

Effects of balance training on balance, gait, and non-motor symptoms in individuals with Parkinson's disease

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Submitted to the graduate degree program in Physical Therapy and Rehabilitation Science and the Graduate Faculty of the University of Kansas in partial fulfillment of the requirements for the degree of Doctor of Philosophy

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Abstract

Postural instability (PI) is one of the most disabling symptoms of Parkinson's disease (PD). PI is a well-known risk factor for falls in individuals with PD that worsens with disease progression. About 50-70% of people with PD fall once or more in a year, which is much higher than the 30% fall rate reported for community dwelling older individuals. Impaired balance associated with PI and fear of falling are factors related to decreased mobility and poor quality of life in individuals with PD. Several studies have examined the effects of exercise particularly strengthening and aerobic training on various motor and non-motor symptoms of PD. However to date, few studies have examined effects of balance specific interventions on balance, spatiotemporal gait, and non-motor symptoms such as fatigue, pain and depression. Moreover, none have used a commercially available device, Biodex Balance System (BSS) to implement a challenging balance training protocol. BSS consists of a moving platform that can be used to progressively challenge one's balance while providing visual feedback. Finally, most of the previous studies did not report information pertaining to clinically meaningful changes in balance and its implications to physical function and quality of life in individuals with PD. The overall objective of this study was to evaluate whether short term progressively challenging balance specific training using the BSS improves balance, spatiotemporal gait and non-motor symptoms including fatigue, pain and depression in individuals with PD compared to usual non-progressive balance exercises. The central hypothesis is that challenging balance exercises, where individuals with PD are challenged out of their comfort zone for static and dynamic balance can significantly improve balance and spatiotemporal gait.

Chapter 2 describes aims 1 and 2, utilizing 4 weeks of BBS balance training to determine changes in sway measures and spatio-temporal gait variables in individuals with PD. Ten individuals in a balance exercise group using the BSS and 10 individuals in general balance exercise group without Biodex (Non-BSS) completed the study. This study showed that 4 weeks

of balance exercises using BSS resulted in significant within group improvement in sway area, center of pressure (CoP), path length in antero-posterior (AP) direction in the BSS group. We also found significant within group improvements in the balance measured by Berg Balance Scale, gait velocity, and step length in both groups. Additionally, we found significant within group improvements in functional scores measured by the Timed Up and Go and 6 Minute Walk Test in both groups. **However**, we did not find significant between group differences for any of the outcome variables. Due to technical failure in the system, we were not able to report force plate data from the non-BSS group.

Chapter 3 describes aim 3, where 4 weeks of BSS training was utilized to determine changes in fatigue, pain, depression, fear of falling and quality of life in individuals with PD. Although motor symptoms of PD are described widely in the literature, and several studies report improvement in motor symptoms following various exercise trainings, little has been done to determine the efficacy of exercise interventions on the non - motor symptoms of PD. Aerobic exercise, strengthening, gait, tai-chi, qigong, and yoga therapy have been shown to improve motor deficits in PD. However, no study has examined the effects of balance training with BSS on non-motor features such as depression, fatigue, pain and fear of falling in individuals with PD. In our study, we determined the effects of balance training on non - motor symptoms of PD. The results demonstrated that 4 weeks of balance training resulted in a non-significant trend toward improvement in depression, pain, and fear of falling, and only the BSS training group demonstrated statistically significant improvement in fatigue.

In summary, this dissertation work provides evidence that the use of the BSS is feasible, safe, and effective in improving balance, gait, and function in individuals with PD. However further study with a larger sample size, randomized control design, and biomechanical (force plate) data in both groups is required to better understand the role of challenging balance training in this population. The findings of this dissertation work have implications about

designing future studies with specific intensity of balance exercises needed to make meaningful changes in balance, gait and non-motor symptoms of not only the individuals with PD but also in individuals with other neurological disorders resulting in PI.

Acknowledgements

I am feeling really happy and emotional at the same time, while writing this note of thank you to every single individual who was responsible in making this successful experience possible. This dissertation work represents my hard work, dedication, and hunger to become an independent researcher. This dissertation is a proof of quality student work performed at the University of Kansas Medical Center (KUMC) and specifically within the Clinical Orthopedic Rehabilitation Research (CORR) Laboratory. This dissertation is a result of excellent teaching, guidance, and support, which I experienced at KUMC, and I would like to take this opportunity to thank every single person who directly or indirectly contributed to this project.

