To my family
ACKNOWLEDGMENTS

I would like to thank my parents, for their continued support and love. I thank my mentor, Chris Hass, and fellow lab members for their assistance and guidance throughout my time here. Lastly, I would like to thank Taylor for starting and finishing this journey with me.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACKNOWLEDGMENTS</td>
<td>4</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>7</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>8</td>
</tr>
<tr>
<td>LIST OF ABBREVIATIONS</td>
<td>9</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>11</td>
</tr>
<tr>
<td>CHAPTER</td>
<td></td>
</tr>
<tr>
<td>1 INTRODUCTION</td>
<td>13</td>
</tr>
<tr>
<td>Background</td>
<td>13</td>
</tr>
<tr>
<td>Specific Aims</td>
<td>18</td>
</tr>
<tr>
<td>Specific Aim 1</td>
<td>18</td>
</tr>
<tr>
<td>Central Hypothesis 1</td>
<td>18</td>
</tr>
<tr>
<td>Specific Aim 2</td>
<td>18</td>
</tr>
<tr>
<td>Central Hypothesis 2</td>
<td>18</td>
</tr>
<tr>
<td>2 REVIEW OF LITERATURE</td>
<td>19</td>
</tr>
<tr>
<td>Parkinson’s Disease</td>
<td>19</td>
</tr>
<tr>
<td>Neuropathology of Parkinson’s Disease</td>
<td>19</td>
</tr>
<tr>
<td>Locomotor Disturbances in Parkinson’s Disease</td>
<td>24</td>
</tr>
<tr>
<td>Gait Variability and Parkinson’s Disease</td>
<td>28</td>
</tr>
<tr>
<td>Muscle Weakness in Parkinson’s Disease</td>
<td>32</td>
</tr>
<tr>
<td>Human Movement and Force Variability</td>
<td>36</td>
</tr>
<tr>
<td>3 METHODS</td>
<td>41</td>
</tr>
<tr>
<td>Participants</td>
<td>41</td>
</tr>
<tr>
<td>Experimental Protocol</td>
<td>42</td>
</tr>
<tr>
<td>Maximum Voluntary Contraction (MVC)</td>
<td>45</td>
</tr>
<tr>
<td>Constant Isometric Force Task</td>
<td>46</td>
</tr>
<tr>
<td>Data Processing</td>
<td>46</td>
</tr>
<tr>
<td>Gait</td>
<td>46</td>
</tr>
<tr>
<td>Maximum Voluntary Contraction (MVC)</td>
<td>47</td>
</tr>
<tr>
<td>Variation of Force</td>
<td>47</td>
</tr>
<tr>
<td>Statistical Analysis</td>
<td>47</td>
</tr>
<tr>
<td>Spatiotemporal Variability</td>
<td>47</td>
</tr>
<tr>
<td>MVC Testing</td>
<td>48</td>
</tr>
<tr>
<td>Force Control</td>
<td>48</td>
</tr>
</tbody>
</table>
4 RESULTS ........................................................................................................50
  Strength and Force Variability ....................................................................50
    Maximal Muscular Strength .....................................................................50
    Isometric Force Control ........................................................................50
  Spatiotemporal and Gait Variability ............................................................51
  Correlation ................................................................................................51

5 DISCUSSION ................................................................................................68
  Strength Deficits Associated with Parkinson’s Disease ...........................68
  Increased Force Variability Associated with Parkinson’s Disease ..........70
  Stride to Stride Variability .......................................................................73
  Relationship between Muscular Capabilities and Gait Variability ..........74
  Clinical Significance ................................................................................78
  Limitations ...............................................................................................78
  Conclusion ................................................................................................79

LIST OF REFERENCES ...................................................................................81

BIOGRAPHICAL SKETCH ..............................................................................95
<table>
<thead>
<tr>
<th>Table</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-1</td>
<td>Participant characteristics and demographic information.</td>
</tr>
<tr>
<td>4-1</td>
<td>Maximal isometric force production.</td>
</tr>
<tr>
<td>4-2</td>
<td>Spatiotemporal Variability (CV)</td>
</tr>
<tr>
<td>4-3</td>
<td>Spatiotemporal Means</td>
</tr>
<tr>
<td>4-4</td>
<td>Correlation matrix between over ground gait and treadmill variability and force control parameters for cohort</td>
</tr>
<tr>
<td>4-5</td>
<td>Correlation matrix between over ground gait and treadmill variability and Maximal isometric force parameters for cohort</td>
</tr>
<tr>
<td>4-6</td>
<td>Correlation matrix between over ground gait and treadmill variability and force control parameters for HOA</td>
</tr>
<tr>
<td>4-7</td>
<td>Correlation matrix between over ground gait and treadmill variability and maximal isometric force parameters for HOA</td>
</tr>
<tr>
<td>4-8</td>
<td>Correlation Matrix between over ground gait and treadmill gait variability and force control parameters for PD</td>
</tr>
<tr>
<td>4-9</td>
<td>Correlation Matrix between treadmill gait variability and maximal isometric force parameters for PD</td>
</tr>
<tr>
<td>Figure</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>4-1</td>
<td>HAB Force Variability</td>
</tr>
<tr>
<td>4-2</td>
<td>HAD Force Variability</td>
</tr>
<tr>
<td>4-3</td>
<td>HE Force Variability</td>
</tr>
<tr>
<td>4-4</td>
<td>HF Force Variability</td>
</tr>
<tr>
<td>4-5</td>
<td>AP Force Variability</td>
</tr>
<tr>
<td>4-6</td>
<td>AD Force Variability</td>
</tr>
</tbody>
</table>
LIST OF ABBREVIATIONS

- AD: Ankle Dorsiflexors
- ADL: Activities of daily living
- ANOVA: Analysis of variance
- AP: Ankle Plantar flexors
- CV: Coefficient of variation
- GV: Gait Variability
- GPe: Globus pallidus externus
- GPi: Globus pallidus internus
- HAB: Hip abductors
- HAD: Hip adductors
- HE: Hip extensors
- HF: Hip flexors
- H&Y: Hoehn and Yahr
- MLR: Mesencephalic locomotor region
- MVC: Maximum voluntary contraction
- OFF Meds: After 12-hour withdrawal of dopaminergic medication
- ON Meds: While optimally medicated
- PD: Parkinson's Disease
- PN: Peripheral neuropathy
- PIGD: Postural instability and gait difficulty
- PPN: Pedunculopontine nucleus
- SNpc: Substantia nigra pars compacta
- SNpr: Substantia nigra pars reticula
- STN: Subthalamic nucleus
UPDRS
Unified Parkinson’s Disease Rating Scale
Parkinson’s disease (PD) is the second most common neurodegenerative
disease. Individuals with PD typically exhibit deficits in motor function, including slow,
shuffling steps, stooped posture and muscle weakness. One of the most significant
consequences of a disturbed gait is the increased incidence of falls. Gait variability (GV)
is one of the only measures that is related to one’s risk of falls. Therefore, the primary
aim of the project was to investigate the differences in joint behavior, in regard to
strength and force variability, in an attempt to ascertain contributing factors of the
increased GV in persons with Parkinson’s disease.

Thirteen participants with idiopathic PD who were being treated with stable doses
of orally-administered levodopa therapy and 13 age matched controls participated in
this study. All participants performed two randomized sessions of testing on separate
days separated by maximum of 1 week: Once performing gait analysis and once
performing motor control task. During session 1, we assessed locomotor performance
by) the magnitude and variability of the stride length, step width and stride time during
normal over ground and treadmill walking. Session 2 consisted testing lower extremity
muscle strength (in terms of maximum voluntary contraction; MVC) testing and relative
force control (5, 10 and 20% of MVC) during isometric contractions.

Diminished isometric force production was observed in those with PD (p<.05). The diminished capabilities in the lower extremity lead to a higher coefficient of variation in force control in the joints of the lower extremity, specifically for hip flexion and ankle plantar and dorsiflexion (p.<05). There was a moderate correlation found between force variability in muscle control and temporal variability observed in gait in those with PD.

The findings from this investigation may have important implications for both clinicians and researchers. Interventions should emphasize increasing lower extremity strength or force production and introducing fine motor task into a therapeutic or rehabilitative or clinical paradigm to reduce the probability of falls and increase quality of life.
CHAPTER 1
INTRODUCTION

Background

Parkinson’s disease (PD) is a progressive neurodegenerative disease that affects over one million Americans and upwards to ten million people worldwide (39); PD is the second most common neurodegenerative disease with approximately 60,000 new Americans diagnosed each year (39). Depletion of dopamine-producing cells in the substantia nigra leads to the manifestation of the cardinal symptoms of PD: resting tremor, rigidity, akinesia(bradykinesia, and postural instability and gait disturbance (PIGD). A number of studies of parkinsonian gait have focused on traditional measures of gait, i.e., gait speed, 6 minute walk, etc..., in order to better understand the effect of a particular intervention (e.g., physical therapy) or understand the ambulatory limitations associated with the disease. However, most clinical observations are not comprehensive enough to detect subtle alterations in gait. Early in the disease gait disturbances are negligible but become a major influence on one’s of quality of life in the later stages; therefore early detection of gait disturbances may only become noticeable when the gait is quantitatively analyzed to examine all aspects of locomotion.

Individuals with PD typically exhibit a characteristic slow gait, often coupled with reduced stride and step length (shuffling gait), a forward-stooped posture and a reduced and asymmetrical arm swing (6, 67, 68, 123). Unfortunately these disturbances in gait progressively worsen as the disease progresses (86, 155). Further, the severity of impairments often worsen with task difficulty (e.g., gait, GI, gait termination, turning. Thus, gait disturbances or abnormalities are among the most disabling symptoms of PD. Gait impairments in PD lead to higher metabolic demand (132), increased relative
effort to perform activities of daily living (ADL) (153) and often result in deleterious decline in mobility and physical activity (60, 155). Not surprisingly, gait impairments have detrimental effects on self-reported motor and psychological quality of life and contributes to decreased functional capacity.

One of the most significant consequences of a disturbed gait is the increased incidence of falls (16, 147). As expected as gait impairment worsens and falls become increasingly common as the disease progresses. Between 40-70% of persons with PD fall during the course of their disease, often resulting in fractures and if hospitalized, they face high morbidity and mortality (128, 153, 173). Unfortunately, research as shown that having a prior history of falling can increase the chance of falling again up to 50% in the months following (128) and 40% within the year (76). Fear of falling or fear of reoccurrence of falling, a self-induced symptom can also lead to kinesiophobia and a reduction in general activity. Reduced physical activity not only leads to declines in musculoskeletal fitness but also drastically increases the risk of cardiovascular disease (139) and increases the difficulty during routine ADL (6, 37, 153). Falls in PD are multifactorial, resulting not only from various disease-specific gait complications (e.g. freezing of gait, shuffling feet)(6), but also from generic age-related risk factors, such as sarcopenia and osteoporosis (164, 165). However, it is uncertain as to why those with PD are more prone to fall. As previously mentioned, many features specific to PD contribute to an increased fall risk: disease severity, polypharmacy, slower ambulation, freezing of gait, rigidity and dyskinesia’s. These features have been associated with falls, either as direct cause of falls or as marker of underlying vulnerability (173). One of the only measures or risk factors that has been shown effective to predict future falls
and serve as a potential utility as a predictive measure of dysfunction in PD is increased gait variability (72, 147).

