Fall Prevention Using Linear and Nonlinear Analyses and Perturbation Training Intervention

by

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ABSTRACT

Injuries and death associated with fall incidences pose a significant burden to society, both in terms of human suffering and economic losses. The main aim of this dissertation is to study approaches that can reduce the risk of falls. One major subset of falls is falls due to neurodegenerative disorders such as Parkinson's disease (PD). Freezing of gait (FOG) is a major cause of falls in this population. Therefore, a new FOG detection method using wavelet transform technique employing optimal sampling window size, update time, and sensor placements for identification of FOG events is created and validated in this dissertation. Another approach to reduce the risk of falls in PD patients is to correctly diagnose PD motor subtypes. PD can be further divided into two subtypes based on clinical features: tremor dominant (TD), and postural instability and gait difficulty (PIGD). PIGD subtype can place PD patients at a higher risk for falls compared to TD patients and, they have worse postural control in comparison to TD patients. Accordingly, correctly diagnosing subtypes can help caregivers to initiate early amenable interventions to reduce the risk of falls in PIGD patients. As such, a method using the standing center-of-pressure time series data has been developed to identify PD motor subtypes in this dissertation. Finally, an intervention method to improve dynamic stability was tested and validated. Unexpected perturbation-based training (PBT) is an intervention method which has shown promising results in regard to improving balance and reducing falls. Although PBT has shown promising results, the efficacy of such interventions is not well understood and evaluated. In other words, there is paucity of data revealing the effects of PBT on improving dynamic stability of walking and flexible gait adaptability. Therefore, the effects

of three types of perturbation methods on improving dynamics stability was assessed. Treadmill delivered translational perturbations training improved dynamic stability, and adaptability of locomotor system in resisting perturbations while walking.

DEDICATION

I dedicate this dissertation to my family,

Keivan - my husband and my love

For making me laugh, hugging me tight, supporting me unconditionally, and keeping me strong.

He is a promise that I will have a friend forever. He is all the love, passion, and comfort of my life.

My mother and my father

For their endless support, patience, unconditional love, and encouraging me in every step of my life.

All that I am or hope to be is because of them.

Alireza and Sepinoud- My brother and sister

For their kindness and devotion, words of encouragement, and precious support throughout my life.

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TABLE OF CONTENTS

CHAPER Page

CHAPER Page

LIST OF ABBREVIATION

ADL: Activities of daily living

AP: Anterior-posterior

CCI: Co-contraction index

CNS: Central nervous system

COP: Center of pressure

CWT: Continuous wavelet transform

FFT: Fast Fourier transform

FOG: Freezing of gait

HC: Heel contact

L_{max}: Maximum Lyapunov exponent

MPT: Mixed perturbation training

ML: Medial-lateral

MLPT: Medial-lateral perturbation training

NPT: No perturbation training

PBT: Perturbation-based training

PD: Parkinson’s disease

PIGD: Postural instability and gait difficulties

SampEn: Sample entropy analysis

SPT: Slip-like perturbation training

TD: Tremor dominant

UPDRS: Unified Parkinson’s disease rating scale

VT: vertical

WT: Wavelet transform

LIST OF TABLES

Table | Page

LIST OF FIGURES

Figure Page

Figure Page

Figure Page

Figure Page

CHAPTER 1: OVERVIEW

1.1 Rationale

There are many daily situations that may challenge individual's ability to stay upright. The cracks in the sidewalks, slippery or uneven surfaces, loose rocks and many other situations which may increase the risk of losing one's balance (i.e., falling). Although many factors increase the likelihood of falling, generally, a fall occurs when a person cannot recover from a loss of balance (Maki & McIlroy 1996). Different recovery strategies are utilized by individuals to regain their balance and to prevent a fall. All individuals who are ambulatory can experience balance losses and falls, but certain diseases and aging processes, as well as fall-risk conditions can make it more difficult for these events to be controlled safely. In this chapter, the rationale of the Dissertation as well as the approaches (i.e., specific aims) that can reduce the risk of falls are further elaborated.

Injuries and death associated with fall incidences pose a significant burden to society, both in terms of human suffering and economic losses. Injuries associated with fall accidents are the leading cause of nonfatal injuries treated in hospital emergency departments and the third leading cause death due to unintentional injury in the U.S. (Center for Disease Control and Prevention, 2014). In the working population, the direct cost of occupational injuries in 2012 due to falls on the same level in the U.S. was estimated to be approximately $9.19 billion or 15.4% of total injury cost (Liberty Mutual Research Institute for Safety, 2014). During 2014, more than 2.8 million older individuals were treated in emergency departments for fall-related injuries, and approximately 800,000 of these patients were subsequently hospitalized (Bergen et al. 2016; Center for Disease

Control and Prevention, 2014). The resulting treatment cost was estimated to be $31 billion annually in the U.S. for older adults (Burns et al. 2016). As such, finding the intervention strategies to reduce fall accidents are paramount to our society.

One major subset of these falls is falls due to neurodegenerative disorders such as Parkinson's disease (PD). Approximately 50-70% of patients with PD fall at least once (Bloem et al. 2003; Allen et al. 2013; Ashburn et al. 2001; Ashburn et al. 2008) and over 50% of these fallers experience two or more falls each year (Wood et al. 2002; Allen et al. 2013). It is estimated that about 630,000 people were diagnosed with PD in 2010 in the United States. This number is anticipated to be double by 2040 (Kowal et al. 2013), meaning PD-related falls can be expected to have a major impact on health care systems in the coming decades.

It should be noticed that there are a variety of reasons for loss of balance in daily life which can have extrinsic sources or intrinsic sources (Robinovitch et al. 2013). Extrinsic sources can be uneven or slippery surfaces while intrinsic sources might be aging or disorder such as PD. Therefore, the causes or circumstances of a fall are important to define the type of approach which could reduce the risk of future falls. For example, freezing of gait (FOG) is a major cause of falls in PD. FOG is defined as a "brief, episodic absence or marked reduction of forward progression of the feet despite having the intention to walk" (Nieuwboer & Giladi 2013; Schlenstedt et al. 2016). Previous studies have shown that external cues such as rhythmic auditory stimulation can help patients to alleviate FOG episodes and resume walking (Bächlin, Plotnik, Roggen, Maidan, Jeffrey M. Hausdorff, et al. 2010; Okuma 2006; Nieuwboer & Giladi 2013). As such, objective measures of FOG have been developed and employed utilizing wearable sensors to detect FOG right after an episode starts (Bächlin, Plotnik, Roggen, Maidan, Jeffrey M. Hausdorff, et al. 2010; Rezvanian & Lockhart 2016; Jeffrey M. Hausdorff et al. 2003a; Horak 2013; Silva de Lima et al. 2017). There are several requirements that must be considered prior to designing any real-time FOG detection systems, such as minimum sensor nodes, sensor placement locations, and appropriate sampling window size and update time. Smaller window size of data allows for better detection of short-duration FOG episodes, since larger window size can average-out shorter FOG episodes. In addition, smaller window size could decrease processing time and allow for faster triggering of external cues to help patients overcome the FOG episodes. Furthermore, the robustness due to the update time variability does not attenuate the levels of detection. It is important that these characteristics are taken into account to create promising systems to detect FOG.

Another approach to reduce risk of falls in PD patients is to correctly diagnose PD motor subtypes. PD can be further divided into two subtypes based on clinical features: tremor dominant (TD), and postural instability and gait difficulty (PIGD) (Chen et al. 2015; Fahn et al. 2011; Thenganatt & Jankovic 2014; Jankovic et al. 1990a). This categorization is of predominant importance at the early stage of PD, since identifying PD subtypes can help to predict the clinical progression of the disease. Several studies have confirmed that the PIGD subtype has a faster disease progression, greater motor function impairment (Jankovic & Kapadia 2001a), and is less responsive to levodopa and deep brain stimulation compared to the TD subtype (Jankovic et al. 1990a; Rajput et al. 1993; Mehanna & Lai 2013; Chen et al. 2015). Additionally, the PIGD subtype can place PD patients at a higher risk for falls compared to TD patients (Rudzińska et al. n.d.). Accordingly, correctly diagnosing subtypes can help physicians, patients and caregivers to initiate early amenable interventions and track the progression of the disease. Differentiation of TD from PIGD is currently based on sub-scores of the Unified Parkinson's Disease Rating Scale (UPDRS) (Stebbins et al. 2013; Chen et al. 2015). The UPDRS is scored by clinicians and is subjective and prone to error (Thenganatt & Jankovic 2014; Stebbins et al. 2013). Subtype-specific biomarkers may improve the accuracy of diagnoses relevant to PD subtypes and PD progression. Several studies have reported a frequency range of 3-7 Hz for PD tremor (Hallett 1998; Lemstra et al. 1999; Timmermann et al. 2003). It can be hypothesized that this frequency range might be seen in whole body center of pressure of patients with TD subtype since a human whole body center of pressure has a frequency lower than 2 Hz (Freitas et al. 2005; Vieira et al. 2009). Therefore, motor subtype of PD might be better identified by using the frequency component of an individual’s center of pressure signal.

Postural and gait perturbation training to prevent future falls has been readily adopted by previous studies. They have shown that participants in these types of training intervention can readily adapt to unpredictable changes or perturbations in environment during different activities, such as standing or walking (Bhatt et al. 2006; Nashner 1976; Horak et al. 1989; Owings et al. 2001; Parijat & Lockhart 2012). This adaptation can be developed by exposing individuals to repetitive external perturbations to create a helpful motor behavior that can be used in the cases of unexpected real-world perturbations (Pai & Bhatt 2007). Perturbation based training (PBT) has been proposed based on this notion and shows promising results in reducing the incidence of falls (Mansfield et al. 2015; Mccrum et al. 2017). In this training method, individuals are exposed to repeated postural perturbations during standing or walking. PBT enhances reactions to balance loss with practice and enriches neuro-mechanical control of stability to prevent balance loss and falls (Pai & Bhatt 2007). A decrease in occurrences of falls in the laboratory from the pre- to post-perturbation training have been reported (Parijat & Lockhart 2012; Y. C. Pai et al. 2014; Tanvi et al. 2012; Mansfield et al. 2015; McCrum et al. 2017). These investigators have shown that there are improvement in control of voluntary movements (Rogers et al. 2003), an increase in the speed of balance reaction (Parijat & Lockhart 2012; Tanvi et al. 2012; Mansfield et al. 2010), and improvement in reactive recovery response to perturbations (e.g., recovery step) (Parijat & Lockhart 2012; Y. C. Pai et al. 2014; Tanvi et al. 2012; Lurie et al. 2013; Pai et al. 2010; Bierbaum & Peper 2010; Bierbaum et al. 2011; Mansfield et al. 2015) following PBT. On another compendium of movement control, PBT also shows positive outcomes within the field of athletic training. It yields promising results in performance, reduces injury, and assists in rehabilitation, as shown in athletes with knee injury (Zech et al. 2010). Rehabilitation with PBT also helps individuals to return to functional activity sooner and maintains their functional status for longer periods as compared to the standard rehabilitation program (Hurd et al. 2006; Chmielewski et al. 2005; Fitzgerald et al. 2000; Rudolph et al. 2000; Williams et al. 2001; Zech et al. 2010).

Although PBT has shown promising results, the efficacy of such interventions is not well understood and evaluated. Most of studies report improvement in some measures (e.g. reaction time, center of mass velocity) of the reactive recovery responses after the training, which may not be transferable to another type of perturbations. In other words, there is paucity of data revealing the effects of PBT on improving dynamic stability of walking and flexible gait adaptability. Additionally, most of the studies applied perturbations while subjects walked over-ground by utilizing the method of movable platform perturbations occurring at the same place, which may lead to a proactive walking pattern, limiting the understanding of the true characteristics associated with motor learning (Y. C. Pai et al. 2014; Parijat & Lockhart 2012). Understanding the effects of PBT on gait stability and complexity will pave the way to developing a better intervention for those who are at a higher risk of losing balance and falls as a result of gait instability.

1.2 Specific aims

The aim of this dissertation is to develop methods to reduce risk of falls in different populations.

Aim #1: Create and validate a new FOG detection method using wavelet transform, testing optimal sampling window size, update time, and sensor placements for identification of FOG events.

> **Hypothesis 1a:** Wavelet transform can detect FOG with higher specificity and sensitivity compared to previous method which used fast Fourier transform.
>
> **Hypothesis 1b:** By using wavelet transform method sampling window size could be as small as 2 s and be robust to changing update time from .5 s to 1 s.
>
> **Hypothesis 1c:** Shank sensor is the best place to detect FOG in compare to thigh and back.

Aim #2: Identify motor subtypes of PD using frequency components of whole body center of pressure

Hypothesis 2a: TD patients have larger frequency in their center of pressure signal in the frequency of 3-7 Hz compared to PIGD patients.

Hypothesis 2b: Wavelet transform is a better tool to diagnose PD subtypes than fast Fourier transform.

Aim #3: Evaluate the effect of slip, mediolateral (ML) and mixed (both slip and ML) perturbation trainings on whole body dynamic stability (as measured by maximum Lyapunov exponent) and gait adaptability (as measured by entropy analysis).

Hypothesis 3a: Slip perturbation training will improve dynamic stability in AP direction.

Hypothesis 3b: ML perturbation training will improve dynamic stability in ML direction.

Hypothesis 3c: ML and slip perturbation training (mixed) will improve dynamic stability in both AP and ML directions.

Hypothesis 3d: Perturbation training will improve gait flexible adaptability.

Hypothesis 3e: Perturbation training on treadmill will improve dynamic stability when tested during over-ground walking.

1.3 Organization

This dissertation has six chapters. Chapter 1 provides the motivations and rationale for conducting this dissertation research as well as the research objectives and hypotheses.

Chapter 2 provides background information and a review of the pertinent literature in regards to the impact and cost of falls, human gait, PD and its symptoms, perturbation training, and a brief background on nonlinear dynamics and stability analyses as well as complexity. In chapter 3, a novel, real-time FOG detection method using the Wavelet transform and wireless accelerometer is proposed and the first aim is explored. The results of this study has been published in journal of Sensors. Chapter 4 provides a method to identify motor subtypes of PD by using frequency component of whole body center of pressure and explores the second aim of this dissertation. The first portion of this study has been published in Biomedical Sciences Instrumentation and the entire study has been published in journal of Sensors. In chapter 5, the effect of slip, ML and mixed (slip and ML) perturbation trainings on the whole-body dynamic stability and flexible gait adaptability are assessed. Finally, Chapter 6 highlights the major findings from all three studies, future directions and conclusions.

CHAPTER 2: BACKGROUND

2.1 Impact and cost of instability and falls

Injuries and death associated with fall incidents pose a significant burden to society both in terms of human suffering and economic losses. Injuries associated with fall accidents are the leading cause of nonfatal injuries treated in hospital emergency departments and the third leading cause of death from unintentional injury in the U.S. (Center for Disease Control and Prevention, 2014). Among all the environmental causes of falls, 47.6% and 20.2% are due to uneven surfaces and slipping on something, respectively (Li et al. 2006). During 2014, more than 2.8 million older individuals were treated in emergency departments for fall-related injuries, and approximately 800,000 of these patients were subsequently hospitalized (Bergen et al. 2016; Center for Disease Control and Prevention, 2014). Outdoor falls happen more often than indoor falls and 47% occur while walking (Li et al. 2006). The resulting treatment cost was estimated to be $31 billion annually in the U.S. for older adults (Burns et al. 2016). In the working population, the direct cost of occupational injuries in 2012 due to falls on the same level in the U.S. was estimated to be approximately $9.19 billion or 15.4% of total injury cost (Liberty Mutual Research Institute for Safety, 2014). Fall often leads to injuries (Bloem et al. 2001; Genever et al. 2005), increased dependency, reduced activity (Bloem et al. 2001), poor quality of life (Bloem et al. 2001; Franchignoni et al. 2005), added caregiver-burden (Schrag et al. 2006), and mortality (Allen et al. 2013).

One major subset of these falls is falls due to neurodegenerative disorders such as Parkinson’s disease (PD). Approximately 50-70% of patients with PD fall at least once (Bloem et al. 2003; Allen et al. 2013; Ashburn et al. 2001; Ashburn et al. 2008) and over

50% of these fallers experience two or more falls each year (Wood et al. 2002; Allen et al. 2013). It is estimated that about 630,000 people were diagnosed with PD in 2010 in the United States. This number is anticipated to be double by 2040 (Kowal et al. 2013), meaning PD-related falls can be expected to have a major impact on health care systems in the coming decades. Although the costs of fall, fall-related injuries, and its consequences have not been separately investigated, it can be estimated that significant percentage of economic burden of PD are caused by falling because PD patients are highly susceptible to fall. The economic burden of PD studies show that PD is costly in view of the fact that the national medical expenses of PD are more than 14.4 billion in 2010 (Kowal et al. 2013; Johnson et al. 2013). As such, finding the intervention strategies to reduce fall accidents are paramount to our society.

2.2 Human gait

The purpose of walking is to transport the body safely and efficiently across terrain. This is achieved through biomechanical constraints of the body and the physical constraints of the environment. Additionally, the central nervous system (CNS) needs to integrate all of the sensory information to generate appropriate motor commands. Normal walking depends on a series of reciprocal movements involving the alteration of the function of each leg supporting the body and advancing into the next position. Apart from individual differences, human gait is constructed of several events which are similar across all individuals. A gait cycle is defined as a time period from when one foot contacts the floor to next time that foot contacts the floor again (Winter 1990). Each gait cycle can be divided into two phases for either leg: swing phase and stance phase. Stance phase (approximately 60% of the gait cycle) starts when the heel of one foot contacts the floor and ends at toe-off of the same foot. Swing phase includes the period when the foot advances forward without touching the floor. Within each gait cycle, there is a period of double support time (20% of the gait cycle), in which both feet are in stance phase, and two periods of single support time, where one foot is supporting the weight of the body while the other is in swing phase.

Forward locomotion is achieved by pushing off the leg in stance phase while swinging other leg forward. At the heel contact phase of the gait cycle, hip and knee extend to prevent body from collapsing (Winter 1990). Forward movement of the body propels the weight on the foot forward from heel to forefoot. At that instance, heel rises and pushes the foot backward. At the same time, muscles extend the hip, flex the knee, and plantar flex the foot (Whittle 1996). In the swing phase, the leg is flexed at hip and knee and dorsiflexed at foot, the limbs move under the influence of gravity alone and a fall is arrested by putting down the contralateral foot.

In normal walking, muscles contract and relax in a rhythmic form. Synchronized EMG and kinematic data can be measured during walking to identify the sequence of muscle recruitment during walking (Rose et al. 1994). At the initial contact of foot, the limbs begin to decelerate the body as it reaches the floor by activating both knee flexor and extensor to stabilize the knee in space. Deceleration of thigh is obtained by hip extensor. Additionally, the anterior tibialis contracts to gradually lower the foot. The limb accepts the weight of body by contracting knee extensors (vasti muscles). The knee bend slightly and begins extending. This is accompanied by plantarflexion of the ankle, which moves the contact point of the limb forward. At mid stance, the center of mass reaches its highest point. As long as the knee remains extended, body mass can fall forward (in line of walking progression). By contraction of soleus muscle, foot is pressed against the floor and allows the knee to remain extended. At terminal stance, knee extension and ankle plantarflexion force couple to keep the knee passively extended, but now the ankle plantar-flexors begin to contract and accelerate the body forward. Pre-swing starts by contracting hip flexors which lifts the limb and swings it forward. Swing phase continues using ankle plantarflexion to allow the foot to clear the floor. At terminal swing, the limb starts to decelerate by contracting hamstrings. This efficiently slows both hip flexion and knee extension. Tibialis anterior continues its activity as it gently float the foot over the floor immediately before foot contact. As the foot contacts the floor, this cycle repeats itself.

2.3 Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder caused by the death of dopaminergic neurons in the substantia nigra, one of the nuclei of the basal ganglia in the midbrain.. The basal ganglia receives signals from the cortex, processes this information and then projects to the motor cortex via the thalamus. Two distinct pathways process signals through the basal ganglia: the direct pathway and the indirect pathway. These two pathways have opposite effect. Activation of the direct pathway increases thalamocortical activity whereas activation of the indirect pathway inhibits thalamocortical neurons. Roughly, activation of the direct pathway facilitates movements and activation of the indirect pathway inhibits movements. Integrated activity of these two pathways modulate movements. The balance of activity between the direct and indirect pathways are modulated by dopamine. The cells of direct pathway have D_1 dopamine receptors. When dopamine binds to these receptors, it excites the neurons and makes them more likely to fire. Therefore, dopamine activates the direct pathway. In contrast, cells of indirect pathway utilize D_2 dopamine receptors. When dopamine binds to these receptors, it inhibits the neurons and makes them less likely to fire. Accordingly, death of dopaminergic neurons in the substantia nigra during PD results in an imbalance towards over activity of indirect pathway and underactivity of direct pathway. This means motor programs are now excessively inhibited, leading to difficulty in initiating movements and thus the characteristic features of PD of slowness of movements (bradykinesia) and rigidity (Davie 2008; Morris 2000; Jankovic 2008; Kendal et al. 2013). The most common motor symptoms of PD include tremor, bradykinesia, akinesia, rigidity, freezing of gait (FOG), and impaired balance and postural control (Davie 2008; Morris 2000; Jankovic 2008; Kandel et al. 2013).

FOG is one of the symptoms of PD which is defined as an inability of a person to move one's feet in spite of the fact that he/she intends to move (Giladi 2008; Nutt et al. 2011). FOG usually occurs during gait initiation and turning or encountering an obstacle (Moore, D. a Yungher, et al. 2013). The occurrence of FOG increases at the later stage of PD; PD patients with mild and advanced stages experience FOG about 10% and 80%, respectively (Macht et al. 2007). FOG not only negative impacts activities of daily living, but is also a common cause of falls in this population (Bloem et al. 2004). As such, specifying a treatment and finding a biomarker of FOG is an important goal of PD clinical research.

PD can be further divided into two subtypes based on clinical features: tremor dominant (TD), and postural instability and gait difficulty (PIGD) (Chen et al. 2015; Fahn et al. 2011;

Thenganatt & Jankovic 2014; Jankovic et al. 1990a). This categorization at the early stage of PD is important, as identifying PD subtypes could help to predict the clinical progression of the disease. Several studies have confirmed that the PIGD subtype has a faster disease progression, greater motor function impairment (Jankovic & Kapadia 2001a), and is less responsive to levodopa and deep brain stimulation of the STN and GPi compared to the TD subtype (Jankovic et al. 1990a; Rajput et al. 1993; Mehanna & Lai 2013; Chen et al. 2015). It has also been reported that there is a correlation between freezing of gait score and PIGD score (Rajput et al. 1993). Additionally, the PIGD subtype can place PD patients at a higher risk for falls compared to TD patients (Rudzińska et al. n.d.). It has been shown that PIGD patients have worse postural control in comparison to TD patients (Rudzińska et al. n.d.; Herman et al. 2013). Accordingly, correctly diagnosing subtypes can help caregivers to initiate early amenable interventions and track the progression of the disease.

2.4 Perturbation-based training

Previous studies have shown that physical exercises which focus on balance training result in fall reduction (Ld et al. 2015; Parijat et al. 2009; Beam et al. 2004; Sherrington et al. 2008). Although these exercises can reduce the risk of falls, greater reduction in fall incidence are not seen because it may need an intervention focusing on one's balance recovery strategies following a balance loss (such as swaying around the ankles or hips, taking a step, or grasping action) (Maki & McIlroy 2006; Hof 2007). Thus, training tasks that focuses on improving the balance recovery strategies may provide a beneficial effect in reducing falls (McCrum et al. 2017; Mansfield et al. 2015).

One intervention method focusing on improving balance recovery that has shown promising results in regard to reducing the incidence of falls is unexpected perturbation-based training (PBT) (Mansfield et al. 2015; Mccrum et al. 2017). This balance-training intervention exposes individuals to repeated external perturbations during walking which might happen in daily life and evokes balance recovery reaction. This empowers individuals to enhance these reactions with practice. PBT can enrich neuro-mechanical control of stability to prevent falls and create a helpful motor behavior that can be used in the cases of unexpected real-world perturbations (Pai & Bhatt 2007). Different studies have shown that there are improvements in control of voluntary movements (Rogers et al. 2003), an increase in the speed of balance reactions (Parijat & Lockhart 2012; Tanvi et al. 2012; Mansfield et al. 2010), and improvements in some measures of the reactive recovery response to perturbations (e.g., recovery step) (Parijat & Lockhart 2012; Y. C. Pai et al. 2014; Tanvi et al. 2012; Lurie et al. 2013; Pai et al. 2010; Bierbaum & Peper 2010; Bierbaum et al. 2011; Mansfield et al. 2015).

