BIOMECHANICAL MARKERS AS INDICATORS OF POSTURAL INSTABILITY
PROGRESSION IN PARKINSON'S DISEASE

By

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Abstract

      The <u>long term objective</u> of this research is to identify quantitative biomechanical parameters of postural instability in patients with Parkinson's disease (PD) that can in turn be used to assess fall risk. Currently, clinical assessments in PD are not sufficiently sensitive to predict fall risk, making a history of falls to be the best predictor of a future fall. Identifying biomechanical measures to predict risk of falls in PD would provide a quantitative justification to implement fall-reducing therapies prior to a first fall and help prevent the associated debilitating fractures or even morbidity. While past biomechanical studies have shown the presence of balance deficits in PD patients, which often include a broad spectrum of disease stages, compared to healthy controls (HC), no studies have assessed whether such parameters can distinguish the onset of postural instability prior to clinical presentation, and if such parameters persist following clinical presentation of postural instability. Toward this end this study had three goals:

- Determine if biomechanical assessment of a quasi-static task, postural sway, could provide preclinical indication of postural instability in PD.

- Define a mathematical model (based on principal component analysis, PCA) with biomechanical and clinical measures as inputs to quantitatively score earlier postural instability presence and progression in PD.

- Investigate if biomechanical assessment of a dynamic task, gait initiation, could provide preclinical indication of postural instability in PD.

    <u>Specific Aim 1</u> determined that some biomechanical postural sway variables showed evidence of preclinical postural instability and increased with PD progression. This aim distinguished mild PD (Hoehn and Yahr stage (H&Y) 2, without postural deficits) compared to HC

suggesting preclinical indication of postural instability, and confirmed these parameters persisted in

moderate PD (H&Y 3, with postural deficits). Specifically, trajectory, variation, and peak measures

of the center of pressure (COP) during postural sway showed significant differences ($p < .05$) in mild

PD compared to healthy controls, and these differences persisted in moderate PD. Schwab and

England clinical score best correlated with the COP biomechanical measures. These results suggest

that postural sway COP measures may provide preclinical indication of balance deficits in PD and

increase with clinical PD progression.

      Specific Aim 2 defined a PCA model based on biomechanical measures of postural sway

and clinical measures in mild PD, moderate PD, and HC. PCA modeling based on a correlation

matrix structure identified both biomechanical and clinical measures as the primary drivers of

variation in the data set. Further, a PCA model based on these selected parameters was able to

significantly differentiate ($p < .05$) all 3 groups, suggesting PCA scores may help with preclinical

indication of postural instability (mild PD versus HC) and could be sensitive to clinical disease

progression (mild PD versus moderate PD and moderate PD versus HC). AP sway path length

and a velocity parameter were the 2 primary measures that explained the variability in the data

set, suggesting further investigation of these parameters and mathematical models for scoring

postural instability progression is warranted.

      Specific Aim 3 determined that a velocity measure from biomechanical assessment of

gait initiation (peak COP velocity towards the swing foot during locomotion) showed evidence

of preclinical postural instability in PD. Because balance is a complex task, having a better

understanding of both quasi-static (postural sway) and dynamic (gait initiation) tasks can provide

further insight about balance deficits resulting from PD. Several temporal and kinematic

parameters changed with increasing disease progression, with significant difference in moderate

PD versus HC, but missed significance in mild PD compared to HC. Total Unified Parkinson's

Disease Rating Scale (UPDRS) and Pull Test clinical scores best correlated with the

biomechanical measures of the gait initiation response. These results suggest dynamic

biomechanical assessment may provide additional information in quantifying preclinical postural

instability and progression in PD.

In summary, reducing fall risk in PD is a high priority effort to maintain quality of life by

allowing continued independence and safe mobility. Since no effective screening method exists

to measure fall risk, our team is developing a multi-factorial method to detect postural instability

through clinical balance assessment, and in doing so, provide the justification for implementing

fall reducing therapies before potentially debilitating falls begin.

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List of Abbreviations

A   anterior

AP   anterior-posterior

AP RMS   anterior-posterior root mean square

AP SPL   anterior-posterior sway path length

AP SRP   anterior-posterior sway path range

BG   basal ganglia

COM   center of mass

COP   center of pressure

DBS   deep brain stimulation

EC   eyes closed

EO   eyes open

GPe   globus pallidus externas

GPi   globus pallidus internas

H&Y   Hoehn and Yahr

HC   healthy controls

kg   kilograms

m   meters

ML   medial-lateral

ML RMS   medial-lateral root mean square

ML SPL   medial-lateral sway path length

ML SPR   medial-lateral sway path range

mm   millimeters

MSS   mean sway speed

n   number

P	posterior
PC	principal component
PCA	principal component analysis
PD	Parkinson's disease
PPN	pedunculopontine nucleus
PSS	peak sway speed
PT	physical therapy
s	seconds
S1	stage 1
S2	stage 2
S3	stage 3
SA	sway area
SD	standard deviation
SNc	substantia nigra pars compacta
SNr	substantia nigra pars reticulata
SPL	sway path length
STN	subthalamic nucleus
UPDRS	Unified Parkinson's Disease Rating Scale
WST	weight shift time

CHAPTER 1: Introduction

Introduction and Motivation

Parkinson's disease (PD) is the second most common neurodegenerative disorder (Wirdefeldt, Adami et al. 2011) and affects approximately 1 million people in the USA and 5 million people worldwide (Olanow, Stern et al. 2009). Around 50-60,000 new cases are diagnosed annually, with the prevalence increasing as the population ages (Huse, Schulman et al. 2005, Lees, Hardy et al. 2009). The etiology of PD is not well understood and is attributed to a combination of genetic and environmental factors (Shulman, De Jager et al. 2011, Wirdefeldt, Adami et al. 2011). Clinically, PD patients typically present with motor symptoms and these include tremor, rigidity, and bradykinesia (slowed movement), and later develop shuffling gait and postural instability (Rascol, Goetz et al. 2002, Dauer and Przedborski 2003, Fritsch, Smyth et al. 2012). There is no cure for PD, but pharmaceutical, surgical, and physical therapy based treatments focus on controlling the symptoms of the disease (Marsden and Obeso 1994, Vingerhoets, Villemure et al. 2002, Fahn, Shoulson et al. 2004, Protas, Mitchell et al. 2005, King and Horak 2009, Schapira, Emre et al. 2009). By 2040, the annual cost to the USA associated with PD is estimated to exceed 50 billion dollars (Huse, Schulman et al. 2005).

In a recent survey of individuals with PD, their caretakers and family members, the participants identified improving research related to balance and falls as their number one priority they would like to see addressed (Deane, Flaherty et al. 2014). Postural instability is generally resistant to current therapies and is one of the most incapacitating symptoms of PD because it increases fall risk (Olanow, Watts et al. 2001, Michatowska, Fiszer et al. 2005). Falls in PD are so debilitating because they lead to further complications like fractures (Martin 2011, Matinolli, Korpelainen et al. 2011), decreased quality of life (Michatowska, Fiszer et al. 2005, Voss, Elm et al. 2012), and increased morbidity (Morens, Davis et al. 1996). Unfortunately, falls

are currently one of the greatest unmet needs in PD because current clinical assessments are not sensitive to predict falls (Bloem, Beckley et al. 1998) and interventions typically do not occur until after a fall episode has occurred (Bloem, Grimbergen et al. 2001). Although there are targeted therapies that may effectively reduce fall risk (Visser, Marinus et al. 2003, Segev-Jacubovski, Herman et al. 2011, Morris, Martin et al. 2012), if not implemented early, falling and often injury have already occurred. Accurate assessment of postural instability and prediction of fall risk is a crucial unmet need in the clinical care of PD patients.

There are some promising preliminary biomechanical assessments of postural instability in those with PD for various tasks including postural sway, gait initiation, and balance recovery (Rosin, Topka et al. 1997, Hass, Waddell et al. 2005, Horak, Dimitrova et al. 2005, Blaszczyk, Orawiec et al. 2007, Matinolli, Korpelainen et al. 2007, Buckley, Pitsikoulis et al. 2008, Blaszczyk and Orawiec 2011, Mancini, Horak et al. 2011, Stylianou, McVey et al. 2011, Ickenstein, Ambach et al. 2012, Mancini, Carlson-Kuhta et al. 2012, Stegemoller, Buckley et al. 2012). However, these studies typically combine a wide range of disease severities (Hoehn & Yahr stages (H&Y) 1-4) so the relation of biomechanical parameters to PD progression remains unknown. While these studies show the presence of balance deficits in PD compared to HC, no studies have assessed whether such parameters can distinguish early onset of postural instability prior to clinical presentation. Biomechanical markers that are sensitive to early onset of postural instability and specific to clinical disease progression could help fulfill this unmet need in fall risk assessment. Further, to ensure more robust measures of postural instability related to fall risk, these biomechanical parameters should likely encompass a range multi-factorial balance assessment tasks (i.e. quasi-static and dynamic tasks).

A pilot study done by our group represents a preliminary step for this type of analysis, assessing postural instability with biomechanical markers in PD participants, compared to healthy controls. This study demonstrated that the biomechanical assessment of the response to a fall provoking balance disturbance exhibited significant differences in mild PD participants compared to the healthy controls (McVey, Stylianou et al. 2009) and these deficits persisted in moderate PD (McVey, Amundsen et al. 2013) . Therefore biomechanical assessment of various balance tasks may show promise as diagnostic markers of postural instability, and therefore fall risk, in PD. The natural next step is to determine if disease progression impacts biomechanical markers for other balance tasks such as postural sway and gait initiation. And further, to see if the combination of such biomechanical parameters with existing clinical measures can provide more information about postural instability onset and progression through the use of increasingly sophisticated mathematical models. Ultimately, using biomechanical parameters along with existing clinical measures may represent an opportunity to refine potential parameters that can predict fall risk, and be valuable in detecting the transition associated with the onset of postural instability and its development with clinical disease progression.

Specific Aims

  <u>**Specific Aim 1**</u> determined that biomechanical postural sway variables showed evidence of preclinical postural instability and persisted with clinical PD progression. Whole body center of pressure (COP) trajectory, variation, and peak measures were calculated for healthy controls (HC), mild PD (H&Y 2, without postural deficits), and moderate PD (H&Y 3, with postural deficits). It was hypothesized that some postural sway COP parameters could distinguish patients with mild PD compared to HC, reflecting evidence of preclinical postural instability and

that these parameters would persist in moderate PD. Chapter 3 addresses Specific Aim 1. Appendix B.i. includes additional analysis and results related to this aim not included in Chapter 3.

      Specific Aim 2 defined a principal component analysis (PCA) model based on a standardized input matrix of biomechanical measures of postural sway and clinical measures of PD progression. A correlation matrix structure PCA was performed for the purpose of selecting the most influential parameters in the data set and determining if PCA could differentiate preclinical postural instability and changes associated with PD progression. We hypothesized that parameter selection would result in both biomechanical and clinical measures as the primary drivers of variation in the data set, and a PCA model based on these selected parameters would be able to significantly differentiate HC, mild PD and moderate PD. Chapter 4 addresses Specific Aim 2. Appendix B.ii includes additional analysis and results related to this aim not included in Chapter 4.

      Specific Aim 3 determined that a velocity measure (peak COP velocity towards the swing foot during locomotion) from biomechanical assessment of gait initiation showed evidence of preclinical postural instability in PD. The biomechanics of gait initiation from cue onset to heel strike of the first step were analyzed and temporal, kinematic, and COP measures were analyzed for several stages of this response. It was hypothesized that some gait initiation parameters could distinguish patients with mild PD compared to HC, reflecting evidence of preclinical postural instability and some parameters would change with increased disease progression (moderate PD). Chapter 5 addresses Specific Aim 3. Appendix B.iii includes additional analysis and results related to this aim not included in Chapter 5.

Dissertation Content

This dissertation contains six chapters. Chapter 1 contains an introduction to the area of research for this study. Chapter 2 consists of an in-depth review and background of relevant published literature related to this study. Chapter 3 contains the manuscript for Specific Aim 1 on postural sway as a measure of preclinical postural instability in Parkinson's disease. Chapter 4 contains the manuscript for Specific Aim 2 related to principal component analysis of postural sway for tracking preclinical onset and progression of postural instability in Parkinson's disease. Chapter 5 is the manuscript for Specific Aim 3 on gait initiation in Parkinson's disease to assess preclinical postural instability and progression. Chapter 6 summarizes the primary findings and future directions of this research.

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CHAPTER 2: Background

Parkinson's Disease Epidemiology and Etiology

Parkinson's Disease (PD) is the second most common neurodegenerative disorder and affects approximately 1 million people in the United States and 5 million people worldwide (Olanow, Stern et al. 2009, Wirdefeldt, Adami et al. 2011). PD is a progressive disease that has no confirmed cause, with approximately 85% of diagnosed patients having no confirmed genetic link to the disease (Corti, Lesage et al. 2011).The average age of diagnosis is approximately 60 years of age, with approximately 10% diagnosed before the age of 40 (Lees, Hardy et al. 2009, Wirdefeldt, Adami et al. 2011). Around 50-60,000 new cases are diagnosed annually, with the prevalence increasing as the population ages (Huse, Schulman et al. 2005, Lees, Hardy et al. 2009). Men are estimated to be about 1.5 times as likely as women to be diagnosed with PD (Wooten, Currie et al. 2004). The etiology of PD is not well understood and is attributed to a combination of genetic and environmental factors (Shulman, De Jager et al. 2011, Wirdefeldt, Adami et al. 2011). Recent research suggests that there is a continuum of overall risk factors for PD which range from familial genetic factors to unknown environmental variants (Shulman, De Jager et al. 2011). By 2040, the annual cost to the United States associated with PD is estimated to exceed 50 billion dollars (Huse, Schulman et al. 2005).

Neurophysiology

PD is caused by the loss of dopamine containing cells in the substantia nigra pars compacta (SNc). The substantia nigra is a component of the basal ganglia, the part of the brain that is involved with voluntary movement. The degeneration of the dopamine containing cells in the SNc ultimately results in decreased stimulation to the motor cortex (Centonze, Calabresi et

al. 1999). Typically when dopaminergic cells in the SNc decrease to around 50% of normal individuals, external symptoms of PD become apparent (Wichmann and DeLong 2003).

Basal Ganglia Anatomy and Function

The basal ganglia (BG) are a group of nuclei located at the base of the forebrain comprised of a complex network of nuclei that innervate the thalamus, which is responsible for motor, sensory, and cognitive function (Middleton and Strick 2002). Although there are several theories as to the precise function of the BG, many theories suggest the BG are responsible for facilitating voluntary movement and the associated learning, planning, execution, and modulation of these movements (Takakusaki, Saitoh et al. 2004, Lehericy, Benali et al. 2005, Obeso, Rodriguez-Oroz et al. 2008, Doyon, Bellec et al. 2009). There are four main nuclei that make up the BG: substantia nigra (composed of the substantia nigra pars compacta (SNc) and the substantia nigra pars reticulata (SNr)), striatum (composed of the caudate and putamen), globus pallidus (composed of the globus pallidus externa (GPe) and the globus pallidus interna (GPi)), and the subthalamic nucleus (STN).

Substantia Nigra

The substantia nigra, composed of the SNc and SNp, has both input (SNc) and output (SNp) nuclei as part of its structure. The SNc provides dopamine input to the striatum, the main input structure of the BG. Some PD motor symptoms are caused by a loss of the dopaminergic cells of the SNc, thus decreasing the input the striatum receives. The SNr is an output pathway of the BG that innervates the thalamus (Wichmann and DeLong 2003, Shulman, De Jager et al. 2011). (Figure 1)

Striatum

The striatum, composed of the caudate and putamen nuclei is the largest input structure of the BG. The striatum receives input from the cortical areas and the SNc and has an inhibitory effect on the GPe and GPi. When there is dopamine loss due to PD in the SNc, the weaker signal sent to the striatum causes the striatum to send an increased inhibitory signal to the GPi and GPe. (Figure 1)

Globus Pallidus & Subthalamic Nucleus

The globus pallidus, comprised of the GPe and GPi, has both input (GPe) and output (GPi) nuclei as a part of its structure. There are two pathways to the output nucleui, the GPi, one that is direct: striatum → GPi and one that is indirect: striatum →GPe→STN→GPi. In PD, the increased inhibitory input signal from the striatum ultimately causes the GPi to send an increased inhibitory signal to the thalamus (Utter and Basso 2008). This over-inhibition of the thalamus causes a decrease in the excitatory signal the thalamus sends to the motor cortex, therefore affecting normal motor function. Once dopamine levels decrease to around 50% of levels found in a normal brain, parkinsonian symptoms begin to become visible (Wichmann and DeLong 2003). (Figure 1)

Symptoms

Motor Symptoms

Once the levels of the dopaminergic cells of the substantia nigra pars compacta decrease to a clinically significant level, the onset of PD motor symptoms starts to occur. Traditionally, there are 4 cardinal symptoms of PD: tremor, rigidity, bradykinesia, and postural instability (Pahwa and Lyons 2013).

Resting Tremor

Resting tremor is a very common symptom and presents in approximately three-quarters of PD patients, with over 70% of patients having tremor as an initial symptom at the time of disease diagnosis(Hughes, Ben-Shlomo et al. 2001). The frequency of the tremor typically ranges between 4 and 6 Hz and is present in the distal part of the extremities(Jankovic 2008). Resting tremor generally does not affect the head, neck or voice in PD. The onset of a tremor typically occurs in just one limb, but over the course of the disease progression expands to affect a wider range of areas. Resting tremor is most apparent when the affected limb is at rest, and improves once active or held in a position against gravity (Simuni, Lyons et al. 2009).

Rigidity

Rigidity, or stiffness of the muscles, affects the majority of PD patients and is consistent with basal ganglia diseases. Rigidity in PD can affect all the muscles and is particularly apparent by a ratchety/jerky feeling during passive movement, referred to as "cogwheel" rigidity (Pahwa and Lyons 2013).

Bradykinesia

Bradykinesia, or the slowness of movement, is a symptom typical of all basal ganglia disorders (Jankovic 2008) and is associated with the depletion of dopaminergic neurons of the putamen. This symptom typically presents before diagnosis of a neurological impairment, and thus is one of the clinical indicators of a PD diagnosis (Simuni, Lyons et al. 2009). Various motor activities are impaired by bradykinesia, namely activities of daily living and writing tasks. Bradykinesia affects the velocity of movements, thus this symptom manifests in slowed reaction times and slower self-paced movements (Berardelli, Rothwell et al. 2001, Hallett 2011). Because

bradykinesia is correlated with dopamine loss, this symptom typically responds well to dopaminergic therapy (Simuni, Lyons et al. 2009).

Postural Instability

Once the first motor symptoms appear, on average it may take 5-10 years for patients to exhibit postural instability symptoms (Zhao et al., 2010). Postural instability, the final cardinal motor symptom of PD is characterized by flexed posture that occurs due to a decrease in postural reflexes. Postural instability typically occurs later in the disease progression (Jankovic and Poewe 2012). Postural instability is a particularly disabling symptom due to its resistance to current therapies and its link to increased fall risk (Olanow, Watts et al. 2001, Michatowska, Fiszer et al. 2005). Additionally, the fear of a future fall can also decrease a PD patients postural control, thus further increasing fall risk and decreasing quality of life (Adkin, Frank et al. 2003). In a recent survey of individuals with PD , their caretakers, and family members, the number one priority participants identified that they would like to see addressed was improving research related to balance and falls (Deane, Flaherty et al. 2014).

Non-motor Symptoms

In addition to the cardinal motor symptoms of PD, there are various non-motor symptoms of the disease that impact quality of life. Namely, neuropsychological, sleep, gastrointestinal, and sensory symptoms are typically present throughout the disease progression (Chaudhuri, Healy et al. 2006, Chaudhuri and Schapira 2009, Tolosa, Gaig et al. 2009). Neuropsychological symptoms like depression, anxiety, apathy, and dementia have been reported (Simuni, Lyons et al. 2009). Some type of sleep disorder such as rapid eye movement sleep behavior disorder, restless leg syndrome, sleep apnea, excessive daytime sleepiness, and insomnia is reported in up to 90% of PD patients (Olanow, Watts et al. 2001, Jankovic 2008). Gastrointestinal disorders such as

constipation can precede a PD diagnosis, and in later stage PD dysphagia and increased urinary

frequency and urgency are also present (Leopold and Kagel 1997, Araki, Kitahara et al. 2000,

Gage, Kaye et al. 2011). Additionally, sensory disorders like decreased olfactory function,

increased pain and impaired visual sensitivity are also common (Tinazzi, Del Vesco et al. 2006,

Jankovic 2008).

Diagnosis and Rating of PD Progression

Diagnosis

Because there is a lack of distinct neuroimaging attributes or biomarkers related to PD,

diagnosis of PD is reliant on clinical presentation of PD symptoms (Wirdefeldt, Adami et al.

2011). Typically, PD is diagnosed by a neurologist based on patient history and physical

examination where the patient exhibits multiple symptoms of PD: tremor, rigidity, bradykinesia,

and postural instability or responds to dopaminergic therapy (Hughes, Daniel et al. 2001,

Chaudhuri, Healy et al. 2006, Savitt, Dawson et al. 2006, Kim, Allen et al. 2013). Additionally,

current research suggests that various other symptoms can precede the typical cardinal symptoms

of PD like sleep disorders, olfactory dysfunction, dysautonomia, depression, anxiety,

constipation, pain, and genitourinary problems (Chaudhuri, Healy et al. 2006, Tolosa, Gaig et al.

2009). Molecular imaging provides some promise in PD diagnostics but is costly and needs to be

done in combination with pre-motor testing (Siderowf and Stern 2008, Stephenson, Siderowf et

al. 2009).

Classification and Rating Scales

As PD is a progressive disorder, there are 3 widely used standardized rating scales, Unified Parkinson's Disease Rating Scale (UPDRS), Schwab & England Scale and Hoehn & Yahr stages (H&Y) to assess disease progression related to a variety of areas such as the impact of PD related to mentation, activities of daily living, and motor control (Factor and Weiner 2007, Pahwa and Lyons 2013).

Specifically, the UPDRS has four scoring components: I. Mentation, behavior, and mood; II. Activities of daily living; III. Motor examination; and IV. Complications of therapy. Components I, II, and IV are historical and based on patient responses to verbal questioning. Component III is completed by a clinician and consists of brief physical tests/examinations to assess motor capabilities such as speech, facial expression, rigidity, tremor, finger tapping, hand and leg movements, rising from a chair, posture, a balance disturbance test, and walking (Goetz, Tilley et al. 2008).

H&Y assesses disease impairment of motor function related to postural stability and consists of stages 0-5. Below is an outline of the H&Y stages criteria.

Stage 0 – No signs of disease.

Stage 1 – Unilateral disease.

Stage 1.5 – Unilateral plus axial involvement.

Stage 2 – Bilateral disease, without impairment of balance.

Stage 2.5 – Mild bilateral disease with recovery on pull test.

Stage 3 – Mild to moderate bilateral disease; some postural instability; physically independent.

Stage 4 – Severe disability; still able to walk or stand unassisted.

Stage 5 – Wheelchair bound or bedridden unless aided. (Hoehn and Yahr 1998)

Therapies

Drug Therapies

Levodopa continues to be the most commonly used and most effective drug for the management of PD symptoms since it was first used in the 1960's by Cotizias et al (Fahn, Shoulson et al. 2004, Fox, Chuang et al. 2008, Jankovic and Poewe 2012). Levodopa was produced with the goal of improving motor symptoms associated with PD through restoring the levels of dopamine that were lost due to PD (Schapira, Emre et al. 2009). Today, levodopa continues to be a successful oral therapy to combat dopamine loss and to treat the motor symptoms of PD (Thanvi, Lo et al. 2007, Jankovic and Poewe 2012). Since the drug's introduction, levodopa has demonstrated efficacy in improving the cardinal PD symptoms including bradykinesia, rigidity and resting tremor Levodopa is combined with a dopa-decarboxylase inhibitor, carbidopa, which improves efficacy increases and reduces side effects, particularly nausea (Schapira, Emre et al. 2009, Jankovic and Poewe 2012).

Despite levodopa's success in treating the majority of the motor symptoms of PD, other motor symptoms, particularly related to gait and balance, are much less responsive. In addition, long-term use of levodopa results in levodopa-induced side effects. Particularly, higher doses and long term levodopa use leads to motor complications such as wearing off of symptom control before the next dose and period when symptoms are not well controlled (motor fluctuations) and involuntary wiggling movements (dyskinesia) (Schapira, Emre et al. 2009). After years of levodopa use, the majority of PD patients will be affected by these levodopa-induced motor complications (Contin, Riva et al. 1998, Rascol, Brooks et al. 2000, Schrag and Quinn 2000, Van Gerpen, Kumar et al. 2006, Antonini, Chaudhuri et al. 2010).

In addition to inducing motor complications like fluctuations and dyskinesias, levodopa also does not sufficiently improve some motor symptoms of PD like postural instability and freezing of gait. There are conflicting reports as to the extent to which levodopa can (Nova, Perracini et al. 2004) or cannot (Bronte-Stewart, Minn et al. 2002, Rocchi, Chiari et al. 2002, Mancini, Rocchi et al. 2008) influence functional postural control. However, some recent studies acknowledge that while there is some improvement to PD induced postural instability while in the "on" medication state, functional postural control deficits still exist causing PD patients to continue to be at increased fall risk despite levodopa use (McNeely, Duncan et al. 2012).

In addition to levodopa, dopamine agonists and MAO-B inhibitors have also been used to treat the motor symptoms of PD either exclusively or in conjunction with levodopa therapy (Chaudhuri and Schapira 2009). Particularly with use during the early stages of PD progression, dopamine agonists and MAO-B inhibitors have been shown to provide symptom relief with a lower rate of drug-induced motor complications (Antonini, Tolosa et al. 2009). However over the long term, dopamine agonists and MAO-B inhibitors compared with levodopa are less effective in managing PD symptoms, but also cause less drug-induced motor symptoms like wearing off and dyskinesia (Stacy and Galbreath 2008).

Surgical Therapy

Deep Brain Stimulation (DBS) of the subthalamic nucleus (STN) or the globus pallidus interna (GPi) was first implemented in the early 1990's as a surgical treatment to improve motor symptoms in advanced PD patients (Bronstein, Tagliati et al. 2011). The DBS leads are most commonly implanted into the STN or GPi (Hickey and Stacy 2011). Studies have also investigated the possibility of the pedunculopontine nucleus (PPN) as a target for DBS in PD

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patients (Thevathasan, Coyne et al. 2011). DBS of the STN and GPi has been demonstrated to improve motor function and reduce dopaminergic drug and PD symptoms like motor fluctuations, dyskinesia, rigidity, tremor and bradykinesia (Benabid, Chabardes et al. 2009, Hickey and Stacy 2011, Thevathasan, Coyne et al. 2011). Eligibility criteria include: a PD diagnosis, motor fluctuations or dyskinesia that cannot be controlled with medication or medication adjustments and no significant behavioral or cognitive disorders (Morgante, Morgante et al. 2007, Bronstein, Tagliati et al. 2011).

Physical Therapy

Studies have investigated the effectiveness of standard physical therapy (PT), exercise, balance and gait training programs on reducing mobility impairments and increasing quality of life in PD(Stankovic 2004, Nieuwboer, Kwakkel et al. 2007, King and Horak 2009, Allen, Canning et al. 2010, Hickey and Stacy 2011, Maki, Sibley et al. 2011, Ransmayr 2011, Morris, Martin et al. 2012, King, Salarian et al. 2013, Harro, Shoemaker et al. 2014). While these studies have not been able to completely prevent falls, improvements have been observed in balance and gait measures for some biomechanical task assessments (Stankovic 2004, Protas, Mitchell et al. 2005, King and Horak 2009).

Specifically, Stankovic et al. studied the effect of a 30 day PT program and reported improvements in balance measures. While this study was not able to show the effect on falls, it did find an improvement in measures used to classify patients as fallers. In addition to PT, gait training involving intensive treadmill training and Nordic walking have been shown to improve quality of life and gait speed in PD (Herman, Giladi et al. 2007). Although mobility impairments caused by PD have been shown to be difficult to treat with medication therapy (Bloem, Beckley et al. 1996, Lang and Lees 2002), when standard PT is provided in addition to medication

therapy, some benefit is realized in quality of life related to mobility (Morris 2000). Therefore standard PT moderately impacts mobility impairments, suggesting that PD specific therapy designed to directly target the source of the mobility impairment may be more effective in addressing mobility impairments in PD.

Postural Instability

Postural instability, one of the cardinal motor symptoms of PD, is characterized by flexed posture that occurs due to a decrease in postural reflexes. Postural stability is regulated by the nervous system through continual adjustments in the body's center of mass due to both internal and external stimuli (Lord 2007). Postural instability is defined as the impairment of these postural reflexes, resulting in decreased balance and increased fall risk (Tugwell 2008). Postural instability typically occurs later in the disease progression and is particularly disabling due to its link to increased fall risk (Bloem, Grimbergen et al. 2001, Olanow, Watts et al. 2001, Michatowska, Fiszer et al. 2005).

Current Clinical Assessments

Current clinical tests to assess postural instability and/or balance impairment include UPDRS item 27 (arising from a chair), item 28 (posture), item 29 (gait), item 30 (response to a posterior displacement, "Pull Test") as well as steady stance positions (2-leg stance, tandem stance, single-leg stance, and single leg stance with arms above head) (Fahn, Elton et al. 1987, Visser, Marinus et al. 2003). Specifically, for example, posture UPDRS testing consists of a rating scale between 0-4 to assess deficits. Below is an outline of the rating scale used to assess posture with the UPDRS:

0 = Normal erect.

1 = Not quite erect, slightly stooped posture; could be normal for older person.

2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.

3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.

4 = Marked flexion with extreme abnormality of posture.(Goetz, Tilley et al. 2008)

Similarly, postural instability is assessed by the Pull Test with a "Response to sudden, strong posterior displacement produced by a pull on the shoulders while the patient is erect with eyes open and feet slightly apart" and is also rated on a scale of 0-4 based on the following criteria:

0 = Normal.

1 = Retropulsion, but recovers unaided.

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

3 = Very unstable, tends to lose balance spontaneously.

4 = Unable to stand without assistance.

While such tests are easily applied in a clinical setting, the qualitative assessment criteria and gross-level rating scale do not allow for a detailed or quantitative analysis of balance and postural deficits. While these tests are proficient at assessing the severity of postural control deficiencies once balance symptoms have progressed, they are less effective in the prediction of a future fall if one has not yet occurred (Bloem, Beckley et al. 1998, Bloem, Grimbergen et al. 2001).

Fall Risk

Effect of Falls

Decreased postural control and the resultant increased fall risk in PD are particularly

incapacitating because of the impact on activities of daily living and quality of life. Falls in PD

are debilitating because they lead to further complications like fractures (Martin 2011, Matinolli,

Korpelainen et al. 2011), nursing home admission (Michatowska, Fiszer et al. 2005, Voss, Elm et

al. 2012), and increased morbidity (Morens, Davis et al. 1996). Even if no serious injuries are

sustained, fear of falling following a fall episode increases a patient's risk of recurring falls and

decreases quality of life (Voss, Elm et al. 2012).

Incidence in PD

PD patients have an increased risk of falls nine-times that of their healthy counterparts.

While fall frequency generally increases with increased clinical progression, as PD progresses

the progressive immobilization may result in a decreased frequency of falls as patients are often

confined to a wheelchair (Bloem, van Vugt et al. 2001). Overall, reported ranges of around 25-

70% of PD patients fall each year, with the majority of them having more than one falling

episode (Wood, Bilclough et al. 2002, Wielinski, Erikson-Davis et al. 2005, Voss, Elm et al.

2012). Of patients who experience a fall, up to 65% sustained an injury, and of the injured, 75%

required assistance from a health care provider (Wielinski, Erikson-Davis et al. 2005). Such high

fall rates and the subsequent injuries and need for assistance in PD patients not only reflect the

risk of serious risk of injury due to a fall, but the expensive cost of falls on the health care system

in general.

Implementation of Fall-Reduction Interventions

Despite the well documented adverse consequences, prevention of falls is still one of the

greatest unmet challenges in PD because interventions typically do not occur until after a fall

episode has occurred (Bloem, Grimbergen et al. 2001), largely due to the fact that current clinical

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assessments are not sensitive enough to predict when a patient first becomes at risk to fall

(Bloem, Beckley et al. 1998). Although there are targeted therapies that can successfully reduce

fall risk (Visser, Marinus et al. 2003, Segev-Jacubovski, Herman et al. 2011, Morris, Martin et

al. 2012), such interventions are expensive and time consuming for both the patient and provider.

Therefore, because current assessments are not predictive of fall risk (Bloem, Grimbergen et al.

2001), such therapies are typically not prescribed until after a fall has already occurred, making

the best current predictor of a future fall a history of falling.

Types of Fall Intervention Therapies

Largely, multi-factorial programs seem to show promise in effectively reducing fall risk

in PD and elderly patients (Rao 2005, Voss, Biglan et al. 2008, Harro, Shoemaker et al. 2014).

Other recent studies have tested some novel and targeted balance and fall-risk therapies such as:

home-based exercise programs (Ashburn, Fazakarley et al. 2007), treadmill gait and step training

(Protas, Mitchell et al. 2005), group exercise (Allen, Canning et al. 2010), tai chi (Marjama-

Lyons, Smith et al. 2002), and virtual reality (Hausdorff, Mirelman et al. 2010). With such a

wide range of therapeutic techniques showing a reduction in fall risk, once a reliable method to

predict fall risk is established, these targeted therapies can provide significant improvements to

PD patient outcomes and quality of life. If targeted biomechanical assessments are utilized that

can detect postural control deficits prior to a history of falling, then fall interventions can be

implemented at the appropriate time. Such an assessment system could help eliminate the current

obstacle to receiving therapy. With an accurate prediction of being at risk of falls, prescribing

patients such interventions could avoid undue cost or time for patients and providers.

Biomechanics

Postural Control

The postural control system of the body is responsible for the maintenance of balance, posture equilibrium, and the biomechanical support to execute movements (Massion 1998). Effective postural control relies on the incorporation of both neural and musculoskeletal systems: namely, the vestibular, visual, proprioceptive, and sensory systems (Palmieri, Ingersoll et al. 2002, Lacour, Bernard-Demanze et al. 2008). Postural position is maintained through adjusting postural control and tone to account for gravity, standing surface, and visual input. Postural balance is maintained following internal or external perturbations to stability through integrating sensorimotor processes to control the body's center of mass (COM) (Horak 2006). The relation of the COM to the body's base of the support (the feet for a standing task) is crucial for the maintenance and control of balance. When the COM is within the base of support during a standing task, the body is in equilibrium- or in a state of balance.

For biomechanical assessments, the whole-body center of pressure (COP) is often used to assess postural control. The COP path is comprised of the point location of the vertical ground reaction force vector obtained from a force platform. The forces of the body on the force plate are dependent on the placement of the foot as well as the motor control of the muscles in the ankle. Physiologically, the COP is considered the neuromuscular response of the body to perturbations or changes of the COM location. Thus, the COP is directly affected by the acceleration of the COM, which is caused by muscle activations and gravity. The COP position is calculated by:

$$COP = \sqrt{\left(-\frac{M_y + F_x * d_z}{F_z}\right)^2 + \left(\frac{M_x - F_y * d_z}{F_z}\right)^2}$$

where F_x and F_y are the force parallel to the top of the force plates, F_z is the force perpendicular to the force plates, M_x and M_y are the moments parallel to the top of the force plates, and d_z is the distance below the top surface at which the origin in located (Palmieri, Ingersoll et al. 2002, Winter 2009). [1]

While current clinical assessments are able to assess postural control deficits later in the disease progression, they are not sufficiently sensitive to predict fall risk in the early stages of PD (Bloem, Beckley et al. 1998, Bloem, Grimbergen et al. 2001). Quantitative biomechanics-based studies have investigated postural instability and balance deficits in PD with laboratory based measures such as force plates, motion systems, and electromyography. Such experimental measures can allow for more quantitative and complex analysis to assess kinematic, kinetic, temporal and muscular responses compared to currently available clinical assessments.

These biomechanical assessments of postural stability in those with PD have focused on a range of quasi-static and dynamic tasks including postural sway, gait initiation, and balance recovery (Hass, Waddell et al. 2005, Horak, Dimitrova et al. 2005, Blaszczyk, Orawiec et al. 2007, Buckley, Pitsikoulis et al. 2008, Mancini, Horak et al. 2011, Stylianou, McVey et al. 2011, Ickenstein, Ambach et al. 2012, Mancini, Carlson-Kuhta et al. 2012, Stegemoller, Buckley et al. 2012, Greve, Luna et al. 2014, Harro, Shoemaker et al. 2014). Because postural control is a multifactorial system, recent studies also suggest incorporating multiple tasks and UPDRS items for the assessment of balance can prove more effective at predicting past fall history. However,

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[1] Appendix B. COP calculations provides an in-depth explanation of the calculation of the center of pressure in the anterior-posterior and medial-lateral directions.

the majority of these studies have not been linked to the effects of disease progression and the ability to use parameters to determine preclinical postural instability if the patient does not have a history of falls (Jacobs, Horak et al. 2006, Kim, Allen et al. 2013).

Postural Sway

Biomechanical assessment of postural control using force plates, that measure the force and moment reactions the body exerts on the ground, has been performed since the 1970's. The effects of biologic factors and pathologies such as age, neurological disease, visual/auditory input, and injuries have been examined using biomechanical parameters extracted from standing tasks (Palmieri, Ingersoll et al. 2002). Specifically, postural sway has been investigated in PD during static, surface translation, and varied visual input standing tasks (Horak, Nutt et al. 1992, Horak, Dimitrova et al. 2005, Blaszczyk, Orawiec et al. 2007, Blaszczyk and Orawiec 2011, Mancini, Horak et al. 2011, Stylianou, McVey et al. 2011, Ickenstein, Ambach et al. 2012, Mancini, Carlson-Kuhta et al. 2012, Revilla, Larsh et al. 2013, Greve, Luna et al. 2014).

Although various studies have assessed the effect of PD on postural control during a quiet standing task, the effect of PD on biomechanical sway parameters, like COP, remains unclear. While some studies report that PD results in a decrease in sway parameters (Horak, Nutt et al. 1992), others suggest that PD increases sway parameters (Blaszczyk, Orawiec et al. 2007, Stylianou, McVey et al. 2011, Ickenstein, Ambach et al. 2012, Mancini, Carlson-Kuhta et al. 2012). In order for biomechanical parameters of postural sway to be a useful clinical tool to assess disease progression and the related fall risk, a better understanding of PD specific deficits in these parameters is needed. Specifically, to identify postural sway parameters that have the potential to diagnose fall risk, significant differences must not only be present early in the

disease (mild PD, H&Y 2), but also that these parameters must increase with disease progression (moderate PD, H&Y 3). Several groups have found significant differences between PD and HC subjects in general, but no groups have isolated mild and moderate PD patients versus healthy controls.

To better quantify and assess postural instability in PD, several groups have performed laboratory based studies to assess how PD affects postural control parameters for quiet stance. Our lab has performed such a study in which Stylianou et al. analyzed biomechanical sway parameters for 19 mild to moderate PD patients (H&Y 1.5-3) compared to HC and found significant differences during eyes open (EO) and eyes closed (EC) static stance on a force platform. Specifically, 4 COP sway parameters were significantly different in PD compared to the age-matched HC: medial-lateral (ML) sway path length, sway area, and anterior-posterior (AP) and ML ranges of motion (Stylianou, McVey et al. 2011). Ickenstein et al. similarly studied 12 mild to moderate PD patients (H&Y <3) compared to HC during quiet EO and EC stance on a force platform and found that mean COP sway, radius and marked area were greater for PD vs. HC (Ickenstein, Ambach et al. 2012). Such findings reinforce the idea that biomechanical markers of postural instability show promise as a diagnostic tool in PD balance assessment.

Other studies have related biomechanical parameters to current clinical assessments of disease progression and fall risk. Blaszczyk et al. studied 55 mild to moderate PD patients (H&Y 1-3) compared to HC during EO and EC quiet stance on a force platform. PD subjects had greater sway area, length, and range compared with HC, with ML sway range magnitude also correlating with H&Y scores (Blaszczyk, Orawiec et al. 2007). Matinolli et al. analyzed the relationship between postural sway parameters and fall status in 120 PD patients (H&Y 1-3.5)

using an inclinometric device. They found that fallers had significantly greater sway area and AP and ML ranges of motion (Matinolli, Korpelainen et al. 2007). Further, increased UPDRS scores correlated with increased postural sway parameters (Matinolli, Korpelainen et al. 2007).

The results of these studies are promising because they further support the idea that postural sway parameters can help to distinguish differences between PD versus HCs as well as fallers versus non-fallers. Having COP parameters that differ depending on fall status and pathology may provide incite as to which parameters are related to disease progression and fall risk. Further, since these parameters correlate with UPDRS, H&Y, or other clinical scores, this suggests that postural sway parameters can be promising candidates for assessing disease progression related to fall risk. Unfortunately however, because these studies do not isolate mild and moderate patients relative to HC, it is still unclear if such deficits can be detected in the early stages of disease progression compared to HC. In order for biomechanical assessment of postural sway to be useful in predicting fall risk, such parameters must be correlated to disease progression, sensitive to a decrease in subclinical postural stability, and specific to fall risk.

Gait Initiation

Gait initiation involves an individual starting in a quasi-static stance, the task described above for postural sway, and then the initiation of a step to begin steady-state gait. Gait initiation involves the postural control system because an individual must transition from a state of equilibrium or balance, where the COP is within the base of support, to a constantly unstable state during gait. Gait initiation is able to assess motor planning in addition to motor programing since there is an execution of a movement (Halliday, Winter et al. 1998). Biomechanical assessment of postural instability through gait initiation using kinetic, kinematic, and

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electromyographic parameters has been studied for a range of populations to investigate the effect of aging, neurological disorders, and injuries (Rosin, Topka et al. 1997, Martin, Shinberg et al. 2002, Chang, Chuang et al. 2004, Brunt, Santos et al. 2005, Hass, Waddell et al. 2005, Delval, Krystkowiak et al. 2007). Specifically, gait initiation has been investigated in PD in a range of conditions including: no cue, visual-cued, and auditory-cued (Rosin, Topka et al. 1997, Martin, Shinberg et al. 2002, Hass, Waddell et al. 2005, King, St George et al. 2010, McCandless, Evans et al. 2010, Muniz, Liu et al. 2010, Hass, Buckley et al. 2012, Muniz, Nadal et al. 2012, Rocchi, Carlson-Kuhta et al. 2012).

Several studies have found significant differences between PD and HCs for both temporal and kinematic parameters. Rosin et al. demonstrated that following an auditory cue, PD patients compared to HCs have an increased preparation time (time from start signal to motion onset) as well as a smaller second step (of the first stride). These findings suggest that postural instability deficits in PD may also be due to motor planning difficulties (Rosin, Topka et al. 1997). Martin et al. investigated the difference between 12 mild to moderate PD (H&Y 1-3) subjects compared to young and age-matched HCs. The group divided the gait initiation movement (from first initiation of movement until immediately prior to toe-off of the first step) into 5 stages, and found that the COM-COP distance for PD during 4 of these 5 events was significantly smaller than the HCs (Martin, Shinberg et al. 2002). Hass et al. studied the difference between PD patients with H&Y ≤ 2 and H&Y ≥2.5 during a verbally cued gait initiation task. Gait initiation was divided into 3 stages, and the COM-COP peak distance was significantly less with increased H&Y score for the final stage of the gait initiation: when the COP moved anteriorly under the stance foot (at the end of the when the first foot takes a step, but before the foot touches the ground) (Hass, Waddell et al. 2005).