First and foremost I wish to thank almighty God, who gave me this opportunity and strength to accomplish this work despite all odds. My belief and my faith in the almighty grew stronger during this educational journey. I would like to start with my chair and my advisor, Neena Sharma, PT, Ph.D. director of CORR lab for her valuable guidance, her patience and encouragement. This project would not have been possible without her continuous efforts, support and guidance throughout this journey. Despite several hurdles on the way, her faith in me motivated me constantly. Dr. Sharma not only provided guidance but also held my hand during the ups and downs in my research and provided the encouragement, without which I would have not made it. I thank her for putting me in challenging situations, which helped me become a better researcher and a better person. I am indebted to her for helping me understand better ways of conducting research and have patience required in research. Her enthusiasm and dedication toward scientific her work and research always inspired me and other students throughout my Ph.D. work, and I am fortunate that I will carry these priceless qualities with me in my future endeavors.

I would like to thank Dr. Kelly E Lyons, PhD. Director of research at Parkinson's Disease and Movement Disorders Center at KUMC, for her endless support throughout my doctoral

studies. Her understanding of my dissertation and my research work was the key factor for successfully completing my dissertation project. She is one of those persons at KUMC, who not only helped complete my dissertation project, but helped me grow stronger and kept my faith in humanity. Her guidance made me understand the core issues related to my dissertation topic. I adore her not only as a great researcher and a guide but also as a wonderful human being. I am deeply indebted to her for everything she did for me during my doctoral studies at KUMC.

I would like to thank Dr. Rajesh Pahwa MD, Director of Parkinson's Disease and Movement Disorders Center at KUMC for several reasons. I always felt very emotional talking or thinking about him. He held my hand during that critical period, when I was about to stray away from PhD. I approached him looking for a work position and guidance for my project. After learning about my financial situation, he created a position in the Parkinson's Disease and Movement Disorders Center, which was pivotal for my dissertation work in Parkinson's. I will forever be indebted to him and anything I write would not express the level of respect I have for him. He always inspired and will keep inspiring me throughout my life. His achievements are always a source of inspiration to students and new researchers like myself. I remember him putting articles on table for me to read. He has always been very supportive of anything I wanted to do. I have no hesitation in accepting that without Dr. Pahwa's extremely valuable guidance and his understanding of the movement disorders, this project would have never occurred. Despite my errors, he kept his faith in me and helped me understand the information, which I needed for my dissertation. I feel extremely fortunate to have worked under Dr. Pahwa's guidance.

I would like to thank my committee members: Wen Liu PhD, Yvonne Colgrove PT, PhD, Lisa Stenho-Bittel PT, PhD, and Henry Yeh, PhD for all of their time, support, suggestions and constructive criticisms in improving my dissertation work. Dr. Liu's extensive knowledge in Biomechanics and Engineering skills were instrumental in writing the basics of this project. Dr.

Colgrove has always been very supportive and provided her valuable suggestions, which improved my project in a better way. She also helped in conducting the project by serving as an external assessor for the outcomes. Dr. Stehno-Bittel has always been an inspiring personality and her guidance helped me to be a stronger person and a good researcher. Dr. Yeh's immense knowledge in statistics helped me understand all the statistical tests needed to complete this dissertation project. This whole document will not be complete, if I do not talk about Dr. Irina Smirnova, PhD. I am extremely thankful to her for her guidance and encouragement throughout my work here at KUMC. Her support and guidance has always helped doctoral students, especially international students in understanding several ins and outs of PhD.

The other faculty members, administrative staff, and DPT students in the Department of Physical Therapy and Rehabilitation Science (PTRS) have also been very helpful in the completion of this project. I really appreciate all the understanding, help and guidance I received through working as a Graduate Research Assistant and a Graduate Teaching Assistant. Additionally, I want to thank other departments and my fellow students in other departments at KUMC that enhanced my knowledge and experience outside of the lab and my dissertation project.

I'd like to thank former and present fellow students in our Ph.D. program for their friendship and moral support. I could not have completed this dissertation without their help and guidance through every step of the process. I am grateful to them for making my Ph.D. memorable in several ways.

I'd like to acknowledge all the former and present members of the CORR lab and the neuromuscular lab in the PTRS Dept.; their help and encouragement will always be remembered. I would like to thank Zaid Mansour, PT, Fahed Mehyar, PT, Christian Busch PT,

Tarang Jain, PT, PhD, and Viswa Gangedulla, PT as well as the members of the Georgia Holland Research Laboratory. Long conversations with fellow lab friends Dr. Tarang Jain, Dr. Saddam Kanaan, Zaid Mansour, and Fahed Mehyar enriched me not only culturally but also as a human being. I would like to thank Zaid and Fahed for spending long hours discussing my problems regarding dissertation and supporting me throughout my stay in Kansas City.

I wish to express my deep gratitude to the Parkinson's Disease and Movement Disorders Center at KUMC for providing me this opportunity to be a part of the program and learn from all the wonderful people at the center. I want to thank my team members at the center, Stephanie Ely, Janet Kirk, and April Langhammer for all the support and encouragement throughout my stay in the center. I can never thank team enough for what they have done. Additionally, I want to thank all the participants, who voluntarily agreed to participate in my research.