Additionally, a decrease in occurrence of falls in the laboratory from the pre- to post-perturbation training has been reported (Parijat & Lockhart 2012; Y. C. Pai et al. 2014; Tanvi et al. 2012; Mansfield et al. 2015; McCrum et al. 2017). Parijat et. al. indicated fall reduction on slippery surface from 42% to 0% (Parijat & Lockhart 2012) and, Pai et. al reported fall reduction from 42.5% to 0%, 8.7% and 11.5% in 6, 9, and 12 months after repeated slip training during the laboratory retest (Y. C. Pai et al. 2014). A few studies also show reduction in number of daily living falls by following up with their participants after several months of PBT (Y.-C. Pai et al. 2014; McCrum et al. 2017). Therefore, an improvement in control of balance may improve response to unexpected real world balance loss and reduce the likelihood of falls (Mansfield et al. 2015).

Along with reducing risk of fall, PBT shows promising results in performance, preventing injury, and rehabilitation (mainly athletes with knee injuries) within the field of athletic training (Zech et al. 2010). Rehabilitation with PBT facilitates return to functional activity sooner and maintains functional status for longer periods compared with a standard rehabilitation program (Hurd et al. 2006; Chmielewski et al. 2005; Fitzgerald et al. 2000; Rudolph et al. 2000; Williams et al. 2001; Zech et al. 2010). The commonly used PBT protocol for this purpose is the one proposed by Chmielewski et. al. (Chmielewski et al. 2005). In their study, they have applied PBT on individual with unilateral anterior cruciate ligament (ACL) (Chmielewski et al. 2005). All subjects participate in sessions of perturbation training which include perturbation on tilt board while subject stands on one leg and ML and AP perturbation with only one foot on a roller board or one on roller board and the other on a static platform. Results indicated that individuals with ACL injures showed improvement in movement patterns and muscle activations, resembling subjects without injuries after training.

Although the results of PBT are promising, the efficacy of such interventions is not well understood. Most studies report the improvement in some measures of the reactive recovery response after the training, which may not be transferable to another type of perturbation. In other words, there is paucity of data revealing the effects of PBT on improving dynamic stability of walking and gait flexible adaptability as a whole. Additionally, most of these studies apply perturbations while subjects walk over ground by utilizing some method like movable platform (Y. C. Pai et al. 2014; Parijat & Lockhart 2012). Therefore, perturbations occur at the same location each time. This might give subjects external cues and cause adaption in gait due to predictions about the location of a possible perturbation, which would affect the results of laboratory induced falls and alter measures of the reactive recovery response to the perturbations.

The main difficulties associated with using PBT as an intervention method to reduce fall incidences are the requirements of this training method (equipment and space). The common method to induce perturbations during walking requires an instrumented walkway and overhead harness system which takes up a large space. Additionally, subjects can predict the location of perturbations in PBT training (e.g. slip induced perturbation by movable platform) since perturbations occur in the exact same location. Furthermore, the starting point of subject's walking needs to be adjusted before starting a training session to secure that foot lands at the exact same location of applied perturbations. These difficulties hinder the use of PBT during walking in the clinical and community settings. In contrast, treadmills offer several advantages such as reduced space requirements, standardized components, and reproducibility in training protocols (Yang et al. 2013). Most importantly, precise foot placement is no longer necessary since every step is recorded. Furthermore, harness systems need to cover a smaller space during treadmill training. Thus, application of a treadmill design may facilitate PBT during walking in the clinical and community settings.

2.5 Adaptive control and training

Previous studies have shown that humans adapt to unpredictable changes or perturbations in environment during different activities, such as standing or walking (Bhatt et al. 2006; Nashner 1976; Horak et al. 1989; Owings et al. 2001; Parijat & Lockhart 2012). A new association between external perturbation (e.g. slip) and motor action is required for this adaptation. For example, experiencing repeated slip perturbations may elicit increased transitional acceleration at the time of heel contact, reducing the risk of backward balance loss and fall upon further perturbation (Lockhart et al. 2003a). This type of change in gait pattern is acquired by repeating movements in the presence of an external perturbation to reconstruct the performance of a task when external perturbations exist (Pai & Bhatt 2007).

Sensory information is integrated by the CNS to calculate required motor commands for postural control and prevent balance loss during movement. For this purpose, CNS constructs internal representation of the world by integrating different sensory systems. This internal representation is known as the internal model (Kandel & Schwartz 2013). The internal model includes two main components; the inverse model and feedforward model. The inverse model computes the motor commands by considering the desired state (preventing balance loss), while the forward model operates as a predictor to estimate the next state based on a copy of the current motor commands (efferent copy). During walking, the inverse model calculates the required motor commands for the desired body position to control stability. The commands from inverse model are sent to neuro-mechanical apparatus (muscles) to control the location of each limb. Additionally, a copy of these commands (efferent copy) are sent to forward models to predict the future state/position. The sensory feedback information is integrated and compared with the predicted posture from the forward model. The comparison gives the error (corollary discharge). If there is an error, it will be fed to the adaptive controller (inverse and forward models) to update the motor commands (Sicre et al. 2008). In this proposal, the internal model is considered as a feedforward control of balance control.

By repeating exposure to perturbations, a new predictive control is developed which reduces the risk of balance loss in the presence of perturbations. The CNS builds, refines, or updates an internal representation of the potential threats that may occur in the external environment (Pai & Bhatt 2007; Kandel & Schwartz 2013). When sensory prediction is consistent with the actual sensory information, there is little command from the feedback controller. Otherwise, these sensory inputs not only elicit corrective commands from the feedback controller but also are utilized to regulate the sensory representation of the environment and the motor commands in a feedforward controller (Pai & Bhatt 2007; Kandel & Schwartz 2013; Morasso et al. 1999). This improves performance in the future motor actions under similar contexts. Thus, PBT decreases dependency on the feedback mechanism as the adaptation process is further developed over repeated exposures to perturbations (Pai & Bhatt 2007; Y. Pai et al. 2003). Furthermore, the CNS explores all the possible patterns of motor neuron requirements for fulfilling a movement task in the presence of an external perturbation (Pearson 2000; Prochazka & Ellaway 2012). Thus, PBT refines neural pathways to effectively recruit motor neuron in order to reduce the risk of balance loss and fall.

2.6 Local dynamic stability

Dynamic stability during gait is defined as the resilience of a subject to infinitesimal perturbations during walking (Dingwell et al. 2000). Perturbations in human gait might have an internal source like sensory or motor noise or an external source such as an uneven surface. If an individual is unstable, they might be at high risk of losing balance and fall when there is larger perturbation. Local dynamic stability is a method that measures the ability of the walking subject to resilience of these perturbations (Toebes et al. 2012). Local dynamic stability is quantified by the maximum Lyapunov exponent (L_{max}). L_{max} measures the average logarithmic rate of divergence and specifies how a system responds to a very small perturbation (Dingwell & Cusumano 2000; Rosenstein ' et al. 1993; Stergiou 2016a). The general concept is that if a system is at nearly the same state as the current state one of these sates might be considered a perturbation for the other state. By tracing the distance between these two states in time, it could be seen whether this distance increases exponentially, an indicator of instability, or decreases, which implies that the system is more stable. One of the advantages of this method is that any source of kinematic data can be utilized to calculate this measure regardless of the reference frame (Bruijn et al. 2010; Gates & Dingwell 2010). Additionally, it doesn't need an actual gross perturbation as walking itself produces a very small perturbation with every step. The disadvantage of this method is that it needs relatively large amount of data (Dingwell & Cusumano 2000; Rosenstein ' et al. 1993; Stergiou 2016a).

Maximum Lyapunov exponents have been used for a while to assess human gait stability by comparing patients to healthy controls, or by comparing younger to elderly subjects (Lockhart & Liu 2008; Buzzi et al. 2003; Dingwell & Cusumano 2000; Kang & Dingwell 2009; Dingwell et al. 2000; Stergiou et al. 2004; Moraiti et al. 2007). Results of LDS (quantified by L_{max}) on older adults show that they are more unstable during walking than young subjects, which is consistent with the association between age and decreased ability of keeping balance (Buzzi et al. 2003; Kang & Dingwell 2009). Additionally, L_{max} could discriminate elderly fallers from elderly non-fallers and young subjects (Lockhart & Liu 2008).

L_{max} defines how the system responds to small perturbations (Dingwell & Cusumano 2000; Rosenstein ’ et al. 1993; Stergiou 2016a) but it does not provide any insight about how it relates to more common sense notions of stability, such as the ability to overcome larger external perturbations. By considering this assumption that patients or elder adults are less stable in the aforementioned studies, this can be a support for this concept. Lockhart et. al. tried to address this by calculating L_{max} for individuals with known balance problems (Lockhart & Liu 2008). They report greater L_{max} for elderly subjects with a history of falling compared to ones without such a history. Another way to assess how well L_{max} relates to notion of stability is to assess L_{max} when there is external perturbation. Young et al. applied random perturbations during walking to put subjects in unstable walking condition. Their results showed an increase in L_{max} which indicates that L_{max} is sensitive to unstable walking (Young 2011).

2.7 Adaptability and complexity

Human movement requires adaptability to different demands since human face different challenges every day. It is hypothesized that variations in human movement might be essential to provide flexible adaptations to everyday disturbances experienced by the body (Goldberger et al. 2002; Otero-Siliceo & Arriada-Mendicoa 2003; Georgoulis et al. 2006; Stergiou & Decker 2011). On the other hand, a lack of this complexity is associated with rigidity and inability to adapt to different demands and challenges. The loss of adaptability is related to lack of complexity and greater regularity in the dynamics of daily living activities (Paraschiv-Ionescu et al. 2012; Ihlen et al. 2016). In human movements, higher levels of entropy reflect a more complex mechanism and greater adaptability to different demands (Stergiou 2016a; Costa & Healey 2003; Costa et al. 2005; Costa et al.

2003; Manor et al. 2010; Karmakar et al. 2007). High level of entropy points to a higher flexibility (complexity) in selecting an action requires for a task at a certain condition. Alternatively, lower entropy determines repetitive behavior and a limited amount of flexibility or complexity. A study of acceleration signals during walking have indicated that older-adult-fallers have lower entropy level in comparison to ones without the history of falls (Ihlen et al. 2016). A decrease in entropy is also shown in toe clearance during walking for older adults at the risk of fall (Karmakar et al. 2007). Additionally, Georgoulis et al. have showed that subject with ACL injuries have lower entropy than controls (Georgoulis et al. 2006). They conclude that deficient knee due to ACL injuries exhibits more regular patterns and therefore, reduces the adaptability of subject to adjust to perturbations. These findings support the hypothesis that lower entropy level leads to loss of complexity in the gait dynamics and accordingly lessens the adaptability of daily life walking and increase the risk of falls (Goldberger et al. 2002; Otero-Siliceo & Arriada-Mendicoa 2003; Georgoulis et al. 2006; Paraschiv-Ionescu et al. 2012; Ihlen et al. 2016).

One speculation regarding how PBT reduces risk of falls could be that it might increase the flexible adaptation of human gait to adapt to different daily challenges. Hence, this speculation is yet to be attested and investigated. A deeper understanding of the reasons is important to suggest new approaches and employ PBT in more effective ways. Evidence to date suggests that the loss of adaptability is associated with lack of complexity and greater regularity in the dynamics of daily living activities (Paraschiv-Ionescu et al. 2012; Ihlen et al. 2016). In human movements, entropy measures are a key indicator of complexity in the system (Stergiou 2016a; Costa & Healey 2003; Costa et al. 2005; Costa et al. 2003; Manor et al. 2010; Karmakar et al. 2007). Therefore, analyzing gait complexity after PBT could evaluate gait flexible adaptability and give us a glimpse of how perturbation training can reduce the risk of falls (i.e., by increasing complexity and improving dynamic stability).

2.8 Nonlinear analysis

Hardware and computing advances have enabled long time-series data to be collected, stored, and analyzed efficiently allowing researchers to utilize complex algorithms in a variety of capacities. Recently, long time-series of biomechanical data have been analyzed using mathematical techniques commonly reserved for dynamical systems (Granata & Lockhart 2008; Bruijn et al. 2009; Young 2011; Dingwell et al. 2001). Gait and postural stability have received a large amount of attention with these new tools in an attempt to understand the motor control strategies of human movements. These specific actions have demonstrated chaotic structure and produced results that are not seen with traditional biomechanical analysis (Terry et al. 2012; Dingwell et al. 2000; McAndrew Young & Dingwell 2012; Georgoulis et al. 2006; Granata & Lockhart 2008; Bruijn et al. 2009; Young 2011; Dingwell et al. 2001; Ihlen et al. 2016; Karmakar et al. 2007).

2.8.1 Lyapunov exponent

Lyapunov exponents determine the average exponential rate of divergence of neighboring trajectories in state space (Rosenstein ' et al. 1993; Kantz & Schreiber 2003; Stergiou 2016). The first step in calculating a Lyapunov exponent is the creation of a state space. A time delay state space is constructed using the original data and its time-delayed copies.

$$S(t) = [v(t), v(t+\tau), \ldots, v(t+(d_E - 1)\tau)] \quad (2\text{-}1)$$

where S(t) is the d_E-dimensional state vector, v(t) is the original 1-dimensional data, τ is the time delay and d_E is the embedding dimension. Time delays are determined from the first minimum of the Average Mutual Information function (Stergiou 2016b). The embedding dimension can be calculated using false nearest neighbors algorithm. The embedding dimension of d_E=5 is mainly used in previous studies on analyzing walking dynamics (Dingwell & Marin 2006; Dingwell & Cusumano 2000; McAndrew et al. 2011).

The maximum Lyapunov exponent can be defined by using:

$$d(t) = d_0 e^{\lambda_1 t} \quad (2\text{-}2)$$

where d(t) is the mean displacement between neighboring trajectories in state space at time t and d_0 is the initial separation between neighboring points. λ_1 which is true Lyapunov exponents are only defined at the limits of $t \rightarrow \infty$ and $d_0 \rightarrow 0$ in above formula. Since experimental data can't reach to these limits, an algorithm for estimating maximum finite-time Lyapunov exponents (λ_*) are proposed (Rosenstein ' et al. 1993). By taking the natural log of both sides of Equation (3), λ_* is defined from:

$$\ln[d_j(i)] \approx \ln\left[d_{0j}\right] + \lambda_*(i\Delta t) \quad (2\text{-}3)$$

where dj(i) is the Euclidean distance between the jth pair of nearest neighbors after i discrete time-steps (i.e. iΔt). The maximum finite-time Lyapunov exponents λ_* can then be estimated from the slope of the linear fit to the curve of:

$$y(i) = \frac{1}{\Delta t}\langle \ln[d_j(i)] \rangle \qquad (2\text{-}4)$$

where $\langle . \rangle$ is the average over all values of j (Stergiou 2016; Rosenstein et al. 1993).

2.8.2 Entropy

Sample entropy (SampEn) analysis is a nonlinear technique for quantifying the regularity of time series data. This method which is an estimate of actual entropy for finite number of data points represents the tendency of a system to visit different states rather than being an a few states. In other words it indicates the complexity of a system (Pincus & Goldberger 1994; Stergiou 2016a; Kantz & Schreiber 2003). Lower values of SampEn reflect more regular time series (less complex) while higher values indicates more complex time series.

Mathematically, SampEn is computed as follows:

Let $\{U_i\} = \{u_1, u_2, \dots, u_i, \dots, u_N\}$ represent a time series of length N. There are also two input parameters, m and r. m is the length of compared runs, and r is a tolerance radius. Vector sequences of x_1 through x_{N-m-1} are formed from $\{U_i\}$, defined by $x_i = [u_1, \dots, u_{i+m-1}]$. These vectors are basically consecutive u values beginning with i^{th} point. The largest difference between corresponding elements of two vectors x_i and x_j is defined the distance between two vectors ($d[x_i, x_j]$). Based on this definition of distance $C_i^m(r)$ is defined as follow:

$$C_i^m(r) = \frac{number\ of\ x(i) such\ that\ d[x_i, x_j] \leq r}{Nim - 1} \qquad (2\text{-}5)$$

Natural logarithm summation of all $C_i^m(r)$ is used to define $\Phi^m(r)$:

$$\Phi^m(r) = \frac{\sum_{i=1}^{N-m+1} \ln C_i^m(r)}{N-m+1} \qquad (2\text{-}6)$$

The calculation of SampEn is then given by the difference:

$$SampEn = \Phi^m(r) - \Phi^{m+1}(r) \qquad (2\text{-}7)$$

CHAPTER 3: TOWARDS REAL-TIME DETECTION OF FREEZING OF GAIT USING WAVELET TRANSFORM ON WIRELESS ACCELEROMETER DATA

Abstract

Injuries associated with fall incidences continue to pose a significant burden to persons with Parkinson's disease (PD) both in terms of human suffering and economic loss. Freezing of gait (FOG), which is one of the symptoms of PD, is a common cause of falls in this population. Although a significant amount of work has been performed to characterize/detect FOG using both qualitative and quantitative methods, there remains paucity of data regarding real-time detection of FOG, such as the requirements for minimum sensor nodes, sensor placement locations, and appropriate sampling period and update time. Here, the continuous wavelet transform (CWT) is employed to define an index for correctly identifying FOG. Since the CWT method uses both time and frequency components of a waveform in comparison to other methods utilizing only the frequency component, I hypothesized that using this method could lead to a significant improvement in the accuracy of FOG detection. I tested the proposed index on the data of 10 PD patients who experience FOG. Two hundred and thirty seven (237) FOG events were identified by the physiotherapists. The results show that the index could discriminate FOG in the anterior–posterior axis better than other two axes, and is robust to the update time variability. These results suggest that real time detection of FOG may be realized by using CWT of a single shank sensor with window size of 2 s and update time of 1 s (82.1% and 77.1% for the sensitivity and specificity, respectively). Although implicated, future studies should examine the utility of this method in real-time detection of FOG.

3.1 Introduction

Injuries associated with fall incidences continue to pose a significant burden to persons with Parkinson's disease (PD) both in terms of human suffering and economic loss. Annual fall incidence rates range from 50% to 70% in patients with PD, and recurrent falls are a major cause of disability in PD (Allen et al. 2013). The resulting loss of independence and treatment costs add substantially to the healthcare expenditures in PD which is estimated to be $27 billion annually in the U.S. (Obeso et al. 2000). This number may rise substantially in the coming decades as the entire U.S. population ages. Furthermore, recurrent falls usually occur later in PD (Allen et al. 2013; Matinolli et al. 2011). Indeed, among the top three priorities presented to the National Institute of Neurological Disorders and Stroke (NINDS) Council (NINDS PD2014) as final recommendations of critical needs for advancing PD research, is to develop effective treatments for dopa-resistant features of PD. These features include motor symptoms such as gait and balance problems and freezing of gait leading to falls.

Freezing of gait (FOG) is one of the cardinal symptoms of the PD which is defined as an inability of a person to move one's feet in spite of the fact that he/she intends to move (Giladi 2008; Nutt et al. 2011). FOG usually occurs during gait initiation and turning or, encountering an obstacle (Moore, D. a Yungher, et al. 2013). The occurrence of FOG increases at the later stage of PD and, the PD patients with mild and advanced stages experience FOG about 10% and 80%, respectively (Macht et al. 2007). Not only FOG causes a negative impact on the activity of daily living, but also it is a common cause of falls in this population (Bloem et al. 2004). As such, specifying a treatment and finding a biomarker of FOG is considered as a goal of the PD clinical research. Several questionnaires have been utilized to assess the severity of FOG conditions. One of the well-known and widely used questionnaires is Unified Parkinson's Disease Rating Scale (UPDRS), Activities of Daily Living (ADL) part 14 (Fahn et al., 1987). This questionnaire rates FOG from scale 0 (no FOG) to 4 (frequent falls from freezing) based on the patient history. The accuracy and validity of this method for detecting FOG is completely subjective and dependent on patient and caregiver's assessments and, they are not as accurate as the objective methods (Shine et al. 2012). As such, objective measures of FOG have been developed and employed utilizing wearable sensors. These methods use pressure sensors or inertial monitoring units (IMU) along with waveform analysis to characterize the episodes of FOG. These studies indicate that the spectral component in the range of 3–6 Hz was associated with FOG episodes (Jeffrey M Hausdorff et al. 2003). Recent wearable sensors, such as inertial measurement unit, could quickly and inexpensively deliver accurate measurements. Due to the form factor they also enable users to wear sensors on the various parts of body (Horak 2013). Additionally, these sensors can be used in any environment rather than the controlled environments (Muro-de-la-Herran et al. 2014). The portability and widespread use of cell phones (with embedded IMUs) may make this method useful and universal.

Furthermore, sensor placement locations as well as calibration methods may influence the accuracy of FOG detection (Nutt et al. 2011). As such, there are several requirements that must be considered prior to designing any real-time FOG detection systems—such as minimum sensor nodes, sensor placement locations, and appropriate sampling period and update time (Moore et al. 2008; Bachlin & Plotnik 2010). For example, FOG episodes have different durations (from 0.5 s to 128 s) (Moore et al. 2008;

Bachlin & Plotnik 2010), and given a short duration of the FOG episodes, use of fast Fourier transform (FFT) with the minimum sample window size of 4 s will erroneously miss the FOG in the signal. However, methods such as continuous wavelet transform (CWT) which employ time domain information in a smaller sample window size may detect the short-duration FOG better than FFT method. The objective of this study is to assess the effects of sampling duration and update time using the CWT for correctly identifying the FOG events in lieu of different sensor placements. The advantage of this method in comparison to other waveform methods (e.g., FFT) is that the CWT method uses both time and frequency components of a waveform and may improve the accuracy of FOG detection. Unlike Fourier transform, the continuous wavelet transform could construct a time-frequency representation of a signal which delivers the time and frequency localization. Furthermore, continuous wavelet transform (CWT) could assess how the frequency content (the power amplitude of specific frequency) of a signal changes over time. This detailed time-frequency analysis provides the ability to localize the transient state of a signal in time well better than FFT method. It is hypothesized that CWT analysis will objectively identify FOG better than the traditional method using power spectral analysis by incorporating appropriate sampling periods and update time with optimal sensor number/placement locations.

3.2 Method

The present work consists of novel analyses performed on the complete dataset obtained from previously published data (Bächlin, Plotnik, Roggen, Maidan, Jeffrey M Hausdorff, et al. 2010). Bachlin and colleagues recruited 10 PD patients (three females; age: 66.5 ± 4.8 years; disease duration: 13.7 ± 9.67 years; H & Y in ON: 2.6 ± 0.65) with the history of FOG and could walk during the “off-medication” stage without additional assistance. All participants except for two individuals (who had frequent FOG experience during the “on-medication” state) performed the tasks in the “off” stage of medication. Different walking conditions were provided to the participants (walking back and forth in a straight line, random walk with several stops and 360″ turns, and walking simulating activities of daily living). All trials were recorded on a video camera. Two physiotherapist analyzed the videos of the patients to detect four different activities: walking, standing, turning, and freezing. The term no-freeze included the activities of walking, standing, and turning. For each FOG episode, they specified the start and end times of FOG. Additionally, three 3-D accelerometers were used to collect the accelerations of shank (just above the ankle), thigh (just above the knee), and lower back. The accelerometers were sampled at 64 Hz sampling rate. In this dataset, there were totally 8 h and 20 min of data with 237 FOG events which were identified by the physiotherapists.

Previous studies (Moore et al. 2008; Bachlin & Plotnik 2010) used Fourier transform to elicit information from the frequency domain of acceleration data in order to detect the FOG episodes. In this study, I applied CWT on acceleration data to extract further features. CWT method provides the information not only in frequency domain but also in temporal domain that may help in defining a better FOG index using an appropriate window size and update rate.

