38, \eta_p^2=.02); steps per day (F_{1.35}=0.00, p=.99, \eta_p^2<.01); sustained phonation maximum duration (F_{1.35}=0.90, p=.35, \eta_p^2=.03) or mean frequency (F_{1.35}=1.15, p=.30, \eta_p^2=.03); Rainbow Passage total time (F_{1.35}=1.45, p=.24, \eta_p^2=.04) or STSD (F_{1.35}=0.15, p=.70, \eta_p^2<.01); or 9HPT dominant (F_{1.35}=1.54, p=.22, \eta_p^2=.04) or non-dominant (F_{1.35}=0.28, p=.60, \eta_p^2=.01).

Table 5.2 Outcome measures.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Post</td>
</tr>
<tr>
<td><strong>Mobility</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forward gait</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Velocity (cm/sec/LL)</td>
<td>1.51 (0.20)</td>
<td>1.57 (0.21)</td>
</tr>
<tr>
<td>Cadence (steps/min)</td>
<td>111.2 (8.7)</td>
<td>111.7 (8.0)</td>
</tr>
<tr>
<td>Stride length (cm/LL)</td>
<td>1.63 (0.18)</td>
<td>1.69 (0.21)</td>
</tr>
<tr>
<td>Fast gait</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Velocity (cm/sec/LL)</td>
<td>2.12 (0.29)</td>
<td>2.17 (0.32)</td>
</tr>
<tr>
<td>Cadence (steps/min)</td>
<td>133.1 (10.6)</td>
<td>132.9 (11.3)</td>
</tr>
<tr>
<td>Stride length (cm/LL)</td>
<td>1.91 (0.20)</td>
<td>1.96 (0.19)</td>
</tr>
<tr>
<td>Steps/day</td>
<td>8,016 (3,197)</td>
<td>7,529 (3,010)</td>
</tr>
<tr>
<td><strong>Speech</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sustained phonation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum duration (sec)</td>
<td>20.09 (7.45)</td>
<td>20.06 (8.06)</td>
</tr>
<tr>
<td>Mean frequency (Hz)</td>
<td>136.4 (42.0)</td>
<td>144.4 (49.2)</td>
</tr>
<tr>
<td>Rainbow Passage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total duration (sec)</td>
<td>123.2 (17.6)</td>
<td>122.2 (19.4)</td>
</tr>
<tr>
<td>STSD</td>
<td>2.08 (0.70)</td>
<td>2.22 (0.91)</td>
</tr>
<tr>
<td><strong>Dexterity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9HPT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dominant (sec)</td>
<td>26.68 (4.32)</td>
<td>26.20 (3.61)</td>
</tr>
<tr>
<td>Non-dominant (sec)</td>
<td>27.37 (4.50)</td>
<td>25.99 (3.28)</td>
</tr>
</tbody>
</table>

Values are mean (SD). Abbreviations: Abbreviations: Leg length, LL; Semitone standard deviation, STSD; 9-Hole Peg Test, 9HPT.
There were no significant main effects of time for MDS-UPDRS-III scores (F\(_{1,35}=2.64, p=.11, \eta^2_p=.07\)); forward gait normalized velocity (F\(_{1,35}=1.71, p=.20, \eta^2_p=.05\)), cadence (F\(_{1,35}=0.15, p=.70, \eta^2_p<.01\)), or normalized stride length (F\(_{1,35}=2.66, p=.11, \eta^2_p=.07\)); fast gait normalized velocity (F\(_{1,35}=0.16, p=.69, \eta^2_p<.01\)), fast cadence (F\(_{1,35}=1.06, p=.31, \eta^2_p=.03\)), or fast normalized stride length (F\(_{1,35}=0.12, p=.74, \eta^2_p<.01\)); steps per day (F\(_{1,35}=2.73, p=.11, \eta^2_p=.07\)); sustained phonation maximum duration (F\(_{1,35}=0.70, p=.41, \eta^2_p=.02\)) or mean frequency (F\(_{1,35}=1.55, p=.22, \eta^2_p=.04\)); Rainbow Passage total time (F\(_{1,35}=1.78, p=.19, \eta^2_p=.05\)) or STSD (F\(_{1,35}=0.43, p=.52, \eta^2_p=.01\)); or 9HPT dominant (F\(_{1,35}=0.93, p=.34, \eta^2_p=.03\)) or non-dominant (F\(_{1,35}=3.50, p=.07, \eta^2_p=.09\)).