Above everything, I want to thank my wife Rupali Singh, PT, PhD (former student of KUMC) and my son Yuvraj Singh for all the love, support, and encouragement throughout my doctoral studies. I could not imagine completing this dissertation without their support. They waited years and years and never asked for anything. I would not be able to express in words, how I feel about them. I want to thank my mother, who allowed me to travel abroad and live my dreams. I feel really emotional and sad while I write this because she was the one who wanted to live for this day but she left us in 2011. Thank you ma for everything; it's because of your hard work, love, support, patience, and faith in me that allowed me to succeed. I know you would have been very proud of me. I want to thank my sisters and apologize to them for not being available to them during the most important events of their lives. I want to thank my father and apologize for being away from him, when he needed me the most. I want to thank all my family members including my uncles, aunts, and my cousins for their continuous support and

encouragement. I want to thank my in-laws, who constantly supported and encouraged me throughout my doctoral studies.

This document will be incomplete, if I do not mention about the person, who is not only financially responsible for my education but the one, who always believed that I can achieve this. I want to thank my uncle Narinder Singh MD, without whom I would have not even arrived to the United States. Despite being a busy doctor himself, he spent years and years teaching me, supporting me and encouraging me for higher studies. I cannot thank you enough. I would like to thank all my friends who have supported me through all these years and made my time here at KUMC enjoyable and memorable. Rock Chalk Jayhawk!

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CHAPTER 1

Introduction

1.1 Definition of Parkinson 's Disease:

Parkinson's Disease (PD) was first described by James Parkinson in 1817, in his essay on "Shaking palsy"¹. The essay included the characteristics of PD including resting tremors, decreased muscle strength, abnormal gait and balance that progressively worsen over time. Jean-Martin Charcot further described the disease of PD, explaining the features of rigidity, weakness, and bradykinesia. At present, both motor and non-motor symptoms of PD are well described in the literature^{2,3}. The main cardinal motor features of PD are tremors, slowness of movement, rigidity, and postural instability.

Tremor is the most prominent symptom of PD defined as rhythmic, oscillatory movements of the extremities. As the name implies, a resting tremor appears during rest and vanishes during active voluntary movements. PD tremors are usually at rest, ranging between 3 -6 Hz with amplitude of 1 -10 cm. A feature of tremor that is "pill rolling" is commonly seen in PD, where the patient rubs the thumb against the index finger. Tremors are also seen in the lower extremities, jaw and tongue. Tremor are basically classified based on when it occurs, either at rest, during an activity or with certain postures ⁴ Type I is classic parkinsonian tremor at rest, Type II tremor is resting and postural and kinetic tremors of different frequencies, ≥ 1.5 Hz, that occur in $\leq 10\%$ of PD patients). Type III are postural or kinetic tremors, 4 -9 Hz and Type IV are mono symptomatic tremors at rest, similar to classic tremor seen in type I PD and which persists for over 2 years)⁵.

Bradykinesia is defined as slowness of movement characterized by loss of amplitude and speed that causes difficulties with the entire movement process, beginning from planning to initiate movement to execution of movements³. The clinical diagnosis of bradykinesia is made by observing difficulty in performing quick repetitive movements such as tapping the foot or functional activities such as moving from sit to stand^{3,6}.

Rigidity is defined as increased stiffness and resistance to passive movements of both flexor and extensor muscle groups. Rigidity can be uniform resistance (lead pipe type) or ratcheting

resistance (cog wheel type)^{3,7}. A combination of tremors and increased muscle tone produces cog wheel rigidity in PD. The increased resistance is felt throughout the range of motion and is independent of movement velocity. In the initial stages of the disease, rigidity is asymmetrical, but progresses to affect the whole body and the ability to move^{3,7}.

Postural instability is one of the main cardinal features, which leads to impaired balance and frequent falls. About 38 - 68% of individuals with PD report at least one fall a year⁸⁶.

In addition to motor features mentioned above, several non-motor features are seen commonly in PD. Some of the non-motor features such depression and sleep disorders appear before the appearance of the motor symptoms. The most common non-motor symptoms of PD are depression, pain and fatigue along with other symptoms such as sleep disturbance, sexual dysfunction, anxiety and cognitive impairment^{8,9}.

1.2 Prevalence of Parkinson's Disease:

PD is the 2nd most common neurodegenerative disorder of the central nervous system following Alzheimer's Disease, with a male to female ratio of 3:2^{10,11}. PD affects approximately 7 -10 million people around the globe¹² and more than 1 million individuals in the USA alone¹¹.