The CWT constitutes a set of scaled and shifted wavelets in the frequency and time domain, respectively (Mojtahedi et al. 2015). Each wavelet is generated by mother wavelet and has a finite length with zero average. Each wavelet could be constructed by stretching or compressing (s, scale) the mother wavelet and transferring it in temporal domain (τ, translational time). The CWT of the acceleration signal (a(t)) is defined as the integral of multiplication of acceleration signal and wavelets over the duration of window:

$$\mathrm{C}(\mathrm{s},\tau) = \int_{0}^{\mathrm{window}} \mathrm{a}(\mathrm{t})\Psi^{*}\left(\frac{\mathrm{t}-\tau}{\mathrm{s}}\right)\mathrm{dt} \qquad (3\text{-}1)$$

where Ψ is a mother wavelet function. $\Psi^{*}\left(\frac{\mathrm{t}-\tau}{\mathrm{s}}\right)$ is the conjugate of mother wavelet which is shifted in temporal domain and scaled. The CWT of acceleration signal (C(s, τ), CWT coefficients) is the function of both scale and translational time. Since the scale is inversely proportional to the frequency, the corresponding pseudo-frequency for a specific scale could be computed by:

$$F_s = \frac{F_c}{s.\Delta} \qquad (3\text{-}2)$$

where F_c is the center frequency of mother wavelet. Δ is the sampling time in data collection from hardware specification and Fs is the pseudo-frequency which corresponds to a specific scale (i.e., s). Throughout the manuscript, I have used the term “frequency” to refer to pseudo-frequency.

During FOG there were frequency components in 3–6 Hz (Jeffrey M. Hausdorff et al. 2003b). Accordingly, I defined two scale ranges to capture the spectral components separately. The two scale ranges which correspond to frequency ranges of 0.5–3 Hz and 3–8 Hz were considered as locomotor and freeze scales, respectively. I computed the locomotor ($\mathrm{LC}(\tau)$ in equation (3-3)) and freeze ($\mathrm{FC}(\tau)$ in equation (3-4)) components at each translational time as the summation of CWT coefficient values of correspondent scale ranges. Therefore, I introduced the percentage ratio (R(τ) in equation (3-5)) of locomotor component to the sum of locomotor and freeze components. The FOG index was defined as the average of R(τ) over the sampled window.

Locomotor component: $\mathrm{LC}(\tau) = \sum_{i=0}^{5} \mathrm{C}\left(s = \frac{F_c}{0.5(1+i)\times\Delta}, \tau\right)$ (3-3)

Freeze component: $\mathrm{FC}(\tau) = \sum_{i=5}^{15} \mathrm{C}\left(s = \frac{F_c}{0.5(1+i)\times\Delta}, \tau\right)$ (3-4)

Ratio: $\mathrm{R}(\tau) = \frac{\mathrm{LC}(\tau)}{\mathrm{LC}(\tau)+\mathrm{FC}(\tau)} \times 100$ (3-5)

As I mentioned above, the two frequency ranges of 0.5–3 Hz and 3–8 Hz were considered for locomotor and freeze components, respectively. I tried different step sizes (e.g., 0.1, 0.25, 0.5, 1, 1.5 Hz) in frequency ranges for calculating the locomotor and freeze components. For any step size above 0.5 Hz, the frequency resolution was not enough to lead to different values for locomotor and freeze components. So, these step sizes were not good at discriminating these two components. However, the discrimination results were obtained by choosing any step sizes equal or below 0.5 Hz. Therefore, I chose 0.5 Hz as the proper step size. Consequently, I needed to calculate CWT coefficients for 6 and 11 frequencies (or scales) in order to compute the locomotor and freezing components, respectively. Note that 0.5 in the denominators of equations (3-3) and (3-4) is the step size in frequency. As in equation (3-2), I could calculate the correspondent scale of each frequency. For example, the term of 0.5(i + 1) for the values of i = 0, 1, 2, . . . , 5 generates the frequencies of 0.5, 1, 1.5, . . . , 3 Hz in the denominator to select the correspondent scales of these 6 frequencies for locomotor component in equation (3-3). In the current study several sample window sizes (1 s, 2 s, 3 s, and 4 s) have been applied to assess the effects of sampling duration on the FOG detection with CWT method. The same sample window size was always used for the locomotor and freezing components in order to calculate the ratio. The smallest sample window size in previous studies (Bächlin et al. 2010) were 4 s. I also want to assess smaller window sizes in order to not miss the short FOG episodes.

The optimal decision threshold for discriminating FOG from the other activities was selected according to the accuracy of diagnostic tests using an interactive dot diagram in MedCalc software (MedCalc statistical software, version 13). In the graph, I defined two groups “FOG” and “No FOG” (the other activities) which were plotted on two vertical axes by dots. A horizontal line in the graph indicated a threshold which illustrates the best separation between the two groups (via obtaining minimal false negative and false positive results). The signals of three axes in each accelerometer were considered as independent variables.

These signals were low-pass filtered using a fourth order, zero lag, Butterworth filter at a cut off frequency of 10 Hz. The FOG index for each axis was calculated. I assumed the clinical assessment from (Bächlin et al. 2010) as the ground-truth and assessed the performance of FOG index via sensitivity and specificity criteria. The sensitivity was the probability that the index detected FOG when FOG was present. Specificity indicated the probability that the index detected normal movement when there was not a FOG.

The type of the mother wavelet ($\Psi(t)$) could also influence the CWT coefficients. I chose db4 (Daubechies wavelets of 4th order) as the mother wavelet in the current study (Martin 2011). I applied CWT on 2 subjects with other wavelet families and orders (e.g., db10, Morlet, Haar, Mexican Hat, and Gaussian) to find the appropriate wavelet. Results showed that db4 could discriminate locomotor and freezing components better and gave a larger values for the sensitivity and the specificity.

3.3 Results

The CWT coefficient values are plotted in Figure 3.1. The profile of accelerations changed during FOG episode (left column, Figure 3.1.) and CWT of accelerations (right column, Figure 3.1.) magnify these changes in order to capture them computationally better. The inside of the red dash rectangle box specifies the FOG episode. The white horizontal line discriminates the two scale ranges of locomotor and freezing activities. In other words, below and above the white line corresponds directly to the frequency ranges of 3–8 Hz and 0.5–3 Hz, respectively. The CWT coefficients in Figure 1 shows relatively larger values (lighter blue values appeared in the below of white line) in the scales corresponding to the pseudo-frequency 3–8 Hz during the FOG episode (in the red dash rectangle box) in comparison to other activities (out of the red dash rectangle box) in all three axes of shank accelerometer. In contrast, the CWT coefficients had larger values in the pseudo-frequency 0.5–3 Hz (lighter blue values appeared in the above of white line) during the normal movement.

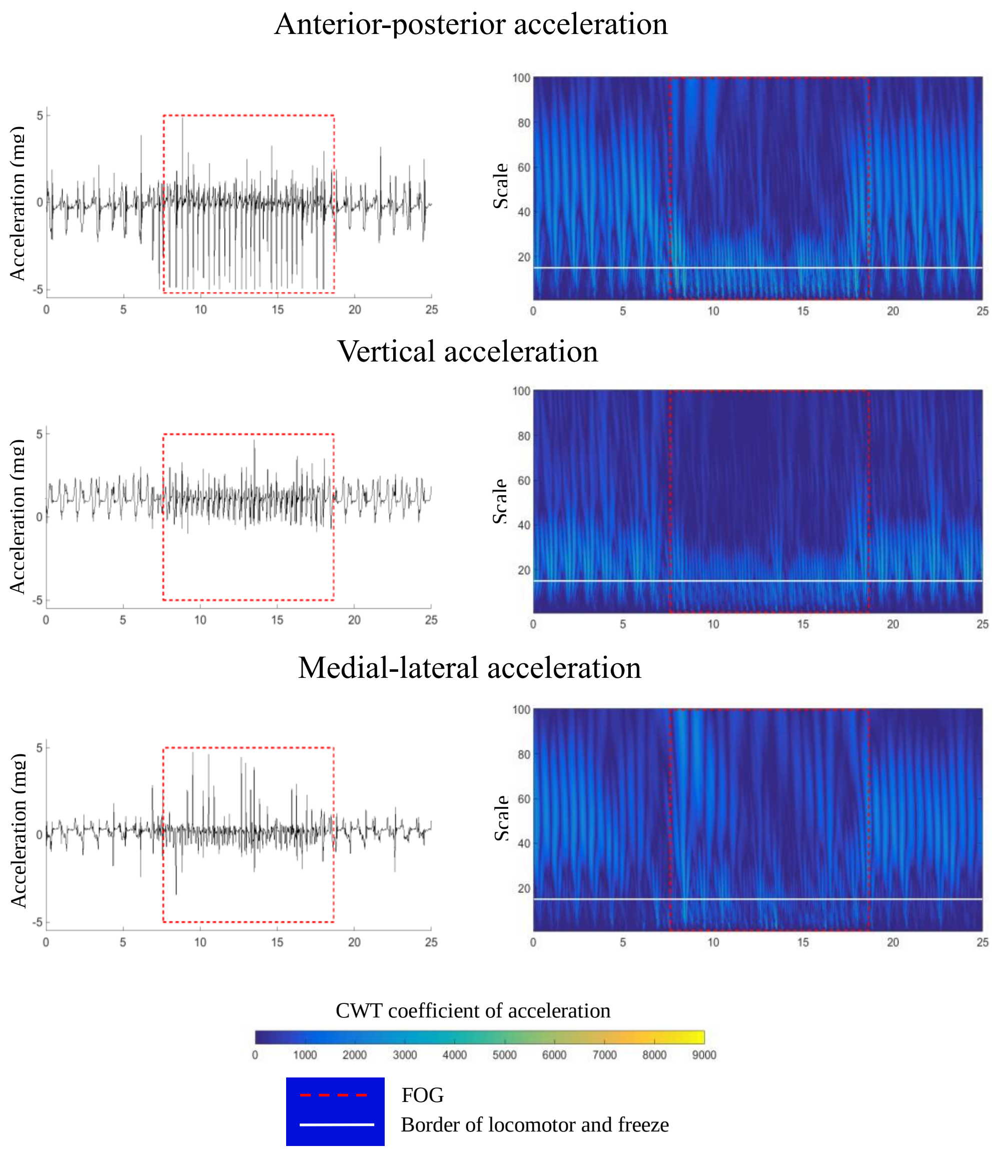

Figure 3.1. Shank acceleration signal and corresponding continuous wavelet transform of 25 s signal extracted from subject 2. The red dash rectangles denoted the true freezing of gait (FOG) episode period which physiotherapists identified by watching the video of a patient during the trials. At each continuous wavelet transform (CWT) plot, the white horizontal dash line indicated scale 15.2 which corresponded to 3 Hz and defined the border between locomotor and freeze scale ranges. The upper and lower sides of the white line indicated the locomotor and freeze scale ranges which corresponded to frequency ranges of 0.5–3 Hz and 3–8 Hz, respectively. The frequencies of 0.5, 3, and 8 correspond to the

scales of 91.4, 15.2, and 5.7, respectively. Milli-gravitational acceleration is denoted by mg (980.665 mm/s^2).

The receiver operating characteristic (ROC) curves of FOG index for all sensors and all of the three axes were provided in Figure 3.2. According to the area under the ROC curve, anterior–posterior direction could discriminate FOG better than the other two axes in any sensor placement locations (Table 3.1.). As such, the anterior–posterior axis of acceleration signal maybe a good candidate for detecting the FOG.

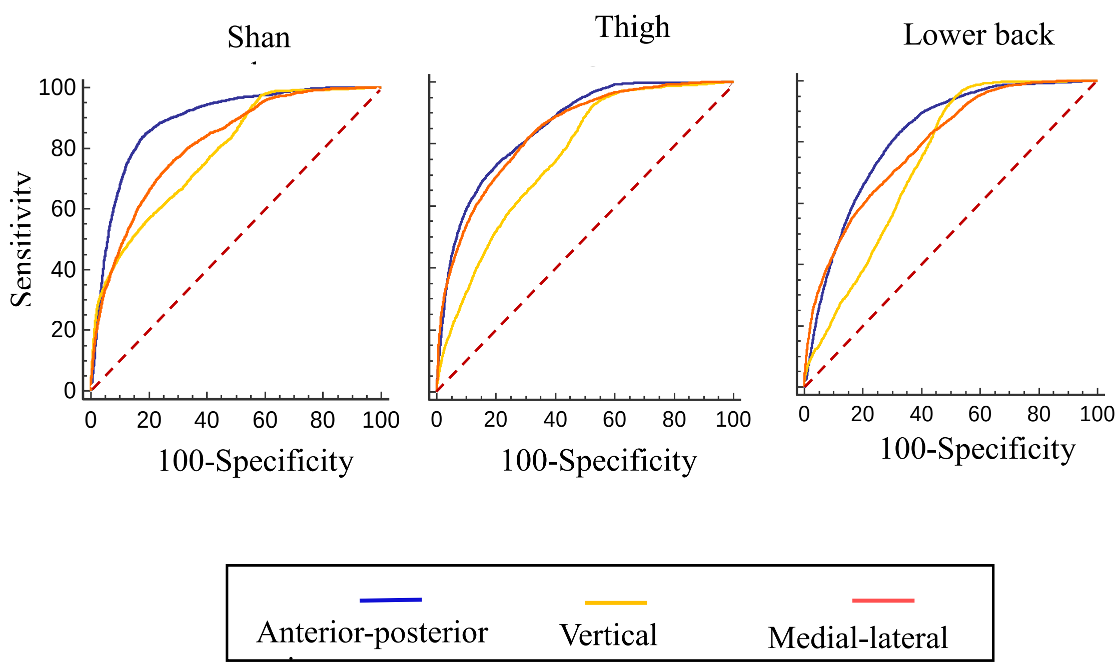

Figure 3.2. Receiver operating characteristic (ROC) curves for all sensors and all the three axes.

Table 3.1. Area under ROC curve across all the subjects for the different sensor positions and axes.

Sensor position	Anterior-posterior	Vertical	Medial-lateral
Shank	0.890	0.786	0.815
Thigh	0.857	0.759	0.842
Lower back	0.821	0.738	0.793

The threshold which discriminated FOG from the other activates was defined from the average data of all subjects based on the results of interactive dot diagram. The interactive dot diagram of FOG index for shank senor of subject 2 is illustrated in Figure 3.3. The horizontal line in each graph shows the best threshold which could discriminate FOG from other activities. In Figure 3, each circle shows the value of the proposed FOG index which are classified in two groups based on the ground truth clinical assessments. So, all circles in the “FOG” group indicate true FOG events and those in the “No FOG” group are true no FOG events (other movements). The overlap between the two sections indicate the false negative (circles located above threshold line in “FOG” group) and false positive (circles located below threshold line in “No FOG” group) of the proposed index.

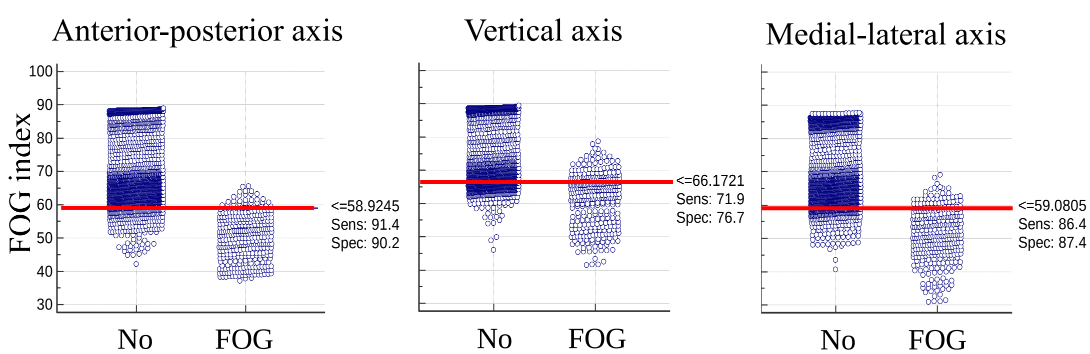

Figure 3.3. Interactive dot diagram of the FOG index for the shank senor of subject 2 for three different axes.

Furthermore, in terms of the real-time detection of the FOG episodes, the assignment of the window size and update time may be critical. Utilizing the results (Bächlin et al. 2010), I used the window length of 4 s with the update time of 0.5 s and applied CWT to all three sensors locations in order to find the best sensor position for detecting the FOG event. The averages of sensitivity and specificity across all subjects are presented in Table 3.2. The results indicate that the shank was the best placement location to detect FOG episodes rather than lower back or thigh positions.

Table 3.2. Sensitivity, specificity, and area under ROC curve across all the subjects for the different sensor positions with the time window size 4 s and the update time 0.5 s.

Sensor position	Sensitivity (%)	Specificity (%)	Area under ROC curve
Shank	84.9	81.0	0.890
Thigh	73.6	79.6	0.856
Lower back	83.5	67.2	0.821

In order to verify the appropriate window size and update times, I applied the FOG detection method on various window sizes that were smaller than 4 s (3, 2 or 1 s) on the anterior–posterior acceleration of the different sensor placements. I also employed larger update time (1 s) to examine the case in which the access to the processor could be limited and fast calculation was not available which would require the larger update time. The averages of sensitivity and specificity of various window sizes, update times, and sensor placements were presented in Figure 3.4.

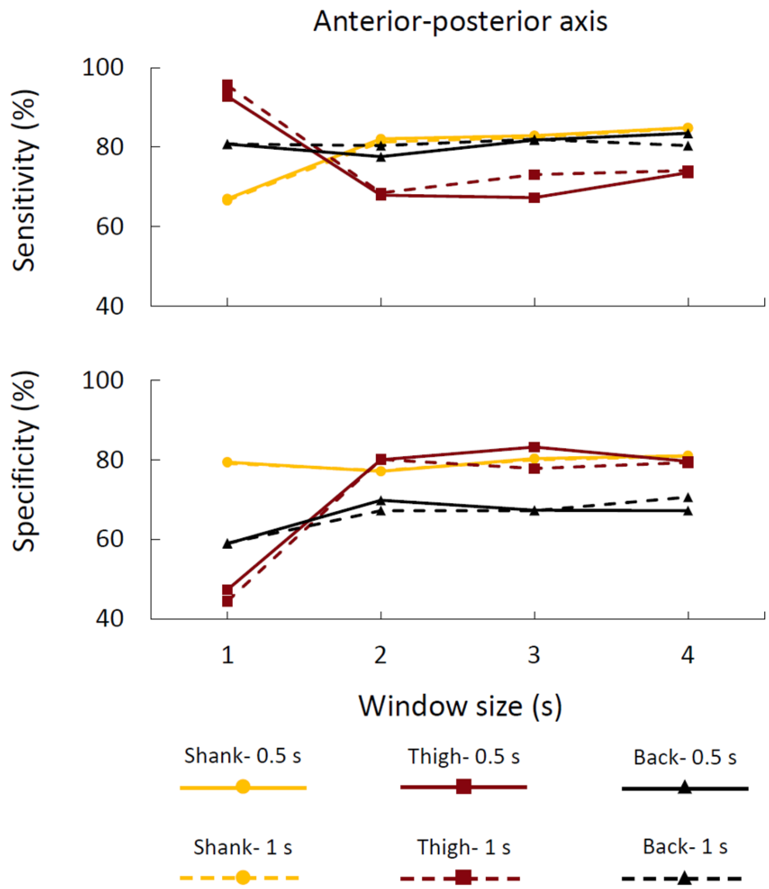

Figure 3.4. The averages of sensitivity and specificity across all subjects as a function of window size, update time, and sensor placement.

The results indicated that the acceptable sensitivity and specificity on the anterior–posterior shank acceleration sensor was achievable even for shorter window sizes (i.e., 2 s; Figure 3.4.) by employing the proposed FOG index. Importantly, the proposed index showed strong robustness to the update time variability. In other words, the sensitivity and specificity were robust to the changes of update time from 0.5 s to 1 s.

One of the design aspects in online detection is the number of false positive rates that may influence user compliance. Since I had different sample window sizes and update times, I provide average false positive percentages of the test results per minute for FOG index in Table 3.3.

Table 3.3. Average false positive percentage of the test results per minute for FOG index, across all the subjects for the anterior–posterior axis of shank senor.

Sample window size (s)	Update time 0.5 s (%)	Update time 1 s (%)
4	16.42	16.35
3	16.52	17.05
2	15.49	18.11
1	15.40	17.78

3.4 Discussion

I applied the CWT on wireless accelerometer signals to acquire real-time FOG detection. The novel FOG index was created to capture the time and frequency components of acceleration signal. To the best of my knowledge, this paper is the first attempt to utilize CWT for real-time detection of FOG events. Additionally, I evaluated the optimal sensor placement locations for identifying FOG. The efficiency of real-time detection of FOG was further investigated by assessing window size and update time. These two variables can be highly important when real time feedback (e.g., auditory, vibratory stimulations) is applied in order to overcome FOG (Lee et al. 2012; Heremans et al. 2013; Bächlin, Plotnik, Roggen, Maidan, Jeffrey M Hausdorff, et al. 2010). The current findings from applying CWT to linear acceleration signals were compared with previous studies (Moore et al. 2008; Jeffrey M. Hausdorff et al. 2003b) and it was found that there was an increase in amplitudes in the frequencies from 3–8 Hz in comparison with normal movements during FOG.

Very small shuffling steps with minimum forward movement and leg trembling in place (some leg trembling but no effective forward motion) were the most common manifestations of FOG (Schaafsma et al. 2003). The previous studies concentrated only on leg trembling in place (Schaafsma et al. 2003; Nutt et al. 2011) and used the frequency information of acceleration signal in the vertical axis which was the axis where the trembling occurred. The current study showed that I could also distinguish FOG by using the capability of the CWT to capture information from both time and frequency domain (Figure 3.1). Interestingly, the novel FOG index could detect FOG in anterior–posterior axis better than the other two axes. Since the shuffling steps had minimum forward movement and the axis of minimum forward movement corresponded to anterior–posterior axis, the proposed index could discriminate FOG in anterior–posterior better. The proposed FOG index detected FOG with 84.9% sensitivity and 81.01% specificity for sensor placed at shank with a window size of 4 s and update time of 0.5 s. Using the proposed method, the sensitivity was much higher than the previously reported result of 73.1%, applying FFT to the same dataset, but the specificity was similar (81.6%) (Bächlin, Plotnik, Roggen, Maidan, Jeffrey M Hausdorff, et al. 2010).

In terms of the location of the sensor placements, shank and lower back positions were preferred as these locations did not interfere with normal walking and produced best results. However, the lower back position could not represent trembling in place effectively during FOG events. As such, detection of FOG events using the shank sensor was better than the lower back sensor location (Figure 3.4). These results were in agreement with the other studies which evaluated sensor placement at the lower back for FOG detections (Moore et al. 2013; Tripoliti et al. 2013). In conclusion, a single sensor at the shank location may be the best sensor placement location for identifying FOG events, as this sensor location will not interfere with gait and allows easy installation of the sensors. In the current study, 48.1% of FOG events lasted less than 5 s. Thus, it was necessary to detect the FOG events with a shorter window size. Additionally, the efficiency of real-time detection could be improved with lowering sampling window and increasing update time. None of the previous studies have reported false positive per minute of their method. This value should be considered during early design phase since false positive signals will limit the usability of the device (i.e., “cry-wolf” effect for user compliance—users may turn the system off if too many false alarms are engaged). Based on the results from Table 3, false positive per minute values might be high from the design aspect, but it should be considered that these results were obtained from global threshold (all subjects have same threshold). By determining the threshold for each subject (i.e., calibrate index for each individual), the false positive rate will notably be decreased. Since I didn’t have access to other activity conditions (walking, standing, and turning), I were limited to improve the proposed index to identify FOG events from all other conditions. The current framework (window size of 2 s and update time of 1 s) achieved the levels of 82.1% and 77.1% for sensitivity and specificity, respectively. This framework had several special characteristics: First, the smaller window size, such as 2 s, allowed detection of short-duration FOG episodes better than a larger window size, since the larger window size can average out shorter FOG episodes. Second, the smaller window size could also decrease the processing time and send the signal to the third party faster (e.g., an assistive device) to help patients overcome the FOG episodes. Third, the robustness due to the update time variability did not attenuate the levels of detection. These characteristics are promising for real time application as these settings will decrease the calculation time and increase the efficiency.

The current work indicates that real-time detection of FOG using CWT of acceleration data is attainable with a small window length of 2 s and the larger update time of 1 s using the single shank sensor. Since a single shank sensor did not interfere with walking and was placed easily, it facilitated gait analysis as well as real-time FOG detection. Although the requirements for FOG detection were well resolved, future studies should implement and examine the utility of this method in real-time detection of FOG and associated feedback stimulations. In other words, future studies should implement this method in a real time fashion to validate the results. One of the limitations of this work was that the data-sets were demarcated as only freezing and non-freezing conditions, limiting the details about non-freezing conditions such as walking, standing, and turning. Given this information, detection of FOG events could be better ascertained by characterizing and distinguishing other non-freezing features/activities prior to applying CWT.