These results support that gait initiation biomechanical postural parameters have potential to distinguish differences between PD versus HCs as well as changes with disease progression. Having parameters that differ depending on pathology or disease severity may provide insight as to which parameters are related to fall risk. However, because these studies either do not isolate mild and moderate patients relative to HC, or only look at these parameters within PD, it is still unclear if such deficits can be detected in the early stages of PD compared to HC. In order for gait initiation parameters to be early indicators of postural instability and therefore fall risk, these deficits must be demonstrated as different from HC in the early stage of the disease.

Balance Recovery

In addition to self-initiated tasks like postural sway and gait initiation, an individual's ability to respond to an external perturbation that disrupts balance and postural stability is another key component of decreasing fall risk. Researchers have looked at the response to a balance disturbance for various populations such as the elderly and those with neurological diseases. Past research has investigated how biomechanical parameters related to a balance disturbance, such as a posterior waist pull, affects those with and without balance impairments. Generally, the elderly compared to the young take more steps, take smaller steps, and have a lower step height clearance in response to a backwards pull (Luchies, Alexander et al. 1994, Schulz, Ashton-Miller et al. 2005).

Balance recovery following an external postural perturbation has also been studied in those with PD and is the basis for the UPDRS postural instability pull test (Dimitrova, Nutt et al. 2004, Jacobs, Horak et al. 2006, King, St George et al. 2010, Smith, Jacobs et al. 2012). Recently, Smith et al. studied 12 mild to moderate (H&Y 2-3) PD patients compared to HC and

their response to a posterior balance disturbance. Those with PD exhibited a slower rate of change response of the COP following the external balance disturbance (Smith, Jacobs et al. 2012). In a study by King et al., they analyzed the biomechanical response to a backwards translational balance disturbance in 17 PD patients (H&Y 1.5-4.0) compared to age-matched HCs. This study found that those with PD, compared to HC took more and shorter steps, used more anticipatory postural adjustments, and their COM was more anterior prior to stepping foot lift-off (King, St George et al. 2010). While it is encouraging that PD patients show biomechanical deficits when compared to HCs, the relation of these variables to disease progression and prediction of fall risk is not addressed. In order for these variables to be helpful in predicting fall risk prior to a first fall, the relationship of the biomechanical parameters to disease progression must be better understood.

A pilot study by our lab, McVey et al., has done the preliminary step for this type of progression-based analysis, assessing postural instability with biomechanical markers in exclusively mild PD patients (H&Y 2, without postural deficits) compared to HC. This study showed that there are several significant differences ($p < .05$) during a balance recovery task in the mild PD group compared to HC. Specifically, during multiple step responses, mild PD caused longer weight shift times (WST), increased dorsiflexion at the ankle, and further posterior displacement of the COP prior to foot landing (McVey, Stylianou et al. 2009). Further, in a follow up study with moderate PD patients (H&Y 3, with postural deficits), longer WST persisted in this group, suggesting that this biomechanical parameter could be a promising diagnostic markers of postural instability, and therefore fall risk in PD (McVey, Amundsen et al. 2013). The natural next step is to determine if disease progression impacts biomechanical markers for additional balance tasks and to see if the combination of such biomechanical

parameters with existing clinical measures can provide more information about postural instability onset and progression through the use of increasingly sophisticated mathematical models.

These quantitative laboratory based studies for a range of balance tasks show that PD patients compared to HC have differences in their response to a range of tasks. However the study populations have a wide range of disease severities (H&Y 1 - 4) so the relationship of these parameters to the early stages of PD is still largely unknown.   By grouping a range of PD patients, it is still unclear if these biomechanical parameters are representative of later stage PD, or are present throughout the disease progression. In order for biomechanical parameters of postural instability to be predictors of fall risk, parameters present across a wide range of the disease must also be present before PD patients have a fall episode, and still present in later stages of the disease. Further research is needed to address how these parameters change with disease severity for a multi-factorial group of balance assessment tasks.

Principal Component Analysis

Because an unmet need in PD is understanding the relationship of biomechanical parameters of postural instability across various balance tasks and throughout disease progression, a method to elicit the correlations between these variables is needed to gain a better understanding of these relationships. Principal Component Analysis (PCA) is such a statistical method used to detect and emphasize the similarities, differences and patterns in a data set in order to make inferences about a population. PCA involves using a data set of various variables to calculate a covariance matrix and the associated eigenvalues and eigenvectors to find the direction of maximum variation in the data. The resultant principal components (eigenvectors)

are orthogonal matrices that are linear combinations of the ordinal variables that are used to make inferences about which variables are primarily responsible for the variation in the data. Because each principal component accounts for the effect of each input variable, trends and patterns in the data that are not detectable with using each variable independently can be determined using PCA (Jolliffe 2002). Therefore, PCA is a useful tool to assess whether patterns in a set of variables exist in order to make inferences about across-task correlations and population groups.

PCA based on biomechanical parameters has recently been shown to help determine identifying features for different ages, pathologies and tasks (Rocchi, Chiari et al. 2004, Rocchi, Chiari et al. 2006, Labbe, de Guise et al. 2010, Muniz, Liu et al. 2010, Muniz, Liu et al. 2010, Mantovani, Lamontagne et al. 2012, Muniz, Nadal et al. 2012, Kobayashi, Hobara et al. 2014). PCA has been successfully applied to biomechanical parameters of postural sway and gait initiation in PD previously, providing driving variable selection and differentiation of groups based on PCA (Rocchi, Chiari et al. 2006, Muniz, Liu et al. 2010, Muniz, Nadal et al. 2012).

Specifically, PCA has been used in analysis of the quasi-static task postural sway to assess feature selection of postural sway characteristics in young healthy adults (Rocchi, Chiari et al. 2004) and to assess the impact of "on" versus "off" medication in PD (Rocchi, Chiari et al. 2006). In these studies, biomechanical measures of the whole body COP were used as the input parameters for the PCA model. COP parameters that reflected the overall COP trajectory and variation were found to be the principal drivers of variation within the data set (Rocchi, Chiari et al. 2004, Rocchi, Chiari et al. 2006). When comparing the effect of drug therapy ("on" versus "off" medication) the 4PCs in the "off" medication state and 3 PCs in the "on" medication state accounted for at least 90% of the original variation in the data set (Rocchi, Chiari et al. 2006).

In addition to applying a PCA model to postural sway in PD, a study that involved members of the current research study (KL and RP) applied PCA modeling to a gait initiation task in PD patients with DBS implantation. PCA was applied to the ground reaction forces during gait initiation in 4 different conditions: without treatment, with medication only, with stimulation only, and with both medication and stimulation. Ten PCs explained the overall variation in the data set, with 8 being attributed to vertical forces and 2 to horizontal ground reaction forces. The standard distance of the resultant PCs was able to differentiate the PD group without treatment from the HC as well as the PD group without treatment from the PD group with stimulation. The results of this study show promise that PCA can be applied to both better understand the variation within a data set, as well as identify attributes related to PD and therapeutic (i.e. DBS and medication) states (Muniz, Liu et al. 2010).

Significance

Since no effective screening method exists to reliably measure fall risk, our team is developing a method using laboratory-based measures to detect postural instability before recurrent falls manifest. Reducing fall risk in PD is a high priority in the effort to maintain good quality of life by allowing continued independence and safe mobility until a treatment is discovered which stops the progression of PD and reverses its neurological effects. Determining if biomechanical markers for balance tasks of various demands on motor function can provide preclinical indication of postural deficits and persist with clinical disease progression is a crucial unmet need in PD. And further, through utilizing mathematical modeling to determine which biomechanical and clinical parameters are also sensitive to disease severity can potentially provide indicators to assess preclinical postural instability and progression. Once the most

significant tasks and parameters are identified, this research also has the long term potential of translating to a bioinstrumentation development study. Applying the results of this research towards a bioinstrumentation device that a clinician can use to assess fall risk quickly and accurately would have a direct and tangible positive impact on patient care and the healthcare system in general.

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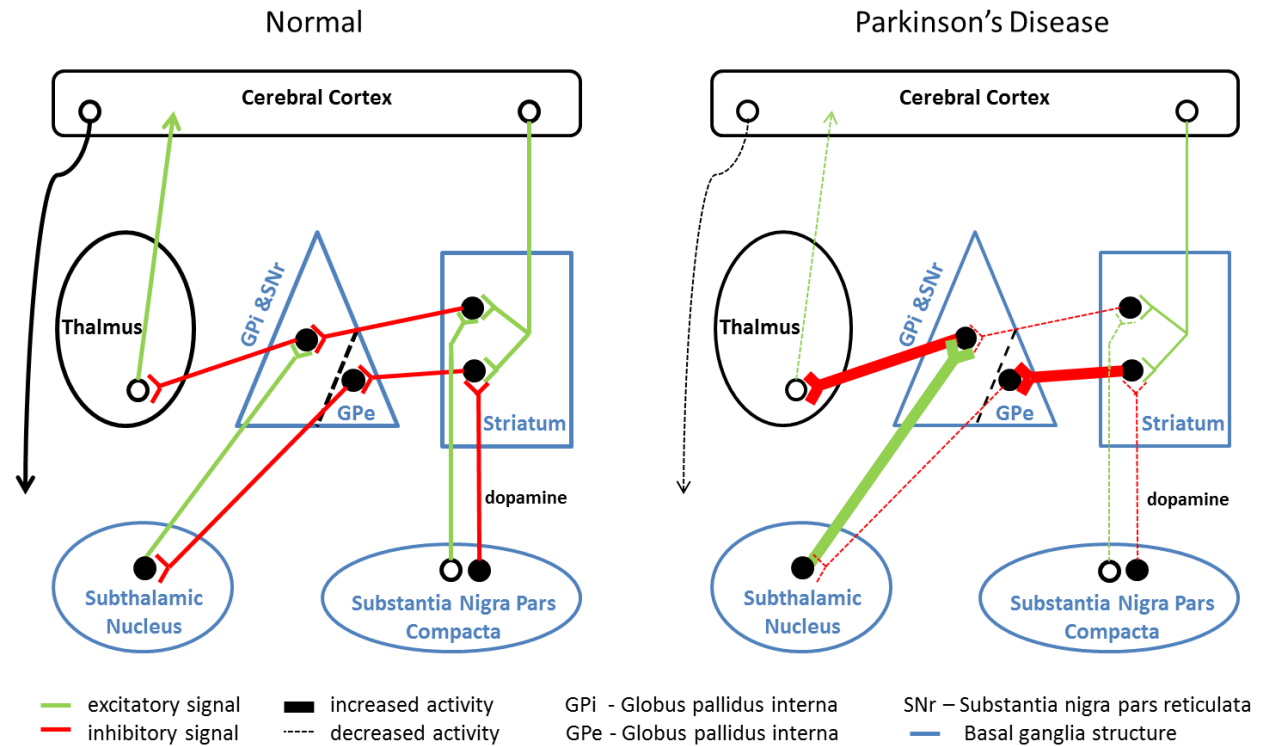
Figure 2.1. Differences in basal ganglia pathways in a normal versus PD brain due to dopaminergic cell loss in the substantia nigra pars compacta (SNc). Ultimately, this dopamine loss of the SNc results in a decreased excitatory signal from the thalmus to the motor area of the cerebral cortex. Note: excitatory connections are depicted as open neurons while inhibitory connections are shown as filled neurons.

CHAPTER 3: Postural Sway as a Measure of Preclinical Postural Instability in Parkinson's Disease

Abstract

Background: Postural instability leading to falls is a debilitating symptom of Parkinson's disease (PD) due to the associated fractures, nursing home placement, and morbidity. However, standard clinical assessments are unable to predict falls. Reducing fall risk and fall-related complications could positively impact quality of life and life expectancy. While previous studies assessed postural instability in PD, an examination of biomechanical parameters to detect preclinical postural instability and measure disease progression is lacking. This work investigates the efficacy of biomechanical parameters as indicators of preclinical balance deficit and their correlation with PD progression.

Methods: Quiet postural sway was measured in mild PD (n=13), moderate PD (n=10) and age-range matched healthy controls (HC, n=21) in eyes open and eyes closed conditions. Foot/floor reactions were measured and linear measures of center of pressure (COP) path and velocity were calculated.

Findings: Trajectory (sway path length, sway path area, mean sway speed), variation (medial-lateral root mean square), and peak (sway path range and peak sway speed) COP measures were significantly greater (p < .05) in mild PD versus HC, and further increased in moderate PD. Schwab and England clinical score best correlated with the biomechanical COP measures.

Interpretation: Biomechanical assessment of postural sway may provide preclinical recognition of postural instability, providing the missing link in PD fall prediction and the opportunity to introduce preventative interventions. To further develop and strengthen postural instability detection, biomechanical parameters need to be investigated across balance tests of varying motor function demands (quasi-static versus dynamic tasks), along with their persistence throughout disease progression and their efficacy in assessing fall risk.

Introduction

Postural instability is a debilitating symptom of Parkinson's disease (PD) as it leads to increased risk of falls (Olanow, Watts et al. 2001, Voss, Biglan et al. 2008). High fall rates in PD patients and the associated increased risk of fracture, nursing home admission and morbidity not only reflect the serious impact of a fall on health and mobility, but also the significant financial impact of falls for both patients and the health care system (Morens, Davis et al. 1996, Rao 2005, Martin 2011). Standard clinical assessments are not sufficiently sensitive to predict falls, and reducing fall risk in PD could not only delay the associated disability and medical cost, but also positively impact patient quality of life and life expectancy (Bloem, Beckley et al. 1998). While targeted therapies that can reduce fall risk are available, they are not commonly implemented until after a fall has already occurred owing to the associated cost and time for both patients and providers (Palmer, Mortimer et al. 1986, Bloem, Grimbergen et al. 2001, Bloem, van Vugt et al. 2001).

Biomechanical assessment of postural control could enhance the efficacy of PD fall assessment through the early detection of postural instability and the ability to monitor its development and progression. Identifying biomechanical measures to detect the onset of postural instability and predict fall risk in PD would provide a quantitative justification to implement fall-reducing therapies earlier and thus help reduce the associated debilitating fall-related consequences (Bloem, van Vugt et al. 2001). Postural instability in PD can be assessed through a range of balance tasks with varying demands on motor control (i.e. quasi-static stance (postural sway), surface translation, balance recovery, and gait initiation) (Bloem, van Vugt et al. 2001, Kim, Allen et al. 2013).

Biomechanical assessment of postural instability during postural sway in eyes open (EO) and/or eyes closed (EC) conditions is an attractive option due to ease for clinical implementation and previous studies demonstrating its efficacy to distinguish postural deficits in a group of PD patients with a range of severities (Hoehn & Yahr stage (H&Y) 1-4) compared to healthy controls (HC) (Horak, Nutt et al. 1992, Horak, Dimitrova et al. 2005, Blaszczyk, Orawiec et al. 2007, Matinolli, Korpelainen et al. 2007, Chastan, Debono et al. 2008, Blaszczyk and Orawiec 2011, Mancini, Horak et al. 2011, Stylianou, McVey et al. 2011, Ickenstein, Ambach et al. 2012, Mancini, Carlson-Kuhta et al. 2012). However, the effect of PD on biomechanical postural sway parameters used to quantify center of pressure (COP) movement characteristics has differed across studies. While some studies have reported that PD decreases some COP postural sway parameters (Horak, Nutt et al. 1992, Horak, Dimitrova et al. 2005), others report that PD increases COP parameters (Blaszczyk and Orawiec 2011, Mancini, Horak et al. 2011, Stylianou, McVey et al. 2011, Ickenstein, Ambach et al. 2012, Mancini, Carlson-Kuhta et al. 2012).

Specifically, previous postural sway studies have shown that COP path trajectory measures (i.e. sway path length and area), variation measures (i.e. root mean squared (RMS) of COP), and peak measures (i.e. sway path range) increase in PD (H&Y 1-4) compared to their HC counterparts (Blaszczyk, Orawiec et al. 2007, Mancini, Horak et al. 2011, Stylianou, McVey et al. 2011, Ickenstein, Ambach et al. 2012). Studies have also found that several COP trajectory and peak measures correlate with total Unified Parkinson's Disease Rating Scale (UPDRS) score and medial-lateral (ML) sway path range correlates with H&Y staging (Blaszczyk, Orawiec et al. 2007, Matinolli, Korpelainen et al. 2007). It is possible that the differences found between PD and HC groups may result from the significant balance deficits often present within the PD group in the more severe stages of disease. While past studies have shown the presence of balance

deficits in PD patients, which often include a broad spectrum of disease stages, compared to HC, no studies have assessed whether such parameters can distinguish the onset of postural instability prior to clinical presentation (mild PD, H&Y 2), and if such parameters persist following clinical presentation of postural instability (moderate PD, H&Y 3).

To determine if biomechanical assessment could detect preclinical balance deficits and the associated changes with disease progression, this study examined the postural sway of PD ("on" medication) and HC participants. Postural sway testing requires minimal space to perform and lesser demands on motor control than dynamic tasks, making it a feasible task to perform in a clinical setting. Further, while the task can be performed "on" or "off "medication, by conducting the experiment "on" medication the results should be similar to the data that could be collected in routine clinical visits (i.e. no withholding medication). Ultimately in order for clinical balance assessment to be comprehensive enough to definitively diagnose the onset of fall risk, likely a multi-faceted approach that would cover several dimensions of functional balance and clinical measures of disease progression would need to be implemented. The present study is a part of a set of studies with the long term goal of developing such a multi-factorial method to detect the onset of postural instability through various clinical balance assessments (McVey, Stylianou et al. 2009, McVey, Amundsen et al. 2013).

To address this unmet need in postural instability assessment, this study had three goals. First, we investigated the differences between HC and PD (PD patients pooled as a single group), a comparison often reported in the literature. We anticipated that PD, compared to HC, would result in greater COP trajectory, variation, and peak measures, consistent with published postural sway studies. Second, we stratified our PD patients into mild and moderate PD subgroups to identify postural sway biomechanical parameters sensitive enough to detect preclinical balance

deficits (mild PD versus HC) and assess their efficacy in monitoring the increasing level of postural instability associated with disease progression (moderate versus mild PD). We hypothesized that a subset of our COP parameters will be sensitive enough to detect the presence of postural instability prior to clinical presentation, and some of these parameters will persist with clinical postural instability progression. Third, we explored how these COP measures correlate with existing clinical measures of PD progression. We hypothesized that some of the postural sway COP measures will correlate with current clinical measures of postural instability and disease progression in PD.

Methods

2.1 Participants

Twenty three patients with PD and twenty one age-range matched healthy controls participated in this study (Table 3.1). A subset of these subjects (n = 12 PD and n = 11 HC) were from a previous study which investigated the effect of visual conditions on young healthy, elderly healthy and PD (Stylianou, McVey et al. 2011). All individuals gave informed written consent as approved by the University's Institutional Review Board. To characterize the effect of PD in general, all PD patients were first considered in a single group; and subsequently in order to analyze the effect of postural instability with disease progression, PD patients were divided into two groups based on their clinical presentation of postural instability: mild PD group (without postural deficits) and moderate PD group (with postural deficits) (Table 3.1).

PD patients were recruited from the University of Kansas Medical Center (KUMC) Parkinson's Disease and Movement Disorder Center. All patients had PD, confirmed by a

neurologist specializing in movement disorders (RP). PD participants were able to walk without assistance, were without severe depression (BDI < 30/63), dementia (MMSE > 24/30), and musculoskeletal or neurologic impairments unrelated to PD, had an H&Y score of 2 (mild PD) or 3 (moderate PD), and had not had neurosurgery for PD. HC participants were recruited from the local community and were without any significant cognitive, musculoskeletal, or neurologic impairment.

2.2 Task

The task for this study has previously been published in detail (Stylianou, McVey et al. 2011). In brief, participants wore standardized footwear and a self-selected natural stance was maintained across repeated trials. Six 30 second postural sway trials (quiet stance with arms at sides) were performed with eyes open (EO) or eyes closed (EC) in random order (3 trials per condition) (Figure 1a). PD participants were instructed to maintain their normal medication schedule and were tested "on" medication (mean (SD) time since last antiparkinsonian dosage: 2.1 (1.0) hours).

2.3 Experimental Measures and Data Analysis

Foot/floor kinetic and video data were collected for all postural sway trials. Kinetic data were collected using AMTI six-channel force plates (Advanced Mechanical Technology Inc., Watertown, MA, USA) and sampled at 1000 Hz using a 16-bit A/D data acquisition system (National Instruments, Austin, TX, USA). Video data were used to ensure subject compliance with postural sway task instructions.

Kinetic data were down sampled to 100 Hz and a low pass second-order Butterworth filter was applied with a 12.5 Hz cutoff frequency. Whole body COP path and velocity was then

calculated for each trial (Figure 1b). COP path was calculated from the output signals of the

force plates in the anterior-posterior (AP) and medial-lateral (ML) direction and COP velocity

was calculated with a fourth order accuracy derivate of the COP path. COP trajectory, variation,

and peak parameters (Table 2) were derived from these measures to quantify postural sway

characteristics for each participant (MATLAB, Natick, MA, USA).

2.4 Clinical Measures

PD subjects were assessed by a specialist from the KUMC Parkinson's Disease and

Movement Disorder Center, using the following clinical measures (Table 1):

Unified Parkinson's Disease Rating Scale (UPDRS): assessment of the overall

progression of PD characterized by: Mentation, Behavior and Mood; Activities of Daily Living;

and a Motor Examination. Scores can range from $0 - 180$, with higher scores reflecting greater

impairment.

Motor Exam: the third section of UPDRS completed by the investigator, that assesses

motor symptoms related to PD. Scores can range from $0 - 108$, with higher scores reflecting

greater impairment.

Pull Test (Postural Stability, UPDRS item 33): assessment of how a patient responds to a

sudden posterior pull in order to characterize the patients' overall postural stability. Scores can

range from $0 - 4$, with higher scores reflecting greater impairment (Fahn, Elton et al. 1987,

Goetz, Poewe et al. 2003).

Schwab and England: estimation of the ability to independently perform activities of

daily living. Scores can range from $100 - 0\%$, with 100% being completely

independent/essentially normal and lower scores reflecting greater dependence (Schwab and England 1969).

2.5 Statistical Analyses:

T-tests were used to compare baseline demographic and disease severity characteristics between groups. Two types of statistical analysis were used to assess the outcome parameters of this study.

First, all individual data means were analyzed using repeated measures Analysis of Variance (ANOVA) with group (mild PD, moderate PD, HC) as factors for both EO and EC trials. Significant group differences ($p < .05$) were determined with an ANOVA, Tukey-Kramer multiple comparison post hoc tests when appropriate, and a Bonferroni correction for multiple comparisons. Second, because we anticipated our PD groups to have high variation (large within group standard deviations) for COP measures as has been observed in past literature (Blaszczyk and Orawiec 2011, Stylianou, McVey et al. 2011, Mancini, Carlson-Kuhta et al. 2012), in order to account for this possibility of systematically high variations, a "normal" threshold was utilized to compare the HC to PD groups.

The HC group mean plus one standard deviation (SD) for each of the biomechanical parameters was calculated and then served as a threshold for comparison of the "normal" parameter values versus the corresponding parameter values within the mild PD and moderate PD groups. Each subjects' parameters were then compared to this "normal" threshold set to determine if the subject fell above (greater than the HC threshold, reflecting increased postural instability compared to controls) or below (less than the HC threshold, no difference in postural instability compared to controls). A Fischer's exact test with a Bonferroni correction for multiple comparisons was used to test for significant differences across groups ($p < .05$) (SAS 9.4, SAS

Institute Inc., Cary, NC). Lastly, a Spearman rank correlation analysis was used to characterize the relationship between the mean experimental postural sway parameters and the clinical parameters for the PD participants (SAS 9.4, SAS Institute Inc., Cary, NC).

Results

The COP trajectory, variation, and peak postural sway measures were first considered for both the general PD (n = 23) versus HC (n = 21) groups and then further analyzed for the mild PD (n = 12) and moderate PD (n = 11) subgroups versus HC (n = 21) to explore the relationship of these parameters to postural instability. No significant differences in anthropometric data (age, height or mass) were found between the groups and these data were not considered further.

3.1 Effect of PD on Postural Sway Parameters

Trajectory Measures: During EO and EC trials, sway path length, AP and ML sway path length, and mean sway speed were significantly greater ($p < .05$) in the PD group compared to HC. Sway area was significantly greater in the PD population compared to HC for EO trials but not for the EC trials ($p = .0556$). (Table 3)

Variation Measures: The PD group compared to HC had significantly greater ($p < .05$) AP RMS of COP during EO and EC trials. ML RMS of COP was significantly greater for PD than HC only during EO trials. (Table 3)

Peak Measures: During EO and EC trials, AP and ML sway path range and peak sway speed were significantly greater ($p < .05$) in the general PD group compared to HC. (Table 3)

3.2 Effect of Postural Instability on Postural Sway Parameters

Trajectory Measures: For both EO and EC trials, the moderate PD group accounted for the differences between the PD population and HC ($p < .05$) for sway path length, AP and ML sway path length, sway area, and mean sway speed. Sway path length, ML sway path length, and mean sway speed were all significantly greater in moderate PD compared to mild PD for EO and EC conditions. While all trajectory measures trended towards higher means for mild PD compared to HC, there were no significant differences between these groups for any trajectory measures. (Table 3)

Variation Measures: For both EO and EC trials, the moderate PD group accounted for the differences ($p < .05$) between the PD population and HC for AP RMS of COP. AP RMS of COP was all significantly greater in moderate PD compared to mild PD for both visual conditions. Both variation measures trended towards higher means for mild PD compared to HC, but there were no significant differences between mild PD and HC for either measure. (Table 3)

Peak Measures: For the EO trials, AP sway path range was significantly greater ($p < .05$) in the mild PD compared to the HC group. AP sway path range further increased for the moderate PD group, and was significantly greater ($p < .05$) than the HC group but was not significantly different from the mild PD group. For the EC trials, the moderate group accounted for the differences from the HC group ($p < .05$) in AP sway path range. The moderate PD group also accounted for the differences from the HC group in ML sway path range for the EO trials. Lastly, while the moderate PD group explained the increased peak sway speed in the EO trials, the mild PD group had a significantly faster peak sway speed compared to the HC population for the EC trials. Peak sway speed further increased for the moderate PD group for EC trials, and was significantly greater ($p < .05$) than the HC group but was not significantly different from the mild PD group. (Table 3)

3.3 Effect of Threshold Analysis on Early Postural Instability Indication for Postural Sway Parameters

　　Trajectory Measures: For the EO trials when comparing the PD groups to the "normal" threshold (mean + SD of the HC mean), there were significantly more mild PD participants above the threshold compared to HC for sway path length, sway area, and mean sway speed (p < .05). There were no significant differences between the HC and mild PD groups for trajectory measures during EC trials (Table 4).

　　Variation Measures: For the EO trials, there were significantly more mild PD participants exhibiting increased postural instability (above the threshold) compared to HC for ML RMS of the COP, however there were no significant differences in these groups during EC trials (Table 4).

　　Peak Measures: While there were no significant differences between the HC and mild PD group for the EO peak parameters, mild PD had a significantly greater frequency of participants above the threshold for ML sway path range compared to HC during EC trials (Table 4).

3.4 Clinical Correlation with Postural Sway Parameters

　　Schwab and England score had the highest correlation with the postural sway parameters with 7/10 (EO condition) and 6/10 (EC condition) biomechanical parameters being significantly correlated (p < .05) with the Schwab and England score. The UPDRS Motor score was significantly correlated (p < .05) with 6/10 biomechanical parameters for EO trials and 1/10 for EC trials. AP sway path range was the only biomechanical parameter that significantly correlated (p < .05) with the total UPDRS score. Only AP RMS of COP for EC trials was significantly correlated with the Pull Test (Postural Stability, UPDRS item 33). (Table 5)

Discussion

This study sought to investigate if a quasi-static biomechanical task could detect preclinical postural instability in PD and if changes in postural instability with disease progression could be observed. Understanding the effect of PD on postural sway has received much attention recently, with studies demonstrating the efficacy of biomechanical parameters to distinguish differences between PD and healthy controls (HC) (Blaszczyk and Orawiec 2011, Mancini, Horak et al. 2011, Stylianou, McVey et al. 2011, Ickenstein, Ambach et al. 2012, Mancini, Carlson-Kuhta et al. 2012), the effects of antiparkinsonian medication (Nantel, McDonald et al. 2012, Revilla, Larsh et al. 2013, Greve, Luna et al. 2014), the effect of surgical intervention (Krishnamurthi, Mulligan et al. 2012, Nantel, McDonald et al. 2012), and the effects of physical therapies (Li, Harmer et al. 2012, King, Salarian et al. 2013).

This work provides the next step in biomechanical assessment of postural sway in PD through investigating if such parameters could serve as biomarkers of early postural deficits. By considering postural sway with both eyes opened and closed, this study provided additional information as to how PD affects postural control with (and without) reliance of vision to stabilize postural control across the clinical progression of postural instability (Chagdes, Rietdyk et al. 2009). Parameters that both identify preclinical postural deficits and measure changes in postural instability over the course of PD would allow clinicians to identify at risk PD patients before they begin to fall and develop interventions to prevent or reduce falling throughout the disease course. Sensitive and specific biomarkers of postural instability would also be valuable for properly placing PD participants in therapeutic clinical trials.

4.1 Effect of PD Compared to HC

The characteristic, variation, and peak measures from this study were all significantly different for the general PD group compared to HC (Figure 1, Quadrant I) and are comparable to previously reported values in the literature for both eyes opened and closed trials (Blaszczyk, Orawiec et al. 2007, Matinolli, Korpelainen et al. 2007, Chastan, Debono et al. 2008, Ickenstein, Ambach et al. 2012, Mancini, Carlson-Kuhta et al. 2012). Some of the means reported in the current study such as sway path length and sway path area are higher than those in previous studies, but this is likely due to the large observed variation (standard deviations) across PD participants for these parameters and differences in the inclusion/exclusion criteria used across studies. This study included PD patients in the H&Y stages 2-3, where other studies often also include PD patients at the less severe H&Y stage 1.

Further, sway measures in the AP direction tended to be better at discriminating between PD and HC than in the ML direction, which is in contrast to studies that have suggested that the ML direction may be an equally effective indicator of postural instability changes in PD. These differences may be related to methodological differences between studies. For example, if the stance width was controlled by placing the feet together, the feet may have been closer compared to a natural stance; or if subjects were barefoot compared to wearing a standard shoe, any of which could affect ML values compared to this study in which subjects self-selected their stance wearing footwear (Mitchell, Collins et al. 1995, Viitasalo, Kampman et al. 2002, Blaszczyk, Orawiec et al. 2007, Matinolli, Korpelainen et al. 2007).

4.2 Effect of Postural Instability Clinical Presentation (mild and moderate PD) Compared to HC

When comparing the groups based on group means per parameter (ANOVA analysis), during both the EO and EC trial conditions the trajectory and variation measures did not reflect evidence of preclinical postural instability (mild PD versus HC). The differences between PD

and HC for these parameters were explained by the moderate PD group (H&Y 3) which had clinical presentation of postural instability (Figure 2, Quadrant II). Sway path length, ML sway path length, mean sway speed and AP RMS of COP were significantly greater in the moderate PD group compared to the mild PD group, and therefore, these parameters may be specific to clinical progression of postural instability (Figure 2, Quadrant III). Yet because the mild PD group was not significantly different compared to the HC group for these parameters, for this mode of analysis they were not sensitive enough to detect preclinical postural instability (Figure 2, Quadrant III and IV).

However, the peak measures of AP sway path range (EO trials) and peak sway speed (EC trials) did show evidence of preclinical postural instability (Figure 2, Quadrant IV). Despite no clinical presentation of postural instability, mild PD had increased AP sway path range and peak sway speed that showed evidence of diminished postural control versus HC, and these parameters progressed in moderate PD. With visual feedback available (EO trials), increased AP sway path range reflected larger excursions of postural control. With visual feedback removed (EC trials), increased peak sway speed reflected larger instantaneous changes, possibly reflecting an adoption of a more stiff postural control strategy.

4.3 Threshold Analysis for Early Postural Instability Indication for Postural Sway Parameters

When comparing the mild and moderate PD groups to the HC group based on the "normal" threshold (HC mean + SD), we sought to eliminate the impact of the large variability present within the PD groups. By definition, H&Y staging bins subjects based on relative postural instability deficit due to PD and is not a continuous measure like postural sway biomechanical measures. As a result, by nature of how our groups were clinically defined in combination with the small sample size of this pilot study, our PD groups as expected had larger

amounts of variability within their groups (larger group standard deviations) compared to the HC group. Through using this "normal" threshold, we hypothesized that similar to the precedent of other clinical measures that also rely on a "normal" threshold (i.e. BMI for obesity classification) that such threshold analysis may help to significantly elicit the observed trends in the overall group means for the mild PD group compared to HC, reflecting preclinical indication of postural instability.

Using the threshold analysis, the frequency of mild PD patients that had larger COP parameter values than the "normal" threshold compared to HC was significantly greater ($p < .05$) for trajectory (sway path length, sway area and mean sway speed for EO trials), variation (ML RMS of COP for EO trials), and peak parameters (ML sway path range for EC trials) (Figure 2. Quadrant IV). However despite these observed differences between the HC and mild PD group, this method of group comparison was unable to differentiate between the mild and moderate PD groups. While this result is expected due to the nature of this pilot study (small sample size) and the definition of the threshold,[2] this suggests that while both statistical methods help to elicit early detection of postural instability in PD, future study with larger sample sizes is needed to better understand the sensitivity and specificity of these parameters related to postural instability and fall risk in PD.

4.4 Parameter Selection of Early Postural Instability Onset Methods

Analysis based on individual subject means (Section 4.2) and thresholds (Section 4.3) uniquely provided evidence of preclinical postural instability in mild PD compared to HC. When comparing individual means, only peak parameters (AP sway path range and peak sway speed)

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[2] A threshold analysis with the mean + 2 SD was also calculated in the preparation of this manuscript to test the robustness of the parameters and to see if mild to moderate PD differentiation could occur, however no results were significant so they are not presented here. See Appendix B.i. for this additional analysis results.

revealed significant differences between mild PD and HC while for the threshold analysis trajectory parameters (sway path length, sway area, mean sway speed) had the most significant differences. These observed trends are likely possible for two reasons. First, the functional limits of sway path range and peak sway speed likely have tighter physiological constraints in order to maintain upright balance. There is most likely a limit to the increase in the COP excursions and/or increase in COP speed before balance is lost, potentially explaining the smaller within group variability for these measures and associated significance when comparing individual means. Conversely, trajectory measures are cumulative and are additive over the whole trial, explaining why small differences in an individual subject can magnify over 30 seconds, potentially explaining the large within group variability and thus significant results only when using threshold analysis. Using multiple methods of feature selection may help to account for these fundamental differences in the overall nature of the parameters observed, providing greater incite as to the subtle changes that may occur early in the disease progression.

Trajectory, variation, and peak COP postural sway parameters show promise as biomarkers for detecting postural instability earlier in PD, however they are unavailable during current clinical assessment of postural stability. Because these parameters cannot be quantified by visual inspection, use of biomechanical technology in the clinical setting may allow for additional information during balance assessment. The ability to detect subtle changes in postural control with these parameters may provide early indication of postural instability onset, providing additional information for PD fall prediction and the opportunity to introduce fall risk interventions.

4.5 Clinical Correlation

Schwab and England scoring had the strongest correlation with the postural sway biomechanical measures, with over half of the biomechanical parameters correlating with this clinical score for both EO and EC trials. The Schwab and England score is a measure of independent performance of activities of daily living and is not directly based on postural stability; however, the correlation of these scores with the biomechanical parameters warrants further exploration into this score and the associated correlation with postural instability during quasi-static stance. Further, AP sway path range, the biomechanical marker that showed earlier evidence of postural instability during the EO trials, was significantly correlated with all measured clinical scores except the Pull Test (Postural Stability, UPDRS item 33). Interestingly, despite AP sway path range appearing to be a good indicator of early postural instability during EO postural sway, the current clinical measure of postural stability (the Pull Test) is not reflective of these differences. If these measures are reflecting task-specific deficits, potentially a static measure of postural instability (like postural sway) coupled with existing dynamic measures of postural instability (i.e. the Pull Test) could provide further information to assess a patient's overall motor control and balance deficits.

Limitations of this study include the small sample size, the potential influence of outliers, that PD participants were tested "on" medication, and that the balance assessment task was quasi-static. While it is recognized that outliers can significantly impact the variability of the data for a small sample size, the systemic large variations within the PD groups (based on H&Y staging) may also demonstrate the need for alternate, more quantitative based parameters to limit within-group variability when scoring patients. Because of the clinically driven nature of this research, these choices were made in order to reflect a potential clinical balance assessment that is possible to implement and does not require patients to alter their dosing schedule ("on" medication) so the

task could be more easily translated to routine clinical care. However, future studies should include "off" medication assessments or inclusion of de novo subjects to determine if medications are masking subtle changes in balance that may further enhance the detection of those at risk for postural instability and falling. In future studies, larger sample sizes are also needed to determine if biomechanical parameters can distinguish preclinical postural instability for activities of varying demands on motor function (e.g. postural sway, balance disturbances, gait initiation, and steady state gait), and if these parameters persist throughout disease progression. Further analysis with increasingly sophisticated mathematical models may help establish the threshold where the onset of postural instability can be confirmed from multiple biomechanical and clinical measures.

Conclusion

This study is a part of an ongoing effort to ascertain biomechanical parameters to identify preclinical postural instability in PD patients. Trajectory, variation, and peak postural sway measures show promise as parameters that may detect postural instability earlier than current clinical assessment as they were significantly greater in the mild PD group compared to HC, and these parameter means increased in moderate PD. Once validated, these biomechanical parameters could serve as part of a multi-faceted fall risk assessment that would cover several dimensions of functional balance and clinical measures of disease progression. Future work with larger sample sizes and additional tasks is needed to ensure such parameters are correlated to disease progression, sensitive to a decrease in subclinical postural stability, specific to fall risk, and simple enough to perform during routine clinical visits.

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Table 3.1. Mean (SD) Demographic and Clinical Data for Parkinson's Disease (PD) Subjects and Healthy Controls (HC)

I. Subject Demographic Data

	Gender	Age (years)	Height (m)	Mass (kg)
HC	M=13, F=8	66 (8)	1.71 (.08)	79 (28)
PD	M=15, F=8	65 (7)	1.70 (.09)	85 (17)
Mild PD	M=7 , F=6	62 (8)	1.67 (.08)	74 (11)
Moderate PD	M=8, F=2	68 (4)	1.73 (.10)	95 (15)

II. Parkinson's Disease Specific Participant Data

	H&Y Score	Years Since Diagnosis	UPDRS Total	UPDRS Motor	UPDRS item 33 (Pull Test)	Schwab & England (%)
PD	2.4 (.5)	6 (4)	37 (16)	24 (9)	1 (.9)	84 (8)
Mild PD	2 (0)	6 (5)	28 (13)	20 (7)	.3 (.4)	88 (6)
Moderate PD	3 (0)	7 (3)	48 (11)	30 (8)	1.8 (.6)	79 (7)

M – male, F – female, H&Y – Hoehn and Yahr, UPDRS – Unified Parkinson's Disease Rating Scale.
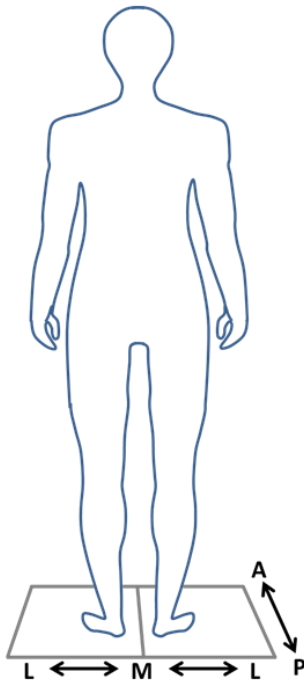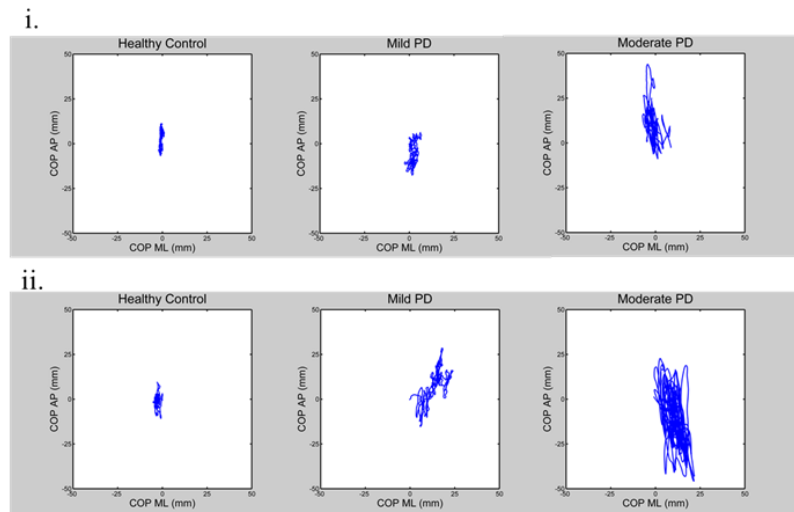
Figure 3.1. a. Schematic of the experimental setup for the postural sway task. b. Representative center of pressure (COP) traces for HC, mild PD, and moderate PD during eyes open (i) and eyes closed (ii) trials.

Table 3.2. Abbreviations and Descriptions for COP Postural Sway Parameters

Abbreviation	Parameter Name (units)	Description
Trajectory Parameters:		
SPL	Sway Path Length (mm)	Total distance the whole body COP travels along its path in any direction during the postural sway task
AP SPL	AP Sway Path Length (mm)	Total distance the whole body COP travels along its path in the anterior-posterior direction during the postural sway task
ML SPL	ML Sway Path Length (mm)	Total distance the whole body COP travels along its path in the medial-lateral direction during the postural sway task
SA	Sway Area (mm^2)	Total area the COP path encompasses during the postural sway task
MSS	Mean Sway Speed (mm/s)	Average rate of change of the magnitude of the center of pressure displacement during the postural sway task
Variation Parameters:		
AP RMS	AP RMS of COP (mm)	Square root of the mean squared deviation from the average COP value in the anterior-posterior direction during the postural sway task
ML RMS	ML RMS of COP (mm)	Square root of the mean squared deviation from the average COP value in the medial-lateral direction during the postural sway task
Peak Parameters:		
AP SPR	AP Sway Path Range (mm)	Maximum displacement the COP deviates from the center point in the anterior-posterior direction during the postural sway task
ML SPR	ML Sway Path Range (mm)	Maximum displacement the COP deviates from the center point in the medial-lateral direction during the postural sway task
PSS	Peak Sway Speed (mm/s)	Maximum change in the magnitude of the center of pressure displacement over time during the postural sway task

Table 3.3. Mean (SD) COP Parameters for Eyes Open and Eyes Closed Postural Sway

	Trajectory				Variation			Peak		
	SPL	AP SPL	ML SPL	SA	MSS	AP RMS	ML RMS	AP SPR	ML SPR	PSS
Eyes Open										
HC	277.8 (48.9)	227.1 (47.5)	115.7 (35.0)	124.2 (84.9)	9.7 (1.7)	3.8 (1.1)	1.3 (1.1)	22.1 (4.9)	8.4 (4.0)	53.3 (22.5)
PD	598.0 (511.4)*	419.8 (298.5)*	329.0 (364.5)*	491.1 (730.0)*	20.5 (17.0)*	5.3 (1.8)*	3.0 (3.7)*	32.3 (11.4)*	19.1 (17.3)*	90.0 (47.8)*
Mild PD	427.7 (172.8)	332.2 (134.1)	201.3 (115.5)	356.2 (292.0)	15.3 (6.2)	4.7 (1.2)	2.9 (1.5)	30.1 (9.7)*	17.0 (8.7)	79.6 (33.6)
Moderate PD	656.7 (415.0)*+	531.9 (328.0)*	279.5 (243.9)*+	628.4 (908.7)*	23.5 (15.0)*+	5.4 (2.0)*+	3.6 (2.8)	35.8 (15.3)*	22.3 (18.9)*	103.5 (61.0)*
Eyes Closed										
HC	390.4 (133.1)	335.3 (129.3)	138.2 (53.4)	197.2 (164.1)	13.6 (4.6)	4.1 (1.4)	1.6 (1.4)	26.4 (8.6)	10.7 (8.0)	72.5 (27.7)
PD	906.2 (677.4)*	671.0 (477.6)*	452.3 (469.4)*	981.0 (1815.6)	31.2 (22.7)*	6.3 (2.5)*	3.9 (6.2)	40.7 (17.5)*	26.5 (31.9)*	143.6 (87.0)*
Mild PD	819.5 (709.3)	533.6 (410.3)	495.0 (502.7)	666.5 (1062.2)	27.4 (23.7)	5.9 (2.1)	3.2 (4.9)	35.1 (13.3)	21.9 (24.9)	128.8 (84.1)*
Moderate PD	1230.6 (827.8)*+	851.9 (591.5)*	676.8 (600.2)*+	1439.4 (2558.1)	41.1 (27.6)*+	7.2 (2.6)*+	4.3 (8.2)	47.1 (19.0)*	32.0 (44.2)	162.9 (91.4)*

COP- center of pressure, HC – healthy controls, PD – Parkinson's Disease, SPL – sway path length, AP SPL – anterior-posterior sway path length, ML SPL – medial-lateral sway path length, SA – sway area, MSS – mean sway speed, AP RMS – anterior-posterior root mean square, ML RMS – medial-lateral root mean square, AP SRP – anterior-posterior sway path range, ML SPR – medial-lateral sway path range, PSS – peak sway speed.

