University of Memphis
University of Memphis Digital Commons

Electronic Theses and Dissertations

5-23-2019

The effects of simulated parkinsonian rigidity on energy expenditure during gait

Sarah Elizabeth Blackmore

Follow this and additional works at: https://digitalcommons.memphis.edu/etd

Recommended Citation
Blackmore, Sarah Elizabeth, "The effects of simulated parkinsonian rigidity on energy expenditure during gait" (2019). *Electronic Theses and Dissertations*. 2017.
https://digitalcommons.memphis.edu/etd/2017

This Thesis is brought to you for free and open access by University of Memphis Digital Commons. It has been accepted for inclusion in Electronic Theses and Dissertations by an authorized administrator of University of Memphis Digital Commons. For more information, please contact khggerty@memphis.edu.

THE EFFECTS OF SIMULATED PARKINSONIAN RIGIDITY ON ENERGY EXPENDITURE DURING GAIT

by

Sarah Blackmore

A Thesis

Submitted in Partial Fulfillment of the

Requirements for the Degree of

Masters of Science

Major: Health Studies

The University of Memphis

May 2019

Abstract

Rigidity is a symptom of Parkinson's disease (PD) that is caused by neural and intrinsic mechanisms. Individuals with PD show increased rates of energy expenditure during walking and it is speculated that intrinsic rigidity is contributing. **Purpose**: Evaluate the effects of intrinsic rigidity on the metabolic cost of walking. **Methods**: 10 experimental subjects were used to create muscle-driven simulations of walking. During the simulations, intrinsic rigidity was increased in the model's lower extremity musculature. Whole-body metabolic power was calculated in each state of increased intrinsic rigidity. **Results**: There were no significant differences (p=.448) in simulated metabolic power between states of intrinsic rigidity. **Conclusion**: It is speculated that the simulated musculotendon system adapted to a more optimal fiber length after alterations to intrinsic rigidity resulting in more efficient movement and that the simulated alterations were not large enough to change systemic energy expenditure at this particular walking speed.

Table of contents

Chapter I: Introduction ……1-4

Chapter II: Literature review…….……5-22

Chapter III: Manuscript……..…...23-46

Introduction……..…….26-27

Methodology……...……...27-31

Results……..…….…….31-32

Discussion…….……32-36

References…….……37-44

Tables and figures…….…….……45-46

Appendices……..……..…47-60

Appendix A: IRB sections…….47-56

Appendix B: Informed consent……..……..….57-60

Chapter I: Introduction

In biological systems, mechanical efficiency is pertinent to minimizing the physiological cost of movement. Efficiency of movement can be gauged by mechanical work which is often considered the external work done by the body on its environment. During human locomotion, most of the mechanical work done is lost in the form of heat (69). Locomotor strategies geared towards efficiency are key in sustaining steady state, progressive movement at minimal cost. During level walking, there is a net positive work being performed by lower extremity muscles (26). During human locomotion, positive work is need to compensate for the energy lost during the cycle (26). This strategy minimizes the energy lost during walking and allows for more efficient movement in positive work production.

Tendinous tissues are primarily composed of collagen but, they also possess a few elastic fibers that allow for tissues to return to its original shape after being stretched. During locomotion, the Achilles tendon undergoes a considerable amount of strain during the early stages of gait due to the stretch of the tendon. The parallel and series elastic components of the triceps surae complex allows the tendon to return to its original length after being stretched. As the gait cycle continues, the stored mechanical energy from the stretched tendon is used to help propel the body forward. As a result, tendon compliance has a large influence on whole-body metabolic power production (120). In tendons, there is an optimal range of stiffness needed to maximize contraction efficiency and reduce the metabolic cost for walking (60, 61). Tendon stiffness is dependent upon its viscoelastic properties and in certain populations, such as rigid or spastic patients, the elasticity of lower extremity musculotendon units are altered (35). It has been shown that mechanical efficiency during gait tends to be significantly decreased in these

populations resulting in increased metabolic cost of walking (76, 90). Within the diseased population, one of the primary pathologically rigid cohorts lie in individuals with Parkinson's disease.

Parkinson's disease (PD) is a progressive neurodegenerative disease that is characterized by rigidity, dyskinesia and fatigue. Rigidity is a cardinal symptom of PD and is defined as an increased resistance to passive movements and is caused by a heightened stretch reflex and altered mechanical properties of connective tissues (8, 32, 80, 99, 111, 119). The neural portion of parkinsonian rigidity is well studied and is primarily treated with dopaminergic interventions. But the proposed soft tissue changes contributing to overall rigidity and this area less analyzed in literature. Through modeling approaches, it has been demonstrated that there are intrinsic contributions to PD rigidity but, it isn't known specifically how these changes are manifested (119). It is hypothesized that the intrinsic changes to these tissues are a result of stiffer musculotendon units that in turn contribute to passive resistance (8, 11 80, 99, 119). When considering the definition of PD rigidity and the analyses from these studies, non-neural contributions to rigidity are only present during passive, 2 degrees of freedom movements. A large amount of the literature supporting the non-neural contributions have only been observed in passive, single joint movements. Little is known about how the non-neural contribution to rigidity influence active movements or even more complex movements such as walking.

As previously mentioned, changes in musculotendon stiffness can have systemic influence on the body by increasing metabolic demand for walking (60, 61). Knowing this influence of musculotendon tissue composition on larger scaled movements, it could be speculated that individuals with PD are experiencing similar mechanisms when performing walking tasks based on their increased level of energy expenditure during walking and the

known presence of intrinsic rigidity within the disease (8, 21, 80, 99, 119). This stiffness-metabolic interaction seems more feasible based on a few of the symptoms reported in PD. With increasing disease severity, rigidity becomes more pronounced and walking economy continues to worsen (21, 52). Furthermore, it has been shown that basal metabolic rate is raised in individuals with PD and that this increased rate is further augmented and positively correlated with both mild and severe rigidity (65). Along with the metabolic findings, individuals with PD report fatigue as a prevalent symptom. Fatigue is common symptom of PD that is thought to originate from increased energy expenditure during rest and activities of daily living (8, 31). It could be speculated that fatigue is being mediated by metabolic mechanisms and augmented by mechanical resistance to passive movements caused by intrinsic rigidity.

The non-neural aspect of parkinsonian rigidity could be facilitating systematic changes that influence metabolic cost during everyday tasks like walking. More research is needed to help clarify the effects of intrinsic rigidity on PD patients during active tasks like walking. Musculoskeletal modelling has become a useful tool for evaluating pathological gait in several different populations (24, 34, 103). Conducting these simulations would allow for preliminary exploration of these proposed ideas without needing to expend resources on bringing actual patients in for experimentation. Most research investigating the influence of tendon compliance on metabolic cost and the presence of non-neural components to PD rigidity have been achieved through similar modeling approaches (61,62,119). Modelling software has advanced since these studies and now allows for gross level musculoskeletal analyses coupled with estimates of total energy and localized muscle energy expenditure. Walking simulations with musculoskeletal models that have the proposed musculotendon properties that resemble PD intrinsic stiffness can now be used to provide specific insight into how the soft tissues may be changing without using

invasive procedures such as buckle transducers to measure tendon stress and strain. The results of these simulations can be corroborated by measured data through comparisons of simulated and measured energy expenditure. In PD, energy expenditure during gait as well as rigidity progresses with disease severity and it could be plausible that changes in intrinsic stiffness are contributing to this trend. Therefore, the purpose of this study is to investigate the effects of intrinsic parkinsonian rigidity on energy expenditure during walking. We hypothesize that with increasing amounts of simulated rigidity, there will be a subsequent increase in total muscle energy expenditure during walking.

Specific aims:

Aim #1: To analyze the effects of simulated parkinsonian intrinsic rigidity on metabolic cost during muscle-driven simulations of walking.

Aim #2: To validate the modeling software's estimates of metabolic power to experimentally collected metabolic data

Chapter II: Literature Review

Background

Parkinson's disease (PD) is the second most common neurodegenerative disease afflicting over 1 million U.S. adults (9). The overall prevalence in the U.S. is small at 0.3% but, rates significantly increase to 1-2% in persons over the age of 65 and 4-5% for people of 85 (112). PD was first described in 1817 by James Parkinson who initially characterized the disease as "involuntary tremulous motions with a propensity to bend the trunk forward" (81). The typical age of onset is 60 years but, onset can begin as early as 21 meaning that both elderly adult and middle-age adult groups can be at risk (112). Individuals with PD encounter several functional limitations that have negative effects on quality of life. Decrements in health-related quality of life (HRQOL) have been documented with increasing disease severity and have even been shown to be lower in PD patients than in people with diabetes, heart failure or stroke (44). Though PD is not considered a fatal disease, signs and symptoms slowly worsen over time and can lead to severe disability and increased reliance on efficient healthcare. It is estimated that the annual direct costs of PD care in the United States can range from $2,000 to $15,000 per patient (53, 112). The number of cases of PD are expected to increase in years to come and more efficient means of care will be required to compensate.

Etiology

PD is pathologically characterized by a loss of dopamine producing neurons in the substantia nigra pars and the presence of aggregated proteins (Lewy bodies) in the surviving neurons (32). PD has either an idiopathic or familial origin with majority of cases being idiopathic. The pathology behind idiopathic PD is largely unknown but, it has been suggested

that exposure to certain risk factors increase an individual's chances of developing PD. The only proven risk factor for PD is advancing age but, environmental risk factors like exposure to rural living, pesticides, herbicides and well-water drinking increase the likelihood of disease onset (10). Unlike idiopathic PD, genetic PD originates from either autosomal dominant or recessive inheritance. There are 18 chromosomal regions (termed PARK) that have been found to be associated with PD onset but, research involving mutations in these areas are considered to be unreliable. PD-related mutations are said to affect a number of molecular processes but have predominately been found to occur in genes that encode proteins like alpha-synuclein and ligases like parkin (9). These genetic mutations are thought to forebode the pathology underlying PD.

The exact cause of the neuronal degeneration in PD is largely unknown but, it is suggested to be a result of several specific cellular and molecular changes. Oxidative stress, inflammation, the accumulation of misfolded proteins and mitochondrial dysfunction have all been linked to the degeneration of dopaminergic neurons (66). These physiological changes are thought to arise from genetic mutations as well as exposure to previously mentioned environmental factors. Protein aggregation plays a key role in neuronal death associated with familial and sporadic PD (20, 50, 67, 112). Lewy bodies are a hallmark pathology found in the brains of parkinsonian patients and are composed of a wide range of proteins. The aggregations are mostly composed of misfolded alpha-synuclein proteins commonly found on the tips of neurons in the brain (67). The aggregation of proteins has not been established as either a neuronal death agonist or a cytoprotective mechanism to preserve remaining neurons but, it is a defining characteristic of Parkinson's disease (67, 85).

Pathology of signs and symptoms

Parkinsonism is characterized by motor dysfunction consisting of symptoms like tremor at rest, rigidity, bradykinesia, postural instability and the freezing of gait (32). These motor symptoms are characteristic of extrapyramidal disorders where abnormal basal ganglia function is the primary cause. The basal ganglia is composed of the substantia nigra pars (reticulum and compacta), subthalamic nucleus (STN), globus pallidus and striatum (comprising the caudate nucleus and putamen respectively). These areas are major contributors to the extrapyramidal motor system and make several synapses with lower motor neurons in order to create appropriate motor responses. Individuals with PD are particularly plagued with dysfunction in the substantia nigra pars compacta (SNc) of the basal ganglia. The SNc is composed of around 220,000 dopaminergic neurons and when over 50% of those neurons are lost, patients start to develop motor dysfunctions like tremor, bradykinesia, postural and gait instabilities associated with PD (32). The neural circuitry of the basal ganglia originates in the striatum, which receives excitatory afferents from the cortex and thalamus. Most cells in the striatum are GABAergic (inhibits neuronal activity) and are characterized by their high spine density and low firing rates that allow for a high degree of neuronal plasticity (54). Individuals with PD have abnormal neural communication in the nigrostriatal pathway that connects the SNc with the dorsal striatum. The progressive loss of dopaminergic neurons in this pathway causes an imbalance of the direct and indirect pathways of movement. The direct and indirect pathways of the basal ganglia function to process external information in an attempt to control movement (113). Research has suggested that the corticostriatal networks that project to these pathways function to control actions that are goal-oriented, sensitive to rewarding feedback, and relatively automatic or habitual by nature (6). These movement pathways work in opposing ways and

involve the motor cortex, basal ganglia and thalamus. The direct pathway originates from the striatonigral neurons that receive excitatory afferents from the sensorimotor cortex and thalamus (23). The direct pathway facilitates disinhibition of the thalamus which leads to increased excitation of the motor areas in the cortex that drives the ability to select appropriate movement patterns. The indirect pathway originates from the striatopallidal neurons and form inhibitory synapses on GABAergic pallidal neurons. The net outcome of the indirect pathway is an inhibition of the thalamocortical neurons which reduces cortical premotor drive and inhibits unwanted movement. Individuals with PD have a reduced capacity to activate dopamine receptors which in turn leads to reduced inhibition of the indirect pathway and decreased excitation of the direct pathway (32, 54, 75). Previous literature has suggested that the imbalances in these pathways are responsible for the difficulty in initiating movements and bradykinesia associated with PD (32, 40).

Rigidity

Rigidity is a cardinal symptom of PD and can be defined as an increase in resistance to passive movements. In individuals with PD, rigidity is considered a continuous increase in muscle tone throughout the entire range of a passive motion (94). Rigidity in PD has been shown to be caused by an enhanced tonic stretch reflex (8, 57). The myotatic reflex (i.e. stretch reflex) is a muscle contraction in response to stretching of the same muscle. Muscle spindles serve as sensory receptors within muscles are the primary facilitators of this reflex. Spindles are often labeled as proprioceptive receptors and are composed of 8-10 intrafusal fibers that are arranged in parallel with extrafusal fibers within the muscle. When intrafusal fibers are stretch (in conjunction with muscle fibers), afferent signals are directed to monosynaptic excitatory

receptors on the alpha motoneurons in the ventral horn of the spinal cord. These alpha motoneurons innervate the homologous and antagonistic muscle and activation of the neurons results in a brief contraction in the stretched muscle as well as relaxation in the antagonistic muscle. The stretch reflex ultimately serves as a protective mechanism and can be quantified by electromyographical (EMG) activity when a muscle is rapidly stretched. The stretch reflex in the form of EMG activity can be broken down into two components: an initial short response, representing the spinal monosynaptic activity, and the long latency response, suggested to have supraspinal origin (8, 59). In parkinsonian rigidity, the long latency aspect of the stretch reflex is impaired. As a result, PD individuals have heightened long latency EMG magnitudes during passive stretching when compared to age matched controls (8). But, it should be noted that PD individuals have normal short latency EMG magnitudes suggesting that the source of issue is at the supraspinal level given that long latency reflex is impaired and commonly thought to be influenced by cortical activity. It should also be noted that patients with PD experience high amounts of EMG activity during passive shortening of the muscle as well (5, 118). This "shortening reaction" can be described as brief EMG activity that occurs when a muscle is passively shortened through a range of motion (8, 92, 117). The overexaggerated long latency reflex and shortening reaction are occurring during flexion and extension of a limb and it is suggested that they significantly contribute to the neural aspect of parkinsonian rigidity and cause an increase resistance to passive movement (5, 87). Reflex magnitudes are also influenced by the velocity and amplitude of the movement where the faster and larger motions create increasing levels of rigidity thus contributing even more to resistive movements (87, 102, 118). This is reportedly due to increased activation of muscle spindles and subsequent monosynaptic pathways.