Although, more common in individuals over 60 years of age, about 5-10% of the cases have a young onset, with early diagnosis between 20 -50 years of age⁷.

1.3 Risk factors and causes of Parkinson's disease:

Although most of the cases are identified as idiopathic with no known specific cause, some of the risks and causes have been related to aging, gender, tobacco and caffeine use, environment stresses (pesticides, occupation) and/or genetic disposition.

1.3.1 Age:

Similar to other neurodegenerative disorders, age is a clear risk factor for PD. The incidence of PD increases with age¹³, which is evident by the fact that only 5.4% individuals under the age of 50 years are diagnosed with PD, whereas the proportion of individuals diagnosed over the age of 65 years is 31.2%. Although earlier research studies reported extremely low prevalence of

PD in population under the age of 40¹⁴, the newer research reports indicate that incidence of young onset of PD (21-49 years) is increasing, with studies currently reporting up to 5-10% of overall cases to be young onset of PD^{7,15,16}.

1.3.2 Gender:

Epidemiological studies in PD have shown that men are 1.5 -2 times more likely to get PD compared to similar aged women¹⁷. Studies have reported that the age of onset in women is slightly later (2.2 years) than men. However, no gender differences in onset of PD have been reported in individuals under the age of 60 years^{18,19}. Higher prevalence rate of Parkinson's PD in men could be related to more toxicant exposure, head injuries, neuroprotection in females by estrogen, mitochondrial dysfunction, or X linkage of genetic risk factors²⁰.

1.3.3 Tobacco and caffeine:

There seems to be inverse relationship between tobacco use and PD²¹. Interestingly, people with more pack-years of smoking have lower risk of developing PD. It is believed that nicotine reduces nigrostriatal damage (neuroprotective) and nicotinic receptor drugs improve abnormal involuntary movements. Conversely, increased mortality in smokers may save these individuals from age related risk for developing PD²². Similar to tobacco, increased coffee consumption was associated with decreased risk of developing PD²¹. Individuals who drink coffee have decreased risk of developing PD as compared to non-coffee drinkers²¹. The protective effect of caffeine is associated with the fact that caffeine protects against the damage to dopaminergic neurons²².

1.3.4 Occupational risk and pesticide exposure:

Farmers and other individuals associated with agriculture and other rural occupations have been reported to have higher risk of developing PD. Although not clear, this could be due to frequent exposure to pesticides. People exposed to pesticides are 3 times at risk for PD, and the risk varies according to the type of pesticide²³. Although there is not enough evidence to associate any specific pesticide to development of PD, however a study by Costello et al. found

that exposure to Maneb and Paraquat increases the risk of PD especially in younger individuals and when exposure occurs in younger ages²⁴.

Another occupation that has been associated with increased risk for developing PD is welding and/or exposure to manganese. However, there is no clear evidence available with some studies confirming this association²⁵ and most refuting exposure to welding and manganese and its association with development of PD²⁶⁻²⁸.

1.3.5 Traumatic brain injury:

Traumatic brain injury has been related to the development of PD. Goldman et al²⁹ reported that the duration of unconsciousness and number of head injuries increased the risk for PD.

Individuals who are unconscious for more than 5 minutes are at 2 fold increased risk of PD.

Although unclear, in another study Goldman et al³⁰ indicated that damage to the blood brain barrier and subsequent neurotoxic injury or overexpression of proteins might lead to a neurodegenerative process.

1.4 Pathology of Parkinson's Disease:

1.4.1 Anatomy:

The dopaminergic system innervates the basal ganglia. The main pathological hallmark of PD is neuronal loss in the substantia nigra (ventral part of pars compacta), which may lead to loss of 70% of the cells by the time first motor symptoms appear³¹. The reduction in dopaminergic neurons leads to reduction of high affinity dopamine (DA) uptake. The reduction in DA uptake forces the DA out of the synapse into the extracellular space which reduces the availability of DA resulting in symptoms of PD.

1.4.2 Pathophysiology:

Five major pathways connect to the basal ganglia including motor, associative, oculomotor, limbic and orbitofrontal pathways. All five pathways are involved in the pathology of PD resulting in multiple symptoms including movement problems, and attention and memory deficits. The motor pathway has been investigated thoroughly and has been a part of research investigation

