MODULATION AND MODELING OF ANTICIPATORY POSTURAL ADJUSTMENTS FOR GAIT INITIATION IN PERSONS WITH PARKINSON'S DISEASE

BY

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DISSERTATION

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ABSTRACT

Parkinson's disease (PD) is a movement disorder traditionally thought to be caused by the degeneration of striatal dopaminergic neurons in the substantia nigra. One of the most devastating symptoms of PD that can decrease mobility and substantially impair quality of life is freezing of gait (FOG). Currently, the treatments for the motor symptoms of PD (e.g., levodopa, deep brain stimulation) are ineffective at managing FOG as the disease progresses. These treatments only target the cortical-striatal pathways of volitional movement that are dependent on dopamine, whereas FOG may be caused by the degeneration of other non-dopaminergic subcortical nuclei that are involved with posture and gait control (e.g., the pedunculopontine nucleus). A well-characterized behavior observed in PD that could contribute to FOG is a diminished ability to properly coordinate anticipatory postural adjustments (APAs) prior to the first step. In particular, diminished muscle activation leads to impaired limb mechanics and slower, less-coordinated gait initiation. Sensory cues have been demonstrated to improve gait initiation behaviors, possibly because they provide relevant information for movement to the motor cortex through cerebellar-thalamo-parietal pathways that remain intact during the disease process. However, sensory cues are not always reliable or effective in all contexts and are unable to directly modulate the force production of the user. Forms of mechanical stimuli can amplify force production during APAs by directly modulating force production and providing relevant timing and magnitude information through afferent sensory pathways. To date, no mechanical assistance that mimics the desired motion during an APA provided at the ankle joint in the form of modest ankle torques has been tested. The **overall research objective** of this dissertation work was to test the hypothesis that mechanical assistance provided at the ankle joint can be an effective paradigm for facilitating the diminished gait initiation behaviors in persons with PD and FOG symptoms. Biomechanical measurements and mechanical modeling techniques were

used to explore the neuromechanical factors (e.g., cognitive, sensorimotor, biomechanical) that could enable this type of intervention or therapy.

(1) The **first research objective** was to provide proof of concept that mechanical assistance provided at the ankle through a powered ankle-foot orthosis can shorten and amplify APAs compared to self-initiated stepping in healthy young adults.

(2) The **second research objective** was to test the hypothesis that mechanical assistance provided at the ankle by a wearable powered ankle-foot orthosis can directly shorten and amplify gait initiation APAs compared to self-initiated and acoustic cued stepping in persons with PD and FOG.

(3) The **third research objective** was to evaluate how cue-induced modulation of APAs in persons with PD and FOG vary based on whether the external cue is initiated exogenously or is self-triggered.

(4) The **fourth research objective** of this dissertation was to simulate the behaviors observed during the early phase of an APA for gait initiation in persons with PD and FOG using mechanical modeling techniques.

Results from these studies may inform future interventions or therapies that can provide mechanical assistance at the ankle during gait initiation for persons with PD and FOG. Such interventions could increase mobility and promote independence, thereby improving quality of life and decreasing morbidity for these patients.

To Family

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TABLE OF CONTENTS

1 INTRODUCTION

1.1 Freezing of Gait in Parkinson's Disease

Parkinson's disease (PD) is the second most common neurodegenerative disease, disproportionally affecting adults over the age of 50 (Pringsheim et al. 2014). According to the Parkinson's Disease Foundation, PD is estimated to affect 10 million people worldwide and 1 million in the United States (Parkinson's Disease Foundation 2016). PD has typically been characterized by the progressive loss of dopamine-producing neurons in the substantia nigra, a concentration of pigmented cells that is a component of the basal ganglia (Kish et al. 1988). This degeneration causes a malfunction of cortical-striatal pathways that control voluntary movement (Albin et al. 1989), leading to cardinal motor symptoms that include akinesia, bradykinesia, rigidity, tremor, and postural and gait dysfunction (Macht et al. 2007). Degeneration in PD is not only confined to the substantia nigra and the dopaminergic system (Braak et al. 2001; Braak et al. 2002; Langston 2006). Other subcortical nuclei and neurotransmitters that are involved with postural control are also subject to degeneration including the locus coeruleus (norepinephrine), raphe nucleus (serotonin), and pedunculopontine nucleus (abbreviated PPN, acetylcholine) (Jellinger 1988; Zweig et al. 1989; Braak et al. 2001; Braak et al. 2002; Langston 2006; Grimbergen et al. 2009). The etiology and pathophysiology of PD remain largely unknown. However, the main candidate for degeneration is the accumulation of Lewy Bodies, which are abnormal protein aggregates made up primarily of alpha-synuclein (Lewy 1912; Spillantini et al. 1997).

One of the most devastating features of PD-associated gait dysfunction is freezing of gait (FOG), which affects up to one-half of persons with PD (Macht et al. 2007). These symptoms typically involve an absence or reduction of voluntary movement, including problems with initiating gait (Berardelli et al. 2001; Giladi and Nieuwboer 2008). Patients describe the feeling as their feet are "glued to the floor" often coupled with a phenomenon known as "trembling knees" (Jacobs et al. 2009). FOG presents in three ways: (1) the inability to take the first step (also known as start hesitation), (2) freezing while walking, or (3) freezing while making a turn (Giladi and Nieuwboer 2008). These symptoms are associated with a decrease in postural stability, and they increase in severity and incidence with disease progression (Lamberti et al. 1997; Giladi 2001; Macht et al. 2007; Vervoort et al. 2013). Like PD more generally, the cause of FOG is also poorly understood. One candidate mechanism is degeneration of nuclei responsible for posture and balance control in the brain stem, namely the PPN, which has been linked to an increased risk of falling in PD (Jellinger 1988; Zweig et al. 1989; Bohnen et al. 2009). Ultimately, FOG decreases mobility, increases the risk for falls, and has a large negative overall impact on quality of life (Giladi 2001; Bloem et al. 2004; Allen et al. 2013).

Currently, there are no therapies or treatments for FOG symptoms. The most common treatment for motor symptoms has been dopamine replacement therapies (e.g., levodopa, dopamine agonists), which can significantly improve motor symptoms but unfortunately have little impact on mitigating FOG (Giladi 2008). Other pharmacological agents have been tested with limited success and they typically lose efficacy over time (Giladi 2001; Macht et al. 2007; Giladi 2008). Recently, deep brain stimulation (DBS) has emerged as a surgical intervention to improve motor symptoms by stimulating the subthalamic nucleus and globus pallidus of the basal ganglia. Despite its effectiveness for improving several motor dysfunctions (i.e., tremor, rigidity, bradykinesia, decreased gait speed) (Rodriguez-Oroz et al. 2005; Roper et al. 2016), DBS can also exacerbate posture and gait dysfunction (Rodriguez-Oroz et al. 2005; St George et al. 2010) or does nothing to improve some gait characteristics (e.g., variability and complexity) (Park et al. 2011). A handful of studies have observed improvements in gait and posture with electrical stimulation of the PPN, but a comprehensive clinical trial has yet to be performed (Morita et al. 2014). Thus, there exists a need for effective interventions that can alleviate the symptoms of FOG.

1.2 Anticipatory Postural Adjustments of Gait Initiation

During healthy, able-bodied gait initiation, a set of anticipatory postural adjustments (APAs) are coordinated to prepare the body to accelerate forward for the first step. The behavior starts with a preparatory "loading – unloading" phase. Beginning at standing posture, the tibialis anterior (dorsiflexor muscle) is activated while the gastrocnemius and soleus (plantarflexor muscles) are deactivated on both legs (Figure 1 and Figure 2) (Carlsoo 1966; Crenna et al. 1991; Elble et al. 1996). At the same time, the stance leg has a similar silencing of the plantarflexor muscles (Elble et al. 1996). This sequence of muscle activations results in a simultaneous loading and unloading of the stepping and stance feet, respectively, which increases the vertical (directed upward, Figure 1), frontal (directed medially), and sagittal (directed anteriorly) ground reaction forces under the stepping foot (Carlsoo 1966; Elble et al. 1996). Also, the center of pressure is moved laterally and posteriorly towards the stepping foot and the center of mass moves slightly forward and laterally toward the stance limb (Figure 1 and Figure 3). Increased gait initiation velocity, posterior center of pressure excursion, and the initial tibialis anterior burst on the stepping foot are positively correlated (Crenna and Frigo 1991; Lepers and Breniere 1995). After the “loading-unloading” phase, the center of mass is accelerated laterally (towards the stance foot) and forward by way of activating the plantarflexor muscles (soleus and gastrocnemius) of the stepping leg, while at the same time deactivating the dorsiflexor muscles (tibialis anterior) in both the stance and stepping legs (Figure 2) (Crenna and Frigo 1991; Lepers and Breniere 1995; Elble et al. 1996; Burleigh-Jacobs et al. 1997). Finally, the tibialis anterior on the stepping leg and the gastrocnemius on the stance leg are activated (Figure 2) as the stepping foot lifts off the ground and the center of mass is propelled forward (Figure 3), resulting in a step (Carlsoo 1966; Crenna and Frigo 1991; Elble et al. 1996).

It has been well established that APAs in persons with PD are diminished and prolonged compared to healthy individuals (Figure 1), especially in patients that suffer from FOG (Burleigh-Jacobs et al. 1997; Halliday et al. 1998; Jacobs et al. 2009; Rogers et al. 2011)**.** In particular, the ability to produce force is attenuated, including diminished activation of the tibialis anterior on the stepping leg during the loading-unloading phase (Figure 1 and Figure 2) (Elble et al. 1996; Rogers et al. 2011). Due to the positive correlation between the diminished initial tibialis anterior activation and posterior excursion of the center of pressure, gait initiation velocity is slower in PD (Burleigh-Jacobs et al. 1997; Halliday et al. 1998). Furthermore, people with PD and FOG have diminished anterior-posterior center of pressure excursions during an APA (Figure 1) and decreased overall postural control compared to people with PD and no FOG symptoms (Vervoort et al. 2013; Alibiglou et al. 2016). These deficits in APAs could be attributed to malfunctioning of cortical-striatal pathways, as well as the lower locomotor regions of the reticular formation containing the PPN in PD (Takakusaki 2008; Nutt et al. 2011). Overall, diminished and prolonged

APAs result in slower gait initiation velocity (Burleigh-Jacobs et al. 1997; Halliday et al. 1998) and disrupts the normal sequence of APAs (Crenna and Frigo 1991; Rogers et al. 2011). Thus, interventions and therapies for start hesitation that focus on facilitating APA generation could be beneficial for persons with PD and FOG.

1.3 Approaches to Facilitating Gait Initiation

The mostly widely recognized approach for alleviating FOG and facilitating gait initiation is by providing external sensory cues. Some of the first quantitative evidence demonstrated that external cues can restore APAs and improve gait initiation (Burleigh-Jacobs 1997). The neural correlates believed to enable cues run through the cerebellum, thalamus, parietal cortex, and finally motor cortex, circumventing the malfunctioning cortical-striatal pathways that are dependent on dopamine (Praamstra et al. 1998; Nieuwboer 2008; Nombela et al. 2013). This theory has been supported by evidence that cues are effective both on and off dopaminergic medication (Burleigh-Jacobs 1997). Over the past couple of decades, cueing has been broadly studied, but with inconsistent results (Dietz et al. 1990; Kompoliti et al. 2000; Cubo et al. 2004; Nieuwboer 2008). For example, after a single session with different forms of visual cues (i.e., lines on the floor and a walking stick that provided a threshold to step over) followed by practice at home with the walking stick, some patients experienced positive benefits in reducing FOG, while others either did not benefit or had a worsening in symptoms of FOG (Dietz et al. 1990). A longitudinal study also demonstrated a positive effect of cueing after three weeks of in-home training, but the cueing effect on posture and gait scores diminished substantially at a 6-week follow up assessment (Nieuwboer et al. 2007). These findings underscore that more attention towards how and when to present cues is needed. The lack of consistent efficacy could be due to a variety of reasons, one being current cueing paradigms do nothing to actively modulate the force production of the user. Moreover, it is still not fully understood what timing and context (i.e., environments, paradigms) are ideal for presenting cues (Nieuwboer 2008). Consequently, there is a need for more reliable cueing interventions capable of facilitating force production while being presented in an effective manner.

The magnitude of APAs can be directly modulated using mechanical assistance to mimic the desired motion of the body during gait initiation. Several studies have shown that floor translations and lateral waist pulls can modulate APAs in persons with PD (Burleigh-Jacobs et al. 1997; Mille et al. 2009; Rogers et al. 2010) and healthy adults (Burleigh et al. 1994; Mouchnino et al. 2012). For example, in persons with PD, a backward floor translation used to facilitate forward body lean resulted in shorter APA timing and increased force production compared to self-initiated stepping (Burleigh-Jacobs et al. 1997). More recently, the use of a lateral waist pull (Mille et al. 2009) and a protocol involving either raising or dropping the floor under the stance foot (Rogers et al. 2010) were associated with a similar shortening of APA duration and earlier step onset in persons with PD. The floor dropping paradigm also amplified vertical ground reaction force magnitudes under each foot. These findings suggest that it is possible to modulate force using externally applied mechanical stimuli during APAs for gait initiation in persons with PD.

Despite several studies focused on different mechanical stimuli, the utility of wearable devices that can specifically provide mechanical assistance during gait initiation has been unexplored. Shoes that provide somatosensory stimulation (vibration) underneath the foot have been developed for gait dysfunction in PD (Winfree et al. 2012), but not mechanical assistance.

Our lab has developed a portable powered ankle-foot orthosis (PPAFO) to investigate applications for untethered gait assistance (Figure 4) (Shorter et al. 2011a; Boes et al. 2013). The most recent Gen 2.0 PPAFO utilizes a bi-directional pneumatic rotary actuator (PRN30D-90-45; Parker Hannifin, Cleveland, OH) to provide dorsiflexor and plantarflexor torque at the ankle (Boes et al. 2013). It is capable of producing up to 12 Nm of torque at 100 psig and the dorsiflexor torque can be down regulated according to the user's needs. The device utilizes an on-board microcontroller (MSP430G2553; Texas Instruments, Dallas, TX) to control two solenoid valves (VUVG 5V; Festo Corp-US; Hauppauge, NY, USA) which control dorsiflexion or plantarflexion actuation. The PPAFO can be powered either as a portable device by a compressed CO_2 gas tank worn at the waist (JacPac J-6901-91, 20 oz capacity; Pipeline Inc., Waterloo, ON, Canada), or by attachment to a stationary air compressor supply and hose line for power within a confined space. The device was built to be modular to accommodate multiple foot sizes (US men's 4 to 14) and tibial sizes (small, medium and large adult male). Control algorithms have been developed for providing assistance at specific times in the gait cycle (Li et al. 2011; Islam et al. 2016) and to adapt to different walking environments (stairs, ramps) (Li and Hsiao-Wecksler 2013). Hence, the PPAFO is a suitable platform to investigate the utility of wearable devices that can provide mechanical assistance during gait initiation.

To improve the viability of a mechanical assistance paradigm, it is important to consider the method and timing of cue triggering. Multiple approaches for exogenously triggering a cue have been investigated with varied results. One technique involves the use of wearable technology (e.g., accelerometers) to detect a freezing episode in order to present cues (Jovanov et al. 2009; Bachlin et al. 2010; Moore et al. 2013; Pepa et al. 2015). Despite a high classification rate (85%), patients reported that the cues were distracting when presented without a FOG episode (Bachlin et al. 2010). Recently, sensory-cue induced gait initiation was improved in PD patients when presented 2.5 seconds after a ready cue (i.e., the “instructed-delay” paradigm) (Rogers et al. 2011). This method is effective because it allows the person to adequately prepare for movement. Use of the instructed-delay may be limited in practical situations where the person needs the cue immediately. One previously unexplored option to eliminate any uncertainty for the user is to self-trigger a cue by pressing a button. Self-triggering could be considered a dual-task due to the multimodal cognitive/motor demands of triggering the cue and stepping simultaneously. Performing a cognitive dual-task has been found to impair motor performance in persons with PD, causing them to resort to conservative movement strategies including slower gait speed and cadence (O'Shea et al. 2002; Spildooren et al. 2010), and decreased center of pressure excursion during upright stance (Holmes et al. 2010). Relying on internal control versus external cues (i.e., self-awareness of the task rule versus the task rule is cued before each trial) can impair tasks that require attentional control (e.g., Stroop task) (Brown and Marsden 1988). Furthermore, people with PD and FOG have decreased cognitive capacity compared to people with PD without FOG (Walton et al. 2015). Another potential limitation of self-triggering is that it may potentiate the malfunctioning self-initiated cortical-striatal neural circuitry in PD, decreasing the effects of external sensory cue due to dysfunctional volitional control. In sum, a comparison between self-triggered versus externally-triggered cues could elucidate if cues (including mechanical assistance) are still effective when the user is able to self-trigger.

In addition to triggering the mechanical assistance, it is also important to consider the magnitudes and timings of the applied assistance. To accurately determine the necessary torque-timing relationship for the initial dorsiflexor torque, a model of the neuromechanics of gait initiation in persons with PD and FOG is necessary. As mentioned in the previous section, the initial TA burst during the “loading-unloading” phase can be diminished or absent in PD, resulting in diminished force production and a decreased excursion of the center of pressure in the sagittal plane (Elble et al. 1996; Burleigh-Jacobs et al. 1997). Despite the wealth of experimental evidence, no computational model of this neuromuscular dysfunction exists for PD. Simplified models of the body as an inverted pendulum in the sagittal plane have been used to calculate the mechanics during the “loading-unloading” phase of an APA in healthy individuals (Breniere et al. 1987; Lepers and Breniere 1995). However, they do not include components specifically related to the neuromuscular system that have also been widely used in postural control inverted pendulum models of healthy individuals (Johansson et al. 1988; Peterka 2000; Maurer and Peterka 2005) and persons with PD (Nogueira et al. 2010). Ultimately, an inverted pendulum model including these components of the neuromuscular system could be used to simulate the abnormal neuromechanics during APAs in persons with PD and FOG and inform interventions that include mechanical assistance provided at the ankle.

1.4 Objectives of Dissertation

The basic hypothesis of this dissertation was that a wearable device, which provides mechanical assistance at the ankle, can be an effective paradigm for facilitating gait initiation in persons with PD and FOG. The first research objective was to provide proof concept that mechanical assistance from the PPAFO can modulate the APAs of gait initiation in healthy young adults (Chapter 2). The second research objective was to investigate how mechanical assistance from the PPAFO can modulate APAs for gait initiation compared to self-initiated and cued stepping in persons with PD and FOG (Chapter 3). The third research objective was to evaluate how cue-induced modulation of APAs in persons with PD and FOG may vary based on whether the external cue (including mechanical assistance from the PPAFO) is initiated exogenously or self-triggered (Chapter 4). The fourth research objective was to simulate the diminished muscle activation and force production during APAs observed in persons with PD and FOG using an inverted pendulum model (Chapter 5). Finally, conclusions and potential future work are discussed (Chapter 6). Results from these studies will inform the successful implementation of interventions or therapies that can provide mechanical assistance at the ankle during gait initiation.

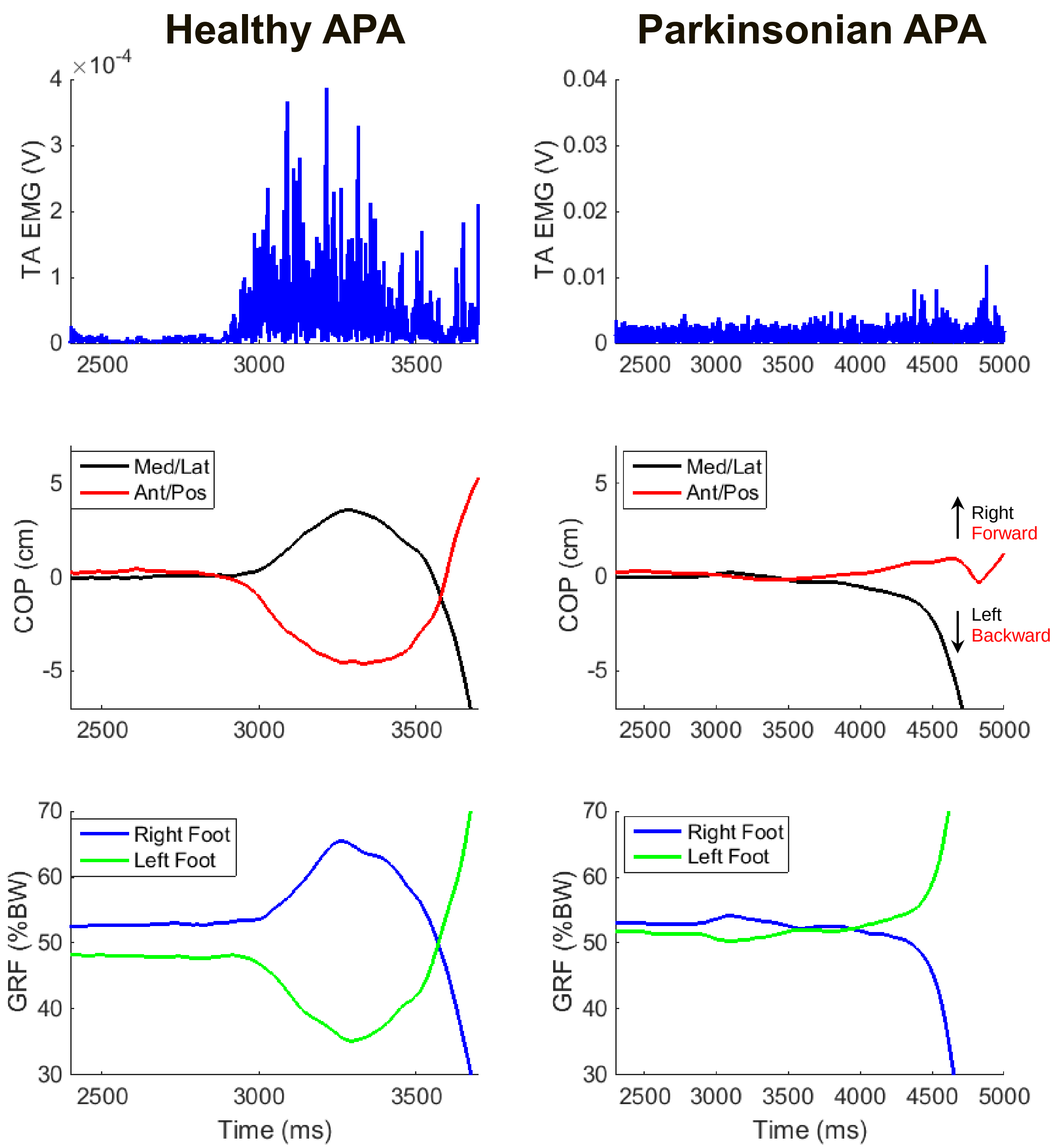

Figure 1: Characteristics of APAs for gait initiation for healthy and Parkinsonian adults. The plots show EMG from the tibialis anterior (TA) muscle of the stepping leg, center of pressure (COP) for total body, and vertical ground reaction forces (GRF) for the right (stepping) and left (stance) limbs. Note that all plots begin at the same time, but the Parkinsonian APAs are prolonged and diminished compared to the healthy APAs.

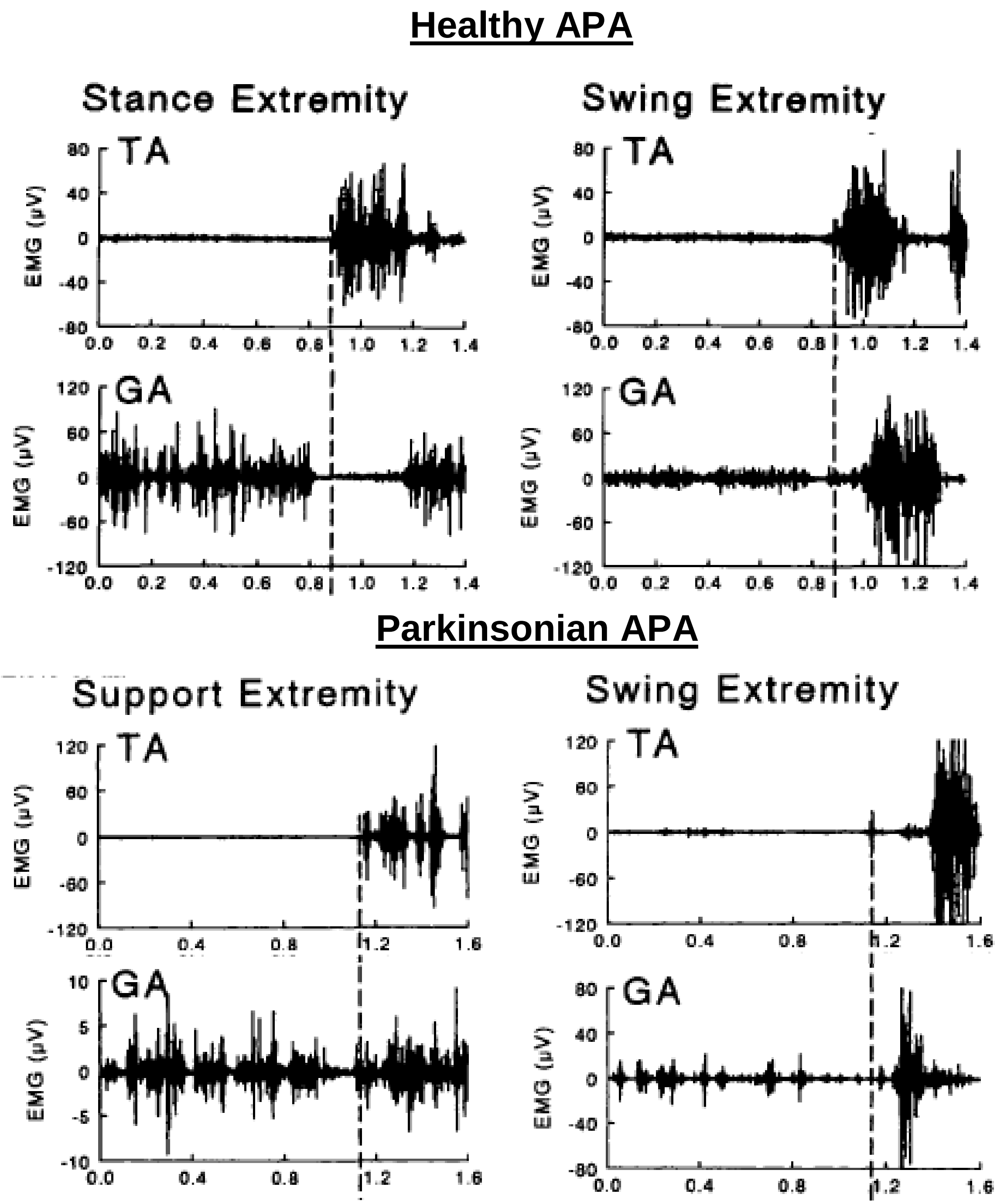

Figure 2: Healthy and Parkinsonian EMG activation patterns of the tibialis anterior (TA) and gastrocnemius (GA) of the swing (stepping) and stance (support) legs during an APA. The vertical dashed line indicates the onset of the APA. Adapted with permission from (Elble et al. 1996).

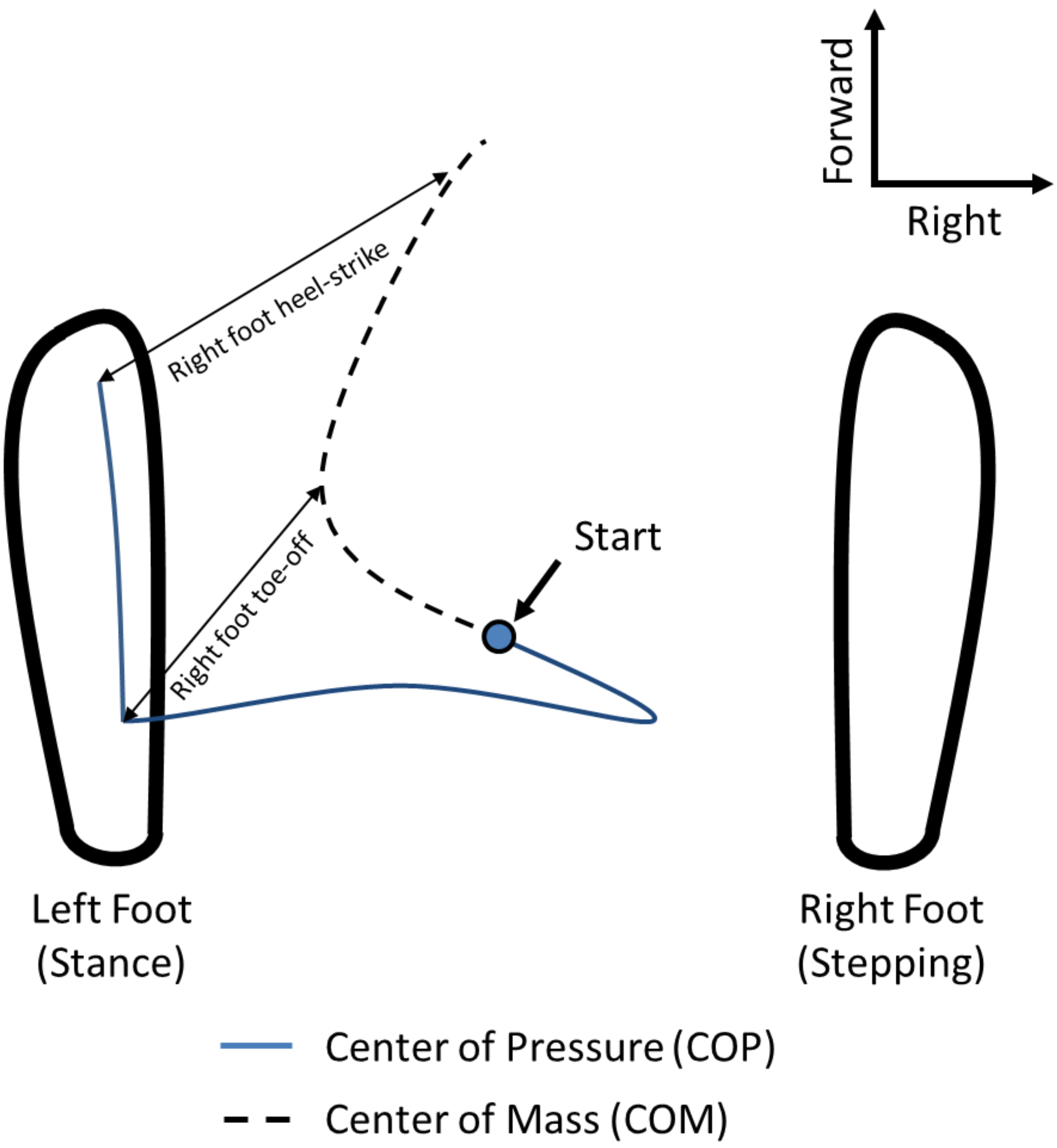

Figure 3: Two-dimensional top-down view of the archetypical center of pressure (COP) and center of mass (COM) trajectories during gait initiation. Adapted with permission from (Hass et al. 2005) and (Remelius et al. 2008).

