THE INFLUENCE OF AUDITORY CUEING TECHNIQUES ON GAIT PERFORMANCE IN PARKINSON’S DISEASE

By

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To the ever-inspiring group of individuals who’ve had the freedom of movement taken from them through the affliction of Parkinson’s disease. Don’t give up the fight. I thank my mentors, formal and non-formal for their advisement, critiques, and contributions. I thank my colleagues for their support and comradery. Most of all, I thank my loving and supportive family, who have endlessly stood by my side through this crazy adventure called life.
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<td>MD/VA</td>
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<td>NC</td>
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<td>PAR-Q</td>
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<td>PD</td>
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<td>PIGD</td>
<td>Postural instability and gait disturbance</td>
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<td>Pedunculopontine nucleus</td>
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<td>RAC</td>
<td>Rhythmic auditory cueing</td>
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<td>RM</td>
<td>Regular metronome condition</td>
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<td>SNc</td>
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<td>STN</td>
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Persons with Parkinson’s disease (PD) walk with slow gait speed, smaller steps, reduced cadence, and altered stride to stride variability. Walking to the beat of a metronome or piece of music often increases cadence, gait speed, and stride length yet there have been few direct comparisons of the efficacy of these techniques, their rhythmic structure, and the effects on the underlying temporal structure of walking variability. The aim of this project was to compare the effects of a regular metronome, fractal metronome, and music on spatiotemporal gait parameters and the structure of temporal gait variability. 15 PD and 15 age-matched controls volunteered. PD participants were tested in the on-medication state. The Ambulatory Parkinson’s Disease Monitoring system recorded gait performance. Participants walked for two minutes and their self-selected cadence was determined. Thereafter, participants walked for 5 minutes at a time under four randomized auditory conditions: no cue (NC), regular-beat metronome (RM), fractal-beat metronome (FM), and music (M), with the beat of RM, FM, and M set to their natural cadence. Detrended fluctuation analysis (DFA) was performed on stride time. Spatiotemporal gait variables and DFA were
compared using repeated measures analysis of variance, p<0.05 for statistical significance. For both groups, α-values were greater in FM compared to RM (p<0.001) and M (p<0.001). α-values increased from baseline during FM (p<0.001) and decreased during RM (p=0.003) while M was unchanged (p=541). Velocity, stride length, and arm swing velocity increased from baseline in M (p<0.0125) compared to RM (p<0.01) and increased in stride length and arm swing velocity compared to FM (p<0.01). Arm swing velocity remained increased after M relative to RM (p=0.006). In conclusion, walking to a fractal-beat metronome improved the temporal structure of variability when compared to a regular-beat metronome and music. Walking to music improved velocity, stride length, and arm swing velocity compared to a regular metronome, and stride length and arm swing velocity compared to a fractal metronome. Future research is warranted to identify musical selections with fractal beat structure in order to optimally improve gait performance in PD.
CHAPTER 1
INTRODUCTION

Background

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by motor dysfunction. Primary motor symptoms including tremor, rigidity, bradykinesia, postural instability and gait dysfunction lead to impaired mobility and decreased quality of life. As walking ability and tasks such as gait initiation, turning, and stopping become increasingly difficult, navigating the natural environment becomes a challenge. While the optimal course of pharmacological treatment and neurosurgical options alleviate many symptoms in PD, posture and gait impairments often persist. Thus, there is a pressing need for adjuvant therapies to enhance walking function.

Cueing is a method used to improve walking through the application of external temporal or spatial stimuli. Various cueing techniques are utilized to elicit a motor response through stimulation of the auditory, visual, or proprioceptive sensory pathways. Rhythmic auditory cueing (RAC) is the most common form of cueing used to enhance gait function in PD. The stimulus is typically a repeated click, beep, or tone such as a metronome at regular intervals. Music, which can contain various rhythmical structures, has also been used as an auditory cueing method to improve gait in PD. Repeatedly, these techniques have been shown to increase gait velocity, stride length, and cadence. The effects of RAC on additional linear measures of gait are inconsistent in the literature while other aspects of locomotion are left unassessed. Indeed, identification of the optimal rhythmic auditory cue for enhancing all gait variables remains unknown.
Gait variable dynamics over time have been identified as an important area of dysfunction in PD through the use of non-linear analysis. A number of studies have shown that in healthy adults, natural stride to stride fluctuations that occur over time are not random, but exhibit long-range correlations that have a fractal-like structure. In other words, there is a pattern in the variability. In PD, this fractal-like structure breaks down and becomes more random, or similar to white-noise. It has been demonstrated in older adults, that listening to an auditory cue with a fractal beat structure restores gait variability closer to that of healthy young adults. The question remains, will listening to an auditory cue with a fractal beat structure restore gait variability closer to that of healthy adults in those with PD? Additionally, what impact does listening to an auditory cue with a regular beat structure have on gait variability in PD?

It is important to identify and compare the acute effects of various auditory cueing techniques on gait, however we must also sequentially assess and compare carry-over effects of each technique. Ultimately, in order for auditory cueing to be advised as a therapeutic training method, it is pertinent to understand the impact of these external stimuli after they have been removed. While the retention of several improved gait parameters has been demonstrated with RAC, it is unknown as to which specific technique is most effective.

**Specific Aims and Central Hypotheses**

The overall purpose of this project was to determine the influence of auditory cueing techniques on gait performance in PD and to identify the acute effects on post-cue gait performance. Specifically, we compared and contrasted the change in gait performance from walking without an auditory stimulus, to walking to a regular-beat auditory stimulus, a fractal-beat auditory stimulus, and music. We additionally
examined the acute post-cue effects on gait during a short walking task performed after the removal of each auditory stimulus.

**Specific Aim 1**

To determine the effects of beat structure within an auditory cue, regular vs. fractal, on over-ground walking performance in PD. This aim was accomplished by comparing changes in spatiotemporal gait parameters while walking to a fixed beat (regular) auditory stimulus and a variable beat (fractal) auditory stimulus. Post-cue gait task performance was also compared.

**Hypothesis 1**

Walking while listening to a fractal-beat metronome will improve gait measures in PD to a greater extent than walking while listening to a regular-beat metronome.

**Specific Aim 2**

To determine the effects of auditory cueing modality, metronome vs. music, on over-ground walking performance in PD. This aim was accomplished by comparing changes in spatiotemporal gait parameters while walking to a regular metronome and music set to the same tempo (beats per minute). Post-cue gait task performance was also compared.

**Hypothesis 2**

Walking while listening to music will improve gait measures in PD to a greater extent than walking while listening to a regular metronome.
CHAPTER 2  
REVIEW OF LITERATURE 

Parkinson’s Disease 

Parkinson’s disease (PD) is a progressive neurodegenerative brain disorder estimated to affect over one million people in the United States and four to six million people world-wide. These numbers have been projected to double by 2030.  

Categorized as a movement disorder, the cardinal motor symptoms of PD include tremor, rigidity (stiffness), akinesia/bradykinesia (loss/slowness of movement), as well as postural instability and gait disturbance. These motor symptoms result primarily from the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc), a region in the midbrain. This degeneration is slow, progressive, and unclear as to why it occurs. Most often, by the time symptoms become apparent and a diagnosis is made, approximately 70% of the dopaminergic neurons are already degenerated hence making treatments and therapies a challenge.  

The typical age of onset in PD is around 60 years of age, it affects males more than females, and appears to be relatively equal among cultures and ethnicities.  

The diagnosis of PD is a collective clinical decision as there is no one definitive test (blood test, imaging test, etc.) that verifies the disorder. A thorough history, physical examination, specific neurological examination, and possible response to dopaminergic medication are all necessary in the development of a working diagnosis. The differential diagnosis is based mostly on the neurological exam. In order to differentiate PD from the atypical Parkinsonian pathologies, the timing of symptom development and course of progression play a vital role. As the disease progresses the
majority of patients will also develop non-motor symptoms in addition to the cardinal motor symptoms, both of which are further defined below.\textsuperscript{11}

Common motor symptoms in PD include tremor, rigidity, akinesia/bradykinesia, and postural instability/gait disturbance (PIGD). Typically, symptoms initially present unilaterally eventually progressing to both sides with the initial side remaining more affected. The presence of bradykinesia and at least one other of the above motor symptoms must be present for diagnosis.\textsuperscript{12} Bradykinesia may be one of the best clinical progression markers in PD.\textsuperscript{13}

Tremor in PD is often described as the “pill-rolling” type. It is present at rest and has a frequency of about 4-6 Hz.\textsuperscript{10,14} It is most often present in the hands, head, and jaw. Postural and action/intention tremor may also be present but are not as likely.\textsuperscript{15} Rigidity refers to stiffness in the limbs and/or trunk. It is caused by an increase in tone of both the flexors and extensors therefore joints become resistant to passive movement.\textsuperscript{14} It may be categorized as “cogwheel” or “lead pipe” rigidity. Akinesia and bradykinesia are described as a loss of movement and slowness of movement respectively. Movements tend to be smaller in amplitude as well, which becomes more evident during repetitive actions. This can include overall body movement, facial movement “masked face”, or even in the hand characterized by micrographia.\textsuperscript{14} PIGD includes impairment in response to postural perturbation, balance difficulty, and slow/irregular characteristics in gait. Posture and gait disturbances often become more present as PD progresses.\textsuperscript{16} The deterioration of overall mobility resulting from the combination of these motor symptoms predicts a poor quality of life.\textsuperscript{17} Non-motor symptoms that develop in PD are also likely to further reduce quality of life.
Several non-motor symptoms including hyposmia, constipation, and sleep disturbance may actually precede the onset of motor symptoms. These are often not recognized as signs of PD until after a diagnosis has been made later in the course of disease. Non-motor symptoms at various stages of the disease can include neuropsychiatric features, dysautonomia, sleep disorders, sensory dysfunction, pain and fatigue. Arising neuropsychiatric features may include anxiety, depression, apathy, memory decline, frontal executive disturbance, and/or dementia. Autonomic disturbances such as orthostatic hypotension, urinary incontinence, constipation, and sexual dysfunction can also occur. Sleep disturbances including insomnia, REM sleep disorder, and excessive daytime sleepiness are common. Hyposmia, paresthesia, and visual impairment (color and contrast) are potential sensory dysfunctions.

Tracking the progression of PD is typically performed with the use of the Unified Parkinson’s Disease Rating Scale (UPDRS). Motor and non-motor symptoms are addressed and rated. The four sections of the UPDRS are comprised of questions designed to assess mentation/behavior, activities of daily living, motor disturbance, and medication effects. The Hoehn and Yahr stage and Schwab and England scale are included measuring stage of disease and independence respectively. These tools are helpful in tracking the progression of the disease as well as assessing potential treatment/intervention effects. All three of these tools are used in this study as inclusion/exclusion criteria and for demographic information.