* indicates the parameter was significantly different (p < .05) than the HC group.

+ indicates the parameter was significantly different (p < .05) than the mild PD group (for mild PD versus moderate PD comparisons).

Table 3.4. Threshold Analysis Results (number subjects greater than threshold/group size) for COP Parameters for Eyes Open and Eyes Closed Postural Sway

	Trajectory				Variation			Peak		
	SPL	AP SPL	ML SPL	SA	MSS	AP RMS	ML RMS	AP SPR	ML SPR	PSS
Eyes Open										
HC	4/21	3/21	3/21	5/21	4/21	5/21	3/21	5/21	5/21	2/21
PD	19/23*	17/23*	17/23*	18/23*	19/23*	12/23	15/23*	13/23	16/23	12/23
Mild PD	11/13*	9/13	8/13	11/13*	6/13	10/13*	6/13	6/13	10/13	6/13
Moderate PD	8/10*	8/10*	9/10*	7/10	8/10*	6/10	5/10	7/10	6/10	6/10*
Eyes Closed										
HC	3/21	3/21	4/21	4/21	4/21	4/17	2/21	4/21	2/21	3/21
PD	14/23	13/23	14/23	14/23	14/23	12/23	9/21	13/23	14/23	14/23
Mild PD	7/13	6/13	7/13	7/13	7/13	4/13	7/13	6/13	8/13*	7/13
Moderate PD	7/10	7/10	7/10	7/10	7/10	8/10	2/10	7/10	6/10	7/10

COP- center of pressure, HC – healthy controls, PD – Parkinson's Disease, SPL – sway path length, AP SPL – anterior-posterior sway path length, ML SPL – medial-lateral sway path length, SA – sway area, MSS – mean sway speed, AP RMS – anterior-posterior root mean square, ML RMS – medial-lateral root mean square, AP SRP – anterior-posterior sway path range, ML SPR – medial-lateral sway path range, PSS – peak sway speed.

* indicates the parameter was significantly different (p < .05) than the HC group.

+ indicates the parameter was significantly different (p < .05) than the mild PD group (for mild PD versus moderate PD comparisons).

Table 3.5. Spearman Rank Correlation Coefficients for Clinical and COP Parameters for PD Subjects

	Trajectory				Variation			Peak		
Eyes Open	SPL	AP SPL	ML SPL	SA	MSS	AP RMS	ML RMS	AP SPR	ML SPR	PSS
UPDRS	0.3326	0.3771	0.2664	0.0865	0.2654	0.2891	-0.1567	0.4225*	0.0395	0.2071
Motor Exam	0.5303*	0.6274*	0.3917	0.3882	0.4818*	0.5373*	0.0347	0.5610*	0.2258	0.4224*
Pull Test	0.2390	0.3023	0.2038	0.1617	0.1617	0.3304	-0.2882	0.1898	-0.0070	0.0633
Schwab & England	-0.5175*	-0.6836*	-0.3772	-0.4246*	-0.4404*	-0.5532*	-0.1056	-0.5823*	-0.2888	-0.4312*
Eyes Closed	SPL	AP SPL	ML SPL	SA	MSS	AP RMS	ML RMS	AP SPR	ML SPR	PSS
UPDRS	0.3099	0.3306	0.2945	0.2308	0.2980	0.3880	-0.0860	0.3647	0.2006	0.3385
Motor Exam	0.4095	0.3872	0.4060*	0.2397	0.3971	0.4729*	0.0099	0.3487	0.1362	0.3387
Pull Test	0.0914	0.0633	0.1406	-0.0352	0.0773	0.4499*	-0.3514	0.1265	-0.1968	-0.0141
Schwab & England	-0.4705*	-0.4746*	-0.4358*	-0.4005	-0.4857*	-0.5006*	-0.0964	-0.3817	-0.2670	-0.4511*

UPDRS – Unified Parkinson's Disease Rating Scale, PD – Parkinson's disease, SPL – sway path length, AP SPL – anterior-posterior sway path length, ML SPL – medial-lateral sway path length, SA – sway area, MSS – mean sway speed, AP RMS – anterior-posterior root mean square, ML RMS – medial-lateral root mean square, AP SRP – anterior-posterior sway path range, ML SPR – medial-lateral sway path range, PSS – peak sway speed.

* indicates the Spearman Rank Correlation Coefficient was significant (p-value ≤ .05) for the comparison listed

I. HC v. PD			IV. HC v. Mild PD		
Trajectory	Variation	Peak	Trajectory	Variation	Peak
SPL	AP RMS	AP SR	SPL	ML RMS	AP SPR
AP SPL	ML RMS	ML SR	SA		ML RMS
ML SPL		PSS	MSS		PSS
SA					
MSS					
II. HC v. Moderate PD			III. Mild PD v. Moderate PD		
Trajectory	Variation	Peak	Trajectory	Variation	Peak
SPL	AP RMS	AP SR	SPL	AP RMS	
AP SPL	ML RMS	ML SR	ML SPL		
ML SPL		PSS	MSS		
SA					
MSS					

Reflects Postural Instability Progression

Earlier Indicator of Postural Instability Onset

Figure 3.2. Quadrant chart depicting the significance of each center of pressure parameter per group comparison and the relative ability of the parameter to reflect progression and preclinical indication of postural instability. Parameters listed in each quadrant are significantly different (p < .05) for the groups being compared. Parameters not listed in a quadrant did not have significant differences for that group comparison.

Legend: HC – healthy controls, PD – Parkinson's Disease, SPL – sway path length, AP SPL – anterior-posterior sway path length, ML SPL – medial-lateral sway path length, SA – sway area, MSS – mean sway speed, AP RMS – anterior-posterior root mean square, ML RMS – medial-lateral root mean square, AP SRP – anterior-posterior sway path range, ML SPR – medial-lateral sway path range, PSS – peak sway speed.

CHAPTER 4: Principal Component Analysis of Postural Sway for Tracking Preclinical Onset and Progression of Postural Instability in Parkinson's Disease

Abstract

Background: Postural instability is a debilitating Parkinson's disease (PD) symptom because it increases risk of falls and is resistant to current therapies; however, standard clinical assessments are unable to predict falls. Biomechanics based assessment with the ability to more quantitatively score postural instability onset and progression in PD could fulfill this unmet need.

Methods: A principal component analysis (PCA) model based on biomechanical center of pressure (COP) measures of postural sway and clinical measures of PD progression for mild PD (n=13), moderate PD (n=10) and age-range matched healthy controls (HC, n=21) for eyes open and closed conditions was calculated. PCA was first used for parameter selection of inputs primarily driving the variation in the data (PCA $_{initial}$ model). Then, a reduced parameter model based on the selected parameters (PCA $_{selection}$ model) was calculated to determine if PCA could detect preclinical postural instability and its changes with clinical PD progression.

Findings: Parameter selection resulted in a combination of biomechanical and clinical measures (n=5) based on the PCA $_{initial}$ model. The scores of the first principal component (PC 1) for the PCA $_{selection}$ models were able to significantly ($p < 0.05$) differentiate both preclinical postural instability (mild PD versus HC) and changes with disease progression (mild PD versus moderate PD and moderate PD versus HC). COP AP sway path length and a velocity measure were the 2 most influential parameters for PC 1 in both the eyes open and eyes closed PCA $_{selection}$ models.

Interpretation: PCA based on postural sway biomechanical parameters and clinical measures shows promise as a potential modeling tool for more quantitative scoring of postural instability progression in PD. Future work that explores PCA for parameter selection and postural instability differentiation in PD with larger sample sizes and predictive modeling is needed.

Introduction

Postural instability is one of the most incapacitating symptoms of Parkinson's disease (PD) because it increases fall risk and is resistant to current therapies (Olanow, Watts et al. 2001, Michatowska, Fiszer et al. 2005). Unfortunately, falls are currently one of the greatest unmet needs in PD because standard clinical assessments are not sensitive to predict falls (Bloem, Beckley et al. 1998) and interventions typically do not occur until after a fall episode has occurred (Bloem, Grimbergen et al. 2001). In a recent survey of individuals with Parkinson's disease, their caretakers, and family members, the number one participant priority for future research was identified as improving balance and falls (Deane, Flaherty et al. 2014). Accurate assessment of postural instability and prediction of fall risk is a crucial need in clinical care of PD patients. Biomechanics based assessment with the ability to more quantitatively score postural instability onset and progression in PD could fulfill this unmet need.

Recognizing that balance maintenance is a complex system, finding a single parameter from a balance assessment task that provides a definitive diagnosis of postural deficit onset in PD is considered unlikely. Rather, considering the cumulative effect of biomechanical parameters with additional clinically available measures is likely necessary. In order to have a means to combine biomechanical and clinical parameters with the goal of subject differentiation, a method to elicit the cumulative effect of the variation within these variables across both healthy controls (HC) and PD participants is needed to gain a better understanding of these relationships. Principal Component Analysis (PCA) is such a statistical method used to detect and emphasize the similarities, differences and patterns in a data set in order to make inferences about a population group.

PCA with a correlation matrix structure involves using a data set of various (normalized) variables to calculate a correlation matrix and the associated eigenvalues and eigenvectors to find the direction of maximum variation in the data. The resultant principal components (eigenvector, PCs) are orthogonal matrices that are linear combinations of the ordinal variables used to make inferences about which variables are primarily responsible for the variation in the data. Because each principal component accounts for the cumulative effect of all the input variables, trends and patterns in the data that are not detectable when considering each variable independently can be determined using PCA (Jolliffe 2002, Abdi and Williams 2010). Therefore, PCA shows promise as a useful tool to assess whether patterns in a set of variables exist in order to make inferences about population groups.

Recent studies have shown the efficacy of using PCA on biomechanical parameters to extract information about the traits of static and dynamic tasks (Rocchi, Chiari et al. 2004, Rocchi, Chiari et al. 2006, Labbe, de Guise et al. 2010, Muniz, Liu et al. 2010, Mantovani, Lamontagne et al. 2012, Muniz, Nadal et al. 2012, Kobayashi, Hobara et al. 2014). PCA based on biomechanical parameters has had the ability to select the primary features and variables driving the variation in a data set, as well as differentiate different pathologies (Landry, McKean et al. 2007, Labbe, de Guise et al. 2010, Muniz, Liu et al. 2010, Muniz, Nadal et al. 2012, Kobayashi, Hobara et al. 2014). Specifically, PCA has been used in analysis of the quasi-static task postural sway to assess feature selection of postural sway characteristics in young healthy adults (Rocchi, Chiari et al. 2004) and to assess the impact of "on" versus "off" medication in Parkinson's disease (Rocchi, Chiari et al. 2006). In these studies, parameters that reflect the overall center of pressure (COP) trajectory and variation were found to be the principal drivers of variation within the data set (Rocchi, Chiari et al. 2004, Rocchi, Chiari et al. 2006).

Additionally, traditional biomechanical assessment of the postural sway task in PD through COP measures has shown promise as this task can distinguish postural deficits in PD for a range of severities (Hoehn & Yahr stage (H&Y) 1-4) compared to healthy controls (HC) (Horak, Dimitrova et al. 2005, Matinolli, Korpelainen et al. 2007, Chastan, Debono et al. 2008, Blaszczyk and Orawiec 2011, Stylianou, McVey et al. 2011, Ickenstein, Ambach et al. 2012, Mancini, Carlson-Kuhta et al. 2012). While no previous studies addressed the use of postural sway for preclinical postural instability indication, a recent study by our laboratory found that several trajectory (i.e. COP sway path length), variation (root mean square of COP) and peak postural sway parameters (peak COP sway path speed) were able to detect preclinical evidence of postural instability in PD patients without clinical presentation of postural instability (mild PD, H&Y 2 versus HC). And further, these parameters continued to increase with disease progression (moderate PD, H&Y 3, with clinically present postural instability, was significantly different than HC, and their mean values trended higher than mild PD). However, no individual parameter was able to reach statistical significance in detecting both preclinical onset of postural instability (mild PD versus HC) and specificity to clinical disease progression (mild PD versus moderate PD) (Barnds Dissertation Chapter 3).

Past studies reflect the ability of PCA to be successfully applied to the postural sway task, and postural sway shows promise as a potential indicator of preclinical postural instability in PD. However, no studies have assessed whether PCA could be a valuable tool to score the overall progression of postural instability related to preclinical onset and clinical disease progression of postural instability. To address this unmet need in tracking the onset and progression of postural instability, this study used PCA modeling toward two goals: parameter selection and group differentiation.

Toward our first goal, our object was to determine if PCA based on biomechanical and clinical parameters could reduce the number of variables needed to explain the overall variation in the data. Based on a PCA model with clinical (i.e. Unified Parkinson's Disease Rating Scale (UPDRS), Schwab and England scores) and biomechanical (i.e. COP trajectory, variation, peak postural sway measures) parameters as inputs, we performed a feature selection process on the PCA model to determine which parameters were primarily responsible for the variation in the overall data set. We hypothesized that a combination of clinical and biomechanical parameters would account for the variation in the data for the HC, mild PD and moderate PD participants. For our second goal, we sought to determine if a PCA model based on parameter selection could not only detect preclinical balance deficit (HC versus mild PD), but that the PCA model would also reflect postural instability progression in PD (mild PD versus moderate PD). We hypothesized that some of the resultant principal component scores (eigenvectors) would be able to differentiate both early onset and progression of postural instability with increasing PD progression.

Methods

2.1 Participants

The methods and materials for the biomechanical task of this study have been previously published in detail (Stylianou, McVey et al. 2011). A brief description of them follows. All participants gave informed written consent as approved by the University's Institution Review Board. Thirteen participants with mild PD (H&Y 2; age 62 ± 8.2 years; height $1.7 \pm .10$ m; mass 76 ± 13 kg), ten participants with moderate PD (H&Y 3; age 68 ± 3.9 years; height $1.7 \pm .10$ m;

mass 95 ±17 kg) and twenty one age-range matched healthy controls (age 66 ±7.5 years; height 1.7 ±.10 m; mass 79 ±28 kg). A subset of these participants (n = 12 PD and n = 11 HC) were a part of a previous study looking at the effect of Parkinson's disease on traditional measures of postural sway during different visual conditions (Stylianou, McVey et al. 2011).

PD participants were recruited from the KUMC Parkinson's Disease and Movement Disorders Clinic and had their PD diagnosis confirmed by a movement disorder specialist (RP). PD participants were able to stand on their own, did not have significant depression (BDI < 30/63), dementia (MMSE > 24/30), musculoskeletal or neurologic impairments unrelated to PD, deep brain stimulators and had an H&Y score of 2 (mild PD) or 3 (moderate PD). HC participants were recruited in the local community and did not have any significant musculoskeletal, neurological or cognition deficits.

2.2 Task

Participants self-selected a natural stance and then foot position was marked and controlled. They were instructed to stand still in a natural upright position with their arms at their sides for a total of six 30 second postural sway trails with their eyes open or eyes closed in random order (Figure 1a). To control the visual field, subjects were instructed to focus on a target six feet in front of them during eyes open trials. PD participants were instructed to maintain their normal medication schedule and were tested "on" medication (time since last antiparkinsonian dosage: 2.1 ± 1.0 hours).

2.3 Experimental and Clinical Measures

Foot/floor kinetic and video data were collected for all postural sway trials. Kinetic data were collected using two six-channel AMTI force plates (Advanced Mechanical Technology Inc., Watertown, MA, USA) and sampled at 1000 Hz using a 16-bit A/D data acquisition system (National Instruments, Austin, TX, USA). Video data were used to ensure subject compliance with postural sway task instructions.

Kinetic data were down sampled to 100 Hz and a low pass second-order Butterworth filter was applied with a 12.5 Hz cutoff frequency. Whole body COP path and velocity was then calculated for each trial (Figure 1b.). COP path was calculated from the output signals of the force plates in the anterior-posterior (AP) and medial-lateral (ML) direction and COP velocity was calculated with a fourth order accuracy derivate of the COP path. COP trajectory, variation, and peak parameters were derived to assess postural sway characteristics for the HC and PD participants (MATLAB, Natick, MA, USA). The total unified Parkinson's disease rating scale (UPDRS), the pull test (UPDRS item #33), and Schwab and England clinical assessments were performed by a movement disorders specialist for all PD participants. Table 1 contains brief descriptions of the clinical and biomechanical parameters obtained in this study.

2.4 Data Processing for PCA Analysis

Because PCA maximizes the variation within the data, the inputs must have equal variance to avoid undue influence of certain parameters caused by different mean values or units. Therefore, because the biomechanical and clinical input data had different units, the data were first centered along their mean using the z-score standardization:

$$z_{score} = (Raw_{Parameter} - Mean_{Parameter})/(STD_{parameter})$$

such that the sample mean equals zero and standard deviation equals one for each input parameter.

2.5 PCA Analysis

The use of PCA to model the data had two goals. First, feature selection to identify which parameters best explained the maximum variation in the overall data set related to the biomechanical postural sway and clinical parameters (PCA $_{initial}$ model). Second, the goal was to see if these selected features were able to provide differentiation across the 3 groups of interest in a reduced data PCA model based on parameter selection (PCA $_{selection}$ model) in order to track both earlier onset and the overall progression of postural instability in PD.

2.5.1 Parameter Selection

For both the eyes open and eyes closed task conditions, an input matrix was compiled for the PCA $_{initial}$ model used as the basis for parameter selection. The standardized (z $_{score}$) biomechanical and clinical parameters were compiled into an *s* x *p* input matrix where the *s* rows corresponded to an individual subject and the *p* columns corresponded to the standardized parameters. PCA was performed on the input matrix with a correlation structure. PCA $_{initial}$ resulted in a total of *p* eigenvectors (PCs). Each PC maximized the variability of the initial input matrix such that it accounted for the weighted linear combination of the initial input parameters in a unique orthogonal dimension. Of the resultant *p* PCs, a total of *m* PCs were retained based off the PCs corresponding eigenvalues such that a certain percentage of the original variance in the input data was explained (Jolliffe 2002). While there are many methods to select the number of PCs to retain, we selected a 95% threshold due to the exploratory nature of this study and to

ensure that our parameter selection captured a significant portion of the overall variation in the input data.

Because the retained m PCs can be difficult to interpret as each PC is a weighted combination of all input parameters, parameter selection was performed to reduce the number of variables and to help provide meaningful interpretation of the driving input parameters of the PCA $_{initial}$ model.[3] In order to interpret the meaning of the retained PCs, the parameters that most explained the derived PCs were binned. There are several methods for feature selection of PCs that are used in a variety of applications. Because the goal of this study was to explain the maximum variation within the initial data matrix, we used a commonly implemented method as presented by Jolliffe et al that has been previously used in postural sway studies (Jolliffe 1972, Jolliffe 1973, Jolliffe 2002, Rocchi, Chiari et al. 2004)[4]. Briefly, parameter selection involved associating one parameter that is most influential (largest coefficient) with each of the m retained PCs that has not already been associated with a previous PC. A total of m parameters were retained and the remaining $p - m$ parameters were discarded. The retained m parameters help to interpret the primary drivers of variation within the data set and were then used as inputs for new reduced parameter PCA $_{selection}$ model to determine if the variation in the data can still be preserved with a fewer number of variable inputs.

2.5.2 PCA Model and Analysis Based on Parameter Selection Data Reduction

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[3] An in-depth analysis of the original PCA $_{initial}$ model (based on all input parameters) related to group differentiation, the physical meaning of the significant principal components, and varimax rotation is included in Appendix B.ii. However because the reduced data set resulted in significant group differentiation as well, only those results are presented in this manuscript.

[4] Multiple methods for parameter selection were used in the data analysis prior to this paper: selection based on the largest coefficients from the first PC, selection based on the largest coefficients for the first m PCs (presented here), deletion based on the largest coefficients from the last $p-m$ PCs, and sparse PCA. Appendix B.ii provides a brief description of these methods and the associated parameter results based on these selection criteria.

Towards our second goal, following parameter selection of the PCA $_{initial}$ model, a new reduced s x m input matrix based on these selected m (standardized) parameters as columns and the s rows corresponding to an individual subject was compiled for the PCA $_{selection}$ model. PCA based on the reduced dimension s x m input matrix with a correlation matrix structure was performed to obtain the PCA $_{selection}$ model. Through considering the reduced parameter PCA $_{selection}$ model, we sought to determine if these retained parameters that influence the variation in the overall data set are also effective in differentiating the onset and progression of postural instability. Of the resultant m PCs, a total of n PCs were retained based off the PCs corresponding eigenvalues such that at least 95% of the original variance in the reduced input data was explained. If the resultant PCs (eigenvectors) result in significantly different confidence intervals for the HC, mild PD and moderate PD groups, the PC and corresponding parameters may be primary indicators of early onset and progression of postural instability in PD. Group differences for PC scores were determined with ANOVA ($p<0.05$) and Tukey-Kramer post hoc tests (SAS).

Results

3.1 PCA $_{initial}$ Model Parameter Selection

3.1.1 Eyes Open Postural Sway Model

For the correlation matrix based PCA $_{initial}$ model with standardized clinical and eyes open biomechanical parameter inputs, $m = 5$ PCs explained 97.3% of the variation in the original input data. Three eyes open postural sway biomechanical parameters (AP sway path length, AP

sway range, and peak sway speed) and 2 clinical parameters (UPDRS and Pull Test) were the parameters with the largest coefficients associated with each subsequent PC. Table 4.2a provides the eigenvectors of the correlation matrix for the first $m = 5$ PCs for the EO PCA model. [5]

3.1.2 Eyes Closed Postural Sway Model

The PCA with a correlation matrix structure for the eyes closed postural sway model also resulted in $m = 5$ PCs that explained 96.9% of the variation in the original input data. For the parameter selection based on the largest coefficient per PC, 4 eyes closed biomechanical parameters (AP sway path length, ML sway path length, mean sway speed and AP RMS of COP) and 1 clinical (UPDRS) were most representative of the first $m = 5$ PCs. Table 4.2b shows the eigenvectors of the correlation matrix for the retained PCs for the EC PCA model. [6]

3.2 PCA $_{selection}$ Model Group Differentiation and Physical Meaning

3.2.1Eyes Open Postural Sway Model

Group Differentiation

Based on the results from the eyes open PCA $_{initial}$ model parameter selection, 5 standardized input parameters (AP sway path length, AP sway range, and peak sway speed, UPDRS, Pull Test) made up the columns for the input data matrix for the correlation structure PCA $_{selection}$ model. The first $n = 4$ PCs explained at least 95% of the overall variation of the

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[5] In Appendix B.ii., the exact values of the eigenvectors per PC are listed for the eyes open PCA $_{initial}$ model; however for the ease of determining overall trends in the data a plus and minus system is presented here to ease interpretation and inferences.
[6] In Appendix B.ii, the exact values of the eigenvectors per PC are listed for the eyes closed PCA $_{initial}$ model; however for the ease of determining overall trends in the data a plus and minus system is presented here to ease interpretation and inferences.

input data matrix. To assess the PCA $_{selection}$ model's differentiation of the three study population groups (HC, mild PD, and moderate PD), the resultant scores (the representation of the input data in the rotated coordinate system for each PC) per group were tested for significant differences. PC 1 scores for all group pairwise comparisons (HC v. mild PD, HC v. moderate PD, mild PD v. moderate PD) were significantly different (mean (SD): HC -1.99 (.56), mild PD 0.47 (1.64), moderate PD 3.56 (3.58), p < .05)[7]. The 95% confidence intervals for PC1 scores for the HC versus Mild PD and Moderate PD groups were unique, with the HC confidence intervals of -2.24 $\leq \theta \leq$ -1.74, mild PD: -0.52 $\leq \theta \leq$ 1.46, and moderate PD: 1.00 $\leq \theta \leq$ 6.02. No other PCs were able to differentiate all group pairwise comparisons for the eyes open PCA $_{selection}$ model.

Physical Meaning of Retained PCs from the PCA *selection* Model[8]

Physical analysis of PC1, the eigenvector that explained 66% of the variance in the data and was able to differentiate between the HC, mild PD and moderate PD groups, shows that AP sway path length and peak sway speed were the 2 primary parameters influencing the PC based on their coefficients. Figure 3a shows representative plots of the 2 primary parameters for this PC for the subjects with the smallest and largest score for this PC. As demonstrated by Figure 3a, PC 1 is representative of the COP motion in the AP direction and the peak sway speed, while it is also affected by the other 3 parameters on similarly high levels, any component could potentially characterize this PC. For PC 2, which explained 18% of the variance in the parameter selection PCA model, this PC was primarily explained by a clinical (Pull Test score) and biomechanical (peak sway speed) measure. PC 3, which explained 9 % of the variation of the model, was

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[7] A comprehensive list of the means and SDs for all n = 5 PCs scores by subgroup for the eyes open PCA $_{selection}$ model is provided in Appendix B.ii. Because no other PCs provided the same level of differentiation as PC 1, only these mean (SD) are mentioned in this paper.

[8] A varimax rotation to the resultant PCs was also performed in an attempt to increase the interpretability of the PCs, but due to the small initial data set the improvement in the interpretation was negligible. The resultant rotated PCs and the corresponding parameter coefficients are provided in Appendix B.ii.

primarily driven by AP sway path range, thus reflecting differences in peak anterior-posterior

excursion across subjects during the eyes open postural sway trials.

3.2.2 Eyes Closed Postural Sway Model

Group Differentiation

Based on the results from the eyes closed PCA $_{initial}$ model parameter selection, 5

standardized input parameters (UPDRS, AP sway path length, ML sway path length, mean sway

speed, and AP RMS of COP) made up the parameter inputs for the reduced data input matrix for

the correlation structure PCA $_{selection}$ model. The first $n = 4$ PCs explained at least 95% of the

overall variation of the input data matrix. In order to assess the ability of the PCA $_{selection}$ model

to score and differentiate the study population groups (HC, mild PD, and moderate PD), the

resultant scores per PC were tested for significant differences. PC 1 scores for all group pairwise

comparisons (HC v. mild PD, HC v. moderate PD, mild PD v. moderate PD) were significantly

different (mean (SD): HC -1.97 (.54), mild PD 0.47 (2.28), moderate PD 3.61 (3.59), p<.05)[9].

The 95% confidence intervals for PC1 scores for the HC group was $-2.22 \leq \theta \leq -1.72$, mild PD: -

$1.85 \leq \theta \leq 0.99$, and moderate PD: $1.04 \leq \theta \leq 6.18$. No other PCs were able to differentiate all

group pairwise comparisons for the eyes closed PCA $_{selection}$ model.

Physical Meaning of Retained PCs from the PCA *selection* Model

Qualitative analysis of PC1 from the eyes closed PCA $_{selection}$ model, which explained

75% of the variance in the input data and was able to differentiate between the 3 study groups

had AP sway path length and mean sway speed as the 2 primary parameters (largest coefficients)

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[9] A comprehensive list of the means and SDs for all n = 5 PCs scores by subgroup for the eyes open PCA $_{selection}$
model is provided in Appendix B.ii. Because no other PCs provided the same level of differentiation as PC 1, only
these mean (SD) are mentioned in this paper.

influencing this PC. Figure 2b shows representative plots of the 2 primary parameters for PC 1

for the subject with the minimum and maximum score for this PC. As demonstrated by Figure

2b, PC 1 is representative of the COP motion in the AP direction and the mean sway speed,

while it is also affected by the other 3 parameters in a similar direction on a lesser level. For PC

2, which explained 11% of the variance in the parameter selection PCA model, this PC was

primarily explained by UPDRS Total score, indicating PC2 primarily is a descriptor of clinical

disease progression. PC 3, which explained 8 % of the variation of the model, was primarily

driven by ML sway path length, thus reflecting differences in overall medial-lateral movement of

the COP across subjects during the eyes closed postural sway trials

Discussion

This work sought to determine if PCA modeling of biomechanical and clinical

parameters could provide more quantitative scoring of both preclinical onset and progression of

postural instability in PD. PCA based on biomechanical parameters has recently been shown to

help determine identifying features for different ages, pathologies or tasks (Rocchi, Chiari et al.

2004, Rocchi, Chiari et al. 2006, Labbe, de Guise et al. 2010, Muniz, Liu et al. 2010, Mantovani,

Lamontagne et al. 2012, Muniz, Nadal et al. 2012, Kobayashi, Hobara et al. 2014). Specifically,

PCA has been successfully applied to postural sway in PD previously, with this PCA application

exclusively looking at biomechanical parameters of PD patients and the effect of drug therapy

("on" versus "off" medication) (Rocchi, Chiari et al. 2006).

This present study had the goal of looking for preclinical indicators of postural instability

in PD compared to HC based on both biomechanical and clinical parameters. This present work

takes the next step towards this goal in PCA modeling of postural sway in PD through investigating if PC scores based on parameter selection of biomechanical and clinical measures could serve as biomarkers of early postural deficits. By modeling postural sway with both eyes opened and closed conditions, this provided additional information as to how PD affects postural control with (and without) reliance of vision to stabilize postural control across the clinical progression of postural instability (Chagdes, Rietdyk et al. 2009). PC scores that both identify preclinical postural deficits and differentiate changes in postural instability across PD progression would allow clinicians to identify at risk PD patients before they begin to fall and develop more timely interventions. Sensitive and specific biomarkers of postural instability would also be valuable for properly placing PD participants in therapeutic clinical trials.

4.1 PCA Feature Selection Analysis

Variable selection of the PCA $_{initial}$ model for both the eyes open and eyes closed models resulted in a combination of biomechanical and clinical parameters as the driving variables of the model. This is a promising result as this may suggest that the biomechanical and clinical parameters are not redundant, and both are providing unique information about the overall variation observed in the HC, mild PD, and moderate PD participants. As the Total UPDRS score is a comprehensive measure of overall disease progression, it is not surprising that this measure is one of the extracted features for explaining the variation across subjects for both the eyes open and eyes closed PCA $_{initial}$ model. More generally, both eyes open and eyes closed PCA $_{initial}$ models resulted in measures that described the overall path trace (i.e. AP sway path length) and the velocity of the COP during the trial (i.e. peak sway speed for eyes open or mean sway speed for eyes closed).

Specifically for the eyes open PCA $_{initial}$ model, the biomechanical features extracted based on variable selection were a combination of COP trajectory and peak measures. While for the eyes closed PCA $_{initial}$ model, the extracted biomechanical measures were a combination of COP trajectory and variation measures. These parameters suggest that during eyes open postural sway, the increased variation in the PCA $_{initial}$ model was at least partially due to larger excursions of postural control (evidenced by AP sway path range and peak sway speed). For eyes closed postural sway, part of the variation in the PCA $_{initial}$ model can be explained by increased variation in the subjects COP movement during the trial (evidenced by AP RMS of COP), perhaps reflecting a stiffer postural control strategy.

4.2 PCA Model Based on Parameter Selection

4.2.1 Group Differentiation and Physical Meaning of the PCs

<u>Eyes Open Postural Sway Model</u>

Although no individual input parameter for the PCA models could provide differentiation of both postural instability onset (HC versus mild PD) and also significantly change with clinical disease progression (mild PD v. moderate PD and HC v. moderate PD), PC 1 score of the PCA $_{selection}$ model was able to do so. PC1 explained 66% of the variance in the model based on the weighted cumulative effects of AP Sway path length, AP sway range and peak sway speed, UPDRS Total score and Pull Test score. The variance in these input parameters across groups are at least partly explained by postural instability progression due to PD as the PC 1 scores resulted in significant differences for all comparisons of mean HC versus mild PD versus moderate PD. While the other PCs for the eyes open PCA $_{selection}$ model missed significance for all pairwise group comparisons, considering the large amount of variation explained by PC 1 it is promising

that the input parameters for this model may have the potential to provide additional information about postural instability progression in PD.

Eyes Closed Postural Sway Model

Similarly to the eyes open PCA models, no individual input parameters could provide differentiation of both postural instability onset (HC v. mild PD) and also significantly progress with disease clinical progression (mild PD v. moderate PD and HC v. moderate PD). However, PC 1 score of the eyes closed model based on the weighted cumulative effects of AP Sway path length, ML Sway path length, mean sway speed, AP RMS of the COP and UPDRS Total score was able to do so. PC 1 of the eyes closed PCA $_{selection}$ model explained 75% of the variance in the model, and considering the significant differences in all group comparisons the variance in these parameters across groups are at least partly explained by postural instability progression due to PD. Despite no other PCs for the eyes closed PCA $_{selection}$ model exhibiting significance in all group pairwise comparisons, considering the very high overall variation explained by PC 1 it is promising that the input parameters for this model may have the potential to retain the variation within the original data while still providing information about postural instability progression in PD.

Interestingly, despite both the eyes open and eyes closed models having some differing input parameters for their respective PCA $_{selection}$ models, in the resultant PC 1 for both eyes open and eyes closed, the two parameters with the largest coefficients for this significant PC were very similar across tasks. In both visual conditions, AP sway path length and a velocity measure (peak sway speed for eyes open and mean sway speed for eyes closed) were the 2 parameters weighted most heavily in PC 1 for their respective PCA $_{selection}$ models. Despite AP sway path length and

COP velocity impacting the variation in the PD and HC groups, and thus helping detect postural

instability earlier in PD, they are unavailable during current clinical assessment of postural

stability. COP path and velocity parameters cannot be quantified by visual inspection, therefore

use of biomechanical technology in the clinical setting may allow for additional information

during balance assessment. Despite this present study having a differing research question and

population group to a recent study by Rocchi et al (where they looked at the effect of levodopa

exclusively in PD participants), our work found similarities to the driving parameters of this

study. Mean sway speed and AP sway path range that explained our overall group variation

(parameter selection) similarly were determined to be driving parameters in the Rocchi study for

the "on" medication PD model from their study (Rocchi, Chiari et al. 2006). Future work that

explores these parameters, and all variables selected via parameter selection would provide incite

as to how sensitive and specific these parameters are to both onset of postural instability and

clinical PD progression.

Limitations of this work included the small sample size, that the balance assessment task

used for the PCA model inputs was quasi-static, and that PD participants were only tested in the

"on" medication state. These task choices were made due to the clinically driven nature of this

research. In order for a balance assessment model to be effective in a clinical setting, not

requiring patients to alter their dosing schedule ("on" medication) could provide easier

implementation in routine clinic visits. However, future studies with larger sample sizes should

also include "off" medication assessments to better understand if medication can be masking

small changes in postural stability that may help facilitate earlier detection of fall risk. With

larger sample sizes, predicting the scores of subjects based on biomechanical and clinical input

parameters could help test the robustness of the confidence intervals for the PCs that are able to

differentiate the PD groups versus controls. Also, applying such methods to a range of functional balance assessments such as gait initiation or balance recovery could provide further information based on how postural instability in PD detection changes with quasi static (i.e. postural sway) versus dynamic (i.e. balance recovery) tasks.

Conclusions

This study investigated the use of PCA based on parameters from a quasi-static biomechanical task and clinical outcome measures for the detection of preclinical postural instability and differentiation of its changes in PD. Parameter selection of the PCA $_{initial}$ model found a combination of biomechanical and clinical parameters were the primary drivers of variation in the HC and PD participants. The PC 1 scores for both the eyes open and eyes closed PCA $_{selection}$ models were able to significantly differentiate early onset and clinical progression of postural instability in PD. In both eyes open and eyes closed models, AP sway path length and a velocity measure were the primary drivers of the PCA that was able to differentiate the HC and PD groups. Future study for a wider range of functional tasks with larger sample sizes as well as predicative PCA modeling to test the robustness of PCA to score patients based on postural instability severity is needed.

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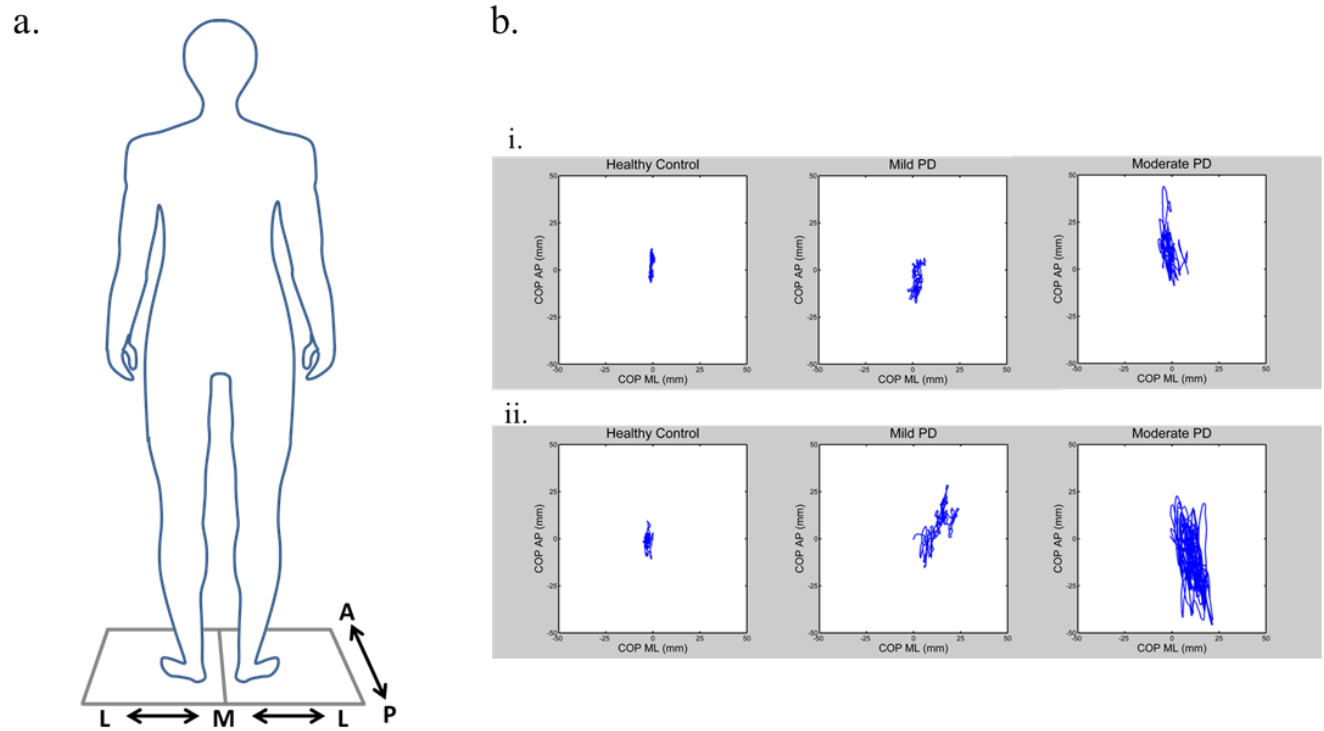
Figure 4.1. a. Schematic of the experimental setup for the postural sway task. b. Representative center of pressure (COP) changes for HC, mild PD, and moderate PD during eyes open (i) and eyes closed (ii) trials. Note the increase in the COP trace with disease progression, and the increase in COP trace with task condition (eyes closed > eyes open).