There were no significant interaction effects of group and time for MDS-UPDRS-III scores (F\(_{1,35}=0.53, p=.47, \eta^2_p=.01\)); forward gait normalized velocity (F\(_{1,35}=3.03, p=.09, \eta^2_p=.08\)), cadence (F\(_{1,35}=0.23, p=.63, \eta^2_p=.01\)), or normalized stride length (F\(_{1,35}=4.10, p=.05, \eta^2_p=.10\)); fast gait normalized velocity (F\(_{1,35}=3.92, p=.06, \eta^2_p=.10\)), fast cadence (F\(_{1,35}=1.01, p=.32, \eta^2_p=.03\)), or fast normalized stride length (F\(_{1,35}=6.60, p=.01, \eta^2_p=.16\)); steps per day (F\(_{1,35}=0.21, p=.65, \eta^2_p=.01\)); sustained phonation maximum duration (F\(_{1,35}=0.91, p=.35, \eta^2_p=.03\)) or mean frequency (F\(_{1,35}=0.92, p=.34, \eta^2_p=.03\)); Rainbow Passage total time (F\(_{1,35}=0.80, p=.40, \eta^2_p=.02\)) or STSD (F\(_{1,35}=6.24, p=.02, \eta^2_p=.15\)); or 9HPT dominant (F\(_{1,35}=0.00, p=.95, \eta^2_p<.01\)) or non-dominant (F\(_{1,35}=3.94, p=.06, \eta^2_p=.10\)).

Qualitatively, based on extracting themes from comments in the exit survey from the 17 participants in the intervention group, seven participants reported perceiving a benefit from one or more exercises in the mHealth application, four participants reported feeling motivated by the
mHealth application, and three participants reported the mHealth application was easy to use. Also, four participants reported the mHealth application was repetitive, nine participants reported that they did not like one or more of the exercises in the mHealth application, and eleven participants reported experiencing technical issues that interfered with their use of the mHealth application.

5.5 Discussion
The present study investigated the usability of an mHealth application to address gait, speech, and dexterity symptoms in people with PD. While previous studies suggest technology can be used to provide at-home treatment for people with PD and rehabilitation and health organizations endorse incorporating mHealth technologies into treatments to overcome difficulties with treatment access,\textsuperscript{35} the results of the present study suggest that targeted treatment using an mHealth application alone may not be adequate to measurably or meaningfully improve gait, speech, and/or dexterity in people with PD.

Based on prior research using mHealth technology to administer therapy to people with PD, we expected to see improvements in the targeted domains for the mHealth application used in the present study. However, differences in experimental design in the present study compared to previous studies may have contributed to differences in outcomes. Previous research incorporating mHealth technology often involves either therapist consultation or performance feedback for users. In the present study participants only received instruction on how to use the mHealth application without receiving a direct therapist intervention, consultation, or performance feedback.
A previous study demonstrated a device administering cued gait training could be successfully implemented in a patient’s home to treat gait impairments. However, the administration of the cueing technology supervised by a trained therapist may have contributed to the benefits reported. The supervision and training from a therapist may have contributed to the benefits seen from the cueing technology. Likewise, LSVT®LOUD treatment, administered in conjunction with at-home technology can be as effective as treatment alone; however, participants received multiple training sessions with a therapist prior to using the technology, which may have contributed to the efficacy of the technology-based treatment. The present study did not show improvements in gait or speech outcomes in the intervention group, suggesting a therapist intervention may still be necessary in order to receive benefit from a treatment that incorporates at-home technology. In a study investigating an at-home dexterity exercise program participants only received feedback once during a four-week intervention and still yielded positive outcomes, suggesting that even limited therapist intervention may be feasible.

Adherence to treatment is important for mHealth interventions. Our participants did not exhibit high adherence rates, unlike a previous study using an mHealth treatment for weight loss. That study noted that participants who received the most benefit from the treatment were those who had the highest number of website logins. The present study’s low adherence demonstrates a limitation in the usability of the application which may have played a role in its lack of effect in treating symptoms of PD.
Qualitatively, participants seemed willing to use an mHealth application and some participants perceived improvements from doing the exercises. However, participants also noted the exercises were repetitive and more than half of the participants did not like one or more of the exercises.