Pathophysiology of Parkinson’s disease

The basal ganglia (BG) are a group of subcortical nuclei involved in motor control as well as a variety of non-motor functions. The disruption of this neural circuitry, primarily due to the degeneration of the substantia nigra pars compacta (SNC), leads to
the development of PD. Extensive research on the anatomy and physiology of the BG has been performed since the late 1960s leading to the current model of BG structure, function, and connectivity that we have today.

The BG consist of the striatum (caudate and putamen), globus pallidus external and internal segments (GPe & GPi), the substantia nigra pars compacta and pars reticulata (SNc & SNr), and the subthalamic nucleus (STN). There are vast series of connections within the BG nuclei as well as to and from other parts of the brain. These connections are known to have distinct functionally segregated parallel loops that are selected for different sets of behavior.\(^{21}\) The loops connect the cerebral cortex to the basal ganglia nuclei and from the basal ganglia nuclei back to the cortex via the thalamus. The voluntary motor and oculomotor loops are the most notably affected in diseases such as PD and Huntington's disease (HD). In addition to the motor loops are non-motor loops. The prefrontal loop is involved in cognitive behaviors and the limbic loop is involved in emotional and motivational behaviors.

The initial cortical input to the striatum is extensive and diverse. The cortical areas tend to “funnel” into the striatum, however they do remain functionally segregated while connecting to the striatum and continuing into the pallidal and thalamic parts of the circuit.\(^{21}\) The thalamus then activates a specific region of the cortex for a refined behavioral output. Further evidence for the support of these pathways was found via a technique using retrograde transneuronal herpes simplex one virus to map out the specific motor and non-motor loops.\(^{22}\) This circuitry is likely involved in selection, initiation, set switching, and termination of the behaviors specified by each separate loop.
The voluntary motor loop initiates with cortical input from the motor cortex, somatosensory cortex, premotor cortex among others arriving at the putamen. The putamen then sends inhibitory signals to GPi so the ventrolateral and ventroanterior thalamus is released to excite specific areas of the premotor cortex, supplementary motor area, and primary motor cortex.\textsuperscript{21} The oculomotor loop initiates with excitatory cortical input from the posterior parietal cortex (involved with identifying the location of objects) and dorsolateral prefrontal cortex (working memory) to the body of the caudate. The caudate inhibits the inhibitory action of the GPi and SNr on the mediodorsal and ventral anterior thalamus along with the superior colliculus. Cortical areas excited by the thalamus include the frontal eye field and supplementary eye field.\textsuperscript{21} These areas activate voluntary saccadic eye movement. The above motor loops become disrupted in PD which eventually leads to gait dysfunction and difficulty navigating through the environment. Auditory cueing is thought to bypass or facilitate these disrupted circuits via another mechanism thereby improving parameters of gait.

The prefrontal loop receives broad excitatory input from, and sends back refined excitatory signals to, the dorsolateral prefrontal cortex via the circuitry through the head of the caudate, GPi, SNr, and MD/VA thalamus as described above.\textsuperscript{22} This loop isn’t quite as well understood as the motor loops however selection, initiation, and termination of various executive functions are involved as well as memory. The limbic loop is initiated from excitatory input from the amygdala, anterior and posterior cingulate cortices, hippocampus, and temporal cortex to the ventral striatum (the nucleus accumbens, an integral component of the limbic system, resides here). The ventral striatum disinhibits the action of the ventral pallidum on the mediodorsal nucleus of the
thalamus. The anterior cingulate and orbitofrontal cortices are then activated. The disruption of these loops in PD can lead to cognitive dysfunction and neuropsychiatric symptoms respectively. These non-motor symptoms may coincide with or compound the existing dysfunctional gait and mobility resulting from the disrupted motor loop.

Observation studies, lesion studies, electrophysiological studies, and imaging studies in animal models and/or patient populations demonstrate the effects of disruption along these pathways. Although functionally separated, the pathways run very close together. In neurodegenerative disorders a mix of symptoms from various behavioral aspects can be seen. In PD, voluntary motor output is decreased, disruption of saccadic eye movements may be present, and in the later stages both cognitive and affective disorders arise.

In order to understand the intricate function and dysfunction of the BG in PD, the details of motor loop will be described in accordance with the work done by Mink. The overall action of the motor loop of the BG when stimulated is to select appropriate voluntary movements for the task at hand and suppress unwanted or potentially competing movements. The primary input structures are the caudate and putamen which contain medium spiny neurons. They receive excitatory input via the neurotransmitter Glutamate from the cortex and the thalamus. The primary output structures are the GPi and SNr, which under resting conditions hold the thalamus and midbrain structures under tonic inhibition via the inhibitory neurotransmitter GABA.

There are two main pathways involved in the basal ganglia circuit, the direct and indirect, as well as a third hyperdirect pathway. The direct pathway is activated when regions of the cortex excite the striatum via glutamate. The striatum then sends an
inhibitory signal via GABA to the GPi/SNr. The GPi/SNr, which under resting conditions are tonically inhibiting portions of the thalamus and midbrain structures (superior colliculus, MLR, PPN), is then disinhibited. The GPi no longer inhibits the thalamus therefore the thalamus is released to send excitatory signals via glutamate to the cortex to activate specific areas of the motor cortex for voluntary movement signals sent via the corticospinal pathways. When the SNr is disinhibited it releases the activation of the superior colliculus for eye movement and other midbrain areas related to posture and gait control.\textsuperscript{26} The overall function of the direct pathway is to facilitate movement.

The indirect pathway is activated when regions of the cortex excite different areas of the striatum than in the direct pathway. In this case the striatum sends inhibitory signals via GABA to the GPe. The GPe under resting conditions holds the STN under tonic inhibition (via GABA). The STN, if not inhibited, sends an excitatory signal via glutamate to the GPi. This in turn increases the inhibition of the thalamocortical pathway and suppresses movement (thought to be suppression of unwanted movement). Therefore, the activation of the indirect pathway causes the disinhibition of the GPe allowing the STN to reduce movement through increasing the inhibitory output of GPi. The 3\textsuperscript{rd} pathway is a hyperdirect pathway.\textsuperscript{27} It is a direct excitatory connection via glutamate from the cortex to the STN causing suppression of movement.

Dopamine modulates the activity of the medium spiny neurons (MSN) in the striatum. Dopamine is produced by the neurons of the SNc. Nigrostriatal projections release dopamine at the base of the dendritic spines of the MSNs. The actions of dopamine on the striatum depend on the type of dopamine receptor present. D1
receptors are in the direct pathway. When dopamine acts on D1 receptors, it facilitates the direct pathway and therefore increases the release of voluntary movement(s). When dopamine acts on D2 receptors, it suppresses the indirect pathway and therefore decreases the suppression of movements. Collectively, dopamine acts to increase movement.

In PD, there is progressive degeneration of the dopaminergic neurons of the SNc. A decrease in dopaminergic activity at the medium spiny neurons in the striatum will act to decrease movement. Without dopamine (or simply less dopamine), there are changes seen in both the direct and indirect pathways. In the direct pathway, the inhibitory action of the striatum on the GPi is no longer facilitated by dopamine. Therefore the GPi strengthens its inhibitory output to the cortex via the thalamus and there is less movement. In the indirect pathway, without the activation of the D2 receptor, the striatum strengthens the inhibition of GPe so GPe no longer inhibits the STN which now increases the inhibitory action of the GPi on the cortex via the thalamus. Physiological studies by Galvan 2007 and Wichmann 2011 have produced further support of these affected pathways. There is evidence of abnormal firing rates, burst patterns, abnormal oscillations, and abnormal synchrony among the basal ganglia nuclei in PD. The Parkinsonian motor signs and symptoms, including gait dysfunction, are thought to be a result of the diminishing levels of dopamine creating disruption in the BG and downstream circuitry as described above.

**Neural Control of Gait**

Walking in humans is a complex motor task requiring synergistic integration across multiple levels of neural control. The most rudimentary contributions to gait begin low in the central nervous system (CNS) and gain progressive complexity as we
ascend into the intricacies of the brain. Therefore, this discussion will use a bottom up approach in the explanation of the neural control of gait. Inherently, it is the direction of evolutionary and developmental progression as well.

Early studies of gait in animals led to the discovery of central pattern generators (CPGs) residing in the spinal cord. CPGs are neuronal networks within the central nervous system that are capable of generating a rhythmic pattern of motor activity without phasic sensory input from peripheral receptors. Eliciting a motor pattern via stimulation of a CPG can look very similar to motor patterns produced in natural volitional behavior. This became evident by work done on lampreys by Grillner, 1985. In spinalized cats, stimulation of several locations in the interneurons of the spinal cord elicits reciprocal flexion and extension pattern in the limbs without dependency on sensory input. These areas within the CPGs are known as half-centers which facilitate extensors when the flexors are inhibited and vice versa allowing an alternating-limb stepping pattern to occur.

Sensory input from proprioceptors of the lower limbs can modulate the CPG. Hip extension activates the Ia fibers in the muscle spindles of the hip flexors, which induces stepping. If hip extension is restricted, no stepping occurs. Also, the golgi tendon organs in the extensors of the weight-bearing limb will be activated when there is enough tension produced in the muscle to bear weight. If the GTOs do not fire on the weight bearing limb, stepping will not occur in the swing limb. Skin receptors have an effect as well. While in swing, if something touches or brushes the foot it will elicit increased flexion as to avoid tripping and complete successful object clearance. If skin receptors are activated during stance, extension is increased which may be a
mechanism for securing a stable base for support. Although these rhythmic patterns of walking and reactions to sensory stimuli can be passively elicited, these actions cannot occur voluntarily without communication with higher level CNS centers.

As we ascend up the CNS from the spinal cord into the brainstem and surrounding areas, three specific locomotor centers have been identified: the mesencephalic locomotor region (MLR), the subthalamic locomotor region (SLR), and the cerebellar locomotor region (CLR). The SLR and CLR have been shown to induce locomotion when stimulated however their mechanisms remain unclear. The MLR on the other hand has been studied more extensively. When stimulated, anticipatory postural adjustments are made and walking is initiated. The rate at which the MLR is stimulated is related to the speed of gait. For example, in a horse, if the MLR is stimulated at a low frequency the horse walks. An increase in frequency will alter inter-limb coordination and phase until the horse steadies into a trot. A continued increase in frequency results in the horse cantering and then eventually breaking into a gallop. The MLR and other locomotor centers are thought to send a descending signal through the reticular formation and terminate on the CGPs. The pedunculopontine nucleus (PPN) is in the vicinity of the MLR. It is known to inhibit muscle tone. A certain amount of muscle tone is necessary for proper movement. Other descending pathways from the locus ceruleus and raphe nuclei are considered to facilitate muscle tone. A balance between these muscle tone pathways are thought to achieve ideal posture and tone to support voluntary movement including locomotion.