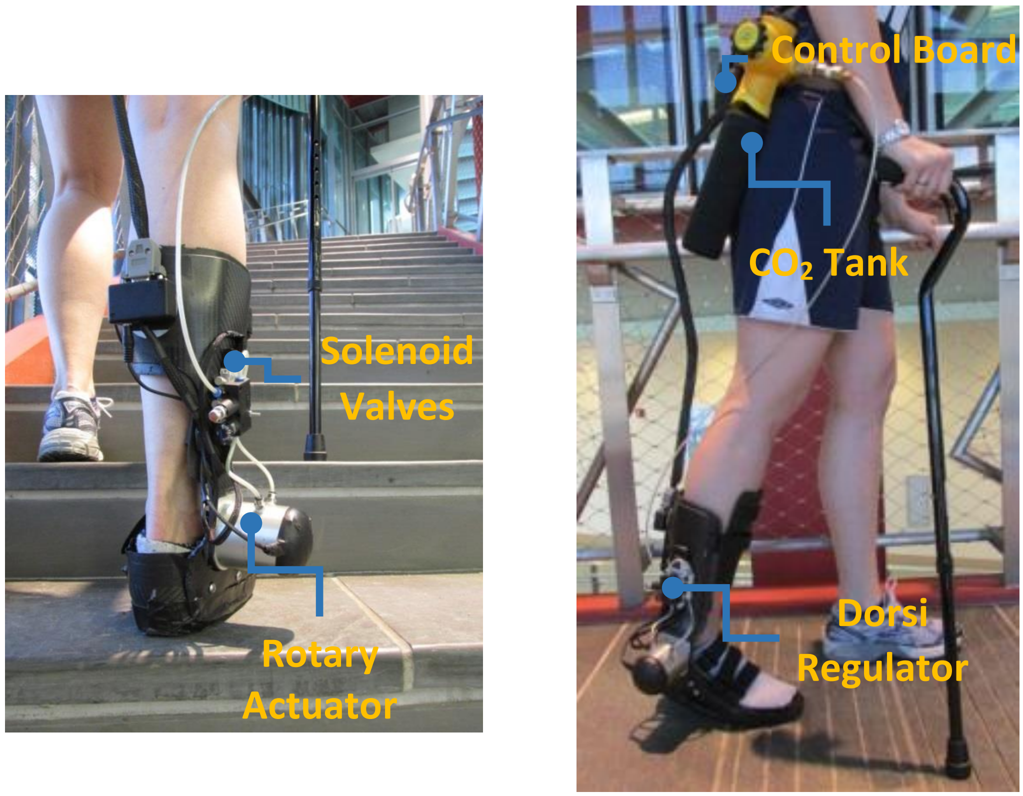

Figure 4: The portable powered ankle-foot orthosis (PPAFO).

2 Modulation of Anticipatory Postural Adjustments of Gait Using a Portable Powered Ankle-Foot Orthosis[1]

2.1 Abstract

Prior to taking a step, properly coordinated anticipatory postural adjustments (APAs) are generated to control posture and balance as the body is propelled forward. External cues (audio, visual, somatosensory) have been shown to facilitate gait initiation by improving the magnitude and timing of APAs in Parkinson's disease (PD), but the efficacy of these cueing strategies has been limited by their inability to produce the forces required to generate an appropriate APA. To date, mechanical cueing paradigms have been relatively underexplored. Using healthy young adults, we investigated the use of a portable powered ankle-foot orthosis (PPAFO) to provide a modest torque at the ankle as a mechanical cue to initiate gait. Subjects were instructed to initiate gait in five test conditions: (1) self-initiated in running shoes [baseline-shoe], (2) self-initiated trial in unpowered passive PPAFO [baseline-passive], (3) with acoustic go-cue in passive PPAFO [acoustic-passive], (4) acoustic go-cue and simultaneous mechanical assist from powered PPAFO [acoustic-assist], and (5) mechanical assist cue only [assist]. APA characteristics were quantified using ground reaction force (GRF), center of pressure (COP), and electromyography (EMG) data. Mechanical cueing significantly increased medial-lateral COP and GRF peak amplitude, and decreased GRF time to peak amplitude, COP and GRF onset times, and time to

[1]This work has been published in (Petrucci et al., 2013)

toe off. Mechanical cueing conditions also demonstrated consistent bimodal EMG behaviors across all subjects. Overall, these data suggest that the mechanical assist from the PPAFO can significantly improve APA timing parameters and increase APA force production in healthy young adults.

2.2 Introduction

During the transition from standing to stepping forward, anticipatory postural adjustments (APAs) are generated prior to the step (Crenna and Frigo 1991). The typical sequence of APAs observed during gait initiation include simultaneous loading of the stepping leg, unloading of the stance leg, movement of the center of pressure (COP) posterior and toward the stepping leg, an initial burst of activity in the tibialis anterior muscle of the stepping leg, and flexion of the stepping limb hip and knee (Figure 5). This motor sequence generates the forces required to accelerate the center of mass forward and laterally toward the stance limb at the start of the step, thus providing both posture and balance control, as well as forward propulsion.

In Parkinson's disease (PD), APAs for gait initiation are reduced in amplitude, prolonged in duration and often inappropriately timed with the forward step, resulting in the termination or shortening of the initial step. Clinicians have long recognized that one of the best methods to facilitate movement initiation in patients with PD is to provide them with a visual, acoustic or somatosensory cue. Laboratory studies have provided quantitative evidence to support this observation by showing that cues can significantly improve the initiation of gait (Burleigh-Jacobs et al. 1997). Despite evidence that cues can facilitate movement initiation in people with PD, the results of studies examining the effectiveness of cues in the home environment have yielded disappointing results (Dietz et al. 1990; Kompoliti et al. 2000; Cubo et al. 2004; Nieuwboer 2008).

This lack of effectiveness could be due in large part that current cueing paradigms do not compensate for reduced capacities to generate the forces necessary to successfully transfer the center of mass laterally during gait initiation. Therefore, there is a need for more reliable cueing interventions that are also able to facilitate force production.

Providing mechanical assistance as a cue has been relatively underexplored. Two recent studies have examined the effects of using an externally applied perturbation. One involved a lateral pull at the waist (Mille et al. 2009) and the other utilized raising/dropping the floor underneath the initial stance foot (Rogers et al. 2010) to facilitate medial-lateral adjustments in posture and balance prior to step initiation in PD patients with FOG. Both interventions were associated with significant shortening of APA duration and earlier step onset. The dropping floor protocol was also able to significantly improve vertical loading (unloading) force magnitude of the stepping (stance) legs, respectively. These results suggest that a mechanical perturbation which augments loading behaviors during an APA can improve gait initiation in individuals with FOG.

We have recently developed a portable powered ankle-foot orthosis (PPAFO) to provide untethered assistance during gait (Figure 6) (Shorter et al. 2011a; Hsiao-Wecksler et al. Patent Pending). It has been demonstrated to restore normative gait function in neurological disorders such as cauda equina syndrome and muscular dystrophy. The PPAFO utilizes a bi-directional pneumatic rotary actuator (CRB2BW40-90D-DIM0065, SMC Corp of America; Noblesville, Indiana) powered by a compressed CO_2 gas tank that can be worn at the belt (JacPac J-6901-91, 20 oz capacity; Pipeline Inc., Waterloo, ON, Canada) to provide dorsi and plantarflexor torque at the ankle. It is capable of producing up to 12 Nm of torque at 0.69 MPa (100 psi). Using on-board electronics, control strategies have been developed to provide assistance at specific times in the gait cycle (Li et al. 2011) and to adapt to different walking environments (stairs, ramps) (Li and Hsiao-Wecksler 2012). The purpose of the current study was to investigate how modest torques at the ankle delivered by the PPAFO can modulate APA behaviors during gait initiation. We hypothesize that by driving the ankle through typical APA movements for gait initiation with the PPAFO, participants will generate more force than that seen in self-initiated conditions.

2.3 Methods

2.3.1 Subjects

Five healthy young adults (4 male, 1 female, age 21±2 yrs, height 183.6±6.1 cm, weight 78.8±11.5 kg) were tested in this study.

2.3.2 Gait Initiation Task

In order to test its efficacy, mechanical cueing from the PPAFO was compared with an acoustic cue in the form of an auditory beep and providing mechanical assistance along with the acoustic cue. Test subjects were asked to initiate gait from a standing position by first stepping with the right leg. Five gait-initiation test conditions were evaluated: (1) self-initiated in personal walking shoes to provide normal baseline [baseline-shoe], (2) self-initiated trial in unpowered passive PPAFO to provide baseline while wearing PPAFO [baseline-passive], (3) acoustic go-cue with passive PPAFO to assess effect of acoustic cue [acoustic-passive], (4) acoustic go-cue with simultaneous mechanical assist from powered PPAFO to assess effect of acoustic and mechanical assist cue [acoustic-assist], and (5) only mechanical assist cue from powered PPAFO [assist]. The PPAFO was fit to the test participant and worn on the right limb. The participant’s personal walking shoe was worn on the left limb (Figure 6).

Blocks of 5 trials were performed for each test condition (total of 25 trials per participant). Trials for test condition (1) were run consecutively before the remaining four conditions. Trial order was randomized for conditions (2-5). Before each trial, subjects were told whether it was a cued or self-initiated trial. For conditions 1 and 2, subjects were instructed to initiate gait with their right foot on their own within 5-10 seconds after hearing the warning signal (Figure 7). For conditions 3-5, they were instructed to initiate gait with their right foot "as quickly as possible" taking a minimum of two steps forward in response to the go-cue. No practice trials were given before the test started.

2.3.3 Cue Presentation

It has been recently shown that gait initiation can be significantly improved in people with PD when the imperative cue to initiate stepping is preceded 2.5 s earlier by a warning cue (an instructed-delay paradigm) (Rogers et al. 2011). For conditions 3-5 we used a similar instructed-delay paradigm consisting of an acoustic warning cue presented 2.5 s before the imperative go-cue (acoustic and/or mechanical) to initiate a forward step with the right foot (Figure 7) (MacKinnon et al. 2007).

The instructed-delay warning, acoustic go-cue, and actuation of the PPAFO for the mechanical assist cue were all controlled with custom software (QUARC, Quanser Consulting Inc, Markham, ON, Canada). Both the acoustic warning and go-cue were clearly audible tones for 500 ms at 80 dB from a speaker. The mechanical assist cue began with a dorsiflexor torque (heuristically tuned to hold the subjects toes at neutral, approximately 3-5 Nm) delivered for 330 ms and followed with a subsequent plantarflexor torque of 9 Nm (based on 90 psig actuated pressure) for 83 ms which terminates at toe-off (timings based on average time to peak from APA onset and toe-off time in healthy control subjects (Rogers et al. 2011)). This pattern of torques matched activities normally seen in gait initiation.

2.3.4 Data Collection

Ground reaction force (GRF), center of pressure (COP), and electromyographic (EMG) data were recorded and sampled at 1000 Hz. The subject stood with each foot on separate force plates. The force plates were embedded in an instrumented treadmill (Bertec Corporation, Columbus, OH). Force data were filtered using a low-pass Butterworth filter with a cut-off frequency of 15 Hz. Net center of pressure under both feet (COP) for the medial-lateral (ML) and anterior-posterior (AP) directions were calculated using filtered GRF data. Bipolar surface EMG signals (Bagnoli 16, Delsys Corp., Boston, MA) were recorded from only the right tibialis anterior (TA).

2.3.5 Data Analysis

To quantify the APA response to the different test conditions, 11 parameters were computed from the vertical GRF and TA EMG of the right leg, and total body AP and ML COP (Figure 8). For the test conditions with acoustic and/or mechanical assistance, the times from the imperative go-cue to the onset of each parameter were determined for vertical reaction force (GRF_t_{onset}), AP center of pressure ($AP\text{-}COP\_t_{onset}$), ML center of pressure ($ML\text{-}COP\_t_{onset}$), and TA EMG signal (EMG_t_{onset}). For all test conditions, the magnitudes of the peak amplitude and the times from onset to the peak amplitude were recorded for vertical GRF (GRF_{pk}, GRF_t_{pk}), AP center of pressure ($AP\text{-}COP_{pk}$, $AP\text{-}COP\_t_{pk}$), and ML center of pressure ($ML\text{-}COP_{pk}$, $ML\text{-}COP\_t_{pk}$). Additionally, the time from onset to the start of toe off was recorded based on the time when the right vertical GRF went below 30 Nm ($t_{toe\text{-}off}$). GRFs were normalized as a percentage of a subject's body weight. Onset times were calculated based on a monotonic change of greater than three standard deviations from the mean signal that was recorded prior to the go-cue. For the baseline conditions that did not contain a go-cue, the mean signal was calculated prior to a point manually picked approximately 300-500 ms before GRF_t_{onset}. These times were further verified by visual inspection.

2.3.6 Statistical Analysis

One-way repeated-measures analysis of variance (ANOVA) tests for each of the 11 APA parameters were conducted with testing condition as the factor. All five testing conditions were compared in the six amplitude parameters (GRF_{pk}, GRF_t_{pk}, $AP\text{-}COP_{pk}$, $AP\text{-}COP\_t_{pk}$, $ML\text{-}COP_{pk}$, $ML\text{-}COP\_t_{pk}$) and time to toe-off ($t_{toe\text{-}off}$), Only the three cued conditions (acoustic-passive, acoustic, assist) were compared for the four onset times (GRF_t_{onset}, $AP\text{-}COP\_t_{onset}$, $ML\text{-}COP\_t_{onset}$, EMG_t_{onset}). Based on a Bonferroni adjustment for multiple statistical comparisons, we regarded *p* values less than 0.010 to indicate a significant association, and *p* values between 0.05 and 0.010 to reflect a "borderline" association. The adjusted *p* value for the onset time ANOVAs was $p = 0.017$, with borderline significant *p* values between 0.05 and 0.017. Post hoc effects were examined using Fisher LSD (Least Significant Difference) test. All data were processed using SPSS statistical software (Version 20, IBM Corp, Armonk, NY).

2.4 Results

Repeated-measures ANOVAs indicated statistically significant ($p < 0.010$ or $p < 0.016$) or borderline significant ($0.010 < p < 0.05$ or $0.016 < p < 0.05$) differences due to testing condition in seven of the 11 APA parameters (Table 1).

2.4.1 Ground Reaction Force

All APA parameters associated with the vertical GRF for the stepping (right) leg were affected due to the use of the mechanical cueing from the PPAFO (Table 1). Onset time (from go-cue to rise of GRF, GRF_t_{onset}) was significantly faster when the mechanical assist from the PPAFO was used compared to only acoustic cueing ($F_{2,8}$ = 11.67, p = 0.004). When the mechanical assist was used alone, the peak amplitude of the GRF (GRF_{pk}) was significantly larger than any condition without the mechanical cueing assistance ($F_{4,16}$ = 8.03, p = 0.001). The times to the peak GRF value (GRF_t_{pk}) tended to be faster for conditions with mechanical assist ($F_{4,16}$ = 5.34, p = 0.006). Similarly, the times to the start of toe-off ($t_{toe\text{-}off}$) tended to be faster in mechanical assist trials ($F_{4,16}$ = 3.31, p = 0.037).

2.4.2 Center of Pressure

Analogous to GRF parameters, mechanical cueing assistance affected both timing and peak displacement of center of pressure parameters. Medial-lateral onset time (ML-COP_t_{onset}) was significantly shortened by mechanical cueing compared to acoustic cueing ($F_{2,8}$ = 12.62, p = 0.003). Medial-laterial peak displacement (ML-COP_{pk}) was signficantly increased by cueing compared to baseline conditions, and mechanical assistance resulted in the largest movement of the COP ($F_{4,16}$ = 11.94, p < 0.001). Likewise, mechanical assitance accompanied by an acoustic cue tended to shorten anterior-poserior onset time (AP-COP_t_{onset}) when compared to acoustic cueing alone ($F_{2,8}$ = 5.87, p = 0.027).

2.4.3 Electromyography (EMG)

Although not significantly different, EMG onset time (EMG_t_{onset}) tended to be consistently shorter with mechanical cueing compared to the other conditions. A bimodal pattern in the TA muscle activity was consistently observed, supporting activation during APA onset, suppression during plantarflexion, and activation during late toe-off (Figure 9).

2.5 Discussion

The main finding of this study was that mechanical assistance provided from a PPAFO can be used as a somatosensory cue to induce consistent normal APA behaviors (Table 1). The increased force production due to the ankle torque assistance from the PPAFO resulted in a larger displacement of the center of pressure in the medial-lateral direction, which reflects the desired lateral weight transfer. Temporal characteristics were also shortened suggesting faster step initiation. EMG activity of the TA muscle also had a consistent bimodal behavior showing distinct activation, as expected during an APA. Overall, the data suggest that a mechanical assist (with or without acoustic cue) may be used as a potential cueing paradigm for gait initiation.

The underlying neural mechanisms that enable cues to work in people with PD are poorly understood. Cues have been demonstrated to elicit improved APAs in PD, i.e., similar or greater performance as compared to when a person is on levodopa medication (Burleigh-Jacobs et al. 1997; Majsak et al. 1998). This result suggests that the neural pathways used to generate motor commands for postural and locomotion are able to function independent of dopaminergic pathways. As proposed by Rogers et al. (2011), cues may act as a way of increasing preparation for movement and are processed in non-dopaminergic pathways in areas within the corticospinal tract. Studies in people with PD show an increase of activity in the lateral premotor and parietal cortices during movement (Samuel et al. 1997; Praamstra et al. 1998; Catalan et al. 1999; Sabatini et al. 2000). This neural activity in the premotor cortex is amplified at the beginning of the intended movement when a cue is given in an instructed-delay paradigm compared to in self-paced trials (Cui and MacKinnon 2009). At the same time, this neural activity is diminished when the cue is given at a random time interval when compared to self-paced trials. Given the instructed-delay paradigm has been shown to elicit APAs in people with PD consistently, using a fixed warning time interval may be a reliable paradigm for inducing gait APAs independent of dopaminergic pathways.

Although these data were recorded on healthy normal young adults, the results of this study may have potential implications for gait initiation in PD. Both healthy and PD subjects have been shown to elicit APA behavior in an instructed delay paradigm in up to 80% of trials (MacKinnon et al. 2007; Rogers et al. 2011). There is little insight into whether the duration of the mechanical assistance would impede or exacerbate APAs due to how little mechanical perturbations have been investigated as a cue. Previous studies used time durations as low as 100 ms to elicit an APA in people with PD (Rogers et al. 2010), which is shorter than what was used in the current protocol for the dorsiflexion torque. Future studies would have to be done to optimize the timing of the PPAFO actuations such that it will only provide assistance and not impede APAs. Most importantly, the amplified and shortened APAs observed using mechanical assistance from the PPAFO may be able to counteract the slower and under-scaled APAs that have been observed in people with PD (Rogers et al. 2011). Thus, a mechanical assist from the PPAFO may be able to induce the necessary loading/unloading behaviors that are absent in people with severe PD.

2.6 Conclusions

These data suggest that the mechanical assist from the PPAFO can signifcantly improve APA parameters and increase APA force production for healthy normal young adults. Future studies should include people with PD to test the feasibility of using the PPAFO for cueing of Parkinsonian gait.

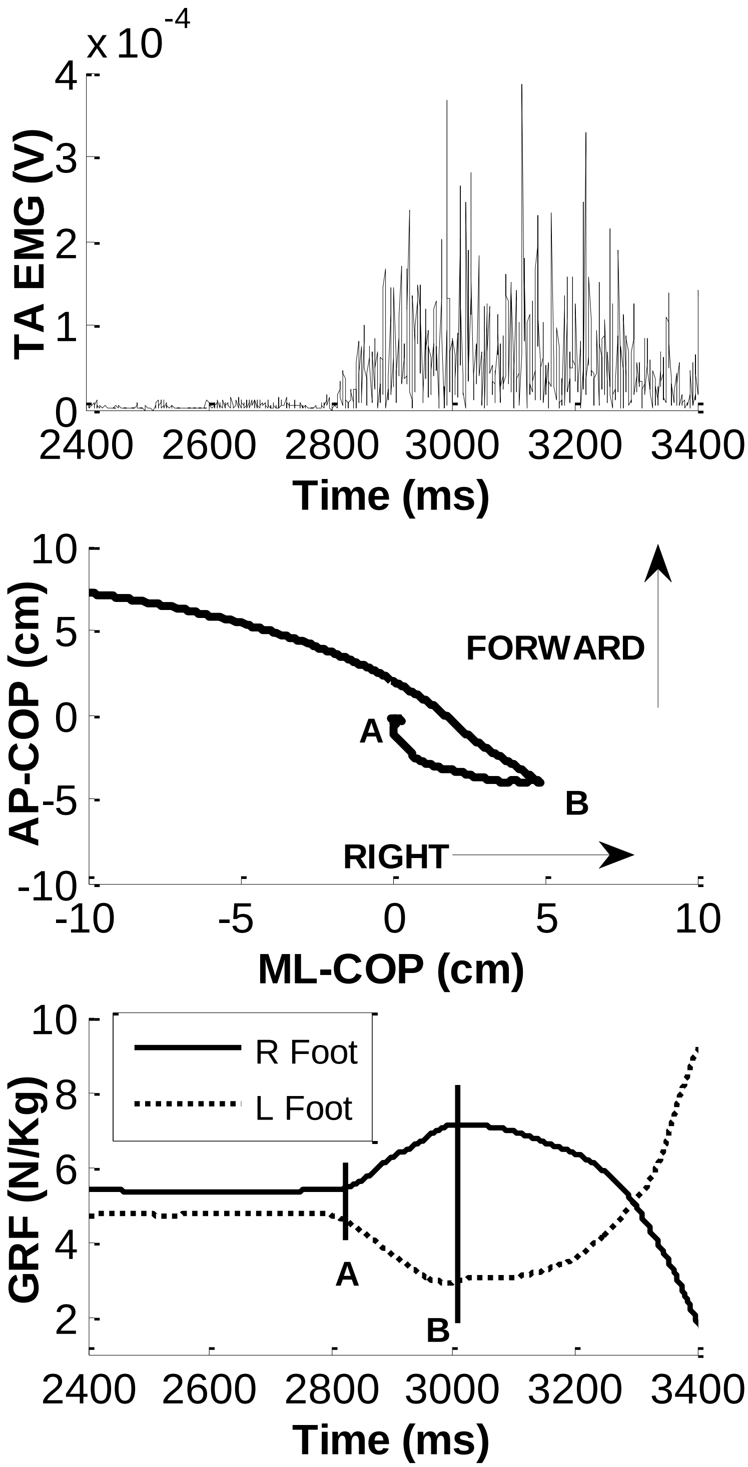

Figure 5: Characteristics of APAs for gait initiation starting with the right leg in a healthy adult that begins at point A. The plots show right tibialis anterior (TA) EMG, center of pressure (COP), and vertical ground reaction forces (GRFs) for the right (stepping) and left (stance) limbs.

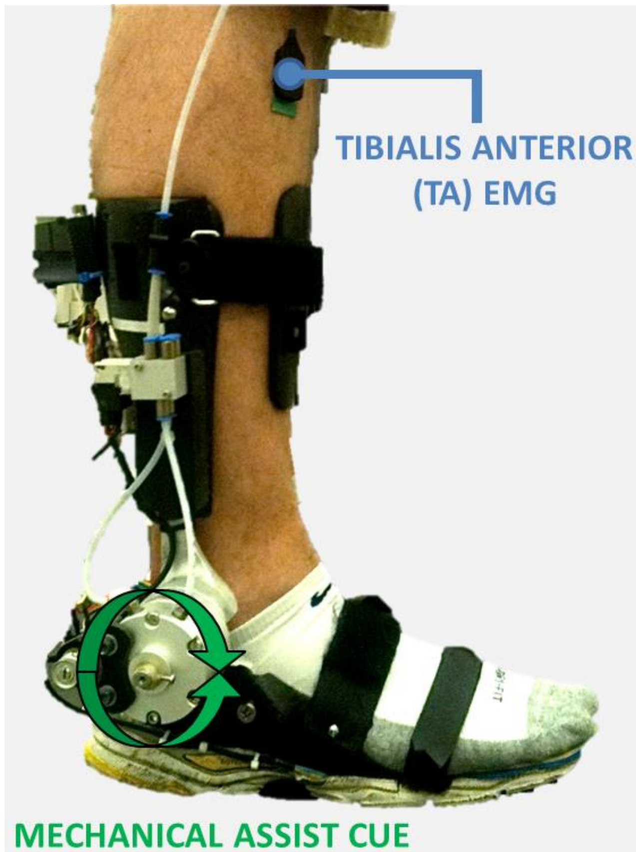

Figure 6: Experimental set up with the PPAFO attached to the right leg. Ground reaction force (GRF) data were recorded from two force plates under each foot. Bipolar surface EMG signals were recorded from an electrode placed over the right tibialis anterior (TA).

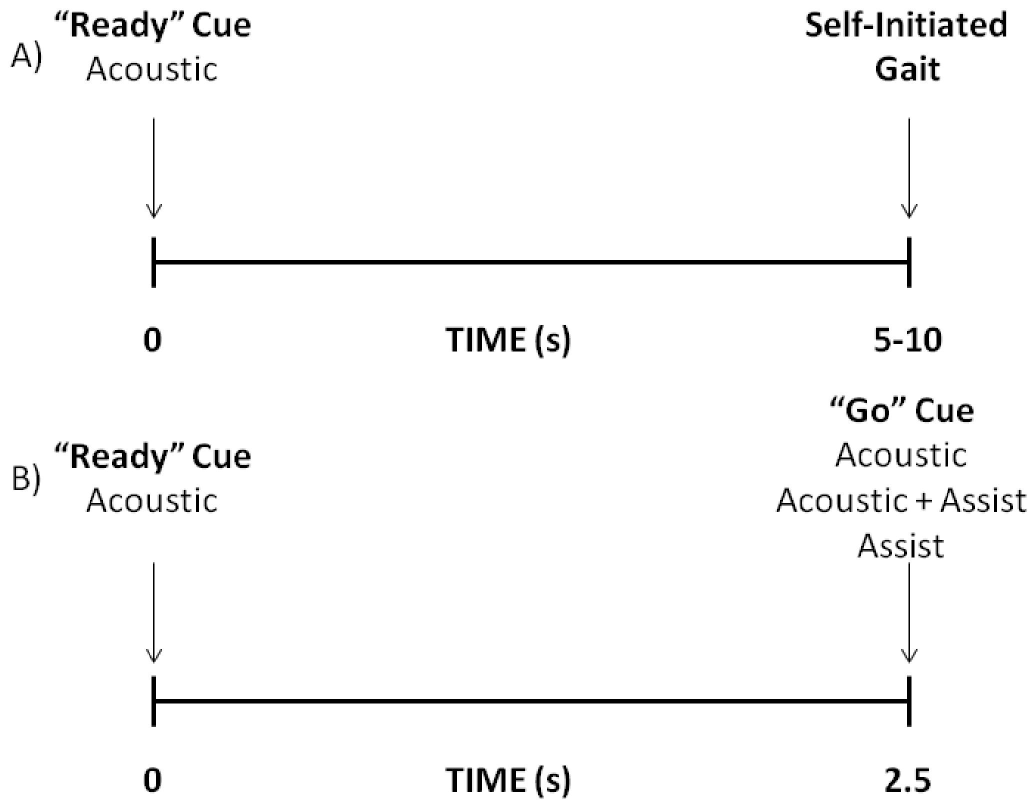

Figure 7: A) Timeline for self-initiated trials. Subject initiates gait within 5-10 seconds of the "ready" warning cue. B) Instructed-delay timeline for the cued trials. The imperative "go" is given 2.5 s after the "ready" warning cue.

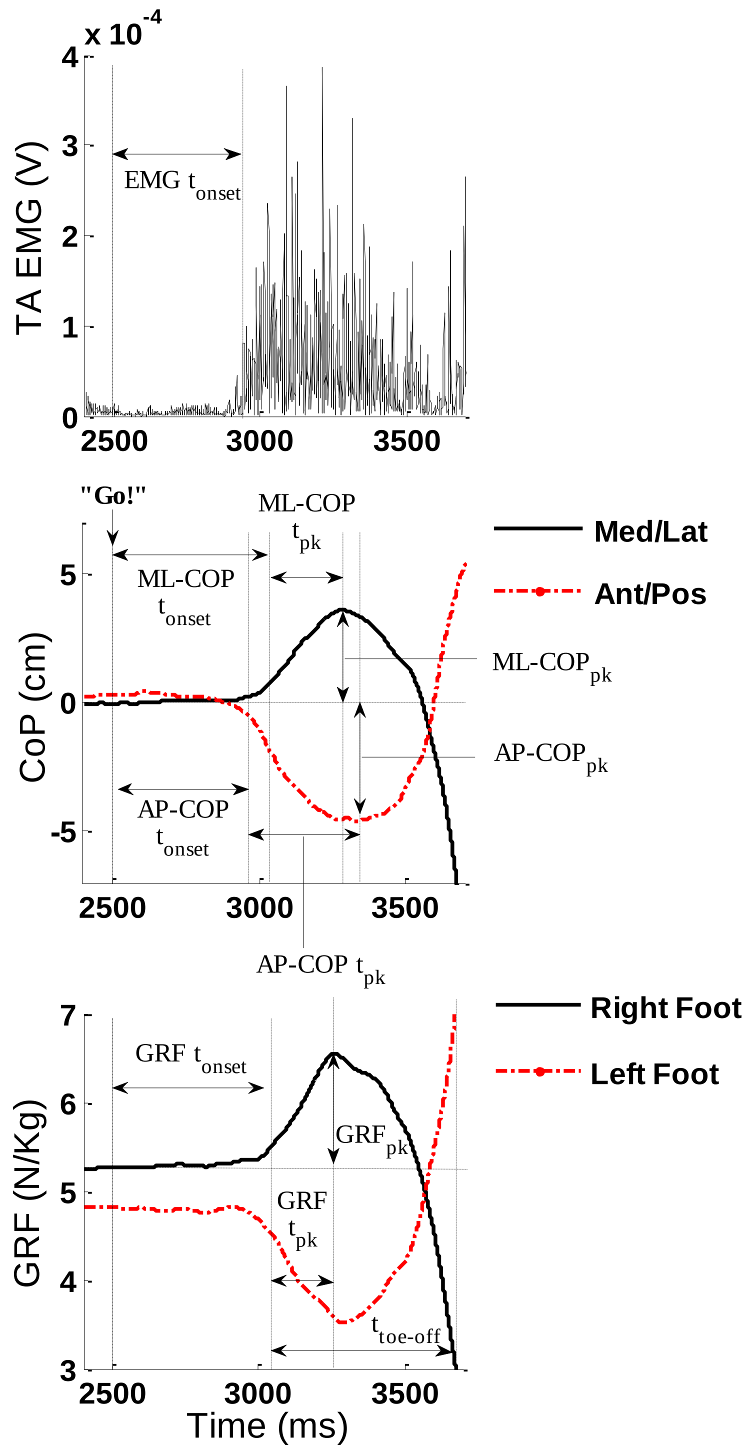

Figure 8. Illustration of the 11 GRF, COP and EMG APA parameters. Go-cue is represented as the thicker dashed line at 2500 ms.