Another suggested contribution to parkinsonian rigidity may be in the form of neuronal inhibition at the spinal cord level (91). As mentioned earlier, muscle spindles elicit both excitatory and inhibitory responses to the homologous and antagonist muscles respectively. The inhibitory drive to the antagonist muscle can be referred to as reciprocal inhibition. But, there is another inhibitory mechanism at the spinal cord level called recurrent inhibition. Recurrent inhibition is centered around Renshaw cells that are located near the alpha motoneurons in the spinal cord. When the alpha motoneurons are activated (in response to muscle spindles), Renshaw cells are also excited and initiate an inhibitory drive to the same activated muscle via Ib afferents. Ib afferent fibers originate in the Golgi tendon organs (GTOs) and they respond to tension in muscle tendons. Activation of this inhibitory pathway results in a diminished efferent drive being delivered to the active muscle. This seems contradictive but, it is a mechanism for finer motor control because it allows for more precise activation and deactivation of certain muscle fibers involved in a movement. In people with PD, it has been suggested that there is a decreased inhibitory drive during both reciprocal and recurrent inhibition in these individuals (25, 68). These differences are mostly seen during voluntary movement as compared to at rest. This suggests that parkinsonian rigidity may in part be due to diminished inhibition at both the supraspinal as well as spinal cord level.

Though most sources of rigidity are attributed to neuronal hyper excitability, there is literature suggesting that there are also changes in the soft tissue adds to an increased amount of resistance during passive movement (8, 70, 99, 100, 110, 121). Some authors have defined this non-neural contribution to be the mechanical resistance of the muscle or joint to external perturbations. The increased resistance during passive movements could be due to an increase in stiffness of the tendons, joints or muscles. Though most of the research around soft tissue

alterations is based on stiffness and spasticity in diseased populations, there is a growing amount of literature suggesting there are non-neural contributions to parkinsonian rigidity as well (110, 119). PD has previously been associated with skeletal muscle alterations with changes in mitochondrial function, type I fiber variability and muscle size (30, 93, 97). Changes in the fiber characteristics could significantly contribute to increased intrinsic rigidity and more research is needed to clarify.

Biomechanics of movement

Gait/Bradykinesia

The basal ganglia is thought to play an important role in regulating motor programs and in the execution of movements involved with gait. PD gait is a product of basal ganglia induced motor dysfunction and it can be described as a slow shuffled movement. The abnormal gait pattern in PD is partially attributed to the decreased inhibitory drive in the dopamine pathway (71). The progressive loss of dopaminergic neurons creates a reduced inhibitory drive from the striatonigral pathways to the internal globus pallidus (GPi) which leads to increased drive to the premotor cortex and supplementary motor area (SMA) (32, 112). It has long been speculated that neuronal activity from the GPi is critical in modulating activity in the SMA to select the appropriate preparatory movement for an action (23). These motor plans are thought to be combinations of movements assembled together with a predetermined timing and amplitude. As a result of overactivity in the SMA, it is speculated that individuals with PD suffer from reduced amplitude of movements with no loss in an ability to complete the activity. This is shown when PD individuals are tasked with walking faster. PD patients walk slower than age matched

controls but, when tasked with faster walking speeds, it has been reported that PD individuals can indeed manipulate the rate at which they step but fail to consistently modulate the length of each stride (71). Normally, when tasked with faster walking, individuals first increase stride length with a subsequent increase in cadence. At a certain point, stride length peaks and the increase in velocity is reliant on increased cadence. Persons with PD retain this strategy when tasked with increasing gait speed but, the stride length is significantly smaller compared to their age matched counterparts. This again suggests that the overall motor strategy remains intact in PD but, the neural drive is too low to sustain movement amplitude (7, 59).

Gait is the fundamental means by which humans move from one point to another. Bipedal walking has often been compared to an inverted pendulum where trunk displacement is the primary force driving forward acceleration of the body (84, 116). Forward acceleration is achieved through manipulation of the center of mass (COM) relative to the center of pressure (COP). There are two phases of gait that include a stance and a swing period. The stance phase is characterized by one or both limbs being planted on the ground whereas swing phase is the period where one limb is being pulled through and not touching the ground. During a normal gait cycle, there are two periods of single support (40%) and two short periods of double-support (60%) in the stance phase (116). Disturbance of this gait cycle is a defining feature of Parkinson's disease and is often used for diagnosis.

Characteristics of parkinsonian gait include reduced gait velocity, reduced stride length, increased time in stride with a particular increase in the amount of time in double stance when compared to age matched controls (7, 11, 14, 78). Reduced gait speed and stride length both contribute to the slow shuffled walk associated with PD and may be a compensatory mechanism for a fear of falling (2). The mechanical cause of this Parkinsonian gait can be attributed to

altered lower extremity joint kinetics and kinematics. Patients with PD are documented to have decreased peak moments and powers in the hip, knee and ankle joints during gait when compared to healthy older adults (33, 72, 101). Patients also have a reduced range of motion in the lower extremity joints in all planes of motion during walking (72). It is theorized that the lack of range and power in the lower extremity joints is responsible for the reduced movement amplitude during walking. Advanced stage PD is associated with more severe gait disturbances that can't be sufficiently controlled with contemporary treatments. In the more advanced stages, gait dysfunction can present itself in the form of freezing of gait (FOG). This phenomenon is described as an abrupt difficulty in starting or continuing a rhythmic movement and is frequently associated with falls and injuries (12, 37, 40). The underlying mechanism is unknown but it has been shown that each case of FOG is unique to the individual in that different stimuli can initiate the phenomena (74).

Another source of instability in gait can be found in the coordination and symmetry of the movements needed to ambulate. Literature suggests that PD patients have a limited ability to switch between coordinative strategies in response to external stimuli (47, 89). Coordination patterns during gait are based on the relative interaction between arm and leg movements and pelvis and thoracic rotations (107, 109). These segmental patterns are chosen based on the nature of the external stimuli, such as walking speed, and an accurate selection and execution of these patterns is critical to stable walking. Individuals with PD are shown to have relatively inflexible coordination during walking which infers less adaptability to when walking (46, 107). Patients with PD not only have limited coordination during walking but, they also display increased variability during gait. An optimal amount of gait variability is necessary for adapting to external and internal environmental disturbances. Individuals with PD have increased stride-to-stride

fluctuations during walking that continually increases with disease severity (7, 11, 14, 42, 44). Gait variability can be described as unsteadiness or inconsistency of stepping and has been associated with risk of falls in elderly adults (41). The increased gait variability in PD suggests that there is a diminished amount of motor control during locomotion that can increase the risk of falling.

Increased gait variability is associated with asymmetry during locomotion in PD and is speculated that there is a cause effect interaction between the two variables (7). Asymmetrical motor strategies can be described as improper timing and size of movements on each side of the body throughout the gait cycle. In individuals with PD, leg swing, arm swing and weight bearing during stance have been found to be a site of asymmetry during gait (7, 58, 74). The deficits in coordination and symmetry further complicates ambulation in this population leaving them more prone to instability.

Energy expenditure and gait

The law of conservation of energy requires that metabolic energy be consumed whenever muscular work is performed. In order to actively move, humans expend varying amounts of Calories to achieve the desired motion. It has long been accepted that movement strategies are selected based on the metabolic cost of the action (3, 19, 69). Efficient movement strategies minimize the energy expended while sustaining the necessary mechanics to complete the task. These strategies are maintained through physiological and mechanical interactions in the human body. Breathing is a great example to highlight how strategies are chosen to preserve energy. Humans select a resting breathing frequency in a manner that utilizes the ability of the alveoli to

store elastic energy that can be used to relieve some of the mechanical demands of breathing at higher frequencies (79). Humans are inherently minimizing the work necessary from the intercostal muscles and diaphragm while still maintaining the necessary oxygen intake for a functional respiratory system. Humans instinctively select the more efficient physiological mechanism that results in a lessened mechanical demand. Movement efficiency is particularly important during continuous motions in that a low metabolic demand is necessary to sustain movement for extended periods of time. Human locomotion requires the progressive advancement of the body through space and is sustained by the continuous displacement of the center of mass (COM) (84, 116). COM is vertically displaced throughout the gait cycle in order to progressively move the body forward. During single leg stance, COM is upwardly displaced causing the body to fall forward. As we approach double support, COM begins to fall. When at heel strike, COM is abruptly raised again signaling the start of the gait cycle. Because of the manner at which COM is displaced, human gait is often described as an inverted pendulum with the stance foot being the axis of rotation and the lower limb acting as the ball and chain. Theoretically in this inverted pendulum design, if movement is not impeded, the continuous motion of the lower extremity will be sustained with little to no net mechanical work being required (49, 55, 110). But, in all actuality, this pendulum design is not the most efficient means of progression (36). Though it is true that energy is conserved during the single support phase of stance, work is required to redirect COM when transition to double support (36). The work needed to redirect the COM using the pendulum model alone would be fourth of a power of step length (36). But, from previous studies we know that the net mechanical work performed during the gait cycle is zero meaning, there must be other energy conserving mechanisms in place.

Muscles are composed of contractile and elastic components. The elastic components of lower extremity musculotendon units (MTUs) have been suggested to significantly contribute to energy conservation during gait (36, 49). The ability of the muscles to store energy without actively performing work is most beneficial to energy conservation (4). During gait, the Achilles tendon (AT) goes through a continuous cycle of stretch and recoil. This is advantageous during gait because the tendon recoil is used to increase power production at the ankle during push off (115). During the stance phase of gait, elastic energy is stored in the AT via stretching of the tendon. The tendon stretch is sustained through both the isometric force produced by the fascicles and the transition of the shank over the ankle causing increased dorsiflexion and subsequent tendon stretch. In this way, potential energy is stored from the tendon and can be utilize to aid in power production at the ankle during push off. The elastic recoil of the tendon allows for a minimum amount of muscle work to be done because activation thresholds are lowered for the muscles due to the lessened need for shortening (38, 60).

The amount of elastic recoil created during walking is influenced by the compliance of the tendon. Compliance can be defined as the elastic deformation of the tendon in response to an applied force initiated by muscle action. Elasticity can be quantified through the relationship between stress and strain of a material. Stress being the force applied to the tendon and strain being the amount of deformation the tendon undergoes after being pulled. Tendon material is relatively consistent between people but, the structure of musculotendon units can influence compliance. Because elastic recoil is an important feature of MTU stiffness, tendon compliance becomes a key contributor to energy expenditure. There is an ideal amount of tendon stiffness associated with optimum energy expenditure during gait (60, 77)

Fatigue

Fatigue is a highly regarded non-motor symptom of PD that impacts daily life. Fatigue is frequently reported in PD and is known to be an important factor for increased distress (44). Disabling fatigue has been reported to occur in 32% of PD cases and has even been reported to predate motor symptoms (83). It should be noted here that individuals with PD experience fatigue and fatiguability. Fatigue is the self-reported sensation that is highly variable depending on the individual. Fatiguability is the relationship between the self-reported fatigue and the level of activity by which the fatigue is associated (31). Fatiguability can be represented in the form of energy expenditure during a given task. It has been shown that resting energy expenditure is higher in PD patients and progressively increases with disease severity (16). Walking economy in PD patients has historically been higher than age matched controls at preferred and faster walking speeds (21, 62). During these walking trials, PD patients consumed 6-10% more oxygen than healthy controls when walking at the same speeds suggesting that patients have higher fatiguability. The source of fatigue in PD is not specifically known but research has suggested that it could be centrally or mechanically driven (82).

Simulation modeling

The modeling approach allows for the creation and analysis of a digital model to predict its performance in the real world. More specifically, computational human models provide a base for mechanical, physiological and energetic analyses. Simulated human models are advantageous because they allow for the quantification of variables that otherwise would be difficult to experimentally measure like bone contact forces, neuromuscular control strategies, etc. (24).

Musculoskeletal models also allow for the manipulation of experimentally collected data and the predicative adjustments made as a result of the new model. For these reasons, simulation modeling has been a useful tool in simulating gait disturbances and motor impairment in various populations while being able to quantify the direct outcomes of modifying these features (34, 39, 73, 95). Within this diverse group of models, multiple parkinsonian models have been created for analysis. For example, modeling software has been used to simulate parkinsonian gait (increased step length variability, reduced stride length, etc.) and abnormal neurotransmitter release in the basal nuclei (modified gain to simulate various neurotransmitter release) in a means to improve early diagnostic protocols as well highlight the importance of door size on freezing of gait (34, 39). These models were able to highlight different variables of interest that were of a direct result of simulated events like walking or abnormal neural processing.

Musculoskeletal modeling can be completed through a number of different software. OpenSim (Simbios 2004) is an open source software with relative popularity in the scientific community. This simulation software boasts a total of 1,947 journal article citations (as of 2018) in academic fields like biomedical engineering, biophysics, computational biology, physiology and biology (96). OpenSim offers a number of different standard musculoskeletal models that can be scaled to experimental data. The standard model used in this study, termed the *gait2392* model, is a three-dimensional, 23-degree-of-freedom computer model of the human musculoskeletal system. This musculoskeletal model features 92 actuators (i.e. muscles and tendons) in the lower extremity and torso which are representative of 76 muscles.

The gait2392 model is further defined by a muscle model termed the *Thelen2003Muscle* model. Muscle models are created in order to simulate an output that is representative of what the real muscle would do under similar circumstances. For this reason, muscle models consist of

actuators with a wide range of distinct architectures and excitation characteristics. The actuators (i.e. muscles) created in the model use an algorithm that transforms muscle activations (i.e. neural excitation) into muscle forces with respect to the specific characteristics of each muscle. The *Thelen2003Muscle* model used in OpenSim is based on the standard Hill-type muscle model. In the standard Hill-type model, the musculotendon complex consists of three components: contractile component, parallel component and the series component that all represent the contractile and elastic attributes of mammalian muscles. The muscle forces generated by these actuators are determined by: activation value, normalized muscle unit length and the normalized velocity of the muscle unit. And finally, the muscles themselves are characterized by: maximum isometric force, tendon slack length, maximum contraction velocity and pennation angle.