As we move up into the cerebrum and subcortical structures, the control of gait becomes more complex. Gait is most often initiated voluntarily (a conscious perception
in the cortex), typically to accomplish a goal-oriented task. Gait can also be initiated by the limbic system as demonstrated most notably during an elicited fight or flight response. In both circumstances, information in the cortex from the areas relevant to the situation links to circuits within the basal ganglia (BG) and thalamus in order to select the appropriate movements and properly initiate and terminate them. The cortex excites the striatum which activates the direct pathway to release the proper movement via disinhibition of the GPi on the thalamus allowing it to send an excitatory signal to the specific areas of the cortex needed for movement. The striatum also acts to suppress any unwanted or competing movements in the indirect pathway via the GPe and STN. The output nuclei of the BG include the GPi and SNr. In addition to inhibiting the thalamocortical pathway at rest, the output nuclei are also thought to inhibit the MLR and PPN in the midbrain. Therefore, when appropriate pathways for locomotion are selected in the basal ganglia circuits, the MLR is released and gait is initiated. The PPN is also released and the muscle tone is appropriately inhibited so that movement is facilitated. Locomotion is terminated when the goal is met, excitation from the cortex ceases, and the basal ganglia return to their “resting state” of tonic inhibition.\textsuperscript{20, 26}

It is apparent that predictive control in human locomotion depends specifically on cerebellar mechanisms.\textsuperscript{26} The cerebellum has the job of taking the intended descending motor output plan and comparing it to how the body is actually interacting with the environment (the actual motor output). The cerebellum must send signals to the brainstem to elicit appropriate real-time alterations in posture and tone and also send signals to the cortex for appropriate real-time alterations in the voluntary movement. The sensory representation of the body in space (body schema) is located
in the posterior parietal cortex due to the integration of visual, somatosensory, and vestibular input.

In PD, the reduced influence of dopamine on the BG leads to the excessive inhibitory output to the thalamocortical loop and the brainstem structures including the MLR and PPN.\textsuperscript{33} This results in hypokinesia and bradykinesia in voluntary movements, increased level of postural tone, and disturbance in gait performance. Consequently, locomotion and mobility become exceedingly difficult throughout the course of the disease.

**Gait Deficits in Parkinson’s disease**

The disrupted neurological circuitry and subsequent impaired function in PD lead to a number of debilitating gait deficits that diminish overall mobility. The classic representation of a person with PD includes a stooped-over forward flexed posture, masked face, deceased to no arm swing (typically asymmetric), short, slow, potentially shuffling uneven steps with a narrow base of support. Not all persons with PD will appear this way, however nearly all will have some level of gait disturbance manifest during the course of the disease.\textsuperscript{16} Particularly those displaying the PIGD-dominant subtype in comparison to the tremor-dominant subtype will be affected.\textsuperscript{34} In persons with PD, the ability to walk is not only a functional issue. It is also intimately linked to their social identity, emotional well-being and integrity.\textsuperscript{35} It is therefore essential to identify the specific gait deficits underlying walking dysfunction, target those parameters with a customized intervention, and restore or improve walking ability.

The quantitative study of movement in research settings has allowed for a deeper understanding of the gait characteristics in PD in addition to clinical analysis. Tools such as EMG, motion capture systems, and force plates have enabled kinematic
and kinetic assessment that can be tracked over time for comparative use.\textsuperscript{36} These technologies facilitate identification and insight into the disrupted motor control strategies of gait in PD. They also provide a valid method of evaluating the effectiveness of gait interventions.

Certain aspects of spatiotemporal gait disturbance appear to be consistent depending on the stage of the disease regardless of medication status. In a group of patients with de novo PD (not yet treated with any anti-parkinsonian medications), patients walked more slowly and with reduced swing times and additionally exhibited increased left/right swing asymmetry when compared to healthy controls.\textsuperscript{37} In another study, a large cohort of persons with PD (on medication) were evaluated and grouped into early, mid, and late stage of the disease.\textsuperscript{1} Spatiotemporal gait changes in PD over time include a progressive decrease in velocity, step/stride lengths, base of support, time spent in single support and therefore contralateral swing time. Findings revealed no significant differences between early and mid-stage PD. However, the late-stage group walked significantly slower with shorter step/stride lengths, and spent more time with both feet on the ground (double support) than the early and mid-stage patients. Less time in single support/swing and more time in double support/stance are indicative of decreased stability during gait.

Many of the disruptions in Parkinsonian gait are thought to manifest as a result of the hypokinesia (reduced movement speed and size) associated with PD.\textsuperscript{38} Movements are slower and smaller, made evident by the decrease in spatiotemporal parameters described above (ie: longer stride time, shorter stride length, etc.) contributing to an overall decreased velocity. People with PD, off medication, have been reported to walk
around 40-60 m/min compared to age matched controls who walk around 75-90 m/min. Additional parameters affected by hypokinesia include a reduction in step height (ground clearance) and decreased arm swing.

Akinesia (the absence or loss of movement), is a less common source of gait disturbance and may result in difficulty with gait initiation as well as freezing of gait (FOG). This can lead to an increased risk of falling. Festination, freezing of gait, and falls are signs of advanced stages of PD. They also appear to be related to cognitive decline. Advanced gait disturbance and dementia tend to occur together. As these advanced stage gait dysfunctions are less common and rather severe, further discussion and review is outside the scope of this project this point in time.

Significant postural changes occur with the progression of PD including impairment in balance/stability and altered joint angle positions, both of which can impact various aspects of gait. Postural instability in this population has been shown to be associated with abnormal patterns of postural responses which include excessive antagonist activity and inflexibility in adapting to changing support conditions. Anticipatory postural adjustments become impaired and therefore decrease the performance of desired movements. During gait, hip and knee flexors are overactive while the extensors are underactive contributing to the forward flexed posture. Impaired/weak plantar flexion during propulsion and limited hip extension contribute to a flat-footed type of landing with minimal roll-off. Hip flexor pull-off action is increased in order to produce forward progression in spite of weak plantar flexion, however foot clearance of the ground is low. This increases the chance for trips and falls. Axial rigidity is increased which decreases the natural trunk rotation that occurs while walking.
Reduced axial rotation prevents the normal out-of-phase motion between the upper and lower body. Motion between the shoulders and hips becomes in phase and reduces gait efficiency.\textsuperscript{45}

**Gait Rhythm and Variability in PD**

Healthy human gait is characterized by rhythmic repetitive movement. The cyclical nature of bipedal ambulation has been described as pendulum-like, uniquely efficient, and functional.\textsuperscript{46} Although this rhythmic form of locomotion appears to be very regular or periodic, all parameters in each gait cycle vary from the next. Variability is a natural part of human movement. Human movement variability has been defined as the normal variations that occur in motor performance across multiple repetitions of a task.\textsuperscript{47} Once considered as noise or error in the system, motor variability has more recently been described as an important informative phenomenon that reflects neural control strategies.\textsuperscript{48}

The use of gait variability as a primary outcome variable in research has been emerging. Conventionally, variability is analyzed across a repetitive task by examining means, standard deviations, and coefficients of variation. This linear method of analysis provides a way to quantify movement over time. While the information derived from this method is useful, the non-linear analysis of gait dynamics over time may provide insight into the neural control of locomotion and enhance functional assessment of aging, chronic disease and their impact on mobility.\textsuperscript{49}

Parkinsonian pathology leads to alterations in both the amount of variability and the nature of variability in gait over time. Increased gait variability has been considered to be an early feature of pathology in PD.\textsuperscript{36} Quantitative measures of variability in temporal gait parameters, including stride time, swing time, percent swing time, double
support time, percent double support time, and step time, have been shown to be significantly increased in PD relative to controls. The degree of variability is correlated to the severity of disease and predicts falling in PD as well.

Non-linear analysis can provide information about the nature of gait variability from stride to stride over the course of a time series. There are many methods of addressing the characteristics of these dynamic gait fluctuations. In regard to PD, an extensive amount of work has established the use of Detrended Fluctuation Analysis (DFA) as an effective tool in assessing the structure of variability in this neurodegenerative population. Originally developed to analyze heart rhythms, DFA provides a method for quantifying the correlation property in non-stationary physiological time series. The use of DFA demonstrated that the beat-to-beat fluctuations in a healthy heart rate display long-range correlations whereas heart rate time series in patients with severe congestive heart failure show a breakdown of this long-range correlation behavior. This repeating self-similar pattern exhibited through the long-range correlations in the healthy heart beat can be described as “fractal.” Similar to the dynamics of a healthy heart beat, fractal dynamics were then also detected in the stride interval of healthy human walking. In PD, the fractal nature of stride to stride fluctuations breaks down and becomes very similar to white noise or random fluctuations.

Auditory Cueing in Parkinson’s disease

The phenomenon that movements in PD patients are less disturbed when triggered by visual or auditory stimuli is well-known. The application of these external sensory stimuli to provoke a physiological response is termed cueing. Cueing has been utilized as a therapy to specifically improve neurologically impaired gait in PD since
It is now well-established that incorporating the use of sensory cueing can be a powerful means of improving gait in PD. Sensory cues are generally either auditory, visual, proprioceptive, or sometimes a combination thereof. The benefit to using the auditory sensory pathway, opposed to other methods using visual or proprioceptive sensory pathways, is that the reaction time is 20-50ms faster. In addition to the difference in reaction time, reviews of the literature revealed that auditory cueing is more effective than visual or proprioceptive cueing for treating gait disorders in PD. Examples of non-auditory cues include strategically placed brightly colored lines on a walkway or stairway, optical stimulating glasses, laser canes, and small vibratory devices. These types of cueing methods are sometimes used in addition to or in place of an auditory cue out of convenience, however will not be discussed further for the purposes of this review.

Modalities of auditory cueing include the use of a metronome, clicks, beeps, auditory tones, rhythmic clapping, music, and music embedded with enhanced beats or patterns. Most often, the cues are presented in a regular rhythmic series that is set closely to the patient’s preferred walking cadence. This is referred to as rhythmic auditory cueing or stimulation (RAC/RAS). RAC techniques have been repeatedly shown to ameliorate the deficits in spatiotemporal parameters of gait in persons with PD.

The implementation of the above mentioned RAC techniques have been studied for their acute effects, longitudinal effects, and to a lesser, although growing extent, long-term motor learning effects in PD. All conditions have supportive evidence of improvement in Parkinsonian gait parameters with this methodology. To assess gait
parameters, during or post RAC, the majority of studies ask participants to perform walking trials on a measureable pathway such as a gym floor, GAITRite instrumented walkway, or treadmill. Motion capture systems are often used as well. The gait variables most often measured to examine the effects of RAC include cadence, step length, and velocity. Repeatedly, one, two, or all three of these measures have been shown to improve during and/or after cueing. In the literature, it is considered an improvement when the magnitude of these parameters increase as well as when the variability of these parameters decrease.\textsuperscript{2, 58, 61, 62, 64-69} Although less often utilized, EMG synchronization, and hip, knee, ankle excursion have also been assessed during RAC and shown to improve.\textsuperscript{61, 70}

In longitudinal studies, various RAC training programs have been implemented in order to examine the effects of RAC training on gait in PD. Pre and post testing is performed in similar conditions as those described above. Examples include a physical rehabilitation program consisting of a variety of motor tasks performed in combination with rhythmic sounds with different cadences 1 hour 5x/week for 4 weeks, a 3 week home-based program in which participants listen to a metronome embedded in music while walking, stair-stepping, and performing stop & go exercises for 30 minutes daily, and an 8 week program in which participants listen to embedded music with increasing cadences 30 minutes 3x/week.\textsuperscript{61, 65, 66} An additional study investigated motor learning in PD with the use of rhythmic auditory cueing. Walking speed and step length significantly increased with cues after training during single- and dual-task gait and were retained after 6 weeks.\textsuperscript{63} All three types of studies investigating the effects of RAC over
various lengths of time (acute, longitudinal, and retention) demonstrate an improvement in gait parameters as discussed above.