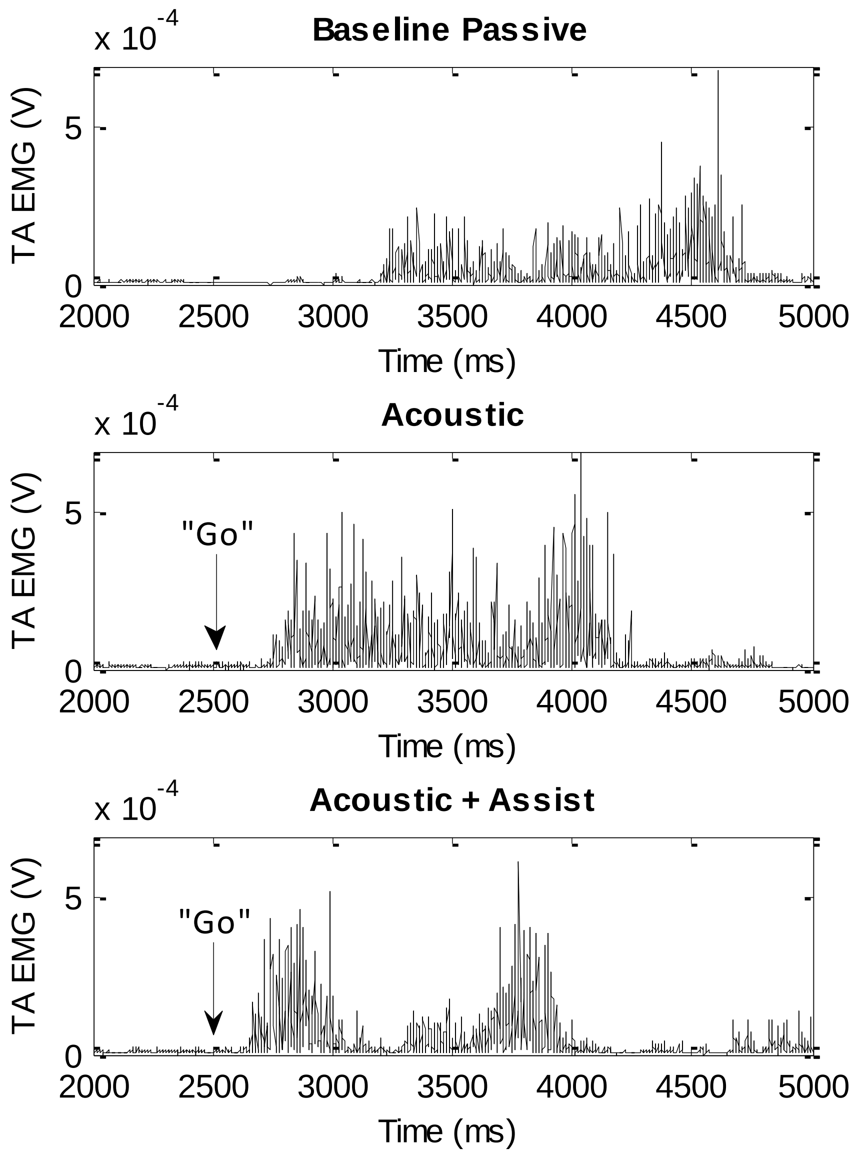

Figure 9: EMG recording from the right TA, during each of the gait initiation conditions.

Table 1: Average values ± standard deviation for all parameters by condition. Superscripts indicate significant difference from indicated condition ($p < 0.010$ or $p < 0.016$, uppercase) or borderline significant ($0.010 < p < 0.05$ or $0.016 < p < 0.05$, lowercase).

Conditions (A-E)	**(A) Baseline Shoe**	**(B) Baseline Passive**	**(C) Acoustic**	**(D) Acoustic + Assist**	**(E) Mechanical Assist**	***p*-value**
GRF_t_{onset} (ms)	-	-	$391 \pm 194^{D,E}$	215 ± 59^{C}	239 ± 83^{C}	**0.004**
GRF_{pk} (N/Kg)	1.3 ± 0.6^{E}	1.4 ± 0.5^{E}	1.9 ± 0.6^{E}	2.5 ± 0.9	$2.7 \pm 0.7^{A,B,C}$	**0.001**
GRF_t_{pk} (ms)	318 ± 125^{d}	356 ± 144^{d}	$317 \pm 120^{d,e}$	$263 \pm 73^{a,b,c}$	284 ± 97^{c}	**0.006**
$t_{toe\text{-}off}$ (ms)	606 ± 152	$584 \pm 195^{d,e}$	582 ± 139^{e}	503 ± 134^{b}	$530 \pm 135^{b,c}$	*0.037*
$AP\text{-}COP\_t_{onset}$ (ms)	-	-	415 ± 167^{d}	244 ± 80^{c}	279 ± 137	*0.027*
$AP\text{-}COP_{pk}$ (mm)	59 ± 16	53 ± 13	61 ± 14	66 ± 12	64 ± 14	0.125
$AP\text{-}COP\_t_{pk}$ (ms)	405 ± 108	462 ± 123	392 ± 131	347 ± 120	330 ± 110	0.054
$ML\text{-}COP\_t_{onset}$ (ms)	-	-	$405 \pm 187^{D,E}$	232 ± 40^{C}	267 ± 72^{C}	**0.003**
$ML\text{-}COP_{pk}$ (mm)	$45 \pm 23^{C,E}$	$47 \pm 18^{C,D,E}$	$57 \pm 25^{A,B,E}$	74 ± 22^{B}	$84 \pm 25^{A,B,C}$	< **0.001**
$ML\text{-}COP\_t_{pk}$ (ms)	350 ± 142	362 ± 142	298 ± 128	241 ± 82	253 ± 83	0.060
EMG_t_{onset} (ms)	-	-	273 ± 128	182 ± 68	164 ± 68	0.115

3 Modulation of Anticipatory Postural Adjustments Using a Powered Ankle Orthosis in People with Parkinson's Disease and Freezing of Gait

3.1 Abstract

Freezing of gait (FOG) during gait initiation may be related to a diminished ability to coordinate anticipatory postural adjustments (APAs) for people with Parkinson's disease (PD). Mechanical assistance that mimics the desired motion of the body during an APA has been demonstrated to shorten and amplify APAs; however, no portable device has been tested. In this study, a portable powered ankle-foot orthosis (PPAFO) testbed was utilized to investigate the utility of mechanical assistance provided at the ankle joint to facilitate APA generation during gait initiation. Thirteen participants with PD and FOG symptoms initiated gait in five test conditions: baseline stepping in walking shoes [Baseline-Shoes], the PPAFO on the right foot in passive mode [Baseline-Passive], and three cued conditions with an acoustic cue and PPAFO in unpowered passive mode [Acoustic-Passive], mechanical assistance from the PPAFO [Assist], or an acoustic cue paired with mechanical assistance [Acoustic-Assist]. An instructed-delay paradigm where the go-cue was preceded by a ready-cue was used in the three cued conditions. Peak amplitudes (and time from onset) of vertical ground reaction force (GRF) and center of pressure (COP), and APA duration from onset to toe-off were compared across conditions. Results suggest that peak amplitudes (GRF and COP) can be increased and timings (to peak amplitude and toe-off) can be shortened with mechanical assistance. Overall, mechanical assistance at the ankle joint (with or

without an acoustic cue) can elicit more consistent, shortened, and amplified APAs in people with PD and FOG.

3.2 Introduction

Freezing of gait (FOG) is a debilitating symptom of Parkinson's disease (PD) that is estimated to affect up to one-half of people with PD (Macht et al. 2007). Symptoms of FOG are defined as the absence or reduction of voluntary movement, including problems with initiating gait (Berardelli et al. 2001; Giladi and Nieuwboer 2008). FOG typically presents in people with PD while taking the first step (a.k.a. start hesitation), walking, or making a turn while walking (Giladi and Nieuwboer 2008). The severity and incidence of FOG symptoms increase with disease progression and are associated with a decrease in postural stability (Lamberti et al. 1997; Giladi 2001; Macht et al. 2007). Also, the pharmacological agents prescribed to PD patients for motor symptoms (levodopa or dopamine agonists) do not alleviate FOG symptoms and there are no adequate therapies or treatments (Giladi 2008). Over the course of the disease, FOG decreases mobility, increases the risk of falls, which all lead to decreased quality of life (Giladi 2001).

During healthy gait initiation, our body coordinates a set of anticipatory postural adjustments (APAs) to propel the body forward during the first step (Carlsoo 1966; Crenna and Frigo 1991; Elble et al. 1996). Beginning at standing posture, forces are generated by the lower limbs to load the stepping foot and unload the stance foot (typically referred to as the loading-unloading or postural phase). During this phase, the tibialis anterior of both legs are activated and the gastrocnemius and soleus are suppressed on the stepping leg (Figure 1 and Figure 2) (Carlsoo 1966; Crenna and Frigo 1991; Elble et al. 1996). This sequence results in an increase (decrease) of vertical ground reaction forces under the stepping (stance) leg and a posterior excursion of the center of pressure towards the stepping foot. The magnitude of the posterior center of pressure excursion and initial tibialis anterior burst on the stepping foot during this sequence are positively correlated with gait initiation velocity (Crenna and Frigo 1991; Lepers and Breniere 1995). After the initial “loading-unloading” phase, forces are generated to accelerate the center of mass of the body towards the stance foot as the stepping leg comes off the ground for the first step (Figure 3). In sum, the APAs for gait initiation are a tightly controlled sequence of movements that are closely related to gait initiation velocity.

In comparison to healthy individuals, people with PD exhibit a diminished capacity to generate APAs necessary for gait initiation (Burleigh-Jacobs et al. 1997; Halliday et al. 1998; Jacobs et al. 2009; Rogers et al. 2011). In particular, the ability to generate force is attenuated, which includes a diminished activation of the tibialis anterior of the stepping leg (Figure 1 and Figure 2) (Elble et al. 1996; Rogers et al. 2011). Furthermore, people with PD exhibit greater variability in APA characteristics (e.g., more variable force production) compared to healthy adults (Lin et al. 2016). Due to the decreased ability to generate APAs, gait initiation velocity is usually slower for people with PD (Burleigh-Jacobs et al. 1997; Halliday et al. 1998) and the normal sequence of gait initiation is disrupted (Crenna and Frigo 1991; Rogers et al. 2011). Therefore interventions or therapies that can modulate APA generation could be beneficial for improving gait initiation and overcoming start hesitation.

Sensory cues can be used to overcome start hesitation and restore APA behaviors in people with PD. The majority of cueing studies have focused on visual, auditory, and somatosensory cues, which include parallel lines on the floor (Dietz et al. 1990), rhythmic auditory stimuli (Cubo et al. 2004) or somatosensory stimulation via vibration (Dibble et al. 2004). Although these cues provide helpful spatial and rhythmic information for the proper coordination of APAs, they do not directly modulate the biomechanics of the user. Consequently, force production during APAs for people with PD are diminished compared to healthy controls when cued to initiate gait (Rogers et al. 2011). Thus, new cueing paradigms, particularly ones that are able to directly modulate force, are needed to effectively amplify APAs in people with PD.

Mechanical assistance mimicking the desired motion of the body during gait initiation has been found to actively modulate the magnitude of APAs. In people with PD, these forms of mechanical stimuli (i.e., vertical or anterior-posterior floor translation, or waist pull in the medial-lateral direction towards the stance limb) were able to facilitate forward body lean, shorten APA timing, and increase force production (Burleigh-Jacobs et al. 1997; Mille et al. 2009; Rogers et al. 2010). An added benefit of these forms of mechanical stimuli is they provide afferent sensory information, which could potentiate the cerebellar-parietal neural circuitries that are believed to enable sensory cues in people with PD (Praamstra et al. 1998; Nieuwboer 2008; Nombela et al. 2013). Taken together, these results suggest mechanical assistance that mimics or facilitates the necessary motions of an APA can effectively modulate APAs for gait initiation in people with PD.

One of the limitations with past mechanical assistance cueing protocols (Burleigh-Jacobs et al. 1997; Mille et al. 2009; Rogers et al. 2010) was that they were restricted to a lab setting. This lack of portability prevents potential interventions during daily active living. A portable powered ankle-foot orthosis (PPAFO) has recently been developed to investigate applications for untethered assistance during gait by providing both dorsiflexor and plantarflexor torques at the ankle (Figure 10) (Shorter et al. 2011a; Boes et al. 2015). The device has been demonstrated to improve gait function in other neurological disorders including cauda equine syndrome, muscular dystrophy, and multiple sclerosis (Shorter et al. 2011a; Shorter et al. 2011b; Boes et al. 2015). Recently, we explored using the PPAFO to actively modulate APAs in healthy young adults (Chapter 2). The results suggest that a similar shortening and amplification in force generation seen in the previous mechanical assistance studies are also possible using the PPAFO. Consequently, the PPAFO is a sufficient platform to test the efficacy of a wearable device that can provide mechanical assistance at the ankle in people with PD and FOG.

The purpose of this study was to investigate how a mechanical stimulus in the form of modest torques at the ankle (with or without an acoustic cue) can modulate APA behaviors during gait initiation in people with PD and FOG. We hypothesize that, by driving the ankle through typical movements of APAs for gait initiation, the PPAFO can shorten APA duration and amplify force production beyond what is observed in self-initiated conditions in people with PD and FOG.

3.3 Methods

3.3.1 Participants

A total of 13 participants with PD and FOG symptoms were recruited for this study (9 male, age 66.8±13.4 yrs, height 170.3±10.8 cm, weight 76.9±15.1 kg, Hoehn & Yahr 2.5-4, tested OFF PD medications). This study was performed at the University of Illinois at Urbana-Champaign (UIUC) and the University of Minnesota (UMN). Institutional Review Board approvals were obtained at both institutions, and all participants signed informed consent forms for the study.

Inclusion criteria included: 45+ years of age; diagnosed with idiopathic PD; Hoehn & Yahr rating scale of 2.5-4; history of start hesitation and freezing episodes based upon the Freezing of Gait Questionnaire (FOG-Q) (Giladi et al. 2009), patients were classified as freezers with start hesitation if they have at least one weekly FOG episode (score of >1 on item 3 of the FOG-Q) (Nieuwboer et al. 2009); no history of musculoskeletal disorders that affect movement of lower limbs; no other significant neurological disorders; able to ambulate independently without use of assistive device (cane, walker) for 50 m, and when in the off-medication state. Exclusion criteria included: history of dementia or cognitive impairment (Mini-Mental Score < 26); clinically significant reductions in vision (when corrected), hearing or cutaneous sensation of the feet; tremor score > 2 on items 20 and 21 of the UPDRS in off-medication state; and implanted deep brain stimulation (DBS) or other neurosurgeries to treat PD.

3.3.2 Portable Powered Ankle-Foot Orthosis (PPAFO)

The mechanical assistance cue used in this study was provided by a portable powered ankle-foot orthosis (Figure 10) (Boes et al. 2013). The PPAFO was capable of providing both dorsiflexor and plantarflexor torque at the ankle through a bi-directional rotary pneumatic actuator (PRN30D-90-45; Parker Hannifin, Cleveland, OH). Two solenoid valves (VOVG and VUVG 5V; Festo Corp-US; Hauppauge, NY, USA) regulated the flow of compressed gas into each vane of the actuator.

3.3.3 Gait Initiation Task

Participants were asked to initiate gait from an upright standing position starting with the right foot for five test conditions. The gait-initiation test conditions were: (1) self-initiated stepping in personal walking shoes to provide a baseline without the PPAFO [Baseline-Shoes], (2) self-initiated trials in unpowered passive PPAFO to provide a baseline while wearing PPAFO [Baseline-Passive], (3) acoustic go-cue with passive PPAFO to assess the effect of acoustic cue [Acoustic-Passive], (4) mechanical assistance from the powered PPAFO to assess its efficacy as a standalone cue [Assist], and (5) acoustic go-cue with simultaneous mechanical assistance from the PPAFO to assess the effect of mechanical assistance provided with another cue [Acoustic-Assist]. For conditions 2-5, the PPAFO was fit to the test participant and worn on the right limb (Figure 10). The participant's personal walking shoe was worn on the left limb.

Blocks of five trials were performed for each test condition (total of 25 trials per participant). Trials for the first test condition (Baseline-Shoes) were run consecutively before the remaining four conditions. Test condition order was randomized for conditions 2-5. Before each test condition, the participant was told whether it was a self-initiated or cued trial. Rest breaks were provided whenever needed by the participant. Also, a fall restraint harness on an overhead track was attached to the participants and 1-2 spotters were available for assistance.

3.3.4 Cue Presentation

For conditions 3-5, an instructed-delay paradigm (MacKinnon et al. 2007) was used consisting of an acoustic ready cue presented 2.5 s before the imperative go-cue (acoustic and/or PPAFO mechanical assist) to initiate a forward step with the right foot (Figure 11B). It has been shown that gait initiation can be significantly improved in people with PD when the imperative go-cue is preceded by a ready cue (Rogers et al. 2011). The instruction was to initiate gait with the right foot "as quickly as possible" taking a minimum of two steps forward in response to the go-cue. In conditions 1 and 2, the participant was instructed to initiate gait "as quickly as possible" with the right foot on their own within 5-10 seconds after hearing the ready cue (Figure 11A).

The ready cue, acoustic go-cue, and actuation of the PPAFO were all controlled with custom software (QUARC, Quanser Consulting Inc, Markham, ON, Canada, and Texas Instruments

Code Composer v5, Texas Instruments, Dallas, TX). Both the acoustic ready and go-cues were clearly audible tones (80 dB, 1 kHz tone) projected from a speaker for 500 ms. The mechanical assist cue began with a dorsiflexor torque (heuristically tuned to hold the participant's suspended foot at neutral position relative to the shank, i.e., approximately 3-5 Nm at 30-50 psig) delivered for 330 ms and followed with a subsequent plantarflexor torque of ~9-10 Nm (based on 90 psig actuated pressure) for 83 ms. These timings and patterns of torques were derived from APAs observed in healthy control subjects (Rogers et al. 2011).

3.3.5 Data Collection

Ground reaction force (GRF), center of pressure (COP), and electromyographic (EMG) data were recorded and sampled at 1000 Hz. The participant stood with each foot on separate force plates. The force plates were embedded in an instrumented treadmill at UIUC (Bertec Corporation, Columbus, OH) and a slightly raised walkway at UMN (Kistler Instrument Corporation, Novi, MI). Force data were filtered using a low-pass Butterworth filter with a cut-off frequency of 20 Hz. Net COP under both feet for the medial-lateral (ML) and anterior-posterior (AP) directions were calculated using GRF data. EMG data were recorded from the tibialis anterior (TA) of the right (stepping) leg (Bagnoli 16 at UIUC, Trigno at UMN, Delsys Corp., Boston, MA).

3.3.6 Data Analysis

EMG parameters were not included in the following data analysis because of challenges with post-processing of the EMG data from this population. Low signal magnitude and high variability of TA EMG signals made consistent identification of TA onset time difficult (Appendix B).

To quantify the APA response to the different test conditions, nine parameters were computed from the vertical GRF of the right leg, and total body AP and ML COP (Figure 12). For all test conditions, the magnitudes and times from onset to peak amplitude were recorded for vertical GRF ($vGRF_{pk}$, $vGRF\_t_{pk}$) and ML center of pressure ($ML\text{-}COP_{pk}$, $ML\text{-}COP\_t_{pk}$). Vertical GRFs were normalized as a percentage of the participant's body weight. For AP center of pressure, two peaks were analyzed. The first peak ($AP\text{-}COP_{pk1}$, $AP\text{-}COP\_t_{pk1}$) occurred during the initial "loading-unloading" phase prior to the forces crossing over after peak loading and before toe-off (Figure 12). The second peak ($AP\text{-}COP_{pk2}$, $AP\text{-}COP\_t_{pk2}$) occurred approximately at toe-off. Additionally, the time from onset to the start of toe-off (of the stepping right foot) was recorded based on the time when the right vertical GRF (normalized by body weight) went below 0.1 %BW ($t_{toe\text{-}off}$). Lastly, the coefficient of variation (COV), sample variance divided by sample mean, for each parameter (except $AP\text{-}COP_{pk1}$ and $AP\text{-}COP_{pk2}$) was calculated from all trials within the participant, for each condition. The COV for the two anterior-posterior COP peaks could not be calculated because these values could be both positive and negative, which invalidates COV.

Thresholds were defined for onsets of each type of data. For a given trial, onset of a measured signal was defined as when a monotonic change of greater than three standard deviations was observed relative to the mean signal that was recorded 1000 ms prior to the go-cue. For the baseline conditions that did not contain a go-cue, the mean signal was calculated prior to a point manually picked approximately 100-300 ms before $vGRF\_t_{onset}$. If there was no monotonic increase in a parameter, it was considered to have "no-APA" behavior and all parameter values were set to zero. All parameters were further verified by visual inspection by a trained researcher.

3.3.7 Statistical Analysis

A one-way repeated-measures multivariate analysis of variance (MANOVA) test was conducted to assess the effect of the five testing conditions on all nine APA parameters. A separate one-way repeated measures MANOVA was run for the COV of the seven parameters. All *p*-values reported for COV data are with a Greenhouse-Geisser correction due to violations of sphericity. If a main effect was found in the MANOVA, follow up univariate ANOVAs were used to evaluate significant parameters. Post-hoc pairwise effects were examined using Fisher Least Significant Difference (LSD) test. All data were processed using SPSS statistical software (Version 20, IBM Corp, Armonk, NY). Significance level was set to $\alpha = 0.05$.

3.4 Results

MANOVA results indicated a main effect of condition ($p < 0.001$). Eight of the nine APA parameters had significant univariate effects of condition (Table 2): the magnitude and time to peak amplitude of vertical ground reaction force ($vGRF_{pk}$, $vGRF\_t_{pk}$), medial-lateral center of pressure ($ML\text{-}COP_{pk}$, $ML\text{-}COP\_t_{pk}$), anterior-posterior center of pressure ($AP\text{-}COP_{pk1}$, $AP\text{-}COP_{pk2}$, $AP\text{-}COP\_t_{pk1}$) as well as time to toe-off ($t_{toe\text{-}off}$). Additionally, a main effect of condition was found in the MANOVA for the coefficient of variation (COV) of five of seven parameters ($p = 0.002$). Decreased coefficient of variation was observed in vertical ground reaction force ($vGRF_{pk}$, $vGRF\_t_{pk}$), center of pressure ($ML\text{-}COP_{pk}$, $AP\text{-}COP\_t_{pk2}$), and toe-off ($t_{toe\text{-}off}$) parameters. Archetypical data for each condition are presented in Appendix A.

3.4.1 Vertical Ground Reaction Force

Follow up univariate ANOVAs indicated significant differences in $vGRF_{pk}$ ($F_{4,48} = 12.76$, $p < 0.001$), $vGRF\_t_{pk}$ ($F_{4,48} = 2.99$, $p = 0.028$), and $t_{toe\text{-}off}$ ($F_{4,48} = 4.62$, $p = 0.003$) across conditions. LSD post-hoc tests found significant increases in peak vertical ground reaction force ($vGRF_{pk}$). First, vGRF was increased in Baseline-Passive condition compared to Baseline-Shoes. Compared to Baseline-Passive, only the Assist conditions (Assist, Acoustic-Assist) were significantly increased for $vGRF_{pk}$ (Figure 13, Table 2). Between cueing conditions, $vGRF_{pk}$ during Acoustic-Assist was significantly larger than the Acoustic-Passive cue alone. For the timing parameters, time to peak vertical ground reaction force ($vGRF\_t_{pk}$) was found to be significantly faster in the Assist condition compared to Baseline-Passive and Acoustic-Passive (Figure 14, Table 2). Similar to $vGRF\_t_{pk}$, time to toe-off ($t_{toe\text{-}off}$) was significantly faster for the Assist and Acoustic-Assist compared to Baseline-Passive. But a significant slowing in $t_{toe\text{-}off}$ was also observed in Baseline-Passive compared to Baseline-Shoes.

Significantly decreased COV was found for $vGRF_{pk}$ ($F_{4,48} = 6.94$, $p < 0.001$), $vGRF\_t_{pk}$ ($F_{4,48} = 3.88$, $p = 0.008$), and $t_{toe\text{-}off}$ ($F_{4,48} = 4.05$, $p = 0.007$) in cued versus baseline conditions. For $vGRF_{pk}$, COV was significantly decreased compared to Baseline-Shoes in the Acoustic-Passive, Assist, and Acoustic-Assist conditions (Figure 13, Table 3). Furthermore, both Assist conditions had significantly reduced COV compared to Baseline-Passive. The COV of this peak time ($vGRF\_t_{pk}$) was decreased in conditions with an acoustic tone (Acoustic-Passive, Acoustic-Assist) compared to Baseline-Shoes (Figure 14, Table 3). Also, Acoustic-Assist was significantly decreased compared to Baseline-Passive. Similar to $vGRF\_t_{pk}$, time to toe-off ($t_{toe\text{-}off}$) had decreased COV in conditions including an acoustic tone (Acoustic-Passive, Acoustic-Assist) compared to Baseline-Shoes.

3.4.2 Center of Pressure

From the univariate ANOVAs, significant differences between conditions in medial-lateral center of pressure parameters ($ML\text{-}COP_{pk}$, $F_{4,48} = 15.00$, $p < 0.001$, $ML\text{-}COP\_t_{pk}$, $F_{4,48} = 3.26$, $p =$

0.019) were found. Post-hoc analyses revealed increases in ML-COP_{pk} for cued conditions compared to Baseline-Shoes (Acoustic-Passive, Acoustic-Assist, Figure 15, Table 2). Additionally, increases in the Assist and Acoustic-Assist conditions compared to Baseline-Passive were observed (Assist, Acoustic-Assist), and Acoustic-Assist was significantly larger than Acoustic-Passive. For the timing of this peak amplitude (ML-COP_t_{pk}), a significant decrease was found in Assist compared to Baseline-Passive and Acoustic-Passive (Figure 15, Table 2). However, a significant increase in timing was observed in Baseline-Passive compared to Baseline-Shoes.

Results from the univariate ANOVAs also demonstrated significant differences existed in anterior-posterior center of pressure parameters (AP-COP_{pk1}, $F_{4,48} = 3.37$, $p = 0.017$, AP-COP_t_{pk1}, $F_{4,48} = 3.30$, $p = 0.018$, AP-COP_{pk2}, $F_{4,48} = 4.23$, $p = 0.005$). A decrease in the first anterior-posterior peak (AP-COP_{pk1}) was observed when the PPAFO was on the participant in passive mode (Baseline-Passive) compared to Baseline-Shoes (Figure 16, Table 2). When an acoustic cue was provided (Acoustic-Passive and Acoustic-Assist), AP-COP_{pk1} was increased compared to Baseline-Passive. No significant increase was observed when the mechanical assistance was provided on its own in the Assist condition. The timing of this peak amplitude (AP-COP_t_{pk1}) was significantly decreased in the Assist conditions compared to Baseline-Passive (Assist, Acoustic-Assist) and further decreased when only the mechanical assistance was given compared to Baseline-Shoes and Acoustic-Passive (Figure 17, Table 2). For AP-COP_{pk2}, significant increases were observed compared to Baseline-Passive in all cued conditions (Acoustic-Passive, Assist, Acoustic-Assist). Mechanical assist conditions were also significantly greater than Baseline-Shoes (Assist, Acoustic-Assist, Figure 16, Table 2). However, the timing of this peak amplitude (AP-COP_t_{pk2}) remained consistent across conditions ($F_{4,48} = 0.53$, $p = 0.714$).

Similar to the vertical ground reaction force parameters, a decrease in COV was observed in the cueing conditions compared to baseline for center of pressure parameters. For ML-COP_{pk}, COV was significantly reduced ($F_{4,48} = 4.67$, $p = 0.003$) in the Assist and Acoustic-Assist conditions compared to Baseline-Shoes and Baseline-Passive (Figure 15, Table 3). Although the average value of AP-COP_t_{pk2} remained constant across conditions, the COV was reduced in the Acoustic-Passive and Acoustic-Assist conditions compared to Baseline-Passive ($F_{4,48} = 3.56$, $p = 0.013$, Figure 17). Furthermore, COV in the Acoustic-Assist condition was also significantly decreased compared to Baseline-Shoes.

3.5 Discussion

Findings from this study suggest that mechanical assistance from the PPAFO induced more consistent, amplified, and shortened APAs in people with PD and FOG. Peak vertical ground reaction force ($vGRF_{pk}$), medial-lateral center of pressure (ML-COP_{pk}), and anterior-posterior center of pressure (AP-COP_{pk2}) amplitudes were increased in mechanical assist conditions (Assist and Acoustic-Assist) compared to baseline (Figure 13, Figure 15, Figure 16, and Table 2). Time to peak amplitudes (vGRF_t_{pk}, ML-COP_t_{pk}, AP-COP_t_{pk1}, Figure 14, Figure 15, Figure 17, and Table 2) were shortened in the Assist condition compared to baseline stepping (Baseline-Shoes and/or Baseline-Passive) or the acoustic cue alone (AP-COP_t_{pk1} only). In addition, decreased COV was observed in both amplitude and temporal characteristics ($vGRF_{pk}$, vGRF_t_{pk}, ML-COP_{pk}, AP-COP_t_{pk2}, $t_{toe\text{-}off}$) (Figure 13-Figure 15, and Figure 17, Table 3) in the Acoustic-Passive and/or Assist conditions compared to baseline stepping (Baseline-Shoes and/or Baseline-Passive). Overall, these effects demonstrate that mechanical assistance from the PPAFO (with or without an acoustic cue) could be used as a viable cueing strategy to effectively modulate APA characteristics in people with PD and FOG.

Several of the results in this study are consistent with previous mechanical assistance protocols that mimic the desired motions of the body during an APA in people with PD. Shortened APA duration from onset to toe-off ($t_{toe\text{-}off}$) with mechanical assistance was also found using an anterior-posterior floor translation (Burleigh-Jacobs et al. 1997), vertical floor translation (Rogers et al. 2010), and a waist pull in the medial-lateral direction (Mille et al. 2009). However, increases were not observed in the peak amplitude of vertical ground reaction force in the anterior-posterior floor translation (Burleigh-Jacobs et al. 1997), and it is unclear if forces were also increased in the waist pull study because they were not reported (Mille et al. 2009). Increased vertical ground reaction force production ($vGRF_{pk}$) and medial-lateral center of pressure excursion ($ML\text{-}COP_{pk}$) with mechanical assistance are consistent with the vertical floor translation study (Rogers et al. 2010). The similarity between our two protocols was that the mechanical assistances directly modulated vertical ground reaction force under the foot. Most importantly, the increased ground reaction force ($vGRF_{pk}$) and medial-lateral ($ML\text{-}COP_{pk}$) magnitudes, and shorter time to peak ground reaction force ($vGRF\_t_{pk}$) and time to toe-off ($t_{toe\text{-}off}$) coincide with the results of the same protocol used in this study on healthy young adults (Chapter 2). These similarities indicate that the same positive effects of APA modulation with the PPAFO in healthy young adults could be elicited in people with PD. Overall, our results further demonstrate that mechanical assistance which mimics APA movements can help counteract the diminished and prolonged APAs associated with PD.

Anterior-posterior center of pressure excursion during the initial "loading-unloading phase" (AP-COP_{pk1}) and approximately toe-off (AP-COP_{pk2}) had different behaviors with the addition of an acoustic cue, mechanical assistance, or both. First, simply wearing the PPAFO in the Baseline-Passive condition significantly reduced AP-COP_{pk1}. However, the addition of a cue (acoustic and/or mechanical) restored this peak amplitude to Baseline-Shoes, with an acoustic cue (in Acoustic-Passive and Acoustic-Assist) significantly increasing the amplitude above Baseline-Passive (Figure 16). The lack of increased AP-COP_{pk1} in the Assist condition compared to Baseline-Passive could have been due to the plantarflexor torque turning on too early in the APA and inhibiting this initial posterior center of pressure excursion. However, the same plantarflexor torque was present in the Acoustic-Assist condition and AP-COP_{pk1} was not inhibited in the same way. The mechanism behind this difference is not necessarily clear, but it suggests that an acoustic-cue is beneficial for increasing AP-COP_{pk1}. The second anterior-posterior peak (AP-COP_{pk2}) was amplified compared to Baseline-Passive in all cued conditions (Acoustic, Assist, Acoustic-Assist), while the assist conditions (Assist, Acoustic-Assist) were significantly increased above Baseline-Shoes as well (Figure 16). Interestingly, the mechanical assistance was not being provided when this peak occurred around toe-off, suggesting that the mechanical assistance induced a larger posterior excursion from the user themselves. Increasing the AP-COP peak excursions are particularly important because they are diminished for people with PD and FOG comparted to healthy controls and people with PD without FOG (Alibiglou et al. 2016). Our results indicate that an acoustic cue paired with mechanical assistance may be necessary to increase both AP-COP peak excursions during an APA.