In OpenSim, additional analyses can be run during dynamic simulations in the form of probes. OpenSim probes perform vector measurements on a model during a simulation and provide results such as internal power of a joint, joint contact forces, etc. In regards to physiological analyses, OpenSim offers a number of different metabolic probes that estimate muscle metabolic power during simulations. Recording muscular tissue temperature during contractions is a well-known procedure that provides insight into muscle energy expenditure during various types of contractions (1,13, 45). Muscle energetic models are developed from these thermodynamic principles and are used to estimate metabolic power during simulations. The *Umberger2010MuscleMetabolics* probe used in OpenSim 3.3 provides an estimation of metabolic power per kilogram of muscle during dynamic simulations of movement. The Umberger probe defines total rate of muscle energy expenditure (W kg^{-1}) as the sum of

activation heat rate ($\dot{h}_A$), maintenance heat rate ($\dot{h}_M$), shortening/lengthening heat rate ($\dot{h}_{SL}$) and the mechanical work rate ($\dot{w}_{CE}$) of the contractile portion of the actuators (Equation 1) (105).

$$\dot{E} = \dot{h}_A + \dot{h}_M + \dot{h}_{SL} + \dot{w}_{CE}. \quad (1)$$

Activation heat can be defined as the metabolic cost needed to transport calcium across the sarcoplasmic reticulum membrane, bind the ions to the myofilament binding sites and reuptake the ions back to the sarcoplasmic reticulum (1, 45, 105). This energy is an important part of muscle metabolic estimations because it is energy expenditure not associated with the contractile elements during a contraction. Activation heat rate is highest at initial muscle activation and steadily decreases as the contraction continues (1). Heat maintenance rate is considered the rate at which heat is being released during a sustained contraction and is thought to primarily arise from actomyosin interactions (45). It is commonly accepted that heat maintenance rate is a product of the summed effects of heat activation that arises from successive stimulus. Due to this interaction, the *Umberger2010MuscleMetabolics* probe combines both the heat activation and maintenance rate into one variable ($\dot{h}_{AM}$) with 40% of the combined variable being attributed to the activation rate and 60% to maintenance rate (105). The combined heat activation and maintenance rate is calculated as follows:

$$\dot{h}_{AM} = 1.28 \times \%FT + 25 \quad (2)$$

%FT is the percent of fast twitch fibers in the muscle and if a muscle were 100% FT, it would have a heat rate of 153 W kg^{-1} and if it were 100% slow twitch muscle fibers it would have a value of 25 W kg^{-1}.

The *Umberger2010MuscleMetabolics* probe also provides an estimation for shortening and lengthening heat rate to contribute to a more robust estimation of muscle metabolic power.

Shortening heat is considered the energy released as soon as a muscle shortens. It differs from activation heat in that it remains constant through the shortening phase of contraction and is therefore considered a part of the actomyosin interaction. Shortening heat is influenced by muscle length and becomes an important part of muscle metabolic calculations when considering the threshold of the contraction as well as the muscle fibers that are predominate in the muscle. Within the OpenSim metabolic probe, the percent of slow twitch fibers in each muscle actuator were estimated based on Johnson et al. 1973 (51). Shortening heat rate is typically suppressed during submaximal contractions when compared to maximal contractions and the rate at which the heat is dispersed is noticeably greater in fast twitch muscle fibers compared to slow twitch fibers (13,15). In the Umberger probe, shortening heat coefficients for fast and slow twitch fibers are defined as follows:

$$\alpha_{S(ST)} = \frac{4 \times 25}{\tilde{V}_{CE(MAX-ST)}} \qquad \alpha_{S(FT)} = \frac{1 \times 153}{\tilde{V}_{CE(MAX-FT)}} \tag{3}$$

$V_{CE\ (MAX\text{-}FT)}$, representing maximum contraction velocity in fast twitch fibers, is assumed to be 2.5 times greater than $V_{CE\ (MAX\text{-}ST)}$, or maximum contraction velocity in slow twitch fibers. The total shortening rate is then calculated as:

$$\begin{aligned} \dot{h}_{SL} = & -\alpha_{S(ST)}\tilde{V}_{CE}(1 - \%FT/100) \\ & - \alpha_{S(FT)}\tilde{V}_{CE}(\%FT/100), \end{aligned} \tag{4}$$

for values of $V_{CE} \leq 0$. At the time of probe development, little information was available on how to quantify lengthening heat rate so, it was assumed that lengthening heat rate could be represented as a product of a coefficient and contraction velocity with a slope somewhat greater than the shortening rate. This algorithm was tested and showed good agreement with experimentally collected data. So, the value used for lengthening heat coefficient is defined as:

$$\alpha_L = 4\,\alpha_{S(ST)} \tag{5}$$

And lengthening heat rate is given by:

$$\dot{h}_{SL} = \alpha_L\,\tilde{V}_{CE} \tag{6}$$

Mass specific mechanical work rate ($\dot{w}_{CE}$) in the Umberger probe is defined as:

$$\dot{w}_{CE} = -\frac{F_{CE}\,V_{CE}}{m} \tag{7}$$

where m is the mass of the muscle being considered. This version of work rate does not account for the mechanical work of the entire musculotendon unit but instead accounts for the work rate of the contractile elements.

Chapter III: Manuscript

Title: The effects of simulated parkinsonian rigidity on energy expenditure during gait

Article type: Full length article

Keywords: Parkinsonian rigidity; non-neural rigidity; tendon compliance; energy expenditure; gait

Corresponding author: Sarah E Blackmore, MS

Corresponding author's institution: University of Memphis

First author: Sarah E Blackmore, MS

Order of authors: Sarah E Blackmore, MS; Douglas W Powell, PhD, Melissa J Puppa, PhD, Deranda B Lester, PhD

Title: The effects of simulated parkinsonian rigidity on energy expenditure during gait

Authors: Sarah E. Blackmore[a], Douglas W. Powell[a], Melissa J. Puppa[a], Deranda B. Lester[a]

[a] University of Memphis, Tennessee, USA

Corresponding Author:

Sarah E. Blackmore, MS

Graduate Assistant | School of health Studies

University of Memphis.Memphis, TN 38152 USA

Email: sblckmre@memphis.edu

Abstract count: 247

Word count: 3140

Tables: 1

Figures: 1

Running head: Increases in non-neural PD rigidity induce no change in simulated whole-body metabolic power

Keywords: Parkinsonian rigidity, non-neural rigidity, tendon compliance, energy expenditure, gait

Conflict of Interest: None

Financial Disclosure: None

Abstract

Rigidity is a hallmark symptom of Parkinson's disease (PD) that is caused by a hypertonic long latency stretch reflex and structural changes to musculotendon tissues. Fatigue is another commonly reported symptom in PD that seems to be mediated by increased rates of energy expenditure during movements like walking. It is speculated that fatigue and its metabolic mechanisms are being augmented by mechanical resistance to passive movements caused by intrinsic rigidity. **Purpose**: To evaluate the effects of intrinsic rigidity on the metabolic cost of steady state walking. **Methods**: We performed muscle-driven simulations in 10 experimental subjects while they were walking at 1.5 m/s. During the simulations, we gradually increased tendon strain and passive muscle strain at maximum isometric force in musculoskeletal model's lower extremity musculature to imitate the speculated intrinsic changes contributing to parkinsonian rigidity. Average whole-body metabolic power (W kg^{-1}) was calculated in each state of increased intrinsic rigidity. **Results**: When walking at 1.5 m/s, the musculoskeletal model showed no significant differences (p=.448) in whole body metabolic power with increasing states of intrinsic rigidity. **Conclusion**: These results suggest that the simulated effects of parkinsonian rigidity in this current study were not significant enough to induce systemic change in metabolic cost. This could be due to the ability of the simulated musculotendon system to adjust to a more strategy unit after the made structural changes or the fact that the simulated changes were not enough to induce significant change whole body metabolic power at this particular walking speed.

Introduction

Parkinson's disease (PD) is a common neurodegenerative disease characterized by symptoms like rigidity, bradykinesia and fatigue. Rigidity is a cardinal symptom of PD that is defined by an increased resistance to passive movements. PD rigidity arises from two sources: a heightened myotatic reflex originating from the loss of dopaminergic cells in the basal ganglia and a non-neural component suspected to be a result of intrinsic changes to soft tissue properties (32, 80, 94, 99, 119). The intrinsic contributions to parkinsonian rigidity are commonly thought to arise from decrements in the mechanical properties of the passive connective tissues (8, 80, 99, 111, 119). These decrements can be manifested in a number of ways but have been extensively explored in literature.

Tendon tissue composition is a potential area of interest when explaining the source of intrinsic contributions to parkinsonian rigidity. Tendons are unique in that they possess elastic properties that allow them to "snap back" to their original shape after being stretched. During walking, these elastic properties are utilized to help contribute to mechanical work without the need for muscle activation. Specifically, the recoil of the Achilles tendon during push off contributes positive mechanical work to the system without the need for a muscle contraction (120). There is an optimal amount of tendon compliance needed to efficiently engage this energy conserving mechanism with too little compliance or too much compliance resulting in an increased need for muscle activation and subsequently whole-body energy expenditure (106). In this regard, tendon compliance has substantial influence on whole-body metabolic demand during tasks like running and walking (120, 61, 106). Tendon compliance is dependent upon its elastic properties and in certain populations, such as rigid or spastic patients, elasticity of lower extremity musculotendon units seem to be altered (35). It has been shown that mechanical

efficiency during gait can be significantly reduced within these diseased populations leading to increased metabolic demand of walking (90). Individuals with Parkinson's disease are one of the primary pathologically rigid cohorts that could also be affected by these same disturbances in tendon compliance.

The intrinsic changes proposed to be contributing to parkinsonian rigidity could be a result of altered tendon compliance that is influencing metabolic cost during walking. More research is needed to help clarify the repercussions of intrinsic parkinsonian rigidity on the metabolic cost of gait. Musculoskeletal modeling software allows for the analysis of data that is experimentally difficult to reach like in vivo tendon compliance, muscle fiber length, muscle metabolic expenditure, etc. Using the modeling approach, tendon compliance can be manipulated in a model representing the human musculoskeletal system and the repercussions of these specific changes can be analyzed. Recent updates in biomechanical modeling software also allows for the estimation of metabolic power consumption during a wide variety of movements at both the local muscular level and the systemic whole-body level. With these resources available, insight can be gained as to how intrinsic parkinsonian rigidity may be influencing the metabolic cost of walking without the need to recruit and subject PD patients to experimental protocols. Therefore, the purpose of this study is to investigate the effects of simulated non-neural rigidity on the whole-body energetic cost of walking. We hypothesize that with increasing amounts of simulated non-neural rigidity, there will be a subsequent increase in total muscle energy expenditure during walking.

Methods

Experimental data collection

10 participants (9M, 1F) between the ages of 20 and 35 years of age were recruited for this study. Participants visited the biomechanics laboratory at the Utah Valley University in Orem, Utah for one testing period. Individuals were screened for inclusion in the study by providing written informed consent and completing a written Physical Activity Readiness Questionnaire (PAR-Q). Following screening and consent, testing occurred in the following order: (1) anthropometric measurements (measurements will include: age, sex, height and mass) (2) placement of measurement sensors (surface EMG, Velcro straps, and reflective markers) (3) completion of 15-minute treadmill walking at 1.5 m/s while simultaneously collecting energetic, metabolic and kinematic data. Kinematic data was measured using a 9-camera motion capture system (240 Hz, Qualisys AB, Goteburg, Sweden). For walking trials, retro-reflective clusters were placed bilaterally on the subject's upper and lower extremity including pelvis, trunk, both legs and feet to measure individual segment motion during the treadmill walking trials. For static trials, anatomical reflective markers were bilaterally placed on bony landmarks to provide a reference to how the dynamic clusters were moving in relation to each other. Reflective markers were placed on the medial/lateral malleoli, medial/lateral knee femoral epicondyles and on the greater trochanters and iliac crests. A pair of force platforms implemented into the treadmill were used to record ground reaction forces (GRFs; 1200 Hz, AMTI Inc., Watertown, MA, USA) during walking trials in order to help predict internal joint moments. During treadmill walking trials, a metabolic measurement system (TrueOne, ParvoMedics, Sandy, UT) was used to perform indirect calorimetry. Through these measurements, energy expenditure was quantified as the amount of oxygen consumed (VO_2) and the number of Calories (kcal/m) used during walking trials with higher values of both variables indicating increased metabolic demand.

Modeling protocol

Experimentally collected motion and force data were fed in to the OpenSim software and used to create muscle-driven simulations of walking. A standard musculoskeletal model was used to simulate 10 seconds of level ground walking at 1.5 m/s. Each standard model was scaled to subject height and weight in order to preserve mass distribution and segmental inertial properties of the experimentally collected bodies. The standard musculoskeletal model used consists of 23 degrees of freedom with 92 muscle actuators representing trunk, pelvis and lower limb musculature. The muscle actuators are driven by estimations of joint torques computed by the OpenSim Inverse Dynamics tool. The Computer Muscle Control (CMC) tool in OpenSim was used to estimate quantities for muscle activation, fiber length and fiber velocity of each muscle. Segment accelerations were estimated and subsequently used to

In order to simulate the musculoskeletal changes associated with PD, four models were formed for each experimentally collected participant: HY0, HY1, HY2 and HY3. The modifications made to these models are listed in Table 1. The HY0 model is representative of a healthy older musculoskeletal system and the HY1, HY2 and HY3 models representing individuals with Parkinson's disease with progressively increased states of rigidity attributed to the non-neural component (connective tissues). In order to simulate intrinsic rigidity, two characteristics within the model were changed: tendon strain at maximum isometric force (F_{max}) and passive muscle strain at maximal isometric force (KshapePassive). Tendon compliance of the tibialis anterior and tricep surae (soleus, gastrocnemius lateral and medial) musculotendon actuators were changed by systematically increasing tendon strain at F_{max} to simulate reduced tendon compliance (Figure 1). KshapePassive factor was also systematically decreased to

recreate passive stiffness suggested to be a result of age-related growth of noncontractile tissue in the muscle (103). Both tendon strain at Fmax and KshapePassive were progressively altered at each HY model to simulate increases in passive tissue concomitant with disease severity. Because compliance in the ankle plantarflexors has been shown to influence muscle metabolics during walking, gastrocnemius (medial and lateral) and soleus compliance were altered. Changes were also made to compliance in the primary ankle dorsiflexor (tibialis anterior) because changes in these soft tissue properties could influence the amount of elastic recoil mediated by the Achilles tendon during walking and could be altered in PD individuals.

Total metabolic power was estimated using an OpenSim metabolic probe based on Umberger's model of human muscle energy expenditure (105, 106). Whole body muscle energy expenditure (W kg^{-1}) was calculated for 2 seconds of each simulated walking trial based on estimations of thermal and mechanical energy during muscle contractions (105). Metabolic power is a measurement of rate that predicts the amount of energy, per kilogram of muscle, required to sustain mechanical work. Within the OpenSim metabolic probe, estimations of metabolic power in each muscle were calculated based on the combined mechanical and thermal energy consumption for each muscle actuator. The sum of the metabolic powers for each muscle actuator were calculated and summed to provide estimations of whole-body metabolic power.

Data Analysis

Experimentally collected kinematic and kinetic data were analyzed using Visual3D software (C-Motion, Germantown, MD, USA). The kinematic and ground reaction force (GRF) data were low pass filtered at 8Hz and 50Hz, respectively, using a zero-lag, fourth-order Butterworth filter. Kinetic and kinematic variables were interpolated if less than ten frames of

data were missing. Inverse dynamics were used to compute net internal joint hip moments and angular power. Angular moments and powers were also normalized to body mass.

In order to corroborate that experimentally collected data was similar to the OpenSim data used in the modelling analyses, inverse dynamics were run in the OpenSim software and compared to moments analyzed through Visual3D. Also, to ensure changes to intrinsic stiffness between the HY models, stress-strain curves were formed for each altered muscle in each model to corroborate differences in compliance.