Among the studies reviewed, several common factors were considered in regard to the inclusion/exclusion criteria for participants with PD. The participants recruited were typically in early to mid-stage PD, did not have any other neuro-musculoskeletal disorders, and did not have injuries that would impact gait. Other factors were variable such as state of medication during testing. In the majority of the studies, participants were tested in the on-medicated state (typically levodopa). Others were asked to abstain from use within a particular time period. In the studies performed during the off-medicated state, velocity, stride length, and cadence still improved. PD does not present equally among all in the population. Cognitive impairment affects some people with PD more than others. The positive potential of cueing as a therapeutic strategy to improve mobility in people with PD and mild cognitive impairment has been demonstrated. Freezing of gait is another characteristic of PD that may only affect a sub-group of the population. It has been found that freezers and non-freezers have a similar response to RAC in regard to changes in speed, however freezers tend to shorten their stride at a 10% increase in step frequency while non-freezers lengthen.

While the current literature provides sound evidence for RAC as a method for improving cadence, step length, and velocity in PD, there are many other gait deficits in the disease that have not been adequately addressed. Inconsistency in findings or simply a lack of testing across other important gait variables has left a gap in the literature in regard to the potential for auditory cueing. Further, the effects of cueing on variables related to efficient and effective gait function are completely missing.
Additionally, certain methods of cueing may improve some aspects of gait, but may also hinder others. As noted in a recent meta-analysis, a wide variety of auditory cueing strategies are used in the research literature and no one cue has been identified to have a more robust effect on gait improvement.² Of the current RAC methods, the modality of cue tends to fall into two categories: a consistent repetitive sound or stimulus set to a fixed tempo (metronome) or music. While music also provides a tempo there are many other components unaccounted for that may provoke physiological responses potentially affecting gait. There is therefore a need to determine the optimal method of auditory cueing techniques among the current RAC methods described as well as in other schools of thought.

Although RAC is the predominant form of cueing in the literature, some would argue that providing a perfectly regular auditory stimulus with identical inter-beat intervals is not ideal for the Parkinsonian population. With RAC, it has been revealed that there is a decrease in the variability of gait parameters which is considered an improvement.⁶⁴,⁶⁵ Typical methods of analysis used to identify improvements in variability in this way use a linear approach with means, standard deviations, and coefficients of variation. Current literature suggests that a more complete picture is missed in this traditional approach. As described above, Parkinsonian pathology leads to alterations in both the amount of variability and the nature of variability in gait over time. In healthy gait, the variability in stride time exhibits long range correlations over time that can be described as fractal in nature. In PD, the fractal nature of stride to stride fluctuations breaks down and becomes very similar to white noise or random
fluctuations. In order to reintroduce the fractal nature of healthy gait in a person with PD, an isochronous stimulus may not be ideal.

In 2006, Stergiou et al presented a theory for Optimal Movement Variability. In this theory it is proposed that, in mature motor skills and healthy states, there is an optimal amount of movement variability that has form and is characterized by a chaotic or fractal structure. This approach, in agreement with previous work done by Hausdorff and colleagues, strongly advocates the use of non-linear measures of analysis in order to identify and analyze this form and structure. It has been suggested that the goal of gait therapy should be to restore optimal gait variability, which exhibits chaotic fluctuations, in addition to the restoration of linear measures such as gait speed or stride length. To this end, a small but growing number of studies have been performed in an effort to manipulate or restore fractal or chaotic structure in gait variability.

A study on healthy young adults (HYA) demonstrated that auditory-motor coupling can be driven by different auditory noise signals, shifting the fractal temporal structure of gait dynamics towards the statistical properties of the signals used. It was shown in another study on HYA that walking to a metronomic beat provided through visual, auditory, tactile or all three cues affects the temporal dynamics of gait, but most notably with the auditory cue. As this was performed in HYA, the auditory metronome condition decreased the natural healthy fractal scaling found during no stimulation to a level similar to that of white noise. Terrier and colleagues have also demonstrated in HYA that RAC induced anti-persistent (or anti-correlated) patterns in stride time series. These results provides evidence that RAC may negatively impact the
variability structure of gait in healthy populations and potentially in neurologically impaired populations as well.

In healthy older adults (HOA) it has been shown that gait variability can also be altered when listening to auditory stimuli with differing temporal structures including white noise, a chaotic rhythm, and a metronome. There has been one study by Hove and colleagues investigating an experimental interactive rhythmic auditory stimulation system designed to re-establish healthy gait dynamics in PD by using foot sensors and nonlinear oscillators. The system uses real-time feedback from its auditory output signal and the participant's step timing, calculates the relative phase difference, and adjusts its phase and frequency (period) to correct a portion of the relative phase difference. It was reported that PD patients were able to synchronize with the interactive system, returning their fractal scaling levels to those of healthy participants, which was retained five minutes after removing the interactive rhythmic stimulation. They suggested that the interaction stabilized the internal rhythm generating system and reintegrated timing networks. These limited yet pivotal studies provide a basis to further explore auditory cueing methods to restore the healthy fractal structure to temporal gait variability in PD.

In the current literature music, as a method of auditory cueing, has been grouped under the category of RAC simply because it provides a rhythmic structure. However, music and a metronome may be far from the same. Music contains multiple features including melodies, chords, themes, riffs, rhythms and tempos making it a challenging topic of research. Traditionally, these features of music are performed by professional musicians via various instruments and/or vocal artists. Therefore, the beat structure is
human-generated from an internal neurological timing mechanism and thereby imperfect. Interestingly, it has been demonstrated that human-generated music exhibits long range correlations in pitch and volume fluctuations. Recently, Hennig and colleagues demonstrated for the first time that temporal fluctuations in complex human rhythmic performances are characterized by long range correlations. Excitingly, these fluctuations exhibit fractal structure paralleling the fractal structure found in the temporal fluctuations of healthy human gait as discussed above. In addition, they demonstrated that music listeners strongly prefer long-range correlated fluctuations in musical rhythms. This explains why perfect beat patterns generated by computers are commonly devalued by listeners.

Not only does human-generated music contain a rich and elaborate structure, it is also has the remarkable capability of evoking emotion. Music by definition, is vocal or instrumental sounds (or both) combined in such a way as to produce beauty of form, harmony, and expression of emotion. Current brain imaging technologies have enabled researches to identify neural substrates of human emotion while listening to a piece of music. Blood and Zatorre demonstrated that pleasurable responses to music correlate with activity in brain regions associated with reward and emotion. The same group later identified that this pleasurable response to music can lead to dopamine release in the striatal system. Anatomically distinct regions, the caudate and nucleus accumbens, were activated during anticipation and experience of peak emotion to music respectively.

Evoking emotion can lead to changes in movement in healthy young adults. More recently, it has also been shown that emotion can affect movement in healthy
older adults and persons with PD.\textsuperscript{90} The majority of these studies were performed with visual stimuli or memory recall to evoke emotion. There is not yet extensive evidence that emotion evoked specifically through auditory stimuli can also impact movement. However, a body of research on improving athletic performance via music does exist\textsuperscript{91-93} and music salience has been demonstrated to increase measures of cadence, velocity, and stride length in HYA.\textsuperscript{94} People with PD have a deficiency in dopamine production, therefore the dopaminergic pathways involved in musically evoked emotion may not function as effectively. However, activating the existing intact portions of the pathway and/or facilitating the use of the pathway through dopaminergic medication may still be advantageous.

The rhythmic and emotional differences between the use of a metronome and music discussed above substantiate specific aim two of this project: determining the effects of metronome vs. music on gait and mobility in PD. In a study on HYA, participants walked faster in time to music than metronome cues throughout a range of matched tempos suggesting that additional elements in the music may have enhanced their gait performance beyond the beat.\textsuperscript{95} Another study by Wittwer and colleagues showed that music but not metronome produced a significant increase in group mean gait velocity and stride length in HOA.\textsuperscript{96} There was no difference in the variability of these measures as analyzed via the coefficient of variation (a method of linear analysis). Non-linear analysis of variability was not performed. The comparison of music and metronome on gait performance in PD has yet to be determined.

The evidence that auditory cueing is an effective method of altering gait parameters in the Parkinsonian population is apparent. However, the mechanisms of
the central processes behind these alterations are not completely clear. The generation of rhythmicity in healthy human gait is suggested to be attributed to a number of structures including central pattern generators within the spinal cord, the basal ganglia, the SMA, the pre-SMA, the pre-motor cortex, inferior parietal cortex, and cerebellum.\textsuperscript{76, 97} In neurologically impaired populations, these structures may be affected either directly or indirectly, thus impairing timing and rhythmicity.

The basal ganglia specifically have received much attention as an internal cue generator. So naturally in PD, which is considered a basal ganglia disorder, rhythm generation and timing are disrupted. It is proposed, that cued walking redirects higher cognitive functions to gait, and compensates for gait regulation deficit.\textsuperscript{76} There is also evidence that rhythmic sound patterns, through the reticulospinal pathway, can increase spinal motor neuron activity.\textsuperscript{69} Auditory cueing is thought to bypass the defective internal rhythm from the basal ganglia\textsuperscript{60} or facilitate the basal ganglia-SMA loop and drive sensorimotor network activity to enable improvements in gait.\textsuperscript{97}

Neuroimaging studies have been performed to broaden the understanding of the effects of auditory stimulation on cortical and subcortical structures and functions. Chauvigne and colleagues performed a meta-analysis on studies designed to identify differences in brain circuitry when tapping the finger to a self-generated beat vs. tapping the finger to match an external beat (audiomotor entrainment).\textsuperscript{98} BOLD signals demonstrated activation of a similar circuitry for both with the exception of the pallidum being activated more so during the self-generated tapping than the externally paced tapping. The spinocerebellum was activated only with the external paced tapping and not during self-generated. This provides support for the theory above suggesting that in
audiomotor entrainment of gait in PD, the defective BG is bypassed (pallidum) but instead, the cerebellum (spinocerebellum) is activated.