Gait variability, the stride-to-stride fluctuations in walking, is a quantifiable feature of walking that is altered (both in terms of magnitude and dynamics) in many clinical populations, such as PD (15, 70, 147). Gait variability has been shown to be a sensitive measure, related to pathology (73) aging (98), and instability (166). Quantifying gait variability also serves important clinical applications that are sensitive enough to identify the subtle pathological gait impairments preceding more readily observed spatio-temporal changes (71, 75); as well as discriminates between older adults with and without mobility and cognitive impairment (71, 72, 174).

Evidence suggest, among fallers, these stride-to-stride fluctuations are increased (76, 165) suggesting a possible role for quantitative measures of gait variability in fall risk assessment. Decades of conventional evidence support that there is an inverse relationship between gait variability and falls (21, 64, 70). For example, Guimaraes and Isaacs observed increased spatiotemporal gait variability in older patients with a history of falls, compared to non-falling older adults (64). Additionally, Hausdroff and colleagues found specific measures of gait variability (e.g., stride and swing time variability) were significantly increased in older adults who fell during a 1 year follow up (76). Hausdroff additionally investigated the relationship between gait variability and predictors of physical performance and functional status as well. In general, the investigation found increased variability correlated with poor health status and decreased performance (76). Thus, previous research clearly documents that gait variability can serve as a useful utility to predict those who are at risk of falling.
A considerable amount of literature has been published on gait variability in those with PD. These studies have demonstrated increased spatial and temporal variability during gait (15, 72, 73, 149). Interestingly, increased gait variability can be seen throughout the disease, even in patients who were only recently diagnosed with PD (72, 155). Similar to the progressive impairment in spatiotemporal patterns of gait performance, the magnitude of the variability increases with disease severity (15, 155). Blin and colleagues observed higher variability in stride length in parkinsonian patients as a function of the clinical stages of Hoehn and Yahr (15) (PD disease severity rating scale). Despite a long list of clinical and literature based evidence to suggest increased gait variability and the consequences that follow in PD populations, the underlying neurophysiological basis of gait variability is still poorly understood.

Investigation of joint behavior i.e., muscle strength and motor control could provide evidence for a more accurate understanding of the underlying mechanisms that contribute to increased gait variability in those with PD. Recent research has suggested that compared to neurologically healthy individuals, persons with PD produced lower extremity force (47), increased co-contraction of muscles (90), specifically at the ankle (13, 37) and displayed increased force production variability (37, 115, 138). Those with PD often have difficulty regulating the amount of force that is required, which could potentially lead to hypometric movements that undershoot the intended goal (42, 65, 115, 158). Sheridan et al. were among the first to speculate that the magnitude of muscle force in PD may not be under scaled but perhaps more variable due to an inability to regulate force in a consistent manner (149). The extant literature supports that damage to structures such as the basal ganglia, cerebellum, or frontal cortex may
interfere with smooth execution of movement, thus potentially leading to increased variability or “noise” in the movement (5, 12, 71, 73, 158). In view of all that has been mentioned so far, my general hypothesis is that the deficits in strength and motor output variability in the lower extremity could potentially lead to increased gait variability in those with PD.

Gait variability is not only related to falls but is one of the only predicative measures for future falls. In spite of the relative importance of gait variability we don’t fully understand underlying neurophysiological basis of gait variability. It is undeniable that a more complete understanding on how variability in force control and strength may influence gait variability in persons with PD is needed. This knowledge could also provide important insight into both the pathologic and age-related alterations in the locomotor control system and motor control of gait, and in improving objective measurement of fall risk and functional status. Therefore, the primary aim of the proposal was to investigate the differences in joint behavior, in regard to strength and motor output variability, in an attempt to ascertain contributing factors of the increased variability observed during gait in persons with PD.

We proposed that this study would provide significant information on the role of strength and motor output variability in connection with gait variability observed in those with PD. Maximal strength, force control, and gait variability are all important parameters of human movement, so it might be predicted that the three parameters would be interrelated. Further, we anticipated that joint specific motor output variability would provide significant insight on potential compensatory mechanisms in those with
PD. Expanding our understanding of motor output variability will provide important information that will ultimately guide appropriate intervention strategies.

**Specific Aims**

**Specific Aim 1**

Determine whether the magnitude and variability of muscle force and motor control abilities differ across the prominent lower extremity joints in persons with PD when compared to neurologically healthy adults.

**Central Hypothesis 1**

We hypothesized that the maximum force produced by those with PD would be lower than their neurologically healthy peers. Additionally, while motor output variability may be similar during coupled movements (flexion and extension, abduction and adduction) at the specific joint, motor output variability would be higher in those with PD.

**Specific Aim 2**

Determine the relationship between the 1) maximal isometric muscle strength in the lower extremity, 2) variability of isometric force, and 3) gait variability observed during over ground gait.

**Central Hypothesis 2**

Strength and variability in force control would significantly relate to stride to stride gait variability.
Parkinson’s Disease

Parkinson disease (PD) is a progressive neurodegenerative disorder caused by a depletion of dopamine-producing cells within substantia nigra that leads to a variety of both motor and non-motor features. The cardinal symptoms of PD include resting tremor, rigidity, akinesia/bradykinesia, and postural instability and gait disturbance (PIGD). The combination of aging, disease specific degeneration, and sedentary lifestyle is often manifested by reductions in muscle strength and postural instability, leading to a decreased functional capacity and an increased risk for falls (37). Difficulties with gait and posture can be one of the most disabling disturbances (1, 6, 108), leading to decreased mobility and increased risk of falling but also significant reduction in quality of life (16, 162). It has been estimated that nearly 70% of persons with PD fall during the course of the disease, which often resulting in hospitalization (128, 164). The lack of physical activity as a secondary consequence of fear of falling can also substantially shorten life expectancy for persons with PD (16). Thus research has been driven to improve the quality of life for persons with PD. A large portion of research studies have evaluated the underlying mechanisms that ultimately contribute to gait and posture deficits and have focused on the evaluation of intervention strategies designed to reverse or alleviate motor deficits associated with the disease.

Neuropathology of Parkinson’s Disease

Over the past several decades, the neuropathology of parkinsonian motor features and the relationships to dysfunction of the basal ganglia and other subcortical structures have becoming increasingly well understood (3, 9, 106). The basal ganglia
are a multifunctional group of subcortical nuclei that form a major center in the complex extrapyramidal motor system. The subcortical structures of the basal ganglia include the striatum, pallidum (globus pallidus internus, GPi and Globus pallidus externus, GPe), subthalamic nucleus (STN), substantia nigra pars reticula (SNpr) and substantia nigra pars compacta (SNpc). The basal ganglia is responsible for a vast series of connections that transmit signals throughout the brain that are involved in many neural pathways contributing to emotional, motivational, associative and cognitive functions. The basal ganglia interact largely with other cerebral motor structures, including the cortex, midbrain, thalamus, and cerebellum, to execute and coordinate voluntary movements such as gait (3, 50, 77). The past thirty years have seen increasingly rapid advances in the understanding of basal ganglia circuitry, outlining not only connections within subcortical structures but also interactions between the basal ganglia and multiple areas of the cortex. Pivotal research was performed in an attempt to explain the complex nature of basal ganglia organization. Using primate models, Delong proposed that basal ganglia function was to control excitation and inhibition of cortex, therefore requiring two distinct pathways: a direct pathway (Cortex → striatum → GPi) which subsequently facilitates the desired motor program for execution of the selected action by exciting the cortex; and an indirect pathway (Cortex → striatum → GPe → STN → GPi) which inhibits motor-cortical firing to suppress competing motor programs (41). This concept was later expanded on to include a shorter route of the indirect pathway (154) (cortex → striatum → GPe → GPi). In addition to the original two pathways, a third pathway, the hyperdirect pathway (Cortex → STN → GPi) was proposed and is thought to reset the system by suppressing both intended and competing actions by inhibiting activity of the
motor cortex (113). The central ideology of basal ganglia organization or functional segmentation of the pathways was conceived based upon evidence that structural convergence and functional integration occurs within, rather than between, each of the identified pathways.

Dopaminergic-cell loss in the substantia nigra disrupts the normal function of the basal ganglia. The basal ganglia circuitry is charged with selecting the motor program and dopaminergic disruption leads to abnormalities in both the spontaneous and sensorimotor responses of neurons in the basal ganglia (40, 42). The resulting effect on basal ganglia circuitry leads to improper enhancement of desired motor programs and faulty inhibition of competing programs. Specifically, the dopamine-deficiency state is associated with excessive excitation through the “indirect” pathway, resulting in excessive glutamatergic drive to the GPi and SNpr and reduced inhibition by “direct” connection from the striatum, which further disinhibits the activity of the GPi and SNpr.

As previously mentioned, the cardinal symptoms of PD are dysfunctional gait, rigidity, bradykinesia, and postural instability. It has been suggested that the excessive thalamic inhibition leads to suppression of the cortical motor system, which could result in akinesia, rigidity, and tremor. However, the inhibitory descending projection to brainstem locomotor areas may contribute to abnormalities of gait and posture (57, 93). Researchers have found that the upper brainstem contains neurons which control both axial and proximal limb musculature for gait through their projections to the lower brainstem and spinal cord via bilateral, midline, descending pathways. Dopaminergic dysfunction has devastating consequences on the structures of the basal ganglia that project into the brainstem; thus it is likely the brainstem motor areas may also be
adversely affected. One structure, the pedunculopontine nucleus (PPN) which is part of the so-called mesencephalic locomotor region (MLR), has been the target of increased research due to its involvement in the regulation of locomotion (18, 94, 103). The PPN provides cholinergic inputs to the basal ganglia, thalamus, cerebellum, several brainstem nuclei, and the spinal cord to influence the initiation, speed manipulation, and termination of gait. Recent investigations have attempted to identify the significance of PPN role in locomotor control in those with PD; as observed by Masdeu and colleagues, who described the inability of a patient, who emphasized damage to the PPN, to stand and to generate stepping (103). A significant amount of research has suggested that gait dysfunction in PD may result from multisystem degeneration, which include degeneration of the PPN (6, 17, 18, 94). These investigations have found evidence that PPN degeneration is a major factor leading to impaired postural control and gait dysfunction in PD (17, 18). Further, research on the influence of PPN has produced intriguing results that suggest that dysfunction of the PPN may be a major contributor to the freezing of gait (FOG) phenomenon frequently observed in persons with PD (53, 96).