Statistical Analysis

A pearson correlation analysis was run in order to observe the association between the collected metabolic data and the simulated metabolic cost for the HY0 model. A positive correlation between these two variables would suggest validity in the OpenSim measurements of metabolic cost. A repeated measures ANOVA was also used to detect any significant differences in simulated metabolic cost in each subject between the 4 HY model conditions. Finally, peak peak plantarflexor moments in Visual3D and OpenSim were analyzed using paired samples t-tests as a means to validate the inverse dynamic calculations in OpenSim.

Results

The Pearson correlation analysis run to measure the strength and direction of the relationship between average whole-body metabolic power (W kg^{-1}) in the simulated condition (HY0) and the experimentally measured VO_2 (ml/kg/min) showed a weak and negative correlation (r=-.277, p=.438) (Figure 2). These results suggest that the metabolic estimations through OpenSim did not produce similar measures to the experimentally collected rate of

energy expenditure. The paired samples t-tests revealed that there were not significant differences in peak plantarflexor moments calculated in Visual 3D and OpenSim (p=.101). The repeated measures ANOVA also showed a nonsignificant difference in average metabolic power in each subject between the four HY conditions (F (3,27) =.991, p=.4487). Though the metabolic probe provided invalid measures of metabolic power, the estimations of metabolic power between each condition in each subject should be considered reliable due to the repeated measures being performed within subject.

Discussion

The purpose of this study was to assess the influence of increasing states of intrinsic rigidity on whole-body metabolic consumption during muscle-driven simulations of walking. The statistical analysis revealed no significant differences in whole-body metabolic power between the different HY models in each subject. This suggests that altering tendon compliance via increasing tendon strain at F_{max} (maximum isometric force) coupled with increasing passive muscle strain at F_{max} had no relevant influence on systemic metabolic power consumption. The findings also showed a weak, negative association between the simulated metabolic cost in the normal musculoskeletal model to the experimentally measured metabolic cost quantified via indirect calorimetry.

Inverse dynamics is a method used in biomechanical analyses to determine measures of net forces around each joint (i.e. torques) during a given movement. Based on Newton's second law of motion, force equals the product of mass and acceleration (F = ma) and within a biomechanical setting, kinematic and kinetic data can both be used to give estimations of force

around a joint (moment) using the Newton-Euler approach. The Newton-Euler method applies rigid body equations of motion sequentially to each body segment, starting at the most distal segment. Using this approach allows for more accurate measurements of acceleration given the validity of kinetic data but, when using this approach, joint forces do not always equal the product of mass and acceleration ($F \neq ma$). This is primarily due to measurement error in the kinematic data and an incomplete musculoskeletal model of the lower extremity. To account for these inaccuracies, loads termed residual forces are needed at the final most proximal segment (i.e. the hip) to satisfy the Newton-Euler equations of motion by providing values of trunk joint forces that are not readily available from the given kinematic data. These residual forces are needed to correct the dynamic equations but, these forces are not a result of any contact with the external environment and can become too large to be reasonably true. When these forces are too large, joint forces are inaccurately estimated. OpenSim provides a tool to reduce the residual forces that may be too large. Within this experiment, the Reduce Residual Analysis (RRA) tool was not implemented before using the Computed Muscle Control (CMC) tool. This means that the potential inaccuracies in the kinematic data were not addressed and could have subsequently provided inappropriate estimations of joint moments that drive the estimates of muscle activation. Inappropriate muscle activations would result in inaccurate predictions of muscle metabolic power that could have potentially skewed the current results. But, it should be noted that post hoc analyses revealed that majority of the residual forces were small in nature and theoretically should not have a huge effect on the accuracy of muscle activation. But, measures were not taken to ensure all the residual forces were minimized and could potentially be providing inaccurate estimation of muscle activations that directly influence the estimates for muscle metabolic power.

A study similar to the current one was conducted by Uchida et al. (2016) and the results from this study were similar results to those found in this experiment (106). Using the same software, experimenters both increased and decreased tendon compliance (1-10% at F_{max}) during simulations of running at 2 m/s and used a similar metabolic probe to estimate whole-body metabolic power. When adjusting tendon compliance between 3-6% strain at F_{max}, no significant differences were found in whole body metabolic power consumption when running at 2 m/s but did find significance running at faster rates (3 and 5 m/s) (106). Based on previous in vivo studies, tendon strain between 3 and 6% at F_{max} is within the physiologically feasible magnitude in the triceps surae complex (soleus, gastrocnemius lateral and medial head and the Achilles tendon complex) (63, 64). With this in mind, it can first be assumed that tendon compliance in the current experiment was increased within a physiologically sound range and is representative of the intrinsic changes that could happen in PD rigidity. But, Uchida et al. suggested that the non-significant changes in whole-body metabolic rate in response to reduced tendon compliance can potentially be attributed to musculotendon adaptation occurring in the model. Post hoc analyses in the current study and results from the Uchida 2016 experiment reveal that muscles of the triceps surae had muscle fiber lengths that changed in response to decreased tendon compliance. These muscle fibers had the tendency to shorten more with greater decrements in tendon compliance. Due to the known relationship between fiber length and tension, it can be theorized that the fibers began operating at more optimal lengths for a muscle force production. These findings suggest that within the simulations, the musculotendon unit started to adjust to the changes made to suit the more mechanically efficient strategy due to lack of compliance in the tendon. This natural adaptation occurring in the model could account for the nonsignificant differences seen in whole-body metabolic power within the parameters of this study. Currently

there is no data suggesting that this is occurring in PD subjects but, given the history of their increased rate of energy expenditure during walking, it could be plausible that they are not making these musculotendon adaptions to a more efficient method if tendon compliance is indeed decreased.

There are several limitations to this study. Though it is outside of the scope of the current experiment, simulations of the neural components of PD rigidity, i.e. a heightened stretch reflex and shortening reaction, were not applied to the models. Within the muscle driven simulations, these neuronal aspects of PD rigidity can contribute to the estimates of muscle activation within the first 100 ms of movement where these neural disturbances have primary influence on movement initiation (57, 59, 94, 118). Even if assuming the PD models are in a ON medication state, where most individuals with PD live their lives, dopaminergic interventions can only alleviate the magnitude of the neural components to parkinsonian rigidity but are not completely abolished and can still have significant influence on early muscle activation. Next, joint moments (forces) were measured via the inverse dynamics tool before using the CMC tool in OpenSim. The joint moments derived from the inverse dynamics tool showed non-significant differences when compared to the measured moments from Visual3D. After running the CMC tool, joint moments are recalculated and are then greatly influenced by the estimations of muscle activation. Post hoc analyses revealed that in some cases, joint moments calculated after running the CMC tool were different from those calculated in Visual3D and within the inverse dynamics tool in OpenSim. The changes in joint moments after the CMC analysis alters the simulated mechanical demand required to be overcome by the musculoskeletal system. The new mechanical demand could therefore influence the algorithm used to estimate metabolic power and create inaccuracies. Also, the fiber type shifts associated with PD were not modeled during the walking

simulations. Individuals with PD tend to have more slow twitch muscle fibers when compared to their age matched controls (30). In the algorithms used by the metabolic probe, estimations were given on slow twitch fiber type in normal human musculature (51). The alterations in fiber type associated with PD could potentially influence the estimated metabolic power within each muscle based on the means of metabolism associated with slow twitch and fast twitch fibers.

Conclusions

Despite these limitations and non-significant findings, a few important conclusions can be drawn from this study. First, the results of this study suggest that the musculotendon complex quickly adapts to induced changes to its structural properties. This has previously been established in literature but, in respect to the aims of this project, it is not known whether or not this is actually occurring in individuals with PD. More research is needed to indicate that the PD musculotendon unit is as a as adaptable as healthy individuals'. Second, the results of this study also suggest that during walking, tendon compliance may no have as significant of an influence on whole-body metabolic cost as initially speculated. Similar analyses that have previously been run suggest that at lower locomotor speeds, tendon compliance may not have a large influence on systemic metabolic cost. Future studies should be done to potentially fine tune the methodology used within this study to assure that estimates for muscle activations and subsequently muscle metabolic power are accurate. It would also be beneficial to investigate how the PD musculotendon unit adapts to certain stimuli given the speculated changes passive tissues.

References

1. Abbott, B. C. (1951). The heat production associated with the maintenance of a prolonged contraction and the extra heat produced during large shortening. *The Journal of physiology*, 112(3-4), 438-445.
2. Adkin, A. L., Frank, J. S., & Jog, M. S. (2003). Fear of falling and postural control in Parkinson's disease. *Movement Disorders*, 18(5), 496-502.
3. Alexander, R. M. (1989). Optimization and gaits in the locomotion of vertebrates. *Physiological reviews*, *69*(4), 1199-1227.
4. Alexander, R. M. (1991). Energy-saving mechanisms in walking and running. *Journal of Experimental Biology*, *160*(1), 55-69.
5. Andrews, CJ., Burke, D., & Lance, JW (1972). The response to muscle stretch and shortening in Parkinsonian rigidity. *Brain*, *95*(4), 795-812
6. Balleine, B. W., Delgado, M. R., & Hikosaka, O. (2007). The role of the dorsal striatum in reward and decision-making. *Journal of Neuroscience*, *27*(31), 8161-8165.
7. Baltadjieva, R., Giladi, N., Gruendlinger, L., Peretz, C., & Hausdorff, J. M. (2006). Marked alterations in the gait timing and rhythmicity of patients with de novo Parkinson's disease. *European Journal of Neuroscience*, *24*(6), 1815-1820.
8. Berardelli, A., Sabra, A. F., & Hallett, M. (1983). Physiological mechanisms of rigidity in Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry*, *46*(1), 45-53.
9. Bertram, L., & Tanzi, R. E. (2005). The genetic epidemiology of neurodegenerative disease. The Journal of clinical investigation, 115(6), 1449-1457.
10. Betarbet, R., Sherer, T. B., MacKenzie, G., Garcia-Osuna, M., Panov, A. V., & Greenamyre, J. T. (2000). Chronic systemic pesticide exposure reproduces features of Parkinson's disease. Nature neuroscience, 3(12), 1301.
11. Blin, O., Ferrandez, A. M., & Serratrice, G. (1990). Quantitative analysis of gait in Parkinson patients: increased variability of stride length. *Journal of the neurological sciences*, *98*(1), 91-97.
12. Bloem, B. R., & Beckley, D. J. (2001). Postural instability and falls in Parkinson's disease. *Advances in neurology*, *87*, 209-223.
13. Bolstad, G., & Ersland, A. (1978). Energy metabolism in different human skeletal muscles during voluntary isometric contractions. *European journal of applied physiology and occupational physiology*, 38(3), 171-179.
14. Bryant, M. S., Rintala, D. H., Hou, J. G., Charness, A. L., Fernandez, A. L., Collins, R. L.,...& Protas, E. J. (2011). Gait variability in Parkinson’s disease: influence of walking speed and dopaminergic treatment. *Neurological research*, *33*(9), 959-964.
15. Buschman, H.P.J., Linari, M., Elzinga, G. and Woledge, R.C. (1997). Mechanical and energy characteristics during shortening in isolated type-1 muscle fibers from Xenopus laevis studied at maximal and submaximal activation. *European Journal of Physiology* 435, 145–150.
16. Capecci, M., Petrelli, M., Emanuelli, B., Millevolte, M., Nicolai, A., Provinciali, L., & Ceravolo, M. G. (2013). Rest energy expenditure in Parkinson's disease: role of disease progression and dopaminergic therapy. *Parkinsonism & related disorders*, *19*(2), 238-241.

17. Carpenter, M. G., Allum, J. H. J., Honegger, F., Adkin, A. L., & Bloem, B. R. (2004). Postural abnormalities to multidirectional stance perturbations in Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry*, *75*(9), 1245-1254.
18. Castrioto, A., Piscicelli, C., Pérennou, D., Krack, P., & Debû, B. (2014). The pathogenesis of Pisa syndrome in Parkinson's disease. *Movement Disorders*, *29*(9), 1100-1107.
19. Cavagna, G. A., & Franzetti, P. (1986). The determinants of the step frequency in walking in humans. *The Journal of physiology*, *373*(1), 235-242.
20. Chau, K. Y., Ching, H. L., Schapira, A. H., & Cooper, J. M. (2009). Relationship between alpha synuclein phosphorylation, proteasomal inhibition and cell death: relevance to Parkinson's disease pathogenesis. *Journal of neurochemistry*, *110*(3), 1005-1013.
21. Christiansen CL, Schenkman ML, McFann K, Wolfe P, Kohrt WM (2009) Walking economy in people with Parkinson's disease. *Mov Disorder*, 24, 1481–1487
22. Connelly, D. M., Rice, C. L., Roos, M. R., & Vandervoort, A. A. (1999). Motor unit firing rates and contractile properties in tibialis anterior of young and old men. *Journal of applied Physiology*, 87(2), 843-852.
23. Cunnington, R., Bradshaw, J. L., & Iansek, R. (1996). The role of the supplementary motor area in the control of voluntary movement. *Human Movement Science*, 15(5), 627-647.
24. Delp, S. Anderson, F. Arnold, A. Loan, P. Habib, A. John, C. Guendelman, E. Thelen, D. (2007). Opensim: Open-source Software to Create and Analyze Dynamic Simulations of Movement. *IEEE Trans Biomed Eng* 54(11), 1940-50.
25. Delwaide, P. J., Pepin, J. L., & De Noordhout, A. M. (1991). Short-latency autogenic inhibition in patients with parkinsonian rigidity. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society*, *30*(1), 83-89.
26. DeVita, P., Helseth, J., & Hortobagyi, T. (2007). Muscles do more positive than negative work in human locomotion. Journal of Experimental Biology, 210(19), 3361-3373.
27. Dietz, V., Berger, W., & Horstmann, G. A. (1988). Posture in Parkinson's disease: impairment of reflexes and programming. *Annals of neurology*, *24*(5), 660-669.
28. Dietz, V., Ziiistra, W., Prokop, T., & Berger, W. (1995). Leg muscle activation during gait in Parkinson's disease: adaptation and interlimb coordination. *Electroencephalography and Clinical Neurophysiology/Electromyography and Motor Control*, *97*(6), 408-415.
29. Doherty, K. M., van de Warrenburg, B. P., Peralta, M. C., Silveira-Moriyama, L., Azulay, J. P., Gershanik, O. S., & Bloem, B. R. (2011). Postural deformities in Parkinson's disease. The Lancet Neurology, 10(6), 538-549.
30. Edström, L. (1970). Selective changes in the sizes of red and white muscle fibres in upper motor lesions and Parkinsonism. *Journal of the Neurological Sciences*, *11*(6), 537-550.
31. Eldadah, B. A. (2010). Fatigue and fatigability in older adults. *PM&R*, *2*(5), 406-413.
32. Fahn S (2003) Description of Parkinson's disease as a clinical syndrome. Ann NY Acad Sci 991:1–14.
33. Ferrarin, M., Rizzone, M., Bergamasco, B., Lanotte, M., Recalcati, M., Pedotti, A., & Lopiano, L. (2005). Effects of bilateral subthalamic stimulation on gait kinematics and kinetics in Parkinson's disease. *Experimental brain research*, *160*(4), 517-527.