Many questions relative to the effects of auditory cueing on gait in PD remain unanswered. The objective of this review encompassing the characteristics of Parkinson’s disease, PD neuropathology, neural control of gait, PD gait deficits, PD rhythm and variability, and an overview of the current literature on auditory cueing, was to provide a thorough background to substantiate addressing specific aims one and two via the methods detailed in the next chapter. Specific aims one and two were designed to fill the gaps in the literature made evident by this review.
CHAPTER 3
METHODS

Participants

A total of 30 participants were recruited for the study: 15 persons diagnosed with idiopathic PD by a movement disorders neurologist and 15 age-matched healthy older adults (HOA). Qualified PD candidates were recruited through the University of Florida Center for Movement Disorders and Neurorestoration. PD participants were tested in the on-medication state. Medication was taken upon arrival to ensure testing was performed during the participant’s optimally medicated state. HOA candidates were recruited via word of mouth from the general community. The inclusion and exclusion criteria are listed below. All participants provided written informed consent prior to participating in the study as approved by the University Institutional Review Board.

Inclusion criteria:

1. Parkinson’s disease - clinical diagnosis of PD with mild to moderate severity (Hoehn & Yahr stages 1 to 3)
   Healthy older adults (control) - gender and age-matched with a PD participant ± 2 years
2. Ambulatory
3. Between the ages of 45-80 years old
4. Capable of providing informed consent
5. Able to comply with trial procedures
6. No history of neurological (other than PD) or unstable orthopedic problems that could impair walking function or upper extremity mobility

Exclusion criteria:

1. Failure to meet the inclusion criteria
2. Regular use of an assistive device
3. The presence of active unstable diabetic, orthopedic, or other medical conditions such as peripheral neuropathy or vestibular dysfunction that would preclude their ability to participate

4. Site accessibility constraints

**Experimental Protocol**

Participants visited the Applied Neuromechanics Laboratory at the University of Florida for testing. Upon arrival to the lab, the investigator reviewed the informed consent document with participants and answered any questions. Once informed consent was provided, participants completed a Medical History Form, Physical Activity Readiness Questionnaire (PAR-Q), and Falls Efficacy Scale (FES). Participants with PD were then evaluated with the Unified Parkinson’s Disease Rating Scale (UPDRS). The UPDRS is a rating tool designed to follow the longitudinal course of the disease. It is made up of 4 sections: (1) Mentation, Behavior, and Mood, (2) Activities of Daily Living, (3) Motor, and (4) Complications of Therapy. These sections are evaluated by interview and as the disease progresses, UPDRS scores increase. The UPDRS was recorded and later rated by a fellowship-trained movement disorders neurologist.

Participants were asked to wear athletic clothing and comfortable walking shoes. After measuring height and weight, participants were instrumented with the six opal Ambulatory Parkinson’s Disease Monitoring system (128 Hz, APDM, Inc., Portland, OR). Opals are small non-invasive sensors, each equipped with an accelerometer and gyroscope, worn via an elastic strap over left and right feet, left and right wrists, trunk, and lumbar spine (Figure 3-1). An access point for wireless data transmission and synchronization of the independent sensors was placed on the perimeter of the walking space to record data.
Participants began by performing a two-minute over-ground walking trial in order to assess each participant’s comfortable walking cadence. Participants were then tested under a total of four different auditory conditions while walking over-ground for five minutes, followed by performing a walking task up to three times with no auditory stimulus (summarized by Table 3-1 and described below). Conditions one through four were randomized using Research Randomizer computer software to create 30 sets of four numbers per set (Urbaniak, G. C. & Plous, S., 2013, Version 4.0). During each condition, participants were asked to wear over-ear headphones that were either silent or provided an auditory stimulus dependent upon the condition.

**No Auditory Stimulus Condition**

**Five Minute Walk:** Participants were asked to walk over-ground at a normal, comfortable walking speed for five minutes. This was performed around the perimeter of a large indoor gym measuring approximately 94 by 50 feet.

**Affect Grid:** At the end of the walking trial the participant was asked to rate their emotional state via an affect grid (appendix a). The rating is determined from the location in the $9 \times 9$ grid in which horizontally (left to right), the scale ranges from “unpleasant” (negative) to “pleasant” (positive) and vertically (bottom to top), the scale ranges from “sleepiness” to “high arousal.”

**Post-Cue Walking Task:** Instrumented Stand and Walk Task (ISAW): Participants were then asked to perform up to three ISAW tasks with no auditory stimulus in order to assess carry-over effects on gait performance. The ISAW is a quick and simple task that is performed with the APDM system in the same location as the over-ground walk. It starts with the participant standing in place, walking seven meters, turning 180 degrees, and walking back.
Participants repeated the above five minute over-ground walking trials, affect grid, and post-cue walking tasks for the remaining three conditions described in detail below. Optional rest was provided between conditions and tasks. The participant was able to stop the protocol at any time if they felt uncomfortable or unsafe.

**Regular Metronome Condition**

A regular metronome in the form of a repeated tone was played via an MP3 player and over-ear headphones. The metronome beat intervals were regular in that the time intervals between beats were all the same. The tempo (beats per minute) was adjusted to match the participant’s self-selected cadence (steps per minute) as measured during the initial two-minute walk. During the five minute over-ground walking task the participant was instructed to “walk to the beat as best they can.”

**Fractal Metronome Condition**

A fractal metronome in the form of a repeated tone was played via an MP3 player and over-ear headphones. The metronome beat intervals in this condition were varied. The variability in the length of time between beats was not random, but exhibited long-range correlations that have a fractal-like structure. The average tempo (beats per minute) was customized to match the participant’s self-selected cadence (steps per minute) as measured during the initial two-minute walk. The magnitude of the variability between beats was determined by the standard deviation of the participants stride time during the initial two-minute walk. This individualized fractal auditory stimulus was created by embedding pink noise (1/f noise representing fractal processes) into a series of repeated tones (same tone as condition two) as done previously by Hunt and colleagues. During the five minute over-ground walking task the participant was
instructed to “walk to the beat as best as they can.” Participants were informed that the beat intervals would be slightly varied.

**Music Condition**

A piece of music was played via an MP3 player and over-ear headphones. The song “Staying Alive” by the Bee Gees (1977) was selected for several reasons. It was a popular upbeat song with the generation of our population and the most popular recording has a bpm of 103.6 which is within range of the average cadence for a person with mild to moderate stage PD.¹ The tempo (beats per minute) of the song was adjusted to match the participant’s self-selected cadence (steps per minute) as measured during the initial two-minute walk. The pitch of the song was not altered. The customized music files were created via the Djay 2 application for iPhone (algoriddim GmbH, version 2.8.1, 2006-2015). During the five minute over-ground walking task the participant was instructed to “walk to the beat as best they can.”

An exit questionnaire, regarding the participant’s subjective opinion of each trial, was given upon completion of the entire protocol.

**Data Processing**

The four, five-minute walking trials were recorded with the APDM system.¹⁰⁰ Gait measures were broken down on a stride-by-stride basis when exported to Excel. Stride velocity was defined as the average gait speed and calculated as stride length divided by stride time. Cadence was defined as steps taken per minute. Stride length was defined as the distance between two consecutive heel strikes. Stride time was defined as the duration of a complete gait cycle (two consecutive heel strikes). Transverse trunk range of motion (ROM) was defined as the range of motion of the trunk in the transverse plane. Arm swing velocity was defined as the peak angular velocity of the
In addition to the linear analysis of the spatiotemporal gait parameters measured above, a Detrended Fluctuation Analysis (DFA) was performed on the stride time series taken from the APDM data. For this particular non-linear analysis it is ideal to use relatively lengthy data sets in order to assess long range correlations. However, it is difficult to obtain walking data for an extended period of time in participants who are clinical patients, therefore we asked them to perform five minute trials. In previous literature, five minute time periods have been used to determine the fractal scaling of stride interval time series. Fractal scaling was determined by a DFA algorithm implemented into MATLAB according to the methods used by Peng et al. By using DFA, a resultant scaling exponent (α) is computed. A scaling exponent α ≈ 0.5 corresponds to rough and unpredictable white noise; α ≈ 1.0 corresponds to 1/f-like noise and long-range correlations. Alpha values were determined for the stride time series during all four auditory conditions.

**Statistical Analyses**

A one-way MANOVA was performed to compare baseline gait characteristics of PD and HOA control groups as determined during the five minute no cue walking condition. In order to determine if participants were able to entrain their steps to the tempo set for each auditory condition, cadence measures during regular metronome, fractal metronome, and music conditions were compared to baseline cadence for both groups using paired t-tests. Gait performance change scores were calculated by subtracting baseline gait parameter values in the no cue condition from the gait
parameter values in the regular metronome condition, fractal metronome condition, and
music condition.

In order to address specific aim one, a 2x2 repeated measures MANOVA was
performed to compare gait performance change score differences in velocity, stride
length, arm swing velocity, and stride time DFA between regular metronome and fractal
metronome conditions within each population (PD and HOA). In order to address
specific aim two, a 2x2 repeated measures MANOVA was performed to compare gait
performance change score differences in velocity, stride length, arm swing velocity, and
stride time DFA between regular metronome and music conditions within each
population (PD and HOA). Change scores in velocity, stride length, arm swing velocity,
and stride time DFA were additionally compared to zero via a one-sample t-test to
determine if the regular metronome, fractal metronome, and music auditory conditions
led to statistically significant changes in gait performance from baseline. Levels of
significance for analyses were set at $\alpha<0.05$. As four dependent variables were chosen
for statistical analysis, the adjusted p-value for significance at the univariate level was
set to $<0.0125$. The above statistical analyses were repeated for all auditory condition
post-cue walking performance measures to compare carry-over effects, however stride
time DFA comparisons among post-cue walking tasks were not able to be performed
due to the short duration of the walking task (<one minute). Affect grid ratings were
assessed for pleasure and arousal scores via two 2x4 (group x auditory condition)
repeated measure ANOVAs.

**Secondary Statistical Analyses**

In order to compare changes from baseline between the fractal metronome
condition and music condition, a 2x2 repeated measures MANOVA was performed to
compare gait performance change score differences in velocity, stride length, arm swing velocity, and stride time DFA between the fractal metronome and music conditions within each population (PD and HOA). Change scores in velocity, stride length, arm swing velocity, and stride time DFA were additionally compared to zero via a one-sample t-test to determine if the fractal metronome and music auditory conditions led to statistically significant changes in gait performance from baseline. Levels of significance for analyses were set at \( \alpha < 0.05 \). As four dependent variables were chosen for statistical analysis, the adjusted \( p \)-value for significance at the univariate level was set to \( <0.0125 \). The above statistical analyses were repeated for all auditory condition post-cue walking performance measures to compare carry-over effects, however stride time DFA comparisons among post-cue walking tasks were not able to be performed due to the short duration of the walking task (<one minute).
Figure 3-1. Six Opal APDM system set-up.