The understanding of PD has evolved to include degeneration of other catecholaminergic systems. Increasing anatomical, pathophysiological and clinical evidence suggested that the cerebellum may contribute substantially to the clinical symptoms of Parkinson’s disease due to the dopaminergic projection from the ventral tegmental area/substantia nigra pars compacta. The cerebellum and basal ganglia are two major subcortical structures that have distinct connections with largely overlapping cortical areas and have been shown to influence multiple aspects of motor, cognitive
and affective behavior. Due to the speculated connections with both the thalamus and the PPN, abnormal cerebellar function has been suggested to also contribute to some of the locomotor changes that occur in persons with PD. Recent investigations have demonstrated pathological changes in the cerebellum following dopaminergic degeneration (141). The cerebellum, specifically the cerebellar locomotor region, which is thought to regulate speed and gives rhythmical impulses to the brainstem and spinal cord, remains a largely unexplored area of research in parkinsonian gait. However, emerging imaging research suggest that those with PD demonstrate exhibited altered activity in the cerebellum (124). Both hyperactivity and hypoactivity of the cerebellum has been observed in persons with PD when walking (66, 80, 110). This altered cerebellar hyperactivity may act to influence cortical mechanisms as necessary compensation for motor control dysfunction of the basal ganglia. For example, Hanakawa et al. found hypoactivation in the left cerebellar hemisphere and suggested it may cause the small shuffling steps seen in parkinsonian gait. Additionally the authors found hyperactivity in the vermis of the cerebellum and could be compensatory effect to maintain better motor and non-motor functions (66). However, the observed abnormal cerebellar function may limit adaptability of gait in PD. Jayaram and colleagues observed cerebellar depression is proportional to the ability to learn and store different gait patterns (81). Thus, altered cerebellar function in PD may contribute to the inflexible gait pattern in parkinsonian gait. The mounting evidence in PD research has added to the understanding that PD is a result from multisystem degeneration and the gait and postural dysfunction in persons with PD seems to be manifested as a multifactorial motor complication involving cortical, subcortical, and cerebellar structures of the brain.
Locomotor Disturbances in Parkinson’s Disease

Efficient human locomotion is a coordinated and complex system of muscle firings and limb movements that produce stable gait and highly consistent walking patterns. The system is regulated by a complex, multi-level neural control system that involves input from the motor cortex, cerebellum, brainstem and basal ganglia. Recent work as shown that gait and postural control has been shown to relate to quality of life, morbidity and mortality (7, 119, 163). Fear of losing the ability to ambulate independently or even to stand or sit in an upright position is prominent and significant concern after the diagnosis of PD. Persons with PD (particularly those classified as PIGD) experience a wide variety of debilitating gait disturbances resulting from aforementioned neurological deficits intrinsic to the basal ganglia and as consequent disruption of signal transmission to structures downstream from these nuclei (6).

During normal gait the lower limbs are charged with two major task; 1) supporting the body against gravity and 2) generating movements to propel the body forward (177, 179). Previous research has shed insight on the functional roles and contributions the muscles at the hip, knee and ankle share during gait (145, 146, 177-179). Muscles of the hip have been primarily characterized as drivers of forward acceleration of the trunk, support during the stance and contribute to forward propulsion (144, 146, 179). The ankle shares many similarities to the hip (in the sagittal plane) in regard to gait. The ankle has been shown to propel the trunk forward and upward, as well as an accelerator which facilitates the movement of the leg into the swing phase (146). Unlike the hip and ankle, the role of the knee is basically to absorb energy during the stance phase, providing stable locomotion rather than being an important source of either control or propulsion (144, 145, 178, 179). Since the primary task of the muscles at the hip and
ankle during gait are to provide support against gravity and contribute to propulsion, examining the control of force at both the hip and ankle may help explain deficits associated with gait in older and pathologic populations and assist in clinical evaluations, rehabilitation and treatment.

As previously mentioned, dysfunctional gait is a common and debilitating symptom of PD, which is characterized by spatial and temporal disturbances when compared with neurologically healthy adults (6, 67, 72, 74, 155, 164). Gait disturbances in PD are typically viewed as either episodic or continuous (6). Episodic events are unpredictable disturbances that occur infrequently and abruptly. These include: festination, hesitation of gait, and freezing of gait (FOG) (6, 16). The unpredictable nature of these events hinders the patient’s ability to adapt to the transient changes in locomotion. Further, these disturbances are often lead to increased incidence of falls, anxiety, fear of falling, and avoidance behavior (1, 86, 164, 181). Gait festination, which is characterized by rapid, hypometric steps that gradually minimize step length while in forward motion and increase double-limb support time. When festination is present, there is an increase in stepping velocity to the state of running which is an attempt to compensate for the hypokinetic steps and prevent falling. The exact cause of the abnormal scaling of gait parameters and dysrhythmic nature of the parkinsonian gait remains unclear, research has suggested that increased stride-to-stride variation could be associated.

Continuous gait disturbances are persistent disturbances that may be the result of neuronal or peripheral dysfunction (6, 16, 58). An example of a continuous gait disturbance is Parkinsonian gait. Parkinsonian gait is characterized by decreased
velocity with hypometric steps (67, 68, 109); increased double-limb support (108, 109); diminished arm swing (95); and decreased dynamic stability (86, 112). Patients often attempt to compensate during continuous gait disturbances by altering their movement pattern to account for the disease specific impairments.

As PD progresses, the features of episodic and continuous often worsen, therapeutic effect of medication wanes, and gait impairment becomes increasingly for more frequent and disabling (38). The decline in gait function generally coincides with loss of independence and increased mortality risk. Although the classification of episodic and continuous events is relatively straightforward there appears to be an underlying association that episodic gait disturbances may be related to continuous and transient changes that may also be occurring in a given patient. For example, Plotnik et al. suggest that although FOG is an episodic event, there is ongoing gait impairment in those who experience FOG compared to those who do not (129, 181). Additionally, Peterson et al. demonstrated in those with PD stepping coordination was significantly worse in freezers compared to non-freezers and controls (125). Since these subdivisions of gait disturbances may co-exist, determination of a complete, multidimensional understanding may help to inform the clinical diagnosis and effective treatment and rehabilitation.

A primary concern of fall prevention is the ability to maintain postural stability during transitions between states of static and dynamic equilibrium, such as during gait initiation, termination, or turning. Evidence suggest that persons with PD, there is a decreased ability to internally control the center of mass (COM) during self-directed activities such as initiating gait, turning, and stopping, and this inability is commonly
associated with falls (27, 52, 69, 140, 143, 153). Each task involves control of the COM whether in response to unexpected perturbations or to planned transitions. This inability to self-regulate postural changes manifests in deficits observed in gait initiation (GI) and gait termination. Research suggest that effective transition from static to dynamic states or vice versa, i.e. GI and GT, can begin with interplay of COM and center of pressure (COP) to separate (GI) or come together (GT) (82). The COP-COM distance measured at a given time may enhance our interpretation of the COP and COM displacements and provide better insight into postural control. Recent studies have found evidence of altered COP-COM displacement in PD during GI (52, 69, 102). The impairments in these transitional states could reflect a need to preserve stability because of impairments in postural control and/or an inability to generate adequate momentum, due to underlying muscle weakness, inappropriate neural drive or neural command (48).

The ability to walk about in a safe and efficient manner is essential for an independent and productive life (118). Gait impairment is a common consequence of Parkinson's disease (PD) that becomes more and more critical with the progression of the disease, in spite of the medication available. For individuals with PD, restoration of walking ability is a primary concern. While many aspects of walking behavior garner the attention of clinicians, gait speed has been singled out as an important target symptom because of its relevance to community independence, and its predictive value for consequential health outcomes and mortality (2, 118, 119). A decreased walking velocity has been associated with disability and falls are a significant cause of injury in people with PD (67, 118, 173). Reductions in stride length is a primary contributor to overall slowness in PD, while temporal characteristics of gait are not (5, 72, 109, 123).
Decreased stride length has been suggested to be a compensatory strategy to maintain stability by limiting the displacement of the COM relative to the base of support.

Interestingly, select research has demonstrated healthy participants increased stride length with each increase in cue rate, whereas PD groups lacked the ability to modulate step length regardless of temporal demand (5). This inability to adapt specific gait patterns suggest underlying pathology in those with PD that increase their susceptibility to falls.

**Gait Variability and Parkinson’s Disease**

Gait analysis, over the course of the past few decades, has transitioned from an almost purely academic discipline to now being a necessary instrument for therapeutic/rehabilitative management for aging adults, orthopedic issues, and those patients with walking disorders. One key characteristic of almost all movements is variability. Historically, gait variability (GV) as seen in stride-to-stride fluctuations has served as a marker for gait performance in addition to further predict future mobility status (7), cognitive status (101), and falls (28, 76). Research suggests that gait variability may provide a more discriminative measure of gait performance than routine spatio-temporal measures such as average gait speed or step time (20, 22). For example, variability in spatiotemporal parameters has been reported to predict mobility deficits and future falls better than the mean of spatiotemporal parameters in older adults (21).

GV was originally thought to be the result of random processes (noise) of instrumentation or physiological noise. However, more recently variability is thought to convey information about the complex nature of the locomotor system that reflect the underlying neural control of gait with demonstrated sensitivity to pathological and ageing
processes (26, 71, 149, 151). Different parameters are used to describe GV. For example, stride time variability reflects the ability to generate consistent rhythmical step cycles, whilst variability in step width and double limb support (DLS) (time spent with both feet in contact with the floor), reflects postural control mechanisms during gait.

Differences in locomotor variability between elderly and young walkers have been previously demonstrated. Early research from Gabell and colleagues quantified variability as CV in stride time, double-support time, step length and stride width and reported no difference in gait variability between younger and older adults (56). However, other groups have reported differences in gait variability between younger and older age groups. For example, Guimaraes and Isaacs found a more variable step length in the elderly when compared to a young group (64). Grabiner et al. observed higher variability in stride width, stride time, stride length and velocity and an increase of stride width variability in older adults (61). Hausdorff et al reported that variability in temporal gait parameters was significantly increased in the elderly compared to the young and it was even larger in a group of elderly fallers (74). Several studies have reported that increased variability of several gait parameters is related with an increased risk of falling in the elderly (22, 76, 99). These results have been attributed to a possible loss of motor control, declining torque production and decline in mobility (6, 22). Based on the above, it can be proposed that the increased falls due to aging may be due to the inability of the elderly to compensate to the natural stride-to-stride variations present during locomotion. In other words, the elderly have increased local instability in stride-to-stride variability.
Despite the mounting evidence supporting use of gait variability, there is no agreed standardized protocol for measuring gait variability, as evidenced by discrepancies in number of strides, instrumentation and inconsistencies in which spatiotemporal measures are reported. The situation is further confused by how to quantify variability e.g., standard deviation (SD), coefficient of variation (CV). Take for example, CV, (SD/mean?100%), is a statistical measure of dispersion of a probability distribution. CV as used to describe variability, is often used to evaluate reliability of measures including gait outcomes and gait variability itself (7). However, another measure of variability that is often reported is SD, a statistical measure used to describe the variation from the mean. Both measures of variability have been used in the literature, however some researchers have proposed that until a consensus can be reached, gait variability should be analyzed multiple ways (7, 98). Regardless, of technique or methodology, measurement of gait variability enhances gait analysis, and future research will compare its utility with other metrics which may prove even more sensitive to early gait pathology.

Traditionally, gait variability has been analyzed using both linear and nonlinear tools. Linear tools reflect the magnitude of variability within the system; this analysis usually reports the range, SD, and CV of a particular time series or in the context walking, over a number of strides. Changes in the CV are indicative of increases or decreases in the amount of relative variability. In the context of this review, gait variability as measured by CV, is related to an individual’s normal variations that occur across multiple strides of gait (70, 73, 84). The use of linear measures of variability is necessary and valuable tool in accessing and identifying the amount of variability,
however linear analysis often limits the understanding of variability and fails to observe how motor behaviors emerge over a period of time (26, 160). Nonlinear tools focus on understanding how variations in the gait patterns change over time and provide crucial information on the structure of the variability. This allows explorations into the mechanisms that are responsible for the state of variability (26, 84, 160). There is increasing evidence that supports the necessity of variability in biological systems, in terms of health and functional movement (160). The relationship between linear and nonlinear tools as described above can provide distinct information on either the structure of the variability or the amount of variability and thus further our understanding of the emergence of functional and adaptive movement.