5.5.1 Limitations
The present study had several limitations. Our sample exhibited mild-moderate symptoms of PD, had higher average steps per day than healthy older adults,\(^3\)\(^7\) and had lower MDS-UPDRS-III scores than scores typically associated with deficits that affect daily living.\(^3\) Thus, participants did not have as much potential for improvement as people with more severe. Compared to the literature, participants in the present sample had higher average steps per day than healthy older adults.\(^3\)\(^7\) Additionally, MDS-UPDRS-III scores also can take up to two years to show significant declines, so three months was not a long enough timespan to see significant changes in disease severity.\(^9\)

The sample size of the present study was small. Examining the usability of the mHealth application was the primary focus and thus the study was not powered to test outcomes or efficacy of the mHealth application. The effect sizes reported should therefore not be used for future sample size calculations.

Another limitation facing research using mHealth applications for rehabilitation is the regulations for therapist-patient interaction, especially when geographic location may prohibit treatment if licensure is not accepted across jurisdictions.\(^3\)\(^6\) In the case of the mHealth application used in this study, support service specialists are typically provided to work with
clients via telephone in order to provide feedback on treatment. However, due to the study design and geographic limitations, these support service specialists were not provided to participants in the present study. Our participants only received technical support for the mHealth application from our staff. The lack of counselor feedback and communication, known to provide motivation and assistance to the patient, may have hindered the efficacy of the mHealth treatment in our study. Also, usability is an important factor that can impact the efficacy of an mHealth treatment, so technological issues experienced by our participants and low adherence may have interfered with their outcomes.

5.6 Conclusion
Here we showed that providing an mHealth application without therapist consultation or intervention was not adequate to improve gait, speech, or dexterity. The results of this study suggest that usability of an mHealth application and incorporating therapist intervention remain important elements of technology-based treatment.

5.7 Future perspective
For future studies, usability of mHealth technology should be enhanced and subjected to continuous quality improvement. In addition, therapist interventions with and without concurrent supplemental mHealth treatments should be investigated to determine the extent to which mHealth treatments may be able to either enhance therapist interventions or maintain the outcomes of interventions, while reducing frequency of therapist contact.
5.8 References


Chapter 6: Conclusion
6.1 Major Findings
Overall, the studies of this dissertation were aimed to answer questions related to gait rehabilitation in people with PD. This chapter will summarize the main findings of these studies and discuss the clinical relevance of these results.

Gait stability is an important factor predicting fall risk in people with PD. The basis for many of the aims in this dissertation was to investigate the effects of cues on gait variability measures, as they have been widely used as indicators of gait stability. In Chapter 2, we aimed to first confirm previously reported findings in the literature, that higher gait variability is associated with increased fall risk, with one of our own study cohorts. We found that this was the case in our sample of people with PD and controls. This finding helps to justify the use of gait variability as an adequate measure of gait stability.

Numerous studies have demonstrated the beneficial effects of rhythmic auditory cueing as a form of gait rehabilitation for older adults and people with neurological conditions such as PD.\textsuperscript{1,2} However, previous studies of rhythmic auditory cueing have been limited in the homogeneous samples of participants with PD being studied. This has yielded conflicting evidence regarding the benefits of rhythmic auditory cueing of gait, particularly in people with PD with and without FOG. In Chapter 2, we investigated these effects of different cue types on gait variability in people with PD with and without FOG. We found that people with PD with FOG were able to use self-generated cues without increasing gait variability measures. This is important to consider when administering different types of rhythmic auditory cues for gait rehabilitation for people with FOG. In this study we also found that participants in all groups with higher baseline
gait variability responded best to rhythmic auditory cueing. In this sample that could be due to ceiling effects from participants already have low gait variability at baseline, however it still suggests that participants who would most benefit from gait rehabilitation responded to rhythmic auditory cues.