for quite some time. Since 1980, a conceptual model of motor programming has been created with many modifications proposed since. According to this model, the basal ganglia controls movement, associative learning, planning of the movement, working memory and emotion. Since Parkinson's is mainly a movement disorder, we will concentrate on the "motor circuit". The basal ganglia primarily consists of a group of nuclei situated at the base of the forebrain. The striatum which is composed of caudate and putamen, is the largest nuclear complex of the basal ganglia³². Normally a balance in neuronal activity causes either the facilitation or inhibition of movement, which occurs within each nucleus of the basal ganglia (Figure 1). There are 2 entry systems to the motor circuitry of basal ganglia: striatum and subthalamic nucleus. Output occurs through the globus pallidus pars interna, which connects to the cerebral cortex via fibers originating from motor thalamus. Any neuronal activation that produces movement activates the basal ganglia via 2 systems, either directly through disynaptic projections to the globus pallidus pars interna or indirectly through trisynaptic projections via globus pallidus pars externa. Corticospinal afferents inhibit spiny neurons in the indirect circuit, thereby facilitating the neurons in the direct circuit in healthy brain. The activity of the globus pallidus pars externa is pivotal in regulating the motor output of basal ganglia. Dopamine assists to make small adjustments in neuronal activity, which in turn modulates globus pallidus pars interna/externa and subthalamic nucleus. Decreased dopamine availability disrupts the normal activity of the corticostriatal afferents, which in turn leads to increased activity of the indirect circuit and decreased activity of the direct circuit (Figure 2). Although the exact events causing increased activity of subthalamic nucleus are not well understood, dopamine is thought to be involved. There is a consensus that the death of midbrain dopaminergic neurons and their striatal projections is the main cause of developing parkinsonian symptoms. Previous research studies suggested reversed trends of pallidal discharge rates following dopamine replacement therapy. Additionally, physiological studies in MPTP treated monkeys suggested dopamine depletion induces abnormal coupling of basal ganglia loops³³. Increased availability of dopamine, as

evident by the studies examining the effects of levodopa, improves motor function, which further strengthens the pathway explained above.

1.4.3 Lewy bodies:

It is believed that abnormal accumulation of alpha synuclein protein and ubiquitin is responsible for damaged dopaminergic cells found in PD. These proteins accumulate inside the neurons in the form of masses called "Lewy bodies". These rounded eosinophilic bodies 5 -25 micrometer in size are seen in case of neuritis or free in extracellular space³⁴. On structural analysis, Lewy bodies are found to have electron dense granular core and a halo on the periphery of radially oriented filaments up to 7-8 nanometers. Lewy bodies are not only found in regions of cell loss, that is the substantia nigra, but are also found in other areas such as locus coeruleus, dorsal motor nucleus of vagus, nucleus basalis of Meynert, neocortex, diencephalon, spinal cord and peripheral autonomic ganglia³⁴.

1.5 Diagnosis of Parkinson's Disease:

The diagnosis of PD is made by neurologist based on clinical symptoms that follow the United Kingdom Parkinson Disease Brain Bank Criteria (Appendix 1). Although there are no objective tests to clearly identify the disease, brain scans are often used to make proper diagnosis.

According to United Kingdom Parkinson Disease Brain Bank Criteria, presence of bradykinesia and either rigidity, resting tremor or postural instability are indicative of PD³⁵. However, there are other causes of these symptoms that can rule out diagnosis of PD.

About 75-90% of the neurologists who specialize in management of PD accurately diagnose the condition³. Additionally, dopamine function can be measured with positron emission tomography (PET) and single photon emission computed tomography (SPECT) radiotracers.

These imaging methods can detect decreased dopamine activity in the basal ganglia seen in PD and assist with diagnosis³⁶. Upon diagnosis, patients are staged according to the Hoehn and Yahr scale. The Hoehn and Yahr Scale was developed in 1967, prior to knowledge about levodopa. It is a simple and descriptive staging scale that provides an estimate of clinical

function in PD patients. The scale has 1 -5 stages (Appendix II) and is based on two concepts, the severity in PD related to bilateral limb involvement and balance problems. A recently modified Hoehn and Yahr scale was introduced to minimize discrepancy in staging the symptom severity. The modified version included 2 additional stages, 1.5 and 2.5 to the initial 1-5 staging criteria. These added stages provide additional steps for categorizing severity of PD and accurate matching of the stage of severity with actual symptoms³⁷.

1.6 Overview

Postural instability (PI) is one of the most disabling symptoms of PD that worsens as the disease progresses causing increased gait abnormalities and falls during middle to late stages of the disease³⁸. The cardinal features of PD including resting tremors, rigidity, bradykinesia and postural instability are primarily associated with loss of dopaminergic neurons from the substantia nigra leading to impaired basal ganglia thalamo-cortical pathway activity. PI leads to disability and poor quality of life. PI correlates strongly with falls and increased fear of falling, which further deteriorates the quality of life. Isolated and recurrent falls occur quite frequently in individuals with PD. Between 35 – 90% of patients with PD report falling once and about 18-65% patients fall more than once in 2 year period. In the US, more than \$23,000 per person with PD is spent annually on healthcare, which is more than double that for similar aged healthy individuals.. Medical management with dopaminergic medications helps in improving postural instability in the early stages, but potency effects tend to decrease as the disease progresses. Surgical options according to eligibility criteria determined by neurologists are limited to a small proportion of patients, have shown to provide modest improvements in postural instability. Whereas, studies focusing on different modes of exercise training including aerobic exercise, strengthening, balance training/exercise or non- traditional forms of exercise such as Tai-chi, Yoga and Qigong have shown promising results for improving balance and postural instability at all stages of the disease. Animal studies have shown that exercise is useful in delaying the onset of symptoms in PD³⁹. Exercise in PD stimulates the production of dopamine in the healthy