The compensatory gait mechanisms described earlier in this section require regularity, rhythmicity and symmetry in both function and motor coordination of one leg with respect to both the function and coordination of the opposite leg. The ability to synchronize these processes bilaterally are disrupted in PD, resulting in increased asymmetry (181), diminished bilateral coordination (130), and high stride-to-stride variability (72). Abnormal gait variability has been shown in all stages of the disease, even as early as those recently diagnosed and seems to increase with disease severity (8, 72). Additionally, analysis of stride variability has been shown to be correlated with FOG in persons with PD (114). The increased variability in PD locomotion is not limited to steady-state gait; data from our laboratory has shown that persons with PD also show increased variability in stepping during GI compared with their neurologically healthy peers (140). Previous research has shown a significant connection between increased variability in both gait and GI and falling in a multitude of healthy and pathologic
populations, including PD (73, 76, 98, 140, 147). Thus, reducing abnormally high gait variability may serve as a target for interventions to reduce falling in persons with PD.

**Muscle Weakness in Parkinson’s Disease**

Persons with PD often suffer from debilitating muscle weakness, a decrease in the amount of force generated during a voluntary contraction (36, 51, 136). In addition, power production and muscle endurance are reduced in persons with PD (148, 153, 161). Lower extremity muscle strength has a major effect on mobility. Such weakness has been suggested to compromise the ability to perform ADL in persons with PD (36, 79, 153). Additionally, the decreased muscle strength can lead to falls among elderly and neurologically impaired patients, causing fractures, joint dislocations, severe soft tissue lesions, and head trauma (74, 85, 164). In elderly PD populations, there is an increase in poverty of movement, impaired muscle function, a decrease in cross sectional area and functional capacity compared to early stage PD (54, 136). Although research has shown that difficulties of functional performance may be associated with the progression of the disease, it is unclear if the muscle weakness appears from central or peripheral manifestations. Other non-disease specific factors may influence functional performance as well. For example, reductions in one’s self confidence in one’s ability to perform activates of daily life may restrict physical activity to avoid potential falls and injury, therefore potentially increasing muscular deficits and atrophy.

In combination with the aforementioned symptoms of PD, research suggest these combined deficits can lead to a loss of functional mobility and increased risk of falling in those with PD, when compared to neurologically healthy age-matched individuals (31, 139, 173). Reduction in muscle power is indicative of deficits in strength, movement speed, or both, and has been shown to be closely related associated to
slower walking speed and increased risk of falls (10, 111, 152). Muscle power, the ability to develop force over a period of time, is crucial for maintaining or responding to an external perturbation and avoiding a fall (100). Prior research has observed that people with PD appear to be significantly weaker and less powerful compared to age matched controls (121, 122). Research from Allen et al. demonstrated that individuals with mild to moderate PD were unable to produce leg extensor power equal to that of the non-PD controls throughout a range of relative intensities (4). The authors concluded that muscle weakness contributed to reduce muscle power at all intensities, however reduced power at lighter intensities was associated with a decreased movement speed. Their findings suggest bradykinesia could contribute to reduced leg extensor power at light intensities (4). Muscle power is the product of force over time, therefore it is not surprising that both bradykinesia and weakness could contribute to reduced muscle power in people with PD. However it is still unclear if the central manifestations of PD or is the reduction in the periphery the prime agonist contributing to muscle weakness and reduced power production.

Muscle weakness has been studied by many researchers using a variety of modalities. One of the most reproducible approaches to quantifying muscle weakness is the isometric (stationary range of motion) strength test. Early research from Stelmach et al. examined force production characteristics during isometric contractions in persons with PD. The investigation found that persons with PD had more irregular force-time curves that were characterized by substantially slower initiation of force production (Stelmach, et al., 1989). Originally, these results, at least in part, were considered to be the result of extraneous noise within the nervous system. Nocera et al. measured the
isokinetic (constant angular velocity throughout a range of motion) muscle strength of knee extension and observed isokinetic strength reduction in PD (116). Pedersen et al. assessed and observed lower isokinetic concentric torque of dorsiflexors for patients with PD compared to control subjects (123). Inkster and colleagues also observed reduced hip strength in those with PD and reported that reduced strength contributed to the difficulty experienced rising from a chair (79). Schilling et al. observed strength deficits using multi-joint isometric testing and compared it to functional outcomes (148). The deficits Schilling observed, specifically at the hip and knee, are important for those functional tasks that involve similar muscular actions, i.e. walking (148). However, these finding are not homogenous across all joints and vary depending on the paradigm of the study. For example, Robichaud et al. found greater impairment of extension movements as compared to flexion movements in PD (137). The authors concluded the increased impairments were based on differential impairment of neural activation of agonist and antagonist muscle groups (137). Additionally previous work done in our lab, found that during isokinetic deficits in peak joint torques were isolated to the ankle, moreover ankle plantar and dorsiflexion, compared to healthy controls (153). This reduction in ankle torque lead to redistribution of joint torques across task (153). While the specific mechanisms remain uncertain; those with PD suffer from the inability to select the appropriate motor program to generate forces in an effective way. Despite continued research, it remains unclear if this phenomenon is due to central or peripheral manifestations of PD (25, 37, 65, 117).

Dopaminergic deficits are central to the pathophysiology of PD. The impaired circuitry of the cortico-thalamic basal ganglia loop results in an exaggerated increases in
tonic inhibition of the thalamus and significant reductions in the excitatory drive to the motor cortex. In those with PD, the motor cortices have limited activation due to the abnormal activation from the basal ganglia to thalamus. Thus it is possible the altered excitatory drive could impede facilitation of the desired motor command (40). The reduced activation of the higher centers can lead to inability to fully activate motoneuron pools, thereby hindering the motor unit recruitment and discharge rate. The reduction in motor unit activity, from impaired neural drive could possibly manifest as the observed general muscle weakness (37).

The hypothesis that persons with PD suffer from impaired neural drive can be deduced by analyzing the final target of cortical output, the muscle. The muscles electromyographic (EMG) activation patterns can provide insight into hypothesized impairments that underlie bradykinesia and muscle weakness. In contrast to healthy subjects, differences in EMG parameters have been observed in persons with PD. EMG activation patterns during ballistic and isometric actions are abnormal and reflect impaired activation of the muscle. A variety of abnormal muscle activation patterns during ballistic and isometric movements have been reported. In an investigation from Pfann and colleagues, attempted to clarify the distinct changes observed in EMG parameters in persons with PD. They found a number of irregularities in EMG activity: First, in contrast to healthy individuals those with PD displayed reduced agonist burst duration despite increase in movement distance (126). Secondly, the authors reported extra cycles of agonist bursting during the initial phase of movement and the number of agonist bursts increased in parallel with increases in movement distance in those with PD (126). Jordan and colleagues observed also this phenomenon in persons with PD.
and found that persons with PD were unable to generate an adequately scaled EMG burst to carry out the successful movement (83). As a consequence, they employ a series of small amplitude bursts to complete the movement. Third, the authors found that in those early in the disease they shared similar trend to that observed in healthy individuals. Specifically a similar magnitude of the first agonist burst. However, as the diseases progresses, the magnitude of the first agonist burst is reduced. Lastly, muscle activation patterns show increased variability when compared to gender and age matched healthy individuals (126).

The aforementioned changes in EMG activation in those with PD, specifically the deficits in the variability, intensity, and frequency can be explained in part by the impaired corticospinal activation of the muscle (138, 169). The exaggerated variability in the EMG signal could stem from downstream effects from an increased variability in motor unit recruitment and activation from the abnormal corticospinal activation (37). This increased motor unit variability could be responsible for disrupted relaxation of actively contracting motor units, contributing to both prolonged deceleration phases during movement and prolonged relaxation times during isometric torque generation (65, 172). Additionally, research has shown longer EMG relaxation times have been associated with higher bradykinesia scores in persons with PD (62). Valls-Sole et al. summarized the described impaired motor unit recruitment to be the result of abnormal corticospinal activation and could contribute both to bradykinesia and muscle weakness (172).

**Human Movement and Force Variability**

Human movement variability can be described as the normal variations that occurs in motor performance across repetitions of a given task, including gait, reaching
and grasping task, etc... (7, 33, 70, 160, 169) However, variability is not isolated to “motor task”; variability is recognizable and inherent across a wide spectrum of biological phenomena such as the heartbeat (46, 55, 127, 135). Variability of force control can be determined by calculating accuracy (constant error and root mean square error; RMSE) and variability (SD and CV) of force production. A conventional perspective on variability in the motor control literature indicates that greater variability and error implies less stable and cooperative behaviors in the motor system (32, 149, 160).

The ability to maintain consistent force production in both the upper and lower extremity is essential for many common ADL. Unintentional fluctuations in voluntary contractions can be quantified and observed in terms of movement (end point and trajectory variability) and force control/steadiness (30, 32, 33, 107, 160, 170). Years of research has attempted to gain a deeper understanding of the mechanisms involved in the generation and regulation of muscle force; much of this research has focused on the effects of normal aging and pathology on motor variability (32, 138). Evidence from multiple studies indicate there is an increase in RMSE, SD, and CV in older adults compared to young adults (32, 34, 169, 170). Historically, a number of these investigations have reported on force variability in terms of relative maximal voluntary contraction (MVC) during both isometric and dynamic task. For example, Vaillancourt et al. observed more variable force contractions in older adults at 5, 10, 20, and 40% of their MVC in both isometric and dynamic (sine wave) tasks in contrast to young adult control subjects (169). Additionally, it was found that the variability in the discharge rate of single motor units contributes to the greater force output variability of the older
subjects. Research from Laidlaw et al. extend the prior observation that older adults have greater motor unit discharge variability and greater force output variability compared to young adults during submaximal contractions. Based on the prior observations, the age-associated augmentation in force variability can impair the ability even of healthy older adults to modulate force to changing environments demands and consequently compromise their independence.

Force control in both healthy and pathological individuals has been well-characterized by the motor control literature. Enhanced variability in movements and force control are commonly reported in neurological populations, including PD, essential tremor (ET) and progressive supranuclear palsy (PSP). Typically PD is complicated by several clinical factors which confound motor performance; slow rate of force development and force relaxation, impaired EMG activation and muscle weakness. These deficits often manifest into unintentional variations in force production or maintenance. As previously mentioned, we hypothesize that these deficits often carry over into locomotive task and cause increased stride-to-stride variability in gait.

Complications extend to discrete hand and arm movements as well; during reaching task patients with Parkinson’s disease show greater inherent variability in the endpoints of their movements than do normal subjects. Decades ago Sheridan et al. examined the execution of arm movements in persons with PD. In their investigation, they found that parkinsonian patients performed movements approximately 37% slower than controls, and their movement times were more variable. Most of the variability in the movement was observed during the initial ballistic phase of the movement.
The effects of PD on motor control suggests that motor planning and execution processes are impaired. Although those with PD suffer from muscle weakness, the magnitude of muscle force available to them is not the primary cause of disability, but rather in the inability to consistently produce for any given movement task (149, 150). These deficits are somewhat dependent on the complexity of the task and when multiple motor programs have to be implemented and executed in parallel (11, 35, 50, 65). Benecke et al. first observed that during multi-joint arm movement in PD there may be an inability to separate motor programs which leads to pronounced slowness and bradykinesia (11). Based on the available evidence Sheridan proposed that motor dysfunction in PD involves a number of components; 1) programming and initiating movements, 2) difficulty in maintaining forces for motor programs over time, 3) bradykinesia or slowness of movements and 4) increased variability of movement in both time and space, presumably caused by the inherent variability in force production (150).