<table>
<thead>
<tr>
<th>AUDITORY CONDITION</th>
<th>Randomized</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO STIMULUS</td>
<td>1 – NO STIMULUS</td>
</tr>
<tr>
<td>a. 2 Minute Walk</td>
<td>a. 5 Minute Walk</td>
</tr>
<tr>
<td>c. ≤ 3 ISAW trials (no stimulus)</td>
<td>c. ≤ 3 ISAW trials (no stimulus)</td>
</tr>
</tbody>
</table>

Figure 3-2. Protocol
CHAPTER 4
RESULTS

Participant characteristics and demographic information are found in Table 4-1. Baseline comparisons of walking performance between individuals with PD and age-matched controls were performed from data obtained during the no cue walking condition (Table 4-2). Individuals with PD walked significantly slower utilizing significantly shorter strides and significantly reduced arm swing velocity. While DFA values were ~8% lower in individuals with PD this did not reach statistical significance. The PD group had a significantly higher fear of falling during daily activities of living as determined by the FES. No significant differences in cadence were found between groups or between auditory cue conditions and baseline (Figure 4-1).

Specific Aim 1

Gait performance change scores were calculated between the regular metronome condition and the no cue condition, and between the fractal metronome condition and the no cue condition. Statistical analyses evaluated the effect of group (PD vs. HOA), auditory cuing rhythm (regular vs. fractal), and their interaction. The repeated measures multivariate analysis identified a significant group main effect (p=0.03) and a significant condition main effect (p<0.001). The interaction term failed to reach statistical significance (p=0.692). At the univariate level, a group main effect was observed for the change in stride time DFA (p=0.005). During the regular metronome condition both groups revealed a decrease in DFA value, more so in controls than PD (Figure 4-2). During fractal metronome, both groups exhibited increased DFA values with larger changes observed in PD (Figure 4-2). Collectively, then the net change was larger and positive in PD and smaller in magnitude and negative in HOA. A condition
main effect was also observed for DFA (p<0.001). The regular metronome caused a
decrease in DFA values whereas the fractal metronome increased DFA values (Figure 4-3). DFA values observed during walking to a regular metronome and fractal metronome were both statistically different from zero (p= 0.003, p<0.001, respectively).

At the univariate level, a condition main effect was not observed for the change in velocity (p=0.083) stride length (p=0.459), or arm swing velocity (p=0.428) (Figures 4-4, 4-5, and 4-6 respectively). Velocity, stride length, and arm swing velocity were not statistically different from zero in the regular metronome condition (p=0.532, p=0.382, p=0.205) or fractal metronome condition (p=0.092, p=0.165, p=0.070) either.

Change scores in the post-regular metronome and post-fractal metronome walking tasks were also calculated and compared. No significant group or condition main effects were found for velocity, stride length, or arm swing velocity (Figures 4-7, 4-8, and 4-9 respectively).

**Specific Aim 2**

Gait performance change scores were calculated between the regular metronome condition and the no cue condition, and between the music condition and the no cue condition. Statistical analyses evaluated the effect of group (PD vs. HOA), auditory cuing modality (regular metronome vs. music), and their interaction. The multivariate analysis failed to identify a significant group main effect (p=0.120), yet revealed a significant condition main effect (p=0.002). The interaction term failed to reach statistical significance (p=0.663). At the univariate level, a condition main effect was observed for the change in velocity (p=0.009), stride length (p=0.001), arm swing velocity (p<0.001), and stride time DFA (p=0.002). Velocity, stride length, arm swing velocity, and stride time DFA were all significantly higher during the music condition.
when compared to the metronome condition (Figures 4-10, 4-11, 4-12, and 4-13 respectively). Velocity, stride length, and arm swing velocity were all statistically different from zero in the music condition (p=0.012, p=0.001, p=0.001), but not during the regular metronome condition. As stated above, stride time DFA values during the regular metronome were statistically different than zero (p=0.003), however walking to music was not (p=0.541).

Change scores in the post-cue walking tasks were also calculated and compared. No significant group main effect was found (p=0.815), however there was a significant auditory cueing modality main effect (p=0.018). The interaction term failed to reach statistical significance (p=0.251). At the univariate level a condition main effect was observed for the change in arm swing velocity, which increased more after the music condition than after the regular metronome condition (p=0.006) (Figure 4-16). Arm swing velocity increased after the music condition relative to baseline as well (p=0.021). Although statistical significance was not reached, it appeared that velocity and stride length values increased from baseline, more so after the music condition than the regular metronome condition (Figures 4-14 and 4-15).

**Secondary Analyses**

Gait performance change scores were calculated between the fractal metronome condition and the no cue condition, and between the music condition and the no cue condition. Statistical analyses evaluated the effect of group (PD vs. HOA), auditory cueing condition (fractal metronome vs. music), and their interaction. The multivariate analysis failed to identify a significant group main effect (p=0.078), yet revealed a significant condition main effect (p<0.001). The interaction term failed to reach statistical significance (p=0.613). At the univariate level, a condition main effect was
observed for the change in stride length (p=0.004), arm swing velocity (p<0.001), and stride time DFA (p<0.001), but not for velocity (p=0.302) (Figures 4-19, 4-18, 4-20, and 4-17 respectively). Stride length and arm swing velocity were higher in the music condition relative to the fractal metronome while DFA was lower. Velocity, stride length, and arm swing velocity were not statistically different from zero in the fractal metronome condition (p=0.092, p=0.165, p=0.070), but DFA was (p<0.001). In the music condition, velocity, stride length, and arm swing velocity were statistically different from zero (p=0.012, p=0.001, p=0.001), but DFA was not (p=0.541).

Change scores in the post-cue walking tasks were also calculated and compared for velocity, stride length, and arm swing velocity (Figures 4-21, 4-22, and 4-23). No significant group main effects or condition main effects were found (p=0.858, p=0.369). The interaction term failed to reach statistical significance (p=0.257). Arm swing velocity increased after the music condition relative to baseline as found in aim two (p=0.021).

Affect grid results revealed the following (pleasure, arousal) ratings for the PD group: no cue (5.3 ± 2.4, 4.2 ± 2.5), regular metronome (5.2 ± 1.9, 4.5 ± 3.0), fractal metronome (4.9 ± 1.7, 5.1 ± 2.7), and music (7.1 ± 0.9, 7.3 ± 1.1). HOA group: no cue (6.6 ± 1.4, 4.9 ± 2.8), regular metronome (5.4 ± 2.2, 4.2 ± 2.9), fractal metronome (5.7 ± 2.1, 6.0 ± 2.7), and music (6.3 ± 1.1, 8.0 ± 0.4). Total group: no cue (6.0 ± 1.2, 4.5 ± 2.6), regular metronome (5.3 ± 2.0, 4.3 ± 2.9), fractal metronome (5.3 ± 1.9, 5.6 ± 2.7), and music (6.7 ± 1.1, 7.6 ± 0.9) (Figure 4-31).

Statistical analyses for the affect grid demonstrated no significant group main effects (pleasure: p=0.382, arousal: p=0.412), however there were significant condition
main effects (pleasure: p=0.006, arousal: p<0.001). Interaction terms failed to reach statistical significance (pleasure: p=0.116, arousal: p=0.691. Pairwise comparisons indicated that the musical condition pleasure rating was statistically higher than no cue, regular metronome, and fractal metronome conditions (P=0.042, P=0.001, P<0.001), and that the musical condition arousal rating was also statistically higher than no cue, regular metronome, and fractal metronome conditions (P<0.001, P<0.001, P<0.001). The fractal metronome had a higher arousal rating than the regular metronome (P=0.038). Results from the exit questionnaire in which participants were asked to rate their level of willingness to train under each auditory cueing condition are posted in Figure 4-32.
Table 4-1. Participant characteristics and demographic information

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parkinson’s disease</th>
<th>Controls</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n)</td>
<td>15</td>
<td>15</td>
<td>--</td>
</tr>
<tr>
<td>Males/Females</td>
<td>11/4</td>
<td>11/4</td>
<td>--</td>
</tr>
<tr>
<td>Age (years)</td>
<td>69 ± 6</td>
<td>69 ± 5</td>
<td>0.87</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>173 ± 9</td>
<td>175 ± 9</td>
<td>0.67</td>
</tr>
<tr>
<td>Weight (lbs)</td>
<td>183 ± 25</td>
<td>183 ± 36</td>
<td>0.96</td>
</tr>
<tr>
<td>Age of PD onset</td>
<td>63 ± 7</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>UPDRS-III</td>
<td>24.4 ± 11.4</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>#28 Posture</td>
<td>1.0 ± 0.8</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>#29 Gait</td>
<td>0.6 ± 0.8</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>#30 Postural Stability</td>
<td>1.0 ± 1.2</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Schwab &amp; England</td>
<td>85.3 ± 10.6</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Hoehn &amp; Yahr</td>
<td>2.3 ± 0.6</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

Values are M ± SD. UPDRS-III: Unified Parkinson’s Disease Rating Scale. * indicates statistical significance.

Table 4-2. Baseline gait characteristics of PD and Control groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parkinson’s disease</th>
<th>HOA Controls</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Velocity (m/s)</td>
<td>1.07 ± 0.22</td>
<td>1.22 ± 0.13</td>
<td>*0.033</td>
</tr>
<tr>
<td>Cadence (steps/min)</td>
<td>112 ± 10</td>
<td>113 ± 8</td>
<td>0.606</td>
</tr>
<tr>
<td>Stride Length (m)</td>
<td>1.15 ± 0.21</td>
<td>1.30 ± 0.11</td>
<td>*0.021</td>
</tr>
<tr>
<td>Stride Time (s)</td>
<td>1.09 ± 0.11</td>
<td>1.06 ± 0.07</td>
<td>0.532</td>
</tr>
<tr>
<td>Trunk Transverse ROM (deg)</td>
<td>9.03 ± 2.33</td>
<td>9.72 ± 2.75</td>
<td>0.466</td>
</tr>
<tr>
<td>Arm Swing Velocity (deg/s)</td>
<td>182 ± 55</td>
<td>237 ± 65</td>
<td>*0.020</td>
</tr>
<tr>
<td>Arm Swing ROM (deg)</td>
<td>43.0 ± 19.9</td>
<td>56.9 ± 17.6</td>
<td>0.052</td>
</tr>
<tr>
<td>DFA of Stride Time (α)</td>
<td>0.76 ± 0.09</td>
<td>0.82 ± 0.08</td>
<td>0.065</td>
</tr>
<tr>
<td>Falls Efficacy Scale</td>
<td>20.0 ± 16.5</td>
<td>10.5 ± 1.1</td>
<td>*0.030</td>
</tr>
</tbody>
</table>

Values are M ± SD. * indicates statistical significance.
Figure 4-1. Total group cadence during all auditory conditions.

Figure 4-2. PD and HOA change scores (mean ± SE) in stride time DFA during regular metronome and fractal metronome conditions. * indicates statistical significance between groups.
Figure 4-3. Total group change scores (mean ± SE) in stride time DFA during regular metronome and fractal metronome conditions. * indicates statistical significance from baseline, ** indicates statistical significance between conditions.

Figure 4-4. Total group change scores (mean ± SE) in arm swing velocity during regular metronome and fractal metronome conditions.
Figure 4-5. Total group change scores (mean ± SE) in stride length during regular metronome and fractal metronome conditions.