Table 4.1. Parameter Name (units, prior to standardization) and Description for the PCA Model Input Parameters

Biomechanical Parameters

Sway Path Length (mm):	Total distance COP travels along its path during postural sway task
AP Sway Path Length (mm):	Total distance COP travels along its path in anterior-posterior (AP) direction during postural sway task
ML Sway Path Length (mm):	Total distance COP travels along its path in medial-lateral (ML) direction during postural sway task
Sway Area (mm²):	Total area the COP path encompasses during postural sway task
Mean Sway Speed (mm/s):	Average rate of change of the magnitude of COP displacement during postural sway task
AP RMS of COP (mm):	Square root of the mean squared deviation from average COP in AP direction during postural sway task
ML RMS of COP (mm):	Square root of the mean squared deviation from average COP in ML direction during postural sway task
AP Sway Path Range (mm):	Maximum displacement COP deviates from center point in AP direction during postural sway task
ML Sway Path Range (mm):	Maximum displacement COP deviates from center point in ML direction during postural sway task
Peak Sway Speed (mm/s):	Maximum change in magnitude of COP displacement over time during postural sway task

Clinical Parameters:

Unified Parkinson's Disease Rating Scale:	Assessment of overall PD progression. Scores can range from 0 – 180, with higher scores reflecting greater impairment.
Motor Exam:	Third section of UPDRS, assesses motor symptoms related to PD. Scores can range from 0 – 108, with higher scores reflecting greater impairment.
Pull Test:	UPDRS item # 33 assessment of how a patient responds to sudden posterior pull to characterize patients' overall postural stability. Scores can range from 0 – 4, with higher scores reflecting greater impairment.
Schwab and England:	Estimation of ability to independently perform activities of daily living. Scores can range from 100 – 0%, with 100% being independent (normal) and lower scores reflecting greater dependence

Table 4.2. Coefficients and Relative Variance Explained for Retained PCs in Eyes Open and Eyes Closed PCA $_{initial}$ Models

Eyes Open	PC 1	PC 2	PC 3	PC 4	PC 5
UPDRS	(+)		(-)*		(-)
Schwab and England	(-)	(+)	(+)		
Motor Exam	(+)		(-)		(-)
Pull Test	(+)		(-)		+*
Sway Path Length	(+)	(+)			
AP Sway Path Length	(+)	(+)*			
ML Sway Path Length	(+)	(+)		(+)	
Sway Area	(+)	(-)	(+)	(+)	
Mean Sway Speed	(+)	(+)			
AP RMS of COP	(+)	(-)		-	(+)
ML RMS of COP	(+)	(-)	(+)	(+)	
AP Sway Path Range	(+)	(-)		-*	
ML Sway Path Range	(+)		(+)	(+)	
Peak Sway Speed	(+)*	(+)			(-)
Variance Explained by PC (%)	61	15.63	14.27	4.08	2.28
Eyes Closed	PC 1	PC 2	PC 3	PC 4	PC 5
UPDRS	(+)	(-)*			
Schwab and England	(-)	(+)	(-)		
Motor Exam	(+)	(-)	(+)		(+)
Pull Test	(+)	(-)		(+)	
Sway Path Length	(+)		(-)	(+)	
AP Sway Path Length	(+)		(-)*		
ML Sway Path Length	(+)			+*	
Sway Area	(+)	(+)	(+)		
Mean Sway Speed	(+)*		(-)	(+)	
AP RMS of COP	(+)				-*
ML RMS of COP	(+)	(+)	(+)		
AP Sway Path Range	(+)		(-)		
ML Sway Path Range	(+)	(+)	(+)		
Peak Sway Speed	(+)		(-)		
Variance Explained by PC (%)	66.1	15.4	9.8	3.1	2.5

Table Key: + signifies a parameter coefficient of 0.5 or greater (strong positive effect)
(+) signifies a parameter coefficient between 0.2 to 0.5 (mild positive effect)
 - signifies a parameter coefficient of -0.5 or less (strong negative effect)
(-) signifies a parameter coefficient between -0.2 to -0.5 (mild negative effect)
* indicates the parameter per PC retained (largest coefficient) for the PCA $_{selection}$ model.

a.
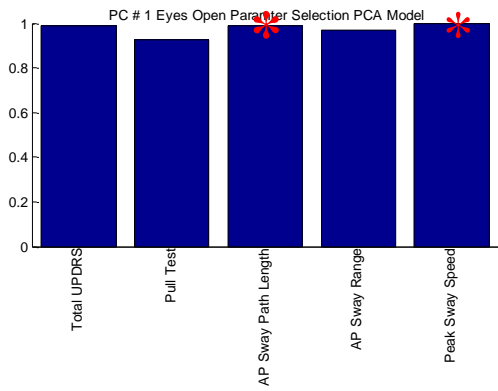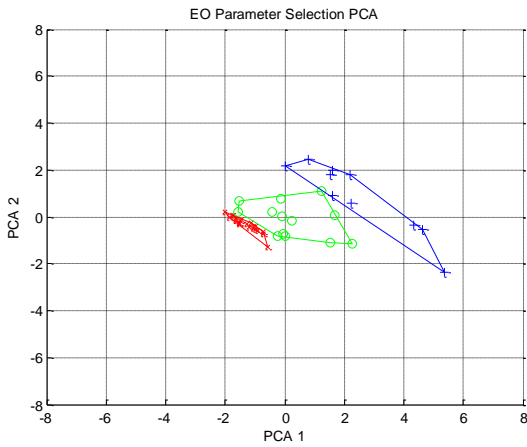
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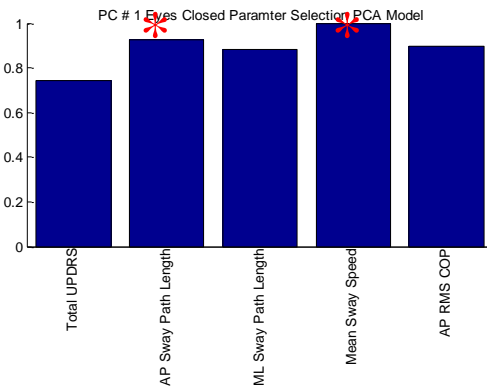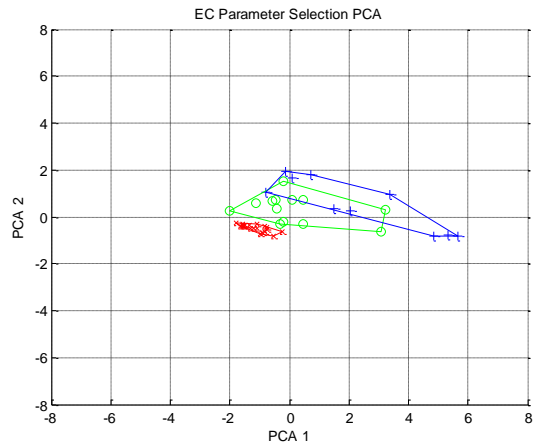
Figure 4.2. a. Transformed subject scores plotted on the principal component (PC) 1 versus PC 2 axes (top) and the relative contribution (coefficients) of each input parameter normalized to the most influential variable (bottom) for the eyes open PCA *selection* model. b. Transformed subject scores plotted on the principal component (PC) 1 versus PC 2 axes (top) and the relative contribution (coefficients) of each input parameter normalized to the most influential variable (bottom) for the eyes closed PCA *selection* model.

A red star on the coefficient bar graphs indicates being one of the 2 most influential parameters for PC 1. Key: red x – HC subject score, green o – mild PD subject score, blue + - moderate PD subject score.

Table 4.3.Coefficients and Relative Variance Explained for Retained PCs in Parameter Selection Based Eyes Open and Eyes Closed PCA Models

Eyes Open

	PC1	PC2	PC3	PC4
UPDRS	(+)	(+)		+
Pull Test	(+)	+	(-)	-
AP Sway Path Length	(+)	(-)	(-)	
AP Sway Path Range	(+)		+	(-)
Peak Sway Speed	(+)	-		
Variance Explained Per PC (%)	66.20	18.36	9.28	3.58

Eyes Closed

	PC1	PC2	PC3	PC4
UPDRS	(+)	+		
AP Sway Path Length	(+)	(-)	(+)	+
ML Sway Path Length	(+)	(-)	-	
Mean Sway Speed	+	(-)		(+)
AP RMS of COP	(+)		(+)	-
Variance Explained Per PC (%)	75.25	11.37	7.93	5.40

Table Key:
 + signifies a parameter coefficient of 0.5 or greater (strong positive effect)
(+) signifies a parameter coefficient between 0.2 to 0.5 (mild positive effect)
 - signifies a parameter coefficient of -0.5 or less (strong negative effect)
(-) signifies a parameter coefficient between -0.2 to -0.5 (mild negative effect)
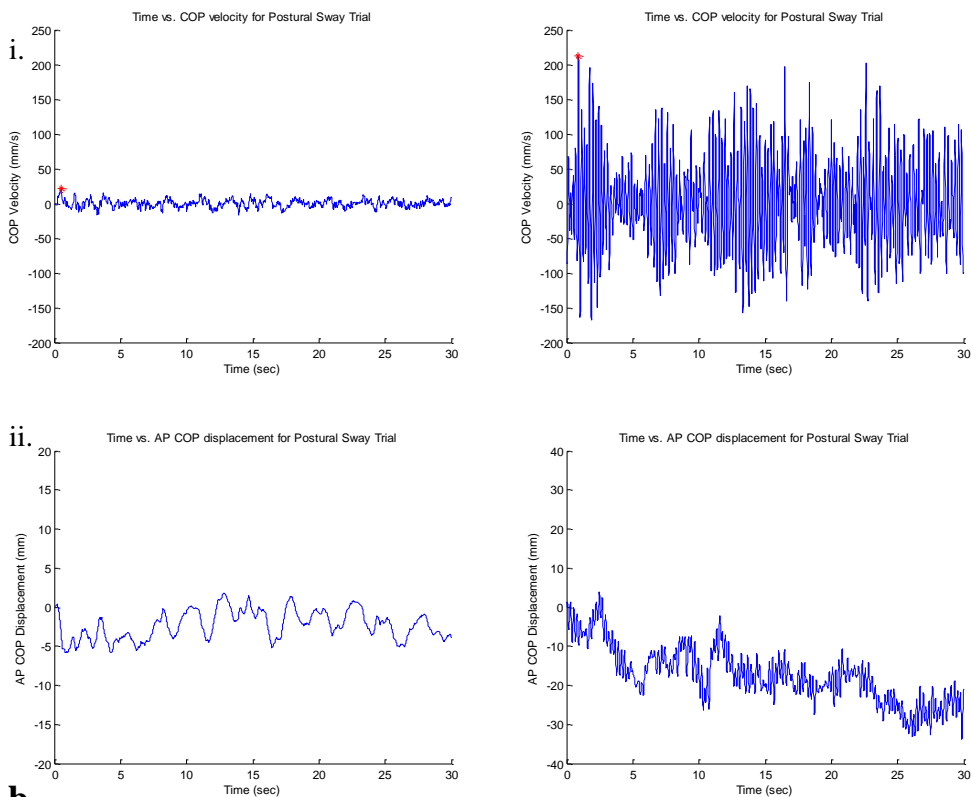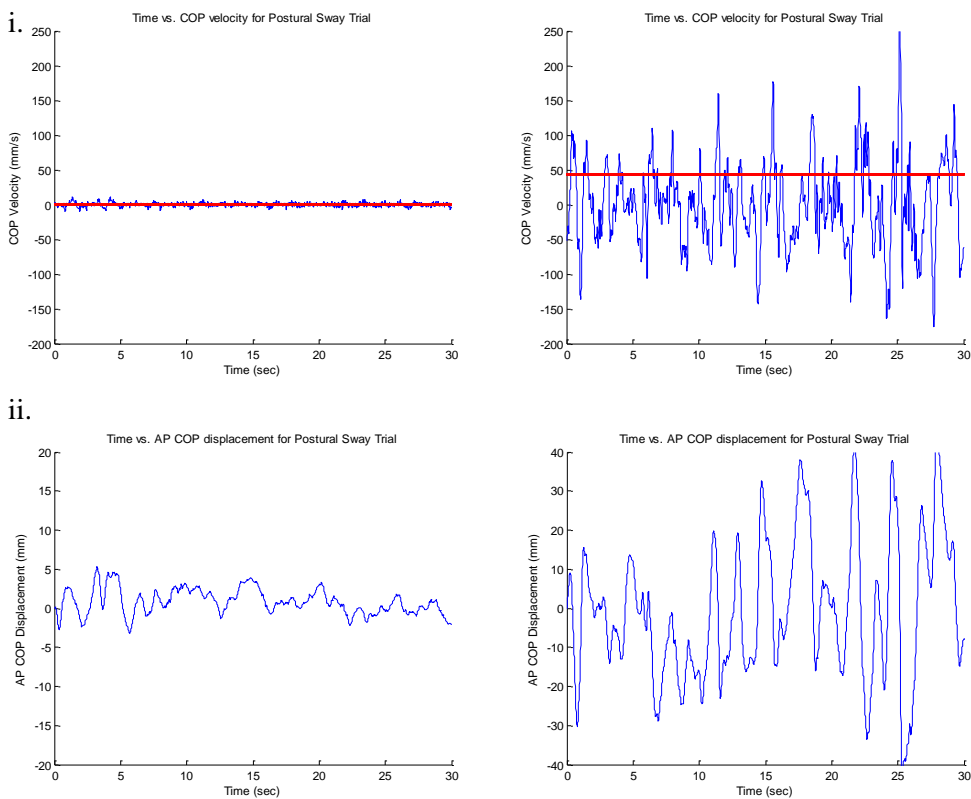
Figure 4.3. a. Representative plots of the 2 variables that are primarily responsible for PC 1 (i. peak sway speed and ii. AP sway path length) for the subjects with the smallest (left) and largest (right) scores in the eyes open PCA $_{selection}$ model. 3b. shows representative plots for the 2 variables that are primarily responsible for PC 1 (i. mean sway speed and ii. AP sway path length) for the subjects with the smallest (left) and largest (right) scores in the eyes closed PCA $_{selection}$ mode

CHAPTER 5: Gait Initiation in Parkinson's Disease to Assess Preclinical Postural Instability and Progression

Abstract

Background: Postural instability leading to falls is a debilitating Parkinson's disease (PD) symptom due to fall-related consequences on quality of life and life expectancy. Standard clinical assessments are unable to predict falls, whereas reducing fall risk through earlier postural instability detection could reduce fall-related complications. Biomechanics based assessment of gait initiation with the ability to more quantitatively assess preclinical postural instability onset and progression in PD could fulfill this unmet need.

Methods: Light-cued gait initiation was measured in mild PD (n=10), moderate PD (n=11) and age-range matched healthy controls (HC, n=19). Foot/floor reactions, motion, and electromyography data were measured and temporal, kinematic, and center of pressure (COP) path and velocity parameters were calculated.

Findings: Peak COP velocity towards the swing foot during locomotion was significantly different ($p < .05$) in mild PD versus HC. Several temporal, kinematic, and COP measures were significantly different ($p < .05$) in HC versus moderate PD, with increasing trends compared to HC in mild PD. Total Unified Parkinson's Disease Rating Scale (UPDRS) and Pull Test clinical scores best correlated with the biomechanical measures of gait initiation.

Interpretation: Biomechanical assessment of gait initiation in PD may provide preclinical recognition of postural instability. To further develop and strengthen postural instability detection, the relationship of biomechanical parameters across balance tests of varying motor function demands (quasi-static versus dynamic tasks), along with their persistence throughout disease progression, is needed to better quantify their efficacy in assessing fall risk.

Introduction

Postural instability, one of the cardinal motor symptoms of PD, is characterized by flexed posture that occurs due to a decrease in postural reflexes. Postural instability is particularly disabling due to its link to increased fall risk (Bloem, van Vugt et al. 2001, Michatowska, Fiszer et al. 2005, Olanow, Stern et al. 2009). Current clinical assessments in PD are not sufficiently sensitive to predict fall risk, making a history of falls to be the best predictor of a future fall. Such retrospective diagnostics are clearly undesirable because nursing home placement increases and quality of life and life expectancy decrease after just one fall (Morens, Davis et al. 1996, Voss, Elm et al. 2012). Targeted therapies that can reduce fall risk are available, but are not implemented without a fall risk diagnosis owing to the associated cost and time for both patient and provider. In a recent survey of individuals with Parkinson's disease, their caretakers, and family members, participants identified improving balance and falls as their number one priority for future research (Deane, Flaherty et al. 2014).

Biomechanical assessment of postural instability during a range of static and dynamic tasks could potentially address this unmet need in fall risk and postural instability diagnostics as recent studies have shown that biomechanical analysis can distinguish postural impairments in patients with PD for a range of severities (H&Y 1-4) from healthy controls (HC). These studies have demonstrated the presence of postural instability in PD compared to HC, however the detection of the onset of preclinical balance deficits remains elusive (Rosin, Topka et al. 1997, Halliday, Winter et al. 1998, Hass, Waddell et al. 2005, Jiang and Norman 2006, McNeely and Earhart 2013). Identifying biomechanical measures to predict fall risk in PD would provide a quantitative justification to implement fall-reducing therapies prior to a first fall and thus help prevent the associated debilitating fractures and morbidities.

Biomechanical assessment of the postural control response during gait initiation could provide such an indication of postural instability onset due to its demonstrated efficacy to distinguish PD and HC groups. Past work by our lab has demonstrated that a quasi-static task (postural sway) can provide such differentiation (Barnds Dissertation Chapter 4) and this work seeks to expand such analysis to a dynamic task. Gait initiation, in contrast to a quasi-static standing task, may provide additional information because it represents a more challenging task involving more complex integration of the postural control system. Gait initiation requires an individual to transition from a quasi-static standing state, where the COP is contained within a fixed base of support, to a dynamic state during gait, with the COP typically located outside of the constantly moving base of support.

Specifically, previous studies have assessed postural instability in gait initiation through using temporal, kinematic, and center of pressure (COP) parameters in PD for a range of conditions including: no cue, visual-cued, and auditory-cued (Rosin, Topka et al. 1997, Martin, Shinberg et al. 2002, Dibble, Nicholson et al. 2004, Hass, Waddell et al. 2005, McCandless, Evans et al. 2010, Hass, Buckley et al. 2012). For temporal variables, recent studies have shown that PD increases the time to respond to a gait initiation stimulus marked by parameters such as delayed onset of movement (Rosin, Topka et al. 1997, Dibble, Nicholson et al. 2004). PD also decreases kinematic parameters like step length when compared to age-range matched healthy controls (Rosin, Topka et al. 1997, Halliday, Winter et al. 1998, Dibble, Nicholson et al. 2004). During step initiation, COP parameters such as COP displacement decrease in PD when compared to their healthy counterparts during the preparatory and locomotor phases of the first step (Martin, Shinberg et al. 2002, Dibble, Nicholson et al. 2004). Hass et al. looked at the center of mass (COM) response in a lesser impaired PD group (HY < 2.0) and a more impaired PD

group (HY >2.5) and found that the peak magnitude of the distance between the COP and COM to be significantly greater during the end of the single-support phase in the less disabled patients, however this study did not compare the findings to age-range matched healthy controls (HC) (Hass, Waddell et al. 2005).

The results of these previous studies provide evidence that quantifying gait initiation using biomechanical parameters has the potential to distinguish differences between PD and HCs as well as some of the parameters being sensitive to disease progression. Parameters that differ depending on pathology or disease severity may provide incite as to which parameters are related to fall risk. However, because these studies either do not isolate mild and moderate PD patients relative to HC, or only look at these parameters within a group of PD, it is still unclear if such deficits can be detected in the early stages of PD progression compared to HC. In order for gait initiation parameters to be useful as early indicators of postural instability and then potentially used to assess fall risk, these deficits must be demonstrated to be different from HC in the early stage of the disease. This study sought to determine if gait initiation could detect preclinical onset and track changes of postural instability with clinical progression in PD during a cued gait initiation task. The assessment of gait initiation could be a valuable component within a multi-faceted approach covering several dimensions of functional balance and clinical measures in the effort to detect the onset and then track the progression of postural instability.

To address this unmet need in the assessment of postural instability in gait initiation, this study had two goals. First, we investigated if the temporal, kinematic or COP parameters of gait initiation were sensitive enough to detect preclinical balance deficits (Mild PD versus HC) and assess their efficacy in monitoring the increasing level of postural instability associated with clinical disease progression (Moderate versus Mild PD). We hypothesized that a subset of our

parameters will be sensitive enough to detect the onset of postural instability prior to clinical presentation, and some of parameters will change with clinical PD progression. Second, of the parameters that exhibited significant differences between, HC, mild PD or moderate PD, we explored how these parameters correlate with existing clinical measures of PD progression. We hypothesized that some of the significant gait initiation measures will correlate with current clinical measures of postural instability and disease progression in PD.

Methods

2.1 Participants

Ten participants with mild PD, 11 participants with moderate PD and 17 age-range matched healthy controls participated in this study (Table 5.1). All individuals gave informed written consent as approved by the University's Institutional Review Board. PD participants were recruited from the University of Kansas Medical Center (KUMC) Parkinson's Disease and Movement Disorder Center. All patients had PD, confirmed by a neurologist specializing in movement disorders (RP). PD participants exclusion criteria were: needing to walk with assistance, severe depression (BDI >30/63), dementia (MMSE < 24/30), musculoskeletal or neurologic impairments unrelated to PD, having neurosurgery for PD, and a H&Y score other than 2 (mild PD) or 3 (moderate PD). HC participants were recruited from the local community and exclusion criteria were significant cognitive, musculoskeletal, or neurologic impairments.

2.2 Task

Participants self-selected a natural stance wearing standardized footwear and stood with arms at their sides. Participants were instructed to initiate gait followed by several steps when a "cue"

light illuminated, which was located at eye level 8 feet in front of them. A total of 5 "good" trials were collected, where a "good" trial was defined as a trial in which the subjects' first step cleanly landed on the force plate directly in front of them.

2.3 Experimental Measures

Kinetic, kinematic, electromyography (EMG) and video data were collected for all gait initiation trials. Foot/floor reaction forces and moments were sampled at 1080 Hz using six-channel AMTI force plates (Advanced Mechanical Technology Inc., Watertown, MA, USA). Kinematic data were sampled at 120 Hz where participants wore bilateral markers on the second metatarsal, lateral malleolus, heel, calf, and lateral femoral epicondyle (Figure 1a, Vicon 512: Vicon Peak, Lake Forest, CA and Optotrak: Northern Digital, Inc., Waterloo, Canada). EMG data were sampled at 1080 Hz where participants had bilateral surface EMG sensors on the tibialis anterior and medial gastrocnemius (Figure 1a, 1080 Hz, Noraxon: Noraxon, Scottsdale, AZ and Delsys: Delsys, Boston, MA, USA). Video data were used to ensure subject compliance with the gait initiation task instructions and ensure a clean strike of the swing foot on the force plate. PD participants were instructed to maintain their normal medication schedule and were tested "on" medication (mean (SD) time since last antiparkinsonian dosage: 2.1 (1.0) hours).

2.4 Data Processing

Kinetic and kinematic data were filtered using a low pass second-order Butterworth filter with a 20 and 30 Hz cutoff frequency, respectively. EMG data were full wave rectified and filtered using a second order low-pass butterworth filter with a 50 Hz cutoff frequency. Temporal, kinematic, and kinetic parameters were calculated for each trial. All data processing was done using a custom-written MATLAB code (MATLAB, Natick, MA, USA).

2.5 Gait Initiation Parameters

All gait initiation trials were analyzed from the time of the cue onset to the heel strike of the first step (of the swing leg). Temporal, kinematic, and kinetic parameters were analyzed for each participant (Table 2). For the kinetic parameters, whole body center of pressure (COP) path and velocity was calculated for each trial. Whole body COP path and velocity was then calculated for each trial (Figure 1b.). COP path was calculated from the output signals of the force plates in the anterior-posterior (AP) and medial-lateral (ML) direction and COP velocity was calculated with a fourth order accuracy derivate of the COP path.   Then, 3 stages based on the COP trajectory were defined similar to the methodology proposed by Hass et al (Hass, Gregor et al. 2004) (Figure 1):

Stage 1 (S1): The onset of the cue light to the most lateral shift in the COP towards the swing leg

Stage 2 (S2): End of Stage 1 to the translation of the COP towards the stance leg when the COP begins to move anteriorly under the stance foot

Stage 3 (S3): End of Stage 2 to the heel strike of the swing foot.

COP step parameters were calculated for events related to the step liftoff and landing, and COP stage parameters were calculated for each of the 3 stages above for all participants (Figure1). Sample COP traces for HC, mild PD and moderate PD are shown in Figure 2.

All parameters that could be affected by subject anthropometry or initial stance conditions were normalized to account for these differences. For example, kinematic step parameters were normalized to subject height. COP parameters were normalized relative to the base of support such that anterior-posterior (AP) parameters were normalized to foot length,

medial-lateral (ML) parameters during Stage 1 and Stage 2 were normalized to initial stance width, and ML parameters during Stage 3 were normalized to stance foot width (Table 2).

2.6 Clinical Parameters

PD subjects were assessed by a specialist from the KUMC Parkinson's Disease and Movement Disorder Center, using the following clinical measures (Table 1):

Unified Parkinson's Disease Rating Scale (UPDRS): assessment of the overall progression of PD characterized by: Mentation, Behavior and Mood; Activities of Daily Living; and a Motor Examination. Scores can range from $0 - 180$, with higher scores reflecting greater impairment.

Motor Exam: the third section of UPDRS completed by the investigator, that assesses motor symptoms related to PD. Scores can range from $0 - 108$, with higher scores reflecting greater impairment.

Pull Test (Postural Stability, UPDRS item 33): assessment of how a patient responds to a sudden posterior pull in order to characterize the patients' overall postural stability. Scores can range from $0 - 4$, with higher scores reflecting greater impairment (Fahn, Elton et al. 1987, Goetz, Poewe et al. 2003).

Schwab and England: estimation of the overall percentage a PD patient is able to function relative to an independent living situation. Scores can range from $100 - 0\%$, with 100% being normal and lower scores reflecting greater impairment (Schwab and England 1969).

2.7 Statistical Analysis: [10]

An ANOVA was used to compare baseline demographic and disease severity characteristics between groups. All gait initiation parameters were analyzed using repeated measures Analysis of Variance (ANOVA) with group (HC, mild PD, moderate PD) as factors for all trials. Significant group differences ($p < .05$) were determined with an ANOVA and Tukey-Kramer multiple comparison post hoc test when appropriate. A Spearman rank correlation analysis was used to characterize the relationship between the biomechanical (gait initiation) and clinical parameters for the PD participants (SAS 9.4, SAS Institute Inc., Cary, NC).

Results

3.1 Temporal Parameters

Step duration and time from the light cue to heel strike of the swing foot trended towards longer durations with increasing PD progression, with cue to heel strike duration being significantly greater in moderate PD compared to HC and mild PD ($p < .05$). Step onset time and weight shift time trended towards increased time in moderate PD, with step onset time being significantly delayed in moderate PD compared to the HC and mild PD groups ($p < .05$) (Table 3a).

3.2 Kinematic Parameters

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[10] Principal component analysis was applied to the gait initiation outcome parameters (combined with clinical parameters) as was done in Barnds Dissertation Chapter 4 for postural sway. Unfortunately, this analysis did not result in any principal components (PCs) that could differentiate both preclinical onset (mild PD v. HC) and progression (mild PD v. moderate PD and moderate PD v. HC) of postural instability, so this analysis is not included in this present chapter. The relative contributions and exact weights of the coefficients per PC as well as mean PC scores by group are in Appendix B.iii.

Moderate PD exhibited significantly decreased (p < .05) total and AP step length compared to the HC and mild PD groups. Step speed and step clearance trended towards decreased values with PD progression; however only step speed of the swing leg in moderate PD was significantly different (p< .05) compared to the HC and mild PD groups. The mild PD group tended to step most laterally with the swing foot, but not significant across group comparisons occurred (Table 3b).

3.3 COP Step Parameters

AP COP position at step heel off trended towards a more anterior position with disease progression, with the moderate PD group being significantly (p< .05) more anterior compared to the HC group. All other COP step parameters were not significantly different across groups (Table 3c).

3.4 COP Stage Parameters

Stage 1: AP and ML COP velocity and peak COP velocity towards the swing foot were significantly slower in moderate PD compared to HC (p < .05). Peak anterior COP velocity was significantly greater in moderate PD compared to HC (p <.05). Stage duration was significantly (p<.05) longer in moderate PD compared to both HC and mild PD. (Table 4)

Stage 2: Mean COP AP velocity was significantly more anterior in moderate PD compared to HC, and mean ML COP velocity was significantly slower in moderate PD compared to HC (p<.05). Peak COP velocity towards the stance foot was significantly slower in moderate PD compared to the HC group (p< .05). Stage duration was significantly longer in moderate PD compared to both the HC and mild PD group (p<.05). (Table 4)

Stage 3: AP COP displacement was significantly less in moderate PD compared to the HC group (p<.05) and ML COP velocity was significantly slower in moderate PD compared to mild PD (p<.05). Peak COP velocity toward the swing foot was significantly less in mild PD compared to the HC and moderate PD groups (p<.05). (Table 4)

3.5 Clinical Correlation with Gait Initiation Parameters

After testing the correlation of the significant gait initiation parameters with the 4 current clinical measures, the Motor Exam score had the highest level of correlation with 78% of significant parameters being correlated with the measure, closely followed by the pull test (72%), and then Motor Exam Score (67%), and Schwab and England (33%). (Table 5)[11]

Discussion

This study sought to determine if gait initiation could detect preclinical onset and track changes of postural instability with clinical progression in PD during a cued gait initiation task. While previous studies have assessed gait initiation in PD for a range of disease severities (H&Y 1-4), no studies have addressed whether gait initiation can differentiate preclinical postural instability (mild PD compared to HC) and quantify the associated progression with disease severity (HC v. moderate PD and mild PD v. moderate PD). The temporal, kinematic, and COP parameters from this study are comparable with previous studies that demonstrated that PD increased the time to respond to a gait initiation cue and decreased step kinematics and COP

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[11] A comprehensive list of the correlation coefficients by PD severity group (mild PD and moderate PD) is included in Appendix B.iii. Because this was a pilot study, we did not have enough subjects per group in order to have robust enough data sets to make inferences about the relative relationships of mild PD versus moderate PD, so they are considered together to increase power and to assess the overall effect of clinical progression for the purpose of this paper.

displacement (Rosin, Topka et al. 1997, Halliday, Winter et al. 1998, Dibble, Nicholson et al. 2004, Rocchi, Carlson-Kuhta et al. 2012).

This work provides the next step in biomechanical assessment of gait initiation in PD through investigating if such parameters could serve as biomarkers of early postural deficits compared to their healthy counterparts. Finding parameters that identify preclinical postural deficits or more quantitatively measure changes in postural instability over the course of PD would enable the clinician to identify PD patients at risk of falling and then implement the appropriate therapy to reduce that risk before the fall event. This could also be valuable for placement of PD participants in clinical trials requiring patient stratification based on the level of postural instability.

4.1 Effect of Mild and Moderate PD Compared to HC: Temporal Parameters

All temporal variables trended towards increased time in moderate PD, while HC to mild PD parameter values remained similar. The findings that moderate PD significantly delays step onset time and the overall duration of the response (from cue to heel strike of the swing foot) is consistent with the idea that PD affects motor planning and programming as the moderate PD participants were not able to plan and execute as efficient of a response as their healthy counterparts(Marsden 1987, Rosin, Topka et al. 1997, Pahapill and Lozano 2000). The mild PD and HC groups were similar in the duration of their response, which may suggest that motor planning and programming are not yet deficit, or evidence that if a change has occurred, then the selected temporal variables are not sensitive enough to detect the change within mild PD group.

4.2 Effect of Mild and Moderate PD Compared to HC: Kinematic Parameters

Step length, speed, and clearance all trended towards decreased values in moderate PD compared to HC (p < .05 for step length and speed), with mild PD exhibiting a trend towards decrease for step speed and clearance but similar values to HC for weight shift time and step onset time. Similar to a recent study by Vitorio et al related to obstacle avoidance in mild and moderate PD, our gait initiation task also exhibited decreased step speed and step clearance with increased disease progression, but as did Vitorio et al. our study comparisons of mild PD to HC for these parameters missed statistical significance (Vitorio, Lirani-Silva et al. 2014). However, these findings may also be limited by this being a pilot study, with a power analysis suggesting that with n ≈ 50 per group for HC and mild PD, this could potentially differentiate this decrease in step clearance. However, the current results from this study suggest that while these kinematic parameters of gait initiation decrease with disease severity, the ability to maintain normal locomotion to their healthy counterparts in statistically unchanged in mild PD.

4.3 Effect of Mild and Moderate PD Compared to HC: COP Step Parameters

At heel off of the swing foot, the location of the normalized COP trended towards being more anterior and towards the stance foot with increasing disease progression (Figure 2), with moderate PD vs HC exhibiting a significantly more anterior position of the COP compared to HC. There was no distinct trend for the normalized COP location at heel strike in either direction. However, the tendency in PD during the preparation phase (S1 and S2) to maintain a more anterior location of the COP location may suggest that the PD groups have an aversion to allowing their COP to move posteriorly or perhaps they are adopting a more stiff postural control response as a compensatory measure to counteract the deficits of PD. Further, the decreased movement of the normalized COP in the ML direction during preparation may suggest impairment to the functionality of the hip abductors and adductors as these muscles are partly

responsible for ML COP movement during gait (Winter 1995). While this trend missed

significance statistically, power analysis suggests that n ≈ 30 per group for HC and mild PD

could differentiate this trend in decreased ML motion of the COP at heel off of the swing foot.

4.4 Effect of Mild and Moderate PD Compared to HC: COP Stage Parameters

Stage 1

In Stage 1, there was a general trend towards less posterior and lateral movement for both

COP displacement and mean COP velocity with increasing PD severity, with significantly less

posterior (AP) and lateral (ML) COP velocity for moderate PD versus HC. This trend towards

less posterior and more lateral movement is also evidenced by the Peak COP velocity, with peak

anterior COP and peak COP toward the swing foot (lateral) velocity reaching significant

differences for HC versus moderate PD. There are several possible reasons that this trend was

observed, such as PD causes a stooped forward posture (Bloem, Beckley et al. 1999), making the

COP more anterior in quasi-static stance (Halliday, Winter et al. 1998), thus evidenced by less

posterior movement in PD. Or this trend also may reflect evidence of decreased efficiency of this

preparation phase of the step initiation response due to PD (Marsden and Obeso 1994, Rosin,

Topka et al. 1997), evidenced by significant differences ($p < 0.05$) in mean COP velocity and

stage 1 duration for moderate PD.

Stage 2

In Stage 2, the PD groups trended towards moving more anteriorly and less quickly

towards the stance foot, with moderate PD having a significantly more anterior velocity and

significantly slower ML velocity compared to HC. Similar to the differences in COP location at

heel off, these differences could be due to an altered postural control strategy, an aversion to

posterior movement (for AP measures), an impairment of the hip adductors/adductors (for ML measures), or some combination of these deficits related to PD. However despite many trends with PD progression for stage 2 parameters, no significant differences were found between the mild PD and HC groups.

Stage 3

In Stage 3, Peak COP Velocity toward the swing foot was significantly less ($p < 0.05$) in mild PD compared to the HC and moderate PD group. During this stage, mild PD tended to move more quickly medially (toward the stance foot), with a trend towards a larger ML displacement, effectively decreasing the effective base of support during locomotion. Conversely, the moderate PD group exhibited an opposite trend- they stepped slower and more laterally, increasing the base of support. Potentially, this can be explained by a bi-phasic effect where there is some early rigidity or stiffening of the muscles that cause a less lateral (toward the swing foot) step and velocity during locomotion in mild PD, and then as PD progresses, compensatory behaviors begin which shortens and decreases the speed of the first step, thus reverting this change observed in the mild PD response compared to HC. This relative change in ML velocity and narrowing of the base of support during the first step in mild PD compared to HC and moderate PD needs further exploration in future studies.

4.5 Clinical Correlation with Gait Initiation Parameters

The total UPDRS and pull test scores had the best level of correlation with the biomechanical measures of gait initiation while Schwab and England score had the lowest level of overall correlation. Interestingly, this observation is the opposite of a previous study by our group on postural sway (quasi-static stance) where Schwab and England had the largest level of correlation and pull test score had the lowest level of correlation with postural sway

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biomechanical parameters (Barnds Dissertation Chapter 3). The differences in the gait initiation clinical correlations in relation to the pull test (compared to postural sway) may be explained by the fact that both gait initiation and the pull test both involve a step response. While the pull test involves backwards compensatory stepping, it nevertheless starts from a quasi-static stance and the participant must then initiate gait, which has many similarities to the light cued gait initiation task used in this study. The Schwab and England score, which reflects a participants ability to do activities of daily living such as getting dressed or showering, may be more closely related to a quasi-static standing task opposed to a dynamic task like gait initiation. Because static versus dynamic biomechanical tasks exhibit different correlations with clinical scores of disease progression, this may provide evidence that different task conditions can provide unique information about the effects of PD on postural control.

Limitations of this study include the small sample size and the associated potential influence of outliers, that PD participants were tested "on" medication, and that initial stance conditions were not controlled. When analyzing data from a small sample size, we recognized that outliers can greatly impact the overall variability in the data; however the systemic large variations within the PD groups that were based on H&Y staging may also demonstrate the need for more continuous or quantitative based parameters to score the PD patients in order to limit within-group variability. The decision to test patients "on" medication without restrictions on their initial stance conditions was done in an effort to simulate routine clinic conditions where cumbersome setup requirements and altering the patient's dosing schedules would be difficult. However, future studies should include "off" medication assessments to check how medications are altering the PD groups' response, thus potentially decreasing the ability to detect early signs of being at risk for postural instability and falling. Although parameters were normalized to the

subject stance conditions, ensuring that stance width and location of the COP at light onset are controlled in future studies may further help differentiate differences between HC, mild PD and moderate PD groups. Further analysis with increasingly sophisticated mathematical models may help establish the threshold where the onset of postural instability can be confirmed from multiple biomechanical and clinical measures.

Conclusion

This study is a part of an ongoing effort to ascertain biomechanical parameters to identify preclinical postural instability in PD patients. Peak COP velocity towards the stance foot during the locomotion phase of gait initiation shows promise as a parameter that may detect postural instability earlier than current clinical assessment as mild PD patients were significantly slower compared to HC. We observed significant differences in temporal, kinematic, and COP parameters for moderate PD compared to HC, with many trends with disease progression in mild PD. However, due to the pilot nature of this study, many of these observed trends missed significance. Once validated with a larger scale study, these biomechanical parameters could serve as part of a multi-faceted fall risk assessment that would cover several dimensions of functional balance and clinical measures of disease progression. Future work is needed to ensure such parameters are correlated to disease progression, sensitive to a decrease in subclinical postural stability, specific to fall risk, and simple enough to perform during routine clinical visits.

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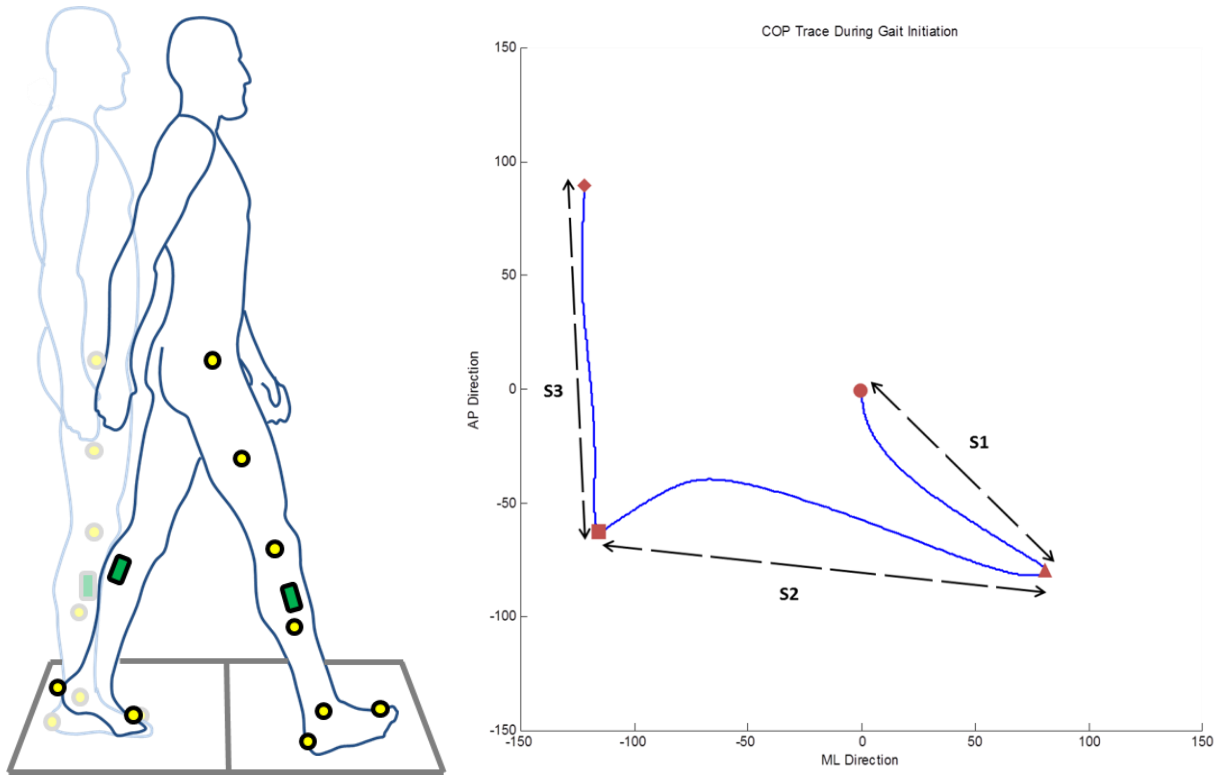
a.

b. Note: AP = anterior-posterior, ML = medial-lateral

Figure 5.1. a. Schematic of the experimental task setup for the gait initiation trials. The yellow markers represent the kinematic markers that were placed bilaterally on the toe, heel, ankle, shank, knee, thigh and hip. The green markers represent the EMG electrodes that were placed bilaterally on the medial gastrocnemius and tibialis anterior. b. Aerial view of an example COP trace during gait initiation (left foot = stance foot, right foot = swing foot) from cue light onset (circle) to swing foot heel strike (diamond). S1, S2, and S3 represent the respective stages based on the COP trace. The triangle marks the transition from stage 1 to stage 2 and the square marks the transition from stage 2 to stage 3.

Table 5.1. Mean (SD) Demographic and Clinical Data for Parkinson's Disease (PD) Subjects and Healthy Controls (HC)

I. Subject Demographic Data

	Gender	Age (years)	Height (m)	Mass (kg)
HC	M=12, F=5	67.7 (4.8)	1.72 (.08)	74 (13)
Mild PD	M=6 , F=5	62.5 (8.7)	1.67 (.08)	76 (14)
Moderate PD	M=8, F=2	67.8 (3.9)	1.73 (.10)	85 (19)

II. Parkinson's Disease Specific Participant Data

	H&Y Score	Years Since Diagnosis	UPDRS Total	UPDRS Motor	UPDRS item 33 (Pull Test)	Schwab & England (%)
Mild PD	2 (0)	4.9 (4.3)	24 (10)	18 (7)	.2 (.4)	90 (5)
Moderate PD	3 (0)	7.6 (3.4)	50 (11)	31 (8)	2 (0)	78 (7)

M – male, F – female, H&Y – Hoehn and Yahr, UPDRS – Unified Parkinson's Disease Rating Scale.

Table 5.2. Names and Descriptions for Gait Initiation Parameters

Parameter (units)	Description
Temporal Parameters:	
Weight Shift Time (s)	Difference between the reaction time and heel off of the swing foot
Step Onset Time (s)	Time from the light cue to heel off of the swing foot
Step Duration (s)	Time from heel off of the swing foot to heel strike of the swing foot.
Cue to Heel Strike Duration (s)	Time from the light cue to heel strike of the swing foot
Kinematic Parameters:	
Step Length (%)	Distance between heel off of the swing foot to heel strike of the swing foot normalized to subject height. Also calculated in the AP and ML direction.
Step Speed (%/s)	Distance divided by time of heel off of the swing foot to heel strike of the swing foot normalized to subject height.
Step Clearance (mm)	Maximum height of the toe from heel off to heel strike of the swing foot.
COP Step Parameters:	
COP Heel Off Location (mm)	Location of the COP at heel off of the swing foot relative to the COP at light onset. Calculated in the AP and ML direction.
COP Heel Strike Location (mm)	Location of the COP at heel strike of the swing foot relative to the COP at light onset. Calculated in the AP and ML direction.
COP Stage Parameters:	
COP Displacement (%)	Maximum displacement of the COP during the gait initiation stage normalized to participant foot length (AP direction) or stance width for Stages 1 and 2 and foot width for Stage 3 (ML direction.
COP Velocity (%/s)	Average of the normalized COP distance traveled over time during the gait initiation stage. Also calculated in the AP and ML directions.
Peak COP Velocity (%/s)	Maximum of the normalized velocity in the anterior, posterior, toward the swing foot, and toward the stance foot directions during each gait initiation stage.
Stage Duration (s)	Total time elapsed during the gait initiation stage.

Table 5.3. a. Mean (SEM) for Gait Initiation Temporal Parameters. b. Mean (SEM) for Gait Initiation Kinematic Step Parameters. c. Mean (SEM) for Gait Initiation COP Step Parameters

Table 3a. Mean (SEM) for Gait Initiation Temporal Parameters

	Weight Shift Time (s)	Step Onset Time (s)	Step Duration (s)	Cue to Heel Strike Duration (s)
HC	.44 (.03)	.68 (.03)	.46 (.02)	1.14 (.04)
Mild PD	.43 (.05)	.66 (.03)	.48 (.04)	1.16 (.06)
Moderate PD	.51 (.05)	.86 (.04)*+	.53 (.03)	1.39 (.06)*+

Table 3b. Mean (SEM) for Gait Initiation Kinematic Step Parameters

	Step Length (%)	AP Step Length (%)	ML Step Length (%)	Step Speed (mm/s)	Step Clearance (mm)
HC	27.6 (.7)	27.5 (.7)	1.64 (0.13)	1057.0 (56.1)	113.0 (3.7)
Mild PD	27.9 (1.7)	27.7 (1.7)	3.18 (0.21)	1005.7 (75.9)	104.4 (6.4)
Moderate PD	21.9 (1.4)*+	21.7 (1.4)*+	1.51 (0.24)	737.2 (64.6)*+	97.4 (6.8)

Table 3c. Mean (SEM) for Gait Initiation COP Step Parameters

	AP COP Heel Off Location (%)	ML COP Heel Off Location (%)	AP COP Heel Strike Location (%)	ML COP Heel Strike Location (%)
HC	-11.8 (2.6)	-26.8 (4.1)	17.0 (2.7)	-65.7 (2.8)
Mild PD	-8.0 (2.4)	-15.8 (4.8)	15.8 (3.2)	-77.0 (7.6)
Moderate PD	-0.1 (1.5)*	-14.7 (4.6)	20.6 (3.5)	-61.3 (2.5)

* indicates the parameter was significantly different ($p < .05$) than the HC group.