Despite extensive research encompassing both gait variability and motor control in those with PD, this literature review outlines an important gap in the literature regarding lower extremity strength and motor control and its relationship with the stride to stride fluctuations in gait. Investigation of lower extremity strength and force control at low forces could provide valuable insight as to how parkinsonian deficits affect gait variability. As gait variability has been shown to be one of the only markers to be predictive of falls, there is merit in exploring the underlying causes of gait variability. These findings could have profound implications in clinical and rehabilitative settings by providing evidence to support whether or not exercise interventions targeted at reducing
low force variability would be useful in combating PD specific gait deficits and provide more clarity to the nature of variability in those with PD.
CHAPTER 3
METHODS

Participants

Thirteen persons with PD (six males and seven females) and 13 (seven males and six females) healthy age-controls (± 2 years) were recruited for the study (Table 3-1). Participants had not experienced any lower-extremity orthopedic injury for at least one year prior to participation. All persons with PD were treated with stable doses of orally-administered levodopa therapy. All participants were provide written informed consent before participating in the study as approved by the University Institutional Review Board. Idiopathic PD was diagnosed by a movement disorders specialist. The initial diagnosis was based on the presence of at least two of three cardinal motor signs of PD: bradykinesia, resting tremor and rigidity, and a demonstrated good response to levodopa medication therapy. A good response to levodopa was defined as a 30% improvement in parkinsonian motor signs. This motor score improvement was based on the Unified Parkinson’s Disease Rating Scale (UPDRS) motor examination sub score, following the administration of levodopa (1.5 times their typical dose) during their screening neurological examination. Such an inclusion criteria was necessary to exclude patients with Parkinson’s plus syndromes (such as progressive supranuclear palsy, multiple system atrophy, striato-nigral degeneration, corticobasal degeneration, and Lewy body disease). The inclusion criteria include:

- Age between 60-90 years.
- Physically healthy by exhibiting pain-free range of motion of the arms and legs and by reporting no orthopedic or neurological problems.
Exclusion criteria for all participants include:

- Failure to meet the inclusion criteria.
- Loss of vision, peripheral neuropathy, vestibular dysfunction, or those taking medications affecting balance or alertness /attention.
- Presence of active unstable medical or psychiatric conditions, diabetes, or any orthopedic condition that would preclude their ability to participate in the exercises.
- Presence of active or unstable/untreated cardiovascular disease.
- Presence of any recent changes in mental and/or physical condition that might affect gait and balance.

**Experimental Protocol**

The experimental design required two testing sessions completed within one week of each other. During both sessions, participants with PD were tested in the optimally medicated state (ON meds). Participants were asked to not participate in any physical activity within the 24 hours prior to both testing visits.

During one of the visits, participants underwent the Unified Parkinson’s disease rating scale while being video-recorded. These videos were scored by a single independent movement disorders-trained neurologist who is blinded to the purpose of the study. After performing the UPDRS, thirty-nine passive retroreflective markers were attached over participant’s boney landmarks in accordance with the Vicon Plug-in-Gait Ai full body marker system. During over ground gait tasks ground reaction forces were collected at 360 Hz using three force platforms (Bertec Corp., Columbus, OH) embedded within a 9-m walkway. Kinematic data was collected at 120 Hz by an 8-camera motion capture system (VICON, Oxford, UK). Kinematic and kinetic collections was time synchronized. During the treadmill gait tasks, participants walked on an instrumented treadmill (Bertec Corporation, Columbus, OH) collecting at 360 Hz.
Kinematic data was collected by an 8 camera motion capture system collecting at 120Hz. The order in which the participants performed the different gait tasks described below was randomized. Fatigue was assessed using a numerically based, self-perceived exertion rating scale (0-10, 0 is no fatigue and 10 is maximal fatigue) at the beginning and end of the testing session. Participants performed 10 over-ground walking trails at both their self-selected speed and fast as possible along the 9-m walkway. Linear measures of gait including; stride length, stance time, step width, and walking speed were calculated using standard definitions according to an algorithm programmed in a custom Matlab program (Mathworks Inc, Natick, Massachusetts). Stride length is defined as the distance traveled by the heel marker along the walking axis from heel-strike to toe-off. Stance time is defined as the percent of the gait cycle between heel-strike and subsequent toe-off of the same limb. Step width is defined as the lateral distance between the heel markers at heel-strike (104). Heel-strikes and toe-offs were found using a custom Matlab program. Marker data was filtered using a 4th-order low-pass Butterworth filter with a cutoff frequency of 10 Hz. After completion of the over ground task, participants underwent walking on the instrumented treadmill. Each subject walked at various speeds to become acclimated to the task. Comfortable walking speed was determined by starting from a relatively slow speed (.5m/s), and slowly increasing the treadmill speed until the subject reports that the current speed was faster than what they determine as “comfortable walking”, once this speed is achieved participants walked continuously for 5 minutes (45). Each subject walked for 30 s at the appropriate speed before data is recorded for the 5 minutes of continuous walking. Subjects were instructed to walk normally and to resist non-walking motions like
scratching or coughing. Subjects rested at least 3 min prior to each trial to avoid fatigue effects before repeating the procedure at 125% of their comfortable speed for another 5 minute trial. All data was secured and processed offline in a secure lab computer in the Applied Neuromechanics Laboratory.

On the second day of testing we examined force control abilities of major muscle groups of the lower extremity, specifically examining the hip extensors (HE), hip flexors (HF), hip abductors (HAB), hip adductors (HAD) and ankle planar (PF) and dorsiflexion (DF). Prior to the experimental session each subject was familiarized with the different task and procedures of the study. Similar to the gait task, fatigue was assessed using the same numerically based rating scale both at the beginning and end of the session. The familiarization period includes a verbal explanation of the task and 3 practice trials with a different force level from the data collection task. After the familiarization period, each subject performed the following movements, bilaterally: 1) Maximum voluntary contraction (MVC) of the hip in 4 directions (HE, HF, HAD, HAB) and at the ankle in 2 directions (DF and PF); and 2) Constant isometric force control tasks at three force levels (5, 10 and 20% MVC). During the isometric task, the targeted position was provided as a red line in the middle of a 32 inch monitor (SyncMaster 320MP-2, resolution: 1360×768 pixels, Samsung Electronics America, NJ, USA) and the force of the ankle joint was shown as a blue line progressing with time from left to right (89). During the ankle testing participants were seated comfortably in the upright position and faced the monitor located 1.25 m away at eye level (89, 107). Before testing, subjects affirmed that they could see the screen and its display clearly, without any obstruction or limitations. The visual gain for the task was 0.05°. We selected this visual feedback to
eliminate the effects of visuomotor corrections on force control (107). Participants hip and knee were positioned at 90° flexion and abducted ~10° (89). The ankle was secured in a customized ankle device with an adjustable foot plate and secured by straps at the level of the metatarsals that isolates the movement of the ankle to the sagittal plane (dorsiflexion and plantar flexion) and was set parallel with the floor. During the hip testing, participants stood upright in a custom frame that isolated the movement of the hip to flexion, hip extension, hip abduction and adduction. Participants pulled horizontally against a strap that was superior to the knee joint that was attached to a strain gauge that could be adjusted based on the participant’s anthropometrics. The force produced was recorded on a one-dimensional force transducer (Capacity 100 lb. (≈ 445 N), Miniature Beam Load Cell, Interface Inc., AZ, USA). The force signal was sampled at 1 kHz with a Power 1401 A/D board (Cambridge Electronic Design, UK) and a NI-DAQ card (Model USB6251, National Instruments, Austin, TX, USA). The data were stored on a secure computer in the Neuromuscular Physiology Lab.

**Maximum Voluntary Contraction (MVC)**

The order of the MVC testing was randomized across subjects. Participants were instructed to increase force of their hip flexors and extensors, abductors and adductors and ankle plantar and dorsiflexors from baseline to maximum as quickly as possible and maintain their maximum force for 7 to 10s. Each subject performed maximal trials until the maximum force of two trials was within 5% of each other (33). A minimum of one minute of rest and maximum of 3 minutes was given between maximal attempts. The peak force was found and the average of the surrounding ten points from the peak was used as the patients maximal value (107). This procedure generated a more
conservative MVC that reflects the capacity to maintain an isometric contraction, which better relates to performance of ADL (107).

**Constant Isometric Force Task**

Based on the maximal value achieved during MVC testing, participants were asked to maintain a continuous isometric force, at three levels of relative intensity (5%, 10% and 20% MVC). The target force (or relative force) was projected as a red horizontal line in the middle of the monitor and subject’s exerted force was projected as a blue line progressing with time from left to right. The visual gain was maintained across all subjects and set at 0.05°. The subjects gradually increased force against the transducer to reach their force to match the target force. When the subjects achieved the target force, subjects were instructed to maintain their force as accurately and as consistently as possible. Subjects performed three different submaximal isometric constant tasks (5%, 10% and 20% MVC), in which the order of specific intensities and muscle groups was randomized across subjects. Subjects had 30 s rest between trials and 3 mins rest between the tasks. A custom-written program in Matlab manipulated the targeted force-level and gain of visual feedback.

**Data Processing**

**Gait**

Participants performed ten continuous over ground walking trials. To appropriately evaluate each participants’ gait (with no acceleration/deceleration phase), the middle two strides of each trial were used for analysis. During the treadmill trial, for each participant, all variables were averaged across all strides of the five minute treadmill trials. Similar to previous literature, the coefficient of variation (CV = SD/mean
× 100%) was used to describe within-subject variability of the stride length, stride time, step width and velocity for both over ground and treadmill trials (19).

**Maximum Voluntary Contraction (MVC)**

For the MVC trials, the average of highest force exerted and the surrounding ten points was used for analysis and computation of relative intensities. At the end of each isometric force task the MVC trial was repeated to determine whether muscle fatigue occurred.

**Variation of Force**

In an attempt to isolate the data to only observe steady force, the first 5 s and last 1 s of force data were removed from all analyses, in hopes to account for any early and late force adjustments. The force signal was filtered using a 20 Hz fourth-order Butterworth filter (97). Standard deviation (SD) was calculated by measuring the changes around the mean force produced by the participants. This study utilized the coefficient of variation (CV) as the measure of variability.

**Statistical Analysis**

Statistical analyses were performed using SPSS statistics version 23.0 (SPSS Inc., Chicago, IL). All analysis were set to a significance level at α<.05.

**Spatiotemporal Variability**

Dependent sample t-test were used to compare mean stride lengths, widths and time of strides during gait between the groups. Additionally, dependent sample t-test were used to compare all CV values between groups.
MVC Testing

A 2x6 repeated measures ANOVA was used to compare between 2 groups (PD and HOA) and 6 conditions (hip flexion, hip extension, hip abduction, hip adduction, ankle plantar flexion and ankle dorsiflexion).