While we have seen the different effects of externally generated and self-generated cues on gait variability in people with PD, we do not fully understand the neural mechanisms that may be associated with these differences in effect. Previous studies have shown similar effects of rhythmic auditory cues on gait and finger tapping variability, however only for externally generated cues. In Chapter 3, we aimed to investigate the effects of these different cues on different movement types that could be used as surrogates for gait in future neuroimaging studies. We found that gait and finger tapping variability were similarly affected by externally generated and self-generated cues. This finding is important for informing a methodology to be used in future neuroimaging studies that will aim to investigate the neural mechanisms involved in these different types of rhythmic auditory cues. We also aimed to investigate the association between movement variability and beat perception. We did not find any associations.

Task-based neuroimaging can yield great insights into the neural mechanisms involved in gait. As has been addressed, the obvious limitation in this methodology is the need to use smaller movements such as finger tapping in place of walking. One neuroimaging method to alleviate this is the use of resting-state functional connectivity MRI. This allows us to associate functional connectivity among brain networks with behavioral measures, such as gait. In Chapter 4, we aimed to investigate associations between gait characteristics and beat perception with strength.
of functional connectivity within and between brain networks in people with PD. The results of this study showed that clinically relevant gait characteristics were associated with functional connectivity of motor and visual networks. However, we did not find any associations between beat perception and gait characteristics or strength of functional connectivity within or between brain networks. Resting state functional connectivity MRI has potential applications for clinical trials by improving diagnostic and prognostic information of patients as well as to cluster heterogeneous patient populations. Chapter 4 addressed implications for strength of functional connectivity to be used as a biomarker for diagnosis and prognosis of PD. The results of a stepwise regression analysis showed that gait velocity was predicted by MDS-UPDRS-III scores as well as strength of functional connectivity between BG and thalamus networks. The use of resting state functional connectivity biomarkers could improve assigning participants to different conditions and treatments in future clinical trials.

A clinical study using an auditory cueing device had beneficial effects on gait for people with PD. While the intervention was effective, the training still required therapist assistance during the intervention and after training was discontinued, the benefits on gait were not retained. In Chapter 5, we aimed to investigate the usability of a mHealth application that could be used daily and independently by people with PD without therapist assistance. The results of the study showed no improvements in gait, speech, or dexterity in people who used the app compared to controls. We also found that level of adherence was not associated with response to using the mHealth application. Overall the study had generally low adherence, and qualitatively, even though participants reported being willing to use the mHealth application, many thought the
exercises were repetitive with over half of the participants not liking one or more of the daily exercises.

Rhythmic auditory cueing would seem to inherently involve beat perception abilities, as participants are supposed to match their footfalls to the beat of the stimulus. In Chapters 3 and 4 we investigated the relationship between beat perception and gait characteristics in people with PD. It was particularly surprising to find in Chapter 3 that beat perception was not associated uncued gait characteristics or response to rhythmic auditory cueing of gait. In Chapter 4 we similarly did not find an association between beat perception and uncued gait characteristics, as well as no associations with strength of functional connectivity within and between brain networks. Previous research has suggested that beat perception is linked to efficacy of response to rhythmic auditory cueing and that beat perception and gait are processed in similar regions of the brain. The results in this dissertation call into question the necessity of beat perception in the efficacy of this form of gait rehabilitation, as well as proposed shared neural mechanisms between them.

6.2 Limitations
There are limitations regarding measures of gait variability and fall risk. Gait variability measures have been validated using computerized walkways, a method used in the studies in this dissertation. However, collecting gait data using these methods confines gait to a laboratory setting with short trials of collecting gait data, limiting the number of steps that go into spatiotemporal calculations of the gait cycle. With the advent of new technologies such as wearable sensors, this allows researchers to collect data continuously in more applicable walking
environments. Falls are also difficult to accurately measure. Many studies, including research in this dissertation, collected data on falls based on retrospective self-reports from participants, which reduces the reliability of the measure. This can be improved in future studies by prospectively tracking falls. These limitations in measuring gait variability and track falls are important to consider for future studies so that we can better investigate their association and in turn more accurately target improvements in gait stability.