CHAPTER 4: MOTOR SUBTYPES OF PARKINSON'S DISEASE CAN BE IDENTIFIED BY FREQUENCY COMPONENT OF POSTURAL STABILITY

Abstract

Parkinson's disease (PD) can be divided into two subtypes based on clinical features—namely tremor dominant (TD) and postural instability and gait difficulty (PIGD). This categorization is important at the early stage of PD, since identifying the subtypes can help to predict the clinical progression of the disease. Accordingly, correctly diagnosing subtypes is critical in initiating appropriate early interventions and tracking the progression of the disease. However, as the disease progresses, it becomes increasingly difficult to further distinguish those attributes that are relevant to the subtypes. In this study, I investigated whether a method using the standing center of pressure (COP) time series data can separate two subtypes of PD by looking at the frequency component of COP (i.e., COP position and speed). Thirty-six participants diagnosed with PD were evaluated, with their bare feet on the force platform, and were instructed to stand upright with their arms by their sides for 20 s (with their eyes open and closed), which is consistent with the traditional COP measures. Fast Fourier transform (FFT) and wavelet transform (WT) were performed to distinguish between the motor subtypes using the COP measures. The TD group exhibited larger amplitudes at the frequency range of 3–7 Hz when compared to the PIGD group. Both the FFT and WT methods were able to differentiate the subtypes. COP time series information can be used to differentiate between the two motor subtypes of PD, using the frequency component of postural stability.

4.1 Introduction

In 2010, approximately 630,000 people in the U.S. were diagnosed with Parkinson's disease (PD), a number estimated to double by 2040 (Kowal et al. 2013). PD is a progressive neurodegenerative disorder which includes motor and non-motor features (Fahn et al. 2011). PD can be further divided into two subtypes based on clinical features: tremor dominant (TD), and postural instability and gait difficulty (PIGD) (Chen et al. 2015; Fahn et al. 2011; Thenganatt & Jankovic 2014; Jankovic et al. 1990a). This categorization is predominant at the early stage of PD since identifying PD subtypes can help to predict the clinical progression of the disease. Several studies have confirmed that the PIGD subtype has a faster disease progression, greater motor function impairment (Jankovic & Kapadia 2001a), and is less responsive to levodopa and deep brain stimulation compared to the TD subtype (Jankovic et al. 1990a; Rajput et al. 1993; Mehanna & Lai 2013; Chen et al. 2015). It has also been reported that there is a correlation between freezing of gait score and PIGD score (Rajput et al. 1993). Additionally, the PIGD subtype can place PD patients at a higher risk for falls compared to TD patients (Rudzińska et al. n.d.). It has been shown that PIGD patients have worse postural control in compare to TD patients (Rudzińska et al. n.d.; Herman et al. 2013). Accordingly, correctly diagnosing subtypes can help caregivers to initiate early amenable interventions and track the progression of the disease. Note that diagnosis would not lead to a different medical treatment. However, another treatment needs to be taken for PIGD patients to reduce loss of balance and fall along with medical treatment since dopaminergic medications may result in limited improvement in postural instability and gait (Stebbins et al. 2013). Thus, diagnosis specifically leads to which path should be taken for the patient to manage symptoms.

Differentiation of TD from PIGD is currently based on sub-scores of the Unified Parkinson's Disease Rating Scale (UPDRS) (Stebbins et al. 2013; Chen et al. 2015). The UPDRS is scored by clinicians and is subjective and prone to error (Mds et al. 2003). Subtype-specific biomarkers may improve the accuracy of diagnoses relevant to PD subtypes and PD progression.

Center of pressure (COP) measure, which is widely employed in assessing postural control, has been utilized for analyzing the disease-related features in PD patients (Schlenstedt et al. 2016; Schmit et al. 2006; Rocchi et al. 2006; Diab et al. 2014). Results of different studies have showed that COP was more variable for PD patients relative to control participants (Schmit et al. 2006; Rocchi et al. 2006) and COP derived velocity were abnormally large for PD patients with freezing of gait in compare to the patients without FOG (Schlenstedt et al. 2016). Thus, COP is considered as a good measure that can represent PD disease-related postural characteristics.

PD tremor is present at the rest and typically dampened with kinetic movement. So, proposing a static test sounds more appropriate in compare to a dynamic task to distinguish between two subtypes (Hallett 1998). Several studies have reported a frequency range of 3-7 Hz for PD tremor (Hallett 1998; Lemstra et al. 1999; Timmermann et al. 2003). It is also demonstrated that the whole body Center Of Pressure (COP) signal has a frequency lower than 2 Hz (Freitas et al. 2005; Vieira et al. 2009; Kanekar et al. 2014). Subtype-specific postural instability in PD may be better identified by the frequencies that make up the COP signal. I hypothesized that the whole body COP frequency may be a better and more objective means of identifying PD subtypes. The most common method to investigate the tremor in PD is Fast Fourier Transformation (FFT) (Jankovic et al. 1990b; Jankovic &

Kapadia 2001b). This mathematical technique transfers a signal from the time domain to the frequency domain. In this method all time information is lost after the transformation. So, a method like wavelet transformation (WT) which includes both time and frequency information of the signal (Rajput et al. 1993) might help to diagnose subtypes better than FFT.

4.2 Method

4.2.1 Participants

Thirty-six participants that were diagnosed with PD by specialists at the Muhammad Ali Parkinson Center at the Barrow Neurological Institute (Phoenix, AZ, USA) were recruited for this study. The participants' demographic information is presented in Table 4.1. The Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) was employed to identify the TD and PIGD groups (Goetz et al. 2008). The designated items for TD (kinetic and postural tremor in both the right and left hand; tremor—while at rest—of either the face and lips or the chain, arms, and legs) and PIGD (freezing, walking, posture, gait, and postural stability) were used to calculate the mean TD and PIGD scores. The ratio of the mean TD score to the mean PIGD score was used to identify the TD group. The patients with a ratio greater than or equal to 1.5 were classified as TD, while those with a ratio less than or equal to 1.0 were classified as PIGD. The patients with ratios ranging from 1.0 to 1.5 were classified as mixed-type, and were considered as an exclusionary criterion for this study (Stebbins et al. 2013; Jankovic et al. 1990b; van der Heeden et al. 2016).

Table 4.1. Demographics of the tremor dominant (TD) and postural instability and gait difficulty (PIGD) groups (mean ± standard deviation—SD). MDS-UPDRS: Movement Disorder Society-Unified Parkinson's Disease Rating Scale.

	TD (n=13)	PIGD (n=23)
Gender (F:M)	0:13	9:14
Age (years)	59.92±9.63	70.43±6.18
Disease duration (month)	20.23±19.14	37.78±54.69
MDS-UPDRS III (ON)	14.85±9.85	15.08±8.48

The study was approved by the Institutional Review Board at the Barrow Neurological Institute and Arizona State University, Tempe, AZ, USA. The participants provided informed consent prior to their inclusion in the study. All of the assessments were performed while subjects were in the "on" medication status—approximately 1 to 1.5 h after taking the PD medication.

4.2.2 Experimental Procedure

The participants were placed with their bare feet on the force platform and were instructed to stand upright with their feet shoulder width apart and their arms by their sides for 20 s, and look straight ahead during the experiment. They were instructed not to talk or bend their knees throughout the experimental trials. Harnesses were fitted onto the participants to avoid falls. This task was performed under two conditions—namely eyes open and eyes closed. For the eyes closed condition, the subjects were asked to close their eyes during the experiment. Each participant performed the experiment under both conditions. Each condition had three trials.

4.2.3 Data Analysis

COP data were derived using force plate data sampled at 100 Hz. Both anterior–posterior (AP) and medial–lateral (ML) COP data were low-pass-filtered using a fourth-order, zero lag Butterworth filter with a cut-off frequency of 10 Hz. Five traditional COP measures were calculated to assess whether or not the two subtypes of PD can be distinguished by using the time domain information. The measures included the following: COP range (the range of COP displacement), resultant COP path length (the total COP trajectory length), resultant mean velocity (the resultant path length divided by the total duration), and a 95% confidence ellipse area (the smallest ellipse that will cover 95% of the points of the COP diagram). Based on previous studies, these traditional parameters are good indicators of postural instability (Schmit et al. 2006; Cavalheiro et al.) and were considered as variables that might help us to distinguish PIGD from TD. All of the analyses were performed in MATLAB version 2015a.

4.2.4 TD vs. PIGD Detection Method

In order to distinguish between the TD and PIGD subtypes, the following two methods were utilized: fast Fourier transform (FFT) and wavelet transform (WT). In the FFT method, the PD subtypes were identified by the frequency spectra of COP signals. Two frequency bands were introduced (Rezvanian et al. 2016; Mojtahedi et al. 2015; Rezvanian et al. 2017): the COP band and the tremor band. The COP and tremor bands were defined as the frequency components from 0–3 Hz to 3–7 Hz, respectively. The detection method was defined as the ratio of the area under the power spectra of the tremor band to the summation of the areas under the power spectra of the COP band and the tremor band. COP data were transformed into the wavelet domain using daubechies mother wavelet (db6). It was chosen because it has been widely employed in different human posture and movement studies (Rezvanian et al. 2016; Lockhart et al. 2013). Various mother wavelets were also applied to ensure that the optimal selection was made appropriately. The results supported the notion that daubechies mother wavelet was the best choice. In the WT method, the COP and tremor bands were defined as the scales that corresponded to the frequency ranges of 0–3 Hz and 3–7 Hz, respectively. The detection method was defined in a similar manner to the way it was defined in the FFT method: the ratio of the averaged WT coefficients of the tremor band to the summation of the averaged WT coefficients of the COP band and the tremor band. This ratio was unit-less because it was a ratio of values with the same unit. In both methods, the defined ratio was multiplied by 100 in order to obtain a value between 0 and 100. Values that were closer to 100 indicated a higher possibility of the TD subtype, while the possibility of the PIGD subtype increased as the values approached 0. The first time derivative of COP time series was defined as COP velocity (V-COP). The ratio that was defined above was applied to COP (RCOP) and COP velocity (RVCOP) in both the AP and ML directions.

4.2.5 Statistical Analysis

Analysis of variance (ANOVA) with repeated measures on the traditional COP measures and the proposed detection ratio (using both the FFT and WT methods) were performed. Different factors—such as condition (two levels: eyes open (EO) and eyes closed (EC)) and group (or subtype) of PD (two levels: TD and PIGD)—were considered as within-subject and between-subject factors, respectively. Comparisons of interest exhibiting statistically significant differences ($p < 0.05$) were further analyzed using post hoc tests with Bonferroni corrections. In all analyses, sphericity assumptions were tested (Greenhouse–Geisser analysis). The diagnostic performance of the proposed method—or the accuracy of a test to discriminate between the subtypes—was further evaluated using receiver operating characteristic (ROC) curve analysis [31] for the directions and factors of both methods. In a ROC curve, the true positive rate (sensitivity) is plotted as a function of the false positive rate (100—specificity) at different cut-off points. Therefore, each point on the ROC curve corresponds to a sensitivity/specificity pair for a particular decision threshold. Therefore, the upper-left corner denotes a test with perfect discrimination (no overlap in the two distributions) in a ROC curve analysis. Accordingly, the closer the ROC curve is to the upper-left corner, the higher the overall accuracy of the test (Zweig & Campbell 1993). In this study, PD subtypes were diagnosed by utilizing UPDRS and were considered as a correct diagnosis. All of the statistical analyses were performed based on this assumption. In all tests, $p < 0.05$ was considered as a significant level. Statistical analyses were performed using IBM SPSS Statistics 22.

4.3 Results

The results of the traditional COP measures—under both the eyes open and eyes closed conditions—are provided in Table 4.2. All of the variables had larger values in the eyes closed condition compared to the eyes open condition. Because these parameters did not have a normal distribution, a Box-Cox transformation was applied and parametric methods were performed. There was no significant difference between the two groups for all the variables. However, there was a significant difference between the conditions for all of the parameters (range AP: $F_{(1,34)} = 4.252$, $p = 0.047$; range ML: $F_{(1,34)} = 60.34$, $p = 0.001$; path length: $F_{(1,34)} = 29.797$, $p = 0.001$; mean velocity: $F_{(1,34)} = 29.795$, $p = 0.001$; area: $F_{(1,34)} = 11.847$, $p = 0.002$).

Table 4.2. Selected postural stability parameters. Range anterior–posterior (AP): center of pressure (COP) range in the AP direction, range medial–lateral (ML): COP range in the ML direction, path length: resultant COP path length, mean velocity: resultant COP mean velocity, and area: 95% ellipse area. The symbols * or ** denote which of the two variables were significantly different at each parameter ($p < 0.05$).

		Range AP (cm)	Range ML (cm)	Mean velocity (cm/s)	Path Length (cm)	Area (cm^2)
Eyes open	TD	0.81±0.15*	1.49±0.10*	1.46±0.27*	29.28 ±5.49*	0.92±0.22*
	PIGD	1.06±0.13**	1.81±0.16**	1.48±0.23**	29.62±4.57**	1.53±0.32**
Eyes closed	TD	1.15±0.24*	2.81±0.39*	2.56±0.66*	51.23±13.16*	2.95±1.05*
	PIGD	1.14±0.14**	2.75±0.36**	2.01±0.20**	40.23±4.01**	2.51±0.45**

A power spectral analysis of the COP and COP velocity of a TD patient and a PIGD patient are plotted in Figure 4.1, revealing that both patients had frequency components ranging from 0 to 2 Hz in their COP and COP velocity signals. However, only the TD patient had an increase in power spectrum in the frequency band of 3–7 Hz. This increase was larger in the ML direction.

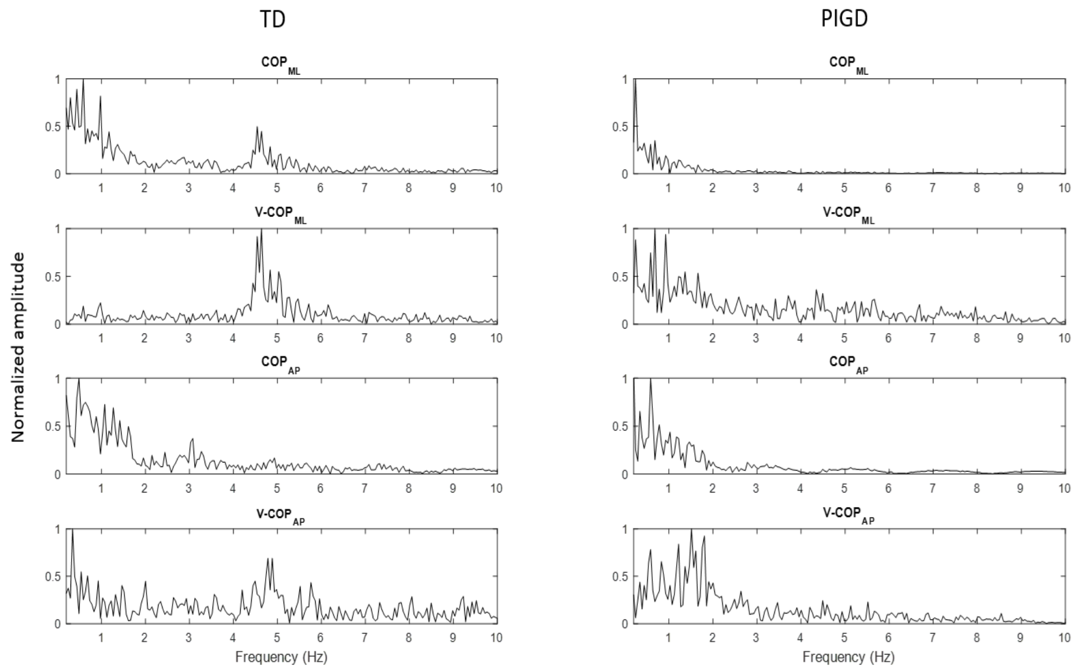

Figure 4.1. Power spectrum of COP and COP velocity of a tremor dominant (TD) patient and a postural instability and gait difficulty (PIGD) patient for both the medial–lateral (ML) and anterior–posterior (AP) directions. The graphs on the left and right sides of the page present the power spectrum signal of a TD patient and a PIGD patient, respectively. COP_{ML}: COP in the ML direction, COP_{AP}: COP in the AP direction, V-COP_{ML}: COP velocity in the ML direction, and V-COP_{AP}: COP velocity in the AP direction.

The WT of COP and COP velocity of a TD patient and a PIGD patient in both the ML and AP directions are plotted in Figure 4.2. The horizontal white lines in each figure indicate the PD tremor scale range corresponding to the frequency range of 3–7 Hz. The WT coefficients in Figure 2 display relatively larger values in the PD tremor scale range (i.e., lighter blue values appeared in between two horizontal white lines) for the TD patient when compared to the PIGD patient. Similar to the power spectral analysis (Figure 4.1), these increases were larger in the ML direction.

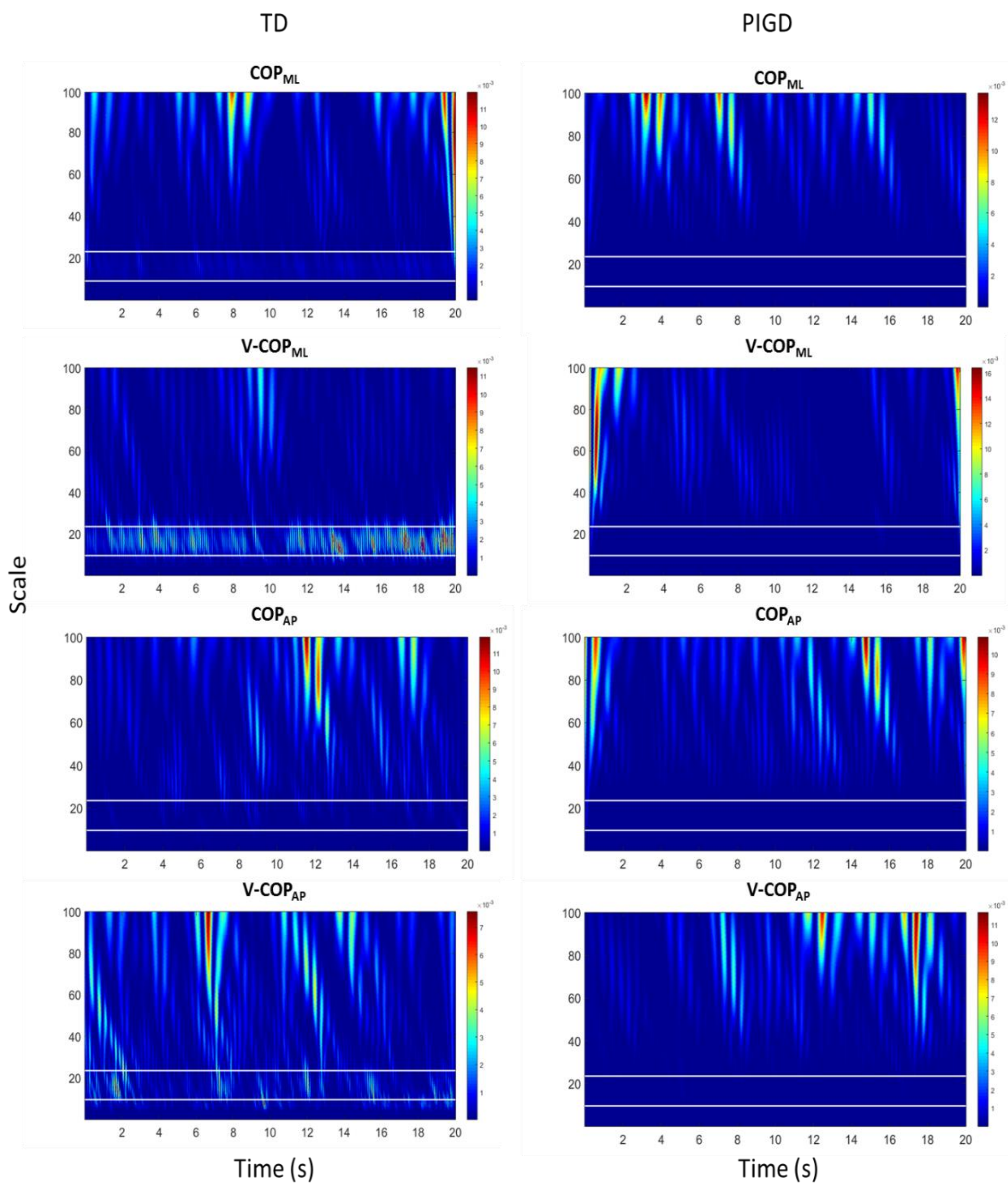

Figure 4.2. Wavelet transform (WT) of COP and COP velocity of a TD patient and a PIGD patient for both the ML and AP directions. The horizontal white lines in each plot indicate the PD tremor scale range corresponding to the frequency range of 3–7 Hz. The frequencies of 3 Hz and 7 Hz correspond to the scales of 24 and 10, respectively. COPML: COP in the ML direction, COPAP: COP in the AP direction, V-COPML: COP velocity in the ML direction, and V-COPAP: COP velocity in the AP direction.

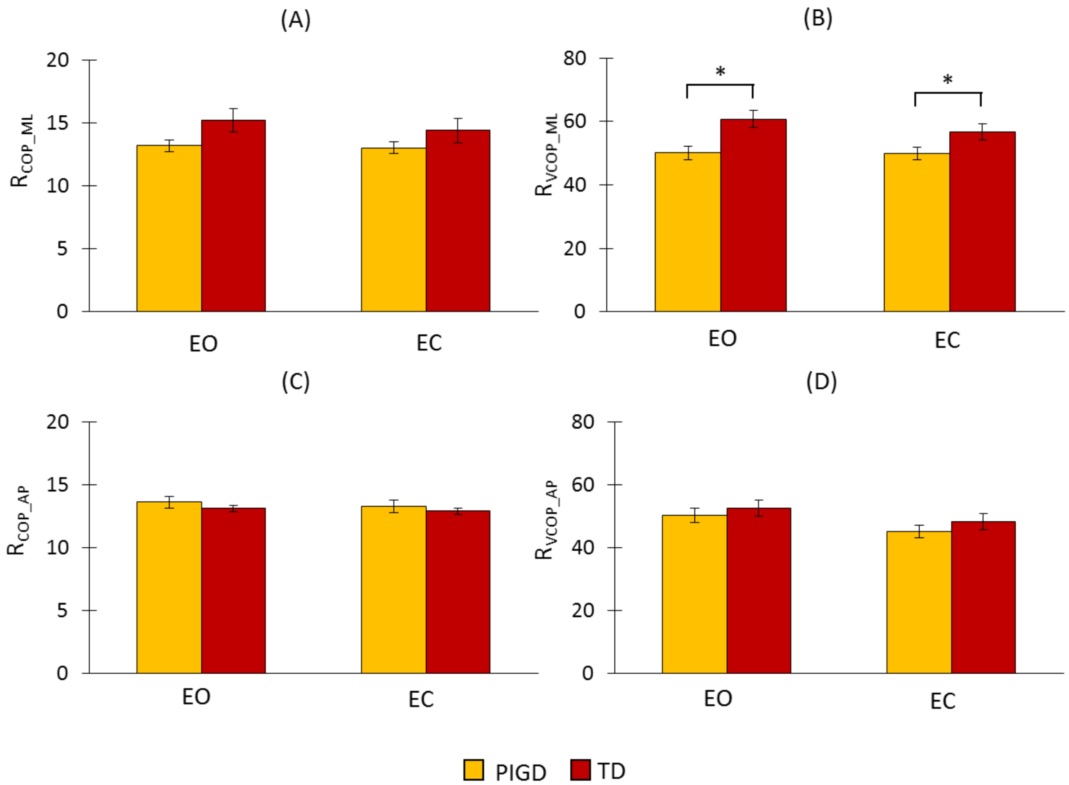

Figure 4.3. The results of proposed detection ratio for FFT method for COP and its velocity and for both medial-lateral (ML) and anterior-posterior (AP) directions. (A) R_{COP_ML}: detection ratio using COP data in medial-lateral direction, (B) R_{VCOP_ML}: detection ratio using COP velocity data in medial-lateral direction, (C) R_{COP_AP}: detection ratio using COP data in anterior-posterior direction, and (D) R_{VCOP_AP}: detection ratio using COP velocity data in anterior-posterior direction. The asterisks (*) placed over the vertical bars show that a significant difference ($p < 0.05$).