Force Control

A repeated measures mixed model ANOVA were used to assess the influence of PD on muscle strength and force variability. Variability of force for the lower extremity was used to compare between 2 groups (PD and HOA) and 6 conditions (hip flexion, hip extension, hip abduction, hip adduction, ankle plantar flexion and ankle dorsiflexion) at 5, 10 and 20% MVC with repeated measures on relative intensities. Pearson's correlations were applied to analyze relationships between variability of gait measures and variability measures of force control and MVC.
Table 3-1. Participant characteristics and demographic information.

<table>
<thead>
<tr>
<th>Participants</th>
<th>Age (yrs)</th>
<th>Height (cm)</th>
<th>Mass (kg)</th>
<th>UPDRS Motor Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD (SD)</td>
<td>71 (5)</td>
<td>174.9 (6.3)</td>
<td>83.5 (6.1)</td>
<td>30 (7)</td>
</tr>
<tr>
<td>HOA (SD)</td>
<td>69 (5)</td>
<td>169.9 (7.9)</td>
<td>85.6 (11.4)</td>
<td>---</td>
</tr>
</tbody>
</table>

UPDRS – Unified Parkinson’s Disease Rating Scale
CHAPTER 4
RESULTS

Strength and Force Variability

All participants were able to successfully complete all testing sessions and conditions. Group means for age, height, and mass did not differ between controls and patients with PD.

Maximal Muscular Strength

Examination of MVC trials indicated that persons with PD generated lower isometric force production at all muscle groups compared to HOA. On average those with PD generated 24% less hip abductor force, 17% less hip adductor force, 11% less hip extensor force, 28% less hip flexor, 48% less plantar flexor force and 21% less dorsiflexor force than age matched controls. Although there was a distinct pattern for those with PD being weaker than HOA, statistically significant differences were only detected for hip flexors (F=6.439, p=.01), ankle dorsiflexors (F=5.299, p=.03) and ankle plantar flexors (F=15.928, p=.001) (Tables 4-1).

Isometric Force Control

Analysis of variability during isometric force testing was conducting by examining the CV of isometric force during sustained force tasks at 5, 10 and 20% of MVC for each muscle group. The repeated measures ANOVA detected significant main effect for condition, i.e. percentages of MVC (F=8.601, p<.001). CV of force decreased as relative intensity increased intensity (5%>10%>20%) of MVC (p<.05). The ANOVA also identified a significant group effect (F=3.608, p=.01) indicating that persons with PD displayed greater variability (p<.05) compared to HOA. Those with PD displayed significantly greater force variability at the hip flexors (F=4.612, p.03) (Figure 4-4), ankle
plantar flexors (F=4.322, p=.03) (Figure 4-5) and ankle dorsiflexors (F=5.986, p=.01) (Figure 4-6) across all most force levels (p<.05). The ANOVA failed to detect a significant interaction (F=1.377, p>.05) between group and conditions.

**Spatiotemporal and Gait Variability**

Variability of gait was assessed examining the fluctuations between strides during both over ground and treadmill walking. Separate dependent sample t-test were used to access normalized gait velocity and found that there were no differences in gait speed between groups during over ground or treadmill walking. Separate dependent t-test indicated that there were no differences in CV for stride length, stride time, step width or velocity between those with PD and HOA (Table 4-2) during over ground gait and treadmill gait. Additionally, a separate dependent sample t-test indicated there were no differences between those with PD and HOA in mean stride length, stride time, step width or velocity (Table 4-3) during over ground gait and treadmill gait.

**Correlation**

In an attempt to answer the second aim, we examined the relationship between strength and force variability on measures of gait variability. Initially, as a combined cohort the statistical analyses found a number of significant correlations (Table 4-4 & 4-5).

We then examined the correlations between muscle strength and control that related to gait variability within the HOA group. The results yielded a number of significant correlations with gait variability and force control in the HOA group during over ground walking and treadmill walking (Table 4-6). Within the HOA group there was only one statistical correlations between MVC and gait variability (Table 4-7).
Further, we then examined the same relationships with the PD group and discovered a much smaller number of significant correlations compared to the cohort (Table 4-8). In the PD group, during over ground walking trials, stride time and force control during the 20% MVC ankle dorsiflexion was the only statistical relationship (p<.05). Additionally, during the treadmill trial, velocity was significantly correlated to CV of force produced by the ankle plantarflexors during the 10% MVC condition (p<.05) and hip flexors in the 20% MVC condition (p<.05). For maximal isometric trials in those with PD (Table 4-9), MVC for the ankle plantar flexors was found to be significantly related to stride time (p<.01) and treadmill stride time (p<.05). MVC for the dorsiflexors was found to be significantly related to stride time (p<.001).
Table 4-1. Maximal isometric force production.

<table>
<thead>
<tr>
<th>Participants</th>
<th>PD N/kg (SD)</th>
<th>HOA N/kg (SD)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankle PF</td>
<td>1.74 (.28)</td>
<td>2.64 (.27)</td>
<td>.001</td>
</tr>
<tr>
<td>Ankle DF</td>
<td>1.92 (.47)</td>
<td>2.34 (.35)</td>
<td>.03</td>
</tr>
<tr>
<td>Hip ADD</td>
<td>1.86 (.61)</td>
<td>2.16 (.55)</td>
<td>.19</td>
</tr>
<tr>
<td>Hip ABD</td>
<td>1.94 (.64)</td>
<td>2.41 (.61)</td>
<td>.07</td>
</tr>
<tr>
<td>Hip Flex</td>
<td>2.01 (.61)</td>
<td>2.58 (.48)</td>
<td>.01</td>
</tr>
<tr>
<td>Hip Ext</td>
<td>2.3 (.68)</td>
<td>2.55 (.47)</td>
<td>.28</td>
</tr>
</tbody>
</table>

Normalized to body mass (N/kg). PF – plantarflexion; DF – dorsiflexion; ADD – adduction; ABD – abduction; Flex – flexion; Ext - extension
<table>
<thead>
<tr>
<th>Participants</th>
<th>Over ground</th>
<th>Treadmill</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PD N/kg (SD)</td>
<td>HOA N/kg (SD)</td>
</tr>
<tr>
<td>Stride Length (m)</td>
<td>.04 (.01)</td>
<td>.04 (.01)</td>
</tr>
<tr>
<td>Stride Time (s)</td>
<td>.04 (.04)</td>
<td>.04 (.04)</td>
</tr>
<tr>
<td>Step Width (m)</td>
<td>.33 (.13)</td>
<td>.36 (.15)</td>
</tr>
<tr>
<td>Gait Speed (m/s)</td>
<td>.05 (.01)</td>
<td>.05 (.01)</td>
</tr>
<tr>
<td>Stride Length (m)</td>
<td>.03 (.01)</td>
<td>.03 (.01)</td>
</tr>
<tr>
<td>Stride Time (s)</td>
<td>.02 (.01)</td>
<td>.02 (.01)</td>
</tr>
<tr>
<td>Step Width (m)</td>
<td>.05 (.02)</td>
<td>.05 (.01)</td>
</tr>
<tr>
<td>Gait Speed (m/s)</td>
<td>.01 (.01)</td>
<td>.01 (.01)</td>
</tr>
</tbody>
</table>
Table 4-3. Spatiotemporal Means.

<table>
<thead>
<tr>
<th>Participants</th>
<th>PD N/kg (SD)</th>
<th>HOA N/kg (SD)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stride Length (m)</td>
<td>1.13 (.13)</td>
<td>1.15 (.15)</td>
<td>.7</td>
</tr>
<tr>
<td>Stride Time (s)</td>
<td>1.05 (.09)</td>
<td>1.1 (.08)</td>
<td>.2</td>
</tr>
<tr>
<td>Step Width (m)</td>
<td>.08 (.03)</td>
<td>.09 (.03)</td>
<td>.6</td>
</tr>
<tr>
<td>Gait Speed (m/s)</td>
<td>1.07 (.16)</td>
<td>1.05 (.20)</td>
<td>.6</td>
</tr>
</tbody>
</table>

Treadmill

<table>
<thead>
<tr>
<th>Participants</th>
<th>PD N/kg (SD)</th>
<th>HOA N/kg (SD)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stride Length (m)</td>
<td>.49 (.10)</td>
<td>.55 (.08)</td>
<td>.1</td>
</tr>
<tr>
<td>Stride Time (s)</td>
<td>1.18 (.09)</td>
<td>1.23 (.17)</td>
<td>.3</td>
</tr>
<tr>
<td>Step Width (m)</td>
<td>.21 (.02)</td>
<td>.23 (.03)</td>
<td>.2</td>
</tr>
<tr>
<td>Gait Speed (m/s)</td>
<td>.62 (.20)</td>
<td>.69 (19)</td>
<td>.4</td>
</tr>
</tbody>
</table>

Gait speed normalized to leg length.
Table 4-4. Correlation matrix between over ground gait and treadmill variability and force control parameters for cohort.

<table>
<thead>
<tr>
<th></th>
<th>Stride Length</th>
<th>Stride Time</th>
<th>Step Width</th>
<th>Gait Velocity</th>
<th>TM Stride Length</th>
<th>TM Stride Time</th>
<th>TM Step Width</th>
<th>TM Gait Velocity</th>
</tr>
</thead>
<tbody>
<tr>
<td>5% HAB</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>10% HAB</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>20% HAB</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>5% HAD</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>0.407*</td>
</tr>
<tr>
<td>10% HAD</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>0.423*</td>
</tr>
<tr>
<td>20% HAD</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>0.531*</td>
</tr>
<tr>
<td>5% HE</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>0.397*</td>
</tr>
<tr>
<td>10% HE</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>0.423*</td>
</tr>
<tr>
<td>20% HE</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>0.531*</td>
</tr>
<tr>
<td>5% HF</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>0.397*</td>
</tr>
<tr>
<td>10% HF</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>0.423*</td>
</tr>
<tr>
<td>20% HF</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>0.531*</td>
</tr>
<tr>
<td>5% AP</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>0.397*</td>
<td>---</td>
<td>0.416*</td>
</tr>
<tr>
<td>10% AP</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>0.457*</td>
<td>0.411*</td>
<td>0.416*</td>
</tr>
<tr>
<td>20% AP</td>
<td>0.46*</td>
<td>---</td>
<td>---</td>
<td>0.382*</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>5% AD</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>0.382*</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>10% AD</td>
<td>0.425*</td>
<td>---</td>
<td>---</td>
<td>0.457*</td>
<td>0.411*</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>20% AD</td>
<td>---</td>
<td>0.351*</td>
<td>0.433*</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

* Correlation is significant at the P < 0.05 level. ** Correlation is significant at the P < 0.01 level.
Table 4-5. Correlation matrix between over ground gait and treadmill variability and Maximal isometric force parameters for cohort.

<table>
<thead>
<tr>
<th></th>
<th>Stride Length</th>
<th>Stride Time</th>
<th>Step Width</th>
<th>Gait Velocity</th>
<th>TM Stride Length</th>
<th>TM Stride Time</th>
<th>TM Step Width</th>
<th>TM Gait Velocity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dorsiflexion</td>
<td>---</td>
<td>0.491*</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

* Correlation is significant at the P < 0.05 level. ** Correlation is significant at the P < 0.01 level.
Table 4-6. Correlation matrix between over ground gait and treadmill variability and force control parameters for HOA.