34. Fox, A. S., Carty, C. P., Modenese, L., Barber, L. A., & Lichtwark, G. A. (2018). Simulating the effect of muscle weakness and contracture on neuromuscular control of normal gait in children. *Gait & posture*, 61, 169-175.
35. Friden, J., Lieber R (2003). Spastic muscle cells are shorter and stiffer than normal cells. *Muscle & Nerve*, 27 (2), 157-164.
36. Fukunaga, T., Kubo, K., Kawakami, Y., Fukashiro, S., Kanehisa, H., & Maganaris, C. N. (2001). In vivo behaviour of human muscle tendon during walking. *Proceedings of the Royal Society of London B: Biological Sciences*, *268*(1464), 229-233.
37. Giladi, N., Treves, T. A., Simon, E. S., Shabtai, H., Orlov, Y., Kandinov, B., ... & Korczyn, A. D. (2001). Freezing of gait in patients with advanced Parkinson's disease. *Journal of neural transmission*, *108*(1), 53-61.
38. Griffiths, R. I. (1991). Shortening of muscle fibres during stretch of the active cat medial gastrocnemius muscle: the role of tendon compliance. *The Journal of Physiology*, *436*(1), 219-236.
39. Haeri, M., Sarbaz, Y., & Gharibzadeh, S. (2005). Modeling the Parkinson's tremor and its treatments. *Journal of theoretical biology*, 236(3), 311-322.
40. Hallett, M., & Khoshbin, S. (1980). A physiological mechanism of bradykinesia. *Brain*, *103*(2), 301-314.
41. Hausdorff, J. M., Cudkowicz, M. E., Firtion, R., Wei, J. Y., & Goldberger, A. L. (1998). Gait variability and basal ganglia disorders: stride-to-stride variations of gait cycle timing in Parkinson's disease and Huntington's disease. *Movement disorders*, *13*(3), 428-437.
42. Hausdorff, J. M. (2007). Gait dynamics, fractals and falls: finding meaning in the stride-to-stride fluctuations of human walking. *Human movement science*, *26*(4), 555-589.
43. Hausdorff, J. M. (2009). Gait dynamics in Parkinson’s disease: common and distinct behavior among stride length, gait variability, and fractal-like scaling. *Chaos: An Interdisciplinary Journal of Nonlinear Science*, *19*(2), 026113.
44. Herlofson, K., & Larsen, J. P. (2003). The influence of fatigue on health-related quality of life in patients with Parkinson's disease. *Acta Neurologica Scandinavica*, *107*(1), 1-6.
45. Homsher, E., Mommaerts, W. F. H. M., Ricchiuti, N. V., & Wallner, A. (1972). Activation heat, activation metabolism and tension-related heat in frog semitendinosus muscles. *The journal of physiology*, 220(3), 601-625.
46. Horak, F. B., Nutt, J. G., & Nashner, L. M. (1992). Postural inflexibility in parkinsonian subjects. *Journal of the neurological sciences*, *111*(1), 46-58.
47. Horstink, M. W., Berger, H. J., Van Spaendonck, K. P., Van den Bercken, J. H., & Cools, A. R. (1990). Bimanual simultaneous motor performance and impaired ability to shift attention in Parkinson's disease. Journal of Neurology, Neurosurgery & Psychiatry, 53(8), 685-690.
48. Hunter, S. K., Thompson, M. W., Ruell, P. A., Harmer, A. R., Thom, J. M., Gwinn, T. H., & Adams, R. D. (1999). Human skeletal sarcoplasmic reticulum Ca2+ uptake and muscle function with aging and strength training. *Journal of Applied Physiology*, 86(6), 1858-1865.
49. Ishikawa, M., Komi, P. V., Grey, M. J., Lepola, V., & Bruggemann, G. P. (2005). Muscle-tendon interaction and elastic energy usage in human walking. *Journal of applied physiology*, *99*(2), 603-608.
50. Jenner, P., & Olanow, C. W. (2006). The pathogenesis of cell death in Parkinson's disease. *Neurology*, *66*(10 suppl 4), S24-S36.

51. Johnson, M.A., Polgar, J., Weightman, D. and Appleton, D. (1973). Data on the distribution of fiber types in thirty-six human muscles: an autopsy study. *Journal of the Neurological Sciences*, 8, 111–129.
52. Katzel, L. I., Ivey, F. M., Sorkin, J. D., Macko, R. F., Smith, B., & Shulman, L. M. (2012). Impaired economy of gait and decreased six-minute walk distance in Parkinson's disease. *Parkinson's Disease*, 2012.
53. Kowal, S. L., Dall, T. M., Chakrabarti, R., Storm, M. V., & Jain, A. (2013). The current and projected economic burden of Parkinson's disease in the United States. Movement Disorders, 28(3), 311-318.
54. Kreitzer, A. C., & Malenka, R. C. (2008). Striatal plasticity and basal ganglia circuit function. *Neuron*, *60*(4), 543-554.
55. Kuo, A. D., Donelan, J. M., & Ruina, A. (2005). Energetic consequences of walking like an inverted pendulum: step-to-step transitions. *Exercise and sport sciences reviews*, *33*(2), 88-97.
56. Lamberti, P., Armenise, S., Castaldo, V., de Mari, M., Iliceto, G., Tronci, P., & Serlenga, L. (1997). Freezing gait in Parkinson's disease. *European neurology*, *38*(4), 297-301.
57. Lee, R., & Tatton, W. G. (1975). Motor responses to sudden limb displacements in primates with specific CNS lesions and in human patients with motor system disorders. *Canadian Journal of Neurological Sciences*, *2*(3), 285-293.
58. Lewek, M. D., Poole, R., Johnson, J., Halawa, O., & Huang, X. (2010). Arm swing magnitude and asymmetry during gait in the early stages of Parkinson's disease. *Gait & posture*, *31*(2), 256-260.
59. Lewis, G. N., Byblow, W. D., & Walt, S. E. (2000). Stride length regulation in Parkinson's disease: the use of extrinsic, visual cues. Brain, 123(10), 2077-2090.
60. Lichtwark, G. A., & Wilson, A. M. (2007). Is Achilles tendon compliance optimised for maximum muscle efficiency during locomotion? Journal of biomechanics, 40(8), 1768-1775.
61. Lichtwark, G. A., & Wilson, A. M. (2008). Optimal muscle fascicle length and tendon stiffness for maximising gastrocnemius efficiency during human walking and running. Journal of theoretical biology, 252(4), 662-673.
62. Maggioni, M. A., Veicsteinas, A., Rampichini, S., Cè, E., Nemni, R., Riboldazzi, G., & Merati, G. (2012). Energy cost of spontaneous walking in Parkinson's disease patients. *Neurological Sciences*, *33*(4), 779-784.
63. Maganaris CN, Paul JP (2002). Tensile properties of the in vivo human gastrocnemius tendon. J Biomech, 35(12):1639–1646.
64. Magnusson SP, Aagaard P, Rosager S, Dyhre-Poulsen P, Kjaer M (2001). Load–displacement properties of the human triceps surae aponeurosis in vivo. J Physiol, 531(1):277–288.
65. Markus, H. S., Cox, M., & Tomkins, A. M. (1992). Raised resting energy expenditure in Parkinson's disease and its relationship to muscle rigidity. *Clinical science*, 83(2), 199-204.
66. Martin LJ, Price AC, McClendon KB, Al-Abdulla NA, Subramaniam JR, Wong PC, Liu Z (2003). Early events of target deprivation/axotomyinduced neuronal apoptosis in vivo: oxidative stress, DNA damage, p53 phosphorylation and subcellular redistribution of death proteins. J Neurochem 85:234 –247

67. McNaught, K. S. P., & Olanow, C. W. (2006). Protein aggregation in the pathogenesis of familial and sporadic Parkinson's disease. *Neurobiology of aging*, *27*(4), 530-545.
68. Meunier, S., Pol, S., Houeto, J. L., & Vidailhet, M. (2000). Abnormal reciprocal inhibition between antagonist muscles in Parkinson's disease. *Brain*, *123*(5), 1017-1026.
69. Minetti, A. E., Capelli, C., Zamparo, P., & Saibene, F. (1995). Effects of stride frequency on mechanical power and energy expenditure of walking. Medicine and Science in Sports and Exercise, 27(8), 1194-1202.
70. Mirbagheri, M., Barbeau, H., Ladouceur, M., & Kearney, R. (2001). Intrinsic and reflex stiffness in normal and spastic, spinal cord injured subjects. Experimental brain research, 141(4), 446-459.
71. Morris, M. E., Iansek, R., Matyas, T. A., & Summers, J. J. (1994). The pathogenesis of gait hypokinesia in Parkinson's disease. Brain, 117(5), 1169-1181.
72. Morris, M. E., McGinley, J., Huxham, F., Collier, J., & Iansek, R. (1999). Constraints on the kinetic, kinematic and spatiotemporal parameters of gait in Parkinson's disease. *Human Movement Science*, *18*(2-3), 461-483.
73. Muralidharan, V., Balasubramani, P. P., Chakravarthy, S., Lewis, S. J., & Moustafa, A. A. (2014). A computational model of altered gait patterns in parkinson's disease patients negotiating narrow doorways. *Frontiers in computational neuroscience*, 7, 190.
74. Nieuwboer, A., Dom, R., De Weerdt, W., Desloovere, K., Fieuws, S., & Broens-Kaucsik, E. (2001). Abnormalities of the spatiotemporal characteristics of gait at the onset of freezing in Parkinson's disease. *Movement disorders: official journal of the Movement Disorder Society*, *16*(6), 1066-1075.
75. Obeso, J. A., Rodriguez-Oroz, M. C., Rodriguez, M., Lanciego, J. L., Artieda, J., Gonzalo, N., & Olanow, C. W. (2000). Pathophysiology of the basal ganglia in Parkinson's disease. *Trends in neurosciences*, *23*, S8-S19.
76. Olgiati, R., Burgunder, J. M., & Mumenthaler, M. (1988). Increased energy cost of walking in multiple sclerosis: effect of spasticity, ataxia, and weakness. *Archives of Physical Medicine and Rehabilitation*, *69*(10), 846-849.
77. Orselli, M. I. V., Franz, J. R., & Thelen, D. G. (2017). The effects of Achilles tendon compliance on triceps surae mechanics and energetics in walking. *Journal of biomechanics*, *60*, 227-231.
78. O'Sullivan, J. D., Said, C. M., Dillon, L. C., Hoffman, M., & Hughes, A. J. (1998). Gait analysis in patients with Parkinson's disease and motor fluctuations: influence of levodopa and comparison with other measures of motor function. *Movement disorders: official journal of the Movement Disorder Society*, *13*(6), 900-906.
79. Otis, A. B., Fenn, W. O., & Rahn, H. (1950). Mechanics of breathing in man. *Journal of applied physiology*, *2*(11), 592-607.
80. Park, B. K., Kwon, Y., Kim, J. W., Lee, J. H., Eom, G. M., Koh, S. B., ... & Hong, J. (2011). Analysis of viscoelastic properties of wrist joint for quantification of parkinsonian rigidity. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, *19*(2), 167-176.
81. Parkinson J. An Essay on the Shaking Palsy. London: Sherwood, Neely, and Jones; 1817.
82. Pasman, E. P., Murnaghan, C. D., Bloem, B. R., & Carpenter, M. G. (2011). Balance problems with Parkinson's disease: are they anxiety-dependent?. *Neuroscience*, *177*, 283-291.

83. Pavese, N., Metta, V., Bose, S. K., Chaudhuri, K. R., & Brooks, D. J. (2010). Fatigue in Parkinson's disease is linked to striatal and limbic serotonergic dysfunction. *Brain*, *133*(11), 3434-3443.
84. Perry, J., & Davids, J. R. (1992). Gait analysis: normal and pathological function. *Journal of Pediatric Orthopaedics*, *12*(6), 815.
85. Petrucelli, L., O'Farrell, C., Lockhart, P. J., Baptista, M., Kehoe, K., Vink, L., ... & Cookson, M. R. (2002). Parkin protects against the toxicity associated with mutant α-synuclein: proteasome dysfunction selectively affects catecholaminergic neurons. *Neuron*, *36*(6), 1007-1019.
86. Powell, D., Hanson, N., Threlkeld, A. J., Fang, X., & Xia, R. (2011). Enhancement of parkinsonian rigidity with contralateral hand activation. *Clinical Neurophysiology*, *122*(8), 1595-1601.
87. Powell, D., Threlkeld, A. J., Fang, X., Muthumani, A., & Xia, R. (2012). Amplitude-and velocity-dependency of rigidity measured at the wrist in Parkinson's disease. *Clinical Neurophysiology*, *123*(4), 764-773.
88. Powell, D. W., Blackmore, S. E., Puppa, M., Lester, D., Murray, N. G., Reed-Jones, R. J., & Xia, R. P. (2018). Deep brain stimulation enhances movement complexity during gait in individuals with Parkinson's disease. *Neuroscience letters*.
89. Praamstra, P., Stegeman, D. F., Cools, A. R., & Horstink, M. W. (1998). Reliance on external cues for movement initiation in Parkinson's disease. Evidence from movement-related potentials. *Brain: a journal of neurology*, *121*(1), 167-177.
90. Ries, A. J., & Schwartz, M. H. (2018). Low gait efficiency is the primary reason for the increased metabolic demand during gait in children with cerebral palsy. *Human movement science*, 57, 426-433.
91. Roberts, R. C., Part, N. J., Farquhar, R., & Butchart, P. (1994). Presynaptic inhibition of soleus Ia afferent terminals in Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry*, *57*(12), 1488-1491.
92. Rondot, P., & Metral, S. (1973). Analysis of the shortening reaction in man. In *Human Reflexes, Pathophysiology of Motor Systems, Methodology of Human Reflexes* (Vol. 3, pp. 629-634). Karger Publishers.
93. Rossi, B., Siciliano, G., Carboncini, M. C., Manca, M. L., Massetani, R., Viacava, P., & Muratorio, A. (1996). Muscle modifications in Parkinson's disease: myoelectric manifestations. *Electroencephalography and Clinical Neurophysiology/Electromyography and Motor Control*, *101*(3), 211-218.
94. Rothwell, J. C., Obeso, J. A., Traub, M. M., & Marsden, C. D. (1983). The behaviour of the long-latency stretch reflex in patients with Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry*, *46*(1), 35-44.
95. Sarbaz, Y., Banaie, M., Pooyan, M., Gharibzadeh, S., Towhidkhah, F., & Jafari, A. (2012). Modeling the gait of normal and Parkinsonian persons for improving the diagnosis. *Neuroscience letters*, 509(2), 72-75.
96. Seth, A., Hicks, J. L., Uchida, T. K., Habib, A., Dembia, C. L., Dunne, J. J., ... & Hamner, S. R. (2018). OpenSim: Simulating musculoskeletal dynamics and neuromuscular control to study human and animal movement. *PLoS computational biology*, 14(7), e1006223.