In addition to changes in the average values, decreased COV was observed in both amplitude and temporal characteristics ($vGRF_{pk,}$ $vGRF\_t_{pk}$, $ML\text{-}COP_{pk}$, $AP\text{-}COP\_t_{pk2}$, $t_{toe\text{-}off}$, Figure 13-Figure 15, Figure 17, and Table 3) in the Acoustic-Passive and/or Assist conditions compared to baseline (Baseline-Shoes and/or Baseline-Passive). Although a direct link between FOG and APA variability has yet to be demonstrated, increased variability in the timing and magnitude of APAs has been found in individuals with PD compared to healthy controls (Lin et al. 2016). An increased amount of variability could interfere with the postural-locomotion coupling during gait initiation (Lin et al. 2016). The amount of variability observed in the vertical ground reaction force peak amplitude and timing parameters ($vGRF_{pk}$, $VGRF\_t_{pk}$, $t_{toe\text{-}off}$) in mechanical assistance conditions was comparable to healthy variability (~ 20%) of the same parameters (Lin et al. 2016). It is possible that reduced APA variability could also make gait initiation more consistent and reduce FOG for people with PD. However, further investigation is needed into the relationship between APA variability and FOG.

A paired stimulus of an acoustic tone and mechanical assistance may be the most effective method for inducing consistent, amplified, and shortened APAs. Peak vertical ground reaction force magnitude and medial-lateral center of pressure amplitudes were increased compared to both baseline conditions and the acoustic condition with the paired stimulus. Similarly, mechanical assistance (alone or paired with an acoustic cue) significantly increased the second AP-COP peak amplitude compared to both baseline conditions. In addition to peak magnitude changes, the coefficients of variance of $vGRF_{pk}$ and $ML\text{-}COP_{pk}$ were decreased the most in the Acoustic-Assist condition and the total duration of the APA ($t_{toe\text{-}off}$) was shortest across all conditions. The potential mechanism behind these improvements could be paired sensory stimuli have an additive effect (i.e., increased neuronal response) making the stimuli easier to detect (Stein and Stanford 2008; Cappe et al. 2009), which could aid in the translation of relevant sensory information to a motor command. In a primate study, paired audio-visual stimuli enhanced the preparation and execution of eye saccades and resulted in larger premotor activity of neurons in the superior colliculus (Bell et al. 2005). Although it was designed to improve continuous gait in people with PD and FOG, a similar benefit of a paired stimulus was observed with the MediGait device, which provided visual cues (i.e., projection of black and white tiled floor within a set of glasses) and auditory feedback (i.e., acoustic tone played in earphone when the ipsilateral foot was in contact with the ground) (Espay et al. 2010). Improved gait velocity, stride length, and freezing of gait questionnaire (FOG-Q) score in people with PD were observed after a two-week period of in-home training. Thus, pairing the assistance with another sensory stimulus (e.g., acoustic tone) should be considered in the development of mechanical assistance paradigms aimed at modulating APAs in people with PD and FOG.

Even though the desired results were attained in this study (shortened and amplified APAs), the optimal timing and magnitude for mechanical assistance provided at the ankle joint need more investigation. Crucially, the timing of the mechanical assistance in relation to the current movement of the user can have direct effect on the modulation of an APA. A medial-lateral waist pull study showed that healthy adults can adapt to a mechanical translation only if it is provided early in the initial loading and unloading phase (Mouchnino et al. 2012). Previous studies in people with PD also provided their respective forms of mechanical assistance beginning at onset of the APA and observed amplified and/or shortened APAs (Mille et al. 2009; Rogers et al. 2010). In addition to timing, the magnitude and direction of assistance are also important to consider.

In the waist pull study in healthy adults, the medial-lateral peak displacement towards the stepping leg was found to be larger when the tug counteracted the motion of the person (Mouchnino et al. 2012). Conversely, if the assistance was pulled in the same direction as the user's intent, the initial medial lateral shift was smaller (Mouchnino et al. 2012). It is not clear if these results would translate when actuating the ankle, but studies focused on different timings and magnitudes of assistance are needed to determine if the desired APA modulation can be consistently attained with mechanical assistance provided at the ankle joint.

The neural mechanisms behind the effects of mechanical assistance are not fully understood. It has been postulated that in pathways through the supplementary motor area and basal ganglia are responsible for delivering the necessary timing and magnitude information to the motor cortex and subcortical locomotor regions (Nutt et al. 2011). It is certainly possible that the feedforward locomotor command for an APA can be altered with the mechanical assistance, given that the assistance is provided during the early portion of an APA (i.e., beginning near APA onset) (Mouchnino et al. 2012). In addition to directly modulating the force production of the ankle, our form of mechanical assistance can also provide relevant timing and magnitude information via proprioceptive and/or somatosensory afferent inputs. This sensory information could be processed through the cerebellar–thalamo–parietal networks that are believed to enable cues (Praamstra et al. 1998; Nieuwboer 2008; Nombela et al. 2013). Overall, more understanding is needed about the neural mechanism that enable mechanical assistance to modulate APA generation in people with PD and FOG.

3.6 Conclusions

In conclusion, mechanical assistance provided at the ankle joint can induce shorter, amplified, and more consistent APAs in people with PD and FOG. Furthermore, the pairing of an acoustic cue with mechanical assistance may result in the best modulation of APA behaviors. Future investigation is need to better understand the mechanism behind these changes and further optimize the assistance.

Figure 10: Experimental set up with the PPAFO attached to the right leg.

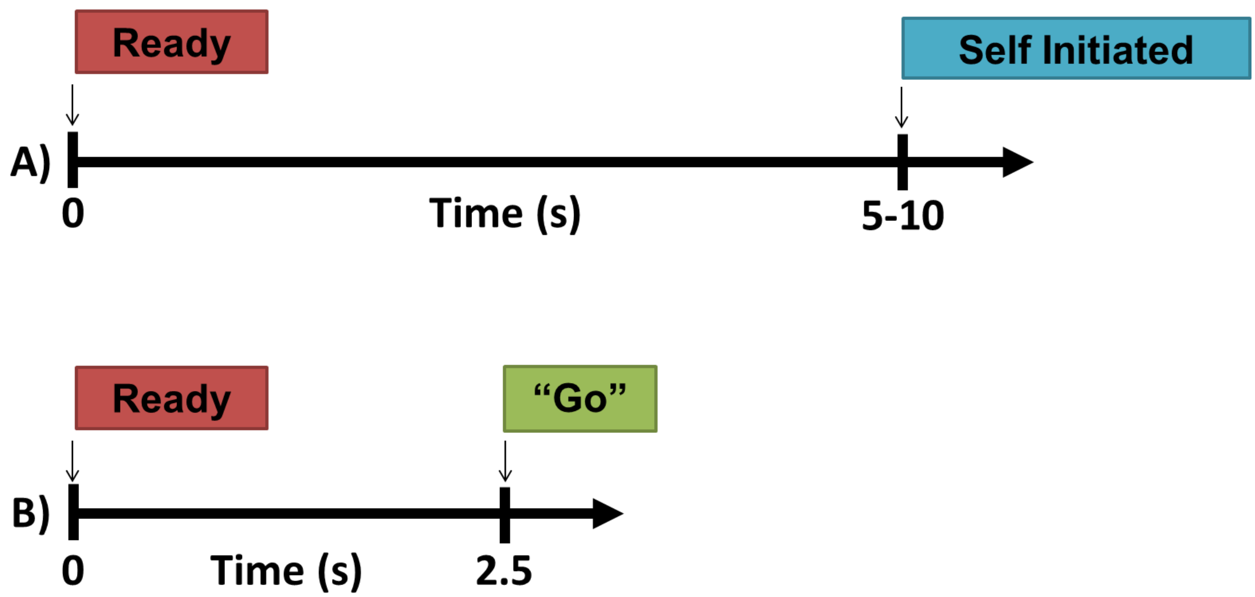

Figure 11: A) Timeline for self-initiated trials. Subject initiated gait within 5-10 seconds of the "ready" cue. B) Instructed-delay timeline for the cued trials. The imperative "go" cue was given 2.5 s after the "ready" cue.

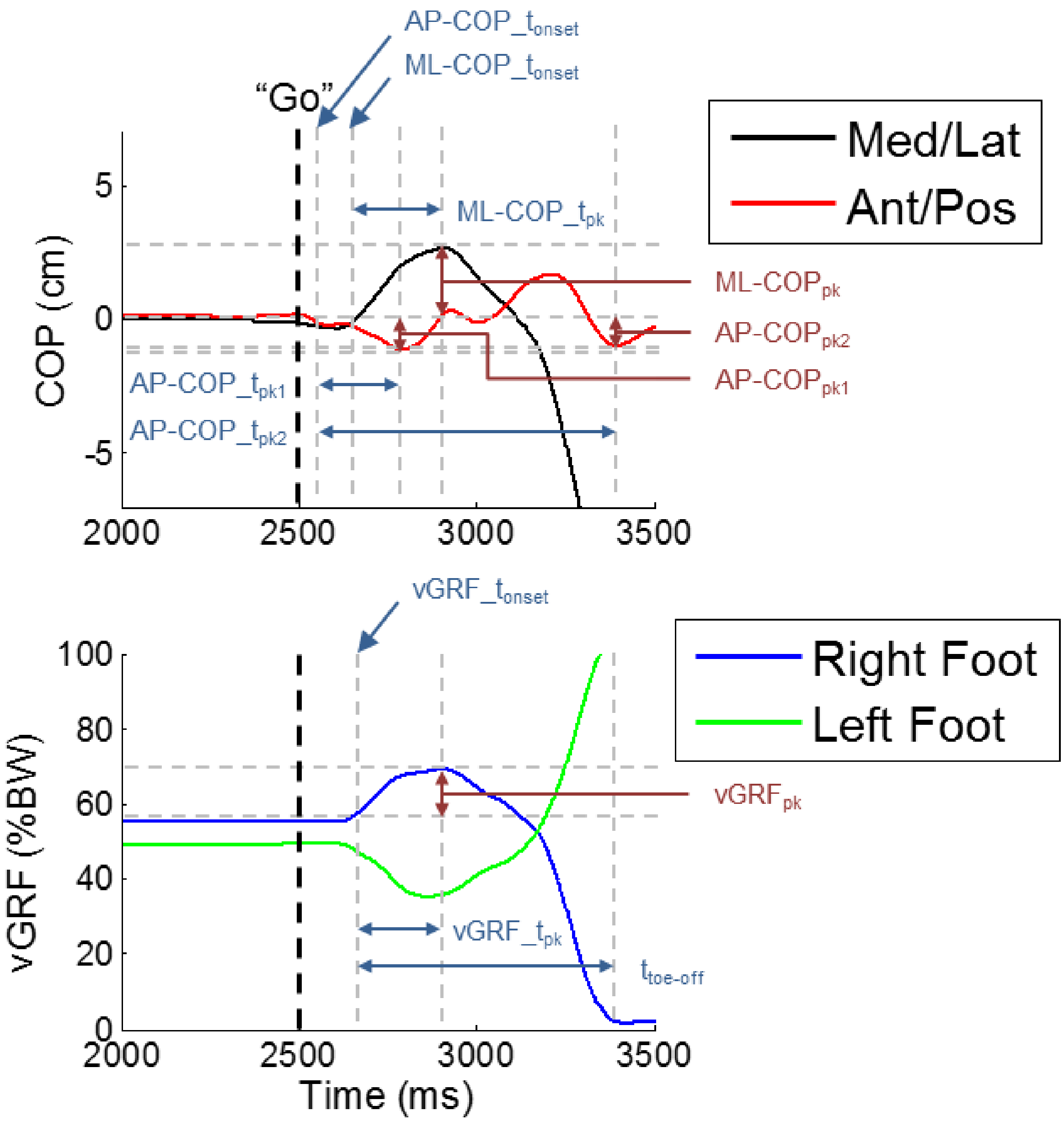

Figure 12: Illustration of the nine APA parameters (vGRF and COP). Timing parameters are in blue and amplitude parameters are in dark red. Go-cue is represented as the thick vertical-dashed line at 2500 ms.

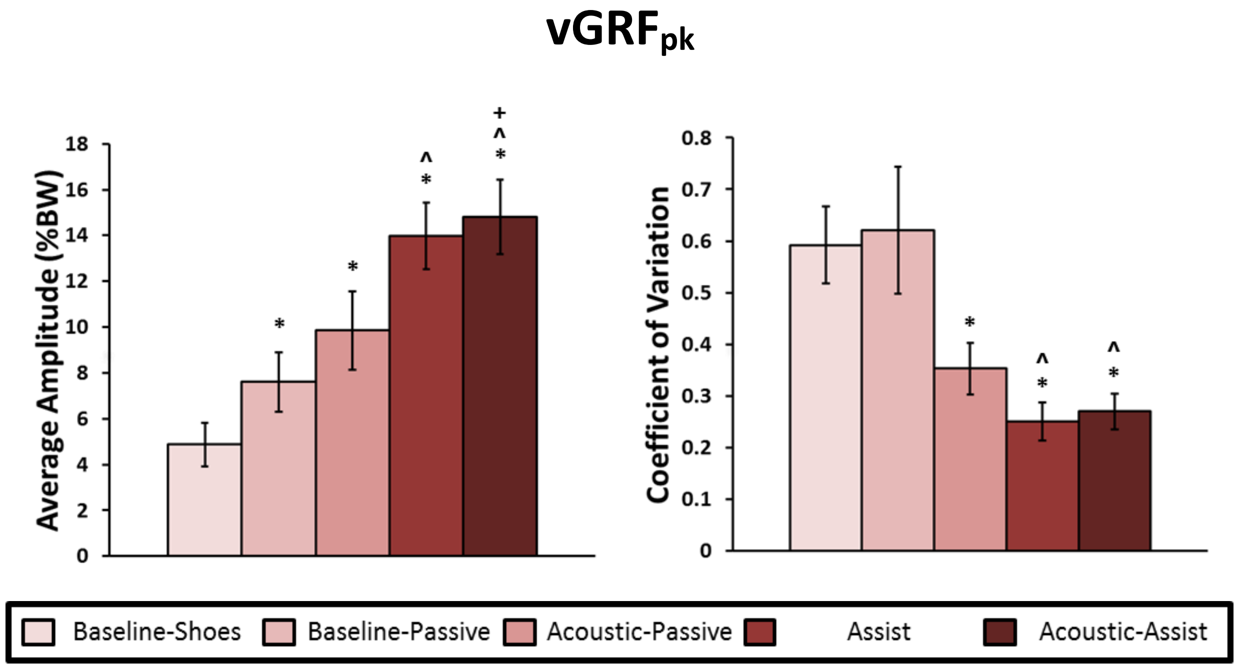

Figure 13: Average peak amplitude and coefficient of variation (± s.e.m) for $vGRF_{pk}$. Significant difference (*p* <0.05) between (*) Baseline-Shoes, (^) Baseline-Passive, and (+) Acoustic-Passive indicated accordingly by condition.

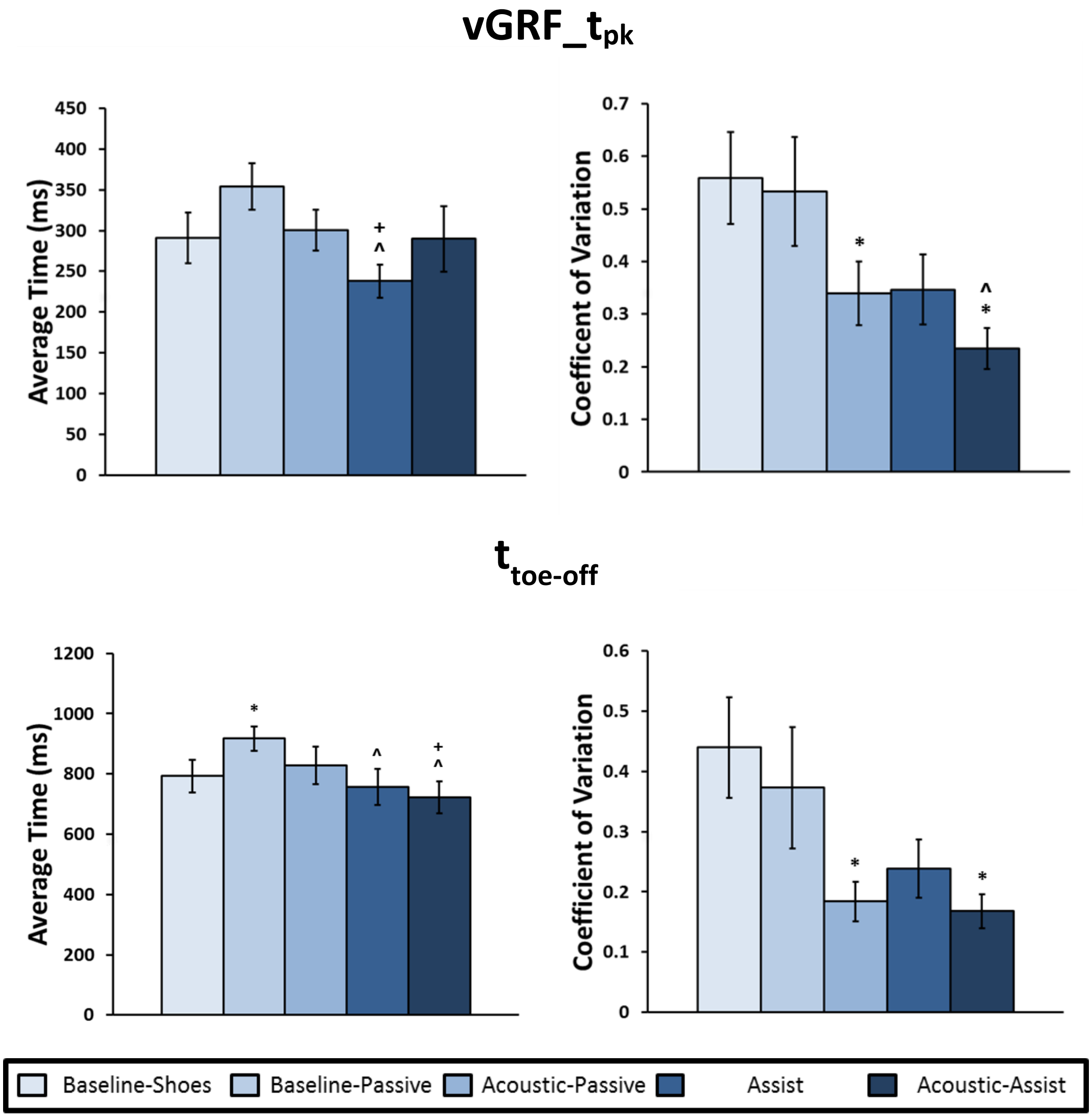

Figure 14: Average time and coefficient of variation (± s.e.m) for vGRF_t_{pk} and $t_{toe\text{-}off}$. Significant difference (p <0.05) between (*) Baseline-Shoes, (^)Baseline-Passive, (+) Acoustic-Passive indicated accordingly by condition.

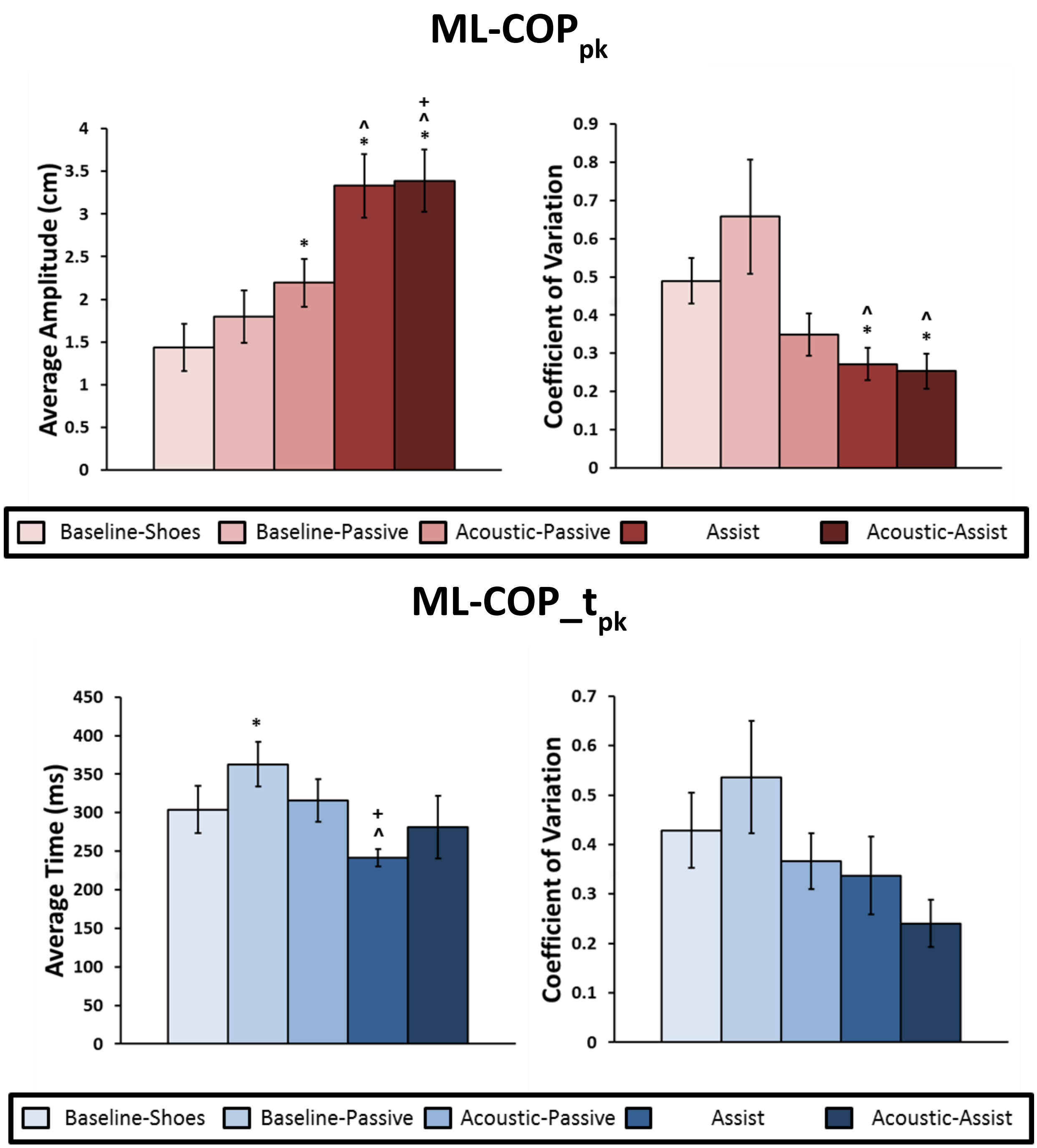

Figure 15: Average peak amplitude and time with coefficient of variation (± s.e.m) for medial-lateral center of pressure ($ML\text{-}COP_{pk}$, $ML\text{-}COP\_t_{pk}$). Significant difference (p <0.05) between (*) Baseline-Shoes, (^) Baseline-Passive, and (+) Acoustic-Passive indicated accordingly by condition.

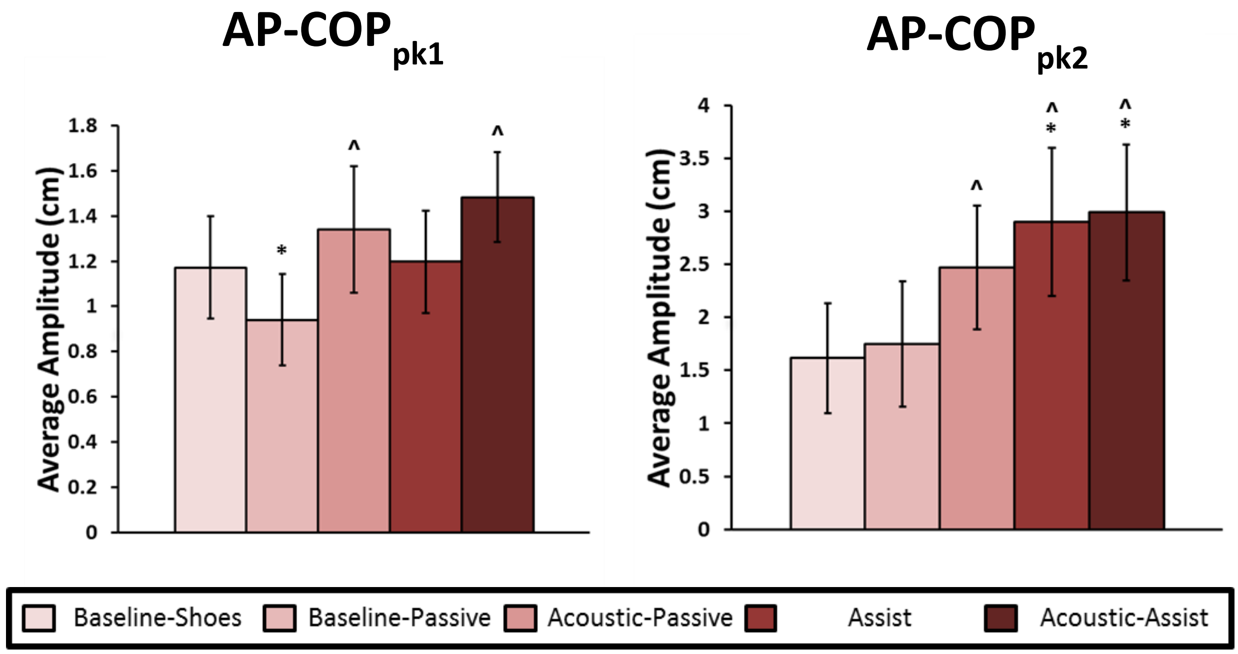

Figure 16: Average peak amplitude (± s.e.m) for anterior-posterior center of pressure (AP-COP$_{pk1}$, AP-COP$_{pk2}$). Significant difference (p <0.05) between (*) Baseline-Shoes, (^) Baseline-Passive, and (+) Acoustic-Passive indicated accordingly by condition.

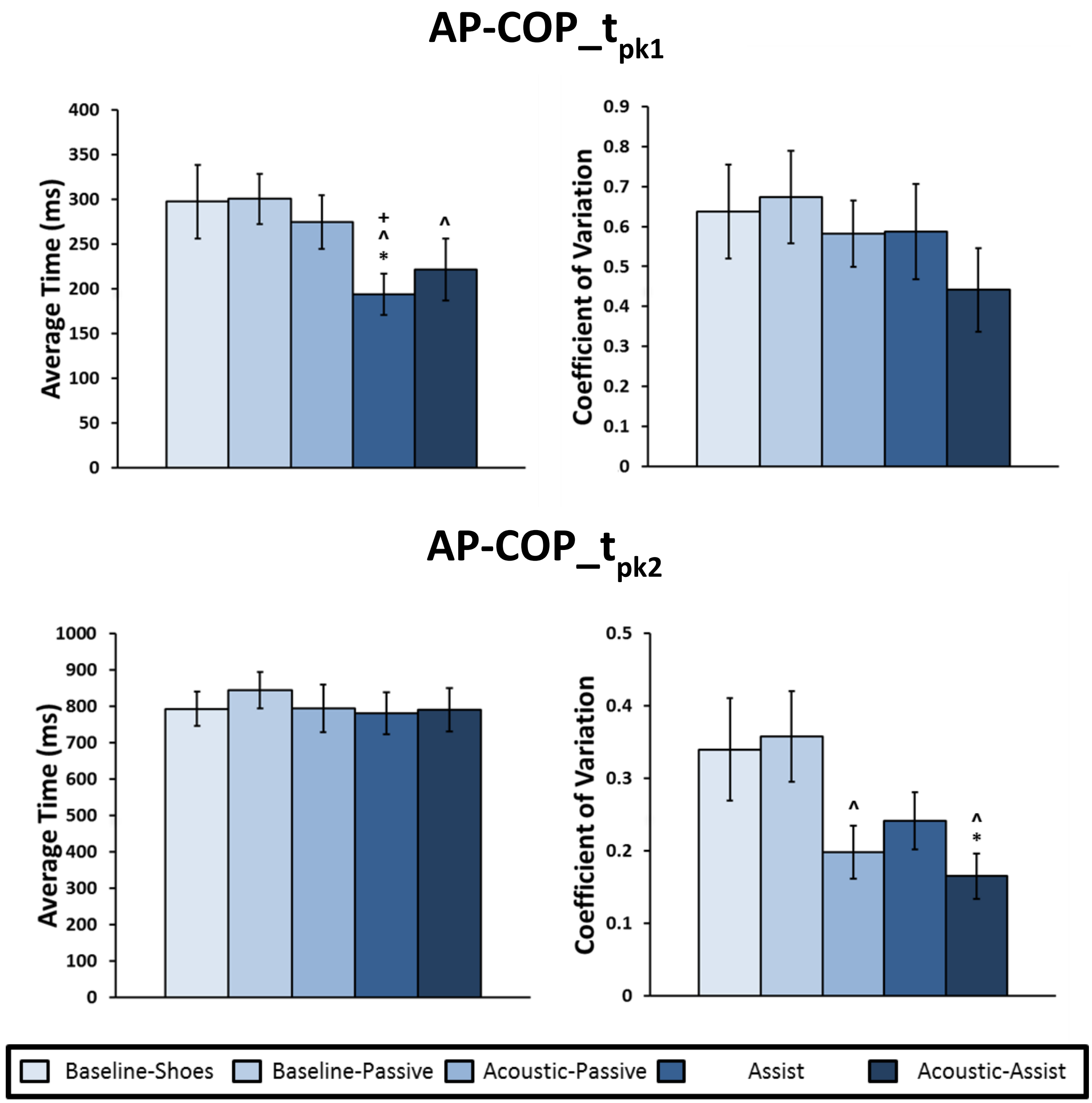

Figure 17: Average peak timing and coefficient of variation (± s.e.m) for anterior-posterior center of pressure (AP-COP_t_{pk1}, AP-COP_t_{pk2}). Significant difference (p <0.05) between (*) Baseline-Shoes, (^) Baseline-Passive, and (+) Acoustic-Passive indicated accordingly by condition.

Table 2: All nine APA parameters (average ± s.e.m) across conditions. Significant univariate *p*-values are bolded and the superscripts indicate a significant difference from the condition specified ($p < 0.05$).

	Baseline Shoes (1)	**Baseline Passive (2)**	**Acoustic Passive (3)**	**Assist (4)**	**Acoustic Assist (5)**	***p*-value**
vGRF_{pk} (%BW)	$4.9 \pm 0.9^{2,3,4,5}$	$7.6 \pm 1.31^{1,4,5}$	$9.9 \pm 1.7^{1,5}$	$14.0 \pm 1.4^{1,2}$	$14.8 \pm 1.6^{1,2,3}$	**<0.001**
vGRF_t_{pk} (ms)	290.8 ± 31.1	354.2 ± 28.5^{4}	300.3 ± 24.9^{4}	$238.2 \pm 20.3^{2,3}$	289.8 ± 40.3	**0.028**
ML-COP_{pk} (cm)	$1.4 \pm 0.3^{3,4,5}$	$1.8 \pm 0.3^{4,5}$	$2.2 \pm 0.3^{1,5}$	$3.3 \pm 0.4^{1,2}$	$3.4 \pm 0.4^{1,2,3}$	**<0.001**
ML-COP_t_{pk} (ms)	304.2 ± 30.7^{2}	$362.9 \pm 28.8^{1,4}$	316.0 ± 27.4^{4}	$241.4 \pm 11.0^{2,3}$	281.3 ± 40.8	**0.019**
AP-COP_{pk1} (cm)	1.2 ± 0.2^{2}	$0.9 \pm 0.2^{1,3,5}$	1.3 ± 0.3^{2}	1.2 ± 0.2	1.5 ± 0.2^{2}	**0.017**
AP-COP_t_{pk1} (ms)	297.2 ± 40.9^{4}	$300.3 \pm 28.2^{4,5}$	274.2 ± 30.0^{4}	$193.6 \pm 23.2^{1,2,3}$	221.5 ± 34.3^{2}	**0.018**
AP-COP_{pk2} (cm)	$1.6 \pm 0.5^{4,5}$	$1.8 \pm 0.6^{3,4,5}$	2.5 ± 0.6^{2}	$2.9 \pm 0.7^{1,2}$	$3.0 \pm 0.6^{1,2}$	**0.005**
AP-COP_t_{pk2} (ms)	794.5 ± 46.4	844.3 ± 50.1	794.3 ± 65.3	780.3 ± 56.7	790.3 ± 59.4	0.714
$t_{toe\text{-}off}$ (ms)	792.5 ± 54.7^{2}	$917.6 \pm 40.7^{1,4,5}$	828.5 ± 62.3^{5}	757.0 ± 60.4^{2}	$722.4 \pm 52.7^{2,3}$	**0.003**

Table 3: Coefficient of variation (COV) for all nine APA parameters (average ± s.e.m) across conditions. Significant univariate *p*-values are bolded and the superscripts indicate a significant difference from the condition specified ($p < 0.05$).