+ indicates the parameter was significantly different ($p < .05$) than the mild PD group (for mild PD vs. moderate PD comparisons).

Table 5.4. Mean (SEM) for Gait Initiation COP Stage Parameters

		Stage 1	Stage 2	Stage 3
AP COP Displacement (%)	HC	18.3 (1.9)	14.7 (1.0)	38.1 (2.5)
	Mild PD	17.1 (2.0)	15.3 (2.9)	31.9 (3.8)
	Moderate PD	13.0 (2.0)	17.8 (1.7)	26.1 (4.1)*
ML COP Displacement (%)	HC	30.8 (1.7)	89.6 (2.6)	16.6 (2.2)
	Mild PD	26.4 (3.0)	85.4 (6.4)	23.7 (4.9)
	Moderate PD	23.2 (2.5)	80.7 (2.0)	11.8 (2.9)
AP COP Velocity (%/s)	HC	-40.2 (4.9)	-10.0 (6.2)	124.6 (11.0)
	Mild PD	-37.8 (5.0)	0.1 (9.7)	99.7 (14.8)
	Moderate PD	-21.8 (4.0)*	16.4 (5.6)*	92.1 (12.6)
Peak A COP Velocity (%/s)	HC	13.9 (3.1)	127.4 (15.1)	307.1 (31.9)
	Mild PD	18.3 (5.7)	145.4 (37.0)	208.2 (32.6)
	Moderate PD	32.2 (5.4)*	126.1 (12.7)	198.9 (21.5)
Peak P COP Velocity (%/s)	HC	-131.9 (7.6)	-146.5 (14.6)	17.2 (2.7)
	Mild PD	-127.0 (15.0)	-132.8 (23.3)	16.6 (5.7)
	Moderate PD	-97.5 (15.2)	-103.0 (19.7)	25.3 (5.6)
ML COP Velocity (%/s)	HC	65.9 (5.4)	-281.5 (12.9)	-38.3 (7.6)
	Mild PD	58.1 (8.5)	-267.7 (27.2)	-70.2 (18.1)
	Moderate PD	44.7 (5.3)*	-191.0 (16.0)*+	-24.6 (11.7)+
Peak COP Velocity toward Swing Foot (%/s)	HC	220.5 (16.9)	5.2 (1.7)	109.4 (21.2)
	Mild PD	199.5 (25.5)	0.3 (0.3)	**22.1 (11.8)***
	Moderate PD	142.2 (23.0)*	5.2 (3.2)	121.2 (32.8)+
Peak COP Velocity toward Stance Foot (%/s)	HC	-8.4 (2.6)	-702.2 (60.2)	-145.2 (18.6)
	Mild PD	-12.9 (3.1)	-588.2 (60.1)	-159.3 (23.8)
	Moderate PD	-11.6 (3.2)	-450.7 (31.8)*	-115.8 (14.9)
Stage Duration (s)	HC	0.49 (.03)	0.33 (.01)	0.32 (.02)
	Mild PD	0.49 (.03)	0.33 (.02)	0.34 (.03)
	Moderate PD	0.64 (.04)*+	0.46 (.03)*+	0.29 (.02)

* indicates the parameter was significantly different ($p < .05$) than the HC group.

[+] indicates the parameter was significantly different ($p < .05$) than the mild PD group (for mild PD vs. moderate PD comparisons).
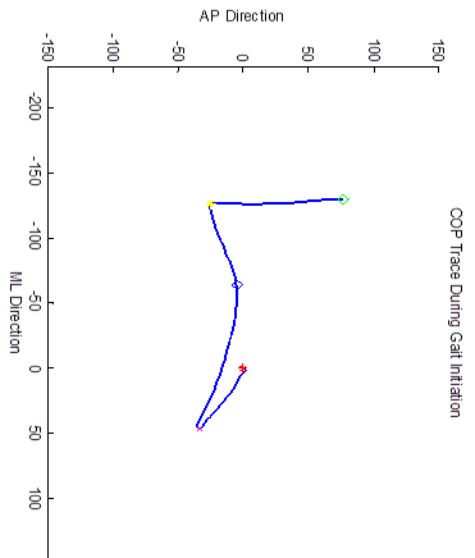
a.
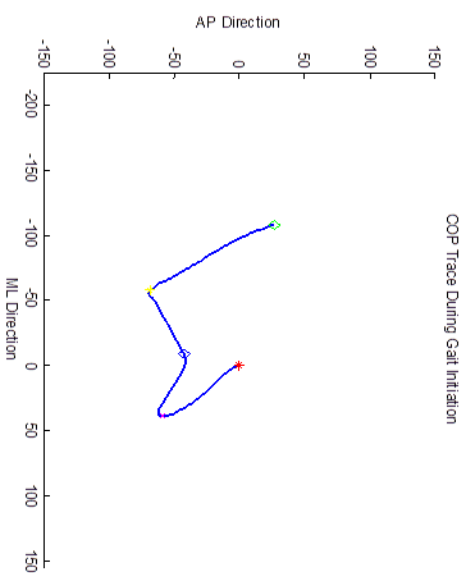
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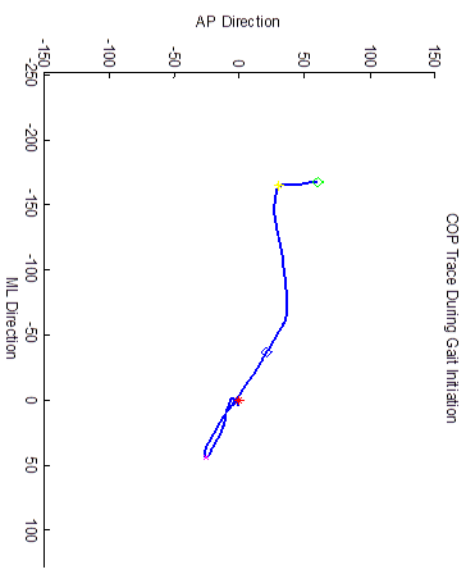
c.

Figure 5.2. Example gait initiation COP traces for a. Healthy Control, b. Mild PD, c. Moderate PD. Red star – light onset, magenta x – transition from stage 1 to stage 2, blue diamond – step heel off, yellow star – transition from stage 2 to stage 3, green diamond – heel strike of the swing foot.

CHAPTER 6: Conclusions

Summary

The primary objective of the research in this dissertation was to investigate quasi-static and dynamic biomechanical tasks as potential indicators of preclinical postural instability and progression in PD. PD patients without postural deficits (mild PD, H&Y 2), those with postural deficits (moderate PD, H&Y 3) and healthy controls (HC) were tested during postural sway and gait initiation toward this goal. Force plate, motion, electromyography, and video data were used to quantify biomechanical measures in terms of center of pressure, kinematic, and temporal parameters. Further, principal component analysis (PCA) models with biomechanical and clinical measures as inputs were utilized to better track and score postural instability progression by considering the cumulative effect of these parameters.

Specifically, postural sway was investigated in mild PD, moderate PD, and HC and whole body COP measures were extracted to determine if a quasi-static task could show evidence of preclinical postural instability (Specific Aim 1, Chapter 3). Then, PCA based on postural sway biomechanical parameters and clinical measures was utilized for 2 goals. First, PCA identified the parameters driving the variation in the overall data set and then determined if the selected variables could differentiate preclinical postural instability and clinical disease progression (Specific Aim 2, Chapter 4). Lastly, gait initiation was investigated through extracting temporal, kinematic, and COP parameters during the first step of the response to determine if a dynamic task could find earlier indication of postural instability in PD (Specific Aim 3, Chapter 5).

Chapter 3 determined if postural sway could differentiate PD patients without clinical presentation of postural instability compared to HC, and if such differences persisted once clinical presentation of postural instability was present. Results showed that multiple measures

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based on the whole body COP path and velocity provided early indication of postural instability in PD. Specifically, trajectory, variation, and peak COP parameters were significantly different in mild PD compared to HC, and these differences persisted in moderate PD. However, despite some measures providing preclinical indication of postural instability (mild PD compared to HC), no individual parameter was also able to differentiate postural instability changes associated with clinical disease progression (mild PD compared to moderate PD). Future work with larger sample sizes and additional tasks is needed to ensure such parameters are correlated with disease progression, sensitive to a decrease in subclinical postural stability, specific to fall risk, and simple enough to perform during routine clinical visits.

Chapter 4 investigated the use of mathematical modeling for more quantitative scoring of postural instability progression in PD. PCA based on a correlation matrix with standardized postural sway biomechanical and clinical measures as inputs was used for both parameter selection and group differentiation. Parameter selection of the PCA $_{initial}$ model found a combination of biomechanical and clinical parameters as the primary drivers of variation in the HC and PD participants. And further, the resultant PCA models based on parameter selection were able to significantly differentiate early onset (mild PD versus HC) and clinical progression (mild PD versus moderate PD and moderate PD versus HC) of postural instability in PD for the first principal component scores. Future study for a wider range of functional tasks with larger sample sizes as well as predicative PCA modeling to test the robustness of PCA to score patients based on postural instability severity is needed.

Chapter 5 determined if gait initiation could differentiate both preclinical onset of postural instability and its associated progression in PD. Peak COP velocity towards the swing foot during the locomotion phase of gait initiation showed promise as a parameter that may

detect postural instability earlier than current clinical assessment as this measures was significantly slower in mild PD group compared to HC. However, this parameter may also be representative of a bi-phasic effect, with moderate PD exhibiting compensatory behaviors in their initial step that reversed this observed change in mild PC compared to HC. Additionally, several significant differences in temporal, kinematic, and COP parameters for moderate PD compared to HC were observed, with many trends in early disease progression in mild PD compared to HC. Once validated with a larger scale study, these biomechanical parameters could serve as part of a multi-factorial fall risk assessment that would cover several dimensions of functional balance and clinical measures of disease progression.

Due to the pilot nature of the studies involved in this research, several limitations exist. The small sample size, the influence of outliers and that PD participants were tested "on" medication all affected the outcomes of this study. Because of the clinically driven goals of this research, this choice was made in order to reflect potential clinical balance assessments that do not require patients to alter their dosing schedule ("on" medication) so that such a task could be more easily translated into routine clinical visits. Future studies with larger sample sizes should include "off" medication assessments or inclusion of de novo subjects to determine if medications are masking subtle changes that may further enhance the detection of those at risk for postural instability and falling.

Overall, postural sway and gait initiation show promise as biomechanical assessment tasks that may provide earlier indication of postural instability in PD, Further, using increasingly sophisticated mathematical models like PCA could provide a method to more quantitative assess the overall progression of postural instability in PD. Particularly, PCA may be helpful in a multi-factorial balance assessment as a means to score a threshold based on multiple measures to

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detect the onset of postural instability in PD. In both quasi-static (postural sway) and dynamic (gait initiation) tasks as well as PCA modeling, COP measures of velocity were found to be significantly different in mild PD compared to HC. Further investigation of all the significant parameters and tasks from this research, and particularly COP velocity measures, warrant further investigation. In order for these biomechanical measures to be useful in predicting fall risk, future study must confirm that such parameters are correlated to disease progression, sensitive to a decrease in subclinical postural stability, and specific to fall risk.

Future Studies

Future studies must address several questions. First, do the responses observed in this research for mild and moderate PD persist in a larger scale study with additional clinical PD stages? Further, can mathematical modeling through PCA be used across multiple levels of functional balance to better assess across and within task correlations? The progression of these changes on a larger scale for both quasi-static and dynamic tasks must be further explored. Also, how do these biomechanical measures of postural sway and gait initiation correlate to fall risk? Future study that longitudinally follows PD patients and relates their biomechanical measures to fall incidence could help better establish the specificity of these parameters to fall risk. Lastly, once certain biomechanical measures are confirmed as sensitive to preclinical postural instability and specific to fall risk, how can these measures be implemented in a clinical setting to better aid clinicians in assessing fall risk, and thus implementing earlier compensatory therapies? The ability of these tasks to be easily and reliably implemented in a clinical setting must be further investigated.

Significance

Timely prediction of risk of falls in those with PD before recurrent falls begin is a crucial need to maintain patient quality of life and increase life expectancy. Because postural instability leads to increased risk of falls, a method to diagnose, assess and score postural instability in PD is a critical unmet need. Since no effective screening method exists to measure fall risk, our team is developing a multi-factorial method to detect postural instability through clinical balance assessment, and in doing so, provide the justification for implementing fall reducing therapies before potentially debilitating patient falls begin. Continued investigation of the significant biomechanical tasks and parameters in postural instability assessment through postural control modeling could help further understanding of the neurophysiology involved in PD progression. Once a set of promising biomechanical markers for a range of balance tasks is identified, these can be streamlined and implemented in a clinical setting. Applying the results of this research towards a bioinstrumentation device that a clinician can use to assess fall risk quickly and accurately would have a direct and tangible positive impact on patient care and the healthcare system in general.

APPENDIX A.Coordinate Systems and Transformations

Landon Center on Aging Experimental Setup
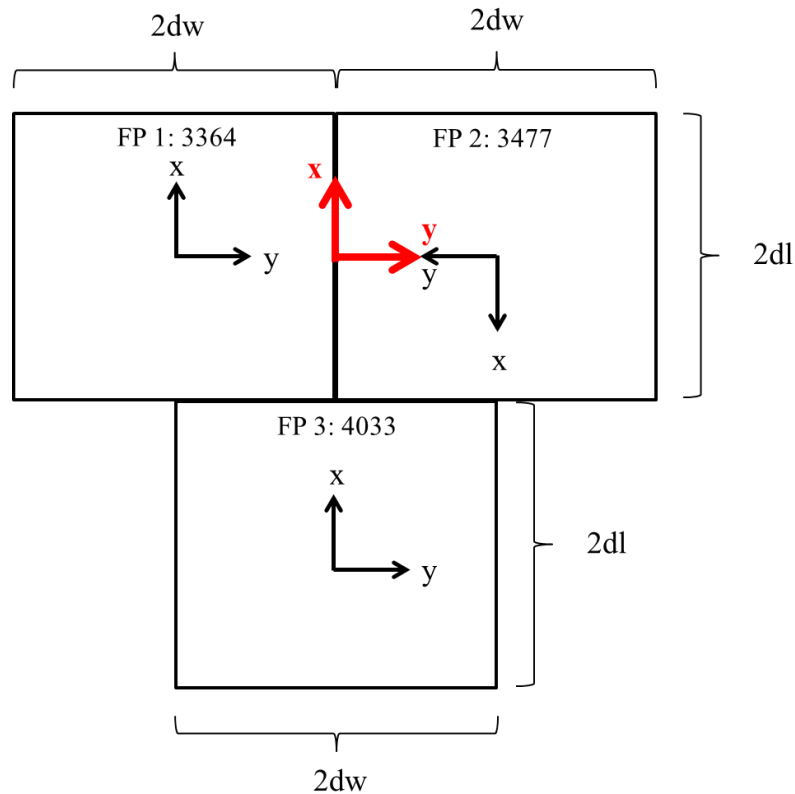
Postural Sway

Black coordinates represent the initial force plate coordinate system; red (bold) coordinates represent the global coordinate system used in the postural sway analysis. Participants stood with their left foot on FP 1 on and right foot on FP 2.

Force Plate Rotations:

FP 1 Rotation: *none*

FP 2 Rotation: $\begin{pmatrix} 1 & 0 & 0 \\ 0 & 0 & -1 \\ 0 & 1 & 0 \end{pmatrix} \begin{pmatrix} 1 & 0 & 0 \\ 0 & 0 & -1 \\ 0 & 1 & 0 \end{pmatrix}$

Force Plate Transformation to Final Coordinate System Alignment:

$Fx_{MAIN} = Fx_{FP1} + Fx_{FP2}$
$Fy_{MAIN} = Fy_{FP1} + Fy_{FP2}$
$Fz_{MAIN} = Fz_{FP1} + Fz_{FP2}$

$Mx_{MAIN} = Mx_{FP1} + Mx_{FP2} - d_w(Fz_{FP1} + Fz_{FP2})$
$My_{MAIN} = My_{FP1} + My_{FP2}$
$Mz_{MAIN} = Mz_{FP1} + Mz_{FP2} + d_w(Fx_{FP1} + Fx_{FP2})$

Gait Initiation

Black coordinates represent the initial force plate coordinate system; red (bold) coordinates represent the global coordinate system used in the gait initiation analysis. Participants stood on FP 1 and then initiated gait onto FP2.

Force Plate Rotations:

FP 1 Rotation: $\begin{pmatrix} 1 & 0 & 0 \\ 0 & 0 & -1 \\ 0 & 1 & 0 \end{pmatrix}\begin{pmatrix} 1 & 0 & 0 \\ 0 & 0 & -1 \\ 0 & 1 & 0 \end{pmatrix}\begin{pmatrix} 1 & 0 & 0 \\ 0 & 0 & -1 \\ 0 & 1 & 0 \end{pmatrix}$

FP 2 Rotation: $\begin{pmatrix} 0 & 0 & 1 \\ 0 & 1 & 0 \\ -1 & 0 & 0 \end{pmatrix}\begin{pmatrix} 0 & 0 & 1 \\ 0 & 1 & 0 \\ -1 & 0 & 0 \end{pmatrix}\begin{pmatrix} 1 & 0 & 0 \\ 0 & 0 & -1 \\ 0 & 1 & 0 \end{pmatrix}$

Force Plate Transformations to Final Coordinate System Alignment:

$Fx_{MAIN} = Fx_{FP1} + Fx_{FP2}$
$Fy_{MAIN} = Fy_{FP1} + Fy_{FP2}$
$Fz_{MAIN} = Fz_{FP1} + Fz_{FP2}$
$Mx_{MAIN} = Mx_{FP1} + Mx_{FP2} + d_l Fz_{FP1} + d_w Fz_{FP2}$
$My_{MAIN} = My_{FP1} + My_{FP2} + (-3d_w)Fz_{FP1} - d_w Fz_{FP2}$
$Mz_{MAIN} = Mz_{FP1} + Mz_{FP2} + 3d_w Fy_{FP1} - d_l Fx_{FP1} + d_w Fy_{FP2} - d_l Fx_{FP2}$

Biodynamics Lab Experimental Setup
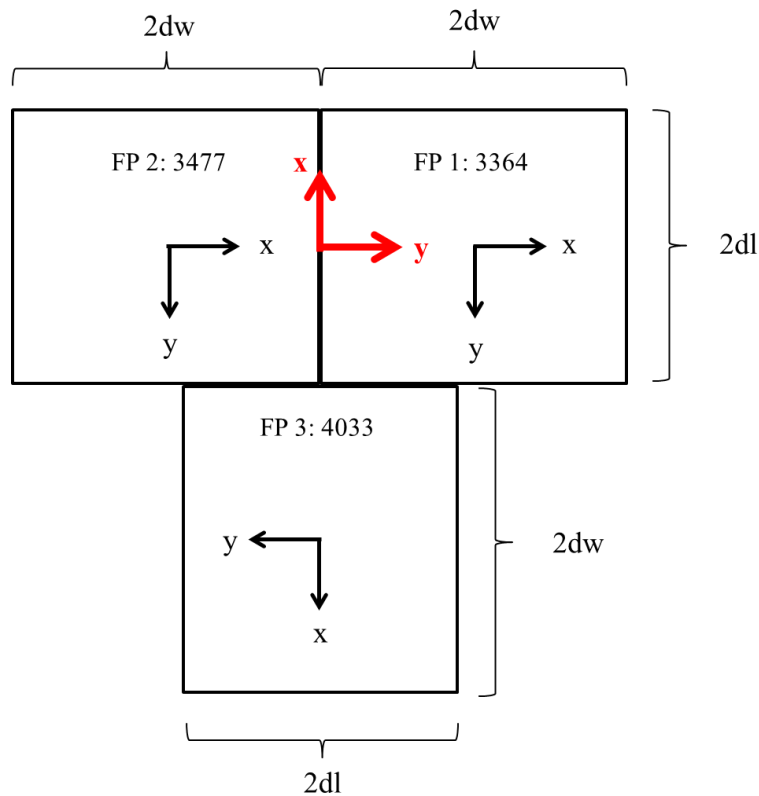
Postural Sway

Black coordinates represent the initial force plate coordinate system; red (bold) coordinates represent the global coordinate system used in the postural sway analysis. Participants stood with their left foot on FP 2 on and right foot on FP 1.

Force Plate Rotations:

FP 1 Rotation: $\begin{pmatrix} 1 & 0 & 0 \\ 0 & 0 & -1 \\ 0 & 1 & 0 \end{pmatrix}\begin{pmatrix} 1 & 0 & 0 \\ 0 & 0 & -1 \\ 0 & 1 & 0 \end{pmatrix}\begin{pmatrix} 1 & 0 & 0 \\ 0 & 0 & -1 \\ 0 & 1 & 0 \end{pmatrix}$

FP 2 Rotation: $\begin{pmatrix} 1 & 0 & 0 \\ 0 & 0 & -1 \\ 0 & 1 & 0 \end{pmatrix}\begin{pmatrix} 1 & 0 & 0 \\ 0 & 0 & -1 \\ 0 & 1 & 0 \end{pmatrix}\begin{pmatrix} 1 & 0 & 0 \\ 0 & 0 & -1 \\ 0 & 1 & 0 \end{pmatrix}$

Force Plate Transformation to Final Coordinate System Alignment:

$Fx_{MAIN} = Fx_{FP1} + Fx_{FP2}$
$Fy_{MAIN} = Fy_{FP1} + Fy_{FP2}$
$Fz_{MAIN} = Fz_{FP1} + Fz_{FP2}$

$Mx_{MAIN} = Mx_{FP1} + Mx_{FP2} - d_w(Fz_{FP1} + Fz_{FP2})$
$My_{MAIN} = My_{FP1} + My_{FP2}$
$Mz_{MAIN} = Mz_{FP1} + Mz_{FP2} + d_w(Fx_{FP1} + Fx_{FP2})$

Gait Initiation

2dw   2dw

FP 2: 3477   FP 1: 3364

x   x

y   y   2dl

FP 3: 4033

y   2dw

x

x

y

2dl

Black coordinates represent the initial force plate coordinate system; red (bold) coordinates represent the global coordinate system used in the gait initiation analysis. Participants stood with their right foot onon FP 1 and left foot on FP 2 and then initiated gait onto FP3.

Force Plate Rotations:

FP 1 Rotation: $\begin{pmatrix} 1 & 0 & 0 \\ 0 & 0 & -1 \\ 0 & 1 & 0 \end{pmatrix}\begin{pmatrix} 1 & 0 & 0 \\ 0 & 0 & -1 \\ 0 & 1 & 0 \end{pmatrix}\begin{pmatrix} 0 & -1 & 0 \\ 1 & 0 & 0 \\ 0 & 0 & 1 \end{pmatrix}$

FP 2 Rotation: $\begin{pmatrix} 1 & 0 & 0 \\ 0 & 0 & -1 \\ 0 & 1 & 0 \end{pmatrix}\begin{pmatrix} 1 & 0 & 0 \\ 0 & 0 & -1 \\ 0 & 1 & 0 \end{pmatrix}\begin{pmatrix} 0 & -1 & 0 \\ 1 & 0 & 0 \\ 0 & 0 & 1 \end{pmatrix}$

FP 3 Rotation: $\begin{pmatrix} 0 & 0 & 1 \\ 0 & 1 & 0 \\ -1 & 0 & 0 \end{pmatrix}\begin{pmatrix} 0 & 0 & 1 \\ 0 & 1 & 0 \\ -1 & 0 & 0 \end{pmatrix}$

Force Plate Translations Following Rotation:

$Fx_{MAIN} = Fx_{FP1} + Fx_{FP2} + Fx_{FP3}$

$Fy_{MAIN} = Fy_{FP1} + Fy_{FP2} + Fy_{FP3}$

$Fz_{MAIN} = Fz_{FP1} + Fz_{FP2} + Fz_{FP3}$

$Mx_{MAIN} = Mx_{FP1} + Mx_{FP2} + Mx_{FP3} + (d_l - d_w)Fz_{FP1} + (d_l + d_w)Fz_{FP2} + d_lFz_{FP3}$

$My_{MAIN} = My_{FP1} + My_{FP2} + My_{FP3} - (2d_w + d_l)Fz_{FP1} - (2d_w + d_l)Fz_{FP2} - d_wFz_{FP3}$

$Mz_{MAIN} = Mz_{FP1} + Mz_{FP2} + Mz_{FP3} + (2d_w + d_l)Fy_{FP1} - (-d_w + d_l)Fx_{FP1} + (2d_w + d_l)Fy_{FP2} - (d_w + d_l)Fx_{FP2} + d_wFy_{FP3} - d_lFx_{FP3}$

APPENDIX B. Outcome Parameter Calculations and Additional Results

COP Calculations

Calculating the Center of Pressure (COP)[12]

Based on the combined (final) coordinate systems, the force plates measures:

- three forces (Fx, Fy, Fz)

- three moments (Mx, My, Mz).

Each moment component measured by the force plate is the summation of the applied couple and the moment-of-force.

A couple, equivalent to two non-collinear, parallel forces acting in opposite directions, is calculated with:

$$M = r \, x \, F$$

r = any vector connecting the line of action of the first force vector with the second force vector, and

F = the second force vector.

The moment-of-force is the moment caused by the force acting at a distance, with:

$$Mo = r \, x \, F$$

r = any vector connecting the origin with line of action of the force vector, and

F = the force vector.

The total moment about the axis normal to the top surface of the force plate (z for AMTI force plates) is equal to:

$$Mz = -Fx * y + Fy * x + Tz$$

The horizontal moments about the axes parallel to the top surface of the force plate (x and y for AMTI force plates) are equal to:

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[12] Adapted from the Luchies ME 751 FORCE PLATES document.

$$Mx = Fz * y + Fy * dz + Tx$$

$$My = -Fz * x - Fx * dz + Ty$$

Where dz in the distance below the top surface at which the origin in located (provided with the calibration).

When an individual stands for walks on an AMTI force plate, the only way to induce a couple about a horizontal axis is to attach a foot (or shoe) to the platform so that it can twist the top surface about the X or Y axis (e.g. similar to the boot on a show board). Otherwise, there are no Tx or Ty torques and these equations can be simplified and used to calculate the x and y coordinates of the center-of-pressure (COP):

$$COP\ x = \left(-\frac{M_y + F_x * d_z}{F_z} \right)$$

$$COP\ y = \left(\frac{M_x - F_y * d_z}{F_z} \right)$$

$$COP = \sqrt{\left(-\frac{M_y + F_x * d_z}{F_z} \right)^2 + \left(\frac{M_x - F_y * d_z}{F_z} \right)^2}$$

i. Specific Aim 1

Table A.i.1.2. SD Threshold Analysis Results (number subjects greater than threshold/group size) for COP Parameters for Eyes Open and Eyes Closed Postural Sway

	Trajectory					Variation		Peak		
	SPL	AP SPL	ML SPL	SA	MSS	AP RMS	ML RMS	AP SPR	ML SPR	PSS
Eyes Open										
HC	0/21	1/21	1/21	1/21	0/21	0/21	2/21	0/21	1/21	1/21
PD	16/23*	13/23*	13/23*	11/23*	17/23*	6/23	9/23	10/23*	11/23*	9/23
Mild PD	8/13*	6/13	5/13	7/13*	9/13*	2/13	7/13	6/13*	7/13*	5/13
Moderate PD	8/10*	7/10*	8/10*	4/10	8/10*	4/10	2/10	4/10	4/10	4/10
Eyes Closed										
HC	1/21	1/21	1/21	1/21	1/21	1/21	1/21	1/21	1/21	2/21
PD	11/23*	10/23	12/23*	9/23	11/23*	7/23	4/23	6/23	6/23	10/23
Mild PD	4/13	4/13	5/13	3/13	3/13	2/13	3/13	2/13	3/13	4/13
Moderate PD	7/10*	6/10	7/10*	6/10*	7/10*	5/10	1/10	4/10	3/10	6/10*

COP- center of pressure, HC – healthy controls, PD – Parkinson's Disease, SPL – sway path length, AP SPL – anterior-posterior sway path length, ML SPL – medial-lateral sway path length, SA – sway area, MSS – mean sway speed, AP RMS – anterior-posterior root mean square, ML RMS – medial-lateral root mean square, AP SRP – anterior-posterior sway path range, ML SPR – medial-lateral sway path range, PSS – peak sway speed.

* indicates the parameter was significantly different (p < .05) than the HC group.

+ indicates the parameter was significantly different (p < .05) than the mild PD group (for mild PD versus moderate PD comparisons).

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ii. Specific Aim 2

PCA _{initial} Model (14 input parameters) in-depth analysis: Eyes Open Postural Sway:

Group Differentiation

To assess the PCA model's differentiation of the three study population groups (HC, mild, and moderate), the resultant scores (the representation of the input data in the rotated coordinate system for each PC) per group were tested for significant differences. PC 1 scores for all group pairwise comparisons (HC v. mild PD, HC v. moderate PD, mild PD v. moderate PD) were significantly different (mean (SD): HC -1.99 (.55), mild PD 0.47 (1.58), moderate PD 3.56 (3.40), p<.05). The 95% confidence intervals for PC1 scores for the HC versus Mild PD group and Moderate groups were unique, with the HC confidence intervals of $-2.24036 \leq \theta \leq -1.73964$, mild PD were $-0.48478 \leq \theta \leq 1.42478$, and moderate PD $1.12779 \leq \theta \leq 5.99221$.

Physical Meaning of PCs

Qualitative analysis of PC1, the eigenvector that was able to differentiate between the 3 study groups, has the mean sway speed and the peak sway speed as the 2 primary parameters influencing the PC based on their coefficients. Figure A.ii.2 shows the 2 primary parameters for this PC for the subject with the smallest and largest score for this PC. As demonstrated by Figures A.ii.1 and A.ii.2, PC 1 is most representative of the overall and peak velocity trajectory; however, the path length and range parameters are also highly correlated with the velocity measures, suggesting most of these parameters could help to describe the variance in the data set across groups. Of the clinical parameters, Schwab and England score has the largest contribution to the PC, with an inverse relationship to the biomechanical parameters. This is to be expected as Schwab and England score decreases with disease progression, while the COP biomechanical parameters are demonstrated to increase with disease progression.

PCA $_{initial}$ Model In-depth analysis: Eyes Closed Postural Sway:

Group Differentiation

To assess the PCA model's differentiation of the three study population groups (HC, mild, and moderate), the resultant scores (the representation of the input data in the rotated coordinate system for each PC) per group were tested for significant differences. PC 1 scores for all group pairwise comparisons (HC v. mild PD, HC v. moderate PD, mild PD v. moderate PD) were significantly different (mean (SD): HC -1.96 (.54), mild PD 0.40 (2.19), moderate PD 3.61 (3.41), p<.05). The 95% confidence intervals for PC1 scores for the HC versus Mild PD group and Moderate groups were unique, with the HC confidence intervals of $-2.20581 \leq \theta \leq -1.71419$, mild PD were $-0.92340 \leq \theta \leq 1.72340$, and moderate PD $1.17063 \leq \theta \leq 6.04937$.

Physical Meaning of PCs

For the eyes close PCA model, qualitative analysis of PC1, the eigenvector that was able to differentiate between the 3 study groups, has mean sway speed and total COP path length as the 2 primary parameters influencing the PC based on their coefficients. Figure A.ii.3 shows the 2 primary parameters for this PC for the subject with the smallest and largest score for this PC. As demonstrated by Figure A.ii.1 and A.ii.3, PC 1 is most representative of the overall path and velocity trajectory; however, the peak velocity and range parameters are also highly correlated with the velocity measures, suggesting most of these parameters could help to describe the variance in the data set across groups. Similarly to the trend observed in the eyes open PCA model, for the clinical parameters in the eyes closed model, Schwab and England score has the largest contribution to the PC, with an inverse relationship to the biomechanical parameters. This is to be expected as Schwab and England score decreases with disease progression, while the COP biomechanical parameters are demonstrated to increase with disease progression.

Table A.ii.1. Mean (SD) Scores for PCs by Group Based on PCA $_{initial}$ Model

EO PCA ANOVA	PC1	PC2	PC3	PC4	PC5
HC	-1.99 (0.55)	0.32 (.37)	0.63 (0.32)	-0.09 (0.54)	0.19 (0.23)
Mild PD	0.47 (1.58)*	-0.4 (0.64)	-0.05 (.79)	-0.03 (.71)	-0.63 (0.55)*
Mod PD	3.56 (3.40)*+	-0.15 (2.85)	-1.26 (2.27)*	0.22 (1.06)	0.43 (0.31)+

EC PCA ANOVA	PC1	PC2	PC3	PC4	PC5
HC	-1.96 (.54)	0.74 (.23)	-0.27 (.43)	0.10 (.26)	-0.47 (.43)
Mild PD	0.4 (2.19)*	-0.19 (0.97)	0.15 (.87)	-0.47 (.49)*	0.47 (.43)*
Mod PD	3.61 (3.41)*+	-1.31 (2.24)*	0.37 (2.05)	0.39 (0.96)+	-0.30 (0.54)+

* indicates the parameter was significantly different ($p < .05$) than the HC group.

+ indicates the parameter was significantly different ($p < .05$) than the mild PD group (for mild PD vs. moderate PD comparisons).

Table A.ii.2. Coefficients and Variance for Retained PCs in Eyes Open and Eyes Closed PCA _initial_ Models

a. Eyes Open	PC 1	PC 2	PC 3	PC 4	PC 5
Parameter Coefficients per PC					
UPDRS	0.262	-0.166	-0.399*	0.082	-0.259
Schwab and England	-0.273	0.207	0.328	-0.158	0.172
Motor Exam	0.26	-0.185	-0.379	0.145	-0.338*
Pull Test	0.238	-0.087	-0.378	0.127	0.73
Sway Path Length	0.282	0.378	0.022	0.038	0.067
AP Sway Path Length	0.271	0.383*	-0.027	-0.193	-0.066
ML Sway Path Length	0.276	0.348	0.06	0.261	0.177
Sway Area	0.263	-0.209	0.368	0.209	0.118
Mean Sway Speed	0.282	0.377	0.028	0.027	0.023
AP RMS of COP	0.261	-0.287	0.051	-0.517	0.277
ML RMS of COP	0.234	-0.283	0.388	0.288	-0.066
AP Sway Path Range	0.28	-0.209	0.102	-0.563*	-0.019
ML Sway Path Range	0.268	-0.195	0.359	0.244	-0.046
Peak Sway Speed	0.285*	0.22	0.117	-0.232	-0.344
Variance Explained by PC (%)	61.00	15.63	14.27	4.08	2.28

b. Eyes Closed	PC 1	PC 2	PC 3	PC 4	PC 5
Parameter Coefficients per PC					
UPDRS	0.247	-0.402*	0.198	-0.135	0.177
Schwab and England	-0.261	0.328	-0.263	0.133	-0.13
Motor Exam	0.244	-0.386	0.237	-0.145	0.264
Pull Test	0.216	-0.382	0.179	0.395	-0.505
Sway Path Length	0.309	0.07	-0.213	0.302	0.087
AP Sway Path Length	0.271	-0.043	-0.457*	0.081	0.12
ML Sway Path Length	0.287	0.168	0.112	0.533*	0.065
Sway Area	0.257	0.349	0.277	-0.049	-0.068
Mean Sway Speed	0.310*	0.076	-0.22	0.262	0.127
AP RMS of COP	0.274	-0.002	-0.175	-0.267	-0.691*
ML RMS of COP	0.22	0.385	0.37	-0.157	-0.039
AP Sway Path Range	0.284	0.025	-0.239	-0.418	-0.13
ML Sway Path Range	0.255	0.351	0.277	-0.099	0.094
Peak Sway Speed	0.286	0.033	-0.333	-0.232	0.275
Variance Explained by PC (%)	66.10	15.40	9.80	3.10	2.50

* indicates the parameter per PC retained (largest coefficient) for the PCA _selection_ model
PC – Principal Component.

Variable Selection

Four methods of variable selection were used to determine the driving parameters for the PCA

$_{initial}$ model. First, due to the observation that PC 1 was driving the majority of the variability in

the model, coupled with the fact that all the parameters were having a mild positive or negative

effect, the most influential parameters (largest coefficients for PC 1) were selected until

significant differentiation occurred in the new PCA model based on parameter selection. Then,

three traditional methods of parameters section were also explored: selection based on the largest

coefficients for the first m PCs (justification and presentation of this in Barnds Dissertation:

Chapter 4), deletion based on the largest coefficients from the last p-m PCs, and sparse PCA.

Table A.ii.3. Variable Selection of Driving Parameters of PCA $_{initial}$ Model

Eyes Open

	UPDRS	S & E	Motor Exam	Pull Test	Sway Path Length	AP Path Length	ML Path Length	Sway Area	Mean Speed	AP RMS	ML RMS	AP Sway Range	ML Sway Range	Peak Speed
Largest coefficients from PC 1*			x		x	x	x		x			x		x
Largest coefficient from significant PCs+			x	x	x	x					x	x		
Largest coefficient from non significant PCs+						x	x	x			x	x	x	
Sparse PCA+				x					x		x	x	x	

Eyes Closed

	UPDRS	S & E	Motor Exam	Pull Test	Sway Path Length	AP Path Length	ML Path Length	Sway Area	Mean Speed	AP RMS	ML RMS	AP Sway Range	ML Sway Range	Peak Speed
Largest coefficients from PC 1*	x				x	x	x	x	x	x		x	x	x
Largest coefficient from significant PCs+		x				x	x	x	x	x				
Largest coefficient from non significant PCs+			x	x		x	x				x			
Sparse PCA+	x								x	x	x	x	x	x

For the largest coefficients from PC1, for eyes open 7 parameters and eyes closed 10 parameters were needed to get significant group differentiation (HC v. mild, HC v. moderate, mild v. moderate). For selecting the parameter with the largest coefficient from each retained PCs, deleting the parameter with the largest coefficient from each non-significant PCs and for sparse PCA, 5 parameters for both eyes open and eyes closed achieved significant group differences in all three sub-comparisons.

* indicates that the number of parameters kept was dictated by continuous iteration until the first n retained parameters resulted in significant subgroup comparisons for the PCA model based on parameters selection (*n* = 7 for eyes open and *n* = 10 for eyes closed).

+ indicates that the number of parameters selected was equal to the number of PCs retained, with *n* = 5 for both eyes open and eyes closed conditions.
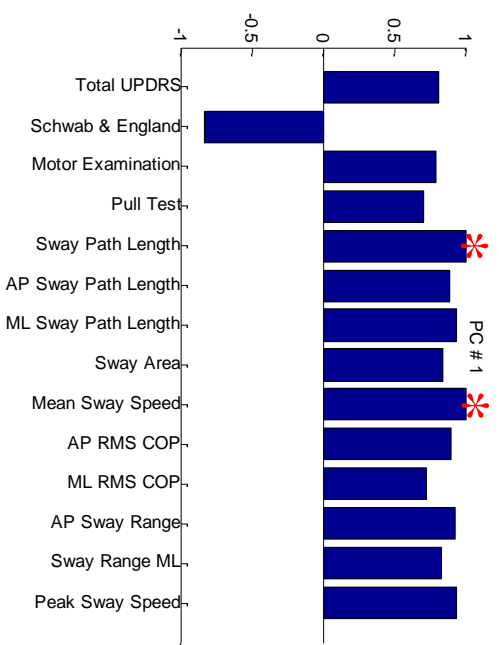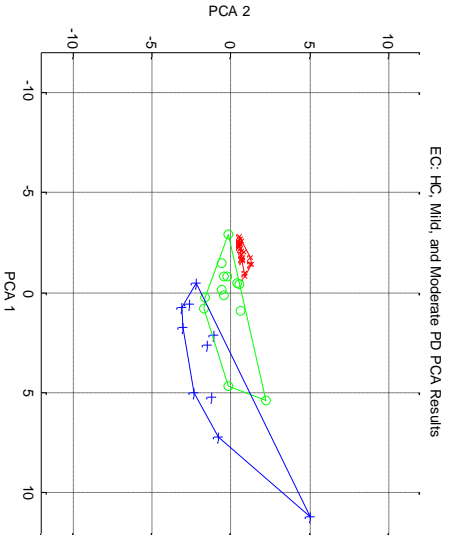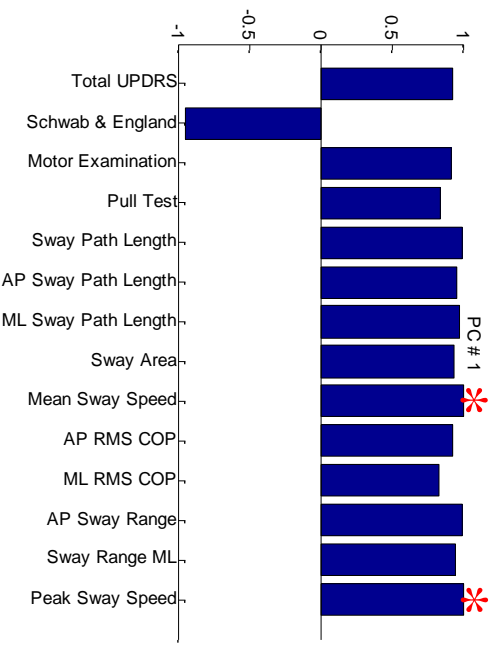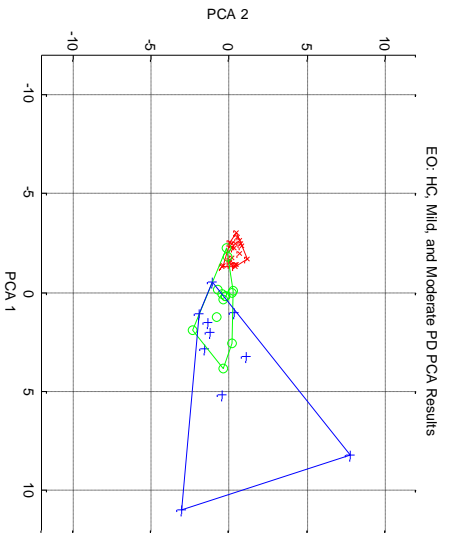
Figure A.ii.1. Upper half: transformed subject scores plotted on the principal component(PC) 1 versus PC 2 axes.(left) and the relative contribution (coefficients) of each input parameter normalized to the most influential variable (right) for the eyes open PCA model. Lower half: transformed subject scores plotted on the principal component(PC) 1 versus PC 2 axes.(left) and the relative contribution (coefficients) of each input parameter normalized to the most influential variable (right) for the eyes closed PCA model.
Key: (left): red x – HC, green o – mild PD, blue + - moderate PD; (right): one of the 2 most influential parameters for PC 1.