dopaminergic cells, which causes improvement in motor as well as non-motor symptoms of the disease. Fox et al. suggested that challenging and complex exercises improve dopamine production and promote learning of motor tasks, if implemented during the early stages of PD⁴⁰. Recent studies identified that physical therapy, which includes balance challenging exercises help improve postural instability and reduce the risk of falls.

1.7 Human Posture and Gait:

1.7.1 Postural control:

Postural control is an important determinant of stability in various positions such as sitting and standing. Human beings have a unique ability to control posture while walking and performing various activities of daily living. The ability to stand up straight is compromised during activities of daily living, due to a smaller base of support of bipedal stance.

Walking becomes even more challenging due to the changing environment around the person such as various walking surfaces, stairs and inclines. In order to maintain upright position and carry out everyday activities, the human body withstands forces of gravity and other external forces. Two postural control mechanisms have been reported⁴¹, one which controls orientation, minimizing the muscular activity required to stabilize the joints against gravity and second that works on maintaining stabilization (equilibrium) via keeping the body's center of mass (CoM) within the base of support. These two postural control mechanisms work in parallel to each other to execute movement⁴². Three processes of the central nervous system are utilized for movement execution: 1) sensory organization, which includes vestibular, visual and somatosensory systems, 2) neuromuscular response and 3) muscle tone⁴³.

1.7.2 Sensory organization:

It is well evident that postural control is dependent on information provided by vestibular, somatosensory and visual systems⁴⁴. The somatosensory system controls posture via proprioceptive input from muscle spindles, joints and cutaneous receptors. To maintain quiet,

erect stance and carry out daily tasks, human beings rely on proprioceptive and cutaneous information. The central nervous system processes the afferent information and integrates the information at various levels resulting in efferent processing for coordinated firing of multiple alpha motor neurons and related muscle fibers. This afferent information processing occurs at spinal cord level and is sent higher up to subcortical or cortical areas for further refinement for voluntary movements⁴⁵.

Muscle spindles are important for proprioception. These stretch sensitive mechanoreceptors provide information about muscle length and speed of contraction to the central nervous system, thus allowing the individual to discern between joint movement and joint position sense. Additionally, muscle spindles provide afferent information that translates into reflexive as well as voluntary movements.

Golgi tendon organs also aids in proprioception. Golgi tendon organs (GTO) in the muscle tendon are sensitive to very minute changes and relay information about the changes in tensile forces caused by active contraction or passive stretching. Activation of GTO results in turn inhibits activity of the alpha motor neurons, resulting in decreased tension of the corresponding muscle and the tendon.

Vestibular system is composed of two types of organs: semicircular canals and the otoliths. Semicircular canals are filled with fluid and detect the angular velocity of the head. Otoliths are present on the hair cells and work as linear accelerometers. These two organs together detect the position and motion of the head. The vestibular system is very unique in its multisensory and multimodal working. For example, the vestibular system interacts with proprioceptive system and corollary discharge, which allows CNS to distinguish between active and passive head movements. Both the visual and proprioceptive pathways work also together with vestibular system throughout the central vestibular pathways in order to control gaze and posture. Afferent input is received by premotor and second order neurons in the brain stem and is relayed to motor neurons, making it a streamlined circuitry for shorter latencies. Some simple pathways

also facilitate the vestibular spinal reflexes that are necessary for maintaining posture and balance. The interaction of multisensory and multimodal systems is vital for some higher functions such as self-motion perception and orientation in space and is basically due to inherent complexity⁴⁶. The visual system, is considered the primary system responsible for balance⁴⁷ has 3 components: the central system, ambient and retinal slip. The central visual system controls the target motion perception and target recognition, whereas ambient or peripheral vision is concerned with movement and is believed to dominate both self-motion perception and postural control. The retinal slip, which is a part of afferent motion perception is concerned with the person's displacement and provides feedback for compensatory sway. Several research studies⁴⁸ have shown that young adults rely on vision for postural control, which strengthens the fact that vision is very important for postural control. However, it is important to note that one can stand upright in the dark or individuals with impaired vision as well.