97. Schapira, A. H., Mann, V. M., Cooper, J. M., Krige, D., Jenner, P. J., & Marsden, C. D. (1992). Mitochondrial function in Parkinson's disease. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society*, *32*(S1), S116-S124.
98. Schlenstedt, C., Muthuraman, M., Witt, K., Weisser, B., Fasano, A., & Deuschl, G. (2016). Postural control and freezing of gait in Parkinson's disease. *Parkinsonism & related disorders*, *24*, 107-112.
99. Sepehri, B., Esteki, A., Ebrahimi-Takamjani, E., Shahidi, G. A., Khamseh, F., & Moinodin, M. (2007). Quantification of rigidity in Parkinson's disease. *Annals of Biomedical engineering*, *35*(12), 2196-2203.
100. Sinkjær, T., & Magnussen, I. (1994). Passive, intrinsic and reflex-mediated stiffness in the ankle extensors of hemiparetic patients. Brain, 117(2), 355-363.
101. Sofuwa, O., Nieuwboer, A., Desloovere, K., Willems, A. M., Chavret, F., & Jonkers, I. (2005). Quantitative gait analysis in Parkinson's disease: comparison with a healthy control group. *Archives of physical medicine and rehabilitation*, *86*(5), 1007-1013.
102. Teräväinen, H., Tsui, J. K., Mak, E., & Calne, D. B. (1989). Optimal indices for testing parkinsonian rigidity. *Canadian Journal of Neurological Sciences*, *16*(2), 180-183.
103. Thelen, D. G. (2003). Adjustment of muscle mechanics model parameters to simulate dynamic contractions in older adults. *Journal of biomechanical engineering*, 125(1), 70-77.
104. Thompson, B. J., Ryan, E. D., Herda, T. J., Costa, P. B., Herda, A. A., & Cramer, J. T. (2014). Age-related changes in the rate of muscle activation and rapid force characteristics. Age, 36(2), 839-849.
105. Umberger, B. R., Gerritsen, K. G., & Martin, P. E. (2003). A model of human muscle energy expenditure. *Computer methods in biomechanics and biomedical engineering*, 6(2), 99-111.
106. Umberger, B. R. (2010). Stance and swing phase costs in human walking. *Journal of the Royal Society Interface*, 7(50), 1329-1340.
107. van Emmerik RE, Wagenaar RC, Winogrodzka A, Wolters EC. Identification of axial rigidity during locomotion in Parkinson disease. Arch Phys Med Rehabil 1999;80:186-91.
108. Vaugoyeau, M., Viel, S., Assaiante, C., Amblard, B., & Azulay, J. P. (2007). Impaired vertical postural control and proprioceptive integration deficits in Parkinson's disease. *Neuroscience*, *146*(2), 852-863.
109. Wagenaar, R. C., & van Emmerik, R. E. (1994). Dynamics of pathological gait. *Human Movement Science*, *13*(3-4), 441-471.
110. Waters, R. L., & Mulroy, S. (1999). The energy expenditure of normal and pathologic gait. *Gait & posture*, *9*(3), 207-231.
111. Watts, R. L., Wiegner, A. W., & Young, R. R. (1986). Elastic properties of muscles measured at the elbow in man: II. Patients with parkinsonian rigidity. *Journal of Neurology, Neurosurgery & Psychiatry*, *49*(10), 1177-1181.
112. Weintraub, D., Comella, C. L., & Horn, S. (2008). Parkinson's disease--Part 1: Pathophysiology, symptoms, burden, diagnosis, and assessment. Am J Manag Care, 14(2 Suppl), S40-S48.
113. Wichmann, T., & DeLong, M. R. (1996). Functional and pathophysiological models of the basal ganglia. Current opinion in neurobiology, 6(6), 751-758.

114. Williams DR, Watt HC, Lees AJ. Predictors of falls and fractures in bradykinetic rigid syndromes: a retrospective study. J Neurol Neurosurg Psychiatry 2006;77:468–73.
115. Wilson, A. M., Watson, J. C., & Lichtwark, G. A. (2003). Biomechanics: a catapult action for rapid limb protraction. Nature, 421(6918), 35.
116. Winter, D. A. (2009). *Biomechanics and motor control of human movement*. John Wiley & Sons.
117. Xia, R., Markopoulou, K., Puumala, S. E., & Rymer, W. Z. (2006). A comparison of the effects of imposed extension and flexion movements on Parkinsonian rigidity. *Clinical Neurophysiology*, *117*(10), 2302-2307.
118. Xia, R., Sun, J., & Threlkeld, A. J. (2009). Analysis of interactive effect of stretch reflex and shortening reaction on rigidity in Parkinson's disease. *Clinical Neurophysiology*, *120*(7), 1400-1407.
119. Xia, R., Muthumani, A., Mao, Z. H., & Powell, D. W. (2016). Quantification of neural reflex and muscular intrinsic contributions to parkinsonian rigidity. *Experimental brain research*, *234*(12), 3587-3595.
120. Zelik, K. E., Huang, T. W. P., Adamczyk, P. G., & Kuo, A. D. (2014). The role of series ankle elasticity in bipedal walking. *Journal of theoretical biology*, *346*, 75-85.
121. Zetterberg, H., Frykberg, G. E., Gäverth, J., & Lindberg, P. G. (2015). Neural and nonneural contributions to wrist rigidity in Parkinson's disease: an explorative study using the NeuroFlexor. *BioMed research international*, *2015.*

Tables and figures

Tables

Table 1: Model characteristics

Feature	HY0	HY1	HY2	HY3	Reference
Max isometric force (N)	F_{max}-30%	F_{max}-30%	F_{max}-30%	F_{max}-30%	30% lower in older adults (103, 104)
Tendon strain at maximum isometric force	.033	.041	.050	.058	Slope increased to simulate tendon stiffness
K shape passive	4	3	2	1	Decreased to simulate intrinsic stiffness
Time to activation (sec)	.012	.012	.012	.012	Unchanged from model
Time to deactivation (sec)	.06	.06	.06	.06	2x as long in older adults (48)
Max contraction velocity (fibers/sec)	8	8	8	8	20% reduction in older adults (22, 103)

Figures

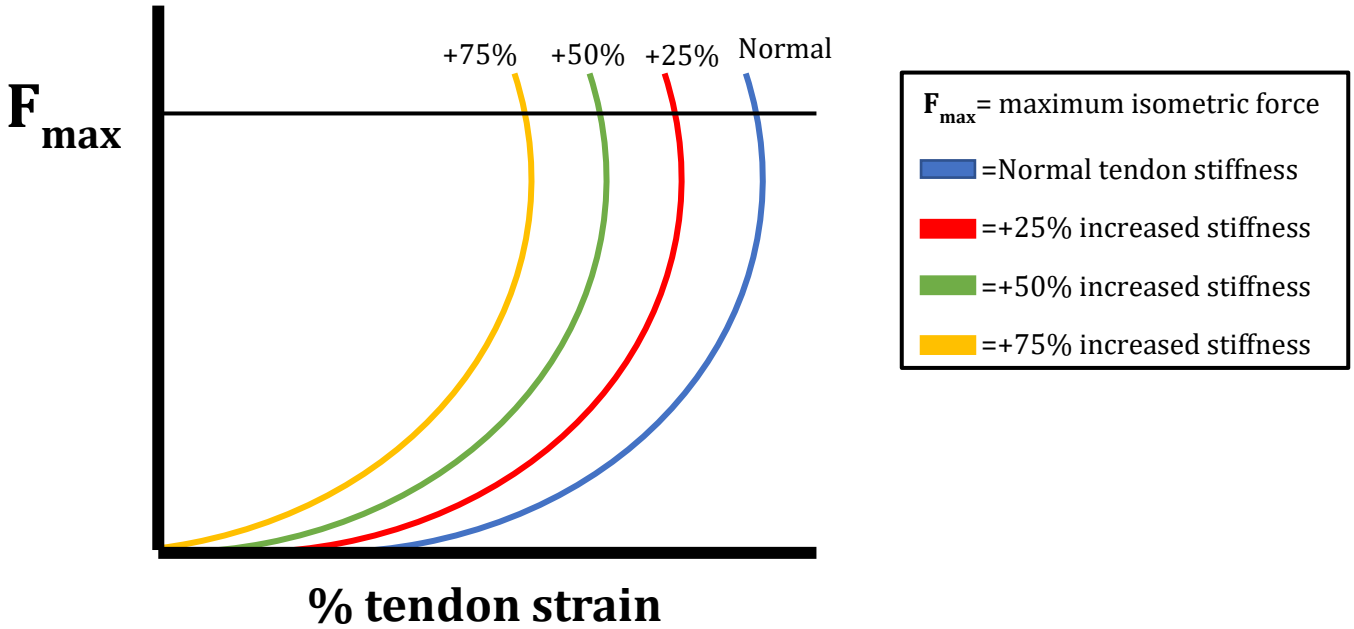

Figure 1: Stress strain curves used for tendon stiffness

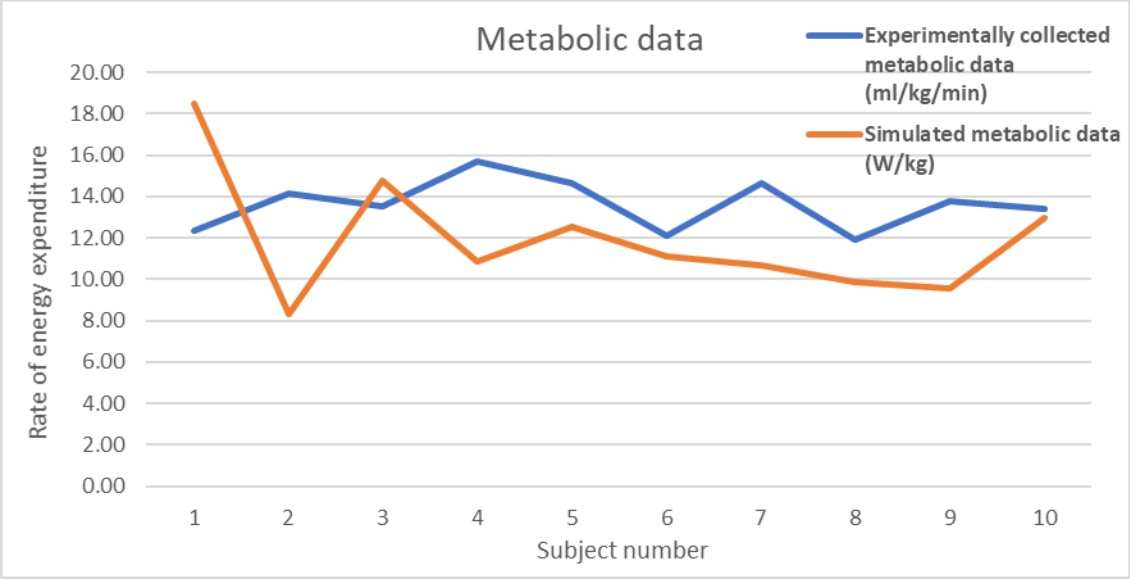

Figure 2: Measured metabolic data and simulated metabolic data

Appendix

Appendix A: IRB sections

TITLE: Quantification of energy expenditure in response to simulated parkinsonian rigidity

PURPOSE

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disease characterized by **rigidity**, ***fatigue***, bradykinesia, resting tremor, and postural instability.[8] Rigidity is defined as an increased resistance to the passive or externally induced movement of a limb persisting throughout its range.[10] Rigidity can be used as a clinical diagnostic criterion, and generally responds well to dopaminergic medication and surgical intervention.[9,11,15] It is widely accepted that increased neural-related muscle resistance to the passive movement of a joint contributes to rigidity in PD as numerous studies have shown that patients with PD exhibit a marked increase in long-latency stretch reflexes, compared to healthy controls.[1,3,11,15] On the other hand, a growing body of literature indicates that increased intrinsic stiffness plays a role in rigidity.[4,5,7,12,16,18] The intrinsic component of rigidity includes the visco-elastic (i.e., mechanical) properties of muscle fibers and passive connective tissues. Evidence clearly suggests that both neural reflex and intrinsic mechanisms operate in parallel and contribute to parkinsonian rigidity.

In Parkinson's disease, fatigue has been described as a "state of tiredness" while physiological fatigue (or fatigability) refers to a reduced capacity to produce force as a result of physiological substrate depletion (i.e. run out of fuel).[6] The relationship between the state of fatigue and the phenomenon of fatigability in individuals with PD is not well understood. However, both fatigue and fatigability are associated with reductions in physical activity and decreased quality of life.[6] It is possible that the state of fatigue exacerbates activity-related fatigability resulting in reduced physical activity purportedly resulting in an increase in the rate of disease progression.[6]

Gait biomechanics are altered in individuals with PD. Our research has previously demonstrated that individuals with PD walk with an increased regularity and decreased complexity of motion.[13] Anti-PD treatments, such as deep brain stimulation, improve movement complexity through improved organization of the motor system. In addition to altered gait biomechanics, individuals with PD also experience reduced metabolic efficiency during walking. Christensen (2010) demonstrated that individuals with PD have greater energy expenditure than healthy, age-matched adults when performing a treadmill walking task. The effect of increasing PD-related rigidity - an increased resistance to motion - on energy expenditure during walking has not been previously investigated. Therefore, the ***purpose of this study*** is to investigate the effects of increasing rigidity on energy expenditure during walking in individuals with PD. To accomplish this, we will perform a preliminary study investigating increasing rigidity on energy expenditure during walking. We will develop a model that predicts the bioenergetics of gait from biomechanical data including gait kinematics, kinetics and muscle activations collected from healthy young adults. Following data collection, we will estimate changes in energy expenditure with increasing rigidity. To simulate PD, we will manipulate muscle activation to mimic hypertonia, and we will decrease tendon compliance to simulate changes in passive connective tissue properties.

REFERENCES

[1] Berardelli, A., & Hallett, M. (1984). Shortening reaction of human tibialis anterior. *Neurology*, *34*(2), 242-242.

[2] Christiansen, C. L., Schenkman, M. L., McFann, K., Wolfe, P., & Kohrt, W. M. (2009). Walking economy in people with Parkinson's disease. *Movement Disorders*, *24*(10), 1481-1487.

[3] Cody, F. W. J., MacDermott, N., Matthews, P. B. C., & RICHARDSON, H. C. (1986). Observations on the genesis of the stretch reflex in Parkinson's disease. *Brain*, *109*(2), 229-249.

[4] Dietz, V., Quintern, J., & Berger, W. (1981). Electrophysiological studies of gait in spasticity and rigidity. Evidence that altered mechanical properties of muscle contribute to hypertonia. *Brain: a journal of neurology*, *104*(3), 431-449.

[5] Dietz V (1987) Changes of inherent muscle stiffness in Parkinson's disease. J Neurol Neurosurg Psychiatry 50:944.

[6] Eldadah, B. A. (2010). Fatigue and fatigability in older adults. *PM&R*, *2*(5), 406-413.

[7] Endo, T., Okuno, R., Yokoe, M., Akazawa, K., & Sakoda, S. (2009). A novel method for systematic analysis of rigidity in Parkinson's disease. *Movement Disorders*, *24*(15), 2218-2224.

[8] Fahn S (2003) Description of Parkinson's disease as a clinical syndrome. Ann NY Acad Sci 991:1–14.