<table>
<thead>
<tr>
<th></th>
<th>Stride Length</th>
<th>Stride Time</th>
<th>Step Width</th>
<th>Gait Velocity</th>
<th>TM Stride Length</th>
<th>TM Stride Time</th>
<th>TM Step Width</th>
<th>TM Gait Velocity</th>
</tr>
</thead>
<tbody>
<tr>
<td>5% HAB</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>10% HAB</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>20% HAB</td>
<td>---</td>
<td>0.62*</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>5% HAD</td>
<td>0.646**</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>10% HAD</td>
<td>0.613*</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>20% HAD</td>
<td>0.576*</td>
<td>---</td>
<td>---</td>
<td>0.543*</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>5% HE</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>10% HE</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>20% HE</td>
<td>0.627*</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>0.643*</td>
<td>0.612*</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>5% HF</td>
<td>0.563*</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>10% HF</td>
<td>0.653**</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>20% HF</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>5% AP</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>10% AP</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>0.583*</td>
</tr>
<tr>
<td>20% AP</td>
<td>0.613*</td>
<td>---</td>
<td>---</td>
<td>0.51*</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>5% AD</td>
<td>0.621*</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>10% AD</td>
<td>0.581*</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>20% AD</td>
<td>0.696**</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

* Correlation is significant at the P < 0.05 level. ** Correlation is significant at the P < 0.01 level.
Table 4-7. Correlation matrix between over ground gait and treadmill variability and maximal isometric force parameters for HOA.

<table>
<thead>
<tr>
<th></th>
<th>Stride Length</th>
<th>Stride Time</th>
<th>Step Width</th>
<th>Gait Velocity</th>
<th>TM Stride Length</th>
<th>TM Stride Time</th>
<th>TM Step Width</th>
<th>TM Gait Velocity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip Abduction</td>
<td>---</td>
<td>-0.609*</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

* Correlation is significant at the P < 0.05 level. ** Correlation is significant at the P < 0.01 level.
Table 4-8. Correlation Matrix between over ground gait and treadmill gait variability and force control parameters for PD.

<table>
<thead>
<tr>
<th></th>
<th>Stride Length</th>
<th>Stride Time</th>
<th>Step Width</th>
<th>Gait Velocity</th>
<th>TM Stride Length</th>
<th>TM Stride Time</th>
<th>TM Step Width</th>
<th>TM Gait Velocity</th>
</tr>
</thead>
<tbody>
<tr>
<td>10% AP</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>.589*</td>
</tr>
<tr>
<td>20% AD</td>
<td>---</td>
<td>0.603*</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>20% HE</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>.63*</td>
</tr>
</tbody>
</table>

* Correlation is significant at the P < 0.05 level. ** Correlation is significant at the P < 0.01 level.
Table 4-9. Correlation Matrix between treadmill gait variability and maximal isometric force parameters for PD.

<table>
<thead>
<tr>
<th></th>
<th>Stride Length</th>
<th>Stride Time</th>
<th>Step Width</th>
<th>Gait Velocity</th>
<th>TM Stride Length</th>
<th>TM Stride Time</th>
<th>TM Step Width</th>
<th>TM Gait Velocity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dorsiflexion</td>
<td>---</td>
<td>.756*</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>.589*</td>
</tr>
<tr>
<td>Plantarflexion</td>
<td>---</td>
<td>.669*</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>.489*</td>
<td>---</td>
<td>.63*</td>
</tr>
</tbody>
</table>

* Correlation is significant at the P < 0.05 level. ** Correlation is significant at the P < 0.01 level.
Figure 4-1. HAB Force Variability.

* Indicates significance between groups. # Indicates significance between 10% for PD. ** Indicates significance between 20% for PD. @ Indicates significance between 10% for HOA. $ Indicates significance between 20% for HOA.
Figure 4-2. HAD Force Variability.

* Indicates significance between groups. # Indicates significance between 10% for PD. ** Indicates significance between 20% for PD. @ Indicates significance between 10% for HOA. $ Indicates significance between 20% for HOA.
Figure 4-3. HE Force Variability.

* Indicates significance between groups. # Indicates significance between 10% for PD. ** Indicates significance between 20% for PD. @ Indicates significance between 10% for HOA. $ Indicates significance between 20% for HOA.
Figure 4-4. HF Force Variability.

* Indicates significance between groups. # Indicates significance between 10% for PD. ** Indicates significance between 20% for PD. @ Indicates significance between 10% for HOA. $ Indicates significance between 20% for HOA.
Figure 4-5. AP Force Variability.

* Indicates significance between groups. # Indicates significance between 10% for PD. ** Indicates significance between 20% for PD. @ Indicates significance between 10% for HOA. $ Indicates significance between 20% for HOA.
Figure 4-6. AD Force Variability.

* Indicates significance between groups. # Indicates significance between 10% for PD. ** Indicates significance between 20% for PD. @ Indicates significance between 10% for HOA. $ Indicates significance between 20% for HOA.
CHAPTER 5
DISCUSSION

Strength Deficits Associated with Parkinson’s Disease

The propose of this investigation was to 1) observe the neuromuscular capabilities, (e.g. maximal strength and magnitude of variability across relative forces) across the prominent lower extremity joints used in locomotion and 2) identify the relationship between the neuromuscular capabilities with stride to stride fluctuations during gait in individuals with PD and their neurological healthy controls. In regards to specific aim 1, persons with PD displayed reduced force generating capabilities during the isometric task and reduced force control across the hip and ankle. In the current investigation all strength measurements were normalized to bodyweight. Specifically, statistically significant strength deficits were found at the hip flexors, ankle dorsi-flexors and ankle plantar flexors. Our findings from the current investigation are consistent with earlier findings that those with PD demonstrated reduced maximal isometric force (4, 116, 148). Recent investigations have provided evidence that muscle weakness is present both bilaterally and unilaterally (79, 134), dependent on velocity (112, 120), and contribute to the increased difficulty performing ADL (134, 153). However, there is disagreement in the literature regarding whether persons with PD are actually weaker than neurologically healthy adults (126, 142). Rose and colleagues found no significant differences in isometric knee extension or flexion force for patients with PD when compared with equally physically active controls (142). In a previous investigation from our lab, we have shown that individuals with PD produced smaller peak ankle plantar flexion moments, but failed to detect differences at the more proximal hip or the knee joints (153). This is may be due in part to methodological differences, such as the type
of assessment performed, (i.e., isometric vs isokinetic), disease severity, medication status, or gender comparison. Although there is some degree of muscular weakness associated with the disease, it remains unclear if the nature of this phenomenon is central or peripheral in its origin. Central to the pathophysiology of PD is the dopaminergic-cell loss in the substantia nigra. The dopamine deficiency ultimately leads to excessive thalamic inhibition, thereby hindering the facilitation of the desired action. This undesired inhibition effectively leads to suppression of the cortical motor system; thereby preventing sufficient activation of motoneuron pools, leading to a downstream effect which would alter motor unit recruitment and discharge rate (59). This may ultimately result in reduced neural drive and lead to general muscle weakness in those with PD. Therefore, based on the results, the observed muscle weakness in PD highlighted in our study appears to be centrally-mediated and separate from the normal effects of aging.

Many of the task that are performed everyday require higher amounts of effort to perform as we age (78). The relationship between function and strength has been reviewed extensively in the literature (43, 78, 180). In those with PD the decrements in performance have been attributed to lower maximum strength (37, 51). Navigating stairs, rising from a chair and locomotion require higher amounts of relative effort, this is a level close to maximal force production capabilities in HOA when compared to young healthy adults and in those with PD when compared to HOA (44, 78, 153). Hortobagyi and colleagues reported in older adults that the difficulty performing ADL is effectively due to working at a higher percentage of relative effort than to the absolute functional demands imposed by the task (78). In previous work, we were able to extend this
finding to PD. We found that individuals with PD had reduced torque generation during maximal isokinetic testing and increased relative effort when performing certain ADL (153); these findings were explained by the redistribution of torque throughout the lower body (ankle, knee and hip) during various task. In particular, we documented reduced capabilities in the ankle plantar flexors and an increased reliance on hip extensors. Nocera and colleagues found impaired knee extensor strength in persons with PD compared to neurologically healthy adults; this deficit extended into performance of functional and ambulatory task (116). The decreased muscular capabilities in those PD appear to be the downstream effects of impaired basal ganglia circuitry (37), and the observed reduction in strength has a negative effect on performance of ADL that involve the lower extremity (134, 153).

**Increased Force Variability Associated with Parkinson’s Disease**

Force control is a vital component in performing many ADL. The inability to control force (force variability), specifically in the upper extremity has been related to decrease in functional performance in many ADL (97, 107). Many investigations have focused on measuring variability, however these findings are limited to expressing upper body movements (i.e., grasping and pinching of the hands) (30, 171). This is the first investigation to quantify force variability across multiple joints and directions in the lower extremity for those with PD. Force variability was found to be higher at the hip flexors, ankle dorsiflexors and ankle plantar flexors in those with PD compared to age matched controls at each submaximal condition. The results from the current investigation mirror the results of previous investigations given the specific joints (hip and ankle) and directions were found to be significantly impaired in PD compared to HOA. Rose and colleagues found that knee extensor torque steadiness was
significantly decreased in patients with PD compared with healthy controls (142). They further explained their results via analyses of EMG data and found increased levels of muscle co-activation in the force-steadiness task in the PD group. Stelmach and Worringham have also shown that PD patients exhibit increased variability when asked to sustain a given force levels during isometric elbow flexion (159). Milner-Brown et al. (1979) theorized that when individuals with PD voluntarily attempt to maintain a force, there is abnormal firing of the motor units, such as hesitation and inconsistent firing rate and firing at abnormally low frequencies (2-3 Hz) (105). PD is complicated by a number of factors that disrupt and impair motor performance; thus leading to abnormal rate of force development and relaxation (158), impaired EMG activation (138) and muscle weakness (161). These deficits in neuromuscular function often manifest into unintentional variations in force production or maintenance (72, 73, 129).

Surprisingly, despite the increasing amount of evidence detailing the importance of force control and how it is utilized for many daily tasks, there is little understanding of brain areas that modulate lower limb force control. It has long been suggested that damage to the structures of the basal ganglia may interfere with efficient and coordinated movement. A recent investigation has attempted to understand key cortical areas associated with control (i.e., steadiness and force) of the ankle (180). In this study, investigators identified several cortical and subcortical regions that increased with contraction intensity; importantly it was found that activation of the putamen (basal ganglia) was associated with both the CV of force and contraction intensity (180). The authors interrupted this the basal ganglia has a dominant role in the control of steady contractions across the range of forces. The results of the investigation from Yoon et al.
suggested that the observed deficits in force control in the PD groups from the current study was due to the impaired cortico-basal ganglia-thalamic loop.

Force control or steadiness has been shown to be reduced in elderly adults compared with young adults, particularly at low levels of force (91, 168). However, there is a bit of ambiguity as to which muscle groups and what levels of force these results extend to. In the current investigation statistical differences in force variability were found at 5, 10 and 20% MVC when comparing PD to HOA; the difference in variability across the relative force values is contrary to what other investigations have found when comparing older adults to younger adults. Christou and Carlton observed no age related differences in the CV for force during isometric contractions of the knee extensor muscles across target forces that ranged from 5 to 90% MVC (33). Galganski and colleagues (53) extended Christou's study and examined smaller relative MVC and found that older adult exhibited increased variability than young adults but the discrepancies were localized at 2% MVC. Contrary to the results of Galganski and Christou, Tracy reported age-related differences in the CV during isometric-force trials at 2%, 5% and 10% of MVC (168). The results from this investigation are similar to other investigations, which follows the general trend that force variability is reduced as relative intensity is increased.