The results of the proposed detection ratio for COP and its velocity in both directions using FFT are presented in Figure 4.3. Neither the ratio of COP (R_{COP_ML}) nor its velocity (R_{VCOP_ML}) in the ML direction were significantly different across the different conditions (R_{COP_ML}: $F_{(1,34)} = 2.006$, $p = 0.112$; R_{VCOP_ML}: $F_{(1,34)} = 2.67$, $p = 0.112$). However, a statistically significant difference in R_{VCOP_ML} across the groups ($F_{(1,34)} = 7.978$, $p = 0.008$) was observed, although no significant difference was found in R_{COP_ML}

($F_{(1,34)}$ = 3.449, p = 0.072). In both R_{COP_ML} and R_{VCOP_ML}, there was no significant interaction between the condition and the group (R_{COP_ML}: $F_{(1,34)}$ = 1.181, p = 0.285; R_{VCOP_ML}: $F_{(1,34)}$ = 2.037, p = 0.163). R_{VCOP_ML} was larger for the TD group than for the PIGD group (Figure 4.3-A,B). This indicated that there were larger amplitudes in the frequency range of 3–7 Hz in this group. In the AP direction, there was no significant difference across the groups (R_{COP_AP}: $F_{(1,34)}$ = 0.498, p = 0.485; R_{VCOP_AP}: $F_{(1,34)}$ = 0.628, p = 0.433) and the conditions (R_{COP_AP}: $F_{(1,34)}$ = 1.306, p = 0.201; R_{VCOP_AP}: $F_{(1,34)}$ = 3.45, p = 0.08) in both R_{COP_AP} and R_{VCOP_AP}.

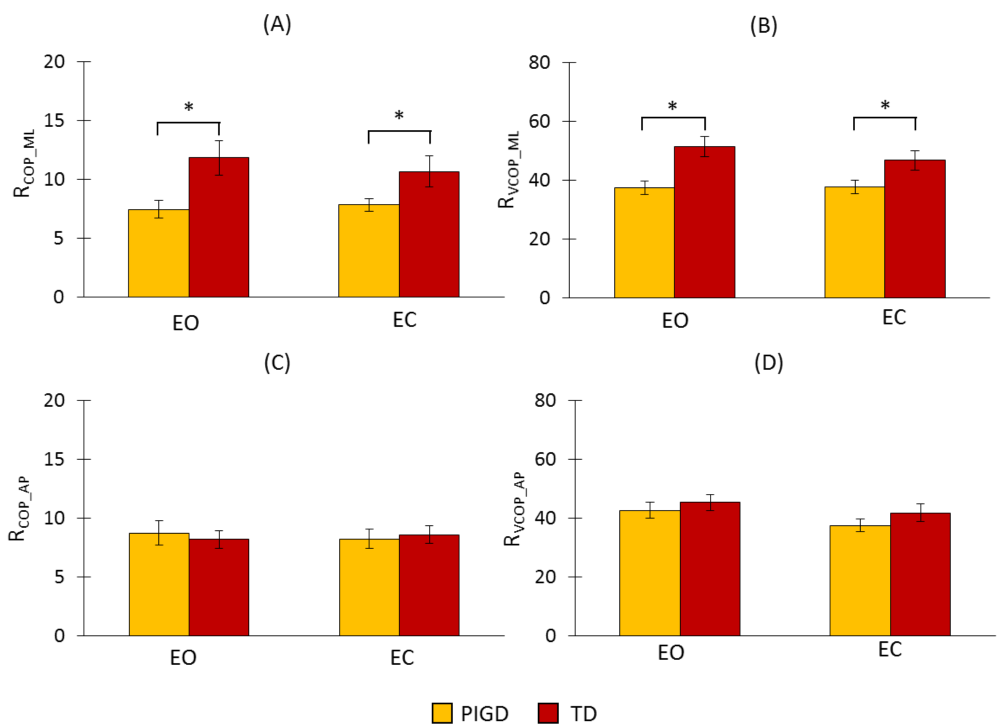

Figure 4.4. The results of proposed detection ratio for WT method for COP and its velocity and for both medial-lateral (ML) and anterior-posterior (AP) directions. (A) R_{COP_ML}: detection ratio using COP data in medial-lateral direction, (B) R_{VCOP_ML}: detection ratio using COP velocity data in medial-lateral direction, (C) R_{COP_AP}: detection ratio using COP data in anterior-posterior direction, and (D) R_{VCOP_AP}: detection ratio using COP velocity

data in anterior-posterior direction. The asterisks (*) placed over the vertical bars show that a significant difference ($p < 0.05$).

The explained WT method was applied to COP and its velocity in both directions. The results are presented in Figure 4.4. I found a significant difference between the groups for R_{COP_ML} and R_{VCOP_ML} (R_{COP_ML}: $F_{(1,34)} = 7.589$, $p = 0.009$; R_{VCOP_ML}: $F_{(1,34)} = 10.066$, $p = 0.003$), but no significant difference between the conditions (R_{COP_ML}: $F_{(1,34)} = 0.373$, $p = 0.814$; R_{VCOP_ML}: $F_{(1,34)} = 2.5$, $p = 0.123$). There was no significant interaction between the conditions and the groups (R_{COP_ML}: $F_{(1,34)} = 3.044$, $p = 0.09$; R_{VCOP_ML}: $F_{(1,34)} = 2.828$, $p = 0.102$). Both R_{COP_ML} and R_{VCOP_ML} had larger values for the TD group than for the PIGD group (Figure 4.3-A,B). These increases occurred because of the larger amplitude values in the scales corresponding to the frequency range of 3–7 Hz. In the AP direction, there were no significant differences across the groups (R_{COP_AP}: $F_{(1,34)} = 0.004$, $p = 0.952$; R_{VCOP_AP}: $F_{(1,34)} = 0.854$, $p = 0.362$) or conditions (R_{COP_AP}: $F_{(1,34)} = 0.011$, $p = 0.916$; R_{VCOP_AP}: $F_{(1,34)} = 3.047$, $p = 0.091$) in both R_{COP_AP} and R_{VCOP_AP}.

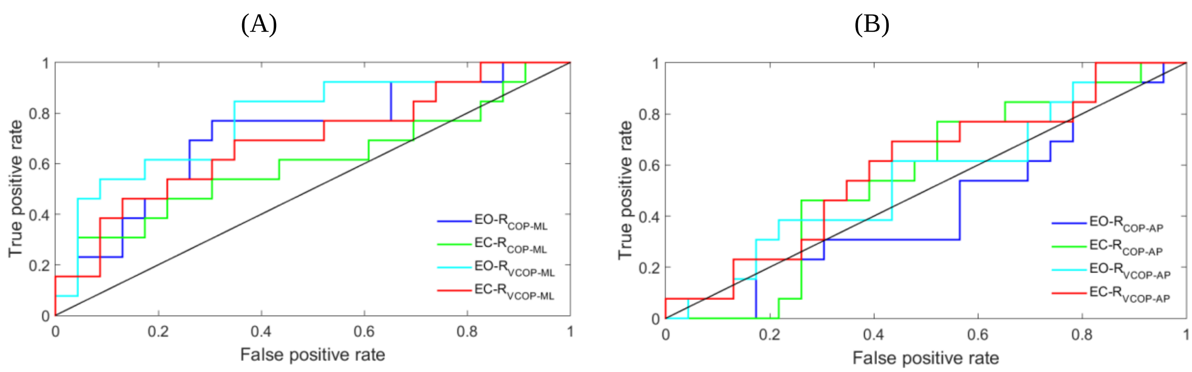

Figure 4.5. Receiver operating characteristic (ROC) curves of proposed detection ratio using FFT method for COP and its velocity; (A) medial-lateral (ML) direction, (B) anterior-posterior (AP) direction. EO-R_{COP_ML}: detection ratio using COP data in ML direction in eyes open condition, EC-R_{COP_ML}: detection ratio using COP data in ML direction in eyes closed condition, EO-R_{VCOP_ML}: detection ratio using COP velocity data

in ML direction in eyes open condition, EC-R_{VCOP_ML}: detection ratio using COP velocity data in ML direction in eyes closed condition, EO-R_{COP_AP}: detection ratio using COP data in AP direction in eyes open condition, EC-R_{COP_AP}: detection ratio using COP data in AP direction in eyes closed condition, EO-R_{VCOP_AP}: detection ratio using COP velocity data in AP direction in eyes open condition, EC-R_{VCOP_AP}: detection ratio using COP velocity data in AP direction in eyes closed condition.

The ROC curves of the proposed detection ratio for COP and its velocity in both directions and under both conditions are plotted in Figures 4.5 and 4.6 for the FFT and WT methods, respectively. In both methods, the ROC curves were closer to the upper-left corner in the ML direction than they were in the AP direction, which indicated a higher overall accuracy of the test in the ML direction (Zweig & Campbell 1993).

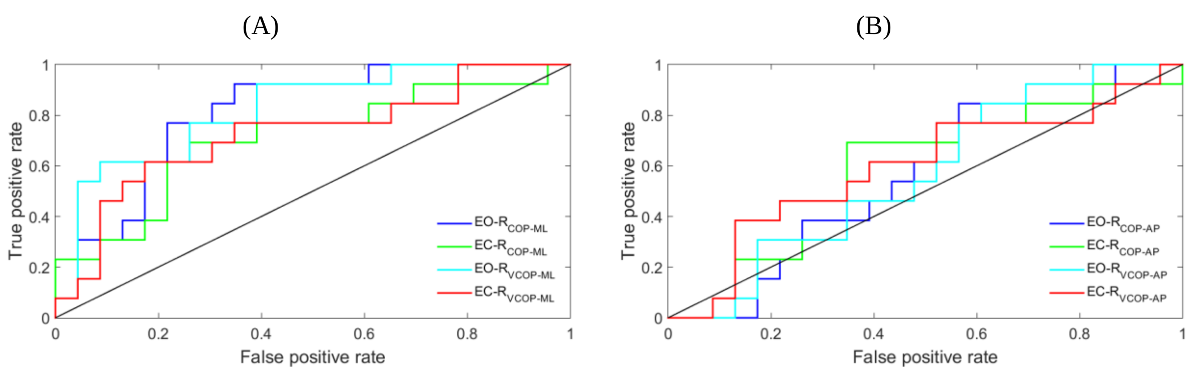

Figure 4.6. Receiver operating characteristic (ROC) curves of proposed detection ratio using WT method for COP and its velocity; (A) medial-lateral (ML) direction, (B) anterior-posterior (AP) direction. EO-R_{COP_ML}: detection ratio using COP data in ML direction in eyes open condition, EC-R_{COP_ML}: detection ratio using COP data in ML direction in eyes closed condition, EO-R_{VCOP_ML}: detection ratio using COP velocity data in ML direction in eyes open condition, EC-R_{VCOP_ML}: detection ratio using COP velocity data in ML direction in eyes closed condition, EO-R_{COP_AP}: detection ratio using COP data in AP direction in eyes open condition, EC-R_{COP_AP}: detection ratio using COP data in AP direction in eyes closed condition, EO-R_{VCOP_AP}: detection ratio using COP velocity data in AP direction in eyes open condition, EC-R_{VCOP_AP}: detection ratio using COP velocity data in AP direction in eyes closed condition.

The ROC curves were further analyzed by calculating areas under each curve. Results were presented in Table 4.3. Only COP velocity data in ML direction could significantly discriminate between two subtypes using FFT method. Results of area under the ROC curves also showed that WT method could significantly discriminate two subtypes by using either COP or COP velocity data in ML direction regard less of eyes conditions.

Table 4.3. Area under the ROC curves of proposed detection ratio for COP and its velocity for both FFT and WT methods, medial-lateral (ML) and anterior-posterior (AP) directions, and two conditions; Eyes open (EO) and eyes closed (EC). Significance levels or P-values of each value are presented in parenthesis. The asterisks (*) indicates the area under the ROC curve is significantly different from 0.5 ($p < 0.05$).

		FFT		**WT**	
		COP	V_COP	COP	V_COP
ML-Direction	EO	0.689 (p=0.05)	0.779 * (p=0.001)	0.809 * (p=0.001)	0.823 * (p=0.001)
	EC	0.602 (p=0.343)	0.712 * (p=0.023)	0.706 * (p=0.033)	0.726 * (p=0.016)
AP-Direction	EO	0.562 (p=0.542)	0.555 (p=0.5873)	0.562 (p=0.529)	0.569 (p=0.482)
	EC	0.555 (p=0.578)	0.592 (p=0.358)	0.579 (0.442)	0.595 (p=0.363)

4.4 Discussion

The present study addressed subtype-specific biomarkers to classify the inherent heterogeneity of Parkinson disease. This categorization can help to predict the clinical progression of the disease. Thus, correctly diagnosing subtypes can assist caregivers to initiate early amenable interventions and manage symptoms. The COP time series of PD patients were analyzed to distinguish the subtypes of PD. To the best of my knowledge, this study is the first to attempt to objectively diagnose TD and PIGD subtypes of PD. Postural stability is maintained through neuromuscular feedback loops and open loop control processes that constantly adapt to internal and external perturbations (Y.-C. Pai et al. 2003; Nallegowda et al. 2004). Utilizing specific statistical and numerical tools, these control mechanisms can be quantified to identify neuromuscular changes that occur with pathology. Thus, traditional linear postural measures and Fourier transformation were applied to the COP time series and the increment of the COP time series both in the AP and ML directions. Furthermore, to quantify the changes in COP dynamics that occur at multiple timescales, a wavelet transform was employed to infer the underlying nature and control mechanisms involved in balance maintenance and disease state.

Traditional measures of postural sway, parameters that denote the magnitude of postural movements, were unable to discriminate the TD and PIGD subtypes (Table 2). However, when visual information was occluded a coincident decrease in postural stability was reflected in both subtypes for the linear postural measures i.e., COP range, mean velocity, path length, and 95% confidence ellipse area; results consistent with previous investigations regarding postural stability in PD patients (Błaszczyk et al. 2007).

Both power spectral density and wavelet transform of the COP time series and its velocity (Figure 1. and 2) revealed an increase in the 3-7 Hz frequency range of the TD group; a frequency spectra reportedly symptomatic of parkinsonian tremor (Hallett 1998; Lemstra et al. 1999; Timmermann et al. 2003). In fact, the ML COP data exhibited greater frequency content than the AP COP, which is consistent with previous investigations that reported PD patients exhibited increased ML sway amplitude, decreased AP sway amplitude and, possibly, postural inflexibility in the AP direction. (Mitchell et al. 1995; van Wegen et al. 2001; Rocchi et al. 2006; Viitasalo et al. 2002). In this context, the preponderance of the ML frequency in the ML direction coupled with the impaired movement in the AP direction suggests an underlying postural inflexibility in PD patients, where the tremor reflected in the ML time domain may be a consequence of the AP direction's inability to contain movements in a higher frequency range (Mitchell et al. 1995; Horak et al. 1992; Schieppati et al. 1994). The proposed ratio wasn't able to show a statistically significant difference between TD and PIGD patients in the AP direction using both methods, even accounting for both the COP and the COP velocity. The reason was that tremor frequency had larger amplitude in ML direction in compare to AP direction as it was shown in the Figure 1 and 2. However, both the FFT and WT methods were able to discriminate TD from PIGD patients using the ML-COP velocity signal, but only the WT method was able to specify the subtype with the COP position time-series was utilized. This could be explained by the fact that FFT method used only frequency information of signals while WT method employed both frequency and time components. Utilized information of signals by WT enabled us to specify subtypes of PD by using both COP and COP velocity. Additionally, FFT showed a significant results when it employed COP velocity not COP in itself. The reason was that a velocity of a signal was a first derivation of the signal which showed more variation of signal. In this way, FFT could assess more information about signals when it employed its velocity. The results of the proposed method was consistent across both conditions (EO and EC) and for both methods (FFT and WT). This consistency indicated the strength of the proposed diagnostic method by using the proposed ratio. Although, proposed method can diagnose TD from PIGD subtypes, further studies are needed to define the threshold value ranges which can classify the patients.

CHAPTER 5: THE EFFECTS OF DIFFERENT TYPES OF PERTURBATION TRAINING ON DYNAMIC STABILITY AND COMPLEXITY

Abstract

Our motor patterns are adaptable to unpredictable changes or perturbations in various environments during different activities (e.g. standing or walking). Unexpected perturbation-based training (PBT) is an intervention method which shows promising results in regard to improving balance and reducing falls. Although PBT has shown promising results, the efficacy of such interventions in improving dynamic stability during walking remains to be evaluated. Numerous studies have reported the improvement in some measures of the reactive recovery responses after the training which might not be transferable to another type of perturbations. In other words, there was paucity of data revealing the effects of PBT on improving dynamic stability of walking and flexible gait adaptability. As such, an experiment was conducted to assess the effects of treadmill delivered translational perturbations training on improving dynamic stability while walking, and adaptability of locomotor system in resisting the perturbations (via evaluating dynamic stability as measured by nonlinear measures of stability and movement complexity as measured by entropy analysis). Three types of PBT were evaluated; medial-lateral (ML), slip-like, and mix (including both medial-lateral and slip-like ones) perturbations. Seventy two participants were randomly assigned into four experimental groups: NPT (control group-receiving no PBT), MLPT (receiving only ML PBT), SPT (receiving only slip-like PBT), and MPT (receiving both ML and slip-like PBT). Results indicated that all types of perturbation training protocols improved dynamic stability as compared to one's prior training level. Additionally, PBT was able to increase the

complexity of the movement and consequently improve flexible gait adaptability. Improved stability and flexible adaptation appear to be brought on by reducing the stiffness of lower extremities as measured by EMG muscle co-contraction index. Understanding the effects of different directional perturbations on gait stability and complexity will pave the way to developing a better intervention for those who are at a higher risk of losing balance and falls as a result of gait instability.

5.1 Introduction

Previous studies have shown that humans are adaptable to unpredictable changes or perturbations in environment during different activities, such as standing or walking (Bhatt et al. 2006; Nashner 1976; Horak et al. 1989; Owings et al. 2001; Parijat & Lockhart 2012). This adaptation is developed by repeating movements in the presence of an external perturbation to reconstruct the performance of a task when external perturbations exist (Pai & Bhatt 2007). Unexpected perturbation-based training (PBT) has been proposed based on this notion and shows promising results in regards to reducing the incidence of loss of balance and falls (Mansfield et al. 2015; Mccrum et al. 2017).

In this training method, individuals were exposed to repeated postural perturbations during walking. PBT not only enhances reactions to balance loss with practice but also enriches neuro-mechanical control of stability to prevent balance loss and falls (Pai & Bhatt 2007). A decrease in occurrence of falls in the laboratory from the pre- to post-perturbation training has been reported (Parijat & Lockhart 2012; Y. C. Pai et al. 2014; Tanvi et al. 2012; Mansfield et al. 2015; McCrum et al. 2017). Different studies have shown that there are improvement in control of voluntary movements (Rogers et al. 2003), an increase in the speed of balance reaction (Parijat & Lockhart 2012; Tanvi et al. 2012; Mansfield et al. 2010), and improvement in some measure of the reactive recovery response to perturbations (e.g., recovery step) (Parijat & Lockhart 2012; Y. C. Pai et al. 2014; Tanvi et al. 2012; Lurie et al. 2013; Pai et al. 2010; Bierbaum & Peper 2010; Bierbaum et al. 2011; Mansfield et al. 2015). PBT also shows positive outcomes within the field of athletic training. It yields promising results in performance, preventing injury, and rehabilitation (mainly athletes with knee injuries) (Zech et al. 2010). Rehabilitation with PBT also helps individuals to return to functional activity sooner and maintains their functional status for longer periods as compared to the standard rehabilitation program (Hurd et al. 2006; Chmielewski et al. 2005; Fitzgerald et al. 2000; Rudolph et al. 2000; Williams et al. 2001; Zech et al. 2010).

Although PBT has shown promising results, the efficacy of such interventions is not well understood and evaluated. Most of studies report the improvement in some measures of the reactive recovery responses after the training which may not be transferable to another type of perturbations. In other words, there is paucity of data revealing the effects of PBT on improving dynamic stability of walking and flexible gait adaptability. Additionally, most of the studies applied perturbations while subjects walked over-ground by utilizing the method of movable platform perturbations occurring at the same place which may lead to proactive walking pattern limiting the understanding of the true characteristics associated with motor learning (Y. C. Pai et al. 2014; Parijat & Lockhart 2012).

In this study, dynamic stability as measured by nonlinear measures of stability (maximum Lyapunov exponent) and movement complexity as measured by entropy analyses were evaluated to assess the effects of treadmill delivered translational perturbations training on improving dynamic stability while walking, and adaptability of locomotor system in resisting to perturbations. Previous studies have shown that gait stability measures in particular direction have changed in greater extend when a perturbation occurred in the same direction (McAndrew et al. 2011; Young 2011; Martelli et al. 2016). As such, a hypothesis that PBT at a specific direction would considerably improve stability measure at that direction was tested. The objective of this study was to evaluate the effects of medial-lateral (ML) and slip-like perturbation training methods on dynamic stability and gait flexible adaptability. Central hypothesis was that (ML) perturbations would influence ML dynamic stability, and slip-like perturbations would influence anterior-posterior (AP) dynamic stability, and that combination of translations perturbations could improve both ML as well as AP dynamic stability. Furthermore, receiving PBT on treadmill would improve dynamic stability during over-ground walking as well. Finally, PBT would increase complexity and consequently improve gait flexible adaptability. Understanding the effects of different directional perturbations on gait stability and complexity will pave the way to developing a better intervention for those who are at a higher risk of losing balance and falls as a result of gait instability.

5.2 Method

5.2.1 Participants

Seventy two healthy young adults were recruited for the study. A written consent form, approved by the Institutional Review Board (IRB) of Arizona state university, was obtained from the participants before participation. Exclusionary criteria included cardiovascular, respiratory, neurological, and musculoskeletal abnormalities as well as any other difficulties hindering normal gait. Participants were randomly assigned into four experimental groups: NPT (control group-receiving no PBT), MLPT (26 lateral perturbation during PBT), SPT (26 slip-like perturbation during PBT), and MPT (13 ML and 13 slip-like perturbations during PBT). No significant differences were found in the demographics of participants between groups (Table 5.1).

Table 5.1. Participants' demographics (Mean ± SD)

	Group				
	NPT(18)	MLPT (18)	SPT (18)	MPT (18)	P-value
Age (year)	23.43±4.12	22.86±2.73	24.10±3.19	23.86±5.48	0.79
Weight (kg)	71.08±12.16	66.85±10.38	71.14±12.18	64.02±11.79	0.16
Height (m)	1.66±0.09	1.74±0.08	1.71±0.08	1.75±.09	0.15

Note. The P value represents the results of an ANOVA test comparing the groups

5.2.2. Apparatus

For this study, GRAIL system (GRAIL, Motek Medical BV, Netherlands) was used to simulate different perturbations. GRAIL was instrumented with dual-belt treadmill with two force plates underneath of each belt (Figure 5.1.). Synchronized VR environment was projected on a semi-cylindrical screen in front of treadmill. A motion capture system ((Vicon Bonita, Vicon, USA) and wireless EMG system (Delsys Trigno Wireless, Delsys Inc.) were incorporated in this system.

Two types of translational perturbations were employed in this study; slip and ML perturbations (Yang et al. 2013; Hurd et al. 2006). To simulate slip perturbation, the method utilized by Yang et al. has been employed (Yang et al. 2013). Initiation of the perturbation was triggered when right heel contact occurs. The perturbation was provided by the treadmill belt for slip types of perturbation (acceleration in opposite direction ($12 m/s^2$) for 200ms then quickly accelerates to the initial direction ($15\ m/s^2$) and back to specified treadmill speed). During ML perturbation, the entire treadmill moved laterally to the right side with a speed of 0.2 m/s and a displacement of 0.05 m. Treadmill was then returns back to its initial position. These perturbations were initiated by right heel contact (Hurd et al. 2006).