[9] Fahn S, Sulzer D, Neurodegeneration and neuroprotection in Parkinson disease, NeuroRx. 1(2004) 139-154.

[10] Fung VS, Thompson PD. Rigidity and Spasticity. 4th ed. Philadelphia: Lippencott Williams & Wilkens; 2002.

[11] Lang, A. E., & Lozano, A. M. (1998). Parkinson's disease. *New England Journal of Medicine*, *339*(15), 1044-1053.

[12] Lee, R., & Tatton, W. G. (1975). Motor responses to sudden limb displacements in primates with specific CNS lesions and in human patients with motor system disorders. *Canadian Journal of Neurological Sciences*, *2*(3), 285-293.

[13] Park, B. K., Kwon, Y., Kim, J. W., Lee, J. H., Eom, G. M., Koh, S. B., ... & Hong, J. (2011). Analysis of viscoelastic properties of wrist joint for quantification of parkinsonian rigidity. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, *19*(2), 167-176.

[14] Powell DW, Blackmore SE*, Puppa MA, Lester DA, Reed-Jones RJ, Xia RP. Deep brain stimulation enhances movement complexity during gait in individuals with Parkinson's disease. Neuroscience Letters, 2018. Accepted.

[15] Prochazka, A., Bennett, D. J., Stephens, M. J., Patrick, S. K., Sears-Duru, R., Roberts, T., & Jhamandas, J. H. (1997). Measurement of rigidity in Parkinson's disease. *Movement Disorders*, *12*(1), 24-32.

[16] Rothwell JC, Obeso JA, Traub MM, Marsden CD (1983) The behaviour of the long-latency stretch reflex in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 46:35–44.

[17] Sepehri, B., Esteki, A., Ebrahimi-Takamjani, E., Shahidi, G. A., Khamseh, F., & Moinodin, M. (2007). Quantification of rigidity in Parkinson's disease. *Annals of Biomedical engineering*, *35*(12), 2196-2203.

[18] Watts RL, Wiegner AW, Young RR (1986) Elastic properties of muscles measured at the elbow in man: II. Patients with parkinsonian rigidity. J Neurol Neurosurg Psychiatry 49:1177–1181.

METHODS & PROCEDURES

Study Setting: Musculoskeletal Analysis Laboratory, School of Health Studies, University of Memphis, Memphis, Tennessee

Interventions:
Participants will be asked to perform over ground and treadmill walking at a self-selected pace.

Experimental Protocol:
Participants will visit the Musculoskeletal Analysis Laboratory (MAL) once for testing. Prior to any data collection, individuals will be screened for inclusion in this study including a written Physical Activity Readiness Questionnaire (PAR-Q; Appendix A) and will provide written informed consent. Following screening and consent, testing will occur in the following order: (1) placement of measurement sensors, (2) completion of maximal voluntary isometric contractions (3) rigidity testing (4) completion of over ground walking task at a self-selected pace, and (5) treadmill walking at a pace equal to their over ground walking pace.

Anthropometric Evaluation
Anthropometric measurements will include: age, sex, height and mass. Participants will be included if they are between the ages of 18 and 35 years of age. All participants will be free of injury for the previous 6 months and will be free of musculoskeletal or neurological condition or injury that may pose a safety risk. Participants will be excluded if they have had a musculoskeletal injury within the past 6 months or if they have a current musculoskeletal or neurological condition that would impair performance of the experimental tasks.

Experimental Equipment
Following anthropometric assessments, retro-reflective markers will be placed bilaterally on the participant's upper and lower extremity and trunk including pelvis, trunk, both legs and feet, both arms and hands to measure individual segment motion during over ground and treadmill walking trials using a 9-camera motion capture system (240 Hz, Qualisys AB, Goteburg, Sweden). Surface electromyography (sEMG) electrodes will be placed bilaterally over muscle belly of the participant's hip, knee and ankle flexors and extensors to record the electrical signals created by the muscles during dynamic movements. sEMG electrodes are non-invasive and record electrical activity created by the participant during muscle contraction. No electrical impulses will be applied to the participants. A pair of force platforms will be used to record ground reaction forces (GRFs; 1200 Hz, AMTI Inc., Watertown, MA, USA) during over ground walking. During treadmill walking a metabolic measurement system (TrueOne, ParvoMedics, Sandy, UT) will be used to perform indirect calorimetry. Indirect calorimetry compares the concentrations of gases within the room to the concentrations of gases expired by the participant to determine the quantity of oxygen consumed by the participant during a given task. In this study, the participant will be performing treadmill walking at their over ground self-selected pace.

Rigidity Testing
After sensors have been applied to the participant, the participant will perform a maximal voluntary isometric contraction (MVIC) for ankle, knee and hip flexors and extensors. The purpose of the MVIC is to provide a scaling measure for electromyography voltages recorded during experimental movements. Participants will be asked to "push as hard as you can" against a manual resistance. Participants will not be restrained in any way and due to the young, healthy nature of the participants, this portion of the protocol presents with minimal risk. Participants will then be placed in an isokinetic dynamometer (HUMAC, CSMi Inc, Boston, MA). The isokinetic dynamometer will move the participant's passive ankle through a range of motion equal to 35 degrees (15 degrees of dorsiflexion; 20 degrees of plantarflexion) while recording the resistance torques applied by the

participant's limb. The participant will be completely passive and generate no active voluntary muscle forces during this testing. The dynamometer will perform the continuous passive motion (dorsiflexion & plantarflexion) for a period of 30 seconds at 60 deg/sec, 120 deg/sec 180 deg/sec and 240 deg/sec. Rigidity testing including dynamometer set up and testing will last approximately 10 minutes.

Over Ground Walking

Following rigidity testing, each participant will be given a five-minute period of rest followed by three over ground walking trials across a 20-meter walkway. A pair of infrared timing gates (Lafayette Instruments) will be used to determine the walking speed of the participant over the center 3 meters of the walkway. An average of the three pacing trials will be used as the participant's self-selected walking pace. This pace will be maintained during over ground and treadmill walking trials. Once the participant's self-selected walking pace has been determined, the participant will perform over ground walking trials across the 20-meter walkway while three-dimensional kinematics and kinetics as well as electromyography are recorded. Each participant will perform 10 trials per limb (20 trials total). Following over ground walking trials, participants will have a five minute period of rest prior to continuation of the experimental protocol.

Treadmill Walking

Once over ground walking trials have been completed, participants will perform a 10-minute treadmill walking task while three-dimensional kinematics and energy expenditure is recorded. Gait kinematics will be recorded for the first 30 seconds of each minute during the 10-minute treadmill walking task while energy expenditure will be collected continuously throughout the treadmill walking task.

The overall testing duration for each participant will be between 60 and 75 minutes. It is anticipated that participant consent and set up will require approximately 30 minutes while experimental testing will require 20 and 15 minutes, respectively.

Data Analysis

- Rigidity will be quantified using the rigidity work score which is calculated as the passive resistance torque integrated with respect to angular displacement.
- Qualisys Track Manager will be used to perform three-dimensional marker tracking and integration of analog (force platform and electromyography) signals into a single file (.c3d).
- Visual 3D will be used to calculate joint angles, velocities, accelerations, moments, and powers.
- MATLAB will be used to calculate joint work values and to quantify muscle activation timing and intensities.
- OpenSim will be used to develop a model to predict energy expenditure during walking based on kinematics, kinetics and electromyography data.
    - This model will be validated by comparing the predicted energy expenditure to measured energy expenditure in healthy young adults.
- OpenSim will be used to estimate changes in energy expenditure as a result of modeled increases in parkinsonian rigidity
    - Four levels of increasing rigidity (correlating to rigidity scores on the Unified Parkinson's Disease Rating Scale) will be modeled.
        - Hypertonia will be modeled as concurrent increases in muscle activation intensities in joint flexors and extensors
        - Increases in passive connective tissue stiffness will be modeled as decreased tendon compliance.
- ParvoMedics software will be used to quantify actual energy expenditure for initial model validation in healthy young adults.

- *Statistical Analysis*
- Student's t-tests will be used to compare predicted energy expenditure to measured energy expenditure during walking in healthy young adults
- Repeated measures ANOVAs will be used to compare the effect of increasing simulated parkinsonian rigidity on energy expenditure during walking.
- Cohen's d effect sizes will be computed to determine the magnitude of differences and changes in dependent variables by experimental condition, respectively.

INVESTIGATOR QUALIFICATIONS

Dr. Powell has been conducting biomechanical and physiological research for 15 years and is trained to collect data on heart rate variability, joint biomechanics, muscle activation and postural stability. Dr. Powell has investigated the biomechanical and physiological underpinnings of impaired motor control associated with advancing age and/or Parkinson's disease for 15 years and has published a number of peer-reviewed research articles pertaining to Parkinson's disease, gait and/or postural stability.

Parkinson's disease

- Powell DW, Blackmore SE*, Puppa MA, Lester DA, Reed-Jones RJ, Xia RP. Deep brain stimulation enhances movement complexity during gait in individuals with Parkinson's disease. Neuroscience Letters, 2018. Accepted.
- Powell, D.W., Muthumani, A., Xia, R.P. Normalization of electromyography signals masks reduction in reflex amplitudes in Parkinson's disease. Journal of Nature & Science, 2017. 3:e315.
- Powell, D.W, Muthumani, A., Xia, R.P. A comparison of the effects of continuous versus discontinuous movement patterns on parkinsonian rigidity and reflex responses to passive stretch and shortening. Journal of Nature & Science, 2016. 2(8): e201.
- Xia, R.P., Muthumani, A., Mao, ZH, Powell, D.W. Quantification of neural reflex and muscular intrinsic contributions to parkinsonian rigidity. Experimental Brain Research, 2016; 234(12):3587-3595. doi:10.1007/s00221-016-4755-9
- Ambati, V.N.P., Murray, N.G., Saucedo, F., Powell, D.W., Reed-Jones, R.J. Constraining eye movement in individuals with Parkinson's disease during walking turns. Experimental Brain Research, 2016. Oct; 234(10): 2957-651. Doi: 0.1007/s00221-016-4698-1.
- Powell, D.W., Muthumani, A., Xia, R.P. Parkinson's disease is associated with greater regularity of repetitive voluntary movements. Motor Control. 2014; 18:263-277.
- Powell, D., Threlkeld, A.J., Fang, X., Muthumani, A., Xia, R.P. Amplitude- and velocity-dependency of rigidity measured at the wrist Parkinson's disease. Clinical Neurophysiology. 2012; 123 (4), p. 764-773.
- Xia, R.P., Powell, D., Rymer, W.Z., Hanson, N.J.*, Fang, X., Threlkeld, A.J. Differentiation between the contributions of shortening reaction and stretch-induced inhibition to rigidity in Parkinson's disease. Experimental Brain Research. 2011; 209: 609-618.
- Powell, D., Hanson, N.J.*, Fang, X., Threlkeld, A.J., Xia, R.P. Enhancement of parkinsonian rigidity with contralateral muscle contractions. Clinical Neurophysiology. 2011; 122: 1595-1601.

Postural Instability

- Reed-Jones, R.J., Carvalho, L. *, Sanderson, C. *, Montelpare, W., Murray, N., Powell, D.W. Examining changes to center of pressure during the first trials of Wii game play. Games for Health Journal, 2017. Accepted.
- Williams, D.S., Murray, N.G., Powell, D.W. Invited Paper: Athletes that train on unstable compared to stable surfaces exhibit unique postural control strategies in response to balance perturbations. Journal of Sport and Health Sciences, 2016; 5: 70-76. doi:10.1016/j.jshs.2016.01.010
- Powell, D.W. & Williams, D.S. Effect of opposing postural feedback paradigms on traditional and nonlinear measures of postural stability. Human Movement Science, 2015; 44: 73-80.
- Murray, N.G.*, Salvatore, A.P., Powell, D.W., Reed-Jones, R.J. Reliability and validity evidence of multiple balance assessments in concussed athletes. Journal of Athletic Training. 2014; 49(4): 540-549.
- Reed-Jones, R.J., Murray, N.G.*, Powell, D.W. Clinical Assessment of Balance in Concussed Adults. Seminars in Speech Language Pathology. 2014; 35(03): 186-195.

Gait Biomechanics

- Williams, D.S., Cole, J.H. *, Powell, D.W. Lower extremity joint work during acceleration, deceleration and steady state running. Journal of Applied Biomechanics, 2017; December.
- Powell, D.W., Andrews, S. *, Windsor, B.A. *, Stickley, C, Williams, D.S. High- compared to low-arched athletes exhibit smaller knee abduction moments in walking and running. Human Movement Science, 2016; 50: 47-53.
- Powell, DW, Walker, M.M.*, Reed-Jones, R.J., Bunn, J.A. Peripheral artery disease and activity-induced shifts in quadriceps median frequency during treadmill walking: a preliminary study. Central European Journal of Sport Science & Medicine, 2015; 10 (2): 5 - 15.
- Powell, D., Williams, D.S. 3rd, Windsor, B.A.*, Butler, R.J., Zhang, S. Dynamic stiffness of the ankle is greater in high- compared to low-arched athletes during barefoot running. Human Movement Science. 2014; 34: 147 - 156.
- Ambati, V.N.P.*, Saucedo, F. *, Murray, N.G. *, Powell, D., Reed-Jones, R.J. Constraining eye movement when redirecting walking trajectories alters turning control in healthy young adults. Experimental Brain Research. 2014; 226(4), 549-556.
- Padulo, J., Powell, D., Milia, R., Ardigo, LP. (2013) A paradigm of uphill running. PLoS ONE, 2013; 8 (7): e69006.
- Powell, D., Williams, D.S., Butler, R. A comparison of two multi-segment foot models in high- and low-arched athletes. Journal of American Podiatric Medical Association. 2013; 103(2): 99-105.
- Powell, D., Clowers, K., Keefer, M., Zhang, S. Alterations in neuromuscular activation patterns in short-leg walking boots. Journal of Sport and Health Science. 2012; 1 (1); 43-8.
- Powell, D., Long, B.*, Milner, C., Zhang, S. Frontal plane multi-segment foot kinematics in high- compared to low-arched females during dynamic loading tasks. Human Movement Science. 2011; Vol. 30, p. 105-14.
- Bice, M.R.*, Hanson, N.J.*, Renshaw, D.*, Eldridge, J., Reneau, P., Powell, D. Neuromuscular adaptations in elderly adults are task-specific during stepping and obstacle clearance tasks. International Journal of Exercise Science. 2011; 4(1), p. 278-86.
- Ruano, C.*, Chalambaga, E.T.*, Renshaw, D.*, Powell, D. The effects of Tempur insoles on ground reaction forces and loading rates in running. International Journal of Exercise Science. 2009; 2 (3), p. 186-190.

- Keefer, M.*, King, J.*, Powell, D., Krusenklaus, J., Zhang, S. Effects of modified short-leg walkers on ground reaction force characteristics. Clinical Biomechanics. 2008; 23 (9): p. 1172-77.
- Powell, D., DeVita, P., Hortobagyi, T. Inertial loading during gait evokes unique neuromuscular adaptations in old adults. Perceptual & Motor Skills, 2008; 107: p. 881-92.
- Zhang, S., Clowers, K.G., and Powell, D. Ground reaction force and 3D biomechanical characteristics of walking in short-leg walkers. Gait & Posture. 2006; 24: p.487-92.