	Baseline Shoes (1)	Baseline Passive (2)	Acoustic Passive (3)	Assist (4)	Acoustic Assist (5)	*p*-value
$vGRF_{pk}$	$0.59 \pm 0.07^{3,4,5}$	$0.62 \pm 0.12^{4,5}$	0.35 ± 0.05^{1}	$0.25 \pm 0.04^{1,2}$	$0.27 \pm 0.03^{1,2}$	**<0.001**
$vGRF\_t_{pk}$	$0.56 \pm 0.09^{3,5}$	0.53 ± 0.10^{5}	0.34 ± 0.06^{1}	0.35 ± 0.07	$0.23 \pm 0.04^{1,2}$	**0.008**
$ML\text{-}COP_{pk}$	$0.49 \pm 0.06^{4,5}$	$0.66 \pm 0.15^{4,5}$	0.35 ± 0.06	$0.27 \pm 0.04^{1,2}$	$0.25 \pm 0.05^{1,2}$	**0.003**
$ML\text{-}COP\_t_{pk}$	0.43 ± 0.08	0.54 ± 0.11	0.37 ± 0.06	0.34 ± 0.08	0.24 ± 0.05	0.093
$AP\text{-}COP\_t_{pk1}$	0.64 ± 0.12	0.67 ± 0.12	0.58 ± 0.08	0.59 ± 0.12	0.44 ± 0.10	0.461
$AP\text{-}COP\_t_{pk2}$	0.34 ± 0.07^{5}	$0.36 \pm 0.06^{3,5}$	0.20 ± 0.04^{2}	0.24 ± 0.04	$0.17 \pm 0.03^{1,2}$	**0.013**
$t_{toe\text{-}off}$	$0.44 \pm 0.08^{3,5}$	0.37 ± 0.10	0.18 ± 0.03^{1}	0.24 ± 0.05	0.17 ± 0.03^{1}	**0.007**

4 MODULATION OF ANTICIPATORY POSTURAL ADJUSTMENTS IN PEOPLE WITH PARKINSON'S DISEASE AND FREEZING OF GAIT USING EXTERNALLY VERSUS SELF-TRIGGERED CUES

4.1 Abstract

One of the most debilitating symptoms of Parkinson's disease (PD) is freezing of gait (FOG). A common impairment associated with FOG is a diminished capacity to generate anticipatory postural adjustments (APAs) for gait initiation. Presentation of sensory cues can significantly improve gait initiation and restore APAs; however, the optimal method for triggering a cue is not fully understood. In the current study, we compared an acoustic and/or mechanical assistance cue with self-initiated stepping in two triggering paradigms: the person was able to trigger the cue with a button press [Self-Triggered] and cues were presented within an instructed-delay paradigm [Externally-Triggered]. Ten participants with PD and FOG performed gait initiation trials in four conditions: self-initiated with no cues provided [No-Cue], acoustic go-cue [Acoustic-Passive], mechanical assistance from a powered ankle-foot orthosis provided as the go-cue [Assist], and acoustic and mechanical assist cues were provided simultaneously [Acoustic-Assist]. Analysis of vertical ground reaction force and center of pressure peak amplitudes, timings, and APA duration (time from onset to toe-off) across cue condition and trigger modality was performed. Results demonstrated that cues (acoustic and/or mechanical assistance) are most effective at increasing peak amplitudes (ground reaction force and center of pressure) using an external-trigger source versus self-triggering. Furthermore, these amplitudes remained

unchanged compared to the No-Cue baseline condition when they were self-triggered. Therefore, this study is the first to suggest that externally-triggered cues may be the better method for facilitating APA generation in people with PD and FOG. However, further investigation into different methods of self-triggering is still needed.

4.2 Introduction

About one-half of the Parkinson's disease (PD) population suffers from the devastating symptoms of freezing of gait (FOG) (Macht et al. 2007). FOG is most commonly defined as the inability to initiate or maintain continuous gait (Berardelli et al. 2001; Giladi and Nieuwboer 2008). These symptoms present in three ways: during the first step (usually termed start hesitation), turning while walking, or when presented with external factors during continuous gait (e.g., transition of environments) (Giladi and Nieuwboer 2008). The incidence and severity of FOG increases throughout the disease progression and is related to decreased postural stability (Lamberti et al. 1997; Giladi 2001; Macht et al. 2007). Currently, there are no adequate therapies or treatments to manage FOG symptoms (Giladi 2008). Ultimately, FOG increases the risk of falls, decreases mobility and independence, and has an overall negative impact on quality of life (Giladi 2001).

People with PD and the symptoms of FOG have difficulty generating and coordinating anticipatory postural adjustments (APAs) during gait initiation (Burleigh-Jacobs et al. 1997; Halliday et al. 1998; Jacobs et al. 2009; Rogers et al. 2011). APAs are generated by the lower limbs to prepare the body to accelerate forward and lift the stepping leg off the ground (Carlsoo 1966; Crenna and Frigo 1991; Elble et al. 1996). The sequence of movements begins with a simultaneous loading of the stepping foot and unloading of the stance foot (Figure 1). This loading-unloading causes the vertical ground reaction forces under the stepping (stance) leg to increase (decrease), and the center of pressure moves towards the stepping foot with a simultaneous posterior shift. After this initial “loading-unloading” phase, the center of mass is accelerated forward and the first step begins.

People with PD and FOG have a diminished ability to generate the necessary forces in the lower limbs during an APA (Rogers et al. 2011) resulting in disrupted gait initiation (Crenna and Frigo 1991; Rogers et al. 2011) and slower gait velocity (Burleigh-Jacobs et al. 1997; Halliday et al. 1998). Thus, it is possible that interventions or therapies that facilitate APA generation could help overcome problems with gait initiation in people with PD and FOG.

Several types of sensory cues have been demonstrated to improve APA generation and alleviate difficulties with start hesitation in people with PD. Visual, auditory, and somatosensory cues have commonly been investigated (Dietz et al. 1990; Cubo et al. 2004; Dibble et al. 2004). APA magnitude can be increased with the use of a visual cue in a lab setting (Rogers et al. 2011). However, translation of these types of cues from the lab setting to the in-home environment has been limited (Nieuwboer et al. 2007) because the ideal cue presentation timing and context (i.e., environments, paradigms) are not fully understood (Nieuwboer 2008). Consequently, further investigations are needed to determine the important factors pertaining to the ideal presentation of sensory cues.

One of these factors relates to the proper method for triggering the sensory cue when it is needed. Most cueing studies have focused on externally triggered cues (i.e. triggered by something/someone other than the user) within a laboratory setting. These paradigms can be successful, improving the timing and magnitude of APA generation and evoking gait initiation

(Dibble et al. 2004; Rogers et al. 2011). Other researchers have used wearable technology (e.g., accelerometers) to detect FOG episodes in order to present cues with classification rates up to 85% (Jovanov et al. 2009; Bachlin et al. 2010; Moore et al. 2013; Pepa et al. 2015). Despite the success of these paradigms, externally-triggered cues have practical limitations. Specifically, cues can be presented without a FOG episode (Bachlin et al. 2010), while other paradigms (i.e., instructed-delay) may be problematic if the person requires the cue immediately. Therefore, there is a need for highly reliable cue delivery methods such that they are only presented when required by the user.

Allowing the person to trigger the cue themselves could eliminate any uncertainty of when the cues would be provided. However, self-triggering could be considered a cognitive dual-task because the person has to trigger the cue and step simultaneously. People with PD and FOG have decreased cognitive capacity compared to people with PD without FOG (Walton et al. 2015). Cognitive dual-tasking can impair gait (O'Shea et al. 2002; Spildooren et al. 2010) and upright stance (Holmes et al. 2010) in persons with PD. Furthermore, tasks that require attention control (e.g., the Stroop task) can be impaired when a person with PD needs to rely on internal control versus external cues to correctly perform the task (i.e., self-awareness of the task rule versus the task rule is cued before each trial) (Brown and Marsden 1988). Self-triggering may also potentiate the dysfunctional neural circuitry for volitional movement in PD, which could attenuate the positive modulatory effects of cues. Altogether, it is unclear if self-triggering a cue would be effective for improving APA generation and gait initiation of people with PD and FOG.

In the current study, we evaluated the effectiveness of an acoustic and a mechanical assistance cue using these two cue delivery paradigms (externally and self-triggered). We hypothesized that externally-triggered cues would result in more effective modulation of APAs than self-triggered cues. Furthermore, we hypothesized that the ability to self-trigger a cue would result in unchanged or diminished APAs compared to self-initiated stepping.

4.3 Methods

4.3.1 Participants

Ten participants with PD and freezing of gait symptoms were recruited for this study (6 male, age 62.1±10.6 yrs, height 170.9±12.0 cm, weight 76.5±15.1 kg). The study was performed at the University of Illinois Urbana-Champaign (UIUC) and the University of Minnesota (UMN). Institutional Review Board approvals were obtained at both institutions and all participants signed informed consent forms for the study.

Participants included in the study were diagnosed with idiopathic PD, 45+ years of age, Hoehn & Yahr rating scale of 2.5-4, and had a history of start hesitation and freezing episodes based upon the Freezing of Gait Questionnaire (FOG-Q) (Giladi et al. 2009). A person was classified as a "freezer" if they have at least one weekly FOG episode (score of >1 on item 3 of the FOG-Q) (Nieuwboer et al. 2009). Furthermore, the participants had to be capable of ambulation without an assistance device (e.g., cane, walker) in the off-medicated state, be free of other neurological disorders, and could not have musculoskeletal disorders that affect movement of lower limbs. Participants were excluded if they had clinically significant reductions in vision (when corrected), hearing, or cutaneous sensation to the feet. Also, a history dementia or cognitive impairment (Mini-Mental Score <26), a high level of tremor off-medication (>2 on questions 20 and 21 of the UPDRS), and any neurosurgeries to treat PD (e.g., deep brain stimulation) were criteria for exclusion.

4.3.2 Portable Powered Ankle-Foot Orthosis (PPAFO)

The mechanical assistance cue used in this study was provided by a portable powered ankle-foot orthosis (PPAFO, Figure 10) (Boes et al. 2013). The PPAFO was capable of providing both dorsiflexor and plantarflexor torque at the ankle through a bi-directional rotary pneumatic actuator. On-board electronics were utilized to control two solenoid valves that regulated the flow of compressed gas into each vane of the actuator.

4.3.3 Cue Presentation

Customized software (Texas Instruments Code Composer v5, Texas Instruments, Dallas, TX) was used to control all cues (ready cue, acoustic go-cue, and actuation of the PPAFO). The same clearly audible acoustic tone (80 dB, 1 kHz tone, 500 ms in duration projected from a speaker) was used for the ready and go-cues. A sequence of a dorsiflexor then plantarflexor torque derived from the APAs of healthy control subjects (Rogers et al. 2011) was used for the mechanical assist cue. The dorsiflexor torque (330 ms in duration) was tuned to hold the suspended participant's foot in neutral position relative to the shank (~3-5 Nm at 30-50 psig). The plantarflexor torque (83 ms in duration) was set to be 9-10 Nm based on 90 psig air pressure.

4.3.4 Gait Initiation Task

Four gait-initiation test conditions were evaluated: (1) self-initiated trials in an unpowered passive PPAFO [No-Cue], (2) acoustic go-cue with PPAFO in passive mode to assess the effect of an acoustic cue [Acoustic-Passive], (3) mechanical assistance from the PPAFO alone to assess its efficacy as a standalone cue [Assist], and (4) acoustic go-cue with simultaneous mechanical assistance from the PPAFO to assess the effect of mechanical assistance provided during another cue [Acoustic-Assist]. Each condition was performed using two different trigger modalities: (1) by the user with a hand held button [Self-Triggered], (2) within an instructed-delay paradigm [Externally-Triggered]. The PPAFO was fit to the test participant and worn on the right limb. The participant's personal walking shoe was worn on the left limb.

Blocks of five trials were performed per trigger modality for each test condition (10 trials per condition, total of 40 trials per participant). Trial order was randomized for each condition and trigger modality. The instructions for all Self-Triggered trials were "Wait approximately 2-3 seconds after the ready cue and press the switch in your hand to receive a cue. The cue will be [nothing (No-Cue), an acoustic beep (Acoustic-Passive), a mechanical assist (Assist), an acoustic beep and mechanical assist (Acoustic-Assist)]." The button press was included in the Self-Triggered No-Cue trials to control for the act of pressing the button while stepping. For Externally-Triggered trials, an instructed-delay paradigm was used with the go-cue provided 2.5 seconds after the ready cue for the cued conditions (MacKinnon et al. 2007; Chapters 2 and 3). The instructions were to initiate gait with the right foot in response to the go-cue. In the baseline condition for this trigger modality, the instruction was to initiate gait 5-10 seconds after hearing the ready tone. Participants were asked to take two steps forward "as quickly as possible" starting with the right foot for all trials.

4.3.5 Data Collection

Ground reaction force (GRF), center of pressure (COP), and electromyographic (EMG) data were sampled at 1000 Hz. Participants stood with each foot on separate force plates embedded in an instrumented treadmill at UIUC (Bertec Corporation, Columbus, OH) and a slightly raised walkway at UMN (Kistler Instrument Corporation, Novi, MI). Force data were filtered using a low-pass Butterworth filter with a cut-off frequency of 20 Hz. Total body COP for the medial-lateral (ML) and anterior-posterior (AP) directions were calculated using GRF data from both feet. EMG data were recorded from the tibialis anterior (TA) muscle of the stepping (right) leg (Bagnoli 16 at UIUC, Trigno at UMN, Delsys Corp., Boston, MA).

4.3.6 Data Analysis

EMG parameters were not included in the following data analysis because of challenges with post-processing of the EMG data from this population. Low signal magnitude and high variability of TA EMG signals made consistent identification of TA onset time difficult (Appendix B).

Nine APA parameters from the vertical GRF of the right leg, and AP/ML COP of the total body were computed for each test condition (Figure 12). Peak amplitudes (magnitudes and timings measured from onset) of vertical GRF ($vGRF_{pk}$, $vGRF\_t_{pk}$), ML center of pressure ($ML\text{-}COP_{pk}$, $ML\text{-}COP\_t_{pk}$), and AP center of pressure ($AP\text{-}COP_{pk1}$, $AP\text{-}COP\_t_{pk1}$, $AP\text{-}COP_{pk2}$, $AP\text{-}COP\_t_{pk2}$) were analyzed. The first AP center of pressure peak was quantified during the "loading-unloading" phase prior to the vertical GRFs of both feet crossing over prior to the step. The second AP peak happened approximately at toe-off. GRF was normalized as a percentage of the participant's body weight. The time from onset to toe-off of the stepping foot ($t_{toe\text{-}off}$) was also analyzed. Toe-off was quantified based on the instant the right vertical GRF (normalized by body weight) went below 0.1 %BW. Finally, the sample variance divided by the sample mean (coefficient of variation (COV)) was calculated from all trials in a condition for each parameter (except for the $AP\text{-}COP_{pk1}$ and $AP\text{-}COP_{pk2}$), per participant. It was invalid to calculate COV for the two anterior-posterior peaks could because values were both positive and negative.

Onsets for each type of data were calculated based on a monotonic change of greater than three standard deviations in relation to baseline signal (mean of 1000 ms prior to the go-cue). For the No-Cue conditions, the mean signal prior to a manually picked point (~100-300 ms before GRF_t_{onset}) was used to calculate the baseline signal. A trial was considered to have "no-APA" behaviors (parameters set to zero) if no clear monotonic increase was observed in a signal. Using visual inspection, all parameters were verified by a trained researcher.

4.3.7 Statistical Analysis

A 2×4 repeated-measures multivariate analysis of variance (MANOVA) was conducted to assess the effect of trigger modality (2) × testing condition (4) on the nine APA parameters. A separate MANOVA was also run for the COV of the seven parameters. Only the interaction effect of the trigger × condition interaction was considered during the analysis because the main effects of trigger and condition alone do not address the research questions of this study. Univariate ANOVAs were run for significant parameters if an interaction effect in the MANOVA existed. Post hoc effects were examined using Fisher Least Significant Difference (LSD) test. These pairwise comparisons were evaluated both between conditions (within trigger modality) and trigger modalities (within testing condition). All data were processed using SPSS statistical software (Version 20, IBM Corp, Armonk, NY). Significance level was set to $\alpha = 0.05$.

4.4 Results

The MANOVAs indicated a significant interaction effect for the average values, but not the COV, of the nine APA parameters. The MANOVA containing the average values of the nine APA parameters indicated a significant trigger × condition interaction ($p = 0.003$, Table 4). No interaction effect of the trigger × condition interaction was observed in the COV parameters (p =

0.648, Table 5). Archetypical data for each condition and trigger modality are presented in Appendix C.

4.4.1 Vertical Ground Reaction Force

Univariate analyses found that $vGRF_{pk}$ had significant changes in the trigger × condition interaction ($F_{3,27} = 4.34$, $p = 0.013$) (Figure 18, Table 4).

4.4.1.1 Pairwise Comparison between Trigger Modalities within Conditions

Significant differences between triggering modalities were observed for $vGRF_{pk}$ (Figure 18, Table 4). Overall, $vGRF_{pk}$ was increased between the cued conditions. Amplitudes were significantly greater in the Assist and Acoustic-Assist conditions within the Externally-Triggered modality compared to Self-Triggered. The same increase was observed in the Acoustic-Passive condition, but it was not significant. No significant differences between triggering modalities was observed for the time to peak amplitude ($vGRF\_t_{pk}$, Figure 18, Table 4) or time to toe-off ($t_{toe\text{-}off}$, Figure 19, Table 4).

4.4.1.2 Pairwise Comparison of Conditions within Trigger Modalities

Several differences between cued and baseline conditions were observed for $vGRF_{pk}$ within the triggering modalities (Table 4). Compared to No-Cue, peak vertical ground reaction force magnitude ($vGRF_{pk}$) was significantly increased in the Assist and Acoustic-Assist conditions within the Externally-Triggered trials. An increase was also observed in the Acoustic-Passive condition compared to No-Cue, but the change was not significant. Within the Self-Triggered conditions, no statistically significant changes were observed in cued conditions (Acoustic-Passive, Assist, Acoustic-Assist) for $vGRF_{pk}$ compared to No-Cue. Finally, no significant differences for the time to peak amplitude (vGRF_t_{pk}) or toe-off ($t_{toe\text{-}off}$) were observed within the two triggering modalities.

4.4.2 Center of Pressure

Univariate ANOVA results revealed significant effects for trigger × condition for the magnitudes and timings of medial-lateral (ML-COP_{pk}, $F_{3,27} = 8.52$, $p < 0.001$, ML-COP_t_{pk}, $F_{3,27} = 3.70$, $p = 0.024$) and anterior-posterior (AP-COP_{pk1}, $F_{3,27} = 5.65$, $p = 0.004$, AP-COP_t_{pk1}, $F_{3,27} = 3.53$, $p = 0.028$) center of pressure (Table 4).

4.4.2.1 Pairwise Comparison between Trigger Modalities within Conditions

Significant increases in medial-lateral peak magnitude (ML-COP_{pk}) were observed in External-Triggering compared to Self-Triggering within conditions (Figure 20, Table 4). In all cueing conditions, significant increases in External-Triggering were observed compared to Self-Triggering (Acoustic-Passive, Assist, and Acoustic-Assist). A significant difference in the timing of ML-COP_t_{pk} was observed between trigger modalities in the No-Cue conditions, but none of the cued conditions.

A significant increase in the first anterior-posterior peaks (AP-COP_{pk1}) was also found between triggering modalities (Figure 21, Table 4). AP-COP_{pk1} was significantly greater in the Acoustic-Passive and Acoustic-Assist when Externally-Triggered compared to Self-Triggering. Similar to ML-COP_t_{pk1}, significant differences existed between trigger modalities in the No-Cue conditions, but none of the cued conditions for AP-COP_t_{pk1}.

4.4.2.2 Pairwise Comparison of Conditions within Trigger Modality

Like the ground reaction force data, ML-COP_{pk} was increased in the Acoustic-Passive, Assist, and Acoustic-Assist conditions compared to No-Cue using External-Triggering (Figure 20,

Table 4). In Self-Triggering, no statistical difference existed between all conditions for ML-COP_{pk}. The timing of the medial-lateral peak (ML-COP_t_{pk}) was significantly shorter in the Assist conditions (Assist, Acoustic-Assist) than Acoustic-Passive in External-Triggering. Across Self-Triggered conditions, ML-COP_t_{pk} remained unchanged.

In the anterior-posterior direction, the first peak (AP-COP_{pk1}) was significantly larger in both conditions including an Acoustic cue (Acoustic-Passive, Acoustic-Assist) compared to No-Cue in External-Triggering (Figure 21, Table 4). Furthermore, significant differences existed between the Assist conditions, with the Acoustic-Assist condition being greater than Assist. No significant differences existed between the Self-Triggering conditions for AP-COP_{pk1}. The timing of this peak (AP-COP_t_{pk1}) was significantly shorter than No-Cue in the Assist condition in External-Triggering. Conversely, the timing of this peak was longer in the Assist condition compared to No-Cue in Self-Triggering.

4.5 Discussion

The results of this study suggest that APAs are amplified when cues (acoustic or mechanical) are externally-triggered, but not self-triggered in persons with PD and FOG (Table 4). Between triggering modalities, increases in peak amplitude magnitudes ($vGRF_{pk}$, ML-COP_{pk}, AP-COP_{pk1}, Figure 18, Figure 20, Figure 21, and Table 4) were observed in at least one of the cued conditions within External-Triggering, suggesting that cues are more effective at increasing APA amplitude when they are triggered by an external source. However, the timing of these peak magnitudes did not vary between triggering modalities except for differences between No-Cue conditions in ML-COP_t_{pk1} and AP-COP_t_{pk1} (Figure 20, Figure 21). Within Self-Triggering conditions, cues did not significantly shorten the timing or amplify the magnitude of APAs compared to not providing a cue. Taking everything into account, external-triggering a cue, not self-triggering, is a more effective at modulating the amplitude of APAs in persons with PD and FOG.

The lack of increased APA magnitudes ($vGRF_{pk}$, $ML\text{-}COP_{pk}$, $AP\text{-}COP_{pk1}$, $AP\text{-}COP_{pk2}$) in Self-Triggering could be due to a variety of reasons. One possibility could be an absence of preparation before the planned movement. Even though participants were instructed to press the button approximately 2-3 seconds after the ready tone, they may have not prepared for the movement as they did in the instructed-delay paradigm (i.e., Externally-Triggered conditions). Without preparation, the planned volitional movement can be diminished or absent in PD (Rogers et al. 2011). Another aspect to consider is when the cue was provided relative to the APA. Due to the dual-task of pressing the button and attempting to step at the same time, the cues may not have been provided before or during the early period of the APA. This misalignment of cues with the APA would have been particularly detrimental in the assist conditions because mechanical stimuli do not modulate APA magnitude when provided after the initial phase of the APA (Mille et al. 2009; Rogers et al. 2010; Mouchnino et al. 2012). Lastly, because self-triggering requires an internally generated motor command, it may have potentiated the impaired cortical-striatal neural pathways responsible for initiating volitional movement (Albin et al. 1989) instead of the cerebellar-thalamo-parietal network believed to enable sensory cues (Nieuwboer 2008; Nombela et al. 2013). These malfunctioning cortical-striatal pathways have been attributed to causing diminished and prolonged gait initiation APAs that are observed in people with PD (Burleigh-Jacobs et al. 1997). In sum, these results highlight factors related to cue triggering that should be considered while developing self-triggering cue paradigms for persons with PD and FOG.

Increases in peak magnitudes ($vGRF_{pk}$, $ML\text{-}COP_{pk}$, $AP\text{-}COP_{pk1}$, Figure 18, Figure 20, and Figure 21) within the Externally-Triggered conditions are consistent with previous external-triggered paradigms (for example, as observed in Chapters 2 and 3). Using the instructed-delay paradigm allowed participants to prepare for the movement, which has been demonstrated to help release the desired volitional movement command through corticospinal excitations (MacKinnon et al. 2007). Furthermore, a more accurate alignment of the cue with the early phase of the APA would have enabled the user to adapt their motor command according to the cue, especially for the mechanical assistance cue (Mille et al. 2009; Rogers et al. 2010; Mouchnino et al. 2012). Therefore, externally-triggered cues may be more effective at modulating the amplitude of APAs compared to self-triggered cues.

Within the trigger modalities, there were a few differences between conditions in timing parameters. For Externally-Triggering, $ML\text{-}COP\_t_{pk}$ was shorter in the Assist conditions (Assist and Acoustic-Assist) compared to the Acoustic-Passive condition. A similar decrease in this parameter was observed between the Assist and Acoustic-Passive conditions in Chapter 3. Furthermore, the timing of the first anterior-posterior peak amplitude ($AP\text{-}COP\_t_{pk1}$) was significantly shorter in the Assist condition compared to the No-Cue condition, also consistent with results from Chapter 3. Time to peak anterior-posterior center of pressure amplitude ($AP\text{-}COP\_t_{pk1}$) was the only significant timing difference between Self-Triggering conditions, with it being longer in the Assist condition compared to the No-Cue condition. The mechanism behind this change is unclear, but it is possible that the manner in which the Assist was triggered by the person slightly lengthened the timing of the peak amplitude from onset. Aside from the amplitude changes, no significant differences between trigger modalities were found for timing parameters except for the time to peak medial-lateral (ML-COP_t_{pk}) and anterior-posterior (AP-COP_t_{pk1}), which were longer in Externally-Triggered, No-Cue condition compared to Self-Triggering. The main differences between these two conditions were the instruction given to the participants and the inclusion of button press. In the Externally-Triggered modality, the instruction to the participant was to initiate gait on their own (without a cue) approximately 5-10 s after the ready-cue. In the Self-Triggered modality, the participants were asked to wait 2-3 seconds and then press the button in their hand and take a step, but no cue was provided with the button press. The purpose of including the button press was to control for that action when comparing it against the cued trials in the same triggering modality. Interestingly, the button press could be considered a dual-task, which can have a negative impact on gait speed (O'Shea et al. 2002; Spildooren et al. 2010) and postural control during upright stance (Holmes et al. 2010). However, ML-COP_t_{pk} and AP-COP_t_{pk1} were longer in the Externally-Triggered modality, not Self-Triggered. In general, the average timing values (vGRF_t_{pk}, AP-COP_t_{pk2}, and $t_{toe\text{-}off}$) were slightly longer in the Externally-Triggered modality for No-Cue, but the difference between trigger modalities were not significant for these parameters. The consequence of the peak happening earlier with Self-Triggering without a concomitant shorter duration in toe-off is unclear, but the results are interesting nonetheless.

The proper method of externally-triggering a cue for a person with PD and FOG is still an open question. Practically, the main obstacle for external-triggered paradigms is that freezing episodes (or precursors to a freeze) need to be accurately classified by the external source, or the cues can be distracting or even provoke a freezing episode if they are not in sync with the user’s desired gait (Bachlin et al. 2010; Nombela et al. 2013). Moreover, what is currently known about precursors of FOG (e.g., spatiotemporal changes in gait, electromyography (EMG) activity) has been performed in controlled laboratory experiments where the participants were presented with freeze provoking scenarios while continuously walking or stopping (Nieuwboer et al. 2001; Nieuwboer et al. 2004). Ideally, walking data (including gait initiation) need to be collected during unconstrained movement in the environment to get an all-encompassing picture of the behaviors that precede a FOG episode. Recent advances in machine learning and wearable technology are being used to extract patterns from a combination of sensors (e.g., accelerometers, EMG) in order to continuously track symptoms (i.e., tremor and dyskinesia) (MacKinnon 2013; Roy et al. 2013). These same sensors could be used to determine predictive factors of FOG (Horak et al. 2015), and/or possibly increase the classification accuracy of FOG. If a freezing episode (or possibly precursor to a freeze) can be automatically detected using sensors with high accuracy, then an intelligent external source might be the most viable method of cue triggering.

At the same time, the method for self-triggering could be adjusted and still attain positive results for APA modulation. For example, instead of directly controlling the cue (i.e., without delay between the button press and cue presentation), the user could have control over starting an instructed-delay paradigm, where the cue is preceded by a ready-cue. In this way, the person would be able to prepare for the movement, which can help elicit APAs with increased magnitude and decreased duration (MacKinnon et al. 2007; Rogers et al. 2011). This strategy would still be subject to the practical concerns because the person would have to wait for a certain duration before receiving their cue. However, the user would only receive the cue when it is deemed needed by the user, and the cognitive burden of pressing the button and stepping at the same time would be reduced.

4.6 Conclusions

The results of this study suggest that self-triggering a cue (acoustic tone and/or mechanical assistance) results in unchanged gait initiation APAs compared to baseline, while externally-triggered cues can result in amplified APAs in people with PD and FOG. Future investigations should look into methods for automatic classification of a freezing episode using sensors to improve the efficacy of externally-triggered cue paradigms. Furthermore, investigations into different methods of self-triggering (e.g., provide a delay from the button press) could be investigated to determine if self-triggering a cue is still plausible.

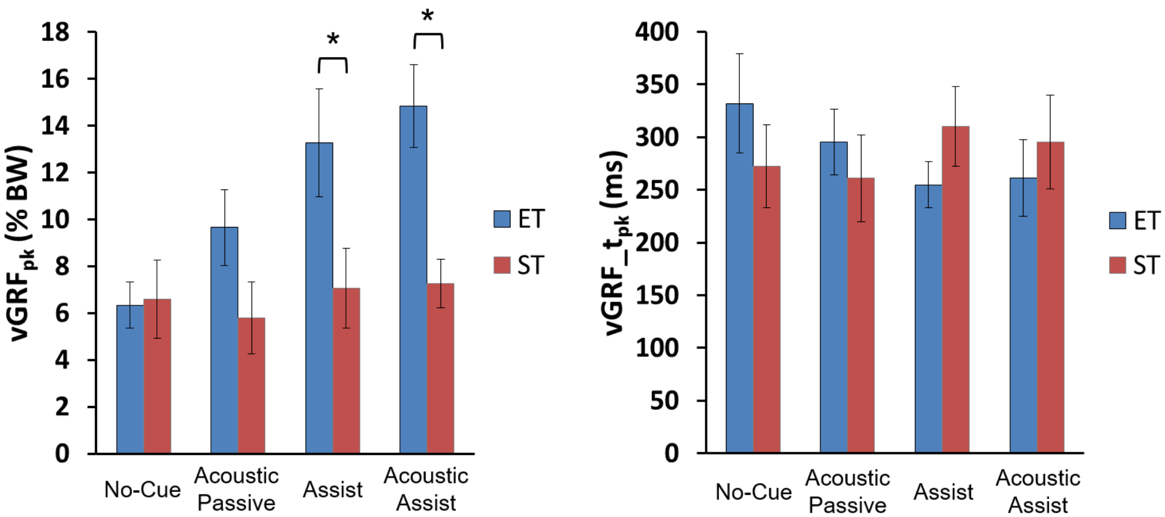

Figure 18: Vertical ground reaction force peak amplitude magnitude ($vGRF_{pk}$) and timing ($vGRF\_t_{pk}$) across external (ET) vs. self-triggered (ST) conditions. An asterisk with a horizontal bar indicates a significant difference between trigger modalities within a condition ($p < 0.05$).