In addition to central processes, it should be noted that peripheral vision plays an important role in maintaining a stable stance. A study by Berensci et. al⁴⁹. showed decreases in postural sway due to over-stimulation of peripheral visual field. This study explained that peripheral vision can be used for visual stabilization of spontaneous or visually induced body sway to control posture.

1.7.3 Mechanism of postural adjustments

Feedback and feedforward are the two types of postural control mechanisms utilized by humans to maintain balance⁵⁰. The type of postural task determines the response elicited. Several studies have documented that feedback postural adjustment occurs following unexpected perturbation. When a person is displaced from one position, an opposite postural response moves the center of mass (CoM) back within the base of support⁵¹. Postural responses occur due to somatosensory feedback from the legs and feet^{52,53}. Several studies have examined the compensatory strategies used by the CNS to regain stable position following perturbation⁵⁴. The

CNS integrates information from various receptors and pathways, to coordinate firing of alpha motor neurons and the corresponding fibers⁴⁵. This eventually initiates stretch signals from the muscles to the spinal cord and cross-neural connections returning to the muscles and resulting in muscle contraction. This mechanism has shorter latency, which does not necessarily affect posture but it affects some simple behaviors⁵⁵. The next important level of feedback for balance involves signals ascending to the midbrain. The brainstem acts as a communication and assimilation center, which receives and sends a large number of sensory and motor signals. Longer conduction paths and a large number of neural synapses, which result in longer latencies than spinal reflexes, is a characteristic feature of mid-level feedback loop. However, accumulation of large numbers of signals and complex connections allows generation of complex automatic movements by the brainstem. The brainstem is modulated by higher CNS levels, and it modulates behavior of spinal reflexes. Finally, signals from the cerebral cortex result in highly complex voluntary movements with much longer latency time than the other two mechanisms (spinal and brain stem) mentioned above⁵⁶. In everyday life, during activities where the CoM moves away from the stable position, postural adjustments must occur prior to the movement execution. To move from one stable position to the other, the CNS uses feedforward model and executes signals to the postural muscles to stabilize the body, within the base of support⁵⁶.

1.7.4 Mechanisms of gait control:

One of the main features of gait and locomotion in humans is the inter-limb coordination. Neural circuits in the spinal cord generate impulses, which control upper and lower limb activities⁵⁷. It is believed that a flexible coordination between thoracolumbar and cervical neural mechanisms allows skilled movements and loco-motor activities. This flexible coordination between thoracolumbar and cervical neural mechanisms signifies a functional task dependent control of neuronal pathways in neural circuits controlling upper and lower extremity muscles during walking. Coordination of muscle activation between both legs ensures the regulation of

locomotion. This inter-limb coordination is in accordance with central pattern generators as well as the half center model proposed by Dietz et al⁵⁷ that indicates upper and lower extremities act differently during gait⁵⁷. According to the half center model, the neuronal circuits that are responsible for coordination of flexor activity on both sides during swing phase (flexor half centers) mutually inhibit one another. On the other hand extensor half centers have no mutual inhibition, as evident in stance phase where extensors on both sides are working simultaneously to allow standing. Similar inter-limb coordination is also seen in upper extremities during walking⁵⁸, which implicates similar control mechanisms in both upper and lower extremities⁵⁸. A functional magnetic resonance imaging study indicated that inter-limb coordination is controlled by the supplementary motor area⁵⁹.

1.8 Pathophysiology relevant to posture and gait problems in Parkinson's Disease:

1.8.1 Postural abnormalities:

Previous studies indicated that both components of postural control; orientation and stability are impaired in PD^{42,60}. Several studies have focused on postural instability in individuals with PD since it leads to impaired balance, impaired gait, frequent falls and poorer quality of life.

1.8.2 Axial orientation as a cause of postural instability:

Postural orientation in the form of a stooped posture is one of the main abnormalities seen in PD. The other common postural abnormalities seen in PD are Pisa syndrome⁶¹, tilt of the trunk in the lateral plane and captoconia⁶², abnormal posture of trunk in antero-posterior (AP) plane with marked flexion of thoracolumbar spine. Animal studies have shown that lesions in substantia nigra result in forced rotations in rats as assessed by unilateral 6-hydroxydopamine lesions of the ascending dopaminergic neurons⁶³. Additionally, lesions of the single caudate nucleus affect the orientation of the body opposite to the side of lesion. These results indicate the importance of substantia nigra and basal ganglia in axial orientation. A recent study⁴² reported impaired proprioceptive stimulation leads to postural abnormality in PD. A study by Vaugoyeau et. al. indicated that if slow perturbations below the semicircular canal threshold are

delivered to young healthy individuals standing on a platform, the individuals tend to stay vertical, even in the absence of vestibular and visual feedback⁶⁴. This suggests that proprioceptive feedback is the main system that controls posture in semi static conditions, and the vestibular system only contributes to large amplitude perturbations. In a following experiment, authors found that individuals with PD had increased trouble in maintaining vertical position than the healthy controls in the absence of visual and vestibular feedback⁶⁴.