Dr. Melissa Puppa has a background and training in applied exercise physiology and molecular biology with a focus in age- and cancer-related reductions in muscle performance. Dr. Puppa will provide perspective to the energy expenditure measurements and the interaction of neuro-metabolic processes with energy expenditure in individuals with Parkinson's disease.

All other investigators on this research project including undergraduate and graduate students will have been properly trained to perform the required tasks and will have completed CITI training prior to working on this project. Most have previously performed similar assessments in this laboratory.

HUMAN SUBJECTS

A. Characteristics

As this study represents the first investigation, it is difficult to determine the number of participants necessary to sufficiently power this study. However, based on experimental data comparing energy expenditure in individuals with PD and healthy, age-matched controls (Christensen 2010), using a calculated effect size (1.96), an alpha level of 0.05 and a power (1-β) of 0.8, we calculated a total sample size of 5 participants. However, as this is a preliminary modeling study, we propose to collect experimental data from 15 participants.

Inclusion criteria: Participants will be aged between 18 and 35 years of age with no history (within 6 months) of musculoskeletal or neurological condition or injury that would negatively affect safety or completion of the experimental tasks. Exclusion Criteria: Participants will be excluded if the participant's indicates the presence or a history of musculoskeletal, or neurological disorders or conditions that would prevent light to moderate exercise.

Participants will be recruited from the University of Memphis and greater Memphis community via advertisements (Appendix C) placed in areas congregated by students and recreational athletes, word of mouth, and social media including Facebook and Twitter (digital version of the advertisement). All participants will be screened via phone or email to assess eligibility based on the previously mentioned criteria (Appendix D). *Prior to participation, each participant will be informed of all procedures, potential risks, and benefits associated with the study through verbal and written form in accordance with the procedures approved by the University Institutional Review Board for Human Participants Research. Following a description of procedures, potential risks and benefits, participants will be offered the opportunity to raise any questions or concerns with the consenting investigator. No data will be collected until participants provide written informed consent.*

B. Vulnerable Populations
No vulnerable populations will be included in this study. Only adults aged 18 to 35 years with no current or recent history of musculoskeletal or neurological condition or injury will be included as participants in the current study.

C. Pre-existing relationship to subject pool.
Participants and researchers may have interacted with each other previously in a classroom or laboratory-based learning environment. However, no pre-existing relationship will influence the selection of participants for this study.

D. Subject selection
All participants who express interest and meet inclusion and exclusion criteria as previously described may be included as participants.

E. Anticipated number of subjects
15; See *a priori* sample analysis in **A. Characteristics** portion of this section.

RECRUITMENT

Participants will be recruited from the University of Memphis and greater Memphis community via advertisements (Appendix B) placed in areas congregated by students and recreational athletes, word of mouth, and social media including Facebook and Twitter (digital version of the advertisement). All participants will be screened via phone or email (See Appendix C: Recruitment Script) to assess eligibility based on the previously mentioned criteria. Prior to participation, each participant will be informed of all procedures, potential risks, and benefits associated with the study through verbal and written form in accordance with the procedures approved by the University Institutional Review Board for Human Participants Research. No data will be collected until participants provide written informed consent.

POTENTIAL RISKS

Recruited participants are young and healthy and regularly engage in walking as a part of their daily routine. There is minimal risk to conducting the experimental protocol listed above. There is always a small risk associated with exercise and the potential risk of tripping over laboratory equipment also exists. However, a research team member will always be present when participants are in the MAL and testing area.

Participants will be informed when giving consent that this project is not a medical treatment. In addition, any need for medical treatment resulting from this project should be obtained from their personal physician. The participants will also be notified that neither the University of Memphis nor the student investigators has budgeted funds to compensate them for injury or illness that may result from participation in this study and thus will not be accountable for illness or injury acquired during the course of this study. If potentially significant clinical findings are observed by the research team during the course of the study, the involved participants will be notified and advised to contact their personal medical doctor. However, it is not possible to detect signs and/or symptoms of an undiagnosed, previously unidentified medical problem during the specific measures being utilized.

Any needed emergency treatment provided by investigators in the laboratory setting will follow the standard procedures of the Human Performance Laboratories (Appendix E). If adverse events occur outside the Human Performance Laboratories (i.e. at home), participants should seek medical attention and notify investigators as soon as possible concerning the event.

POTENTIAL BENEFITS

Direct benefits to participants include a greater understanding of their walking economy and gait biomechanics. Potential benefits include improved understanding of individual anatomy through anthropometric measurements as well as improved understanding of their personal movement biomechanics.

DIFFERENTIAL EVALUATION OF RISKS & BENEFITS

Though there is a risk of potential injury from participating in this study, the age and health status of the participants serves to limit this risk. The risk posed to participants is no greater than would be encountered in their regular daily activities.

PRIVACY

To protect the privacy of the participants, contact will be made via email to an address provided by the participant. Participants will interact with the investigator in the Musculoskeletal Analysis Laboratory of the investigator's office. All personnel present for research activities will either be a participant or an investigator on this study. Images will be electronic representations of reflective markers placed on the participant's anatomical landmarks and will not include any identifying image of the participant. These images appear to be a configuration of dots and cannot be used in any manner that would endanger participant privacy.

Prospective participants will be screened via phone or email to determine their eligibility based on the previously-mentioned criteria. Prior to participation, each volunteer will be informed of all procedures, potential risks and benefits associated with this study through both verbal and written form in accordance with the procedures approved by the University Institutional Review Board for Human Participants Research. No data will be collected until participants sign the informed consent document.

The research procedures will be conducted at the University of Memphis in the Musculoskeletal Analysis Laboratory located in FH171 of the Elma Neal Roane Fieldhouse.

The principal investigator (Dr. Powell) has a PhD from the University of Tennessee, Knoxville. He has experience in conducting human subject research, is a Fellow of the American Heart Association (FAHA) and is certified as a Certified Strength & Conditioning Specialist (CSCS) and Tactical Strength & Conditioning Facilitator (TSAC-F) through the National Strength and Conditioning Association (NSCA).

Participants should not take part in this study if they have had any previous injury or condition that might predispose them to further injury. If the participant has any past or current health conditions diagnosed by a physician that would not permit them to perform running, jumping and landing

activities and/or that would limit their movement capabilities in any way, they should not participate. Finally, if the volunteer is under 18 or over 35 years of age, they will be ineligible to participate. Informed Consent Form and PAR-Q forms will be used to obtain this information from each prospective participant.

CONFIDENTIALITY

Data from this study may be used in reports, presentations and publications but results will be reported in aggregate and each individual's results will be kept confidential. All materials will be kept in a key-locked file cabinet in a locked room (Fieldhouse 309) when not being used by investigators. The key to the file cabinet remains in Dr. Powell's office at all times and only he has access to the key. No participant names will be included in any data analysis files, nor will participants names be included in any presentation data. hence, there will be no way to identify participants other than a unique, generic participant ID number provided at the time of study inception. The participant ID will be assigned to each participant at random and the ID number will be written at the top of the informed consent document which will be locked in the file cabinet. Following all analyses, materials associated with individual participants will be shredded. Study data will be maintained on password protected computers located in the Musculoskeletal Analysis Laboratory (Fieldhouse 171). Only study investigators will have access to study data. Again, no name identifiers will be included in the data analysis files.

COLLABORATION, ENGAGEMENT & SPONSOR RELATIONSHIPS

N/A

PROPOSAL

N/A

Appendix B: Informed Consent

Consent to Participate in a Research Study

Quantification of energy expenditure in response to simulated parkinsonian rigidity

WHY ARE YOU BEING INVITED TO TAKE PART IN THIS RESEARCH?

You are being invited to take part in a research study in which we are assessing how changes in the connective tissues effect the energy it takes to walk. The data that we collect from you will then be used to mimic walking in individuals with Parkinson's disease. In this study you will be asked to sit relaxed in a chair while a robot moves your foot, push against my hand as hard as you can with your ankle, knee and hip and to walk on the ground and on a treadmill. We will measure the forces that you create and the air that you breathe out. You are being invited to participate in this study because you have told the investigator that you are physically healthy, are between the ages of 18 and 35 and that you are both familiar with and confident in safely performing walking. If you volunteer to take part in this study, you will be one of about 15 people to do so at the University of Memphis.

WHO IS DOING THE STUDY?

The person directly in charge of this study is Dr. Douglas Powell, PhD of the School of Health Studies at The University of Memphis. There may be other people on the research team assisting at different times during the study.

WHAT IS THE PURPOSE OF THIS STUDY?

The overall purpose of this study is to assess how changes in the connective tissues that occurs with Parkinson's disease effects the energy cost of walking. Your data will then be used to simulate walking in people with Parkinson's disease. The outcome may better inform medical professionals regarding the diagnosis and treatment of Parkinson's disease.

ARE THERE REASONS WHY YOU SHOULD NOT TAKE PART IN THIS STUDY?

Before you participate in this study, you will complete the Physical Activity Readiness Questionnaire (PAR-Q). If you report any condition that would increase your risk of injury, you will be excluded from participating in the study. Finally, if you are under 18 years of age or over 35 years of age, you will be ineligible to participate.

WHERE IS THE STUDY GOING TO TAKE PLACE AND HOW LONG WILL IT LAST?

The research procedures will be conducted at the University of Memphis in the Musculoskeletal Analysis Laboratory located in FH171 of the Elma Neal Roane Fieldhouse. Once preliminary paperwork and screening have been completed, you will be asked to come to the Musculoskeletal Analysis Laboratory one time for testing purposes. This visit will take approximately 60 to 75 minutes. You will only be asked to volunteer for this study during this one visit.

WHAT WILL YOU BE ASKED TO DO?

During this 75 minute testing session, you will be asked to let us measure your body including height, weight and age. We will then ask you to sit relaxed in a chair while a robot moves your foot and then walk over a walk way and on a treadmill at the same speed. We will measure your muscular and lung performance during these walking tasks. You will need to dress in a manner that will enable us to identify various anatomic landmarks so that measurements can be taken and so that you may perform the walking tasks.

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORT?

Since you already accustomed to walking every day, the tasks you will be doing will not expose you to increased risk of injury. In fact, since fatigue will be minimized, the testing is likely to be less risky than if you were unhealthy. However, walking on a treadmill may present some risk of injury in the unlikely scenario in which you trip and fall down on the treadmill. Risks will be minimized by clear instructions and supervised practice following appropriate guidelines as described by the American College of Sports Medicine (ACSM) and the National Strength and Conditioning Association (NSCA). If any abnormal signs or symptoms appear during participation, the exercise will be terminated and you will receive immediate attention.

WILL YOU BENEFIT FROM TAKING PART IN THIS STUDY?

There is no guarantee that you will get any benefit from taking part in this study. However, some people may find it beneficial to know their average amount of energy expended during everyday walking. You may also learn more about your walking movements and how these movements might place you at a greater risk of injury. Your willingness to take part may help society gain a better understanding of this research topic.

DO YOU HAVE TO TAKE PART IN THE STUDY?

If you decide to take part in the study, it should be because you want to volunteer. You will not lose any benefits or rights you would normally have if you choose not to volunteer. You can stop at any time during the study and still keep the benefits and rights you had before volunteering. If you are a student at The University of Memphis, whether or not you decide to take part in this study, your choice will have no adverse effect on your academic status or grade in any class in which you are enrolled.

IF YOU DON'T WANT TO TAKE PART IN THE STUDY, ARE THERE OTHER CHOICES?

If you do not want to be in the study, you do not have to participate. There are no other choices.

WHAT WILL IT COST YOU TO PARTICIPATE?

There are no costs associated with taking part in the study.

WHO WILL SEE THE INFORMATION THAT YOU GIVE?

We will make every effort to keep private all research records that identify you to the extent allowed by law. However, there are some circumstances in which we may have to share your information with other people. We may be required to provide the Physical Activity Readiness Questionnaire (PAR-Q) to medical professionals in the case of a serious injury occurring during the study. Also, we may be required to show information which identifies you to people with research oversight authority from The University of Memphis who need to be sure we have done the research appropriately.

Your study-related information will be combined with information from other people taking part in the investigation. When we share the study design and findings with others in written and/or oral form, we will only report the combined information we have gathered and you will not be personally identified. We will make concerted attempts to publish the results of this study; however, we will keep your name and other identifying information private.

We will make every effort to prevent anyone who is not on the research team from knowing that you gave us information, or what that information is. All paper records and portable storage devices will be secured in a locked file cabinet that is accessible only to the investigators of the study.

CAN YOUR TAKING PART IN THE STUDY END EARLY?

If you decide to take part in the study, you still have the right to decide at any time that you no longer want to continue or have us include your data in any statistical analysis. You will not be treated differently if you decide to stop taking part in the study.

The individuals conducting the study may need to withdraw you from it. This may occur if you are not able to follow the directions they give you or if they find that your being in the study is more risk than benefit to you.

ARE YOU PARTICIPATING OR CAN YOU PARTICIPATE IN ANOTHER RESEARCH STUDY AT THE SAME TIME AS PARTICIPATING IN THIS ONE?

You may take part in this study if you are currently involved in another research study that does not require strenuous physical activity. It is important to let the investigator/your doctor know if you are in another research study. You should also discuss with the investigator before you agree to participate in another research study while you are enrolled in this study.

WHAT HAPPENS IF YOU GET HURT OR SICK DURING THE STUDY?

If you believe you are hurt or if you get sick because of something that may be due to the study, you should contact Douglas Powell, PhD at dwpowell@memphis.edu or (901) 678-5209 immediately. In the case of a life-threatening emergency, you should call 911.

It is important for you to understand that the University of Memphis does not have funds set aside to pay for the cost of any care or treatment that might be necessary because you get hurt or sick while taking part in this study. Also, the University of Memphis will not pay for any wages you may lose if you are harmed by this study.

Medical costs that result from research-related harm cannot be included as regular medical costs. Therefore, the medical costs related to your care and treatment because of research-related harm will be your responsibility. A co-payment/deductible from you may be required by your insurer or Medicare/Medicaid even if your insurer or Medicare/Medicaid has agreed to pay the costs. The amount of this co-payment/deductible may be substantial. *You do not give up your legal rights by signing this form*.

WHAT IF YOU HAVE QUESTIONS, SUGGESTIONS, CONCERNS, OR COMPLAINTS?

Before you decide whether to accept this invitation to take part in the study, please ask any questions that might come to mind now. Later, if you have questions, suggestions, concerns, or complaints about the study, you can contact the investigator, Douglas Powell, PhD, at dwpowell@memphis.edu. If you have any questions about your rights as a volunteer in this research, contact the Institutional Review Board staff at the University of Memphis at (901) 678-2705. We will give you a signed copy of this consent form to take with you.

WHAT IF NEW INFORMATION IS LEARNED DURING THE STUDY THAT MIGHT AFFECT YOUR DECISION TO PARTICIPATE?

If the researcher learns of new information concerning this study that might change your willingness to continue as a participant, the information will be provided to you. You may be asked to sign a new informed consent form if the information is provided to you after you have joined the study.

_____ _____

Signature of person agreeing to take part in the study Date