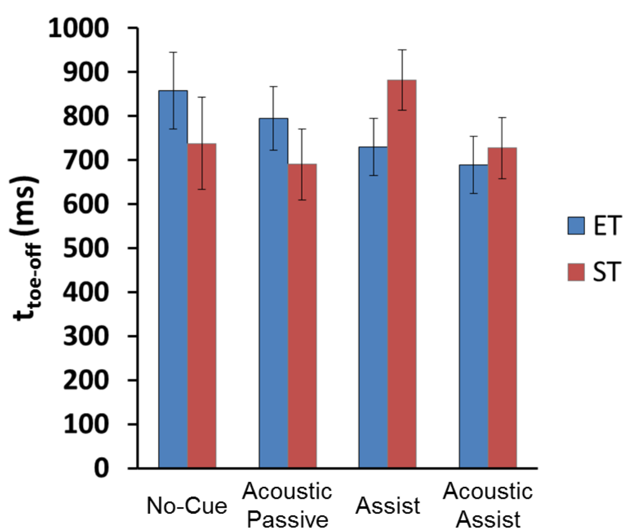

Figure 19: Time from onset to toe-off ($t_{toe\text{-}off}$) across external (ET) vs. self-triggered (ST) conditions. An asterisk with a horizontal bar indicates a significant difference between trigger modalities within a condition ($p < 0.05$).

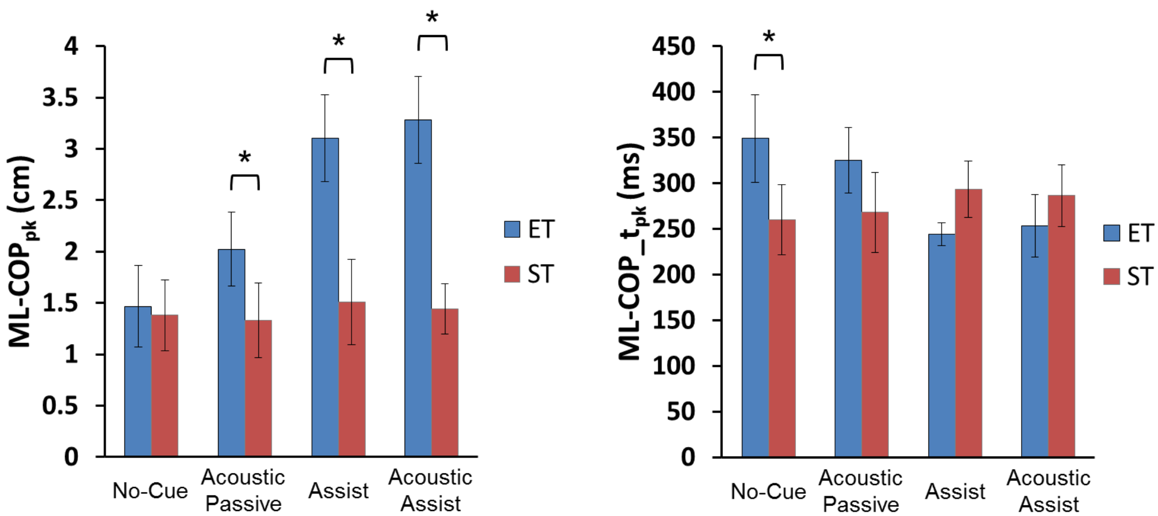

Figure 20: Medial-lateral center of pressure peak amplitude magnitude (ML-COP$_{pk}$) and timing (ML-COP_t$_{pk}$) across external (ET) vs. self-triggered (ST) conditions. An asterisk with a horizontal bar indicates a significant difference between trigger modalities within a condition ($p < 0.05$).

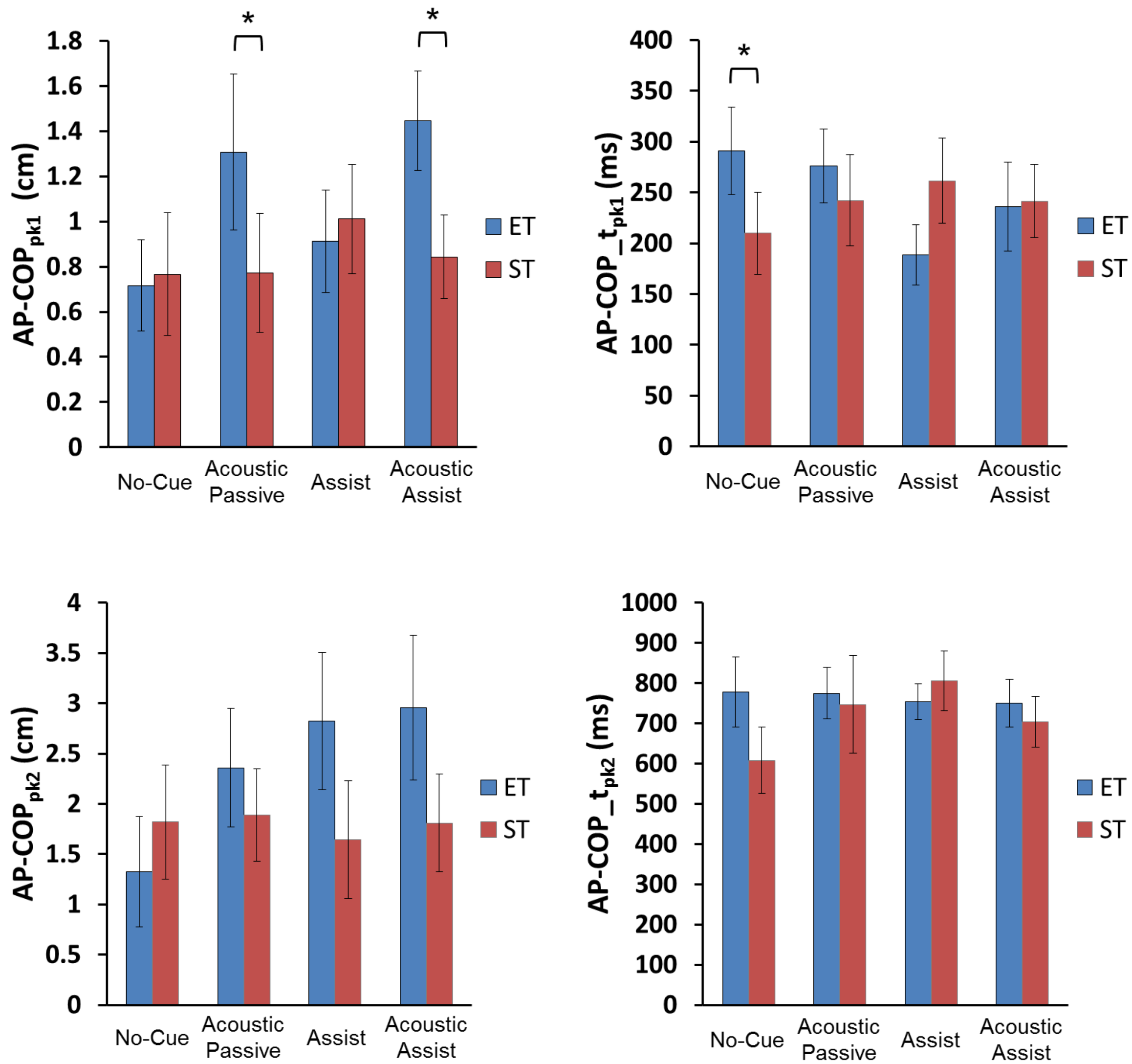

Figure 21: Magnitudes and timings of the anterior-posterior peak amplitudes (AP-COP$_{pk1}$, AP-COP_t$_{pk1}$, AP-COP$_{pk2}$, AP-COP_t$_{pk2}$) across external (ET) vs. self-triggered (ST) conditions. An asterisk with a horizontal bar indicates a significant difference between trigger modalities within a condition ($p < 0.05$).

Table 4: All nine APA parameters (average ± s.e.m) across conditions and trigger modalities (ET – External-Triggering, ST – Self-Triggering). Significant univariate *p*-values (trigger × condition) are bolded in the far right column. Numerical superscripts indicate a significant difference from the condition specified (within a trigger modality, $p < 0.05$). Significant differences within conditions (between trigger modalities) are indicated with ‡ ($p < 0.05$).

	Trigger Type	No Cue (1)	Acoustic Passive (2)	Assist (3)	Acoustic Assist (4)	p-value
$vGRF_{pk}$ (%BW)	ET	$6.3 \pm 1.6^{3,4}$	9.7 ± 2.3^{4}	$13.3 \pm 1.8^{1‡}$	$14.8 \pm 2.0^{1,2‡}$	**0.013**
	ST	6.6 ± 1.7	5.8 ± 1.5	$7.1 \pm 1.7^{‡}$	$7.3 \pm 1.0^{‡}$	
$vGRF\_t_{pk}$ (ms)	ET	331.8 ± 47.1	295.3 ± 31.0	254.8 ± 22.0	261.2 ± 36.1	0.081
	ST	272.7 ± 39.4	261.2 ± 41.2	310.2 ± 37.5	295.6 ± 44.3	
$ML\text{-}COP_{pk}$ (cm)	ET	$1.5 \pm 0.4^{2,3,4}$	$2.0 \pm 0.4^{1,3,5‡}$	$3.1 \pm 0.4^{1,2‡}$	$3.3 \pm 0.4^{1,2‡}$	**<0.001**
	ST	1.4 ± 0.3	$1.3 \pm 0.4^{‡}$	$1.5 \pm 0.4^{‡}$	$1.4 \pm 0.2^{‡}$	
$ML\text{-}COP\_t_{pk}$ (ms)	ET	$349.2 \pm 48.2^{‡}$	$325.1 \pm 35.7^{3,4}$	244.3 ± 12.2^{1}	253.5 ± 34.3^{1}	**0.024**
	ST	$260.1 \pm 38.5^{‡}$	268.1 ± 44.0	293.8 ± 30.9	286.4 ± 34.0	
$AP\text{-}COP_{pk1}$ (cm)	ET	$0.7 \pm 0.2^{2,4}$	$1.3 \pm 0.3^{1‡}$	0.9 ± 0.2^{4}	$1.4 \pm 0.2^{1,3‡}$	**0.004**
	ST	0.8 ± 0.3	$0.8 \pm 0.3^{‡}$	1.0 ± 0.2	$0.8 \pm 0.2^{‡}$	
$AP\text{-}COP\_t_{pk1}$ (ms)	ET	$291.0 \pm 43.0^{3‡}$	276.0 ± 36.5	188.5 ± 29.9^{1}	236.1 ± 44.1	**0.028**
	ST	$209.8 \pm 40.8^{3‡}$	242.3 ± 45.0	261.6 ± 41.7^{1}	241.6 ± 35.9	
$AP\text{-}COP_{pk2}$ (cm)	ET	1.3 ± 0.5	2.4 ± 0.6	2.8 ± 0.7	3.0 ± 0.7	0.054
	ST	1.8 ± 0.6	1.9 ± 0.5	1.6 ± 0.6	1.8 ± 0.5	
$AP\text{-}COP\_t_{pk2}$ (ms)	ET	777.7 ± 87.4	775.2 ± 63.5	753.9 ± 45.1	750.1 ± 58.7	0.168
	ST	608.2 ± 83.0	747.4 ± 121.0	806.0 ± 73.5	704.3 ± 63.6	
$t_{toe\text{-}off}$ (ms)	ET	858.2 ± 87.6	795.4 ± 72.3	729.4 ± 65.1	689.5 ± 65.4	0.052
	ST	737.5 ± 104.8	690.2 ± 80.4	881.5 ± 68.3	727.5 ± 69.0	

Table 5: Coefficient of variation for all nine APA parameters (average ± s.e.m) across conditions and trigger modalities (ET – External-Triggering, ST – Self-Triggering). No univariate *p*-values are provided because the MANOVA interaction (trigger × condition) was not significant.

	Trigger Type	**No Cue (1)**	**Acoustic Passive (2)**	**Assist (3)**	**Acoustic Assist (4)**
$vGRF_{pk}$ (%BW)	ET	0.77 ± 0.22	0.32 ± 0.06	0.26 ± 0.05	0.26 ± 0.05
	ST	0.84 ± 0.23	0.86 ± 0.20	0.49 ± 0.09	0.66 ± 0.15
$vGRF\_t_{pk}$ (ms)	ET	0.78 ± 0.21	0.28 ± 0.05	0.28 ± 0.06	0.24 ± 0.04
	ST	0.69 ± 0.22	0.80 ± 0.19	0.48 ± 0.09	0.50 ± 0.10
$ML\text{-}COP_{pk}$ (cm)	ET	0.82 ± 0.24	0.27 ± 0.05	0.24 ± 0.05	0.22 ± 0.05
	ST	0.90 ± 0.23	0.79 ± 0.19	0.56 ± 0.16	0.65 ± 0.12
$ML\text{-}COP\_t_{pk}$ (ms)	ET	0.73 ± 0.22	0.30 ± 0.05	0.24 ± 0.06	0.19 ± 0.04
	ST	0.74 ± 0.21	0.74 ± 0.19	0.52 ± 0.14	0.47 ± 0.08
$AP\text{-}COP\_t_{pk1}$ (ms)	ET	0.87 ± 0.20	0.52 ± 0.09	0.71 ± 0.14	0.40 ± 0.13
	ST	1.04 ± 0.25	0.99 ± 0.19	0.64 ± 0.14	0.62 ± 0.12
$AP\text{-}COP\_t_{pk2}$ (ms)	ET	0.57 ±0.20	0.20 ± 0.04	0.27 ± 0.05	0.16 ± 0.04
	ST	1.86 ± 2.04	1.94 ± 1.03	0.74 ±0.27	0.73 ± 0.23
$t_{toe\text{-}off}$ (ms)	ET	0.63 ± 0.22	0.14 ± 0.03	0.27 ± 0.08	0.12 ± 0.02
	ST	0.55 ± 0.23	0.66 ± 0.21	0.41 ± 0.11	0.39 ± 0.09

5 Modeling of Parkinsonian Anticipatory Postural Adjustments During Gait Initiation

5.1 Abstract

People with Parkinson's disease (PD) and freezing of gait (FOG) have difficulty generating anticipatory postural adjustments (APAs) for gait initiation. An initial burst of the dorsiflexor muscle (tibialis anterior) of the stepping leg is essential for the posterior center of pressure excursion and forward body lean angle that are typically observed during the "loading-unloading" phase of a typical APA during gait initiation. Tibialis anterior activation can be diminished or absent in people with PD; however, the neuromechanical consequence of this diminished dorsiflexor torque on appropriate APA generation is not fully understood. Computational models of gait initiation that include components of the neuromuscular system may provide additional insight. In this study, an inverted pendulum model of the APAs for gait initiation was created to simulate reduced dorsiflexor torque during the "loading-unloading" phase. Forward body lean angle and center of pressure were assessed over various settings of decreased dorsiflexor torque. Results from the model demonstrate that reducing the peak dorsiflexor torque by as little as 8 Nm may alter forward body lean and the center of pressure excursion from their nominal trajectories. These results can help inform how much torque is needed from an external device (e.g., a powered ankle-foot orthosis) to effectively modulate APAs during gait initiation, as well as provide insight into neuromechanical factors contributing to FOG.

5.2 Introduction

Among the many motor symptoms of Parkinson's disease (PD), freezing of gait (FOG) can be the most debilitating for people with PD. Typically defined as the absence or inability to maintain or initiate continuous gait (Berardelli et al. 2001; Giladi and Nieuwboer 2008), FOG is related to postural instability and becomes more severe and increases in incidence with disease progression (Lamberti et al. 1997; Giladi 2001; Macht et al. 2007). FOG presents in patients when they encounter freeze provoking scenarios during continuous gait (e.g., a transition in the environment), the first step (start hesitation), and turning while walking (Giladi and Nieuwboer 2008). Current therapies or treatments for PD (e.g., levodopa medication, deep brain stimulation) cannot effectively manage FOG symptoms (Giladi 2008). Eventually, people with FOG have an increased risk of falling, leading to decreased mobility, which has an overall negative impact on quality of life (Giladi 2001).

Anticipatory postural adjustments (APAs) are generated by the lower limbs to accelerate the body forward for the first step during gait initiation of healthy, able-bodied adults (Figure 1 and Figure 2) (Carlsoo 1966; Crenna and Frigo 1991; Elble et al. 1996). An APA starts with a "loading-unloading" phase that puts the body in the correct alignment for accelerating forward during the first step. The sequence of muscle activations during this initial phase is a deactivation of plantarflexor muscles (gastrocnemius and soleus) and activation of the dorsiflexor muscle (tibialis anterior) of both the stepping and stance legs (Carlsoo 1966; Crenna and Frigo 1991; Elble et al. 1996). This results in a concomitant increase (decrease) of the vertical ground reaction forces underneath the stepping (stance) foot and an excursion of the center of pressure backwards and laterally towards the stepping limb. The magnitude of the initial tibialis anterior

(TA) burst of the stepping leg and posterior center of pressure excursion have been shown to be highly correlated with gait initiation velocity (Crenna and Frigo 1991; Lepers and Breniere 1995). After the preparatory "loading-unloading" phase, forces are generated by the plantarflexor muscles of the stepping leg to accelerate the center of mass towards the stance foot and forward. Lastly, the dorsiflexor muscle (tibialis anterior) of the stepping leg is activated to lift the stepping leg off the ground for the first step (Carlsoo 1966; Crenna and Frigo 1991; Elble et al. 1996).

In PD, force production of the lower limbs is impaired and gait initiation APAs are diminished in magnitude (Burleigh-Jacobs et al. 1997; Halliday et al. 1998; Jacobs et al. 2009; Rogers et al. 2011). The initial TA burst of the stepping leg can be diminished or absent, resulting in a decreased excursion of the center of pressure in the sagittal plane, reduced dorsiflexor torque, and slower gait initiation velocity (Elble et al. 1996; Burleigh-Jacobs et al. 1997). Furthermore, people with PD and FOG have a diminished posterior excursion of the center of pressure during the "loading-unloading" phase when compared to people with PD without FOG and healthy controls (Alibiglou et al. 2016). However, the neuromechanical significance of this behavior has yet to be fully understood. Some have proposed that the decreased center of pressure excursion may be a way of maintaining stability (Martin et al. 2002). On the other hand, diminished TA activation could also be due to a malfunction of the central nervous system in PD. For instance, the inability to appropriately scale muscle activation to movements has been observed in PD (Pfann et al. 2001). Additionally, persons with PD can have difficulty switching between sequences of movements (Benecke et al. 1987). A model of diminished TA activation during gait initiation could be utilized to better understand the neuromechanical significance and guide the development of modulation strategies for gait initiation in persons with PD and FOG (e.g., cues or externally applied mechanical assistance).

Currently, no computational models exist for PD during gait initiation. Inverted pendulum models have been widely used for studying upright standing postural control (Johansson et al. 1988; Peterka 2000; Maurer and Peterka 2005), including for persons with PD (Nogueira et al. 2010). These models contain terms that effectively model the physiology of the human body, including the neuromuscular system (e.g. sensory feedback, neural controller). Inverted pendulum models have also been used to calculate the mechanics of gait initiation in healthy individuals (Breniere et al. 1987; Lepers and Breniere 1995). However, these gait initiation models do not include elements specifically related to the neuromuscular system. In this study, we aimed to utilize the neuromuscular components of postural control inverted pendulum models to effectively model the "loading-unloading" phase of gait initiation in persons with PD and FOG. We also aimed to investigate the neuromechanical consequences of reduced dorsiflexor torque on overall forward body progression and anterior-posterior excursion of the body's total center of pressure.

5.3 Methods

5.3.1 Model Definition

To study the effects of reduced dorsiflexor torque, the upright body during gait initiation was modeled as a single-link inverted pendulum in the sagittal plane (Figure 22). It was assumed that both ankles pivoted around the same point and the feet were anchored to the ground (Lepers and Breniere 1995). The equations of motion for the body segment pivoting around the ankles were:

$$\sum F_x = R_x(t) = m_B a_{Bx}(t) \tag{1}$$

$$\sum F_z = R_z(t) - m_B g = m_B a_{Bz}(t) \tag{2}$$

$$\sum T = T_{Ank}(t) + T_G(t) = J_B \ddot{\theta}(t) \tag{3}$$

where R_x and R_z were the reaction forces at the ankle, m_B was the body mass (excluding the feet), a_{Bx} was the acceleration of the body segment in the horizontal direction, a_{Bz} was the acceleration of the body in the vertical direction, g was acceleration due to gravity, $J_B = \frac{1}{3} m_B L_B^2$ was the moment of inertia about the ankles (under the assumption of the body being a uniform rod), and L_B was the body length. L_B was defined as the Euclidian distance between motion capture markers placed on the left acromion (shoulder, L_{ACR}) and lateral malleolus (ankle, L_{LMA}) of one participant (age 30, ht. 180 cm, wt. 86 kg) during gait initiation experimental trials. T_{Ank} was the torque applied at the ankle by the person (plantarflexor defined as positive), and T_G was the torque due to gravity of the body. Body lean angle (θ) and torque due to gravity (T_G) were calculated using equations 4 and 5:

$$\theta(t) = -\left(\arctan\left(L_{ACRz} - L_{LMAz}, L_{ACRx} - L_{LMAz} \right) - \frac{\pi}{2} \right) \tag{4}$$

$$T_G(t) = m_B g L_{COM} \sin\theta(t) \approx m_B g L_{COM} \theta(t) \tag{5}$$

where L_{ACRx}, L_{LMAx}, L_{ACRz}, L_{LMAz} were the horizontal and vertical positions of the motion capture markers placed on the left acromium and lateral malleolus, and L_{COM} was the position of the center of mass (assumed to be half of L_B because the pendulum was assumed to be a uniform rod). Small angle approximation was used for equation 5. The transfer function from applied ankle torque (T_{Ank}) to body lean angle (θ_{Model}) in the Laplace domain was derived from equation 3:

$$\frac{\theta_{Model}(s)}{T_{Ank}(s)} = \frac{1}{J_B s^2 - m_B g L_{COM}} \tag{6}$$

5.3.2 Neuromuscular Terms

Multiple terms related to the neuromuscular system were included in the model in order to calculate T_{Ank} (Figure 23). First a feed-forward ankle torque (T_F) was calculated based on solving equation 3 for T_{Ank} and setting it equal to T_F:

$$T_F\left(t\right) = J_B \ddot{\theta}_{ref}^2\left(t\right) - m_B g L_{COM} \theta_{ref}\left(t\right) \tag{7}$$

The nominal trajectory (θ_{Ref}) was generated using equation 4 from the average behavior of 10 self-initiated gait initiation trials (right foot steps) from the test participant. Several experimental studies and computational models have demonstrated that the nervous system develops a predictive feedforward model for movements that can make online corrections with delayed sensory feedback within a neural circuit that involves the cerebellum (Wolpert et al. 1998; Kawato 1999).

Similar to postural control inverted pendulum models (Maurer and Peterka 2005; Nogueira et al. 2010), sensory feedback detecting body lean angle (e.g., vestibular, proprioceptive) was modeled using position feedback (Figure 23). Stiffness (K_p), integrative (K_i), and damping (K_d) feedback gains were included to model corrective torques generate by the neuromuscular system based on sensory feedback. The delay of sensory transmission in the central nervous system was modeled with a time delay block (T_d) of 0.171s (Maurer and Peterka 2005; Nogueira et al. 2010). The feedback gains were heuristically tuned to reduce the sum of squared error between experimental (θ_{Ref}) and simulated (θ_{Model}) body lean angle data. The sum of four neuromuscular terms equals T'_{Ank}:

$$T'_{Ank}(t) = T_F(t-T_d) + K_p\left[\theta_{ref}(t-T_d) - \theta_{Model}(t-T_d)\right] + \ldots$$
$$K_i \int_0^t \left[\theta_{ref}(t-T_d) - \theta_{Model}(t-T_d)\right] dt + K_d\left[\dot{\theta}_{ref}(t-T_d) - \dot{\theta}_{Model}(t-T_d)\right] \tag{8}$$

Lastly, the maximum amount of dorsiflexor torque available for T_{Ank} was limited using a saturation value (T_{SAT}) defined in equation 9. At each time step, the value of T'_{Ank} was compared to ($T_{DFmax} - T_{SAT}$), where T_{DFmax} was an integer value slightly greater than the maximum experimentally-observed dorsiflexor torque and the value of T_{SAT} was incrementally increased by 2 Nm (starting at 0 Nm). For example, from the experimental data of the pilot test participant, the maximum dorsiflexor torque was -22.3 Nm, then T_{DFmax} could be set to -22 Nm. The resultant value based on equation 9 (T_{Ank}) was fed into the transfer function for the body (equation 6). This saturation procedure effectively modeled the diminished or absent TA activation by the central nervous system in people with PD. All simulations were performed using Simulink software (MathWorks Inc. Natick, MA).

$$T_{Ank} = \begin{cases} T'_{Ank} & \text{if } T'_{Ank} < (T_{DF\max} - T_{SAT}) \\ (T_{DF\max} - T_{SAT}) & \text{if } T'_{Ank} \geq (T_{DF\max} - T_{SAT}) \end{cases} \tag{9}$$

5.3.3 Center of Pressure

Along with body lean angle (θ_{Model}), another biomechanical measurement that has been calculated in other postural control models is the center of pressure (COP), or the point at which the total resultant ground reaction force (*GRF*) is acting on the feet, in the sagittal plane (Maurer and Peterka 2005; Nogueira et al. 2010). The position of center of pressure (COP) was calculated using the following equation derived from the equations of motion for the feet and body (Appendix D):

$$COP(t) = \frac{-J_B \ddot{\theta}_{Model}(t) + m_B g L_{COM} \theta(t) + m_F g x_F - m_B a_{Bz}(t) z_F}{m_B a_{Bz}(t) + m_B g + m_F g} \tag{10}$$

Where m_F mass of the feet, z_F height of the ankle joint, x_F horizontal distance between ankle joint and foot center of mass. The last three terms (m_F, z_F, x_F) were based on values for an average adult male used by Maurer and Peterka (2005).

5.4 Results

Prior to presenting the results, a clarification about the convention used to create presented plots of T_{Ank} is needed. Dorsiflexor torque was defined as positive within the model for T_{Ank} (equation 8) in accordance with positive theta; however, T_{Ank} was plotted (Figure 24 and Figure 25) with plantarflexor positive to follow the typical biomechanics convention (i.e., extensor moments are presented as positive values).

With $T_{SAT} = 0$ (no limit on dorsiflexor torque), the model simulation for body lean angle and ankle torque matched the experimental data (Figure 24). Heuristic tuning of the feedback gains (to minimize the difference between experimental and simulated data) resulted in gain values of K_p = 1 Nm·rad^{-1}, K_i = 194 Nm·s^{-1}·rad^{-1}, and K_d = 10 Nm·s·rad^{-1}. Using these gain values, the general behavior for body lean angle was almost identical in the simulation, starting from a slight forward lean of 3.3 degrees progressing to 5.2 degrees at heel-off (Figure 24). Due to a slightly forward lean at the beginning, 33 Nm (of plantarflexor torque) was the initial ankle torque value. As the APA was generated, the model achieved the lowest torque (most dorsiflexor directed) at 22.3 Nm. Finally, the model went into increasing plantarflexor torque before heel-off (Figure 24). The only subtle differences in the simulated ankle torque existed after 0.4 seconds, but the general behavior was the same as the experimental data. Overall, the model was able to accurately simulate the experimental data for body lean angle and ankle torque.

Application of the saturation block ($T_{SAT} \neq 0$) revealed a possible threshold for decreased body lean angle and center of pressure excursion (Figure 25 and Figure 26). Limiting the dorsiflexor torque up to 6 Nm (T_{SAT} ≤ 6 Nm) did not result in large differences in body lean angle or ankle torque. However, when the dorsiflexor torque was limited by 8 Nm, a decrease of body lean angle (0.3°) became apparent and the posterior excursion of center of pressure was decreased by 0.9 cm. When dorsiflexor torque was almost fully limited with a saturation of 10 Nm (33 Nm (starting ankle torque) – 22.3 Nm (max dorsiflexor torque) = 10.7 Nm), the body lean angle was nearly a degree less (0.7°) than the no saturation condition, and the center of pressure excursion was diminished by 1.1 cm. Consequently, reduced dorsiflexor torque resulted in diminished forward progression and decreased posterior excursion of center of pressure.

5.5 Discussion

In this study, an inverted pendulum model of the "loading-unloading" phase of an APA for gait initiation was developed. Furthermore, simulations of reduced dorsiflexor torque during this phase of an APA were performed. The findings highlight the possible consequences of this dorsiflexor torque limitation, including diminished forward progression and posterior excursion of the center of pressure. Specifically, limiting the dorsiflexor torque up to 6 Nm did not result in large differences in forward body lean angle or center of pressure excursion. However, fully limiting the dorsiflexor torque by 10 Nm resulted in reduced forward body lean angle and center of pressure excursion similar to what is observed in PD. Ultimately, this APA model provides an initial basis for understanding the neuromechanical factors that may be important for gait initiation modulation strategies and possibly FOG.

Without any limitation of dorsiflexor directed torque ($T_{SAT} = 0$), the model was able to simulate the experimental body lean angle. The combination of feedback gains (K_p = 1 Nm·rad^{-1}, K_i = 194 Nm·s^{-1}·rad^{-1}, K_d = 10 Nm·s·rad^{-1}) and the addition of a feedforward torque (T_F) resulted in a low amount of error between experimental and simulated body lean angle and ankle torque profiles. Physiologically, a similar online modification of the feedforward movement command through delayed sensory feedback has been demonstrated in several experimental studies (Shadmehr et al. 2010). By comparison to postural control models, our proportional (K_p) and derivative (K_d) gains were smaller and the integrative gain (K_i) was larger. For example, the same three gains in a healthy postural control model were K_p = 957 Nm·rad^{-1}, K_i = 34 Nm·s^{-1}·rad^{-1}, and K_d = 277 Nm·s·rad^{-1} (Maurer and Peterka 2005). Another study that only used proportional (K_p) and derivative (K_d) gains were K_p = 773 Nm·rad^{-1} and K_d = 286 Nm·s·rad^{-1} for healthy individuals and K_p = 667 Nm·rad^{-1} and K_d = 286 Nm·s·rad^{-1} for people with PD (Nogueira et al. 2010). A key difference between these previous postural control models and the model of this study is the desired movement. For postural control, the reference trajectory is set to zero (no body lean angle) because the goal is to maintain standing posture. Consequently, per the feedforward torque equation for T_F (equation 7), the feedforward torque would also be zero and the movement would be controlled with larger proportional (K_p) and derivative (K_d) gains. In our model, the feedforward torque was able to generate the desire forward body lean (θ_{Ref}) with a small amount of error that accumulated due to the sensory time delay. Thus, a higher amount of integrative gain (K_i) was needed to eliminate the error. The difference in gains between these types of models may suggest that feedback gains are different for postural versus volitional movement. Overall, the APA model of this study was able to track the nominal trajectory with a minimal amount of error due to the inclusion of a feedforward torque.

The simulations of the reduced dorsiflexor torque was able to reproduce the typical diminished APA behaviors observed in people with PD. As it has been demonstrated experimentally, decreased posterior excursion of center of pressure and dorsiflexor torque were modeled, which would result in slower gait initiation velocity (Lepers and Breniere 1995; Burleigh-Jacobs et al. 1997). Interestingly, the simulations suggest that there might be a threshold for decreased dorsiflexor torque before the body lean angle was considerably reduced. Between a 0-6 Nm reduction of dorsiflexor torque, body lean angle remained nearly the same as the nominal trajectory. However, when the dorsiflexor torque was limited by 8 Nm, forward body lean angle was slightly decreased and the posterior center of pressure excursion was diminished. At 10 Nm of limitation, forward body lean was almost one degree less than the nominal trajectory and the posterior center of pressure excursion was diminished similar to what is observed in people with PD. Furthermore, the behavior of ankle torque remained relatively constant across different values of saturation aside from the dorsiflexor torque limitation (Figure 25). These results suggest that a certain amount of reduced dorsiflexor torque is allowable before it is has a considerable effect on forward progression. Moreover, these findings give insight into the amount of external assistance that might be needed during the “loading-unloading” phase from an ankle torque device (e.g., a powered ankle-foot orthosis) to maintain a desired nominal trajectory for body lean angle and posterior center of pressure excursion.