Another limitation of Chapters 2 and 3 is the cross-sectional comparison of the effects of externally and self-generated cues on gait variability. It may be clinically important to consider the principles of motor learning and adaption\(^6\) when investigating gait rehabilitation for people with neurological deficits. Movement variability is indicative of the early stages of motor learning and is reduced when automaticity is reached.\(^7,8\) Gait is considered an automatic movement, however people with PD lose this automaticity. While people with PD have a lower capacity for motor learning compared to controls,\(^9\) they are still able to achieve automaticity of gait with cued training.\(^10\) Previous research has shown increased cerebellar activity in people with PD is associated with reaching automaticity of a learned motor skill.\(^7,9\) In research from our group, we have studied externally generated and self-generated auditory cues as novel tasks in a laboratory setting. Considering the reduced capacity for motor learning in people with PD, increases in gait variability could be due to cognitive demands of using the novel cue. While our research shows increased gait variability with the use of externally generated auditory cues, previous research has shown externally generated auditory cues reduce gait variability,\(^3\) which could be the result of motor learning. Future studies should compare the effects of externally and
self-generated cues on gait variability in an intervention to determine whether the same differences we have seen cross-sectionally are maintained with training.

Sample sizes and homogeneity of study cohorts inevitably present limitations in the generalizability of study results. In Chapter 2, we were able to recruit larger number of participants than has been previously used in studies comparing the effects of auditory cues on gait between people with PD with and without FOG. However, the participant cohorts used in the studies in this dissertation were generally homogeneous, excluding a wide range of disease severities and various symptoms. Therefore, we were not able to draw strong conclusions about the generalizability of the results. For instance, in Chapter 4 we found strength of functional connectivity was predictive of clinically relevant gait characteristics. But the small, homogenous sample does not allow us to determine the impact factors such as, cognitive impairment, which is a symptom many people with PD experience, but this sample did not have evidence of cognitive impairment.

6.3 Clinical Implications and Future Research
It is important to consider the effects of cue types on gait variability measures for people with PD because negative effects on gait variability can put people with PD at higher risk of falls. Clinical studies have shown that rhythmic auditory cueing of gait can reduce incidence of falls and reduce gait variability in people with PD. However, these outcomes have not been investigated concurrently in a randomized controlled trial. Considering the differential effects external and self-generated cues on gait variability, it would be important to investigate these effects in a clinical study, which has not been done. Future studies should investigate
interventions using different cue types and investigating their effects on different groups of people with PD, such as people with and without FOG. This would help to optimize and personalize the use of rhythmic auditory cueing to optimize gait rehabilitation. Our previous research has shown factors such as cue rate can affect outcomes,\textsuperscript{13} and other researchers have shown cue rate affects people with and without FOG differently.\textsuperscript{11} Another future direction for clinical trials would be to determine the optimal cue rate for different cue types for a heterogeneous sample of people with PD.

Future studies should use task-based neuroimaging to investigate the neural mechanisms involved in external and self-generated cues. Externally and internally guided movements may involve different pathways for people with PD,\textsuperscript{14} suggesting self-generated cues may work through different neural mechanisms than externally generated cues. This is supported by an intervention showing the effects externally generated cues on gait variability and its related changes in neural activity,\textsuperscript{3} however self-generated cues have not been studied in this way.

Regarding beat perception and rhythmic auditory cueing, future studies should investigate the effects of synchronization on responsiveness to cued gait. None of the studies in this dissertation investigated the effects of synchronization to the auditory cue on gait and few studies of rhythmic auditory cueing have investigated this. Therefore, its necessity is not fully understood and would be important to know in order to better understand the implications of beat perception on response to rhythmic auditory cueing of gait.
Resting state functional connectivity MRI has the potential to be used for diagnostic and prognostic purposes in neurological disorders. A study investigating rehabilitation in stroke showed improvements in connectivity between motor and executive networks, suggesting functional connectivity could be used as a biomarker to improve the efficacy of rehabilitation interventions. Future studies should consider investigating the reliability of resting state functional connectivity and compare its outcomes to already established clinical measures that are used to assess diagnosis, prognosis, and selection of who may respond best to rehabilitation interventions.

Finally, new technologies such as wearable sensors and mHealth technologies will help us investigate rehabilitation by providing more data on movement in real-world environments that may be more relevant to outcomes. This can also increase accessibility of treatment options by allowing participants to use devices independently in order to administer gait rehabilitation exercises. Future studies should incorporate the use of these new technologies to improve the design and implementation of gait rehabilitation interventions.
6.4 References