In agreement to our findings, Kouzaki and Shinohara observed amplified variability in older adults (88). However, Kouzaki and Shinohara extended this finding to establish a relationship between increased variability with one’s ability to perform ADL (88). Kouzaki reported that the increased force variability in older adults during low-intensity lower extremity isometric contractions could accurately predict variability of
center of pressure during quiet standing (88). This is significant for both clinical and research groups that wish to reduce the variability. Investigations of force variability between young and older populations have yielded several interesting theories (32, 33). It is clear from previous investigations, in older populations force variability is higher during relatively low intensities. This conclusion extends to pathological populations as well, namely PD (115, 171). Although the mechanisms of increased force variability remain ambiguous in those with PD, it begs the question on whether improvements in variability can improve ADL and ultimately increase quality of life.

**Stride to Stride Variability**

In the current investigations, there was no statistical difference in gait variability between those with PD and HOA. The lack of increased variability in PD, does not support the original hypothesis that patients with PD would have increased amounts of gait variability. It is important to note, that all patients in the current investigation participants performed walking trials during their self-reported optimally medicated state. Levodopa as mentioned earlier, a precursor to dopamine, is used as a pharmalogical treatment to manage the motor symptoms of PD by replacing endogenous dopamine at the striatum and has been shown to reduce gait variability in individuals with PD (23, 24). This suggest that gait variability may be dopamine dependent. Previous investigators have reported evidence to support the dependence of certain gait characteristics from dopamine, suggesting that gait dysfunction in PD has a complex pathophysiology, with both spatial and temporal components of gait variability responding favorably to levodopa (14, 24). For example, Bryant et al. found both spatial and temporal variability to be improved while ON medication when compared to OFF medication (14, 24). Although there still appears to be some ambiguity regarding the
effects of medication on both the spatial and temporal components of gait variability, it appears in general administration of levodopa improved gait patterns in persons with PD shifting their values toward more normal values. Albeit future research still needs to include examination in both the ON- and OFF-states to better understand the sensitivity of gait variability to dopamine.

In recent years several studies have identified that use of gait variability in distinguishing fallers from non-fallers in both normal (64, 99) and pathological populations (70, 176). Weiss and colleagues found that “fallers”, both the older adult fallers and the PD fallers walked with increased variability, compared to their non-faller counter parts. In the current investigation, none of the participants, both HOA and PD reported having previously fallen with in the past year (176). Interestingly, the results of the current investigation are not consistent with our original hypothesis or previous studies that suggested those with PD would exhibit increased gait variability compared to controls. One possible explanation for our findings is that increased gait variability may be related to those with PD that are at risk of falling. In PD fall risk increases with disease severity and disease duration (63, 128). Thus it is possible the homogeneity and mild nature of disease severity with in the PD group could have contributed to the lack of statistically difference in gait variability between groups.

**Relationship between Muscular Capabilities and Gait Variability**

This is the first investigation to quantify lower extremity force control and its relationship with locomotor variability in those with PD. Previous investigations have reported on the relationship between muscle strength and performance of gait tasks in neurologically healthy adults (29, 92, 133, 151, 156, 175). These investigations shared a general theme, that lower-extremity strength and/or power were significantly related to
almost every measure of functional limitations. However, the vast majority of these investigations relied solely on time to completion and did not quantify spatiotemporal markers of gait or gait variability. It may be noteworthy to mention, Shin et al. reported a positive statistical correlation between muscular strength and gait variability; strength was related with step width variability during normal-paced walking (151). Although the muscles of the lower extremity are shown to be important contributors to functional performance in healthy adults, the association between lower extremity strength and force control on gait variability in those with PD has not been previously demonstrated. The novel aspect of this study was to determine the relationship between max strength and force control in connection with the stride to stride variability observed in those with PD. In the present investigation when we evaluated the relationship between strength and force control on measures of gait variability as a combined cohort, we found that ankle dorsi-flexor strength and force control had significant correlations with spatial and temporal gait variability. Additionally, ankle plantar flexor force control had significant correlations with spatial and temporal gait variability and hip flexion force control had significant correlation with temporal gait variability. However, within the PD group, significant correlations were isolated to temporal gait variability, additionally there were half as many statistically significant correlations identified than compared to the collective cohort and controls. These results are quite interesting, in older adults it appears that force control contributes to gait variability; alternatively in those with PD, strength and force control, specifically in the weaker muscle groups were significantly correlated to gait variability.
Based on the relationship between the muscular capabilities of those with PD and the variability during gait, our evidence suggest that muscle strength and force control is more related to the temporal parameters of gait variability i.e., stride time and speed than spatial parameters. This relationships helps establish an underlying connection between the intrinsic rhythmicity and the neuromuscular capabilities in those with PD. These connection is plausible based on the key roles that the basal ganglia have in both the control of regulation of force (12, 65) and in the timing and sequencing of movements (5). Stelmach and Worringham first suggested that the basal ganglia are involved in the regulation of both time and force (159). Their findings found that PD subjects had deficits in regulating force and inability to maintain specific rhythm in tapping (159). Additionally, Stelamch and Phillips suggested that the spatial and temporal organization of a movement relied heavily on control over the applied forces and any deficits in either parameter could lead to improper movement control (157).

Although our data showed no relationship with spatial aspects, we suggest that the deficits associated in force control in those with PD have a greater relationship with the temporal component of movement (i.e., gait). Additionally, one must consider that PD patients may develop strategies to emphasize spatial accuracy (49). Stelamch et al. has suggested that spatial accuracy is an important aspect of performing many ADL (158). Although this investigation did not test for any alternative strategies, we have observed individuals with PD can adapt their joint torques to perform movements, such as gait initiation and stair ascension (153) and thus preserve many spatial and temporal components.
The findings from the current investigation, in addition to previous findings suggest the importance of basal ganglia in the regulation of movement timing and force regulation during walking. Additionally, it appears that the ankle is the primary agonist muscle group that contributes to gait variability in PD. This is based on the current findings involving the magnitude and number of relationships the muscular capabilities of the ankle (e.g., strength and force control) have with the temporal parameters of variability. In support of the current findings, we have previously reported in our lab, that the ankle plantar flexors were more adversely effected than other muscle groups in those with PD, which lead to redistribution of joint torques and increased relative effort in performing ADL (153). It is unclear why those with PD display weakness of the voluntary distal muscles, but it is possible that the strength deficits are in part due to the presence of underlying neuropathy (87), differences in dosage of medication (24, 36) or differences methodologies (37). In a recent investigation, Toth et al 2010 found that in a large cohort of PD patients, symptoms of peripheral neuropathy (PN) were present in approximately 43% of the PD (167). The Toth et al. study demonstrates an unexpectedly high prevalence of PN in PD. The authors suggest that one explanation of the high prevalence of PN symptoms was mediated by continuous exposure to Levodopa (167). These results suggest that undiagnosed PN could be a contributing factor to the distal to proximal muscle strength gradient (167). The combined results from the current investigation in addition the results from previous studies mentioned above, support the notion that those with PD have deficits in the muscular strength, more so in distal muscle groups (i.e., ankle) compared to controls.
Clinical Significance

The findings from this investigation may have important implications for both clinicians and researchers. As mentioned earlier, falls can be one of the most debilitating injuries in older and pathological populations; leading to a broad spectrum of physical and psychological symptoms and injuries (173). There is an abundant amount of literature that has linked falls with the stride to stride variability observed in gait. The evidence from this investigation should be applied to improving lower body motor control. The ankle appears to be the prime driver for increased gait variability during walking in those with PD. The interventions should emphasize increasing lower extremity strength or force production and introducing fine motor task into a therapeutic or rehabilitative or clinical paradigm to reduce the probability of falls and increase quality of life. Research involving weakness of the lower extremity is of considerable interest, and provides merit into the investigation of therapeutic interventions that encompass both strength and functional ambulation of ADL.

Limitations

The present study is not without limitations. The limitations in this study include a small sample size, strength testing modality and homogeneity of the cohort. Future studies need to examine these correlations along the spectrum of patients with PD (e.g., disease duration, motor subtypes, and greater disease severity). Further, in the current investigation PD patients performed gait trails during the individuals best medicated state, future investigations should focus on accessing strength and gait variability ON and OFF medication. It is likely that the differences would have been more profound if the investigation would have controlled for medication. The amount of levodopa taken by the subjects was not standardized because the subjects were instructed to come in
on their normal dosage during what they describe as their best medicated state. It is possible the different amount of medication might have influenced gait changes to different degrees.

When performing isometric muscle contractions have been used in numerous investigations however, these values tend to be inflated and often over estimate an individual’s maximal capabilities. Examining muscular strength through alternative modalities i.e. isokinetic or isotonic movements may have had a more relative effect on muscular performance, due to the dynamic nature of the task. Additionally, examining different relative intensities that encompassed the relative muscular contributions to a given task, i.e. walking could provide more accurate effect on the relationship between muscular force in the lower extremity and GV. Lastly, the use of linear measures of variability allows for a quantitative assessment of gait performance, however the use of non-linear measures of variability may provide a better detailed description if the underlying causes of variability and may be sensitive enough to detect the subtle changes in gait variability.

**Conclusion**

Older individuals with PD are confronted with the challenges of normal aging as well as disruption in the basal ganglia. Disruption of dopaminergic pathways are responsible for coordination and performance of gross movement and presents as bradykinesia, rigidity, and tremor. Secondary to the basal ganglia deficits, individuals with PD demonstrate impaired motor function (variability) and capacity that lead to muscle and bone weakness. Temporal control is essential to human movement in many of the routinely performed activities of daily living (e.g. gait). However, those with PD often have increased difficulty performing these ADL. The current investigation found
that individuals with PD have reduced muscular strength and force control at the hip (hip flexion) and ankle (dorsi and plantar flexion). Additionally, it was found that the muscular capabilities in those with PD are related to the temporal variables of gait variability. Further, it appears that force variability at the ankle was significantly associated with gait variability and thus this method of evaluation could prove useful as an index to examine potential fall risk and access the impact of or usefulness of interventions.


BIOGRAPHICAL SKETCH

Jared received his Ph.D. from the University of Florida in May 2016. During his graduate career, his research interests have grown to focus on developing strategies to improve neuromuscular control, balance, and improve quality of life in older adults and those with neurological disease. This research involves development of rehabilitation interventions that are based on biomechanical deficits in lower body mechanics and the concept of neuroplasticity. During his time as a graduate student he has developed a background in human anatomy, physiology and human mechanics, with specific training and expertise in key research areas for this application. He has had the opportunity and honor of collaborating with a diverse group of professors, medical doctors and students. These collaborations have allowed him to develop his research experience and scientific background to better contributing to the collective knowledge of these impairments and ultimately lead to improving quality of life. In summary, he has worked with an experienced and diverse group and ready to move forward with his project which will fill the gaps in our understanding of the underlying neural adaptations in the motor cortex.