The implications of reduced forward body lean angle for the stepping phase of gait initiation (after heel-off) remain unclear. People with PD may simply choose to decrease forward body lean angle and reduce the posterior excursion of center of pressure to avoid instability and maintain balance through the initiation of the step (Martin et al. 2002). In contrast, it is also possible that people with PD and FOG move slower and reduce the magnitude of their APAs to avoid scenarios that provoke a freezing episode. For example, if the desired body lean angle cannot be achieved due to a lack of dorsiflexor torque during the "loading-unloading" phase, the motor command after heel-off would need to be adapted, which could be disruptive to posture-gait coupling and particularly difficult for people with PD (Benecke et al. 1987; Pfann et al. 2001). Furthermore, people with PD and FOG have deficits in set switching (e.g., changing direction of walking rapidly) (Smulders et al. 2015). For that reason, set shifting can increase the incidence of freezing episodes for people with PD and FOG (Knobl et al. 2012). Due to the assumptions of our model, we could not investigate what would happen after heel-off of the stepping foot. Future models would require more degrees of freedom (i.e., hip, knee, and ankle joints) and separated feet. This type of model could elucidate if reduced forward body lean during the postural phase could be a catalyst for a freezing episode prior to the stepping foot lifting off the ground.

Several limitations of our model should be considered for interpreting the results and developing models of gait initiation in the future. First, only the ankle joint was modeled, so alternative strategies for producing forward body lean through other joints (e.g., the hip joint) could not be investigated. For example, a common symptom of PD is a forward body lean around the hip joint, which may be a way to improve postural stability (Jacobs et al. 2005). Furthermore, we assumed that all motion was produced around the ankle joint and the feet did not move through the entire "loading-unloading" phase up to heel-off. It is possible that as the model approached heel-off that the model lost approximation of the true behavior of both limbs (Lepers and Breniere 1995). Beyond the mechanics of the model, the feedback gains that were optimized in this model were based on healthy able-bodied behavior. Although our model was able to reproduce the APA behaviors of people with PD, it is possible that the feedback gains would be different in a person with PD due to sensory deficits (e.g., proprioception) (Vaugoyeau et al. 2007; Tan et al. 2011). Experimental data of gait initiation from people with PD and FOG, and if possible, during a freezing episode, are needed to determine the gains for a person with PD. Having the gains appropriately tuned to a person with PD would be necessary for simulating how the central nervous system would respond to externally applied assistance. Finally, future models could investigate different values of sensory time delay. The time that was used in our model was based on previous postural control models (0.171 s) (Maurer and Peterka 2005; Nogueira et al. 2010); however, it is possible that the sensory time delay during gait initiation would be different, especially in response to external assistance. Previous mechanical perturbation studies have demonstrated that adaptations could occur as fast as 88 ms depending on when the perturbation is provided in the APA (Mouchnino et al. 2012). Overall, our model provides an initial basis for future studies, but several factors should be considered in the development of APA models.

5.6 Conclusions

In conclusion, an inverted pendulum model of the "loading-unloading" phase of an APA was created using neuromuscular components. Moreover, the consequence of reduced dorsiflexor torque in people with PD was simulated. The results suggest that there may be a threshold of diminished dorsiflexor torque that results in diminished forward progression and posterior center of pressure excursion. Future models could investigate the consequences of these diminished APA behaviors to the subsequent stepping phase and/or FOG episodes.

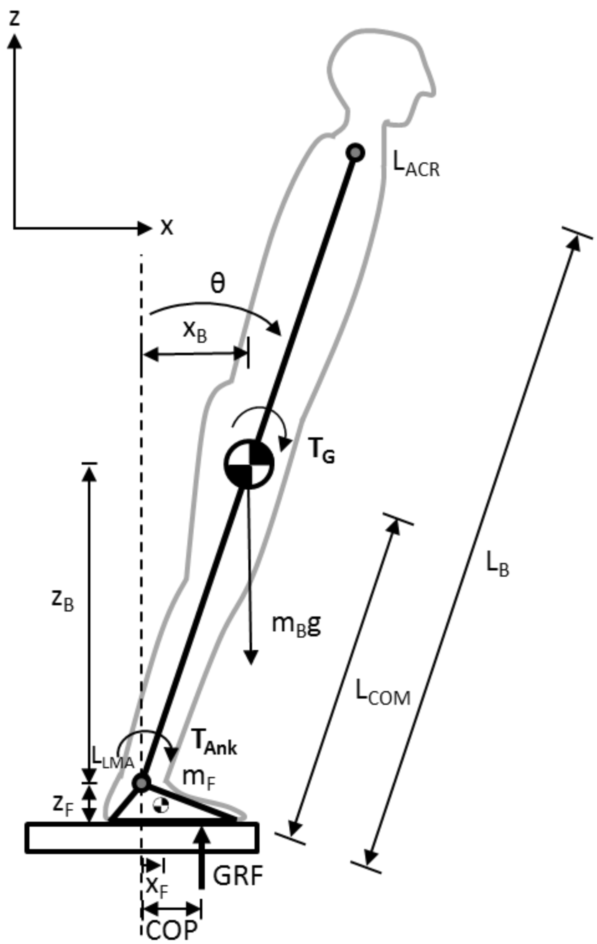

Figure 22: Inverted pendulum model. List of terms: L_{ACR} left acromion marker, L_{LMA} left lateral malleolus marker, θ forward body lean angle, x_B horizontal position of the body center of mass, m_B the mass of the body without the feet, L_B length of the body, L_{COM} length of the body up to the center of mass, z_B vertical position of the body center of mass, m_F mass of the foot, z_F height of the ankle joint, x_F horizontal position of the center of mass of the foot, COP position of center of pressure, GRF vertical ground reaction force, T_{Ank} applied ankle torque generated by the neuromuscular system, and T_G torque due to gravity of body segment.

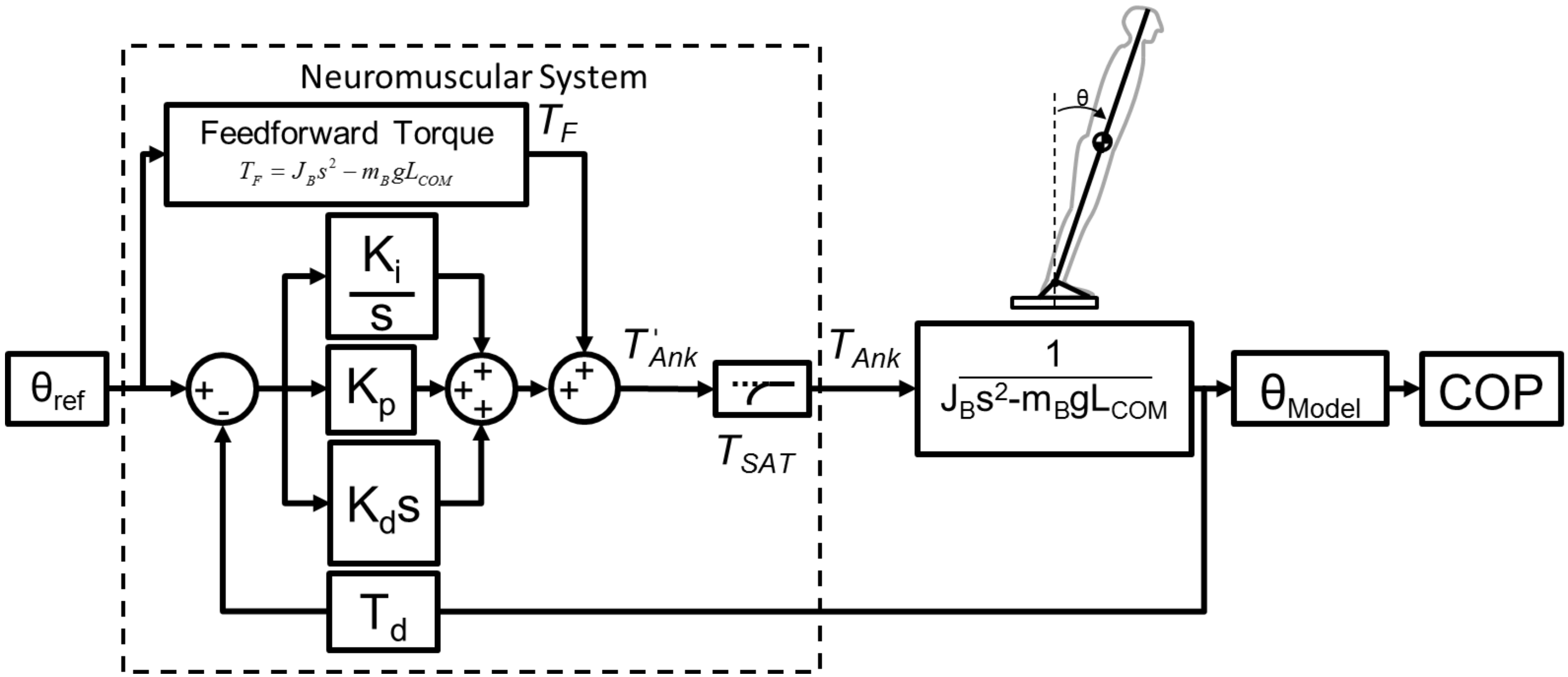

Figure 23: Block diagram of the inverted pendulum model of gait initiation.

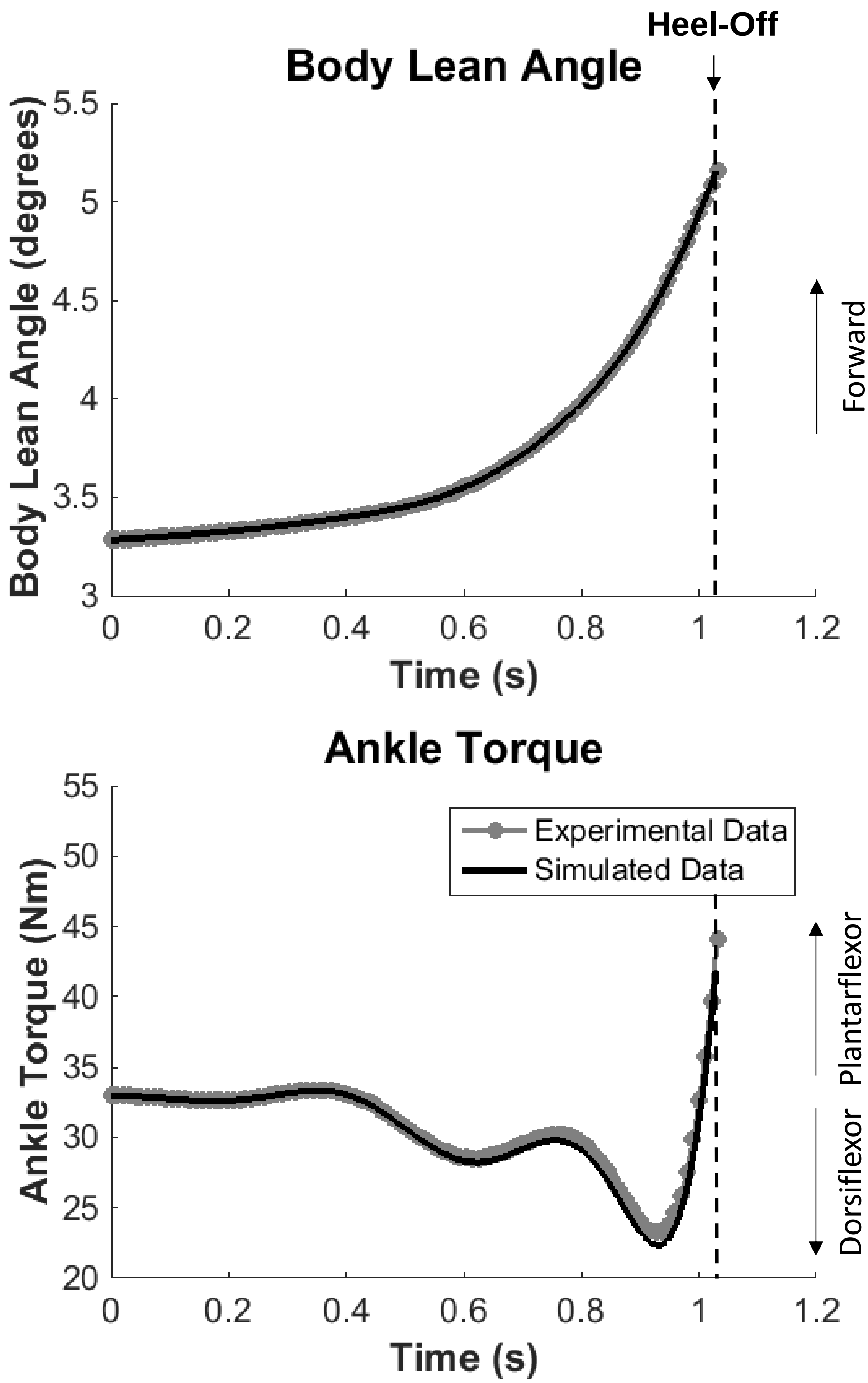

Figure 24: Body lean angle and ankle torque for experimental and simulated data. Note the simulated data are based on the no-saturation condition ($T_{SAT} = 0$).

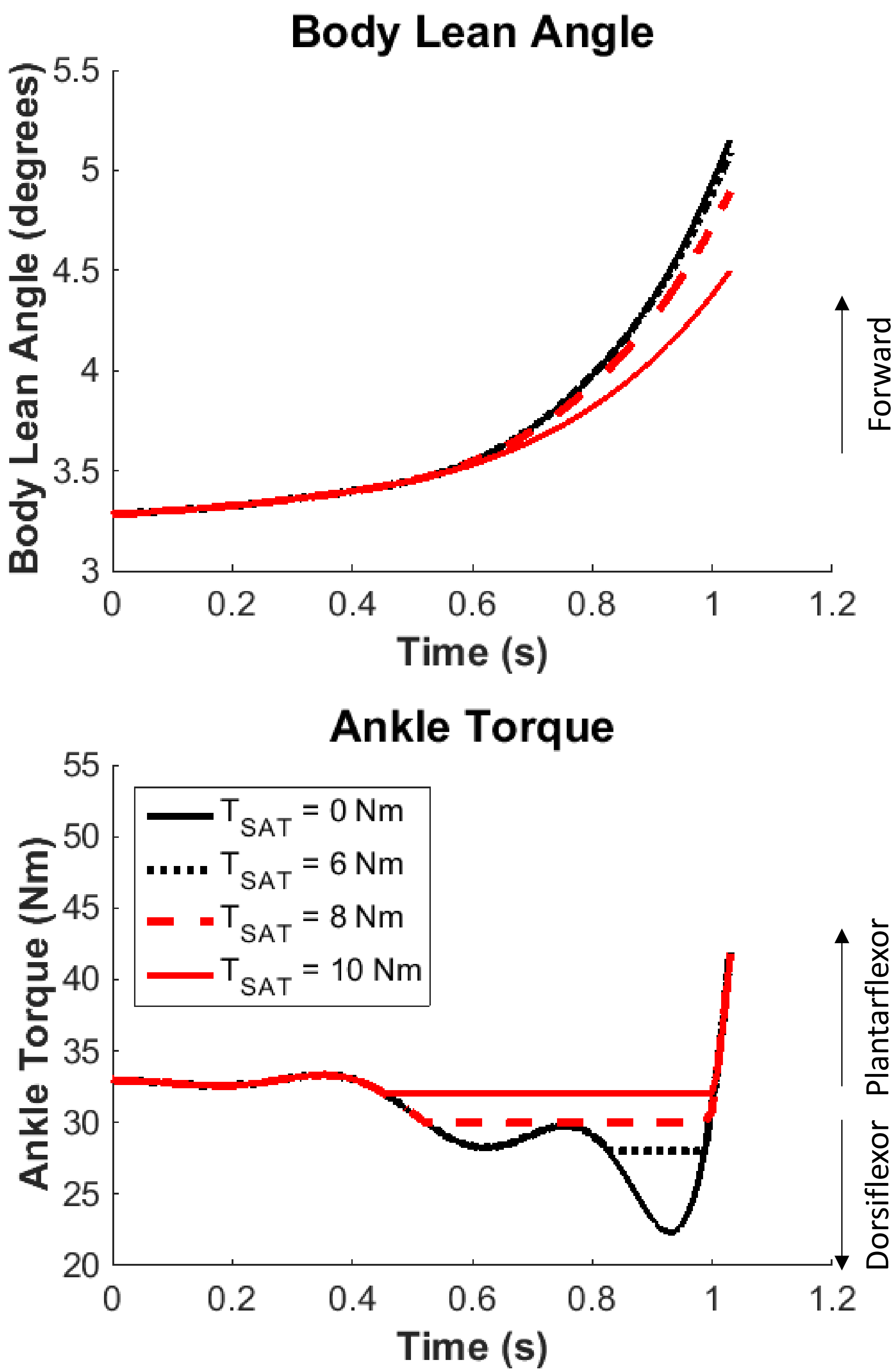

Figure 25: Body lean angle and ankle torque at different dorsiflexor torque saturation values.

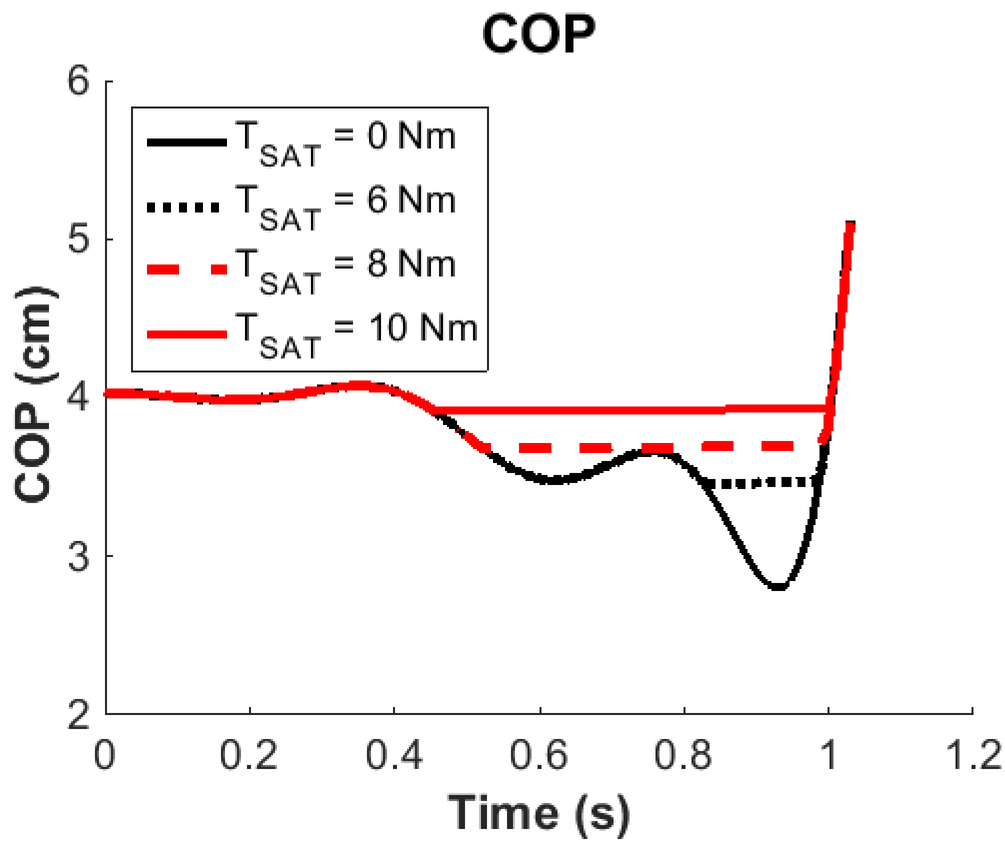

Figure 26: Center of pressure data at various saturation values.

6 CONCLUSIONS AND FUTURE WORK

The main objective of this dissertation was to investigate areas related to the application of mechanical assistance provided at the ankle joint for modulating anticipatory postural adjustments (APAs) in people with Parkinson's disease (PD) and freezing of gait (FOG). The first research objective was to provide proof of concept that mechanical assistance delivered at the ankle joint by a powered ankle-foot orthosis could modulated the APAs during gait initiation in young healthy adults (Chapter 2). Increased force production and shortened timing of APAs were observed with mechanical assistance compared to baseline. The second research objective was to examine how mechanical assistance provided at an ankle joint by a powered ankle-foot orthosis could modulate APAs in people with PD and FOG (Chapter 3). Results suggest that mechanical assistance can amplify, shorten, and improve the consistency of APAs. Moreover, pairing the assistance from the device with an acoustic cue may result in the best modulation of APA behaviors. The third research objective was to evaluate how different methods of cue (acoustic tone and/or mechanical assistance) triggering (externally vs. self-triggered) impacts APA modulation in people with PD and FOG (Chapter 4). Overall, APAs remained unchanged from baseline stepping when cues were self-triggered by the user with a button press. Moreover, APAs were diminished in magnitude when they were self-triggered compared to being externally-triggered within an instructed-delay paradigm. The fourth research objective was to create a neuromechanical computational model of an APA to simulate the diminished muscle activation and force production typically observed in people with PD and FOG (Chapter 5). An inverted pendulum model of movement in the sagittal plane was successfully created using terms that modeled neuromuscular components of the body. Additionally, simulations of reduced muscle activation demonstrated that there may be a threshold of reduced dorsiflexor torque where forward body lean angle and the posterior center of pressure excursion are considerably decreased. Findings from all four studies could help inform the successful implementation of devices that can provide mechanical assistance at the ankle joint to improve gait initiation and possibly help alleviate symptoms of FOG for people with PD.

6.1 Future Work

Ultimately, sensory cue paradigms are currently the best option for people with PD and FOG to overcome these symptoms and maintain mobility and independence. The studies in this dissertation provide an initial basis for the development of novel mechanical assistance paradigms that can be delivered through a wearable device for the ankle joint. This type of mechanical assistance could be translated into daily living; however, several factors pertaining to the mechanical assistance, cue delivery, and modeling the neuromechanics of gait initiation need further investigation.

6.1.1 Mechanical Assistance

Although results from Chapters 2-4 demonstrate that mechanical assistance provided at the ankle joint can amplify and shorten APAs, the torque-timing sequence of the assistance could be further optimized. Within the instructed-delay paradigm, the mechanical assistance was being provided early in the APA sequence, which enabled the person to adapt their APAs accordingly (Mille et al. 2009; Rogers et al. 2010; Mouchnino et al. 2012). However, the sequence of externally applied torques were of fixed durations and magnitudes that may not have aligned with the current movement of the user. This misalignment of torque sequence may have inhibited the first anterior-posterior peak amplitude with the plantarflexor torque turning on too early in the Assist condition. In contrast, if the torque sequence was better aligned with the person's movement, it is possible that smaller peak amplitudes of center of pressure excursion than what was found with the current controller may be observed. A previous lateral waist pull study suggested that the peak medial-lateral center of pressure magnitude was larger (smaller) when the assistance was directed opposite (same) of the desired movement (Mouchnino et al. 2012). However, it is unclear if a similar response to the direction of assistance would be observed when actuating the ankle instead of the entire body at the hip.

In addition to proper timing of assistance, different magnitudes of dorsiflexor and plantarflexor torque could be investigated to explore if improved modulation of APAs observed in this study could be achieved with less assistance. Using less assistance would require a smaller actuator, which would allow future designs of a powered ankle-foot orthosis (or other devices that can provide ankle torque through a wearable device) to be smaller and lighter. Currently, the magnitudes for dorsiflexor and plantarflexor torque were based on values used in previous walking studies with our portable powered ankle-foot orthosis (PPAFO) (Li et al. 2011; Shorter et al. 2011a). Future studies could experimentally increment different durations and magnitudes of mechanical assistance to determine the optimum timing and magnitude for modulating APAs. Additionally, the results of the APA model in Chapter 5 and/or future models could help inform the necessary amount of mechanical assistance. Overall, there are several future directions of research regarding the optimization of mechanical assistance provided at the ankle to consistently modulate APAs of people with PD and FOG.

In combination with an optimized mechanical assistance torque sequence, pairing the assistance with another sensory cue could result in the most consistent APA modulation. Results from Chapters 3 and 4 using the instructed-delay paradigm suggest that pairing the mechanical assistance with an auditory cue may result in the most effective modulation of APAs across all parameters in people with PD and FOG. A similar benefit of paired sensory stimuli had been observed with the MediGait device, which improved gait measures (gait velocity, stride length) and reduced freezing of gait episodes in people with PD (Espay et al. 2010). The potential mechanism behind these improvements is that paired sensory stimuli could have an additive effect (i.e., increased neuronal response) making the stimuli easier to detect (Stein and Stanford 2008; Cappe et al. 2009). The increased neuronal activation could aid in the translation of relevant sensory information to a motor command. Future wearable devices could easily deliver an acoustic cue to a pair of headphones for the user when actuation is provided by a powered ankle-foot orthosis and/or another device. In sum, future research should consider a paired sensory stimulus to increase the efficacy of mechanical assistance at the ankle joint for modulating APAs.

The neural mechanisms that enable mechanical assistance to improve APA generation remain unclear and need further investigation. Pathways through the supplementary motor area and basal ganglia are believed to be responsible for delivering the necessary timing and magnitude information to the motor cortex and subcortical locomotor regions (Nutt et al. 2011). It is possible that the feedforward locomotor command for an APA can be altered with mechanical assistance, given that the assistance is provided during the early portion of an APA (i.e., beginning near APA onset) (Mouchnino et al. 2012). In addition to directly modulating the force production of the ankle, mechanical assistance at the ankle can also provide relevant timing and magnitude information via proprioceptive and/or somatosensory afferent inputs. This sensory information could be processed through the cerebellar-thalamo-parietal networks that are believed to enable cues (Praamstra et al. 1998; Nieuwboer 2008; Nombela et al. 2013). Fundamentally, a better understanding of the neural mechanisms that enable mechanical assistance could further elucidate the pathways that are intact and enable cues in people with PD and FOG.

6.1.2 Cue-Triggering

The proper method for triggering sensory cues, including mechanical assistance, remains an open question. Results from Chapter 4 suggest that self-triggering a cue with a button press results in diminished and prolonged APAs, probably because the dual task of pressing a button and stepping at the same time is cognitively demanding. However, self-triggering may be a viable option for providing a cue on demand if the timing between the button press and the cue was lengthened. Essentially, this would create an instructed-delay paradigm for the user where the go-cue is preceded by a ready-cue. In this scenario, the dual-task of controlling the cue and stepping simultaneously would be reduced, and the person would be given the ability to prepare for the movement, which can help elicit APAs more consistently (MacKinnon et al. 2007; Rogers et al. 2011). In addition to investigating different methods of self-triggering, improved detection of a freezing episode (or possibly precursors to a freeze) using wearable sensors could also be a viable method for determining when a cue needs to be triggered. Currently, classification rates of a freezing episode using accelerometers can be as high as 85% (Jovanov et al. 2009; Bachlin et al. 2010; Moore et al. 2013; Pepa et al. 2015). However, the drawback of this approach is that misclassification of a freezing episode could result in cues being presented to the user when they are not needed. Providing cues without a FOG episode can be distracting and may even cause a freeze (Bachlin et al. 2010). Future research in this area should focus on improving FOG classification so that cues would only be provided when needed by the user. Finally, no studies have attempted to use an instructed-delay paradigm to present cues in real world scenarios. The results of the externally-triggered conditions in Chapter 4 further demonstrate that preparation can be beneficial to eliciting APAs more consistently (MacKinnon et al. 2007; Rogers et al. 2011). A potential drawback of the instructed-delay paradigm is that the person would need to wait for the cue when they need it. However, this delay of cueing may only be a problem in situations where the person needs the cue immediately. Overall, several potential avenues of research regarding cue triggering need further investigation in order to effectively translate the benefits of sensory cues and/or mechanical assistance to daily living.

6.1.3 Modeling of Gait Initiation APAs

Future APA models should focus on the neuromechanical factors that contribute to FOG in order to understand the causes of these symptoms and inform the development mechanical assistance paradigms. The model in Chapter 5 was able to focus on contributions of ankle torque to forward body lean ankle and center of pressure excursion during the "loading-unloading" phase of the APA. However, one limitation of this model was it was unable to model the stepping phase after the "loading-unloading" phase because certain assumptions would be violated (e.g., the ankles pivoted around the same axis). Future models could include more degrees of freedom (i.e., hip and knee) to model the stepping phase of gait initiation to determine how decreased forward body lean angle and center of pressure excursion may affect the ankle torque sequence prior to the stepping foot coming off the ground. One possibility would be to create a hybrid model where the body is modeled differently during the two phases of the motion. For example, the body could be modeled as inverted pendulum during the “loading-unloading” phase and then switch to a model with multiple degrees of freedom in the lower limbs during the stepping phase. Alternatively, a model with additional degrees of freedom could be used for both the “loading-unloading” and stepping phases to determine if alternative strategies for forward body lean angle, namely leaning forward at the hip, would be used in the absence of the initial dorsiflexor torque. Another limitation of the model in Chapter 5 is that the feedback gains were tuned to healthy able-bodied gait initiation, as opposed to a person with PD and FOG. Alternate gains that better represent the behavior of a person with PD and FOG might be necessary if the model was used to determine the necessary amount of ankle torque needed from a wearable device (e.g., powered orthosis). Furthermore, accurate feedback gains for the stepping phase of gait initiation would help elucidate how the central nervous system may adapt to diminished APAs during the “loading-unloading” phase. Ultimately, a better model of APAs could reveal the potential mechanisms behind FOG and inform device design development for alleviating these symptoms.

In conclusion, the studies in this dissertation have increased the understanding of several factors related to modulating the APAs of gait initiation in people with PD and FOG. Initial evidence supporting the utility of mechanical assistance delivered at the ankle joint as a viable strategy for improving APA generation was provided. Moreover, the results also demonstrated that the method of triggering mechanical assistance (or an acoustic cue) can directly impact its effectiveness in modulating APAs of gait initiation. Lastly, a model of the initial phase of an APA was developed to inform future mechanical assistance protocols and investigate the neuromechanical factors that may contribute to FOG. Several aspects of providing mechanical assistance, including a fundamental understanding of the neuroscientific and biomechanical principles that makes it effective in people with PD and FOG, still need further investigation. Furthermore, advances in wearable technology are needed to enable devices that actively modulate ankle torque and can be worn a daily basis. Successful implementation of these devices could potentially transform the lives of people with PD and FOG by increasing mobility and promoting independence.