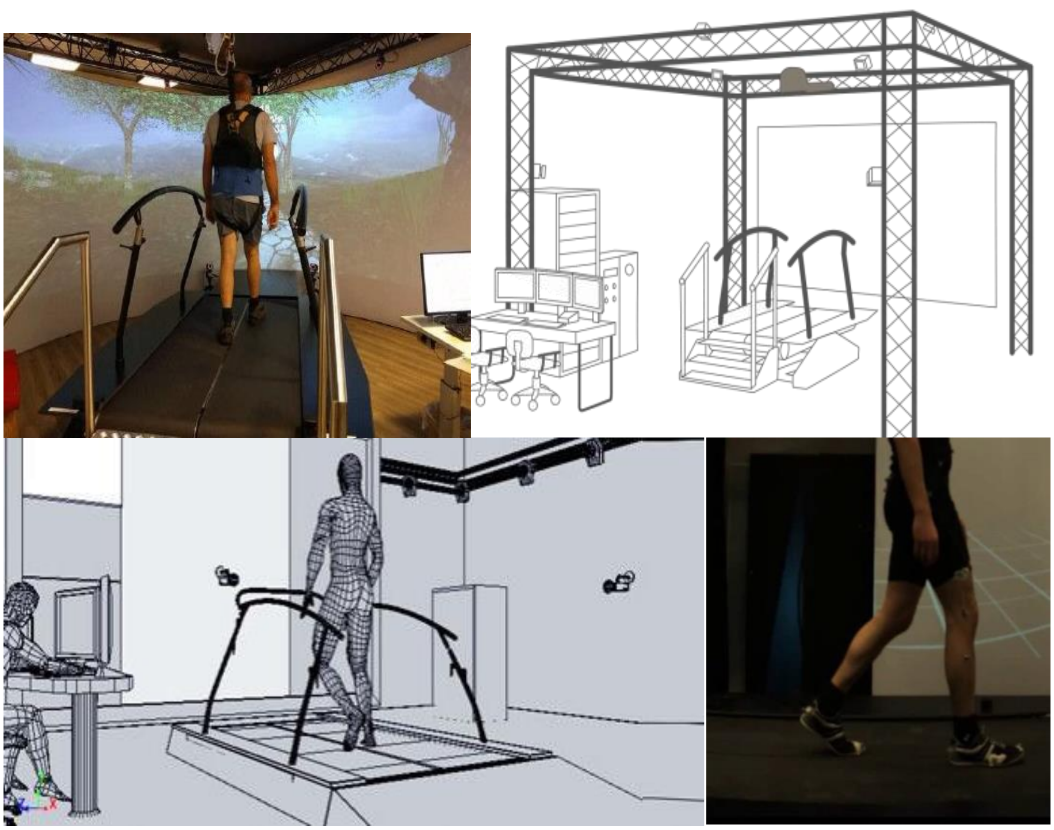

Figure 5.1. Schematic drawing and photo of GRAIL system (Motek medical).

5.2.3 Protocol

All subjects, regardless of group, performed five trials; two over ground walking, two treadmill walking, and one PBT for training groups or just a treadmill walk for control group. Experimental procedure was similar for all groups except for the type of perturbations which they were experienced. At the beginning of the experiment, subjects were asked to walk on a long level indoor walking track at his/her own self-selected walking speed (OG1) and have been instructed “to walk with their regular pace and not to walk very fast or slow”. This was considered as their over-ground walking baseline. In the second trial, subjects walked on treadmill for three minutes (TW1). After this trial, there were a treadmill walking trial with mechanical perturbations for subjects in MLPT, SPT, and MPT groups and no perturbation for participants in control group. Twenty six perturbations with random time intervals were applied. This number was chosen based on the previous studies showing that there were improvement in some measures of the reactive recovery responses or number of falls when they applied about twenty four perturbations in their PBT (Mccrum et al. 2017; Tanvi et al. 2012; Y.-C. Pai et al. 2014; Pai et al. 2010; Y. C. Pai et al. 2014). Participants in MLPT group received 26 lateral perturbations and participants in SPT group experienced 26 slip perturbations during PBT. Perturbations in MPT group included 13 lateral and 13 slip perturbations with random order. At the beginning of this trial, subjects in all groups were informed that they might or might not experience lateral or slip perturbations to prevent any prediction. They were instructed if a perturbation happened, they should try to recover their balance and avoid a fall. After this, subjects again walked on treadmill for another three minutes (TW2). Each subject wore a full-body harness during treadmill walking trial and the length of its tether was set so that, in the event of a fall, the subject's hands and knees would not contact the treadmill surface. Before starting treadmill walking trials, participants were instructed to walk on the treadmill for a few minutes to get familiarized with the harness and GRAIL system. The speed of treadmill's belts was set to the subjects' over ground walking speed. The last trial was another over ground walking similar to the first trial (OG2). Graphical depiction of the experimental procedure was presented in Figure 5.2.

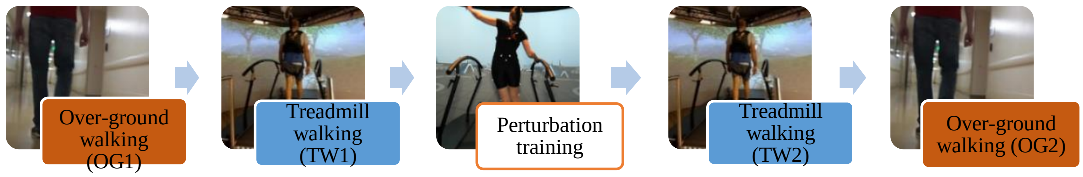

Figure 5.2. Graphical depiction of the experimental procedure.

5.2.4 Measurement

Lower body kinematic were recorded at 100 Hz using a ten-camera motion capture system (Vicon Bonita, Vicon, USA). Reflective markers were placed over participants' bony landmarks to capture gait parameters (van den Bogert et al. 2013) during treadmill walking trials. Subjects were instrumented with 3-D inertial measurement units (IMU – Xsens MTW, Xsens, Netherlands) secured to individuals' sternum with elasticized straps during the whole trials. Its sampling frequency was set to 100 Hz. Six Wireless surface EMG electrodes (Delsys Trigno Wireless, Delsys Inc.) were also placed over Vastus Lateralis (VL), Medial Hamstring (MH), Tibialis Anterior (TA), Medial Gastrocnemius (MG), Gluteus Medius (G-Med), and Gluteus Maximus (G-Max) muscles of right leg to capture muscle activations.

5.2.5 Data Analysis

For dynamic stability and complexity measures, unfiltered data were utilized since the spatio-temporal fluctuations within these signals have been considered for the examination and, to get a more accurate representation of variations within the system (Mees & Judd 1993). To calculate gait parameters and estimate the whole body center-of-mass (COM) velocity, marker data were low-pass filtered using a fourth order, zero lag, Butterworth filter at a cut off frequency of 7 Hz (Winter et al. 1990; Lockhart et al. 2003b).

5.2.5.1 Local dynamic stability

Lyapunov exponents determine the average exponential rate of divergence of neighboring trajectories in state space (Figure 5.3.) (Rosenstein ' et al. 1993; Kantz & Schreiber 2003; Stergiou 2016). The first step in calculating a Lyapunov exponent is the creation of a state space. A time delay state space is constructed using the original data and its time-delayed copies.

$$S(t) = [v(t), v(t+\tau), \ldots, v(t+(d_E-1)\tau)] \qquad (5\text{-}1)$$

where S(t) is the d_E-dimensional state vector, v(t) is the original 1-dimensional data, τ is the time delay and d_E is the embedding dimension. Time delays were determined from the first minimum of the Average Mutual Information function (Stergiou 2016b), yielding average time lags of 15, 20 and 10 samples for the AP, ML and VT directions, respectively. An embedding dimension of d_E=5 was used as previously employed by other studies on analyzing walking dynamics (Dingwell & Marin 2006; Dingwell & Cusumano 2000; McAndrew et al. 2011). For local dynamic stability analysis, each gait cycle was normalized to 100 data points (Bruijn et al. 2009; Dingwell & Marin 2006; England & Granata 2007).

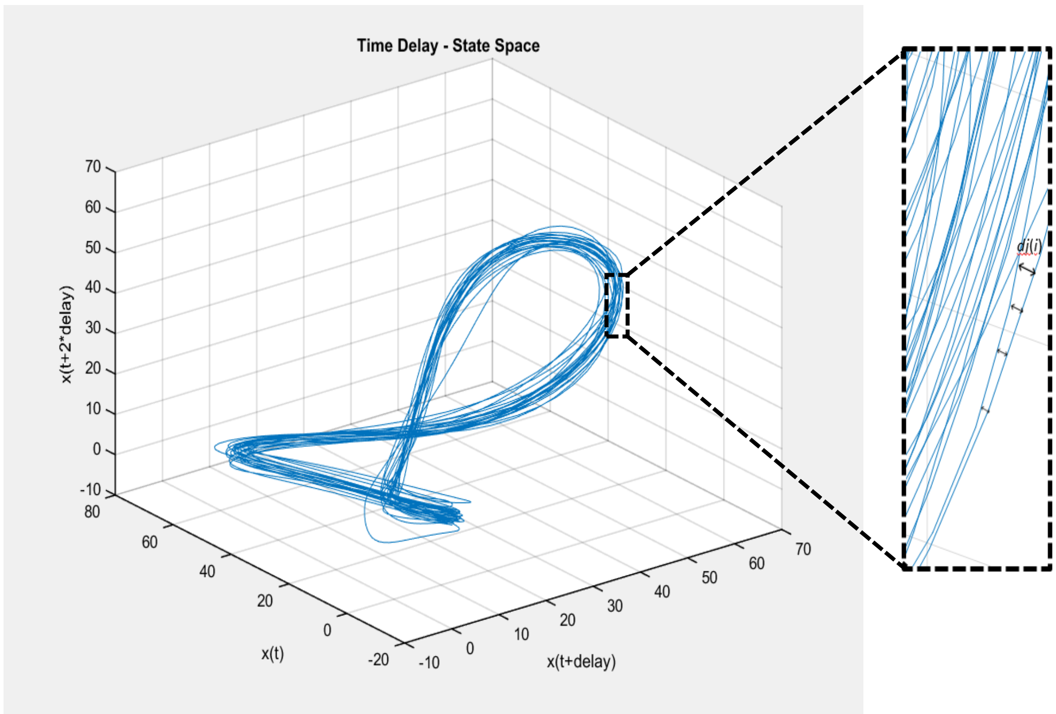

Figure 5.3. Schematic representation of local dynamic stability analysis. (A) Reconstruction of a 3-dimensional attractor for a time series like x(t) such that S(t) = [x(t), x(t+τ), x(t+2τ)]. (B) Expanded view of a local section of the attractor shown in A. An initial naturally occurring local perturbation to a given trajectory (its nearest neighbor) diverges across time steps as measured by $d_j(i)$.

The maximum Lyapunov exponent can be defined by using:

$$d(t) = d_0 e^{\lambda_1 t} \tag{5-2}$$

where d(t) is the mean displacement between neighboring trajectories in state space at time t and d_0 is the initial separation between neighboring points. λ_1 which is true Lyapunov exponents are only defined at the limits of $t \to \infty$ and $d_0 \to 0$ in above formula. Since experimental data cannot reach to these limits, an algorithm for estimating maximum finite-time Lyapunov exponents (λ_*) are proposed (Rosenstein ' et al. 1993). By taking natural log of both sides of Equation (5-2), λ_* is defined from:

$$\ln[d_j(i)] \approx \ln\left[d_{0j}\right] + \lambda_*(i\Delta t) \qquad (5\text{-}3)$$

where dj(i) is the Euclidean distance between the jth pair of nearest neighbors after i discrete time-steps (i.e. iΔt). The maximum finite-time Lyapunov exponents λ_* can then be estimated from the slope of the linear fit to the curve of:

$$y(i) = \frac{1}{\Delta t}\langle \ln[d_j(i)] \rangle \qquad (5\text{-}4)$$

where $\langle . \rangle$ is the average over all values of j (Stergiou 2016; Rosenstein et al. 1993).

5.2.5.2 Entropy analysis

Sample entropy (SampEn) analysis is a nonlinear technique for quantifying the regularity of time series data. This method which is an estimate of actual entropy for finite number of data points represents the tendency of a system to visit different states rather than being an a few states. In other words it indicates the complexity of a system (Pincus & Goldberger 1994; Stergiou 2016a; Kantz & Schreiber 2003). Lower values of SampEn reflects more regular time series (less complex) while higher values indicates more complex time series.

Mathematically, SampEn is computed as follows:

Let $\{U_i\} = \{u_1, u_2, \ldots, u_i, \ldots, u_N\}$ represent a time series of length N. There are also two input parameters, m and r. m is the length of compared runs, and r is a tolerance radius. Vector sequences of x_1 through x_{N-m-1} are formed from $\{U_i\}$, defined by $x_i = [u_1, \ldots, u_{i+m-1}]$. These vectors are basically consecutive u values beginning with i^{th} point. The largest difference between corresponding elements of two vectors x_i and x_j is defined the distance between two vectors ($d[x_i, x_j]$). Based on this definition of distance $C_i^m(r)$ is defined as follow:

$$C_i^m(r) = \frac{number\ of\ x(i) such\ that\ d[x_i, x_j] \leq r}{Nim - 1} \qquad (5\text{-}5)$$

Natural logarithm summation of all $C_i^m(r)$ is used to define $\Phi^m(r)$:

$$\Phi^m(r) = \frac{\sum_{i=1}^{N-m+1} \ln C_i^m(r)}{N - m + 1} \qquad (5\text{-}6)$$

The calculation of SampEn then given by the difference:

$$SampEn = \Phi^m(r) - \Phi^{m+1}(r) \qquad (5\text{-}7)$$

To calculate SampEn, stride time interval is employed based on previous studies (Costa et al. 2003; Georgoulis et al. 2006). It is recommended that the selected value for m (length of compared runs) depends on N (total number of data points) where N needs to be at least 10^m (Pincus & Goldberger 1994; Stergiou 2016a). Tolerance radius, r, is suggested to be a value of about 0.1-0.25 times the standard deviation in the data (Pincus & Goldberger 1994; Stergiou 2016a). Since the length of the data is 100, m=2 is chosen and 0.2 times the mean of standard deviation across all subjects' data is utilized for r. In previous studies on human movement similar values were also used (Vaillancourt & Newell 2000; Georgoulis et al. 2006; Stergiou 2004).

5.2.5.3 EMG measures

EMG data are band pass filter at 10-45 Hz then are rectified and low pass filtered by using fourth-order, zero lag, Butterworth filter at 7 Hz to create linear envelop (Parijat et al. 2015; Chambers & Cham 2007). Each EMG channel are peak normalized within subject by using the average of maximum (peak) activity of that channel from all gait cycles in the first trial (Kadaba et al. 1989).

Co-contraction index (CCI) or coactivity is calculated based on the integrated from (-20% to 20% into stance, with HC being 0%) ratio of the EMG activity of antagonist/agonist muscle pairs (TA/MG and VL/MH) multiplied by the sum of activity found in the two muscles using the following equation proposed by Rudolph et al. (Rudolph et al. 2001). The ratio was multiplied by the sum of activity found in the two muscles. This value is calculated for both ankle and knee flexor and extensor muscles for each gait cycle.

$$CCI = \int_{i=-20\%}^{i=20\%} \frac{\text{Antagonist EMG}_i}{\text{Agonist EMG}_i} \times (\text{Antagonist EMG}_i + \text{Agonist EMG}_i) \qquad (3\text{-}3)$$

Power of muscle activation (PMA) were calculated for G_Med and G-Max because of inability to collect hip adductor muscles and calculate CCI. The power of muscle activity was determined from the integrated EMG, calculated by taking the integral from -20% to 20% into stance, with HC being 0% (Chambers & Cham 2007).

5.2.5.4 Gait parameters

Step length (SL) was calculated as the distance between the heel markers in the AP direction at heel strike. Step width (SW) was calculated as the lateral distance between the two heel markers at heel strike. Stride time (ST) was the amount of time between consecutive heel strikes of the same foot. Means and standard deviations of SL, SW and ST were then calculated for TW trials. Center of mass (COM) position was estimated as the average position of the four pelvis markers (right and left anterior and posterior superior iliac spine) (Whittle 1997; McAndrew Young et al. 2012; Peebles et al. 2016). COM velocity was found by computing the first derivative of the COM position.

5.2.6 Statistical analysis

To test the hypotheses, a repeated-measure analysis was performed using a mixed designed ANOVA model on the defined variables (dynamic stability AP and ML directions, complexity, co-contraction index at ankle and knee, power of muscle activation, center of mass velocity in ML and AP, and gait parameters). In this model subjects were considered as random effects. Types of PBT were considered as between-subject factor (4 groups: NPT, MLPT, SPT, and MPT) and before and after PBT (treadmill walking before and after PBT and over-ground walking before and after PBT) have been recognized as within-subject factors. Comparisons of interest for statistically significant differences (p= 0.05) were further analyzed using post hoc with Tukey test. All statistical analyses have been performed using JMP Pro 14 (SAS Institute Inc, Cary, NC).

5.3 Results

All subjects participated in a single session of PBT protocol. Experimental procedure were consistent across trials and participants to eliminate the possible confounding factors. The results indicated that PBT could change gait dynamic stability since there were no changes in NPT group. In addition, there were an increase in gait flexible adaptability after receiving PBT which enhances individuals in selecting an action requires for a task at a certain condition.

Acceleration data collected from subjects' sternum have been used to calculate L_{max} in ML and AP directions for TW1 and TW2 trials. L_{max} results for both directions of treadmill walking before and after PBTs were presented in Figure 5.4. There were interactions between groups and TW trials for both ML ($F_{(3,68)}$=5.51, p=0.002) and AP ($F_{(3,68)}$=4.85, p=0.004) directions. This could be concluded that the difference between measurements depends on group membership. Post-hoc analysis revealed that there were no significant changes in gait dynamic stability of control group for both ML (p=0.999) and AP (p=0.987) directions. However, all types of PBT could significantly improve dynamic stability in ML direction (MLPT: p=0.020; SPT: p=0.001; MPT: p=0.002) but only SPT and MPT could significantly decrease L_{max} and improve dynamic stability in AP direction (SPT: p=0.001; MPT: p=0.001).

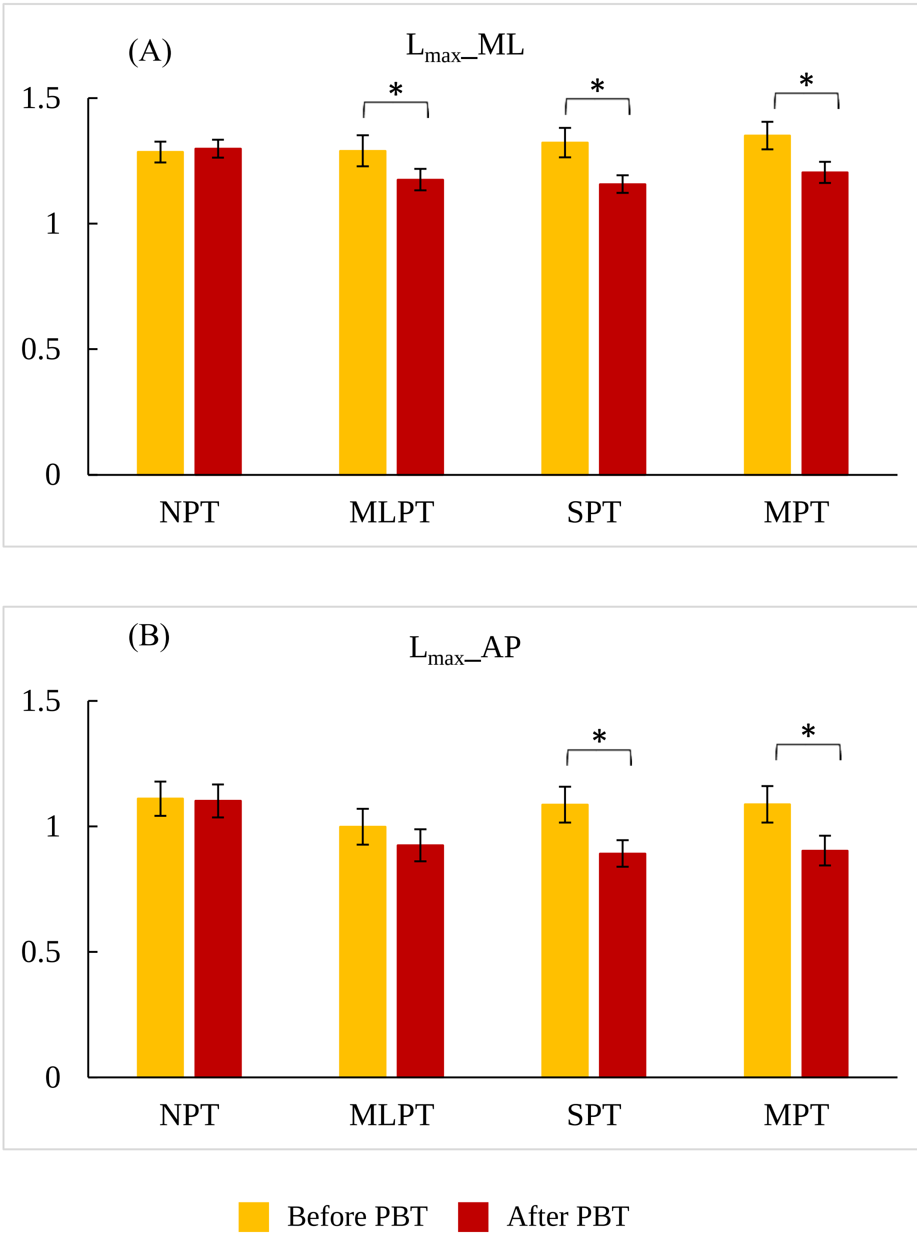

Figure 5.4. Treadmill walking gait dynamic stability before and after receiving a PBT for (A) Medial-lateral (ML) and (B) Anterior-posterior (AP) directions. NPT: NO Perturbation Training, MLPT: Medial-lateral Perturbation Training, SPT: Slip Perturbation Training, MPT: Mix Perturbation Training. The asterisks (*) placed over the vertical bars denote a significant difference ($p < 0.05$).

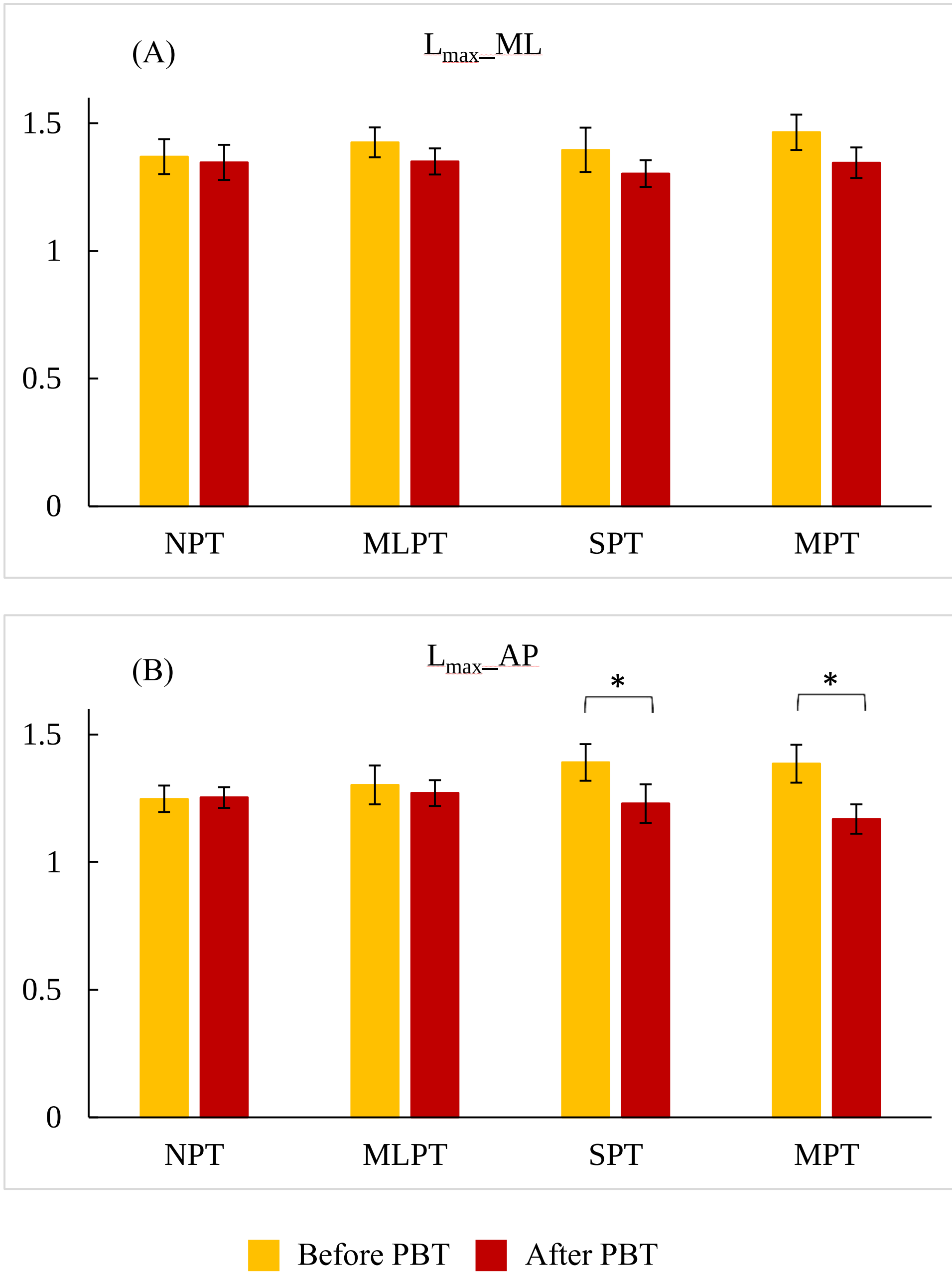

Figure 5.5. Overground walking gait dynamic stability before and after receiving a PBT for (A) Medial-lateral (ML) and (B) Anterior-posterior (AP) directions. NPT: NO Perturbation Training, MLPT: Medial-lateral Perturbation Training, SPT: Slip Perturbation Training, MPT: Mix Perturbation Training. The asterisks (*) placed over the vertical bars denote a significant difference ($p < 0.05$).