Figure 4-6. Total group change scores (mean ± SE) in arm swing ROM during regular metronome and fractal metronome conditions.
Figure 4-7. Post task total group change scores (mean ± SE) in velocity after regular metronome and fractal metronome conditions. —**— indicates statistical significance between conditions.

Figure 4-8. Post task total group change scores (mean ± SE) in stride length after regular metronome and fractal metronome conditions.
Figure 4-9. Post task total group change scores (mean ± SE) in arm swing velocity after regular metronome and fractal metronome conditions.

Figure 4-10. Total group change scores (mean ± SE) in velocity during regular metronome and music conditions. * indicates statistical significance from baseline, —*—— indicates statistical significance between conditions.
Figure 4-11. Total group change scores (mean ± SE) in stride length during regular metronome and music conditions. * indicates statistical significance from baseline, --**-- indicates statistical significance between conditions.

Figure 4-12. Total group change scores (mean ± SE) in arm swing velocity during regular metronome and music conditions. * indicates statistical significance from baseline, --**-- indicates statistical significance between conditions.
Figure 4-13. Total group change scores (mean ± SE) in stride time DFA during regular metronome and music conditions. * indicates statistical significance from baseline, ††† indicates statistical significance between conditions.

Figure 4-14. Post task total group change scores (mean ± SE) in velocity after regular metronome and music conditions.
Figure 4-15. Post task total group change scores (mean ± SE) in stride length after regular metronome and music conditions.

Figure 4-16. Post task total group change scores (mean ± SE) in arm swing velocity after regular metronome and music conditions. * indicates statistical significance from baseline, ** indicates statistical significance between conditions.
Figure 4-17. Total group change scores (mean ± SE) in velocity during fractal metronome and music conditions. * indicates statistical significance from baseline, —*— indicates statistical significance between conditions.

Figure 4-18. Total group change scores (mean ± SE) in stride length during fractal metronome and music conditions. * indicates statistical significance from baseline, —*— indicates statistical significance between conditions.
Figure 4-19. Total group change scores (mean ± SE) in arm swing velocity during fractal metronome and music conditions. * indicates statistical significance from baseline, −*−* indicates statistical significance between conditions.

Figure 4-20. Total group change scores (mean ± SE) in stride time DFA during fractal metronome and music conditions. * indicates statistical significance from baseline, −*−* indicates statistical significance between conditions.
Figure 4-21. Post task total group change scores (mean ± SE) in velocity after fractal metronome and music conditions.

Figure 4-22. Post task total group change scores (mean ± SE) in stride length after fractal metronome and music conditions.
Figure 4-23. Post task total group change scores (mean ± SE) in arm swing velocity after fractal metronome and music conditions. * indicates statistical significance from baseline, −*− indicates statistical significance between conditions.

Figure 4-24. Affect grid of emotional state during all auditory conditions (total group). NC = no cue, RM = regular metronome, FM = fractal metronome, M = music.
Figure 4-25. Willingness to train under all auditory cueing conditions (total group).
CHAPTER 5
DISCUSSION

The primary purpose of this project was to determine the influence of commonly utilized auditory cueing techniques on gait performance in PD. Aim 1 focused on understanding the impact of altering the regularity of a metronome beat on gait spatial-temporal parameters and the underlying structure and complexity of stride time variability, a variable highly related to falls and the ability to adapt gait. Aim 2 focused on a direct comparison of the impact of walking to a metronome or music while controlling for the timing of the beat. The primary findings of these experiments are: both healthy older adults and persons with Parkinson’s disease are able to adapt their walking to an auditory cue; metronomes with a regular fixed beat interval significantly reduce the complexity and structure of stride time variability whereas walking to a fractal beat enhances this complexity; and walking to music is more efficacious for impacting walking performance than walking to a metronome with the same beat. These major findings are discussed in detail below.

**Specific Aim 1**

Healthy human locomotion is characterized by repetitive rhythmic stepping in order to produce forward progression. Gait parameters remain relatively stable and consistent from stride to stride even during unconstrained walking.\(^49\) Due to neurodegeneration in PD, strides become progressively slower, smaller, and irregular over time. PD patients have difficulty producing a steady gait rhythm which, along with increased stride to stride variability, is linked to falling.\(^49,51\) In an effort to amend these symptoms, auditory cueing has become a commonly utilized therapy for improving gait in the PD population. The traditional auditory cue provides a regular, isochronous,
rhythmic stimulus with the intention of restoring the rhythmic flow to gait. However, upon close examination, healthy gait is not perfectly regular but in fact contains stride to stride fluctuations that are self-similar over time described as fractal in nature. In aging and PD, this fractal structure breaks down as gait performance becomes impaired. Our data reveal that walking to the metronome with a fractal beat structure successfully drove the temporal dynamics of gait back to healthy levels in both PD and controls. Conversely, walking to the regular metronome drove temporal dynamics further away. Additionally, walking to a metronome matched to self-selected cadence (regular or fractal), did not result in any other significant benefits to gait.

The primary findings for aim one demonstrate that the use of metronomes, with regular or fractal rhythmic structures, significantly impact stride time DFA values in PD as well as controls. Despite baseline differences between groups, both demonstrated similar gait performance changes during the regular metronome condition. PD and controls exhibited a significant decrease in the fractal dynamics of stride time fluctuations while walking to the regular metronome, as evidenced by the scaling exponent became closer to that of white noise (0.5). This indicates a break down in the long-range correlations in stride to stride variability as fluctuations became more random. These results suggest that the use of an isochronous cue, such as a regular metronome, may be detrimental to gait performance in both PD and healthy older adults. Similar results have been reported when healthy young adults walk to a metronome and in another study when healthy older adults walked to a metronome. Deviations away from optimal variability structure, as found while walking to a regular metronome, reduce the ability to adapt to perturbations encountered in daily walking.103
The regular metronome condition decreased the fractal scaling in the controls to a greater extent than the PD group, however this difference was not statistically significant and baseline DFA values were already lower in PD. Rhythmic entrainment to external stimuli is thought to involve activation of cerebellum-thalamic-cortical circuitry, circumventing the internal rhythmic generating basal ganglia which are dysfunctional in PD.\textsuperscript{97, 98} This may explain why both groups were able to react similarly. Walking to an isochronous beat such as a regular metronome is the most common form of auditory cueing, as patients with PD are able to entrain their steps to the beat and increase their speed as cadence increases. Our results suggest that this type of rhythmic cue, which may aid certain aspects of gait, is in fact detrimental to other important parameters and should therefore be reconsidered as a commonly recommended therapy.

In the fractal metronome condition, it was revealed that both PD and control groups had significantly higher scaling exponents when compared to their respective baselines, and even more so when compared to their respective RM conditions. Our results are in agreement with previous work which demonstrated the ability to alter gait variability in older adults via listening to auditory stimuli with differing temporal structures.\textsuperscript{6} In our data, the effectiveness of the fractal metronome to acutely reinstate fractal scaling in PD produced similar results to another group who used an interactive system on PD to generate rhythmic pacing sequences using nonlinear limit-cycle oscillators in real-time.\textsuperscript{77} In both studies, the interventions successfully brought the scaling exponents close to 1.0 revealing long-range correlations in stride time. However, in our study, baseline scaling exponents were initially lower in our PD sample. This may be explained by the fact that our data was collected and analyzed over five
minute walking periods, while the other study was only collected over three minutes. It has been recommended that, when studying within-subject stride-to-stride changes, the methods used must be able to record a relatively large number of strides. While the optimal number of strides to collect is subject to debate, it is generally accepted that more is better. As it is difficult for neurologically impaired populations to walk for long periods of time, five minute periods have been frequently used in the PD literature for non-linear analyses.

Walking to a metronome with a fractal beat structure effectively drove the $\alpha$-values up to $\sim 1.0$, indicating that it is possible to acutely reinstate healthy long-range correlations in the stride to stride fluctuations of gait of both PD and controls. While promising, it will be pertinent to further investigate the use of a fractal auditory stimulus on carry over effects, long term training programs, and if restored, how fractal dynamics would translate to functional activities. As increased stride to stride variability and reduced long-range fractal dependence in both elderly and PD are linked to falls, there is hope that training with a FM may be a useful preventative measure to increase adaptability and prevent falls in those who are prone. Although encouraging, it is also necessary to examine the behavior other gait parameters during both RM and FM conditions.

Neither the regular nor fractal metronome conditions significantly increased spatiotemporal parameters of gait such as velocity, stride length or arm swing velocity. This is not surprising as our stimuli were intentionally matched to the participant’s self-selected cadence. It has already been well established in previous literature that providing a stimulus at a higher tempo than a person’s self-selected cadence will
increase gait speed as they entrain to the beat. The purpose for holding cadence constant in aim one, was to identify the ability of metronome stimuli to alter the complexity and structure of gait dynamics independent of pace, and to identify any secondary effects on gait parameters in doing so. Entraining steps to the FM likely requires increased attention, or cognitive demand, as the slight variations in tempo are not perfectly predictable like in the RM condition. This may have caused participants to become tense and in doing so restrict their movement. It will be important to determine if repetitive practice walking to a FM leads to changes in spatiotemporal parameters over time.

In summary, the acute impact of a regular metronome on the fractal dynamics of gait is negative while the acute impact of a fractal metronome on the dynamics of gait is positive. There is cause for concern regarding the potential for the regular metronome to break down healthy long-rang correlations in gait variability even further in PD and older adults if used chronically. More research is needed to study the effect of long-term training with a regular metronome on the fractal scaling of gait to form conclusions. The fractal metronome appears to be a superior method of cuing when compared to RM as it acutely re-instates the healthy fractal dynamics of stride time variability.

The post-cue walking task did not demonstrate significant differences between groups or conditions in aim one. As the spatiotemporal gait parameters tested during the post-cue condition were not significantly impacted by the metronome conditions, this was to be expected. The most prominent findings for this aim were in reference to the results of stride time DFA. Unfortunately, the relatively short walking duration of the post-cue task did not provide a stride time series long enough to run this this type of
testing gait performance in the PD population has limitations due to the neurologically impaired state. In order to prevent fatigue and decrease risk of falling, walking trials were kept to five minutes so that all conditions could be performed. For this particular protocol, the addition of five-minute post-cue walking trials after all four auditory conditions would likely have made the protocol challenging to complete. Future studies designed specifically to investigate the carry-over effect of temporal gait dynamics are in need.

Specific Aim 2

Few direct comparisons of the efficacy of metronomes and music have been conducted and little is known about their effects on the underlying structure of walking variability. The second aim of this project was to determine which auditory cueing modality, metronome vs. music, is most beneficial for PD gait. Our results indicate a clear distinction between the effects of metronome and music on gait.

While PD and control groups had several statistically different spatiotemporal gait parameters at baseline, both groups reacted similarly to regular metronome and music conditions. In agreement with our hypothesis, gait velocity, stride length, arm swing velocity, and stride time DFA were all significantly increased in the music condition when compared to the regular metronome condition. Furthermore, walking to music resulted in statistically significant increases in gait velocity, stride length, arm swing velocity, and stride time DFA from baseline. Our results provide evidence that music stimulates alterations in gait that are beyond the effect of a simple auditory rhythmic stimulus in both PD and controls.