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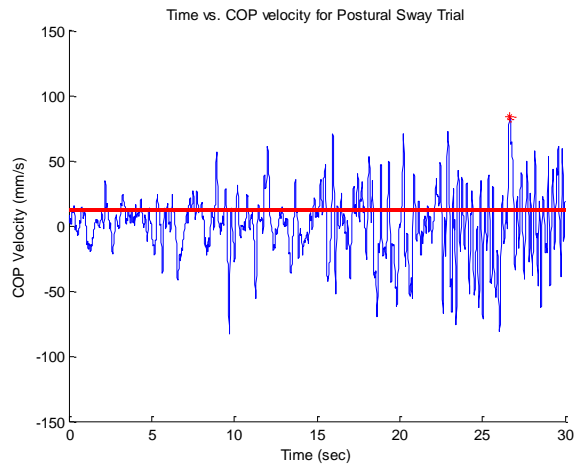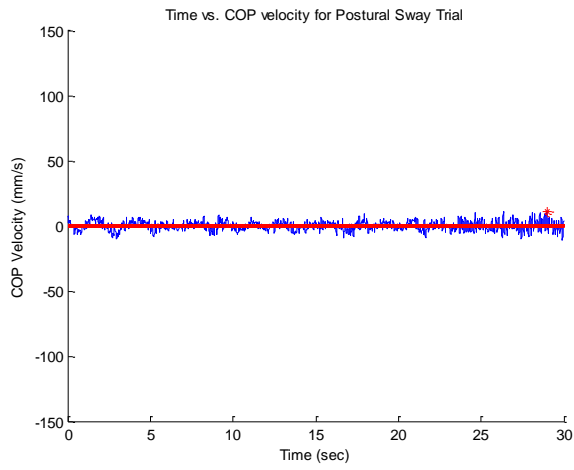
Figure A.ii.2. Eyes Open PCA *initial* model: representative plots for the two most influential parameters (peak sway speed and mean sway speed) of PC 1for the PCA *initial* model for the minimum (left) and maximum (right) PC 1 subjects scores.

Key: peak Sway Speed - red *, Mean Sway Speed -red line.
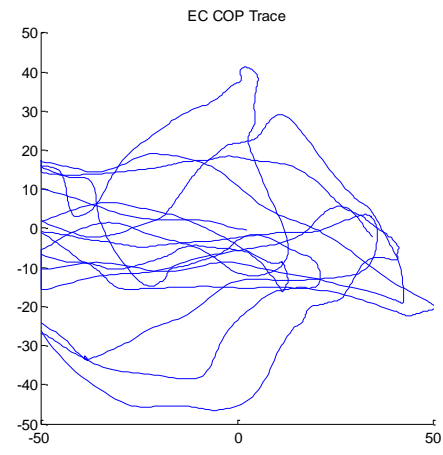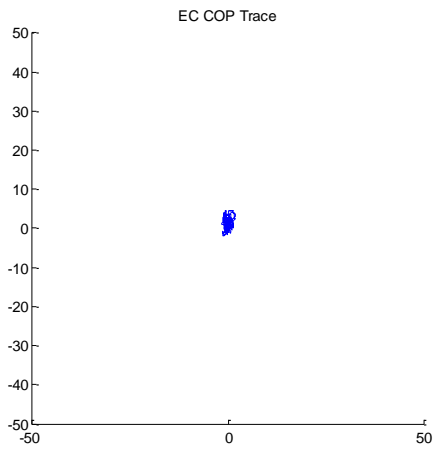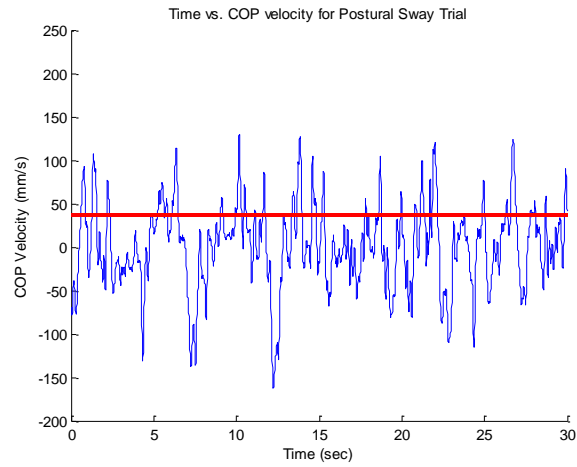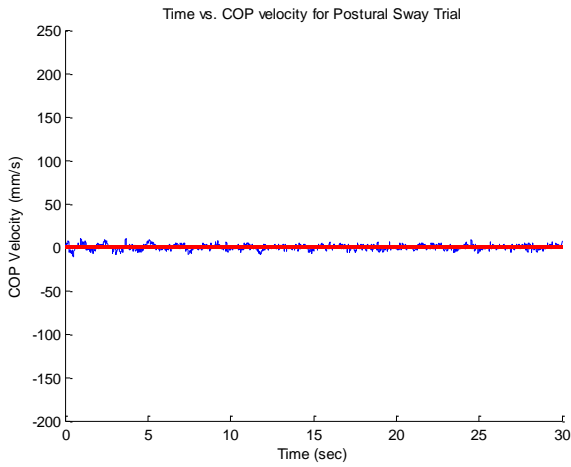
Figure A.ii.3.Eyes Closed PCA $_{initial}$ model: representative plots for the two most influential parameters (mean sway speed- upper half, COP path length, lower half) of PC 1for the PCA $_{initial}$ model for the minimum (left) and maximum (right) PC 1 subjects scores.

Key: Mean Sway Speed -red line, upper half; COP trace aerial view -blue line, lower half.

PCA Results
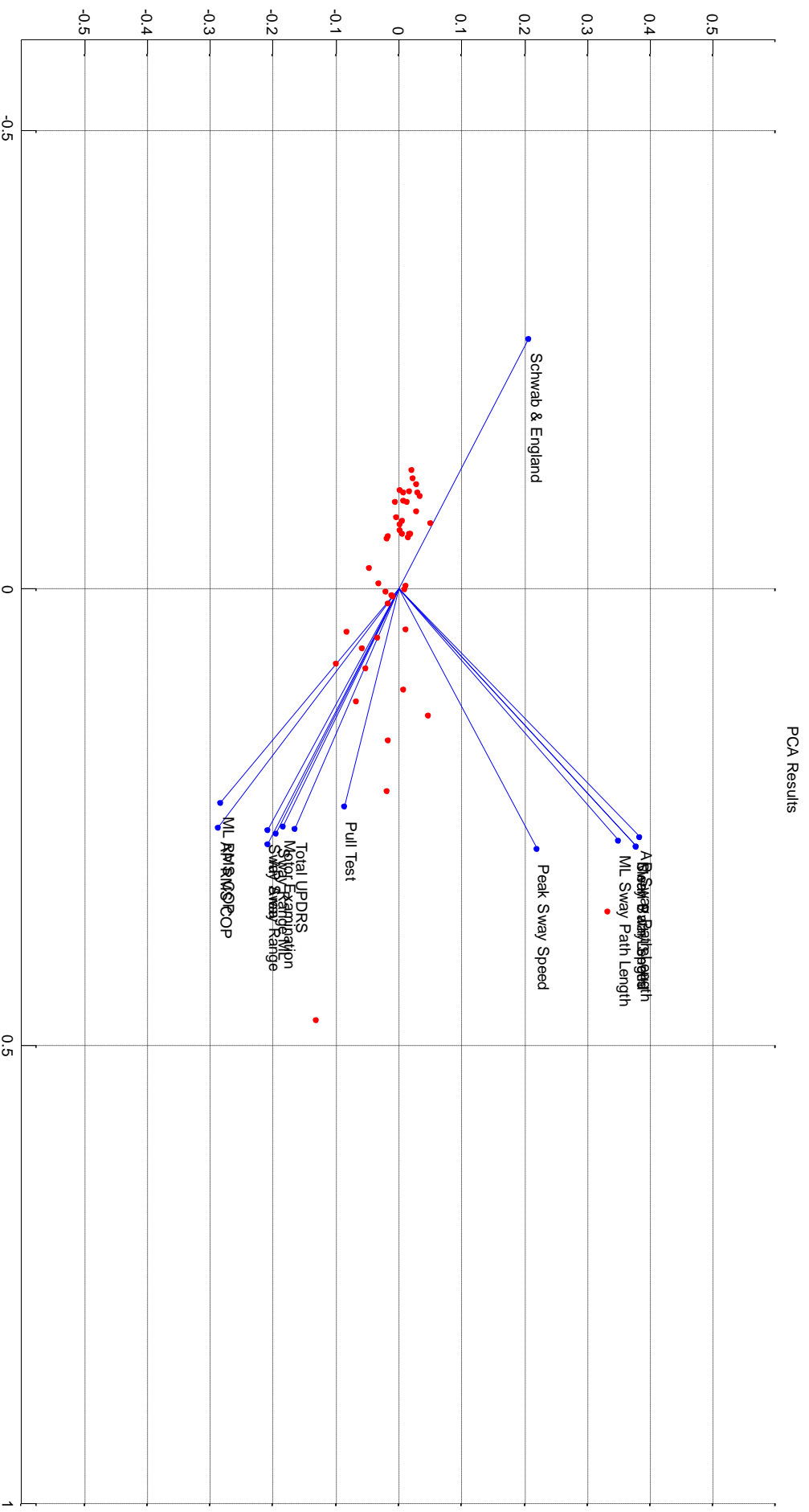
a.
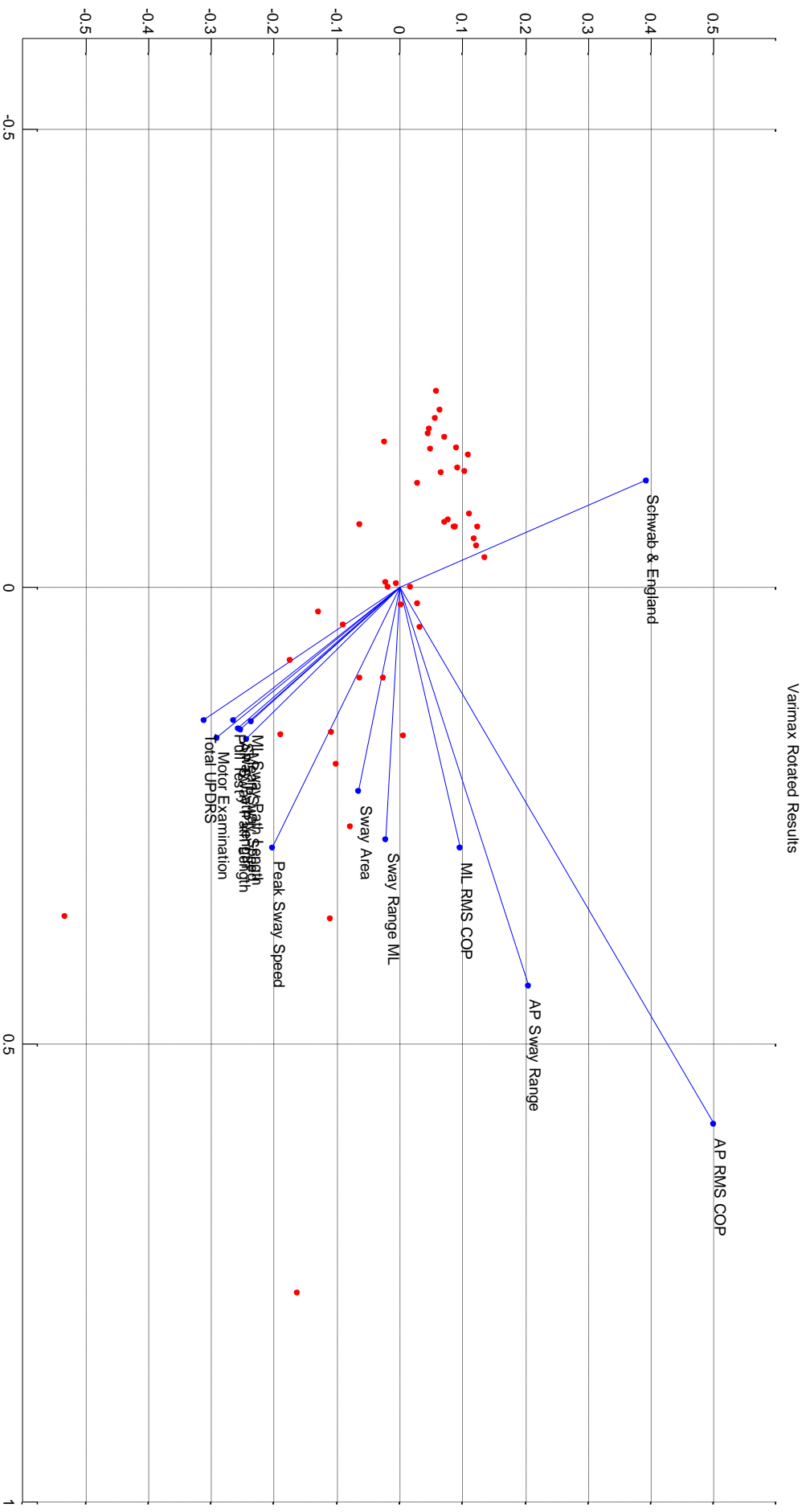
b.

Figure A.ii.4. Eyes Open PCA _initial_ model: biplot of contribution of each parameter for the PCA _initial_ model (a. top) and the varimax rotated PCA _initial_ model (b. bottom) for PC 1 versus PC 2. Because of the smaller number of variables, coupled with the strong contribution of most parameters to the PC 1 eigenvector, the relative continutions of each component does not change or aid the interpretation of the PCs with varimax roation.

a.

PCA Results

Schwab & England

Total UPDRS
Motor Examination
Pull Test

AP Sway Path Length
AP RMS COP
AP Sway Range
Peak Body Speed
Mean Body Speed
Sway Length
ML Sway Path Length
Sway Range ML
Sway Area
ML RMS COP

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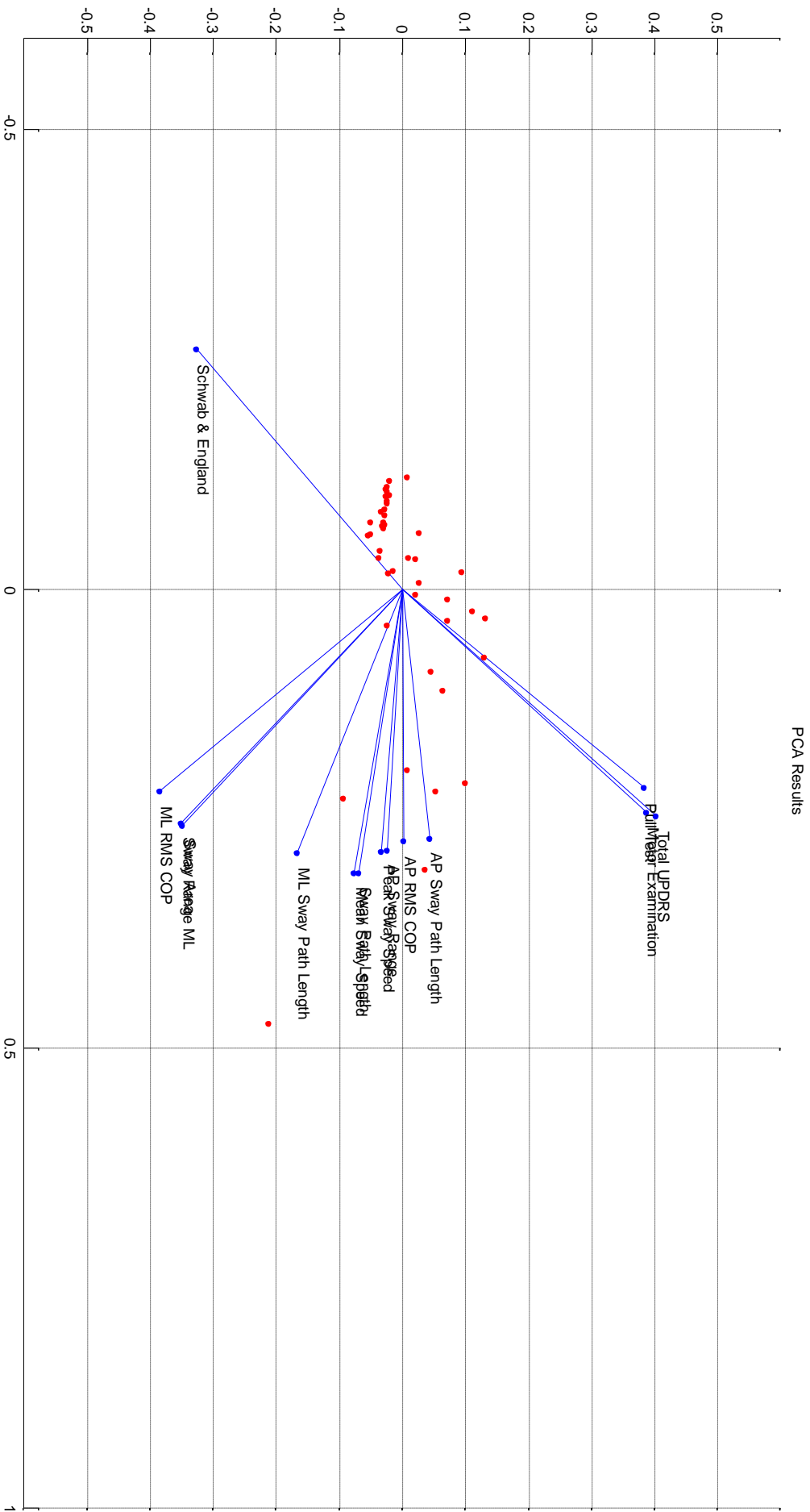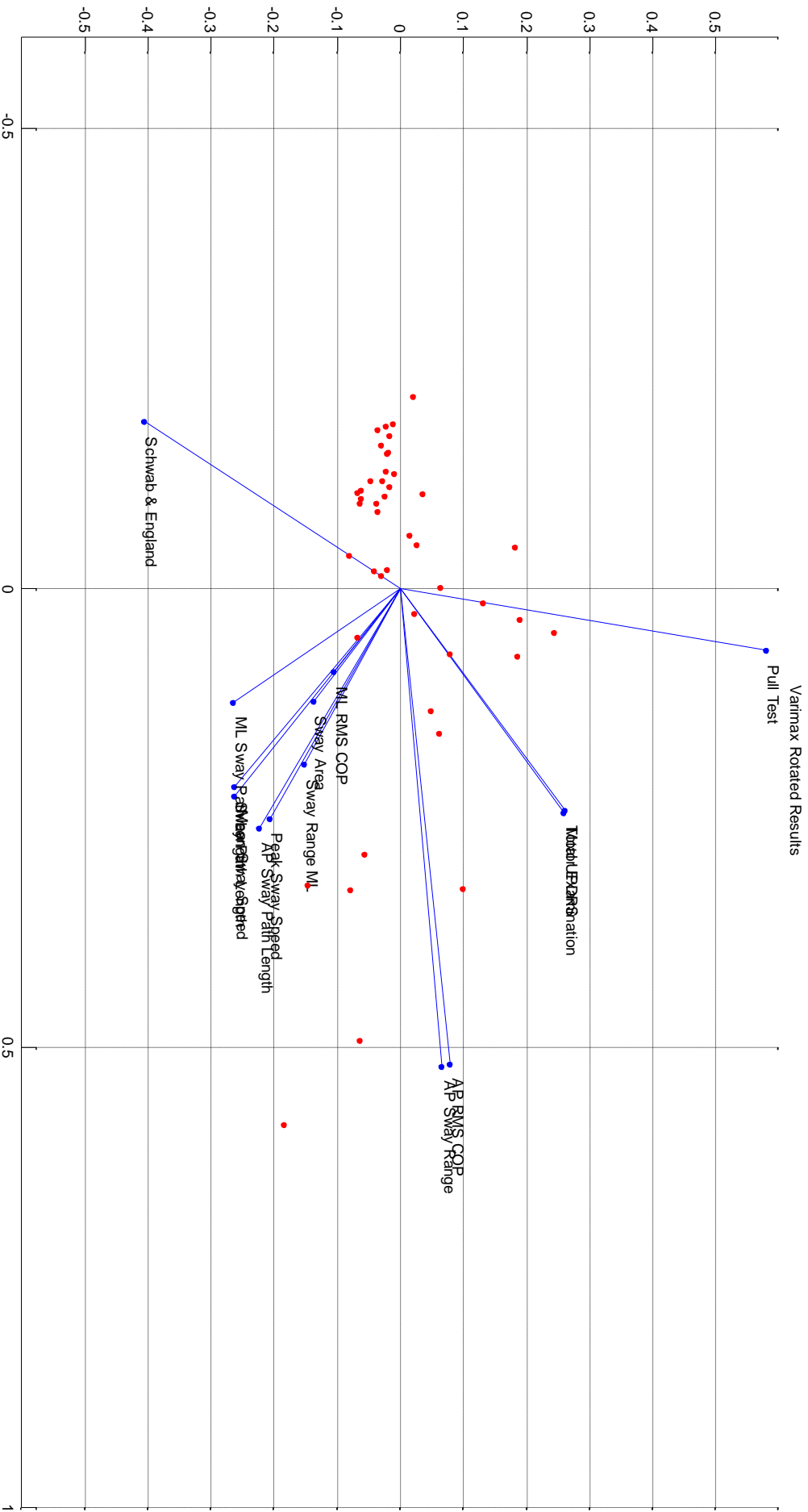
b.

Figure A.ii.5. Eyes Closed PCA $_{initial}$ model: biplot of contribution of each parameter for the PCA $_{initial}$ model (a. top) and the varimax rotated PCA $_{initial}$ model (b. bottom) for PC 1 versus PC 2. Because of the smaller number of variables, coupled with the strong contribution of most parameters to the PC 1 eigenvector, the relative continutions of each component does not change or aid the interpretation of the PCs with varimax roation.

Table A.ii.4. Mean (SD) Scores for PCs by Group Based on PCA *selection* **model**

EO PCA ANOVA	PC1	PC2	PC3	PC4
HC	-1.99 (.56)	0.32 (.37)	0.63 (.32)	-0.09 (.55)
Mild PD	0.47 (1.64)*	-0.4 (1.64)	-0.05 (.82)	-0.03 (.74)
Mod PD	3.56 (3.58)*+	-0.15 (3.01)	-1.26 (2.39)	0.22 (1.12)

EC PCA ANOVA	PC1	PC2	PC3	PC4
HC	-1.97 (.54)	0.74 (.23)	-0.27 (.44)	0.1 (.27)
Mild PD	0.4 (2.28)*	-0.19 (1.01)	0.15 (.91)	-0.47 (.45)*
Mod PD	3.61 (3.59)*+	-1.31 (2.37)*	0.37 (2.16)	0.39 (1.02)*

* indicates the parameter was significantly different (p < .05) than the HC group.

\+ indicates the parameter was significantly different (p < .05) than the mild PD group (for mild PD vs. moderate PD comparisons).

Table A.ii.5. Coefficients and Variance Explained for Retained PCs in Eyes Open and Eyes Closed PCA *selection* **Models**

Eyes Open

	PC1	PC2	PC3	PC4
UPDRS	0.453	0.491	-0.009	0.741
Pull Test	0.425	0.562	-0.293	-0.618
AP Sway Path Length	**0.454**	-0.430	-0.456	-0.055
AP Sway Path Range	0.445	-0.080	0.837	-0.228
Peak Sway Speed	**0.459**	-0.502	-0.080	0.115
Variance Explained Per PC (%)	66.20	18.36	9.28	3.58

Eyes Closed

	PC1	PC2	PC3	PC4
UPDRS	0.371	0.914	-0.078	0.143
AP Sway Path Length	**0.463**	-0.225	0.465	0.536
ML Sway Path Length	0.442	-0.214	-0.763	-0.159
Mean Sway Speed	**0.500**	-0.259	-0.088	0.240
AP RMS of COP	0.450	-0.023	0.434	-0.781
Variance Explained Per PC (%)	75.25	11.37	7.93	5.40

PC – Principal Component

Bolded coefficients reflect the two most influential parameters for PC 1 of the PCA *selection* model for eyes open (top) and eyes closed (bottom).

iii. Specific Aim 3

Table A.iii.1. a. Mean (SEM) for Gait Initiation Kinematic Parameters. b. Mean (SEM) for Gait Initiation Stage COP Parameters

a. Mean (SEM) for Gait Initiation Kinematic Parameters

	Ankle Ang at Heel Off (deg)	Ankle Ang at Heel Strike (deg)
HC	7.6 (1.5)	-2.9 (1.9)
Mild PD	3.0 (2.2)	-6.2 (2.8)
Mod PD	3.4 (0.4)	-4.6 (1.2)

b. Mean (SEM) for Gait Initiation Stage COP Parameters

Stage 1			
	COP Displacement (%)	COP Velocity (%/s)	COP Peak Velocity (%/s)
HC	36.3 (2.3)	78.1 (6.9)	249.0 (20.4)
Mild PD	32.3 (3.2)	71.2 (8.9)	234.0 (28.1)
Mod PD	27.2 (2.7)	44.7 (5.4)*	164.2 (24.6)*

Stage 2			
	COP Displacement (%)	COP Velocity (%/s)	COP Peak Velocity (%/s)
HC	91.0 (2.5)	283.5 (12.9)	716.2 (59.8)
Mild	87.1 (6.6)	269.8 (26.8)	610.1 (63.7)
Mod	82.94 (1.8)	192.9 (16.4)*+	466.2 (33.6)*

Stage 3			
	COP Displacement (%)	COP Velocity (%/s)	COP Peak Velocity (%/s)
HC	42.6 (2.6)	135.4 (10.5)	346.6 (33.6)
Mild	41.5 (5.2)	129.1 (19.2)	253.9 (36.8)
Mod	29.3 (4.7)	101.8 (13.4)	258.1 (31.6)

* indicates the parameter was significantly different ($p < .05$) than the HC group.

[+] indicates the parameter was significantly different ($p < .05$) than the mild PD group (for mild PD vs. moderate PD comparisons).

Table A.iii.2. Correlation coefficients for the significant temporal, kinematic, and kinetic COP parameters during gait initiation

	SOT	C HS	SL	AP SL	SS	AP COP HO	AP COP V S1	ML COP V S1	AP COP V S1	L P COP V S1	S1 Dur	AP COP V S2	ML COP V S2	M P COP V S2	S2 Dur	AP COP S3	ML COP V S3	M P COP V S3
Total UPDRS	0.53*	0.46*	-0.57*	-0.57	-0.51*	0.31	0.47*	-0.55*	0.62*	-0.51*	0.50*	0.13	0.57*	0.57*	0.44*	-0.17	0.18	0.44*
Motor Exam	0.48*	0.47*	-0.55*	-0.55*	-0.56*	0.28	0.50*	-0.53*	0.51*	-0.52*	0.43	0.06	0.52*	0.53*	0.46*	-0.17	0.07	0.28
Pull Test	0.59*	0.46*	-0.63*	-0.63*	-0.49*	0.42	0.50*	-0.48*	0.52*	-0.46*	0.53*	0.40	0.51*	0.49*	0.57*	-0.33	0.07	0.43
Schwab England	-0.30	-0.31	0.53*	0.53*	0.49*	-0.20	-0.36	0.40	-0.48*	0.35	-0.29	0.08	-0.49*	-0.50*	-0.40	0.12	0.07	-0.20

List of abbreviations: SOT – Step onset time, C HS- cue to heel strike time, SL – step length, AP SL – anterior-posterior step length, SS- step speed, AP COP HO- anterior posterior center of pressure displacement at heel off, AP COP V S1- anterior-posterior center of pressure velocity in stage 1, ML COP V S1- medial-lateral center of pressure velocity in stage 1, A P COP V S1- peak anterior center of pressure velocity in stage 1, S1 Dur- duration of stage 1, AP COP V S2- anterior-posterior center of pressure velocity in stage 2, L P COP V S1 – peak center of pressure velocity toward the swing foot during stage 1, S1 Dur- duration of stage 1, AP COP V S2- anterior-posterior center of pressure velocity in stage 2, ML COP V S2- medial-lateral center of pressure velocity in stage 2, M P COP V S2 - peak center of pressure velocity toward the stance foot during stage 2, S2 Dur- duration of stage 1, AP COP S3 - anterior posterior center of pressure displacement during stage 3, ML COP V S3- medial-lateral center of pressure velocity in stage 2, S2 Dur- duration of stage 1, AP COP S3 - anterior posterior center of pressure displacement during stage 3, M P COP V S3- peak center of pressure velocity toward the stance foot during stage 3.

* reflect significant correlation coefficients for the associated biomechanical parameter

Table A.iii.3. Correlation coefficients exclusively for the mild PD group for significant temporal, kinematic, and kinetic COP parameters during gait initiation

	SOT	C HS	SL	AP SL	SS	AP COP HO	AP COP V S1	ML COP V S1	AP COP V S1	L P COP V S1	S1 Dur	AP COP V S2	ML COP V S2	MP COP V S2	S2 Dur	AP COP S3	ML COP V S3	MP COP V S3
Total UPDRS	0.245	0.328	-0.436	-0.436	-0.464	0.082	0.518	-0.191	0.509	-0.291	0.118	-0.309	0.382	0.418	0.155	-0.182	-0.436	-0.427
Motor Exam	0.242	0.330	-0.411	-0.411	-0.489	0.087	0.557	-0.192	0.516	-0.311	0.100	-0.279	0.329	0.420	0.219	-0.160	-0.374	-0.507
Pull Test	-0.075	-0.075	-0.671*	-0.671*	0.000	-0.149	0.087	-0.192	-0.311	0.000	-0.149	0.000	0.075	0.149	-0.075	-0.373	-0.149	-0.522
Schwab England	0.441	0.153	0.140	0.140	-0.035	0.271	0.010	-0.165	-0.311	-0.085	0.451	0.626*	-0.015	0.075	0.185	-0.095	0.782*	0.717*

List of abbreviations: SOT – Step onset time, C HS- cue to heel strike time, SL – step length, AP SL – anterior-posterior step length, SS- step speed, AP COP HO- anterior posterior center of pressure displacement at heel off, AP COP V S1- anterior-posterior center of pressure velocity in stage 1, ML COP V S1- medial-lateral center of pressure velocity in stage 1, A P COP V S1 – peak center of pressure velocity toward the swing foot during stage 1, S1 Dur- duration of stage 1, A P COP V S2- anterior-posterior center of pressure velocity in stage 2, ML COP V S2- medial-lateral center of pressure velocity in stage 2, M P COP V S2 - peak center of pressure velocity toward the stance foot during stage 2, S2 Dur- duration of stage 2, M P COP V S2 - peak center of pressure velocity toward the stance foot during stage 3, ML COP V S3- medial-lateral center of pressure velocity in stage 3, M P COP V S3- peak center of pressure velocity toward the stance foot during stage 3.

* reflects significant correlation coefficients for the associated biomechanical parameter

Table A.iii.4. Correlation coefficients exclusively for the moderate PD group for significant temporal, kinematic, and kinetic COP parameters during gait initiation

	SOT	C HS	SL	AP SL	SS	AP COP HO	AP COP V S1	ML COP V S1	AP COP V S1	L P COP V S1	S1 Dur	AP COP V S2	ML COP V S2	M P COP V S2	S2 Dur	AP COP V S3	ML COP V S3	M P COP V S3
Total UPDRS	-0.170	-0.036	0.043	0.043	0.182	-0.450	-0.207	-0.377	0.152	-0.280	-0.073	-0.395	0.055	0.231	-0.328	0.365	-0.280	0.255
Motor Exam	0.018	0.182	-0.067	-0.067	0.006	-0.280	0.061	-0.413	-0.213	-0.340	0.061	-0.359	0.109	0.243	-0.024	0.085	-0.389	-0.018
Pull Test	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Schwab England	0.220	-0.006	0.272	0.272	0.220	0.440	-0.032	0.213	0.084	0.162	0.136	0.679*	-0.136	-0.356	0.103	-0.149	0.575	0.039

List of abbreviations: SOT – Step onset time, C HS- cue to heel strike time, SL – step length, AP SL – anterior-posterior step length, SS- step speed, AP COP HO- anterior posterior center of pressure displacement at heel off, AP COP V S1- anterior-posterior center of pressure velocity in stage 1, ML COP V S1- medial-lateral center of pressure velocity in stage 1, A P COP V S1- peak anterior center of pressure velocity in stage 1, L P COP V S1 – peak center of pressure velocity toward the swing foot during stage 1, S1 Dur- duration of stage 1, AP COP V S2- anterior-posterior center of pressure velocity in stage 2, ML COP V S2- medial-lateral center of pressure velocity in stage 2, M P COP V S2 - peak center of pressure velocity toward the stance foot during stage 2, S2 Dur- duration of stage 1, AP COP S3 - anterior posterior center of pressure displacement during stage 3, ML COP V S3- medial-lateral center of pressure velocity in stage 3, M P COP V S3- peak center of pressure velocity toward the stance foot during stage 3.

* reflects significant correlation coefficients for the associated biomechanical parameter

Gait Initiation Correlations by Parameter Type

Temporal Parameter Correlations

Step onset time and cue to heel strike duration were significantly correlated (p < 0.05) with total

UPDRS score (ρ = .53, ρ = .46), Motor Exam score (ρ =.48, ρ = .47), and the Pull Test (ρ =.59, ρ

=.46), respectively, with increased duration reflecting increased clinical PD progression. (Table

A.iii.2)

Kinematic Parameter Correlations

Step length, AP step length, and step speed were significantly correlated (p < 0.05) with total

UPDRS score (ρ = -.56, ρ = -.56, ρ =-.51), Motor Exam score (ρ = -.55, ρ = -.55, ρ =-.56), the

Pull Test (ρ =-.63, ρ =-.63, ρ =-.49), and Schwab and England score, (ρ = .53, ρ = .53, ρ =.49),

respectively, with a decreased step length and speed reflecting an increased UPDRS, Motor

Exam, and Pull Test score and a decreased Schwab and England score (increased clinical PD

progression). (Table A.iii.2)

COP Step Parameter Correlations

COP AP position at step heel off of the swing foot was significantly correlated (p < 0.05) with

the Pull Test (ρ = .55), with a less posterior COP displacement at step heel off reflecting an

increased Pull Test score. (Table A.iii.2)

COP Stage Parameter Correlations

<u>Stage 1</u>

Average AP COP velocity, ML COP velocity, and peak anterior and toward the swing foot COP velocity were significantly correlated ($p < 0.05$) with total UPDRS score ($\rho = .47$, $\rho = -.55$, $\rho = .62$, $\rho = -.51$, respectively), and the motor exam ($\rho = .50$, $\rho = -.53$, $\rho = ..51$, $\rho = -.52$, respectively), with increased velocity reflecting increased UPDRS and motor exam scores. The Pull test was significantly correlated ($p < 0.05$) with ML COP velocity, stage 1 duration, and peak anterior and toward the swing foot COP velocity ($\rho = -.48$, $\rho = -.52$, $\rho = -.46$, $\rho = .53$, respectively) with increased velocity and duration reflecting increased Pull Test scores. Duration of Stage 1 was also significantly correlated ($p < 0.05$) with the total UPDRS score ($\rho = .50$), with an increased stage duration reflecting increased UPDRS score. Only peak anterior COP velocity was significantly correlated ($p < 0.05$) with Schwab and England score ($\rho = -.48$), with a more anterior velocity reflecting a decreased Schwab and England score (increased clinical PD progression). (Table A.iii.2)

Stage 2

Average ML COP velocity and peak COP velocity toward the stance foot were significantly correlated ($p < 0.05$) with all clinical parameters (Total UPDRS: $\rho = .57$, $\rho = .57$; Motor Exam: $\rho = .52$, $\rho -.53$; Pull Test: $\rho = .51$, $\rho = .49$; Schwab and England: $\rho = -.49$, $\rho = -.50$; respectively), with increased velocity reflecting increased clinical progression. Duration of Stage 2 was significantly correlated ($p < 0.05$) with Total UPDRS, motor exam and the Pull test ($\rho = .44$, $\rho = .46$, $\rho = .57$, respectively), with an increased stage duration reflecting increased clinical progression. (Table A.iii.2)

Stage 3

Peak COP velocity towards the swing foot was significantly correlated ($p < 0.05$) with total

UPDRS score ($\rho = .44$) , with an increased velocity correlating with increase in Total UPDRS

score. (Table A.iii.2)

Table A.iii.5. Mean (SD) for PCs by Group Based on Principal Component Analysis (PCA) Model

	PC 1	PC 2	PC 3	PC 4	PC 5	PC 6	PC 7	PC 8	PC 9	PC 10
HC	-2.03 (3.06)	-0.76 (1.76)	-0.85 (1.5)	0.42 (1.49)	0.27 (1.27)	-0.57 (1.31)	0.26 (1.21)	-0.27 (0.94)	-0.18 (1.19)	0.16 (0.7)
Mild PD	-0.55 (3.4)	0.98 (2.82)	-0.43 (2.41)	0.01 (1.92)	-1.12 (1.69)*	0.56 (1.53)	-0.47 (1.66)	0.13 (1.18)	0.27 (0.96)	-0.26 (0.65)
Moderate PD	4.05 (2.48)*+	0.22 (1.77)	1.92 (1.38)*+	-0.72 (2.02)	0.77 (1.11)+	0.35 (0.93)	0.07 (1.08)	0.31 (1.4)	0.00 (1.15)	0.00 (1.47)

PC – principal component

* indicates the parameter was significantly different (p < .05) than the HC group.

+ indicates the parameter was significantly different (p < .05) than the mild PD group (for mild PD vs. moderate PD comparisons).

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HC, Mild, and Moderate PD PCA Results

HC, Mild, and Moderate PD PCA Results

HC, Mild, and Moderate PD PCA Results

33
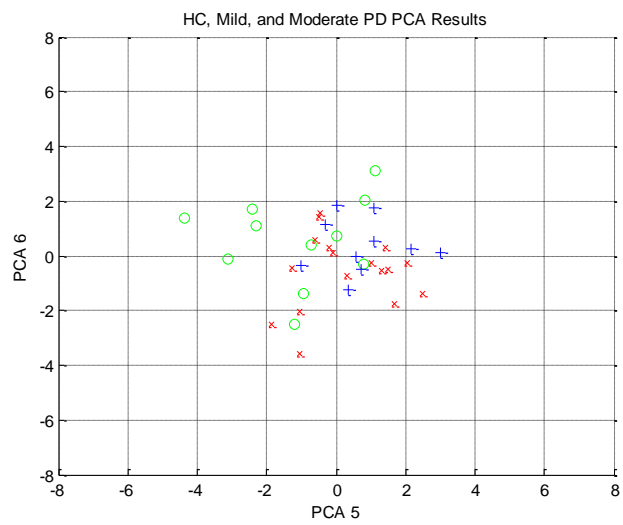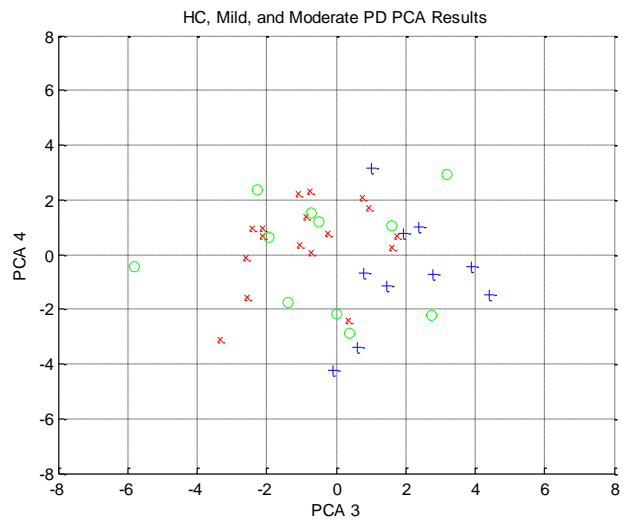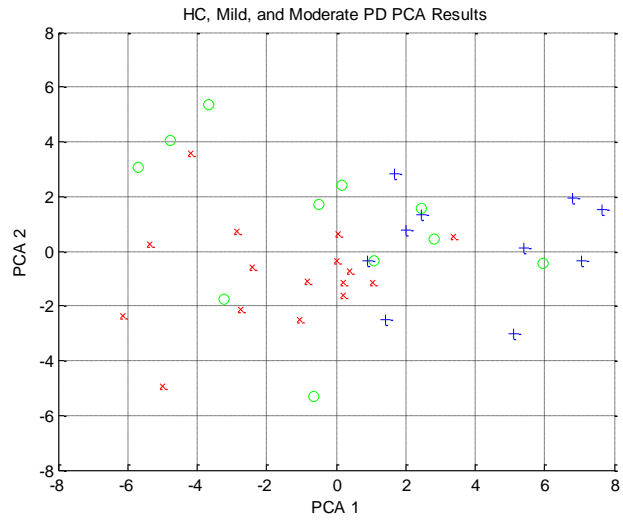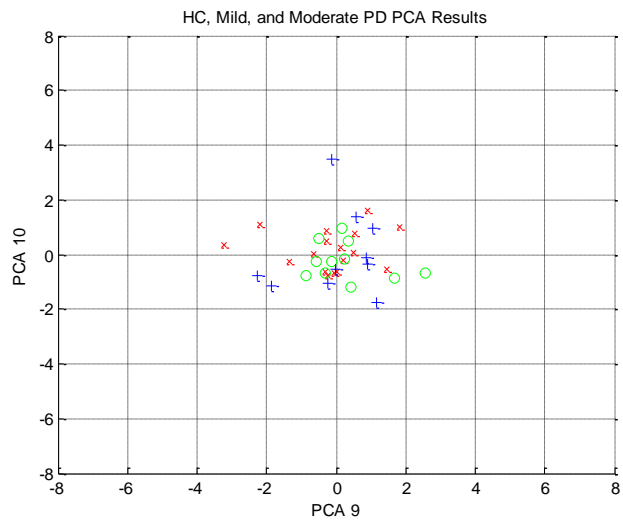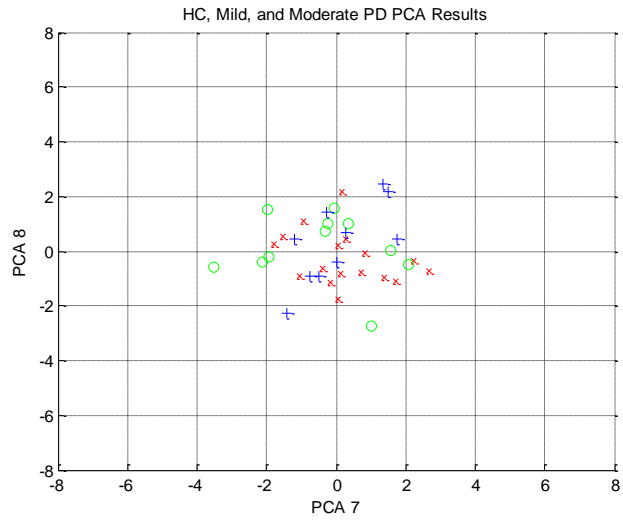
Figure A.iii.1. Transformed subject scores plotted on the principal component(PC) 1 versus PC 2 axes, PC 3 v. PC 4, PC 5 v. PC 6, PC 7 v. PC 8, and PC 9 v. PC 10 (all significant prinicpal components, from top to bottom).