Dynamic stability of subjects have been calculated during over-ground walking trials (OG1 and OG2) to assess whether changes in L_{max} can be transferred to over-ground walking. Results are shown in Figure 5.5. There were no interaction between groups and OG trials for ML direction. ($F_{(3,68)}=1.09$, $p=0.36$) and trials had significant effect on L_{max} ($F_{(1,68)}=19.69$, $p < 0.001$). Results of post-hoc analysis haven't shown any statistical significant change of dynamic stability in ML direction for each experimental group. In AP direction there were an interaction between groups and trials ($F_{(3,68)}=5.04$, $p=0.003$). Similar to treadmill walking trials, post-hoc analysis have indicated that only SPT and MPT could significantly improve dynamic stability in AP direction (SPT: $p=0.004$; MPT: $p=0.001$).

SampEn analysis was applied on the stride interval times series derived from TW1 and TW2 of each participant to assess the effect of PBT on individual's flexible gait adaptability. Results were presented in Figure 5.6. PBT effects were investigated using mixed linear ANOVA conducted on the SampEn values. Statistical analysis showed an interaction between PBTs (between subject factors) and treadmill walking trials (within subject factors), ($F_{(3,68)}=3.58$, $p=0.018$). Therefore, post-hoc analysis was conducted. Results indicated that all types of PBTs significantly increased the complexity level (MLPT: $p=0.044$; SPT: $p=0.004$; MPT: $p=0.009$) while no statistically significant change have shown for NPT group.

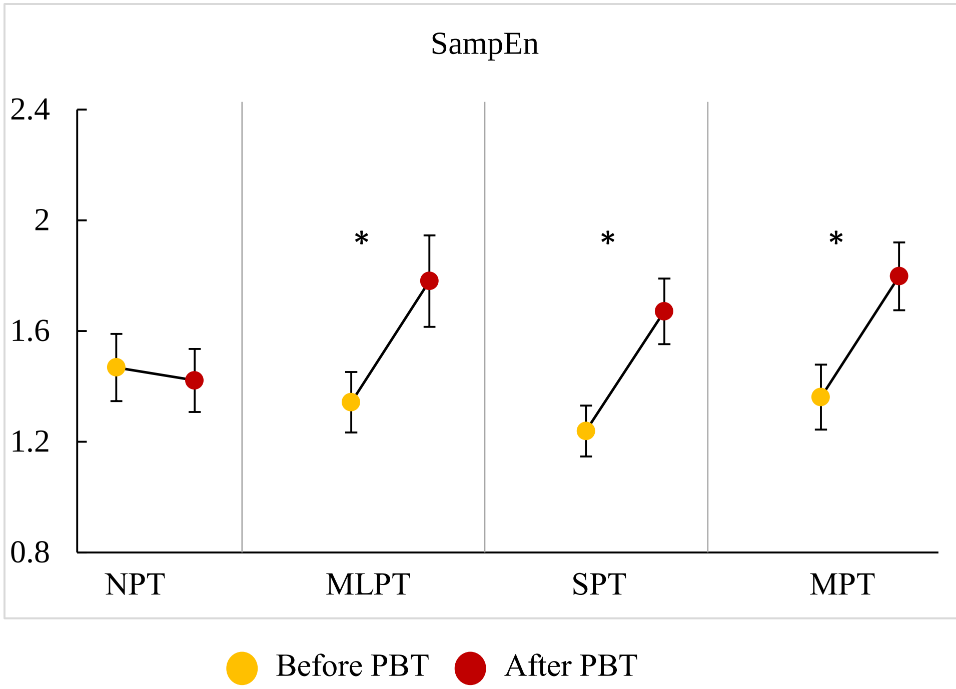

Figure 5.6. Sample entropy analysis (SampEn) before and after PBT. NPT: NO Perturbation Training, MLPT: Medial-lateral Perturbation Training, SPT: Slip Perturbation Training, MPT: Mix Perturbation Training. The asterisk (*) denote a significant difference ($p < 0.05$).

EMG signals of only fifty six subjects (fourteen per group) could be utilized for EMG measure analysis because of some technical issues during data collection. Results of ankle and knee CCI were shown in Figure 5.7. Both ankle and knee CCI reduced after receiving PBTs regardless of types of it. Statistical analysis indicated that all types of PBT could significantly reduce ankle CCI (MLPT: p=0.026; SPT: p=0.045; MPT: p=0.019) while only SPT and MPT could significantly change knee CCI (MLPT: p=0.103; SPT: p=0.034; MPT: p=0.029). Both ankle and knee CCIs haven't changed in NPT group.

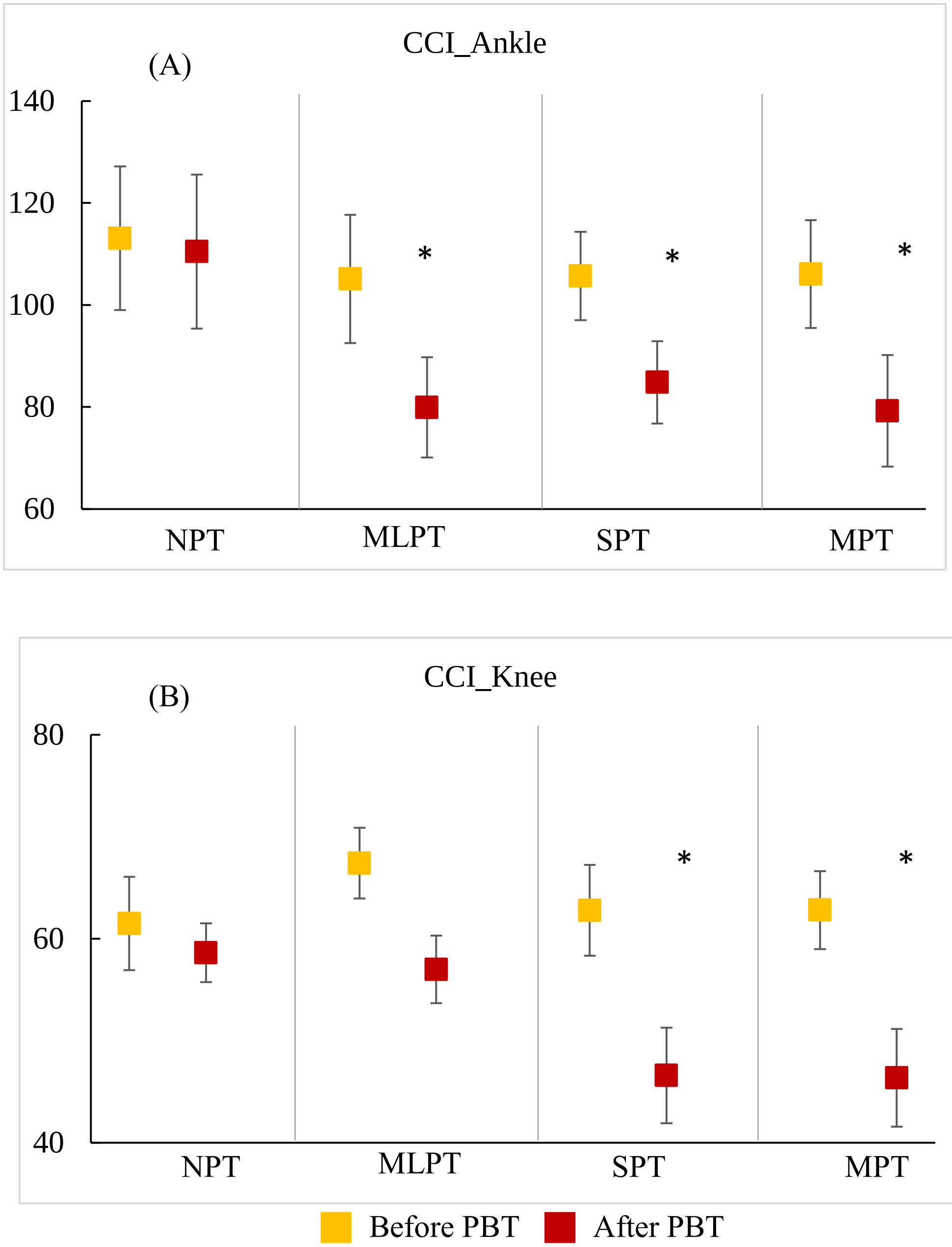

Figure 5.7. Ankle (A) and Knee (B) CCI before and after PBT. NPT: NO Perturbation Training, MLPT: Medial-lateral Perturbation Training, SPT: Slip Perturbation Training, MPT: Mix Perturbation Training. The asterisks (*) denote a significant difference ($p < 0.05$).

Power of muscle activation around heel contact were calculated for G_Med and G_Max muscles around HC for treadmill walking trials. Their results were presented in Figure 5.8. The ANOVA indicated no statistically significant change in PMA of participants' G_Max muscle after receiving any types of PBT (TW*group: $F_{(3,52)}$=6.79, *p*=0.485; TW: $F_{(1,52)}$=0.26, *p*=0.613). However, PMA of participants' G_Med muscle significantly decreased only after receiving MLPT (NPT: *p*=0.999; MLPT: *p*=0.039; SPT: *p*=0.99; MPT: *p*=0.818).

Average position of the four pelvis markers (right and left anterior and posterior superior iliac spine) were utilized to calculate COM_Vel in ML and AP directions. These values were plotted in Figure 5.9. There was no interactions between groups and TW trials for COM_Vel in AP direction ($F_{(3,68)}$=2.57, *p*=0.06) while there was a significant effect of TW trials ($F_{(1,68)}$=14.69, *p*=0.001). Post-hoc analysis indicated that COM_Vel statistically increased in AP direction after SPT (SPT: *p*=0.018) and very close to significant level after MPT (MPT: *p*=0.053). In ML direction, there was an interactions between groups and TW trials for COM_Vel ($F_{(3,68)}$=4.065, *p*=0.01). Further analysis showed that only individuals who have received MLPT could statistically decrease their COM_Vel in ML direction (*p*=0.028).

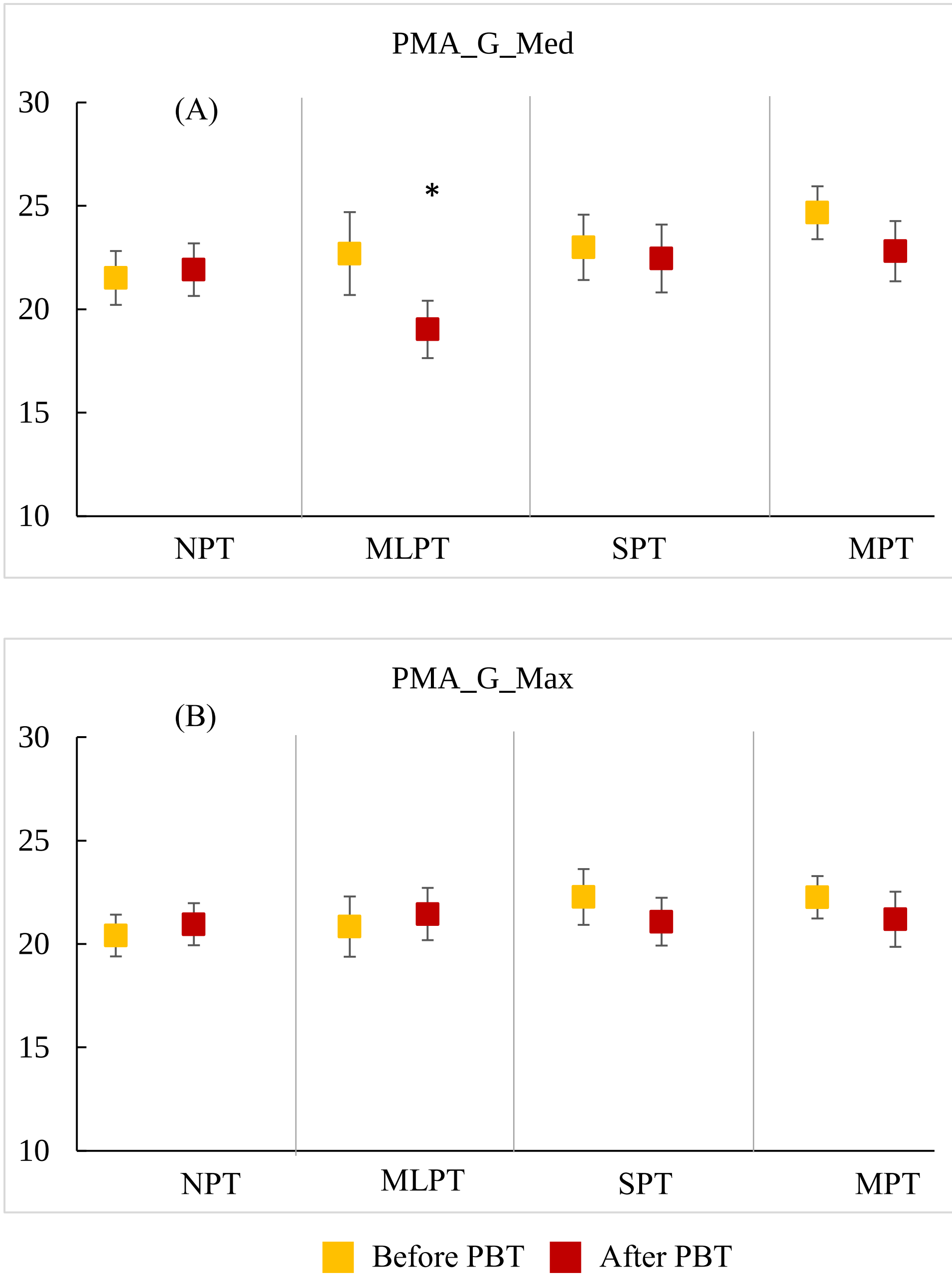

Figure 5.8. PMA of G_Med (A) and G_Max (B) before and after PBT. PMA: power of muscle activation, NPT: NO Perturbation Training, MLPT: Medial-lateral Perturbation Training, SPT: Slip Perturbation Training, MPT: Mix Perturbation Training. The asterisks (*) denote a significant difference (p < 0.05).

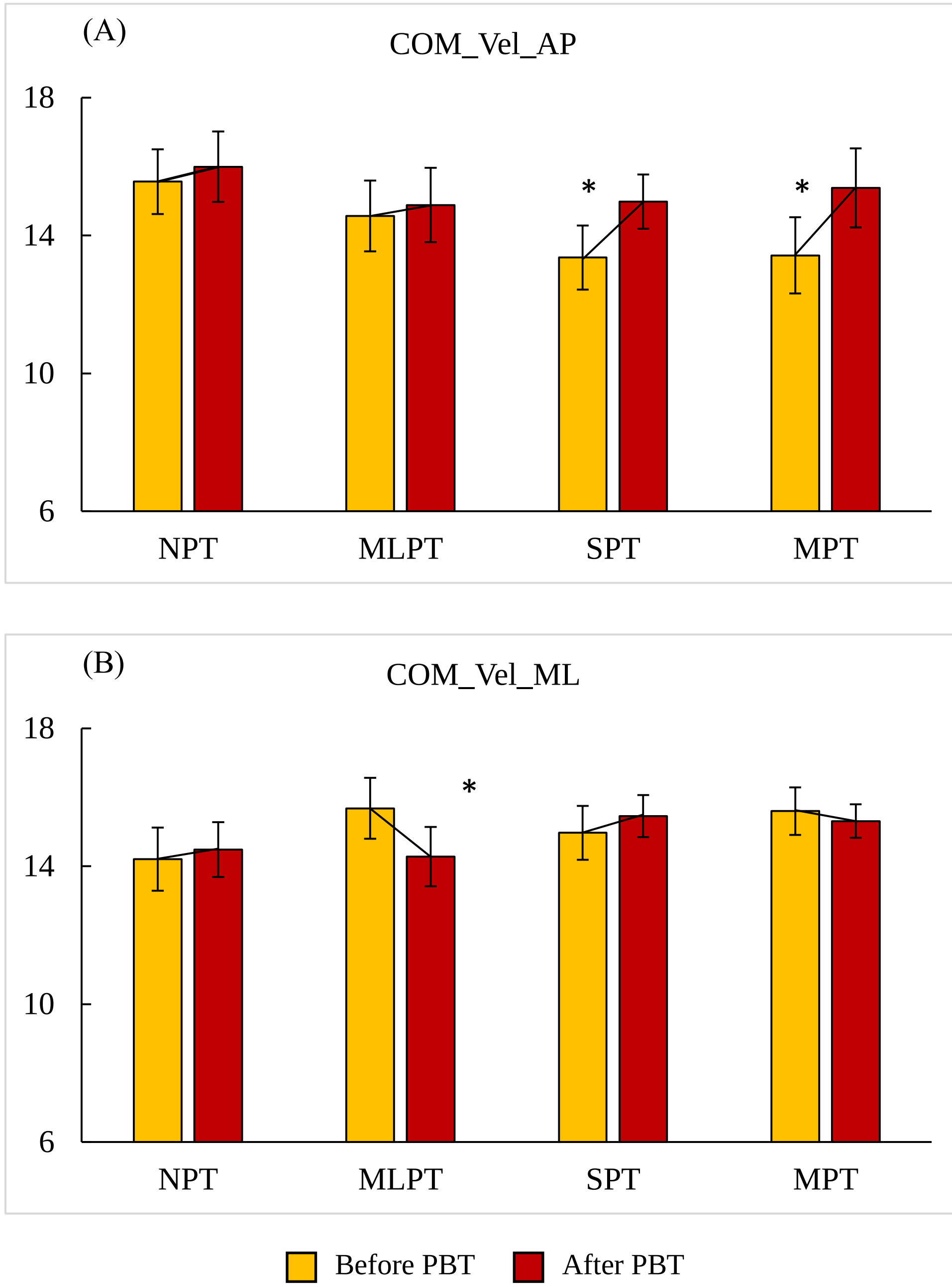

Figure 5.9. Center of mass velocity (cm/s) at the time of heel contact in (A) Medial-lateral (ML) and (B) Anterior-posterior (AP) directions before and after receiving a PBT. NPT: NO Perturbation Training, MLPT: Medial-lateral Perturbation Training, SPT: Slip Perturbation Training, MPT: Mix Perturbation Training. The asterisks (*) placed over the vertical bars denote a significant difference ($p < 0.05$).

Participants' step width and stride time haven't changed after receiving PBT. However, subjects in SPT and MPT groups significantly reduced their step length after receiving PBT (SPT: p=0.001; MPT: p=0.01). These results were shown in Table 5.2.

Table 5.2. Mean ± SD of gait parameters during TW1 and TW2 trials for all training group. Asterisks (*, **) placed close by each of two values denote a significant difference between those two values ($p < 0.05$).

Gait parameters	NPT		MLPT		SPT		MPT	
	TW1	TW2	TW1	TW2	TW1	TW2	TW1	TW2
Step length (cm)	59.51 ±4.77	60.05 ±5.41	59.16 ±4.17	59.62 ±3.79	* 60.35 ±3.61	*58.52 ±3.94	**60.82 ±4.09	**59.26 ±3.32
Step width (cm)	13.98 ±2.01	13.83 ±2.17	14.63 ±3.54	14.10 ±2.79	14.53 ±2.33	15.23 ±2.26	14.74 ±2.17	14.30 ±2.22
Stride time (s)	1.14 ±0.055	1.15 ±0.059	1.11 ±0.062	1.11 ±0.061	1.16 ±0.067	1.15 ±0.068	1.14 ±0.060	1.14 ±0.046

5.4 Discussion

This study examined the effects of PBT on dynamic stability and gait complexity. Three types of PBT interventions were studied. The findings from the study support the hypotheses that PBT could improve gait stability. Additionally, there were an increase in gait flexible adaptability which may enhance the ability of an individual in selecting appropriate motor actions required for a certain fall-risk condition. As such, the PBT intervention appears to support fall prevention effort by improving one's dynamic stability and to resist perturbations associated with daily activities.

Previous studies have shown that humans adapt to unpredictable changes or perturbations in environment during different activities, such as standing or walking (Bhatt et al. 2006; Nashner 1976; Horak et al. 1989; Owings et al. 2001; Parijat & Lockhart 2012).

A new association between external perturbation (e.g. slip) and motor action is required for this adaptation. Some changes such as increasing transitional acceleration at the time of heel contact after experiencing repeated slip perturbations is an example of these adaptations which reduces the risk of backward balance loss and the fall (Lockhart et al. 2003). This type of changes in gait pattern is acquired by repeating movements in the presence of an external perturbation to reconstruct the performance of a task when external perturbations exist (Pai & Bhatt 2007).

By repeating exposure to perturbations, a new predictive control is developed which reduces the risk of balance loss in the presence of future perturbations. For this, CNS builds, refines, or updates an internal representation of the potential threats that may occur in the external environment (Pai & Bhatt 2007; Kandel & Schwartz 2013). When sensory prediction is consistent with the actual sensory information, there is a little commands from the feedback controller. Otherwise, these sensory inputs not only elicit corrective commands from the feedback controller but also are utilized to regulate the sensory representation of the environment and the motor commands in a feedforward manner (Pai & Bhatt 2007; Kandel & Schwartz 2013; Morasso et al. 1999). This improves performance in the future motor actions under similar contexts. Thus, PBT decreases dependency on feedback mechanism as the adaptation process is further developed over repeated exposures to perturbations (Pai & Bhatt 2007; Pai et al. 2003). Furthermore, CNS explores all the possible patterns of motor neuron requirements for fulfilling a movement task in the presence of an external perturbation (Pearson 2000; Prochazka & Ellaway 2012). Thus, PBT refines neural pathways to effectively recruit motor neuron in order to reduce the risk of loss of balance and fall.

Dynamic stability results indicated that PBT can change L_{max}. All three types of PBT (MLPT, SPT, and MPT) improved gait dynamic stability in ML direction while SPT and MPT could improve it in AP direction (Figure 5.4.). Previous studies have shown that gait stability measures in particular direction have changed in greater extend when a perturbation occurred in the same direction (McAndrew et al. 2011; Young 2011; Martelli et al. 2016). For example, L_{max} has significantly larger value in AP direction while AP perturbations were applied during walking but not during ML perturbations and, significantly larger L_{max} in ML direction while ML perturbations were applied during walking but not during AP perturbations (McAndrew et al. 2011). This may indicate that applied perturbations at each direction significantly changed the stability of that direction. As such, PBT at a specific direction would considerably change L_{max} at that direction. Accordingly, MLPT, SPT, and MPT would substantially change L_{max} in ML, AP, and both directions, respectively. This was the hypothesis. However, the results for SPT was not supported. L_{max} in both directions increased. Movement of left belt at the time of perturbation might be a potential reason for this “dual” training. Once a slip perturbation is triggered, right belt start to accelerate in opposite direction to simulate a slip like perturbation while the left belt is still moving at the same speed and direction. So, there would be a rotational movement if subjects put down their contralateral foot while a perturbation movement is still occurring (which is true in most of cases) because left and right belts have opposite direction. In this case, perturbation doesn’t occur in only AP direction but also on ML component as well. Although, further study is needed to understand the mechanisms associated with the improvement of gait dynamic stability in both directions after slip like perturbation.