As gait dysfunction in PD is classically characterized by decreased velocity, step length, reduced arm swing, the above findings suggest that walking to music may
indeed ameliorate these specific symptoms more effectively than a metronome. Additionally, axial rigidity is related to quality of life and the risk of falls in PD.\textsuperscript{106} Here we demonstrate that PD patients, along with controls, appear to improve axial range of motion while walking to music. Of note, is that PD participants were tested while in their best "on-mediated" state which may have contributed to the reason there were no differences in change scores between PD and controls.

In PD, a "motor motivation" problem exists in which patients can produce normal movements when specifically instructed to do so, however the nature of the disease causes movements to be scaled down in speed and amplitude.\textsuperscript{107} Dopamine is thought to set the level of motor motivation. Therefore, when dopamine becomes depleted in PD, bradykinesia and hypokinesia are observed as manifestations of the reduced scaling of movements.\textsuperscript{107} Reintroducing dopamine into the system via pharmaceuticals can be effective in restoring many motor symptoms closer to normal.\textsuperscript{108} While pharmacotherapy has been shown to only have limited effects on gait disturbance, the use of external cues such as metronome and music can successfully stimulate the relatively intact motor programs.\textsuperscript{109} External cues are beneficial to people with PD as the decline in motor function substantiates their use. The effects of cueing however are not PD specific as these methods have similar effects on healthy older adults.\textsuperscript{110} Although metronome and music have been compared in healthy participants,\textsuperscript{96} these comparisons have not yet been published in PD. Our results, for the first time, demonstrate that music when compared to metronome, is more effective at improving gait parameters in PD, similarly to HOA. In addition to demonstrating improved velocity and stride length as reported in the study on HOA,\textsuperscript{96} we found further benefits of music
compared to metronome on arm swing and gait dynamics. This indicates that there are elements in music, beyond rhythm, that further elicit a motor response.

Music is a rich and complex structure, containing many properties that may contribute to the stimulation of movement. Rhythm, as we’ve established, is perhaps the most obvious component, in which compensatory neural circuits are facilitated in order to match the pace oriented goal and entrain movement to the set beat. The amplitude of rhythm, or beat strength, may additionally impact gait. High groove music elicits better gait synchronization and fast gait velocity. Our chosen piece of music may be classified as high-groove music as “groove” is considered the experience of wanting to move when hearing music, often found in music intended for dancing. Staying Alive, by the Bee Gees, was selected due to its popularity with the particular generation of our population. It was released during the disco era in the 1970s during which dancing became a favorite leisure activity. As music familiarity and enjoyment may also have a role in eliciting gait, it is likely that this played a role.

Another perhaps more profound, but fundamentally essential characteristic of music is its ability to evoke emotion. The music selection for the study was chosen for its uplifting and positive nature in addition to its popularity with the generation of our population. In order to assess the emotional impact of the music, along with that of the metronome, an affect grid was used. The music condition elicited high ratings in both pleasantness and arousal as compared to the relatively neutral ratings in both categories during the metronome condition. The positive emotional response elicited by this musical selection may have contributed to the increased gait parameters, as the manipulation of emotion has been previously reported to affect movement in PD.
Our results beg the question: from a neurological standpoint, how does emotion as evoked through musical stimuli increase movement amplitude? It is well known that voluntary movement, including gait, is initiated by an intentional motor command from the cerebrum, which then travels to the brainstem and down the spinal cord. However, this is not the only way to elicit locomotion. Sensory signals from internal and external stimuli, including emotional stimuli, may contribute to what is termed emotional motor behavior. Studies from animal models have revealed a ventral system for emotional locomotor control. In this model, the amygdala and hippocampus project to the nucleus accumbens. These brain structures are the primary components of the limbic system and are also involved in fight or flight mechanisms. Inhibitory neurons from the nucleus accumbens project to ventral pallidum and the SNr. These structures in turn control activity of the MLR, which includes the PPN and cuneiform nucleus (CNF). When stimulated, the PPN suppresses muscle tone and the CNF elicits locomotion. In the emotional locomotor system, dopaminergic projections come from the ventral tegmental area (VTA) and are thought to contribute to reward-oriented locomotor behaviors.

Brain imaging technologies have further validated these models. The use of music specifically, has enabled researchers to identify neural substrates of human emotion. Blood and Zatorre demonstrated that pleasurable responses, induced by listening to music, correlate with activity in brain regions associated with reward and emotion. In particular, the caudate and nucleus accumbens are activated during anticipation and experience of peak emotion to music respectively. The same group later identified that this pleasurable response to music can lead to dopamine release in
the striatal system.\textsuperscript{84} In our study, as all participants rated the music condition as pleasurable, it is quite possible that a release of dopamine in this ventral system of locomotor control led to the amplification of gait parameters seen in our results.

We observed an increase in gait parameter measures in the music condition with both HOA and PD. In PD however, the natural production of dopamine is diminished due to neurodegeneration of the substantia nigra pars compacta leading to motor impairment. What then, happens to the VTA in PD? Is the VTA, which also produces dopamine spared in PD therefore an emotional response can still effectively stimulate locomotion? In advanced PD, there is atrophy of the NA which is proposed to be related to neuropsychiatric decline.\textsuperscript{117} It was later found that in PD with mild cognitive impairment (MCI), there is a significant decrease in the volume of the amygdala and nucleus accumbens over time relative to PD without MCI and healthy controls.\textsuperscript{118} The same group also revealed that dopamine depletion in Parkinson's disease progresses from the dorsal striatum to the ventral striatum, and in the early stage of the disease the dorsal striatum is severely depleted, whereas the ventral striatum is relatively intact.\textsuperscript{118} From this, we can hypothesize that stimulating emotion to improve gait parameters in PD may be effective in the earlier stages of the disease while the ventral emotional locomotor control system is still intact. However later in the course of disease, when neuropsychiatric impairments arise, a blunted emotional response may dampen the beneficial effects.

As determined in specific aim one, the regular metronome condition significantly reduced the fractal scaling of stride time from baseline, while aim two revealed that music did not. This indicates that relative to the regular metronome condition, music is a safer
method of cueing as it did not have detrimental effects on the fractal scaling of gait. Musical pieces have layers of rhythms, with the use of a variety of instruments, and often vocals. Furthermore, unless the music is synthesized, the rhythms in most pieces are human generated and therefore imperfect in timing. Thus there are long-range correlated fluctuations in human-produced musical rhythms. The musical selection for the study may have had an electronically generated baseline beat, as it was made in the disco era, however were human generated components in the piece as well. While the scaling exponent of “Staying Alive” recording was not able to be determined, it is probable that the value is more fractal in nature than that of the regular metronome. Perhaps using an entirely human generated piece of music tested for long-range correlations would have produced significantly higher DFA values and should be recommended for cueing.

During the post-cue walking tasks, arm swing velocity was significantly higher after the music condition than after the regular metronome condition. Although statistical significance was not reached, it appeared that stride length values were longer after the music condition as well. This provides evidence for the potential to retain improved gait parameters following music. Longitudinal training studies are needed to further evaluate carry-over and long-term motor effects.

Secondary statistical analyses were performed to directly compare the effects of walking to the fractal metronome and music. Similar results were found to the regular metronome and music comparison in that music significantly improved stride length and arm swing velocity compared to the fractal metronome and baseline. Velocity was different from baseline in music as stated previously and not during the fractal
metronome. Interestingly, the velocity during music was not significantly faster than during the fractal metronome as it was when compared to the regular metronome. This may be attributed to the fact that the fractal metronome had a higher arousal rating than the regular metronome. The fractal metronome also improved the temporal structure of gait variability more so than music, and from baseline as previously stated. No carry-over effects were found apart from music increasing arm swing velocity from baseline.

Baseline gait characteristics were determined during each participant’s five-minute no cue walking condition. Several significant gait parameter differences were identified between PD and HOA control groups during this condition. The PD group walked slower, with shorter strides, and decreased arm swing velocity. These findings are consistent with the current literature on PD gait.\textsuperscript{1,16} Stride time DFA values were lower in the PD group compared to the HOA group, yet the difference was not statistically significant. This may in part be due to low UPDRS gait disturbance ratings (question #29: 0.6 ± 0.83) and the early disease stage of the PD participants (H&Y: 2.3 ± 0.65), as gait difficulty often arises later in the course of disease.\textsuperscript{16}

While PD and control stride time DFA values were not statistically different from each other, they both exhibited a breakdown in the fractal scaling of gait when compared to previously reported values of healthy young controls,\textsuperscript{54} more so in PD. Our results coincide with the current literature demonstrating that fractal scaling decreases with maturation in older adults\textsuperscript{101} and becomes further uncorrelated in neurologically impaired populations such as PD.\textsuperscript{50,102}

**Limitations**

There are several limitations in the present study. The duration of walking trials was limited to five minutes due to the number of conditions tested and PD population
restraints. It would be ideal to assess fractal scaling measures over a longer time-series. Walking was performed around the perimeter of an indoor gym in a repeated counterclockwise pattern, therefore, gait measures were recorded as participants were continuously slightly turning left. We opted not to use treadmill however, as it is inherently a sensory cue. This study included all PD subtypes, however auditory cueing may be most relevant to the PIGD subtype. PD participants were asked to perform the protocol on-medication to assess the impact of cueing during their usual functional state. It would have been more informative about the nature of the disease to perform the protocol off-medication. The translation of our music results cannot be applied to all music as our results are limited to this one specific piece. Future work is needed on various genres of music also taking personal preference into account.

**Conclusions**

Specific aim one revealed that the use of a fractal metronome acutely re-instates long-range correlations in stride time fluctuations to levels found in healthy young adults whereas the commonly utilized regular metronome, drives scaling levels down to levels found in fallers and freezers. Specific aim two revealed that music, as an auditory cueing modality, is superior to a regular metronome as evidenced by the improvement in many spatiotemporal parameters of gait, some of which were retained post cue. Additionally, when participants were asked to rate their willingness train under the three auditory conditions, music was rated the highest. Regardless of how well an intervention works, its effectiveness ultimately depends upon patient compliance. Collectively, our results indicate that the ideal auditory cue is an upbeat musical selection composed of human generated rhythms containing long-range correlations.
with fractal dynamics. Future studies should be performed to determine optimal musical selections for auditory cueing in PD.
APPENDIX
AFFECT GRID


12. Foundation NP. [http://www.toolkit.parkinson.org/content/diagnostic-criteria](http://www.toolkit.parkinson.org/content/diagnostic-criteria).


BIOGRAPHICAL SKETCH

Kristen Sowalsky received her Bachelor of Science degree at Appalachian State University in 2002. She then went on to Logan College of Chiropractic to receive her Doctor of Chiropractic in 2006 after which, she practiced for six years. Her experience in practice inspired her to research movement in the aging population, in particular those with Parkinson’s disease. She enrolled in a doctoral program at University of Florida in 2012 in order to become a research scientist.