Key: red x – HC, green o – mild PD, blue + - moderate PD

Table A.iii.6. Coefficients and Variance Explained for Retained PCs in Gait Initiation PCA Model

	PC 1	PC 2	PC 3	PC 4	PC 5	PC 6	PC 7	PC 8	PC 9	PC 10
Total UPDRS	0.15	0.14	0.24	-0.16	0.09	0.18	0.09	0.09	0.11	-0.11
Schwab and England	-0.13	-0.18	-0.23	0.18	-0.10	-0.19	0.08	-0.14	-0.13	0.06
Motor Exam	0.15	0.17	0.23	-0.15	0.06	0.20	-0.04	0.10	0.11	-0.12
Pull Test	0.15	0.06	0.29	-0.12	0.14	0.08	0.03	0.09	-0.01	0.05
Weight Shift Time	0.03	-0.08	0.20	0.17	-0.12	0.16	0.31	0.15	-0.32	0.06
Step Onset Time	0.20	-0.06	0.04	-0.15	0.04	0.26	0.13	0.13	-0.03	-0.25
Step Duration	0.18	0.01	-0.23	-0.17	0.04	-0.10	-0.05	0.05	0.08	0.08
Cue to Heel Strike Duration	0.21	-0.03	-0.09	-0.18	0.04	-0.14	0.14	0.11	0.08	-0.12
Step Length	-0.15	-0.14	-0.20	-0.22	-0.18	0.11	0.00	0.04	-0.09	-0.09
Step Length AP	-0.15	-0.14	-0.20	-0.22	-0.17	0.00	0.15	0.03	0.03	-0.09
Step Length ML	-0.04	0.03	0.10	0.04	0.41	0.04	0.13	0.13	-0.11	-0.28
Step Speed	-0.23	-0.10	0.04	-0.04	-0.10	0.07	0.07	0.07	-0.03	-0.13
Step Clearance	-0.12	-0.19	-0.11	-0.25	-0.13	-0.01	0.05	0.08	0.04	0.04
AP COP Heel Off Location	0.21	-0.06	0.07	-0.09	-0.23	-0.03	0.06	-0.03	0.07	0.07
ML COP Heel Off Location	0.11	0.06	0.09	-0.17	-0.22	-0.21	-0.35	-0.17	0.20	-0.09
AP COP Heel Strike Location	0.08	-0.17	-0.13	-0.23	0.07	0.37	0.21	-0.08	-0.08	0.05
ML COP Heel Strike Location	0.08	-0.32	0.02	0.13	0.20	-0.01	-0.18	-0.02	0.20	0.00
AP COP Displacement S1	-0.20	-0.15	0.19	0.04	-0.02	0.08	-0.07	0.07	0.13	-0.08
ML COP Displacement S1	-0.19	0.07	0.09	-0.07	0.06	-0.16	0.28	0.04	0.20	0.07
AP COP Velocity S1	0.22	0.08	-0.13	-0.07	0.02	-0.11	0.12	-0.07	-0.10	-0.03
ML COP Velocity S1	-0.22	0.10	0.05	0.01	0.01	-0.01	0.15	0.04	0.12	0.20
Peak A COP Velocity S1	0.08	0.09	0.15	-0.26	0.01	-0.09	-0.35	-0.01	-0.01	0.36
Peak P COP Velocity S1	0.20	0.08	-0.20	0.01	0.01	-0.04	0.13	0.03	-0.24	0.06
Peak M COP Velocity S1	0.00	-0.15	0.06	0.04	-0.02	-0.15	0.28	-0.11	0.55	0.19
Peak L COP Velocity S1	-0.22	0.09	0.04	-0.04	0.05	0.02	0.09	0.09	0.15	0.02
Stage Duration S1	0.18	-0.06	0.04	-0.19	0.05	-0.27	0.11	0.07	0.08	-0.37
AP COP Displacement S2	0.01	-0.10	0.20	-0.27	-0.29	-0.13	-0.04	0.02	-0.28	0.13
ML COP Displacement S2	-0.13	0.15	0.12	-0.08	-0.09	-0.23	0.40	-0.05	-0.10	0.04
AP COP Velocity S2	0.12	-0.21	0.15	0.10	-0.18	0.22	0.13	0.21	0.21	0.02

Continued.

	PC1	PC2	PC3	PC4	PC5	PC6	PC7	PC8	PC9	PC10
ML COP Velocity S2	0.21	-0.11	-0.05	0.02	0.04	0.13	-0.15	0.19	0.04	0.11
Peak A COP Velocity S2	-0.07	-0.27	0.21	-0.12	-0.28	0.03	-0.09	0.16	0.01	-0.06
Peak P COP Velocity S2	0.16	0.02	-0.13	0.24	0.08	0.24	0.18	0.04	0.18	0.08
Peak M COP Velocity S2	0.22	-0.03	-0.09	0.00	-0.07	0.17	-0.14	-0.06	-0.04	0.02
Peak L COP Velocity S2	-0.03	-0.12	0.00	-0.17	0.31	-0.09	-0.11	0.34	-0.09	0.52
Stage Duration S2	0.20	0.00	0.06	-0.05	0.02	-0.02	0.10	0.22	0.00	0.24
AP COP Displacement S2	-0.15	-0.11	-0.13	-0.25	0.20	0.20	0.05	-0.14	-0.09	-0.04
ML COP Displacement S3	-0.10	0.31	-0.15	-0.18	-0.01	0.10	0.02	0.11	0.01	0.02
AP COP Velocity S3	-0.18	-0.12	0.08	-0.18	0.21	0.12	-0.05	-0.13	-0.06	-0.06
ML COP Velocity S3	0.11	-0.35	0.06	0.09	0.09	-0.07	0.02	-0.15	-0.07	-0.04
Peak A COP Velocity S3	-0.18	-0.14	0.06	-0.05	0.25	-0.12	-0.10	0.05	-0.05	-0.08
Peak P COP Velocity S3	-0.01	0.07	0.16	-0.13	0.03	0.31	0.15	-0.48	0.04	-0.03
Peak M COP Velocity S3	0.13	-0.27	0.06	0.11	-0.01	-0.02	0.13	-0.19	-0.05	-0.02
Peak L COP Velocity S3	0.02	-0.26	0.02	-0.18	0.26	-0.13	0.05	-0.16	-0.09	0.05
Stage Duration S3	0.07	0.00	-0.38	-0.13	0.02	0.07	0.10	-0.07	0.11	-0.03

Table A.iii.7. Coefficients and Relative Variance Explained for Retained PCs in Gait Initiation PCA Model

	PC1	PC2	PC3	PC4	PC5	PC6	PC7	PC8	PC9	PC10
Total UPDRS		(+)								
Schwab and England		(-)								
Motor Exam		(+)			(+)					
Pull Test		(+)								
Weight Shift Time		(+)				(+)	(-)			
Step Onset Time										
Step Duration		(-)					(+)		(+)	(-)
Cue to Heel Strike Duration	(+)									
Step Length			(-)	(-)						
Step Length AP			(-)	(-)						
Step Length ML					(+)					(-)
Step Speed	(-)									
Step Clearance				(-)						
AP COP Heel Off Location	(+)					(-)				
ML COP Heel Off Location			(-)		(-)					
AP COP Heel Strike Location				(-)		(+)	(+)			
ML COP Heel Strike Location		(-)							(+)	
AP COP Displacement S1										
ML COP Displacement S1							(+)			
AP COP Velocity S1	(+)									
ML COP Velocity S1	(-)									(+)
Peak A COP Velocity S1				(-)		(+)		(-)		(+)
Peak P COP Velocity S1			(-)						(-)	
Peak M COP Velocity S1							(+)			
Peak L COP Velocity S1	(-)									
Stage Duration S1						(-)				(-)
AP COP Displacement S2			(+)	(-)					(-)	
ML COP Displacement S2							(+)			
AP COP Velocity S2		(-)		(-)		(+)			(-)	(+)

Continued.

	PC1	PC2	PC3	PC4	PC5	PC6	PC7	PC8	PC9	PC10
ML COP Velocity S2	(+)									
Peak A COP Velocity S2		(-)	(+)		(-)					
Peak P COP Velocity S2				(+)		(+)				
Peak M COP Velocity S2	(+)					(+)				
Peak L COP Velocity S2					(+)					
Stage Duration S2	(+)				(+)					(+)
AP COP Displacement S3	(+)			(-)						
ML COP Displacement S3			(+)							
AP COP Velocity S3					(+)					
ML COP Velocity S3			(-)		(+)					
Peak A COP Velocity S3						(+)				
Peak P COP Velocity S3						(+)				
Peak M COP Velocity S3			(-)				(+)			
Peak L COP Velocity S3			(-)			(+)		(-)		
Stage Duration S3			(-)							

Table Key: + signifies a paraemter coefficient of 0.5 or greater (strong positve effect); (+) signifies a parameter coefficient between 0.2 to 0.5 (mild positive effect); - signifies a paraemter coefficient of -0.5 or less (strong negative effect); (-) signifies a parameter coeffient between -0.2 to -0.5 (mild negative effect).

Figure A.iii.2. Gait initiation PCA model: biplot of contribution of each biomechanical gait initiation and clinical parameter for the PCA model.

APPENDIX C.Recruitment and Testing Materials

Health Screen: Healthy Controls

Subject Identification Number:

Date of Screen:

Subject name: _____

Last   First

"My name is _____. I am calling from the Biodynamics Laboratory at the University of Kansas. I was given your name as someone who had indicated an interest in participating in a research study. We are now beginning a study looking at how the brain controls our balance and how that might be related to risk of falling. If you think you might be interested in participating, and you have a few minutes, I'd like to describe the study to you."

Is subject interested?   YES   NO

Comments:_____

_____

If NO: "Thank you for your time. Would you be interested in being contacted for future studies or do you prefer that your name is removed from our list?"

Comments:_____

_____

If YES: "Please feel free to ask questions at any time. This study is a one-time evaluation that will look at how Parkinson's disease affects the ability of the brain to control our balance. We will be looking at those with Parkinson's compared to healthy adults in the same age range. There are two parts to this study. First, there is a medical screening procedure. The first part is done over the phone and will take approximately 20 minutes. This will include questions about current and previous health conditions. Once that is completed we will schedule you for a visit to the Biodynamics Laboratory at KU in Lawrence where we will do a physical assessment that and then do the balance testing. For the balance testing, we will ask you to do four different tests: one that just involves standing still, one that involves starting to walk from rest, one that involves walking on a treadmill for about 5 minutes, and a balance recovery test. For the balance recovery test, we will pull you backwards from the waist and you will have to regain your balance. During all of the tests, you will be wearing a protective harness to ensure your safety. The whole test will take approximately 3 hours. There is no cost for participating in this study, nor are there any direct benefits to you. We will pay you $30 for your participation. If you are still interested, I would like to ask you some questions to see if you would be able to participate in this study."

Notes:_____

_____

**If subject is excluded by any questions, stop the interview and explain to the subject the reason for exclusion. Thank them for their time and willingness to participate.

Name: _____ Age:_____
Birthdate:_____
Gender: M   F
Address: _____

Phone: _____

Schooling/Occupation: _____

Height: _____Weight: _____

Are you currently participating in any other research studies?

This study will require one trip to the University of Kansas in Lawrence. Would you have transportation for this visit?

Are you able to get out of bed and also use the bathroom without assistance from anything or anyone?

Are you able to stand on your own for 10 minutes without assistance?
(ex. Can you stand at the bathroom sink to do your morning care without having to hold to something?)

SUMMARY OF MEDICAL SCREEN:

Pass? If no, why not?   Height: _____ Weight:_____Age:_____Gender: _____   Comments:

Have you been diagnosed with:	Yes	No	When	Details	Exclude?
Ever had major surgery or amputation?					Yes if affects legs, not recovered completely
Osteoporosis					Yes
Brittle Bones					Yes
Fibromyalgia? Constant aches and fatigue?					Yes if constant
Arthritis					Yes if in legs
Nerve Damage					Yes if in legs
Heart Attack					Yes
Heart Disease or problems (surgeries, valve replacement, angina, pacemaker?)					Yes
Chest Pain from heart disease?					Yes
Polio or Post Polio Syndrome					Yes
Broken Bones? Compression fractures?					Yes if < 2 years ago and in leg or spine
Ever had a hip, knee, or ankle replacement or surgery?					Yes
Ever had a joint fusion?					Yes
Diabetes? Thyroid conditions?					Yes if not controlled or if have neuropathy
High Blood Pressure					Yes if not controlled on meds
Neurological Disease (MS, ALS, Dementia, Seizure disorders, PD)					Yes
Stroke or TIA					Yes
Cancer, Leukemia, Lymphoma?					Yes if currently being treated
Anemia					Yes if has had blood transfusion in last year
Seizure					Yes
Meniere's Disease? Inner Ear Damage? Vertigo? Ear infection now?					Yes
Acoustic Neuroma? Tinnitus? (ringing, buzzing in ears) Do you feel pressure in ears?					Yes if constant

Do you have any problems with:	Yes	No	How does it affect ADL?	Exclude?
Pain or stiffness in hips? Knee? Ankles? Back? Shoulder?				Yes if affects walking, standing
Hip, Knee, or Ankle injury?				Yes if affects walking, standing
Back Problems? If yes: What motions cause pain (bending, twisting, lifting, quick movements?) How irritable is the pain? How do you treat the pain? Have you seen a doctor?				Yes if brought on by walking, standing, quick movements, if brought on easily
Muscle Problems in leg? Weakness in legs? Does it limit how far you can walk or how long you can stand?				Yes if affects walking, standing
Poor circulation in legs causing them to become cold, numb, or causes cramping while walking, been diagnosed with PVD? Claudication?				Only if causes problems when walking or standing
Lung disease? Emphezema? Chronic Bronchitis? SOB? DOE?				Yes if affects walking, standing
Ever had a head or neck injury?				Not necessarily
Gout or Psuedogout?				Not necessarily
Foot problems?				Not necessarily
Hearing Problems? Hearing aid? Last hearing exam?				Not necessarily
Have you been hospitalized in the past year? Major illness in last year?				Not necessarily
Headaches				Not necessarily
Neuropathy				Not necessarily
Vision				Not necessarily
Falls				Not necessarily
Driving				Not necessarily
Night Driving				Not necessarily
Shortness of Breath				Not necessarily

Edema (swelling of legs)				Not necessarily
Fainting or lightheadedness?				Not necessarily
Memory				Not necessarily
Burning pain or weakness anywhere				Not necessarily
Depression				Not necessarily

MEDICATIONS:
What medications are you currently taking?
Name: _____ Amt _____Time_____
Name: _____ Amt _____Time_____
Name: _____ Amt _____Time_____
Name: _____ Amt _____Time_____
Name: _____ Amt _____Time_____
Name: _____ Amt _____Time_____
Name: _____ Amt _____Time_____
OTC Medications:

ACTIVITY:
Are you able to leave house / apartment on your own? How often?
_____

When you walk, do you walk with :   Self   walker/cane   person assist   unable
How far do you walk on a daily basis? _____
How often do you walk? _____
How long do you walk (duration) _____

Do you participate in any exercise/Activities?
Type _____
Sessions per week   _____
Minutes / hours per session _____

When you transfer from a sitting to standing position, do you do it:
Alone   With assistive device   With person assist   Unable

When you transfer from lying down to sitting, do you do it:
Alone   With assistive device   With person assist   Unable

Hand dominance   L   R   Leg dominance L   R
(Are you right or left-handed?)   (Which leg would you kick a ball with?)

Recent vision screen? If yes, when?

BARTHEL INDEX: SEE FULL VERSION

	With Help	Independent
1. Feeding	5	10
2. Moving from wheelchair to bed and return	5-10	15
3. Personal toilet (wash face, comb hair, etc.)	0	5
4. Getting on and off toilet (handling clothes, flush, wipe)	5	10
5. Bathing self	0	5
6. Walking on level surface	10	15
7. Ascend and descend stairs	5	10
8. Dressing (includes tying shoes, fastening)	5	10
9. Controlling bowels	5	10
10. Controlling bladder	5	10

Is there anything else you can think of about your current or past health state that we might need to know?

"With these initial questions it appears that you are eligible for the next step in the study. The next step involves a physical evaluation by a physical therapist and geriatrician here at the Center on Aging. The evaluation will take approximately one hour. We are now scheduling participants for _____. Would you be able to come to the Center on Aging to participate during this time?"

If NO: "We will be continuing to test more participants in the coming weeks and months. Can we contact you to schedule a time in future?"

"We like to schedule to start in the morning or after lunch around 1:00…..*schedule a time with them.

Is participant interested?
   a. Visit scheduled _____

   b. Visit delayed (specify reason)_____

   c. Subject requests delay and reinquiry at a later date: _____

   d. Subject and/or family expresses wish for no further contact.

Notes:

Health Screen: PD Participants

Phone #:

Address:

Subject Identification Number:
Date of Screen:
Subject name: _____
                    Last   First

"My name is _____. I am calling from the Biodynamics Laboratory at the University of Kansas. I was given your name by Dr. Lyons and Dr. Pahwa in the Parkinson's Disease Center at KUMC as someone who had indicated an interest in participating in a research study. We are now beginning a study looking at how Parkinson's disease affects the ability of the brain to control our balance and how that might be related to risk of falling. If you think you might be interested in participating, and you have a few minutes, I'd like to describe the study to you."

Is subject interested?   YES   NO
        Comments:_____
_____

If NO: "Thank you for your time. Would you be interested in being contacted for future studies or do you prefer that your name is removed from our list?"
        Comments:_____
_____

If YES: "Please feel free to ask questions at any time. This study is a one-time evaluation that will look at how Parkinson's disease affects the ability of the brain to control our balance. We will be looking at those with Parkinson's compared to healthy adults in the same age range. There are two parts to this study. First, there is a medical screening procedure. The first part is done over the phone and will take approximately 20 minutes. This will include questions about current and previous health conditions. Once that is completed we will schedule you for a visit to the Biodynamics Laboratory at KU in Lawrence where we will do a physical assessment that and then do the balance testing. For the balance testing, we will ask you to do four different tests: one that just involves standing still, one that involves starting to walk from rest, one that involves walking on a treadmill for about 5 minutes, and a balance recovery test. For the balance recovery test, we will pull you backwards from the waist and you will have to regain your balance. During all of the tests, you will be wearing a protective harness to ensure your safety. The whole test will take approximately 3 hours. There is no cost for participating in this study, nor are there any direct benefits to you. We will pay you $30 for your participation. If you are still interested, I would like to ask you some questions to see if you would be able to participate in this study."
        Notes:_____
_____

**If subject is excluded by any questions, stop the interview and explain to the subject the reason for exclusion. Thank them for their time and willingness to participate.

Name: _____ Age:_____
Birthdate:_____
Gender: M   F
Address: _____
Phone: _____
Schooling/Occupation: _____
Height: _____Weight: _____
Are you currently participating in any other research studies?

This study will be done at the University of Kansas Lawrence Campus. Would you have transportation for this visit?

Are you able to get out of bed and also use the bathroom without assistance from anything or anyone?

Are you able to stand on your own for 10 minutes without assistance?
(ex. Can you stand at the bathroom sink to do your morning care without having to hold to something?)

SUMMARY OF MEDICAL SCREEN:

Pass? If no, why not?

Height: _____ Weight:_____Age:_____Gender: _____

Comments:

Have you been diagnosed with:	Yes	No	When	Details	Exclude?
Ever had major surgery or amputation?					Yes if affects legs, not recovered completely
Osteoporosis					Yes
Brittle Bones					Yes
Fibromyalgia? Constant aches and fatigue?					Yes if constant
Arthritis					Yes if in legs
Nerve Damage					Yes if in legs
Heart Attack					Yes
Heart Disease or problems (surgeries, valve replacement, angina, pacemaker?)					Yes
Chest Pain from heart disease?					Yes
Polio or Post Polio Syndrome					Yes
Broken Bones? Compression fractures?					Yes if < 2 years ago and in leg or spine
Ever had a hip, knee, or ankle replacement or surgery?					Yes
Ever had a joint fusion?					Yes
Diabetes? Thyroid conditions?					Yes if not controlled or if have neuropathy
High Blood Pressure					Yes if not controlled on meds
Neurological Disease (MS, ALS, Dementia, Seizure disorders)					Yes
Stroke or TIA					Yes
Cancer, Leukemia, Lymphoma?					Yes if currently being treated
Anemia					Yes if has had blood transfusion in last year
Seizure					Yes
Meniere's Disease? Inner Ear Damage? Vertigo? Ear infection right now?					Yes
Acoustic Neuroma? Tinnitus? (ringing, buzzing in ears) Do you feel pressure in ears?					Yes if constant
Do you have any problems with:	Yes	No	How does it affect ADL?		Exclude?

Pain or stiffness in hips? Knee? Ankles? Back? Shoulder?				Yes if affects walking, standing
Hip, Knee, or Ankle injury?				Yes if affects walking, standing
Back Problems? If yes: What motions cause pain (bending, twisting, lifting, quick movements?) How irritable is the pain? How do you treat the pain? Have you seen a doctor?				Yes if brought on by walking, standing, quick movements, if brought on quickly
Muscle Problems in leg? Weakness in legs? Does it limit how far you can walk or how long you can stand?				Yes if affects walking, standing
Poor circulation in legs causing them to become cold, numb, or causes cramping while walking, been diagnosed with PVD? Claudication?				Only if causes problems when walking or standing
Lung disease? Emphezema? Chronic Bronchitis? SOB? DOE?				Yes if affects walking, standing
Ever had a head or neck injury?				Not necessarily
Gout or Psuedogout?				Not necessarily
Foot problems?				Not necessarily
Hearing Problems? Hearing aid? Last hearing exam?				Not necessarily
Have you been hospitalized in the past year? Major illness in last year?				Not necessarily
Headaches				Not necessarily
Neuropathy				Not necessarily
Vision				Not necessarily
Falls				Not necessarily
Driving				Not necessarily

Night Driving				Not necessarily
Shortness of Breath				Not necessarily
Edema (swelling of legs)				Not necessarily
Fainting or lightheadedness?				Not necessarily
Memory				Not necessarily
Burning pain or weakness anywhere in body?				Not necessarily
Depression				Not necessarily

MEDICATIONS:
What medications are you currently taking?
Name: _____ Amt _____Time_____
Name: _____ Amt _____Time_____
Name: _____ Amt _____Time_____
Name: _____ Amt _____Time_____
Name: _____ Amt _____Time_____
Name: _____ Amt _____Time_____
Name: _____ Amt _____Time_____
**Testing should occur 1-2 hours after last dose of medication.

OTC Medications:

ACTIVITY:
Are you able to leave house / apartment on your own? How often?
_____

When you walk, do you walk with :   Self   walker/cane   person assist   unable
How far do you walk on a daily basis? _____
How often do you walk? _____
How long do you walk (duration) _____

Do you participate in any exercise/Activities?
Type _____
Sessions per week   _____
Minutes / hours per session _____

When you transfer from a sitting to standing position, do you do it:
Alone   With assistive device   With person assist   Unable

When you transfer from lying down to sitting, do you do it:
Alone   With assistive device   With person assist   Unable

Hand dominance   L   R   Leg dominance L   R

(Right or left-handed?)   (Which leg would you kick a ball with?)

Recent vision screen? If yes, when?

Is there anything else you can think of about your current or past health state that we might need to know?

When were you first diagnosed with Parkinson's disease?

What was the first symptom you experienced? When did you experience the first symptom?

Are you affected on one or both sides of your body? Which side is more affected?

Do you feel like you have bad balance? Do you have difficulty maintaining your balance while: standing still, walking, changing positions?

Have you fallen in the past year?
Event: _____Date:_____Injury:_____
Circumstances: _____
Event: _____Date:_____Injury:_____
Circumstances: _____
Event: _____Date:_____Injury:_____
Circumstances: _____

How often do you fall?

Do you currently use any devices to assist you (canes, walker, etc?)

"With these initial questions it appears that you are eligible for this study. We are now scheduling participants for _____. Would you be able to come to the Center on Aging to participant during this time?"

If NO: "We will be continuing to test more participants in the coming weeks and months. Can we contact you to schedule a time in future?"
"We like to schedule to start in the morning or after lunch around 1:00…..*schedule a time with them.
Is participant interested?
          a. Visit scheduled _____
          b. Visit delayed (specify reason)_____
          c. Subject requests delay and reinquiry at a later date: _____
          d. Subject and/or family expresses wish for no further contact.
Notes:

Appointment Letter

KU THE UNIVERSITY OF KANSAS

Dear _____,

Thank you for agreeing to participate in our research study! This study looking at how Parkinson's disease affects balance will be conducted in the Biodynamics Lab, which is located on the second floor of Learned Hall on the University of Kansas Lawrence Campus.

Your appointment is scheduled for Wed, Oct. 20th at 3pm and will be about 3 hours long. Directions and a campus map are included with this letter. Parking is located on the east side of Eaton Hall (Learned is adjacent to Eaton Hall), and one of four meters will be hooded and marked "Reserved"- this is for you. A research associate will be there to meet you and take you up to the research lab. If you have any problems finding anything please give me a call at the number below.

If you have any questions or need to reschedule your appointment, please contact Molly McVey at 785-218-2714.

Thanks again for participating.

Sincerely,

Molly McVey

Graduate Research Assistant

Biodynamics Laboratory- Mechanical Engineering Department

The University of Kansas

Barthel Index

INSTRUCTIONS: The Barthel Index is a record of what a <u>patient does</u> **not** a record of what a patient could do. Full credit is not given for an activity if the patient needs even minimal help/supervision. A score of (0) is given when a patient cannot meet the criteria as defined. Circle the appropriate answer to each question.

1. Today, are you able to feed yourself?

   10: Independent; feeds self from tray or table; can put on assistive device if needed; accomplishes feeding in reasonable time.

   5: Assistance necessary with cutting food, etc.

   0: Cannot meet criteria

   88: Contraindicated due to
   _____

2. Today, are you able to get out of bed or into a chair?

   15: Independent in all phases of this activity

   10: Minimal help needed or patient needs to be reminded or supervised for safety of one or more parts of this activity.

   5: Patient can come to sitting position without help of second person, but needs to be lifted out of bed and assisted with transfers

   0: Cannot meet criteria

   88: Contraindicated due to _____

3. Today, are you able to wash your face, brush your teeth, brush your hair, etc.?

   5: Can wash hands, face; combs hair, cleans teeth. Can shave (males) or apply makeup (females) without assistance; females need not braid or style hair.

   0: Cannot meet criteria

   88: Contraindicated due to_____

4. Today are you able to get on and off the toilet?

   10: Able to get on and off the toilet, fastens/unfastens clothes; can use toilet paper without assistance. May use wall bar or other support if needed; if bedpan is necessary, patient can place it on chair, empty, and clean it.

   5: Needs help because of imbalance or other problems with clothes or toilet paper

   0: Cannot meet criteria

88:     Contraindicated due to

_____

5.   Today, are you able to bathe yourself?

     5:     May use tub, shower, or sponge bath. Patient must be able to perform all functions without another person being present.

     0:     Cannot meet criteria

     88:     Contraindicated due to

_____

6.   Today, are you able to walk without help?

     15:     Patient can walk at least 50 yards without assistance or supervision; may use braces, prostheses, crutches, canes, or walker, but not a rolling walker. Must be able to lock/unlock braces, assume standing or seated position, get mechanical aids into position for use and dispose of the mechanical aids when seated (putting on and off braces should be scored under dressing).

     10:     Assistance needed to perform above activities, but can walk 50 yards with little help.

     0:     Cannot meet criteria

     88:     Contraindicated due to _____

7.   Today, are you able to use a wheelchair? (Do not score if patient competes score for walking- item #6).

     5:     Patient cannot ambulate, but can propel wheelchair independently; can go around corners, turn around and maneuver chair to table, bed, toilet, etc; must be able to push chair 50 yards.

     0:     Cannot meet criteria

     88:     Contraindicated due to_____

8.   Today, are you able to walk up and down stairs?

     10:     Able to go up and down flights of stairs safely without supervision; using canes, handrails, or crutches when needed and can carry these items as ascending/descending.

     5:     Needs help or supervision of any of the above items.

     0:     Cannot meet criteria

     88:     Contraindicated due to _____

9.   Today, are you able to dress and undress yourself?

10: Able to put on, fasten, and remove all clothing; ties shoelaces unless necessary adaptations used. Activity includes fastening braces and corsets when prescribed; suspenders, loafer shoes, and dresses opening in the front may be used when necessary.

5: Needs help putting on, fastening, or removing clothing; must accomplish at least half of task alone within reasonable time; women need not be scored on use of brassiere or girdle undless prescribed.

0: Cannot meet criteria

88: Contraindicated due to _____

10. Today, are you able to control your bowels?

10: Able to control bowels and have no accidents. Can use a suppository or take an enema when necessary (as for spinal cord injury patients who have had bowel training).

5: Needs help in using a suppository or taking an enema or has occasional accidents.

0: Cannot meet criteria

88: Contraindicated due to _____

11. Today, are you able to control your bladder?

10: Able to control bladder day and night. Spinal injury patients must be able to put on external devices and leg bags independently, clean and empty bag, and must stay dry day and night.

5: Occasional accidents occur, cannot wait for bedpan, does not get to toilet in time or needs help with external device.

0: Cannot meet criteria

88: Contraindicated due to _____

12. Information for today's Barthel data gathered from:

01: Patient

02: Proxy- Caregiver

03: Proxy- Other

04: Chart

05: Both patient and proxy

Beck Depression Inventory

1. Sadness

0   I do not feel sad.

1   I feel sad much of the time.

2   I am sad all of the time.

3   I am so sad or unhappy that I can't stand it.

2.   Pessimism

0   I am not discouraged about my future.

1   I feel more discouraged about my future than I used to be.

2   I do not expect things to work out for me.

3   I feel my fortune is hopeless and will get only worse.

3.   Past Failure

0   I do not feel like a failure.

1   I have failed more than I should have.

2   As I look back I see a lot of failures.

3   I feel I am a total failure as a person.

4.   Loss of Pleasure

0   I get as much pleasure as I ever did from the things I enjoy.

1   I don't enjoy things as much as I used to.

2   I get very little pleasure from the things I used to enjoy.

3   I can't get any pleasure from the things I used to enjoy.

5.   Guilty Feelings

0   I don't feel particularly guilty.

1   I feel guilty over many things I have done or should have done.

2   I feel quite guilty most of the time.

3   I feel guilty most of the time.

6. Punishment Feelings

0   I don't feel I am being punished.

1   I feel I may be punished.

2   I expect to be punished.

3   I feel I am being punished.

7. Self-Dislike

0   I feel the same about myself as ever.

1   I have lost confidence in myself.

2   I am disappointed in myself.

3   I dislike myself.

8. Self-Criticisms

0   I don't criticize or blame myself more than usual.

1   I am more critical of myself than I used to be.

2   I criticize myself for all of my faults.

3   I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes

0   I don't have any thoughts of killing myself.

1   I have thoughts of killing myself, but I would not carry them out.

2   I would like to kill myself.

3   I would kill myself if I had the chance.

10. Crying

0   I don't cry anymore than I used to.

1   I cry more than I used to.

2   I cry over every little thing.

3   I feel like crying, but I can't.

11. Agitation

0   I am no more restless or would up than usual.

1   I feel more restless or would up than usual.

2   I am so restless or agitated that it's hard to stay still.

3   I am so restless that I have to keep moving or doing something.

12. Loss of Interest

0   I have not lost interest in other people or activities.

1   I am less interested in other people or things than before.

2   I have lost most of my interest in other people or things.

3   It's hard to get interested in anything.

13. Indecisiveness

0   I make decisions about as well as ever.

1   I find it more difficult to make decisions than usual.

2   I have much greater difficulty in making decisions than usual.

3   I have trouble making any decision.

14. Worthlessness

0   I do not feel I am worthless.

1   I don't consider myself as worthwhile and useful as I used to.

2   I feel more worthless as compared to other people.

3   I feel utterly worthless.

15. Loss of Energy

0   I have as much energy as ever.

1   I have less energy than I used to have.

2   I don't have enough energy to do very much.

3   I don't have enough energy to do anything.

16. Changes in Sleeping Patterns

0   I have not experienced any change in my sleeping pattern.

1   I sleep somewhat more/less than usual.

2   I sleep a lot more/less than usual.

3   I sleep most of the day.

   I wake up 1-2 hours early and can't get back to sleep.

17. Irritability

0   I am no more irritable than usual.

1   I am more irritable than usual.

2   I am much more irritable than usual.

3   I am irritable all the time.

18. Changes in Appetite

0   I have not experienced any change in my appetite.

1   My appetite is somewhat greater/lesser than usual.

2   My appetite is much greater/lesser than usual.

3   I crave food all the time or I have no appetite at all.

19. Concentration Difficulty

0   I can concentrate as well as ever.

1   I can't concentrate as well as usual.

2   It's hard to keep my mind on anything for very long.

3   I find I can't concentrate on anything.

20. Tiredness or Fatigue

0   I am no more tired or fatigued than usual.

1   I get more tired or fatigued more easily than usual.

2   I am too tired or fatigued to do a lot of the things I used to do.

3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

0 I have not noticed any recent change in my interest in sex.

1 I am less interested in sex than I used to be.

2 I am much less interested in sex now.

3 I have lost interest in sex completely.

Environmental Assessment

1. Do you live in a home, apartment, or assisted living facility?

2. Do you have stairs in your home? How often do you use them?

Staircase #1: _____ Frequency: _____

Staircase #2: _____ Frequency: _____

Staircase #3: _____ Frequency: _____

Staircase #4: _____ Frequency: _____

3. Do you live alone? With a spouse or partner? Do you have a caretaker (live-in or otherwise)?

4. Do you use any type of assistive devices at any time during a normal day? (Walkers, canes, etc?)

5. Do you ever use assistance from someone else during a normal day? (Taking a hand to go down steps, get out of a car, etc.)?

6. Have you ever modified anything in your home to reduce the risk of falling? When?

Modification: _____ Date: _____

Modification: _____ Date: _____

Modification: _____ Date: _____

Modification: _____ Date: _____

Modification: _____ Date: _____

Mini-Mental State Examination

Mini-Mental State Examination (MMSE)[1,2*]

Make the patient comfortable and establish rapport. Ask questions in the order listed. *Total possible score is 30.*

Maximum Score	Score		
			ORIENTATION
5	( )	1.	"What is the (year) (season) (date) (day) (month)?"
5	( )	2.	"Where are we?" (state) (county) (town or city) (hospital) (floor).

REGISTRATION

3 ( ) Ask the patient if you may test his/her memory. Then say the names of 3 unrelated objects, clearly and slowly, about one second for each (eg, "apple," "table," "penny"). After you have said all 3, ask him/her to repeat them. This first repetition determines the score (0-3), but keep saying them until he/she can repeat all 3, up to 6 trials.

ATTENTION AND CALCULATION

5 ( ) Ask the patient to begin with 100 and count backwards by 7. Stop after 5 subtractions (93, 86, 79, 72, 65). Score the total number of correct answers. If the patient cannot or will not perform the serial 7s task, ask him/her to spell the word "WORLD" backwards. The score is the number of letters in the correct order (eg, DLROW = 5; DLRW = 4; DLORW, DLW = 3; OW = 2; DRLWO = 1).

RECALL

3 ( ) Ask the patient to recall the 3 items repeated above (eg, "apple," "table," "penny").

LANGUAGE

2 ( ) **Naming:** Show the patient a wristwatch and ask him/her what it is. Repeat for pencil.

1 ( ) **Repetition:** Ask the patient to repeat the phrase "No ifs, ands, or buts" after you.

3 ( ) **3-Stage Command:** Give the patient a piece of blank paper and ask him/her to "take a piece of paper in your right hand, fold it in half, put it on the floor." Score 1 point for each part correctly executed.

1 ( ) **Reading:** On a blank piece of paper, print the sentence "CLOSE YOUR EYES" in letters large enough for the patient to see clearly. Ask him/her to read it and do what it says. Score 1 point only if he/she actually closes his/her eyes.

1 ( ) **Writing:** Give the patient a blank piece of paper and ask him/her to write a sentence. Do not dictate a sentence; it is to be written spontaneously. It must contain a subject and verb and be sensible. Correct grammar and punctuation are not necessary.

1 ( ) **Copying:** Ask the patient to copy the figure of intersecting pentagons exactly as it is. All 10 angles must be present and 2 must intersect to form a 4-sided figure to score 1 point. Tremor and rotation are ignored.
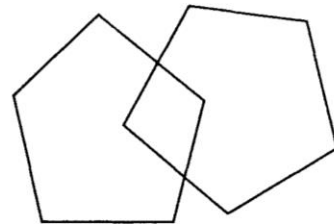
Maximum Total Score	Total Score	Suggested guideline for determining the severity of cognitive impairment:
30	(_____)	Mild: MMSE ≥21 Moderate: MMSE 10-20 Severe: MMSE ≤9

Expected decline in MMSE scores in untreated mild to moderate Alzheimer's patient is 2 to 4 points per year.[3,4]

References: 1. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12:189-198. **2.** Cockrell JR, Folstein MF. Mini-Mental State Examination (MMSE). *Psychopharm Bull.* 1988;24:689-692. **3.** Becker JT, Huff FJ, Nebes RD, Holland A, Boller F. Neuropsychological function in Alzheimer's disease: pattern of impairment and rates of progression. *Arch Neurol.* 1988;45:263-268. **4.** Mortimer JA, Ebbit B, Jun S-P, Finch MD. Predictors of cognitive and functional progression in patients with probable Alzheimer's disease. *Neurology.* 1992;42:1689-1696.

Physical Examination

Height		Weight			
Sitting BP-P					
Supine BP-P		Standing BP-P			

Strength	*Left*	*Right*		*Left*	*Right*
Shld Abd			Hip Ext		
Biceps			Hip Abd		
Triceps			Hip Add		
Wst Flex			Knee Ext		
Wst Ext			Knee Flex		
Grip			Ankle Df		
Hip Flex			Ankle Pf		
Reflexes			Patellar		
Biceps			Achilles		
Triceps			Babinski		

Sensory	Position		Vibration		Pin Prick	
	Left	*Right*	*Left*	*Right*	*Left*	*Right*
Upp Ext						
Low Ext						

Cerebellar	*Left*	*Right*
Fing-Nose		
Heel-Shin		

Other/comments

Examiner Name:

_____

UPDRS Assessment

The Unified Parkinson Disease Rating Scale (UPDRS)

I. Mentation, Behavior and Mood

1. Intellectual Impairment

0 = None

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

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

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

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

problems.

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

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

2. Thought Disorder

0 = None

1 = Vivid dreaming.

2 = "Benign" hallucinations with insight retained.

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

activities.

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

3. Depression

0 = Not present

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

2 = Sustained depression (1 week or more).

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

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

4. Motivation / Initiative

0 = Normal

1 = Less assertive than usual; more passive.

2 = Loss of initiative or disinterest in elective (non-routine) activities.

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

4 = Withdrawn, complete loss of motivation.

II. Activities of daily living (Determine for ON and OFF medications)

5. Speech

0 = Normal

1 = Mildly affected. No difficulty being understood.

2 = Moderately affected. Sometimes asked to repeat statements.

3 = Severely affected. Frequently asked to repeat statements.

4 = Unintelligible most of the time.

6. Salivation

0 = Normal

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

2 = Moderately excessive saliva; may have minimal drooling.

3 = Marked excess of saliva with some drooling.

4 = Marked drooling, requires constant tissue or handkerchief.

7. Swallowing

0 = Normal

1 = Rare choking.

2 = Occasional choking.

3 = Requires soft food.

4 = Requires NG tube or gastrostomy feeding.

8. Handwriting

0 = Normal

1 = Slightly slow or small.

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

3 = Severely affected; not all words are legible.

4 = The majority of words are not legible.

9. Cutting food and handling utensils.

0 = Normal

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

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

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

4 = Needs to be fed.

10. Dressing

0 = Normal

1 = Somewhat slow, but no help needed.

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

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

4 = Helpless.

11. Hygiene

0 = Normal

1 = Somewhat slow, but no help needed.

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

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

4 = Foley catheter or other mechanical aids.

12. Turning in bed and adjusting bed clothes

0 = Normal

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

2 = Can turn alone or adjust sheets, but with great difficulty.

3 = Can initiate, but not turn or adjust sheets alone.

4 = Helpless.

13. Falling (unrelated to freezing)

0 = None

1 = Rare falling.

2 = Occasionally falls, less than once per day.

3 = Falls an average of once daily.

4 = Falls more than once daily.

14. Freezing when walking

0 = None

1 = Rare freezing when walking; may have start-hesitation.

2 = Occasional freezing when walking.

3 = Frequent freezing. Occasionally falls from freezing.

4 = Frequent falls from freezing.

15. Walking

0 = Normal

1 = Mild difficulty. May not swing arms or may tend to drag leg.

2 = Moderate difficulty, but requires little or no assistance.

3 = Severe disturbance of walking, requiring assistance.

4 = Cannot walk at all, even with assistance.

16. Tremor (score right and left side separately)

0 = Absent

1 = Slight and infrequently present

2 = Moderate; bothersome to patient.

3 = Severe; interferes with many activities.

4 = Marked, interferes with most activities.

17. Sensory complaints related to parkinsonism

0 = None

1 = Occasionally has numbness, tingling, or mild aching.

2 = Frequently has numbness, tingling, or aching; not distressing.

3 = Frequent painful sensations.

4 = Excruciating pain.

Motor Exam

III. Motor Examination

18. Speech

0 = Normal

1 = Slight loss of expression, diction and/or volume.

2 = Monotone, slurred but understandable; moderately impaired.

3 = Marked impairment, difficult to understand.

4 = Unintelligible.

19. Facial expression

0 = Normal

1 = Minimal hypomimia, could be normal "poker face".

2 = Slight but definitely abnormal diminution of facial expression.

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

4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted ¼ inch or more.

20. Tremor at rest (score face, lip and chin; right upper; left upper; right lower; left lower)

0 = Absent

1 = Slight and infrequently present.

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

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

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

21. Action or postural tremor of hands (score right and left separately)

0 = Absent

1 = Slight; present with action

2 = Moderate in amplitude, present with action.

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

4 = Marked in amplitude; interferes with feeding.

22. Rigidity (Judged on passive movement of major joints relaxed in sitting position. Cogwheeling to be ignored.

Score neck; right upper, left upper; right lower; left lower)

0 = Absent

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

2 = Mild to moderate.

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

4 = Severe, range of motion achieved with difficulty.

23. Finger taps (tap thumb with index finger in rapid succession, with widest amplitude possible, score each hand

separately)

0 = Normal

1 = Mild slowing and/or reduction in amplitude

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

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

4 = Can barely perform the task.

24. Hand movements (Patient opens and closes hands in rapid succession with widest amplitude possible, score

each hand separately).

0 = Normal

1 = Mild slowing and/or reduction in amplitude.

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

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

4 = Can barely perform the task.

25. Rapid alternating movements of hands (Pronation/supination movements of hands, vertically of horizontally,

with as large an amplitude as possible, both hands simultaneously but score each hand separately.)

0 = Normal

1 = Mild slowing and/or reduction in amplitude.

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

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

4 = Can barely perform the task.

26. Leg agility with knee bent (Patient taps heel on ground in rapid succession, picking up entire foot. Amplitude

should be about 3 inches, score each leg separately).

0 = Normal

1 = Mild slowing and/or reduction in amplitude.

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

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

4 = Can barely perform the task.

27. Arising from chair (Patient attempts to arise from straight backed chair with arms folded across chest)

0= Normal

1= Slow; or may need more than one attempt.

2 = Pushes self up from arms of seat.

3 = Tends to fall back and may have to try more than one time, but can get up without help.

4 = Unable to rise without help.

28. Posture

0 = Normal erect

1 = Not quite erect, slightly stooped posture; could be normal for older person.

2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.

3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.

4 = Marked flexion with extreme abnormality of posture.

29. Gait

0 = Normal

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

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

propulsion.

3 = Severe disturbance of gait, requiring assistance.

4 = Cannot walk at all, even with assistance.

30. Postural stability (Response to sudden posterior displacement produced by pull on shoulders while patient erect

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

0 = Normal

1 = Retropulsion, but recovers unaided.

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

3 = Very unstable, tends to lose balance spontaneously.

4 = Unable to stand without assistance.

31. Body bradykinesia and hypokinesia (Combining slowness, hesitancy, decreased arm swing, small amplitude,

and poverty of movement in general).