Similar changes in gait dynamic stability in AP direction occurred during over-ground walking after PBT. Individuals who received SPT and MPT have shown an improvement in their gait dynamic stability during over-ground walking (Figure 5.5-B). It indicates that changes in gait dynamic stability in AP direction acquired from treadmill-PBT successfully transferred to over-ground walking. Similar finding has been reported by Yang et. al. 2013 (Yang et al. 2013). They have assessed whether treadmill-slip training could reduce the likelihood of falls during a novel slip in over-ground walking. Their results clearly demonstrated the feasibility of fall reduction during a novel slip in an over-ground walking after treadmill-slip training which is consistent with this study's finding. However, improvement of gait dynamic stability in ML direction acquired from any types of treadmill-PBTs wasn't significantly improved during over-ground walking (Figure 5.5-B). A study of waist-pull perturbations during walking has reported the similar results (Martelli et al. 2016). In this study, healthy young subjects were divided into two groups and were exposed to a single training session. Each group received perturbations in ML or AP direction applied to subjects' pelvis when a heel strike was detected. They found that the margin of stability change has been observed only in the first minutes after exposing to ML perturbations during unperturbed walking and got closer to base line level toward the end (about seven minutes after receiving ML perturbations). However, the margin of stability improvement in AP direction was preserved during unperturbed walking after exposing to AP perturbations. This could be explained by control mechanism which is employed at each direction. Mathematical modeling suggests that human walking could be passively stable when restricted to sagittal plane (2-D model) (McGeer 1990). However, lateral motion is unstable (with high tendency to fall laterally) when lateral motion was considered in the model (3-D model) (Kuo 1999; Bauby & Kuo 2000). Hence, there was a need for active feedback control of lateral motion. It has been suggested that feedback control of lateral foot placement is an effective method for stabilizing lateral balance (Kuo 1999). Accordingly, lateral motions requires higher-level integration of sensory inputs (mainly, vision vestibular and proprioceptive systems) during gait (Dean et al. 2007). As such, it increases the computational and metabolic costs. Bauby et al. has evaluated this notion by assessing the effect of removing visual feedback of foot placement (Bauby & Kuo 2000). Their results have shown an inappropriate lateral foot position when visual feedback was removed compared to AP foot position. This suggests that humans actively stabilize lateral motion using medio-lateral foot placement and that this active control mechanism was less precise when there was less sensory information. If subjects were passively stable, they would be expected to have no sensitivity to sensory information (Bauby & Kuo 2000). Another experiment assessed lateral active control by externally stabilizing subjects' posture (Donelan et al. 2004). They applied external lateral stabilization, through elastic cords attached to subjects at the waist and pulling laterally during treadmill walking. Their results showed a decrease in metabolic cost when subjects were externally stabilized. They concluded that external stabilization of the body would reduce the active control needed and decrease metabolic cost. Similarly, when walking during continuous pseudo-random perturbations, subjects were more sensitive to ML perturbations than to AP perturbations (McAndrew et al. 2011). As such, active control from higher centers is necessary for lateral stabilization of gait, but the limbs and spinal cord are sufficient to provide other passively stable properties for AP motion during walking. Based on this, sensory inputs do not send any source of perturbation during unperturbed walking. As a result of that, adaptation mechanism acquired from PBT are not required. So, stability starts to get back to its baseline level (before receiving PBT). This doesn't happen immediately and it takes time based on the previous study (Martelli et al. 2016). Therefore, ML stability improvement could not been seen during over-ground walking but it was observed during treadmill walking. Accordingly, the extent of adaptation mechanisms to repeated perturbations are dependent on the direction. Further study is needed to assess this mechanism in AP direction.

It is hypothesized that variations in the human movement might be essential to provide flexible adaptations to everyday disturbances placed on the human body (Goldberger et al. 2002; Otero-Siliceo & Arriada-Mendicoa 2003; Georgoulis et al. 2006; Stergiou & Decker 2011). The loss of adaptability is related to lack of complexity and greater regularity in the dynamics of daily living activities (Paraschiv-Ionescu et al. 2012; Ihlen et al. 2016). So, a lack of this complexity is associated with rigidity and inability to adapt to different demands and challenges. The higher level of entropy reflects a more complex mechanism in human movements which empowers it to have a greater adaptability to different demands (Stergiou 2016a; Costa & Healey 2003; Costa et al. 2005; Costa et al. 2003; Manor et al. 2010; Karmakar et al. 2007). In other words, high level of entropy points to a higher flexibility in selecting an action requires for a task at a certain condition. Alternatively, lower entropy determines repetitive behavior and a limited amount of flexibility or complexity. Results of Sample entropy analysis has shown an increase in this measure after perturbation training (Figure 5.6). This indicates that PBT increases complexity which enables individuals to have higher level of flexible adaptability. This empowers an individuals to have a quick reaction to a perturbation since it is more flexible to adapt to a new situation. This flexibility is required since a rigid system cannot react very fast and it may cause a fall.

According to the EMG assessments, increased gait flexible adaptability might be attained by reducing co-contraction and power of muscles around heel contact (Figure 5.7. and Figure 5.8.). PBTs affected muscle co-contractions around heel contact of the gait cycle (Figure 5.7.). Increased muscle co-contraction is beneficial to decrease the risk of a hazardous fall (Chambers & Cham 2007) but too much co-contraction would result in stiffening a joint and hindering a quick reaction. According to the previous studies during a PBT there is an initial (approximately first three trials) increase and subsequent decrease in muscle co-contractions which remained unaffected after 6-7 training trials (Parijat & Lockhart 2012; Parijat et al. 2015; Carolan & Cafarelli 1992; Enoka 1997). As a result, stabilization strategy change from stiffening pattern to a pattern that may allow individuals to dynamically stabilize themselves to unexpected perturbations. The initial increase in muscle co-contraction is a primitive strategy when mastering a new skill which freezes degrees of freedom. When learning and skill acquisition take place, rigid control over the degrees of freedom is released. Therefore, a more selective pattern to react to a perturbation would be available by lowering muscle co-contraction (Bernstein 1967; Chmielewski et al. 2005; Kandel & Schwartz 2013). Accordingly, during PBT the CNS chose the most effective muscle synergy organization to achieve a common goal which is keeping balance and avoid a fall (Kandel & Schwartz 2013). Ankle and step strategies are the main tactics which individuals employed to maintain their lateral balance during walking (Hof et al. 2010). Results of current study support this by showing a reduction in ankle CCI in the case of ML PBT.

In the presented study, there was an increase in the COM velocity at the time of heel contact in AP direction after SPT (Figure 5.9.). It has been reported that increased COM velocity helps individuals to maintain their balance when experiencing a slip (Pai & Patton 1997; Lockhart et al. 2003a; Lockhart et al. 2005a; Parijat & Lockhart 2012; You et al. 2001). Body weight should be transfer to the leading foot at the time of heel contact during a normal gait. When there is a slipping condition at time of heel contact and stability cannot be regained, it would result in a backward fall. During this time, the whole body COM moves from behind to ahead of the base of support. So, faster COM velocity would result in a faster transferring body weight and reduce the likelihood of a backward fall. However, velocity of COM in ML direction reduced after MLPT and MPT at the time of heel contact (Figure 5.9.B). Similar finding has been reported in a study of applying repeated multidirectional waist-pull perturbations which subjects have reduced the ML displacement of the extrapolated center of mass after repeated ML perturbations (Martelli et al. 2016). Subjects may have reduced their COM velocity in ML direction in order to adjust to a slower proactive adjustment of ML perturbations applied at heel strike. Additionally they might use less energy to stop lateral displacement of COM and bring it to medial direction when a lateral perturbation occurs. Reduction in PMA of G_Med around heel contact might be the mechanism which reduces COM velocity in ML direction after MLPT based on the results (Figure 5.10.).

Our results have shown that individuals who received SPT or MPT reduced their step length after PBT (Table 5.2). It has been reported that people of all ages shorten step length to reduce the likelihood of slipping (Fong et al. 2005; Chang et al. 2017; Lockhart et al. 2005b; Bhatt 2006; Cham & Redfern 2002). As the step length is increased the ratio of shear to horizontal forces at heel contact would increases (Redfern et al. 2001). Ratio of shear to horizontal forces represented the general friction demand at the shoe floor interface to prevent initiation of forward slipping (Redfern and Andres 1984). In other words, this ratio defines the minimum coefficient of friction that must be available or ‘required to avoid a slip (Lockhart et al. 2003a; Perkins 1978). Thus, reducing step length was an approach to reduce the likelihood of a slip during walking (Redfern et al. 2001). In addition, a longer step length puts COM more posterior to the leading foot at the time of heel contact. It increases required displacement of COM to prevent a slip and increase the likelihood of a slip (Pai & Patton 1997; Bhatt et al. 2005).

In summary, findings from this study indicated that PBT could improve gait dynamic stability. Results also supported the hypothesis that these improvements can be transfer to over-ground walking. In addition, there were an increase in gait flexible adaptability which enhances individuals in selecting an action requires for a task at a certain condition. One of the significant contributions of this study is assessing gait dynamic stability of individuals which has not been evaluated in the previous PBT studies. One of the main advantage of gait dynamic stability is that individuals can measure themselves by just using a smartphone. Nowadays, smartphones are affordable and majority of people use them. So, gait dynamic stability can be measured at certain time points to assess when an individuals need to repeat PBT. In this way a more customized training will be provided although further studies are needed to assess the retention of the training effects after a period of time.

Several limitations exist in the study. Due to the location of hip adductor muscles, collection of those muscle activities to calculate co-contraction at hip level was difficult. Furthermore, simulated slip perturbation was not exactly similar to over-ground slip. Additionally, current system which was used in this study did not have the capability of making vertical movement. As a result, vertical perturbation couldn't be applied. Future studies can address this. Despite its limitations, employing a treadmill for PBT training on treadmill is highly beneficial. Being portable and versatile overcome space limitations in most of clinical setup by using a treadmill. Additionally, the treadmill can deliver precise and reproducible perturbations and, avoids the possibility of predicting obstacles or slippery surfaces.

Future studies may examine the effects of proposed PBT on different populations (athletes or older adults who are at high risk of injuries due to high chance of losing their balance). Additionally, future studies may explore the retention of the training effects after a period of time. Furthermore, future studies may explore and compare the effects of over-ground PBT vs treadmill PBT on dynamic stability and gait complexity.

CHAPTER 6: SUMMARY AND CONCLUSION

6.1 Summary and conclusion

Injuries and death associated with fall incidences pose a significant burden to society, both in terms of human suffering and economic losses. Finding methods to reduce the risk of falls and improve individuals' stability is paramount in our society. In this dissertations, a few methods were studied that may reduce the risk of falls in both PD patients and healthy individuals.

FOG is one of the main causes of falls in PD patients. Previous studies have shown that external cues like auditory cues could help patients to overcome FOG (Bächlin, Plotnik, Roggen, Maidan, Jeffrey M. Hausdorff, et al. 2010; Okuma 2006; Nieuwboer & Giladi 2013). As such, a fall due to FOG could be prevented by detecting FOG immediately after it starts. In the first study of this dissertation, a new method to detect FOG in real time by using wearable sensor has been proposed. Three different sensor locations: shank, thigh, and back were also assessed. Wavelet transform was utilized to define an index to detect FOG. Two hundred and thirty seven FOG events collected from ten PD patients were employed to evaluate the proposed FOG detection index. Suggested index could detect FOG smaller sampling window of data in compare to previous studies. Smaller window size of data allows for better detection of short-duration FOG episodes, since larger window size can average out shorter FOG episodes. In addition, smaller window size could decrease processing time and allow for faster triggering of external cues to help patients overcome the FOG episodes. In addition changing update time from 0.5 s to 1 s didn't attenuate the levels of detection. In terms of the location of the sensor placements, shank sensor showed better sensitivity and specificity in compare to two other locations. In conclusion, the results suggested that real time detection of FOG could be realized by using wavelet transform of a single shank acceleration data with window size of 2 s and update time of 1 s with 82.1% and 77.1% sensitivity and specificity, respectively.

In the second study of this dissertation, a new method was proposed to identify PD motor subtypes. This categorization was important at the early stage of PD, since identifying the PD subtypes could help to predict the clinical progression of the disease. Thirty-six participants diagnosed with PD were evaluated, with their bare feet on the force platform, and were instructed to stand upright with their arms by their sides for 20 s. Standing center of pressure time series data were utilized to separate two subtypes of PD by looking at the frequency component of COP. Fast Fourier transform and wavelet transform were performed to distinguish between the motor subtypes using the COP measures. Both the power spectral density and the wavelet transform of the COP time series and its velocity revealed an increase in the 3–7 Hz frequency range of the TD group, a frequency spectra that has reportedly been symptomatic of parkinsonian tremor. This finding was employed to define a ratio to identify PD motor subtypes. Results indicated that both the FFT and WT methods were able to differentiate the subtypes. Therefore, COP time series information can be used to differentiate between the two motor subtypes of PD, using the frequency component of postural stability.

In the last study, the effects of treadmill delivered translational perturbations training on improving dynamic stability while walking and adaptability of locomotor system in resisting to perturbations were evaluated by using nonlinear measures of stability and movement complexity. Three types of PBT were studied; medial-lateral (ML), slip-like, and mix (including both medial-lateral and slip-like ones) perturbations. Seventy two healthy young adults were recruited for the study and randomly assigned into four experimental groups: NPT (control group-receiving no PBT), MLPT (receiving only ML PBT), SPT (receiving only slip-like PBT), and MPT (receiving both ML and slip-like PBT). Results indicated that all types of perturbation training protocols improved dynamic stability as compared to prior training level. Additionally, PBT could increase complexity and consequently improve gait flexible adaptability. Improved stability and flexible adaptation appear to be brought on by reducing the stiffness of lower extremities as measured by EMG muscle co-contraction index. Understanding the effects of different directional perturbations on gait stability and complexity will pave the way to developing a better intervention for those who are at a higher risk of losing balance and falls as a result of gait instability.

6.2 Future recommendations

While outcomes from this study have shown promising results in reducing the risk of falls, there are areas that still need further investigation. Employing proposed FOG and PD motor subtype detections on larger population is one of them. Specifically, FOG section should be tested in at home environment since it has been shown that some patients doesn't exhibit FOG episodes in clinical environments.

In PBT study, vertical perturbation haven't been assessed due to system limitation. Future studies can assess and evaluate the effect of vertical perturbation on dynamic stability and gait complexity. Future studies may examine the effects of proposed PBT on different population like athletes or older adults who are at high risk of injuries due to high chance of losing their balance. Additionally, future studies may explore the retention of the training effects after a period of time. Furthermore, future studies may explore and compare the effects of over-ground PBT vs treadmill PBT on dynamic stability and gait complexity.

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APPENDIX A

HOEHN AND YAHR SCALE

The Hoehn and Yahr scale is a commonly used system for describing how the symptoms of Parkinson's disease progress.

Stage	Hoehn and Yahr Scale
1	Unilateral involvement only usually with minimal or no functional disability
2	Bilateral or midline involvement without impairment of balance
3	Bilateral disease: mild to moderate disability with impaired postural reflexes; physically independent
4	Severely disabling disease; still able to walk or stand unassisted
5	Confinement to bed or wheelchair unless aided

APPENDIX B

UPDRS SCALE

Unified PARKINSON Disease Rating Scale (UPDRS)

The UPDRS is a rating tool to follow the longitudinal course of Parkinson's disease. It is made up of the 1) Mentation, Behavior, and Mood, 2) ADL and 3) Motor sections. These are evaluated by interview. Some sections require multiple grades assigned to each extremity.

I. Mentation, Behavior, Mood

o *Intellectual Impairment*

0-none

1- Mild (consistent forgetfulness with partial recollection of events with no other difficulties)

2- Moderate memory loss with disorientation and moderate difficulty handling complex problems

3-severe memory loss with disorientation to time and often place, severe impairment with problems

4-severe memory loss with orientation only to person, unable to make judgments or solve problems

o *Thought Disorder*

0-none

1-vivid dreaming

2-"benign" hallucination with insight retained

3-occasional to frequent hallucination or delusions without insight, could interfere with daily activities

4-persistent hallucination, delusions, or florid psychosis.

o *Depression*

0-not present

1-periods of sadness or guilt greater than normal, never sustained for more than a few days or a week

2-sustained depression for >1 week

3-vegetative symptoms (insomnia, anorexia, abulia, weight loss)

4-vegetative symptoms with suicidality

o *Motivation/Initiative*

0-normal

1-less of assertive, more passive

2-loss of initiative or disinterest in elective activities

3-loss of initiative or disinterest in day to say (routine) activities

4-withdrawn, complete loss of motivation

II. Activities of Daily Living

o *Speech*

0-normal

1-mildly affected, no difficulty being understood

2-moderately affected, may be asked to repeat

3-severely affected, frequently asked to repeat

4-unintelligible most of time

o *Salivation*0-normal

1-slight but noticeable increase, may have nighttime drooling

2-moderately excessive saliva, hay minimal drooling

3-marked drooling

o *Swallowing*

0-normal

1-rare choking

2-occasional choking

3-requires soft food

4-requires NG tube or G-tube

o *Handwriting*

0-normal

1-slightly small or slow

2-all words small but legible

3-severely affected, not all words legible

4-majority illegible

o *Cutting Food/Handing Utensils*

0-normal

1-somewhat slow and clumsy but no help needed

2-can cut most foods, some help needed

3-food must be cut, but can feed self

4-needs to be fed

o *Dressing*

0-normal

1-somewhat slow, no help needed

2-occasional help with buttons or arms in sleeves

3-considerable help required but can do something alone

4-helpless

o *Hygiene*

0-normal

1-somewhat slow but no help needed

2-needs help with shower or bath or very slow in hygienic care

3-requires assistance for washing, brushing teeth, going to bathroom

4-helpless

o *Turning in Bed/ Adjusting Bed Clothes*

0-normal

1-somewhat slow no help needed

2-can turn alone or adjust sheets but with great difficulty

3-san initiate but not turn or adjust alone

4-helplesso *Falling-Unrelated to Freezing*

0-none

1-rare falls

2-occasiona, less than one per day

3-average of once per day

4->1 per day

o *Freezing When Walking*

0-normal

1-rare, may have start hesitation

2-occasional falls from freezing,

3-frequent freezing, occasional falls

4-frequent falls from freezing

o *Walking*

0-normal

1-mild difficulty, day drag legs or decrease arm swing

2-moderate difficultly requires no assist

3-severe disturbance requires assistance

4-cannot walk at all even with assist

o *Tremor*

0-absent

1-slight and infrequent, not bothersome to patient

2-moderate, bothersome to patient

3-severe, interfere with many activities

4-marked, interferes with many activities

o *Sensory Complaints Related to Parkinsonism*

0-none

1-occasionally has numbness, tingling, and mild aching

2-frequent, but not distressing

3-frequent painful sensation

4-excruciating pain

III. Motor Exam

- *Speech*

  0-normal

  1-slight loss of expression, diction, and, volume

  2-monotone, slurred but understandable, mod impaired

  3-marked impairment, difficult to understand

  4-unintelligible

- *Facial Expression*

  0-Normal

  1-slight hypomymia, could be poker face

  2-slight but definite abnormal diminution in expression

  3-mod. hypomimia, lips parted some of time

  4-masked or fixed face, lips parted 1/4 of inch or more with complete loss of expression

- *Tremor at Rest*

  + Face

    0-absent

    1-slight and infrequent

    2-mild and present most of time

    3-moderate and present most of time

    4-marked and present most of time

  + Right Upper Extremity (RUE)

    0-absent

    1-slight and infrequent

    2-mild and present most of time

    3-moderate and present most of time

    4-marked and present most of time

  + LUE

    0-absent

    1-slight and infrequent

    2-mild and present most of time

    3-moderate and present most of time

    4-marked and present most of time

  + RLE

    0-absent

    1-slight and infrequent

    2-mild and present most of time

    3-moderate and present most of time

4-marked and present most of time

+ LLE

0-absent

1-slight and infrequent

2-mild and present most of time

3-moderate and present most of time

4-marked and present most of time

o Action or Postural Tremor

+ RUE

0-absent

1-slight, present with action

2-moderate, present with action

3-moderate present with action and posture holding

4-marked, interferes with feeding

+ LUE

0-absent

1-slight, present with action

2-moderate, present with action

3-moderate present with action and posture holding

4-marked, interferes with feeding

o Rigidity

+ Neck

0-absent

1-slight or only with activation

2-mild/moderate

3-marked, full range of motion

4-severe

+ RUE

0-absent

1-slight or only with activation

2-mild/moderate

3-marked, full range of motion

4-severe

+ LUE

0-absent

1-slight or only with activation

2-mild/moderate

3-marked, full range of motion

4-severe

+ RLE

0-absent

1-slight or only with activation

2-mild/moderate

3-marked, full range of motion

4-severe

+ LLE

0-absent1-slight or only with activation

2-mild/moderate

3-marked, full range of motion

4-severe

o *Finger taps*

+ Right

0-normal

1-mild slowing, and/or reduction in amp.

2-moderate impaired. Definite and early fatiguing, may have occasional arrests

3-severely impaired. Frequent hesitations and arrests.

4-can barely perform

+ Left

0-normal

1-mild slowing, and/or reduction in amp.

2-moderate impaired. Definite and early fatiguing, may have occasional arrests

3-severely impaired. Frequent hesitations and arrests.

4-can barely perform

o *Hand Movements (open and close hands in rapid succession)*

+ Right

0-normal

1-mild slowing, and/or reduction in amp.

2-moderate impaired. Definite and early fatiguing, may have occasional arrests

3-severely impaired. Frequent hesitations and arrests.

4-can barely perform

+ Left

0-normal

1-mild slowing, and/or reduction in amp.

2-moderate impaired. Definite and early fatiguing, may have occasional arrests

3-severely impaired. Frequent hesitations and arrests.

4-can barely perform

o *Rapid Alternating Movements (pronate and supinate hands)*

+ Right

0-normal

1-mild slowing, and/or reduction in amp.

2-moderate impaired. Definite and early fatiguing, may have occasional arrests

3-severely impaired. Frequent hesitations and arrests.

4-can barely perform

+ Left

0-normal

1-mild slowing, and/or reduction in amp.

2-moderate impaired. Definite and early fatiguing, may have occasional arrests

3-severely impaired. Frequent hesitations and arrests.

4-can barely perform

o *Leg Agility (tap heel on ground, amp should be 3 inches)*

+ Right

0-normal

1-mild slowing, and/or reduction in amp.

2-moderate impaired. Definite and early fatiguing, may have occasional arrests

3-severely impaired. Frequent hesitations and arrests.

4-can barely perform

+ Left

0-normal

1-mild slowing, and/or reduction in amp.

2-moderate impaired. Definite and early fatiguing, may have occasional arrests

3-severely impaired. Frequent hesitations and arrests.

4-can barely perform

o *Arising From Chair (pt. arises with arms folded across chest)*

0-normal

1-slow, may need more than one attempt

2-pushes self-up from arms or seat

3-tends to fall back, may need multiple tries but can arise without assistance

4-unable to arise without help

o *Posture*

0-normal erect

1-slightly stooped, could be normal for older person

2-definitely abnormal, mod. Stooped, may lean to one side

3-severely stooped with kyphosis

4-marked flexion with extreme abnormality of posture

o *Gait*

0-normal

1-walks slowly, may shuffle with short steps, no festination or propulsion

2-walks with difficulty, little or no assistance, some festination, short steps or propulsion

3-severe disturbance, frequent assistance

4-cannot walk

o *Postural Stability (retropulsion test)*

0-normal

1-recovers unaided

2-would fall if not caught

3-falls spontaneously

4-unable to stand

o *Body Bradykinesia/ Hypokinesia*

0-none

1-minimal slowness could be normal, deliberate character

2-mild slowness and poverty of movement, definitely abnormal, or some reduced amplitude of movement

3-moderate slowness, poverty, or small amplitude

4-marked slowness, poverty, or amplitude