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APPENDIX A: ARCHETYPICAL BEHAVIORS OF DATA IN CHAPTER 3

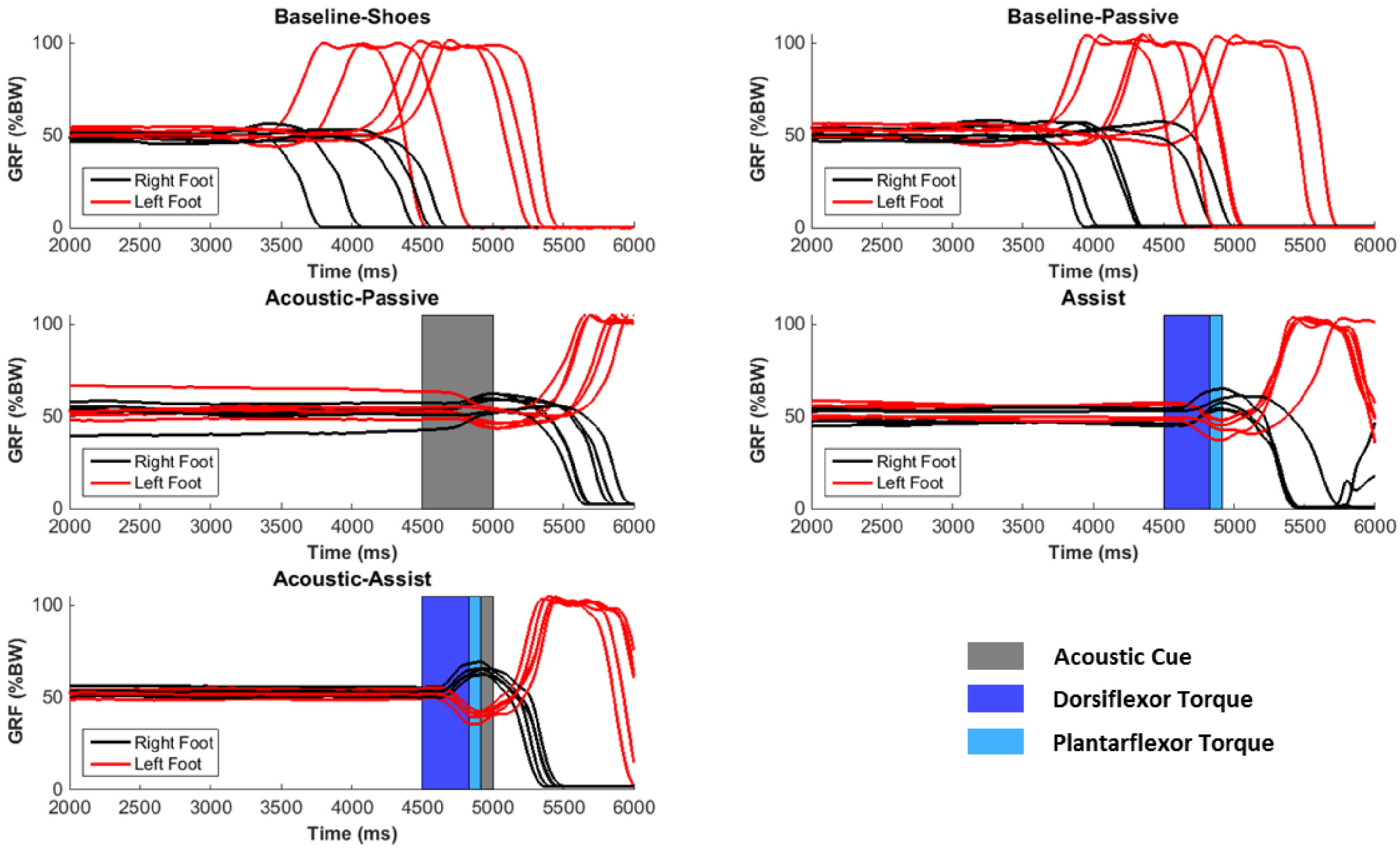

Figure 27: Archetypical ground reaction force data across all conditions for a participant with PD and FOG.

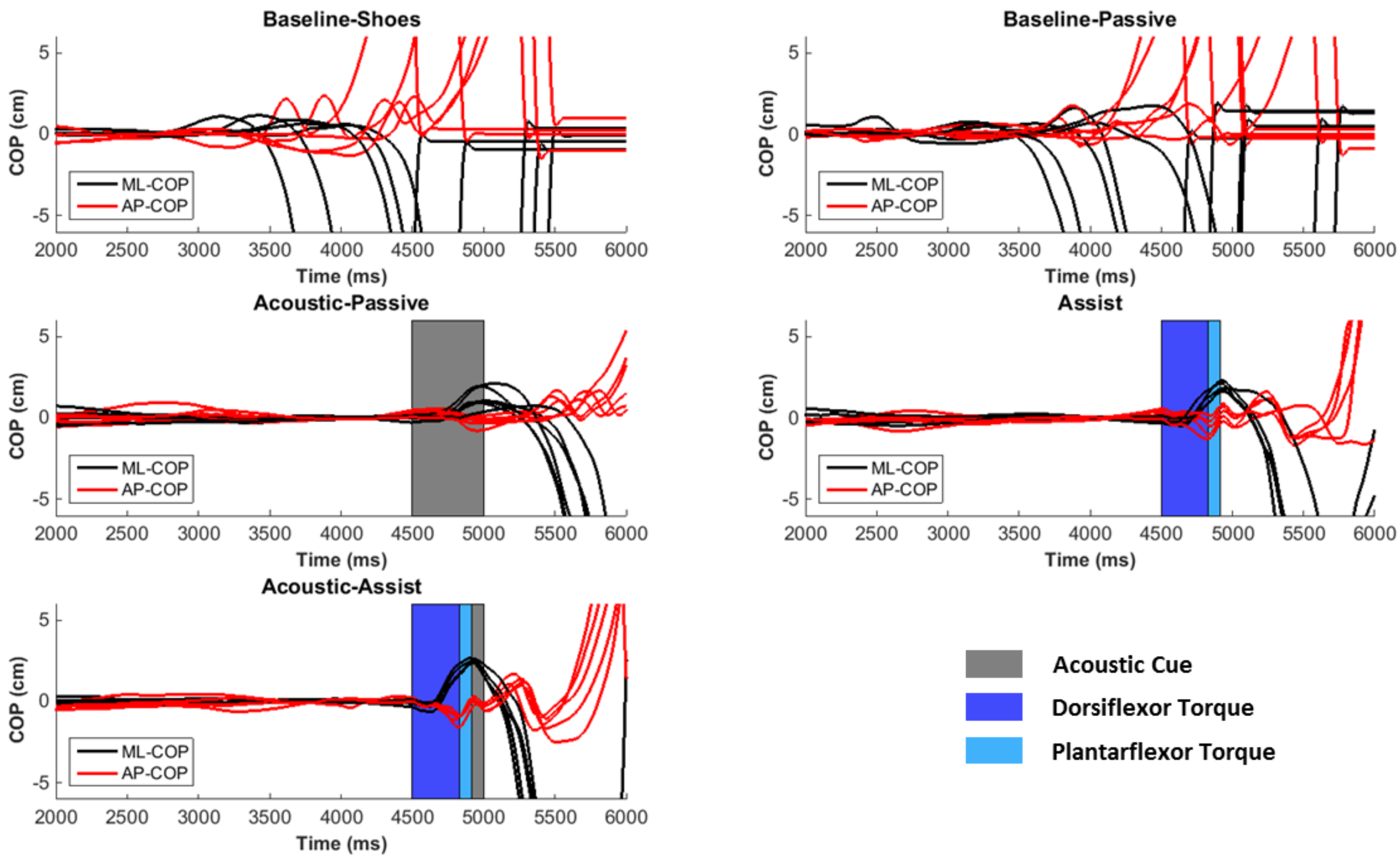

Figure 28: Archetypical center of pressure data across all conditions for one participant with PD and FOG.

Appendix B: Examples of EMG data analysis for Chapters 3 and 4

Due to low signal amplitude and high variability, EMG data were not analyzed in Chapters 3 and 4. In this Appendix, two examples have been provided. The first example demonstrates a trial where low signal amplitude was observed (two small and short bursts) near ground reaction force onset, making it difficult to determine which one is correct to quantify. The second example demonstrates a high amount of variability before GRF onset, making it difficult to establish a baseline for picking EMG onset.

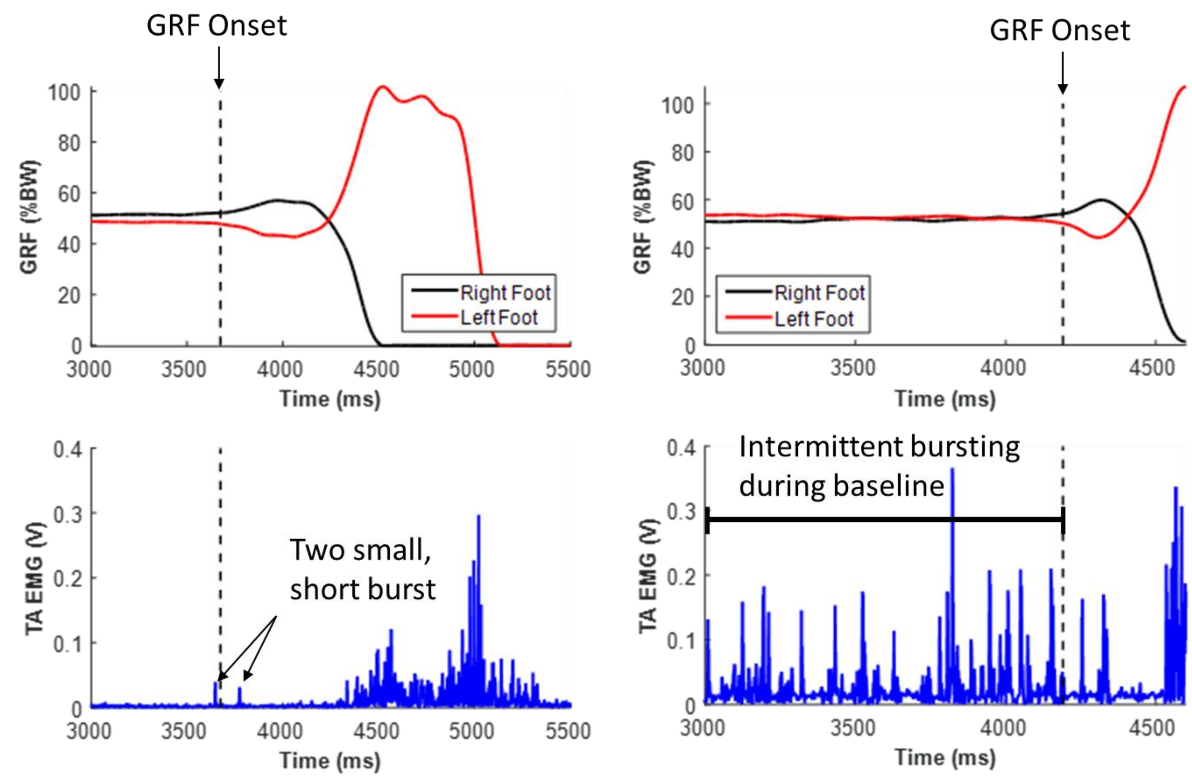

Figure 29: Examples of low signal amplitude (left) and high variability (right) in EMG data. Vertical ground reaction force data are plotted with the onset time indicated with a vertical dashed line.

APPENDIX C: ARCHETYPICAL BEHAVIORS OF DATA IN CHAPTER 4

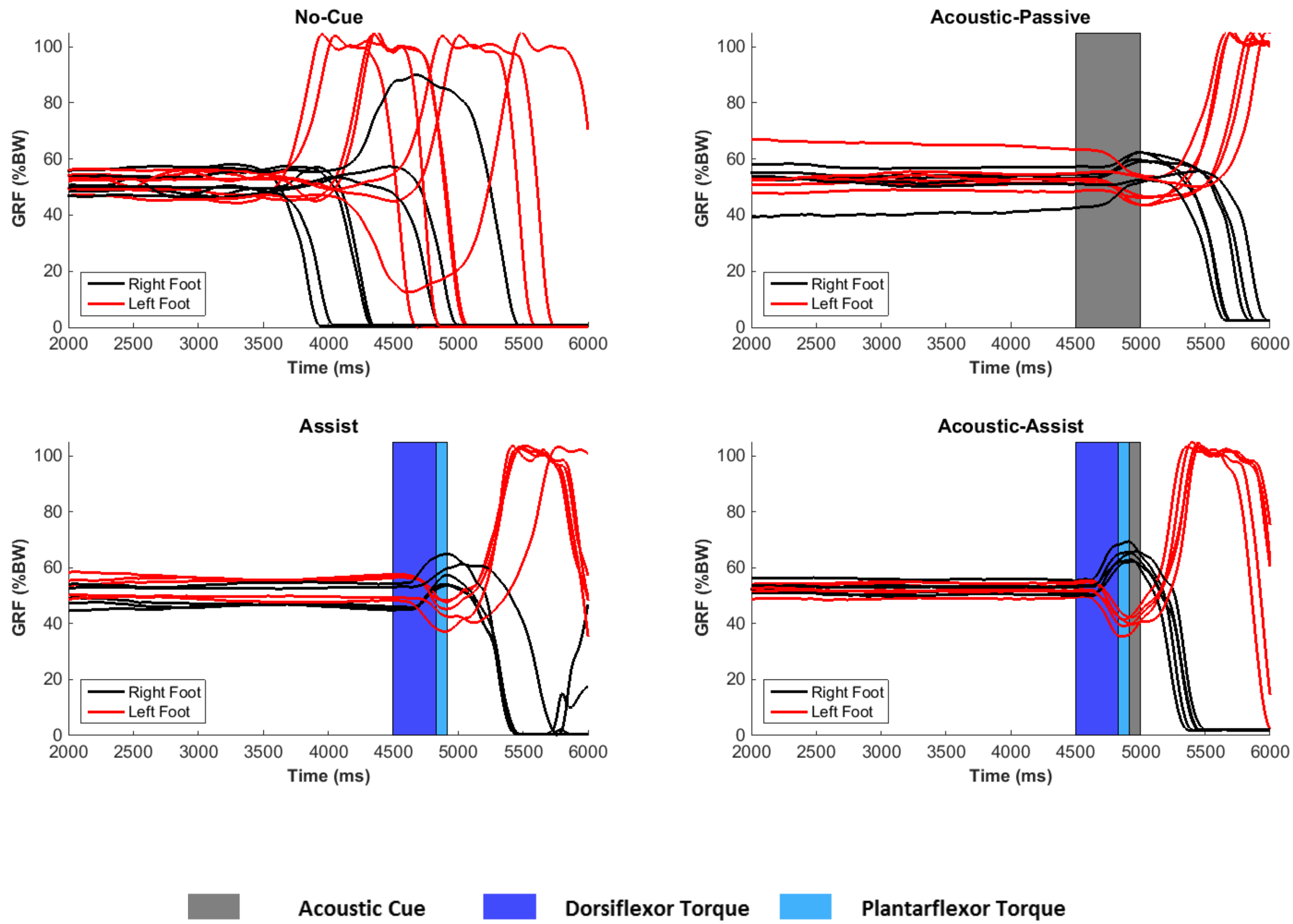

Figure 30: Archetypical ground reaction force data across all externally-triggered conditions for one participant with PD and FOG.

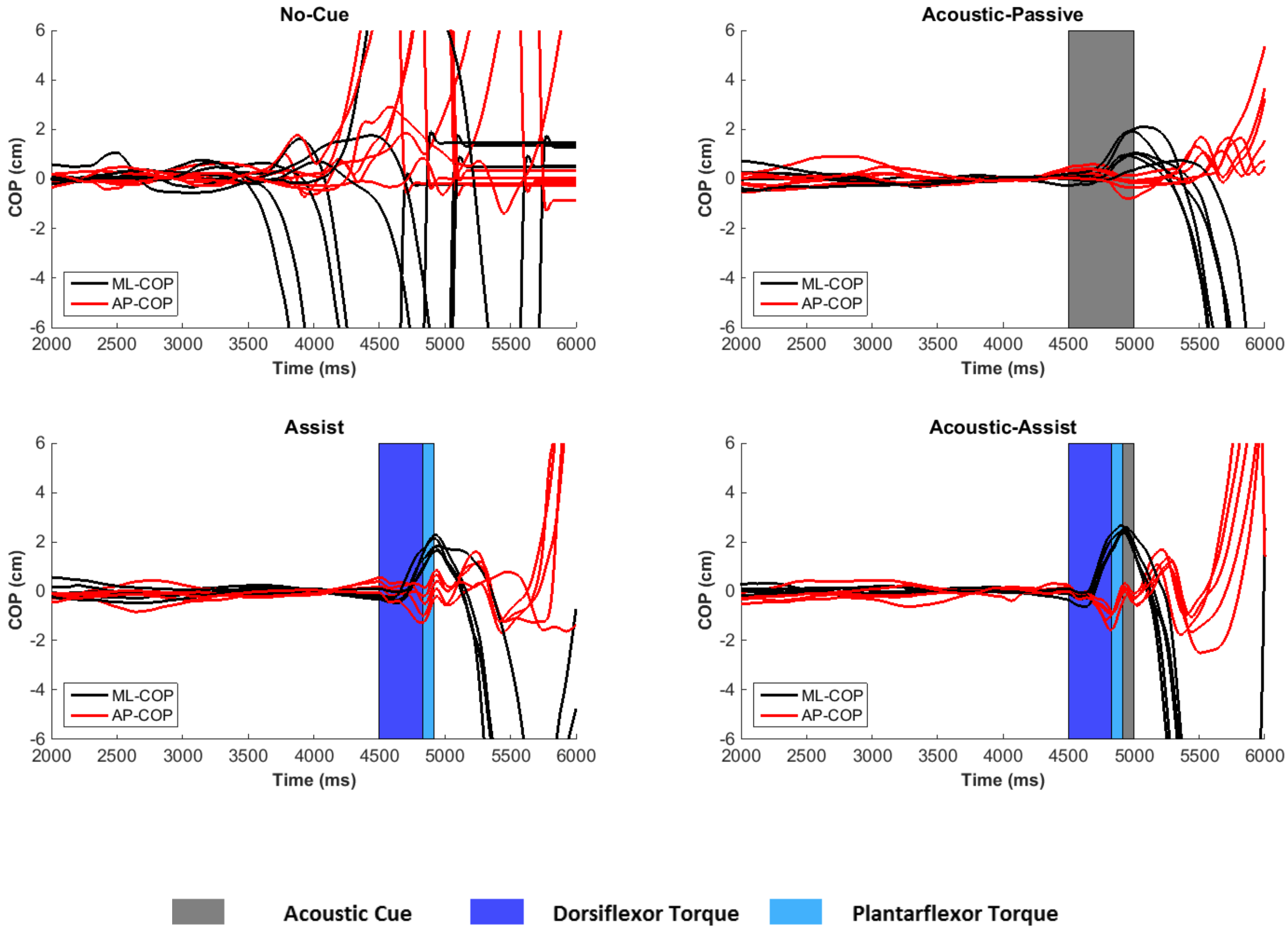

Figure 31: Archetypical center of pressure data across all externally-triggered conditions for one participant with PD and FOG.

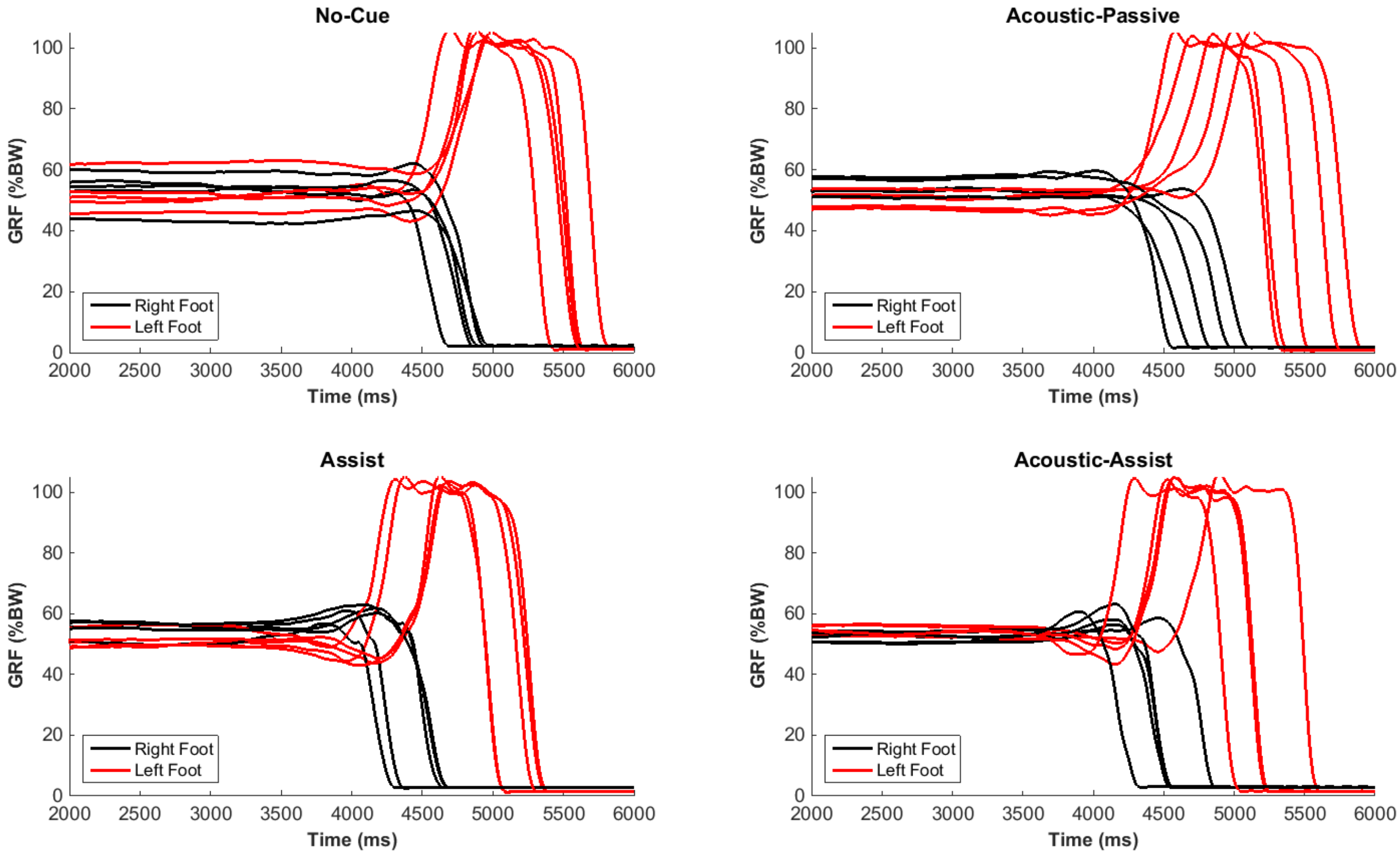

Figure 32: Archetypical ground reaction force data across all self-triggered conditions for one participant with PD and FOG.

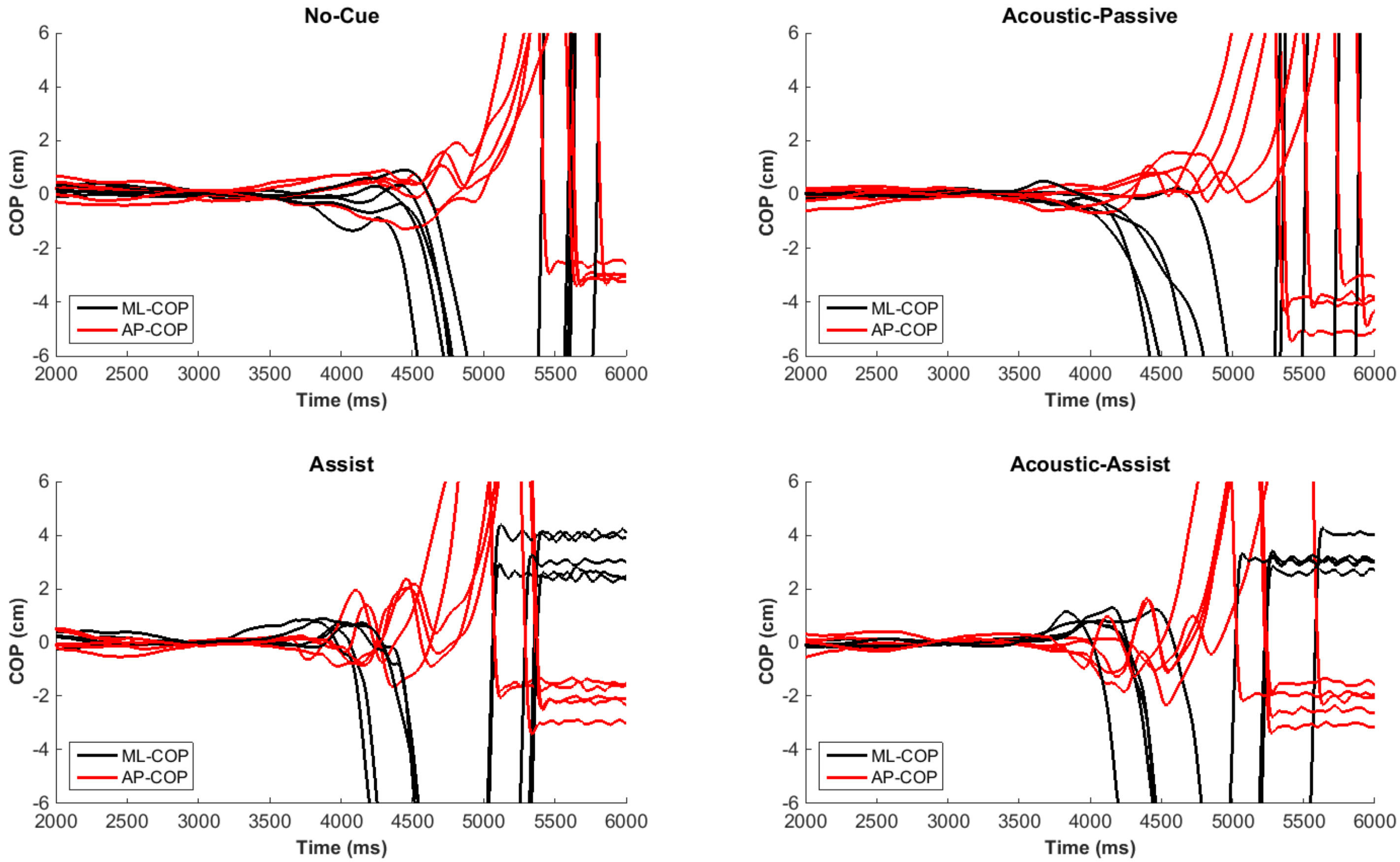

Figure 33: Archetypical center of pressure data across all self-triggered conditions for one participant with PD and FOG.

Appendix D: Derivation of the Center of Pressure Equation for Chapter 5

In order to determine the equation for the center pressure in the sagittal plane (COP), the equations of motion for the body and foot segments needed to be defined.

Body Segment:

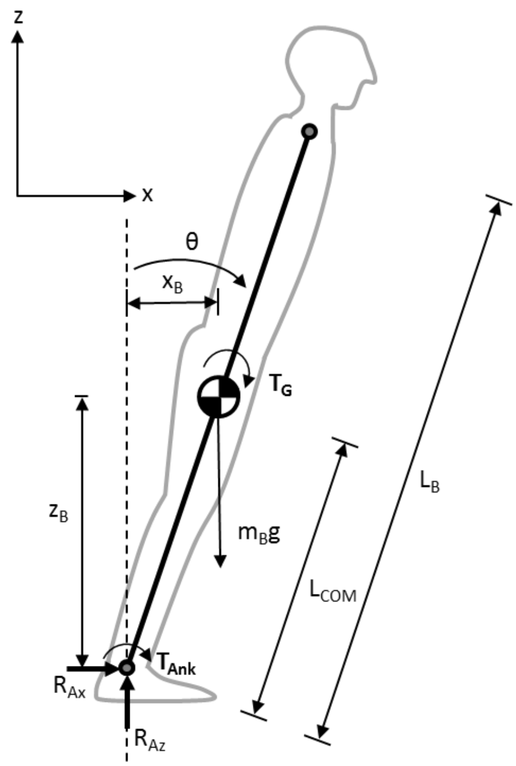

Figure 34: Body segment model. List of terms: θ forward body lean angle, x_B horizontal position of the body center of mass, m_B the mass of the body without the feet, L_B length of the body, L_{COM} length of the body up to the center of mass, z_B vertical position of the body center of mass, R_{Ax} horizontal reaction force at the ankle, R_{Az} vertical ground reaction force at the ankle, T_{Ank} applied ankle torque generated by the neuromuscular system, and T_G torque due to gravity of body segment.

Equations of motion of the body, represented as a uniform rod, about the ankle joint:

$$\sum F_x = R_{Ax}(t) = m_B a_{Bx}(t) \quad \text{(D1)}$$

$$\sum F_z = R_{Az}(t) - m_B g = m_B a_{Bz}(t) \quad \text{(D2)}$$

$$\sum T = T_{Ank}(t) + T_G(t) = J_B \ddot{\theta}(t) \quad \text{(D3)}$$

Foot Segment:

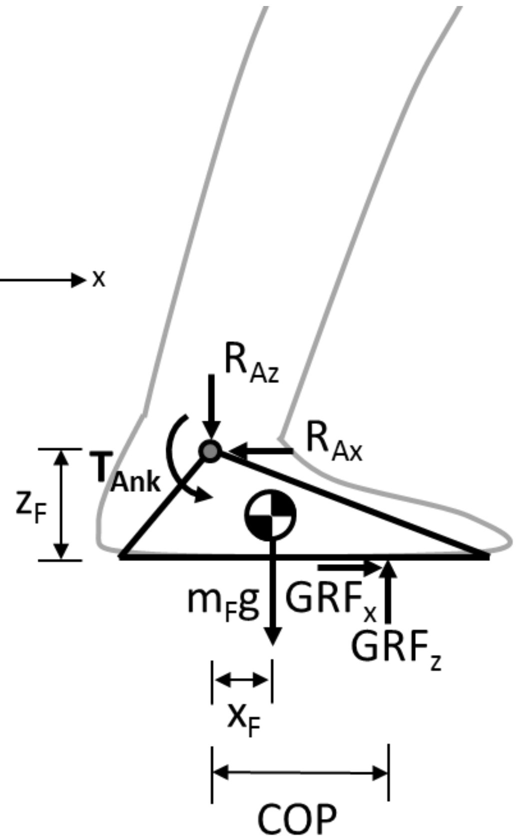

Figure 35: Foot segment model. List of terms: m_F mass of the foot, z_F height of the ankle joint, x_F horizontal position of the center of mass of the foot, GRF_x horizontal ground reaction force, GRF_z vertical ground reaction force, and COP position of center of pressure, R_{Ax} horizontal reaction force at the ankle, R_{Az} vertical ground reaction force at the ankle, and T_{Ank} applied ankle torque generated by the neuromuscular system.

Equations of motion of the foot segment, about the ankle joint:

$$\sum F_x = -R_{Ax}(t) + GRF_x(t) = 0 \tag{D4}$$

$$\sum F_z = -R_{Az}(t) - m_F g + GRF_z(t) = 0 \tag{D5}$$

$$\sum T = -T_{Ank}(t) + m_F\, g * x_F - GRF_x(t) * z_F - GRF_z(t) * COP(t) = 0 \tag{D6}$$

Derivation of *COP* equation:

- Solve equation D3 for T_{Ank}. Small angle approximation was assumed for the T_G term:

$$T_{Ank}(t) = J_B\ddot{\theta}(t) - T_G(t) = J_B\ddot{\theta}(t) - m_B g L_{COM}\theta(t) \tag{D7}$$

- Substitute equation D1 into equation D4 and solve for GRF_x:

$$m_B a_{Bx}(t) = GRF_x(t) \tag{D8}$$

- Solve Equation D2 for R_{Az}:

$$R_{Az}(t) = m_B a_{Bz}(t) + m_B g \tag{D9}$$

- Solve Equation D5 for GRF_z and substitute in R_{Az} from equation D9:

$$GRF_z(t) = m_B a_{Bz}(t) + m_B g + m_F g \tag{D10}$$

- Substitute, T_{Ank} (equation D7), GRF_x (equation D8), and GRF_z (equation D10) into equation D6:

$$-J_B\ddot{\theta}(t) + m_B g L_{COM}\theta(t) + m_F g x_F - m_B a_{Bx}(t) * z_F - \left(m_B a_{Bz}(t) + m_B g + m_F g\right) * COP(t) = 0 \tag{D11}$$

- Solve equation D11 for COP:

$$COP(t) = \frac{-J_B\ddot{\theta}(t) + m_B g L_{COM}\theta(t) + m_F g x_F - m_B \mathrm{a}_{Bz}(t) * z_F}{m_B a_{Bz}(t) + m_B g + m_F g} \tag{D12}$$