0 = None

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

Possibly reduced amplitude.

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

reduced amplitude.

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

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

IV. Complications of Therapy

A. Dyskinesia

32. Duration What proportion of the waking day are dyskinesia present? Historical information.

0 = None

1 = 1%-25% of day.

2 = 26%-50% of day.

3 = 51%-75% of day.

4 = 76%-100% of day.

33. Disability How disabling are the dyskinesia? Historical information; may be modified by office examination

0 = Not disabling.

1 = Mildly disabling.

2 = Moderately disabling.

3 = Severely disabling.

4 = Completely disabling.

34. Painful dyskinesia How painful are the dyskinesia?

0 = No painful dyskinesia

1 = Slight

2 = Moderate

3 = Severe

4 = Marked

35. Presence of early morning dystonia Historical information

0 = No

1 = Yes

B. Clinical fluctuations

36. Are any "off" periods predictable as to timing after a dose of medications?

0 = No

1 = Yes

37. Are any "off" periods unpredictable as to timing after a dose of medication?

0 = No

1 = Yes

38. Do any of the 'off" periods come on suddenly, e.g. over a few seconds?

0 = No

1 = Yes

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

0 = None

1 = 1%-25% of day.

2 = 26%-50% of day.

3 = 51%-75% of day.

4 = 76%-100% of day.

C. Other complications

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

0 = No

1 = Yes

41. Does the patient have any sleep disturbances, e.g. insomnia or hypersomnolence?

0 = No

1 = Yes

42. Does the patient have symptomatic orthostasis?

0 = No

1 = Yes

Hoehn and Yahr

V. Modified Hoehn and Yahr Staging

Stage 0 = No signs of disease

Stage 1 = Unilateral disease

Stage 1.5 = Unilateral plus axial involvement

Stage 2 = Bilateral disease, without impairment of balance

Stage 2.5 = Mild bilateral disease, with recovery on pull test

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

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

Stage 5 = Wheelchair bound or bedridden unless aided

Schwab and England
VI. Schwab and England Activities of Daily Living Scale

100% - Completely independent. Able to do all chores without slowness, difficulty or impairment. Essentially

normal. Unaware of any difficulty.

90% - Completely independent. Abe to do all chores with some degree of slowness, difficulty and impairment.

Might take twice as long. Beginning to be aware of difficulty.

80% - Completely independent in most chores. Takes twice as long. Conscious of difficulty and slowness.

70% - Not completely independent. More difficulty with some chores. Three to four times as long in some.

Must spend a large part of the day with chores.

60% - Some dependency. Can do most chores, but exceedingly slowly and with much effort. Errors; some

impossible.

50% - More dependent. Help with half, slower, etc. Difficulty with everything.

40% - Very dependent. Can assist with all chores, but few alone.

30% - With effort, now and then does a few chores alone or begins alone. Much help needed.

20% - Nothing alone. Can be a slight help with some chores. Severe invalid.

10% - Totally dependent, helpless. Complete invalid.

0% - Vegetative functions such as swallowing, bladder and bowel functions are not functioning. Bedridden.

APPENDIX D. Experimental Protocol Documentation

Landon Center on Aging

Protocol

Subject Setup
Participants will be set up at the start of the session. This setup will remain the same for all protocols.

Consent
Clarify history (falls in previous 3 months, severity and duration, medication status)
Mini-mental exam
Change into standard shorts, shoes, and socks.

Measurements and EMG Placement
Have subject lie down in setup room; take the following measurements while subject is lying down:
Leg Length (distance from ASIS to medial ankle via knee)
Inter-ASIS Distance
Place EMGs: bilateral TA, solius, hamstring, quad
        Tips for placement:
        Solius:
Hamstring: have subject lay on side, then hold their lower leg and ask them to try to bend their leg while you resist.
Have subject stand for the following measurements:
Knee Width (between femoral condyles)
Ankle Width (align measuring device with axis of ankle)
Ankle Height
Foot Width
Foot Length
Calf Circumference
Thigh Circumference
Height
Weight

EMG:
Bilateral application of electrodes to the following muscles:
Gastroc, solius, quadriceps, anterior tib, hamstring.

Connect EMG as follows:

EMG lead	Muscle	EMG out-> Vicon BNC in
#1	R TA	9 – 1
#2	R gatroc	10 – 2
#3	R solius/ham	11 – 3
#4	R quad	12 – 4
#5	L TA	13 – 5
#6	L gatroc	14 – 6
#7	L solius/ham	15 – 7
#8	L quad	16 – 8
Black	ground	17 – 9

Vicon markers

15 14 mm markers will be placed on the lower body as follows (see Vicon PlugIn Gait marker placement guide for more information about specific placement methods):
Complete Setup: Bilateral – ASIS, sacrum, thigh, knee, shin, ankle, heel, toe
Knee alignment devices (KADS) will be used during the patient setup to establish the knee joint coordinate system.
Modified Setup: Bilateral- greater trochanter, thigh, knee, shin, ankle, heel, toe

Marker Placement Tips:
        ASIS/Sacrum: tape around the waist, and then attach markers to the tape
Thigh: Find greater trochanter, have subject rotate their foot to make sure you have it, then place marker on the line between the greater troch and knee. Place the marker on the right side higher than the left side.
Knee: Identify tibial plateau, then move back and up to find the femoral condyle- Place KADS first, then replace with individual markers.
Shin: Place on line between axis of knee and axis of ankle, marker on the right side higher than left
        Heel: Place on shoe, at same height of toe marker
        Ankle: Place marker in line of joint
        Toe: 2nd metatarsal head

- Put harness on
- Put EMG belt on

Data Collection
Walk the subject over to the forceplates for the EMG check and subject calibration trials.

- Subject Calibration Trial
- Remove KADs and replace with knee markers
- EMG check trial

Sway (trial type: PD_sway/ trial name: sway1)
Sway testing consists of three trials in each of two different conditions, eyes open (EO) and eyes closed (EC). Force plate, EMG, and motion data will be collected. Each test will last 30 seconds with 30 seconds of rest in between trials.
Should have complete marker setup, EMG on gastroc, SOLEUS, TA, quads

- Have participant stand comfortably with one foot on each force plate. Feet should be shoulder wide and at a self-selected angle. Arms rest to the side and the subject is looking at a marker placed 5 feet in front of the at approximately eye height.
- Attach safety harness
- Check EMG and visibility of markers
- Read script to the participant
- Before each test, remind the participant of the condition being tested (EO or EC).
- Disconnect Solius EMG channel and connect to hamstring electrode

Balance Recovery (trial type: general w/analog/ trial name: pull1)
The balance recovery testing consists of 3 backwards pull trials. Force plate, EMG, and motion data will be collected during all trials. The weight-drop device will be used to pull the participant.
Should have modified marker setup (no sacrum or ASIS, but including great troch markers), EMG on gastroc, hamstring, TA, quad

- Attach safety harness
- TAKE STATIC TRIAL IN MODIFIED MARKER SETUP

- Put on the rigid belt
- Measure waist height, adjust pull device to 8.7% of waist height
- Attach pull device cable
- Read script, explaining task (no practice trials)
- Research assistant should spot the participant throughout all trials
- Once subject is ready, release the weight-dropping mechanism
- Tell the subject to relax after they have regained their balance for three seconds
- Check trial in Vicon for marker visibility
- Perform a total of 3 trials with 30 seconds rest in between trials
- Disconnect safety harness, cable to pull device, and remove belt

Gait Initiation (trial type: general w/analog/ trial name: gait_ini1)
Participants will perform 5 gait initiation trials, all starting from standing on a forceplate. EMG, force and movement data will be collected.
Should have complete marker setup, foot switches, EMG on gastroc, hamstring, TA, quad

- Attach foot switches and foot switch belt
- Attach foot switches to scope to check and monitor foot switch signal
- Have participant stand in collection area.
- Attach safety harness
- Read the script to the participant.
- Do a few practice trials to get a good starting location ensuring clean FP strikes.
- Participant should start each trial with their feet in a comfortable stance and their arms relaxed at their sides.
- At the end of the trial, remove the light switch cable and replace with a grounding resistor to AUX 4.
- A research assistant should be spotting the participant throughout.

Gait (trial type: PD_gait/ trial name: gait)
Participant will walk on the treadmill for 3 minutes at a self-selected speed. EMG and movement data will be collected.
Should have complete marker setup, foot switches, EMG on gastroc, hamstring, TA, quad

- Move treadmill into the Vicon collection volume under the safety support.
- Have participant put on safety harness.
- Attach foot switches and foot switch belt
- Attach foot switches to scope to check and monitor foot switch signal
- Instruct participant to step onto the treadmill.
- Attach the cable to the safety harness.
- Attach kill switch to subject's clothing.
- Power up the treadmill.
- Read the script to the participant, explaining the tasks.
- Slowly increase the speed of the treadmill until the desired speed is reached. Record the final speed on the data collection sheet.
- Once the participant has reached a comfortable gait begin data collection.
- At the end of data collection, inform participant they are finished and then stop the treadmill (manually decrease the speed to zero).
- Remove safety cable and assist the participant in stepping off the treadmill.

Take another subject calibration trial (should have two subject calibration trials- one for use with br, one for all others)

Take another force plate zero trial

Technical Setup

Camera and Volume setup

- Set camera locations based on Vicon Camera Setup Sheet for study.
- Check that the volume and surrounding area is free of reflective objects.

Check connections with peripheral equipment

- Force plates: Attach the cables labeled "Vicon Raw" to the force plate amplifiers. These terminate at the Vicon BOB. Make sure the cable from the Vicon BOB is connected to the data station. Power on force plates at least 15 minutes before collection.
- EMG: Attach BNC to the Vicon BOB using channels 1-8.
- Pull device input: Connect to the Vicon BOB - normal to AUX1, shear to AUX2.
- Video (If using): Attach fire wire from camera to the fire wire port of PC. If the camera cord length is too short, you may use the Dazzle, connecting the fire wire from the camera to Dazzle and fire wire from Dazzle to the PC. Make sure the Dazzle and camera are powered on. The Dazzle should be set at "Pass through".

Power up

- Power up and log into computer 1st, then power up Vicon Datastation. If you do not do this in the correct order, the computer will not be able to find the network.

Turn on all equipment, including cameras and strobes at least 15 minutes before start of a session.

Session setup:

- Start Workstation
- Open Eclipse. In the correct database (Browse→ D: Capture\Data\ **Antonis**.enf), double click on the project level (green icon) to activate it. With this level highlighted, select System| System Configuration
    - Select "**MJF_pilot**" system configuration (not a bad idea to check analog setup to confirm the change in the system settings). The session settings are taken from the active config, so if you build the session before making this change, your settings will be incorrect and you will need to start over.
- Click System | Control Setup and ensure that no remote triggers are enabled (no checks).
- Click System | Start Link to establish a connection to the datastation. This should illuminate the camera strobes. Allow the cameras to be on for 10 minutes before calibrating.
- Click System | Live Monitors to look at the capture volume. Check and adjust camera placement to ensure your capture space is covered and viewed by cameras (a quick check of the volume by walking through it with the wand).
    - If you are not receiving data from a camera, unplug the line to the datastation for that camera (1-3 or 4-6) and replug it in. This will reinitialize that group of cameras.
- Check camera angles and camera sensitivity in Workstation
- Go to System | Calibrate cameras. Make sure all cameras are selected and that the proper calibration props are selected (clinical L-frame and 500mm wand).
- Set the calibration L-frame in place to create the desired coordinate system.
- Perform a static calibration followed by dynamic calibration* and check for acceptable calibration values.
    - Make sure the wand stays in the calibration volume during the capture.
- Enter the calibration information in the log.

    Wand visibility – measure of whether both markers are visible to each camera. Higher is better (<50% = failed).

    Static reproducibility – how well the L frame measured matches expected measurements. Lower is better.

    Residuals - < 0.1% of the distance from the cameras to the center of the capture volume. Check the log for acceptable values, typically 1-1.6 for larger volumes.

- Build the session (add a new patient, and a new session).
- With the session highlighted, go to System | Calibrate Analog Zero Levels and select the force plate channels. Make sure that the force plates are completely setup before this step (powered on, balanced, etc.) and that there is no load on them.
- Go to System | Live Movie to check the view of the video camera if using it.

Begin Capture with Subject

- Once subject is set up with markers, have them stand in the capture volume. Make sure there is nothing besides markers which appear on the subject (reflective jewelry etc).
- To capture a trial:
    - Select the appropriate trial type
    - Check that the appropriate data will be collected by clicking Types.
    - Give the trial a name and any description desired.

*Note 1: make sure that the person performing the calibration is not wearing anything reflective. This can be checked in live monitor by having the person walk around the capture volume. Also, ensure that your subject is not in view of the cameras if he/she has markers on.

Note 2: if a camera is moved at all during testing you must recalibrate!

**Checking and preliminary processing

- You may want to use diagnostic mode to check video quality.
- Analog data can be checked using Graph | Analog. This data will be the analog data as acted on by the scale factors specified for each channel in the analog setup. The raw data can be visualized by Window | New Analog Data or by double clicking the 'A'.
  Control the data presentation by the following keys with or without shift key:

    L - # of traces

    T – timeline

    G – gain

Protocol Checklist

Start Equipment Setup:

_____Check Vicon camera positions

_____Cables from force plate amplifiers are labeled "Vicon BOB"

_____BNC connectors from EMG are connected to Vicon BOB.

_____Connect video camera

_____Connect pull device – normal (AUX1), shear (AUX2)

_____Balance force plates

Start Subject Setup:

_____Consent

_____Clarify history (falls in previous 3 months, severity and duration, medication status)

_____Mini-mental exam

_____5 Self-Report Tests

Complete Equipment Setup:

_____Complete Vicon session start-up as in Vicon Collection Procedures (do not calibrate more than 30 minutes prior to testing)

_____Check system configuration (MJF Pilot), analog setup and control setup

_____Zero analog channels for the force plates while in correct session

_____Collect a FP zero trial for tracking drift (trial name: FPzero)

_____Calculate appropriate weight for pull and load pull device (see paper)

_____Test Pull Device

_____Place "GO" switch box and target

Complete Subject Setup:
_____Measurements and EMG Placement
_____Vicon markers

_____Put harness on

_____Put EMG belt on

_____Place KADs for subject calibration trial

Data Collection:

_____Check to make sure Vicon is setup for this experiment

_____Collect a subject calibration trial (trial type: subject calibration/ trial name: static)

_____Check that movie camera is working

_____Check to make sure all markers are visible

_____Remove KADs and replace with knee markers

_____Collect EMG trial (trial type: analog only/ trial name: EMGcheck)

_____Check EMG signal (view→new analog data) (shift-t to zoom)

Sway **(trial type: PD_sway/ trial name: sway1) *Comment EO/EC in Vicon***

3 EO/3 EC Each test will last 30 seconds with 30 seconds of rest in between trials.

Should have complete marker setup, EMG on gastroc, SOLEUS, TA, quads

_____Disconnect Solius EMG channel and connect to hamstring electrode

Balance Recovery **(trial type: general w/analog/ trial name: pull1)**

3 Backward Pull Trials

Should have modified marker setup (no sacrum or ASIS, but including great troch markers), EMG on gastroc, hamstring, TA, quad

_____Change markers: move calf and thigh markers out of alignment with knee, ankle, and hip markers. Add a great troch marker if not already in place. Remove ASIS markers.

_____Take a static trial for use with BR (w/troch markers)

_____ Put on the rigid belt

_____Calculate weight drop height (8.7% of waist height) and adjust- measured from brushes

_____Perform a total of 3 trials with 30 seconds rest in between trials

_____Check each trial in Vicon

_____Remove belt

Gait Initiation (trial type: general w/analog/ trial name: gait_ini1)

5 trials, all starting from standing on a force plate.

Should have complete marker setup, foot switches, EMG on gastroc, hamstring, TA, quad

_____Connect foot switch to Vicon BOB- AUX3

_____Connect light switch to Vicon BOB- AUX4

_____Adjust safety harness so that it is moveable

_____Attach foot switches and foot switch belt

_____Attach foot switches to scope to check and monitor foot switch signal

_____Check each trial in Vicon

_____At the end of all trials, remove the light switch cable and replace with a grounding resistor to AUX 4.

Gait (trial type: PD_gait/ trial name: gait)

Participant will walk on the treadmill for 3 minutes at a self-selected speed.

Should have complete marker setup, foot switches, EMG on gastroc, hamstring, TA, quad

_____Attach foot switches and foot switch box, check signal on scope.

_____Take another force plate zero trial

_____Make sure that you have two static trials

Study Scripts
Postural Sway

"For this set of tests you will stand here with your hands to your sides and have either your eyes focused on the target in front of you or have them closed. We will do several trials with rest in between. I will tell you when to begin each trial and I will tell you when to relax."

EO:

Instructions to subject:

"For this test, you will stand as still as possible. Focus your gaze at the target in front of you"

EC:

Instructions to subject:

"For this test, you will stand as still as possible with your eyes closed. Keep your eyes closed until the end of the trial."

Gait Initiation

5 trials start with feet on forceplates (capture push off and first step.

Instructions to subject:

"For this set of tests you will start standing still and then begin walking when you see the green light. Keep walking until I tell you to stop. You will take approximately 3-4 steps. We will do several trials with rest in between and there will be two different starting positions."

Repeat for each trial:

"For this test, you will stand here as still as possible and when you see the green light you will start walking forward, looking ahead while you walk."

Balance Recovery

Instructions to subject:

"This study will let us look at your response to a balance disturbance. You will be asked to stand here on these force plates and a cable will be attached to your waist. The cable will pull you backwards and you need to regain your balance. We will have you repeat this several times. We will explain each step and give you a rest between trials."

"First we will have you put on this waist belt, which will be attached to the cable that will pull you for each trial. For your safety, you will wear a safety harness. The harness will catch you if you are unable to regain your balance."

"Now, we will have you place your right foot on this plate and your left one on this plate. Stand comfortably with your feet approximately shoulder-width apart. Please stand quietly with your hands at your sides. Please remain as still as possible before and after you regain your balance, until I tell you to relax. Do you have any questions?

"Okay, now we will start the test. Please remember to stand up straight and remain still before the pull and after you step."

Gait

Instructions to subject:

"For this test you will walk on this treadmill for approximately 3 minutes at a pace that is comfortable for you. First we will determine a pace and then the test will begin. Again, you will wear a safety harness that will catch you in the event that you lose your balance. Also, if at any time you feel uncomfortable, you can push this button and the treadmill will stop abruptly."

"First, we will start the treadmill slowly and choose a speed that feels like a comfortable, normal walking pace to you. Do you have any questions?"

(Choose pace)

"Now, we will start the test. Just continue to walk normally. The test will last approximately 3 minutes."

Data Collection Sheet

Parkinson's Test

Date: _____   **Time:** _____   **Subject #:** _____
Engineer: _____
Engineer: _____
PT: _____

PD Duration: _____

Medications:
Name: _____ **Frequency:** _____   **Last Dose:** _____
Name: _____ **Frequency:** _____   **Last Dose:** _____
Name: _____ **Frequency:** _____   **Last Dose:** _____

Fall History:
Falls in previous 3 months:
Date: _____ **Description:** _____
Date: _____ **Description:** _____
Date: _____ **Description:** _____
Date: _____ **Description:** _____

Mini-Mental Score: _____

Measurements:
Leg Length (ASIS to medial ankle via knee):   **L:** _____   **R:** _____
Inter ASIS distance: _____
Knee Width (between femoral condyles):   **L:** _____   **R:** _____
Ankle Width: **L:** _____   **R:** _____
Ankle Height: **L:** _____   **R:** _____
Foot Width: **L:** _____   **R:** _____
Foot Length: **L:** _____   **R:** _____
Calf Circumference: **L:** _____   **R:** _____
Calf Length: **L:** _____   **R:** _____
Thigh Circumference: **L:** _____   **R:** _____
Thigh Length: **L:** _____   **R:** _____
Height: _____
Weight: _____
Waist Height: _____

Testing Notes:

Subject Calibration Trial
Static 1: _____
Static 2: _____
EMG Check: _____

Sway(PD_sway)
Sway1: _____
Sway2: _____
Sway3: _____
Sway4: _____
Sway5: _____
Sway6: _____

Balance Recovery (general w/analog capture)
Pull1: _____
Pull2: _____
Pull3: _____

Gait Initiation (general w/analog capture)
Gait_ini1: _____
Gait_ini2: _____
Gait_ini3: _____
Gait_ini4: _____
Gait_ini5: _____

Gait (PD_gait)
Gait: _____

Biodynamics Labratory

Protocol
      0-45 minutes: Subject Paperwork, Health Assessments, Measurements
Location: subject setup area

-Consent Form
-Take weight on force plates
-Questionnaires
-Offer a bathroom break!
-Change into shorts, socks, shoes, T-shirt
-Health Assessment, take weight and height
-Measurements
Laying down: Leg Length, ASIS distance, ankle width
Sitting up: calf circumference
Standing: knee width, ankle height, food width, foot length, thigh circumference
*While taking measurements, mark placement for Knee Marker, ASIS, great troch, and hamstring EMG.

Measurement Descriptions:
Weight: When the subject first arrives, weigh with shoes and clothes on on force plates. Then, after the subject has changed into testing clothing, weight without shoes on on force plates again.
ASIS Breadth: Measure the horizontal distance between the two ASIS
Thigh length: Measure the vertical distance between the top of the great troch and the top of the lateral tibia (can use tibial plateau).
Thigh Circumference: Measure mid-thigh
Calf Length: Measure the vertical distance between the top of the lateral tibia and the lateral malleolus (ankle).
Calf Circumference: Measure the circumference of the calf at the largest spot.
Knee Diameter: Measure the maximum breadth of the knee across the femoral epicondyles.
Foot Length: Measure the distance from the back of the heel to the tip of the longest toe.
Ankle height: Measure the vertical distance from the floor to the lateral malleolus.
Ankle width: Measure the maximum distance between the medial and lateral malleoli.
Foot width: Measure the width across the distal ends of metatarsals 1 and 5.

45-90 minutes: Sensor placement and Equipment Setup
Location: Platform Area

Put safety harness on.

Place EMGs: bilateral TA, gastroc, hamstring, quad
Connect EMG as follows:

EMG lead	Muscle	EMG out-> DAQ Board Channel in
#1	R TA	1 – 22
#2	R gastroc	2 – 23
#3	R solius/ham	3 – 24
#4	R quad	4 – 25
#5	L TA	5 – 26
#6	L gastroc	6 – 27
#7	L solius/ham	7 – 28
#8	L quad	8 – 29

Test EMGs, take sitting break

Optotrak Markers
15 markers will be placed on the lower body as follows (see Vaughan's Gait Model and Helen Hayes Marker Set for more information about specific placement methods):
Complete Setup: Bilateral – ASIS, sacrum, thigh, knee, shin wand, ankle, heel, toe
Modified Setup(for balance recovery only): Bilateral- greater trochanter, thigh, knee, shin wand, ankle, heel, toe

Marker Placement Tips:
ASIS/Sacrum: tape around the waist, and then attach markers to the tape. Use a foam piece to orient the sacrum towards one of the cameras.
Thigh: Find greater trochanter, have subject rotate their foot to make sure you have it, then place marker on the line between the greater troch and knee (along the long axis of the thigh). Marker should be on lower thigh and in line with the flexion/extension axis of the knee.
Knee: Identify tibial plateau, then move back and up to find the femoral epicondyle- along the flexion/extension axis of the knee.
Shin Wand : Place on lower shank, on long axis, and in line with flexion/extension axis of the ankle.
Heel: Place on shoe, at same height of toe marker, use a foam piece to orient the marker towards the cameras.
Ankle: Place marker in line of flexion/extension axis of ankle.
Toe: 2nd metatarsal head on joint closest to body (2nd biggest) Use a foam piece to orient the marker towards the cameras.

Walk subject into data collection area and test to make sure all markers are visible.
Subject calibration trial (stand still)
Take a sitting break

90-180 minutes: Experimental Testing/Data Collection
Location: Platform Area
Balance Recovery (trial type: general w/analog/ trial name: pull1)
The balance recovery testing consists of 3 backwards pull trials. Force plate, EMG, and motion data will be collected during all trials. The weight-drop device will be used to pull the participant.
Should have modified marker setup (no sacrum or ASIS, but including great troch markers)

Attach safety harness
TAKE STATIC TRIAL IN MODIFIED MARKER SETUP
Mark foot position with tape
Put on the rigid harness
Measure waist height, adjust pull device to 8.7% of waist height
Take a still trial
Mark the feet so they stay in the same position as for the "still trial."
Attach pull device cable
Read script, explaining task (no practice trials)
Start the video camera
Research assistant should spot the participant throughout all trials
Once subject is ready, release the weight-dropping mechanism
Replace weights and tell the subject to relax after they have regained their balance for three seconds
Check trial for marker visibility
Perform a total of 3 trials with 30 seconds rest in between trials
Disconnect safety harness, cable to pull device, and remove rigid harness

Take a sitting break

Sway (trial type: PD_sway/ trial name: sway1)
Sway testing consists of three trials in each of two different conditions, eyes open (EO) and eyes closed (EC). Force plate, EMG, and motion data will be collected. Each test will last 30 seconds with 30 seconds of rest in between trials.
Should have complete marker setup

Have participant stand comfortably with one foot on each force plate. Feet should be shoulder wide and at a self-selected angle. Arms rest to the side and the subject is looking at a marker placed 5 feet in front of the at approximately eye height.
Attach safety harness
Check EMG and visibility of markers
Read script to the participant
Before each test, remind the participant of the condition being tested (EO or EC).
Take a sitting break

Gait Initiation (trial type: general w/analog/ trial name: gait_ini1)
Participants will perform 5 gait initiation trials, all starting from standing on a forceplate. EMG, force and movement data will be collected.
Should have complete marker setup

Have participant stand in collection area with one foot on each force plate. They will be oriented so that they are looking at the South wall.
Take a static trial
Mark foot position
Attach safety harness
Read the script to the participant.
Subject will start with one foot on each force plate, then step forward when the light comes on.
Participant should start each trial with their feet in a comfortable stance and their arms relaxed at their sides.
A research assistant should be spotting the participant throughout.
Take a sitting break

Gait (trial type: PD_gait/ trial name: gait)
Participant will walk on the treadmill for 3 minutes at a self-selected speed. EMG and movement data will be collected.
Should have complete marker setup, foot switches, EMG on gastroc, hamstring, TA, quad

Move treadmill into the collection volume under the safety support.
Instruct participant to step onto the treadmill.
Attach the cable to the safety harness.
Attach kill switch to subject's clothing.
Power up the treadmill.
Read the script to the participant, explaining the tasks.
Slowly increase the speed of the treadmill until the desired speed is reached. Record the final speed on the data collection sheet.
Once the participant has reached a comfortable gait begin data collection.
At the end of data collection, inform participant they are finished and then stop the treadmill (manually decrease the speed to zero).

Remove safety cable and assist the participant in stepping off the treadmill.

Take another subject calibration trial (should have two subject calibration trials- one for use with br, one for all others)

Take another force plate zero trial

Optotrak Data Key

Marker	Location	Columns
1	Right Thigh	2:4
2	Right Knee	5:7
3	Right Shank	8:10
4	Right Ankle	11:13
5	Right Heel	14:16
6	Right Toe	17:19
7	Left Thigh	20:22
8	Left Knee	23:25
9	Left Shank	26:28
10	Left Ankle	29:31
11	Left Heel	32:34
12	Left Toe	35:37
13	Right ASIS/Great Troch	38:40
14	Sacrum	41:43
15	Left ASIS/Great Troch	44:46

Pre Data Collection Tasks

Recruitment:
Once a participant has passed the health screen and is scheduled, send them a confirmation letter and directions to the lab.
If it is a PD participant, also email them to ask them to see Dr. Lyons within 3 months of the testing date. Attach the letter called "UPDRS Appt."
Email David to confirm testing dates/times.
Misc:
Email David Moore, parking guy, about reserving a parking meter. His email is moore-ku@ku.edu and phone number is 785-864-7293 (office) or 785-840-5693 (cell).
Make sure David Thomas has a parking pass for the week of testing. If there are 3 or more tests in a week it makes sense to get him a weekly parking permit. A red weekly visitor permit is $8.00/week. Contact Mary Olson at KU Parking. I just sent an email to kupark@ku.edu and that is who responded to me. You can either pay for the permit and get reimbursed or ask them to invoice the ME department (specify that this is for Luchies's PD Pilot project so the office knows what it is). If there are 2 or fewer tests in a week, it makes sense for him to just park in the parking garage and pay $1/hour. In this case, we add the parking fee to his timesheet (there is a column for parking). Just note the number of hours he parked for.
Email Kelly Lyons (klyons@kumc.edu) to let her know if we are testing a PD patient so she can make sure and see them in clinic in case they happen to have an appointment before they come in for testing.
Make sure the laundry is all clean (sheets, shorts, socks, etc).

Post Data Collection Tasks

File Backup:

Take "PD Project Data Transfer" external hard drive from out of Molly's desk and transfer the optotrak files to the hard drive.

Connect the video camera to the Labview computer and turn it on.

Connect the external hard drive to the Labview computer.

Copy the video and optotrak data to the appropriate folder in the Labview computer.

Copy all files from the labview computer folder to the "Master Backup Hard Drive" (the 1 TB one that sits on the desk by the labview computer) as well as on the PD Project Data Transfer hard drive.

Double check that you have complete sets of data on both the labview computer, the master backup hard drive, and the transfer drive.

Take the transfer drive home with you.

DT Timesheet

Update the spreadsheet "DT Timesheet" with the date and hours that he worked and any parking that we owe him for.

Payment and Thank You's:

At the end of a testing week, collect all of the payment forms out of the folders of each participant.

Complete the back side of the forms, and take to Carl to sign.

Make copies of the signed forms for our records and turn in the originals to Leslie in the ME office.

Write and send a thank-you card from our lab to the participant.

PD Patient Appt. with Dr. Lyons Record

Dr. Lyons needs to know about each patient that we test and when we test them. Update the spreadsheet called "Testing Dates" to include each PD participant. Really this should be updated as soon as the patient is scheduled in case they go in to see Dr. Pahwa between scheduling and testing.

Technical Setup
Data Acquisition Setup

Setup data files on both the labview and optotrak computers. For the labview computer, setup a folder for each subject in each task folder. My documents→Research→Molly→PD Project 2010→Data→BR, GI, Sway, Gait, etc. For the optotrak computer, just setup a subject folder in the PD Project→Data folder. It is imperative to keep track of which optotrak file goes with which data file from the other computer. I usually do this on the data collection sheet.

Decide the order of tasks for the experiment and order of EO/EC trials for sway. Balance Recovery will always go first. Use "randperm(3)" to determine the order of the other tasks. 1= gait initiation, 2= sway, 3= gait. For sway, use "randperm(6)" and each even number it gives= eyes open trial, and each odd number= eyes closed trial. Write the orders on the data collection sheet and on the the whiteboard.

Loading the Pull Device

Take the subject's weight on the force plate. Add 10 lbs to account for the weight of all of the sensors and rigid harness.

Go to the "Pull Weight Combinations" sheet and look up the weight to add amount. Remember that the actual amount of weight you will add is 7 lbs less than what it says in the "weight to add" column. If you add the weight together from the weight combinations that it gives, that is the right amount to add. Or, you can just subtract 7 lbs from the amount it tells you to add.

To determine the drop distance, measure the distance from the middle of the waist harness loop that the rope connects in to the floor. Take 8.7% of this number and then add 0.5cm. So the calculation is waist height*.087 + 0.5 cm.

To set the drop distance, note that a "zero" distance is 11cm on the meter stick that is in the device. So you will want to move the brushes to whatever drop distance you calculated + 11cm.

Optotrak Setup

Place Optotrak sensors in location- 12 feet from midline of force plates on East and West sides

Connect 3020 and Certus sensors to the SCU using the correct cables (they are labeled). Ensure that the cable from the SCU to the computer is connected, and that the power is connected.

Turn on both sensors and the SCU unit.

Start up the optotrak computer, logon, and open First Principles

Choose File→New Experiment

Perform a new registration and alignment with coordinate system origin at the SE corner of force plate #3.

*Note- if the software does not detect both sensors it will not ask you to perform a registration- make sure that it finds both sensors. If it doesn't, try "Query System," and then start the setup over again.

Note that sensor 3-03-63 is the 3020 system.

Connect all markers and strobers and make sure the software recognizes the correct number of markers. You can go through and name them here as well if you want to.

Choose to enable the trigger

Setup your data collection parameters

Make sure that all markers are visible.

Force Plate Setup

Turn on and leave alone for 10-15 minutes

Balance amplifiers

Take zero trial prior to data collection

EMG Setup

Scrub area with pumice stone and rub with alcohol wipe

Place sensors and arrange wires

Connect output cables

Ensure that the gain is turned to 1k on all 8 channels

Check signal using labview

Labview Startup

Open My Documents→Research→Molly→PD Project 2010→Labview Vis and open the

"PD_data_collection_allinone."

After balancing force plates, take a force plate zero trial.

-Set collection time to 1 sec

-Select "no" for "Use Trigger?"

-Select "no" for "Do you want to track the COP before data collection?"

-Save the zero trial as My Documents→Research→Molly→PD Project 2010→Data→

Then choose the appropriate experiment folder and label file as "fp_zero"

For the balance recovery experiment,

Have the subject stand on force plates one and two in the same position as they will stand for the

balance recovery task. Mark the feet with tape. Take a trial and label it "still" This will serve as the static

trial, too- so make sure that all markers are visible and use the trigger to collect optotrak data.

Run "zero trial calculation simplify" VI to calculate the still position COP. Save the file as

"still_cop."

Now open PD_data_collection_allinone and select "yes" to monitor the COP and "yes" to use the

trigger. Set the collection time to 5 seconds.

Make sure that the drop mechanism is ready to go (hit "open cleats" and front "drop" and front

"cleat" to arm it.

Begin the VI by pushing the start arrow on the upper left hand side of the window.

When the green light comes on (indicating they have met the COP requirements), click on the

"GO" button. Now the program is waiting for your trigger.

Press the red trigger button to trigger optotrak, labview, and to drop the weights. Weights are dropped 500ms after data collection begins.

Save the trial as br1. Note on the data collection sheet which optotrak file goes with which data file.

Check that all of the data looks good

For all other tasks,

-Select "no" for "Do you want to track the COP before data collection?"

Take another fp_zero trial (1 sec), and save it in the correct task folder.

Gait Initiation trials are 5 seconds (unless they need to be adjusted for a very slow subject), Sway trials are 30 seconds, and we don't need to collect data through labview for gait trials.

Gait initiation also needs a static trial- only marker data is needed, but all markers must be in view. Static trials are 5 seconds long.

Post Data Collection Tasks

File Backup:

Take "PD Project Data Transfer" external hard drive from out of Molly's desk and transfer the optotrak files to the hard drive.

Connect the video camera to the Labview computer and turn it on.

Connect the external hard drive to the Labview computer.

Copy the video and optotrak data to the appropriate folder in the Labview computer.

Copy all files from the labview computer folder to the "Master Backup Hard Drive" (the 1 TB one that sits on the desk by the labview computer) and also to the transfer hard drive.

Double check that you have complete sets of data on both the labview computer, the transfer hard drive, and the master backup hard drive.

Someone should take the transfer hard drive home with them each night.

DT Timesheet

Update the spreadsheet "DT Timesheet" with the date and hours that he worked.

Payment and Thank You's:

At the end of a testing week, collect all of the payment forms out of the folders of each participant. Complete the back side of the forms, and take to Carl to sign.

Make copies of the signed forms for our records and turn in the originals to Leslie in the ME office.

Write and send a thank-you card from our lab to the participant.

PD Patient Appt. with Dr. Lyons Record

Dr. Lyons needs to know about each patient that we test and when we test them. Update the spreadsheet called "Testing Dates" to include each PD participant. Really this should be updated as soon as the patient is scheduled in case they go in to see Dr. Pahwa between scheduling and testing.

Protocol Checklist

Start Equipment Setup:
_____Check camera positions
_____Turn on force plates, cameras, SCU
_____Verify force plates (channels 0-11,16-21), EMG (channels 22-29), pull device load cell (channels 12-13), gait initiation light (channel 14), and trigger (PFIO) are connected to DAQ board
_____Connect video camera
_____Connect pull device – normal (channel 12), shear (channel 13)
_____Balance force plates

Start Subject Setup:
_____Consent
_____Physical Screening
_____Clarify history (falls in previous 3 months, severity and duration, medication status)
_____Mini-mental exam
_____5 Self-Report Tests

Complete Equipment Setup:
_____Complete Optotrak startup (registration, calibration)
_____Collect a FP zero trial for tracking drift (trial name: FPzero1)
_____Calculate appropriate weight for pull and load pull device (see paper)
_____Test Pull Device
_____Place "GO" switch box and target

Complete Subject Setup:
_____Measurements and EMG Placement
_____Optotrak markers
_____Put harness on
_____Put EMG belt on

Data Collection:
_____Connect markers and make sure they are all seen in Optotrak
_____Collect a subject calibration trial (static trial)
_____Check that movie camera is working
_____Check to make sure all markers are visible
_____Check EMG signal

Sway (trial name: sway1EO)
3 EO/3 EC Each test will last 30 seconds with 30 seconds of rest in between trials.
Should have complete marker setup, EMG on gastroc, SOLEUS, TA, quads

_____Disconnect Solius EMG channel and connect to hamstring electrode

Balance Recovery (trial name: pull1)
3 Backward Pull Trials
Should have modified marker setup (no sacrum or ASIS, but including great troch markers), EMG on gastroc, hamstring, TA, quad

_____Change markers: move calf and thigh markers out of alignment with knee, ankle, and hip markers. Add a great troch marker if not already in place. Remove ASIS markers.
_____Take a static trial for use with BR (w/troch markers)
_____ Put on the rigid belt
_____Calculate weight drop height (8.7% of waist height) and adjust- measured from brushes
_____Perform a total of 3 trials with 30 seconds rest in between trials
_____Check each trial in Optotrak
_____Remove belt

Gait Initiation (trial name: gait_ini1)
5 trials, all starting from standing with one foot on each force plate
Should have complete marker setup, EMG on gastroc, hamstring, TA, quad

_____Check each trial in Optotrak

Gait (trial name: gait)
Participant will walk on the treadmill for 3 minutes at a self-selected speed.
Should have complete marker setup, foot switches, EMG on gastroc, hamstring, TA, quad

_____Take another force plate zero trial
_____Make sure that you have two static trials

Study Scripts

Postural Sway
"For this set of tests you will stand here with your hands to your sides and have either your eyes focused on the picture in front of you or have them closed. We will do several trials with rest in between. I will tell you when to begin each trial and I will tell you when to relax."

EO:
Instructions to subject:
"For this test, you will stand as still as possible. Focus your gaze at the target in front of you"

EC:
Instructions to subject:
"For this test, you will stand as still as possible with your eyes closed. Keep your eyes closed until the end of the trial."

Gait Initiation **:**6 trials start with feet on force plates and check for clean strike on back force plate (capture push off and first step)

Instructions to subject:
"For this set of tests you will start standing still and then begin walking when you see the green light. Keep walking until I tell you to stop. You will take approximately 3-4 steps. We will do several trials with rest in between.

Repeat for each trial:
"For this test, you will stand here as still as possible and when you see the green light you will start walking forward, looking ahead while you walk."

Balance Recovery**:** 3-5 trials
Instructions to subject:
"This study will let us look at your response to a balance disturbance. You will be asked to stand here on these force plates and a cable will be attached to your waist. The cable will pull you backwards and you need to regain your balance. We will have you repeat this several times. We will explain each step and give you a rest between trials."
"First we will have you put on this waist belt, which will be attached to the cable that will pull you for each trial. For your safety, you will wear a safety harness. The harness will catch you if you are unable to regain your balance."
"Now, we will have you place your right foot on this plate and your left one on this plate. Stand comfortably with your feet approximately shoulder-width apart. Please stand quietly with your hands at your sides. Please remain as still as possible before and after you regain your balance, until I tell you to relax. Do you have any questions?
"Okay, now we will start the test. Please remember to stand up straight and remain still before the pull and after you step."

Gait**:** 1 trial
Instructions to subject:
"For this test you will walk on this treadmill for approximately 3 minutes at a pace that is comfortable for you. First we will determine a pace and then the test will begin. Again, you will wear a safety harness that will catch you in the event that you lose your balance. Also, if at any time you feel uncomfortable, you can push this button and the treadmill will stop abruptly."

"First, we will start the treadmill slowly and choose a speed that feels like a comfortable, normal walking pace to you. Do you have any questions?"
(Choose pace)
"Now, we will start the test. Just continue to walk normally. The test will last approximately 3 minutes."

Data Collection Sheet

Date: _____   Time: _____   Subject #: _____

Engineer: _____   Testing Order: _____

Engineer: _____

PA: _____

PD Duration: _____

PD Medications (list other medications on health screen):

Name: _____Dosage: _____ Frequency: _____ Last Dose: _____

Name: _____Dosage: _____ Frequency: _____ Last Dose: _____

Name: _____Dosage: _____ Frequency: _____ Last Dose: _____

Name: _____Dosage: _____ Frequency: _____ Last Dose: _____

Name: _____Dosage: _____ Frequency: _____ Last Dose: _____

Name: _____Dosage: _____ Frequency: _____ Last Dose: _____

Fall History:

Falls in previous 3 months:

Date: _____ Description: _____

Date: _____ Description: _____

Date: _____ Description: _____

Date: _____ Description: _____

Mini-Mental Score: _____

Measurements:

Height:	_____	
Weight:	_____	
Leg Length (ASIS to medial ankle via knee):	L: _____	R: _____
Inter ASIS distance:	_____	
Knee Width (between femoral condyles):	L: _____	R: _____
Ankle Width:	L: _____	R: _____
Foot Width:	L: _____	R: _____
Foot Length:	L: _____	R: _____
Thigh Length (troch. to lat'l tibial plateau):	L: _____	R: _____
Calf Length (lat'l tibial plateau to lat'l mall.):	L: _____	R: _____
Ankle Height:	L: _____	R: _____
Calf Circumference (largest pt.):	L: _____	R: _____
Thigh Circumference (mid-thigh):	L: _____	R: _____
Waist Height:	_____	
Weight loaded for pull device:		

Drop distance for pull device:

Testing Notes:

EMG Check: _____

Sway (30 seconds @ 1000Hz EMG/FP, 100Hz Opto)
Need 3 EO and 3EC perfect trials
*Most important data- force plates and EMG

Trial	Video File Name	Labview File Name	Optotrak File Name	Trial Notes
FPzero				
Sway1				
Sway2				
Sway3				
Sway4				
Sway5				
Sway6				

Balance Recovery (5 seconds @1000 Hz EMG/FP, 100Hz Opto)
Need 3 perfect trials
*Most important data- force plates, EMG (TA), markers (up to knee, both sides), load cell channels, video

Trial	Video File Name	Labview File Name	Optotrak File Name	Trial Notes
FPzero				
Static Trial				
Pull1				
Pull2				
Pull3				

Gait Initiation (5 seconds @1000 Hz EMG/FP, 100Hz Opto)

Most important data: force plates, gait initiation light, EMG (all), markers (all). Watch for a clean force plate strike on fp3 for the first step. If it is not a clean strike, the trial is not good.

Need 5 perfect trials

Trial	Video File Name	Labview File Name	Optotrak File Name	Trial Notes
FPzero				
Static Trial				
Gait_ini1				
Gait_ini2				
Gait_ini3				
Gait_ini4				
Gait_ini5				

Gait (100 Hz Opto only)

Most important data: Markers (all)- this is all we have for gait.

Trial	Video File Name	Labview File Name	Optotrak File Name	Trial Notes
Static Trial		n/a		
Gait		n/a		