1.8.3 Postural instability in PD:

Postural becomes a major concern during middle to late stages of PD³. Postural instability results in change of postural strategies during unexpected and expected voluntary destabilization conditions⁶⁵. Since it is difficult to treat, postural instability becomes a major concern leading to frequent falls⁶⁶. Although postural instability in PD is not well understood; it is believed that several neural levels are involved. Pathophysiological studies in PD suggested abnormalities exist in processing circuits from visual, vestibular and proprioceptive systems. The abnormal postural strategies during the destabilizing conditions leads to postural instability⁴³, which involve both feedforward and feedback reactions^{67,68}. Individuals with PD have normal timing and excessive muscle activity in destabilizing conditions, suggesting that people with PD do not lose global proprioception⁶⁹. However, kinesthetic changes were shown to correlate with the affected side according to severity of the disease and UPDRS. Since the BG are responsible for perception of movement and its direction and proprioception plays an important role in control of postural reactions due to unexpected perturbations. It is suggested that kinesthetic problems may cause problems with postural responses to counteract external perturbations leading to postural instability. Dopamine deficiency causes worsening of kinesthetic abnormalities⁷⁰ but not postural reactions⁷¹, which suggest that kinesthetic deficits may be partially responsible for postural instability in PD.

Deep brain stimulation surgery results in subtle improvements in kinesthesia⁷² but not during postural reactions⁷³, further strengthening the argument that kinesthesia may not be responsible

for postural instability in PD. Postural instability in PD is also evident by the presence of retropulsion (pushing backwards). Horak et. al⁷⁴ reported that stability margins were smallest in the backward direction both with narrow and wide stance. The decreased stability margin was due to slower rise and smaller peak of center of pressure (CoP) in PD patients. Effects of PD on postural sway measures remain a matter of debate, with studies reporting either increase⁷⁵, decrease⁴³ or no difference^{68,76} between individuals with PD and healthy controls.

Previous studies have suggested that impairment in sensory inputs could contribute to postural instability. Kitamura et al⁷⁷ suggested that in the absence of visual feedback, CoP shifted backwards significantly as compared to forward shift in age matched controls. This supports the concept that impaired visual feedback contributes to impaired upright posture.

Similarly individuals with PD resulted in abnormally increased postural responses caused by slow perturbation visual environment⁷⁸. Vangoyeau et al⁴⁴ suggested that increased vision dependence in PD is considered as a compensatory strategy for impaired proprioception. However with progression of the disease, the ability to use compensatory sensory feedback with visual sensory feedback may not provide adequate compensation with increased proprioceptive deficits. Additionally, postural instability in PD is not related to dopamine deficiency⁷⁹. Previous studies have shown that dopaminergic medications result in limited improvement⁷³ in velocity of postural transitions and automatic postural responses.

1.8.4 Gait problems in Parkinson's Disease:

Dopamine deficiency in PD has been associated with increased neuronal activity in the basal ganglia⁸⁰. Increased activity in basal ganglia with increased output from globus pallidus pars interna via indirect loop that inhibits thalamo-cortical circuitry, leads to movement deficiency (Figure 2)⁸⁰. Increased basal ganglia output inhibits brainstem initiated movements. Other motor abnormalities such as simultaneous movements, sequencing of movements, and reduction in amplitude have not been linked directly to pathophysiology of basal ganglia⁸⁰. However, decreased leg extensor muscle activity and poor balance due to impaired proprioception and

deficits in neuronal coordination of upper and lower limbs have been linked to gait problems⁸¹.

Gait problems in PD are present in many forms such as initial movement hesitation, freezing and festination.

Due to delay in phasic firing from the globus pallidus to the cortex, gait speed decreases.

Furthermore, freezing of gait occurs if phasic firing becomes slower or is completely absent.

Freezing of gait is defined as a brief, episodic absence or marked decline in forward progression of legs, leading to no movement. Festination is described as rapid, small steps in order to keep the CoG in between the feet that results in reduced gait speed⁸², has been shown to be related to impaired movement cues from the globus pallidus⁸³. Another alteration which occurs in gait is slowness (hypokinesia). The major contributor to gait problems in PD is the reduced amplitude of movement leading to decreased stride length (Morris 1994). A shortened stride length can be linked to other gait abnormalities such as decreased walking speed, increased cadence and double limb support time. All these gait problems lead to increased fall risk in PD⁸⁴.

1.9 Falls in Parkinson's Disease:

It has been shown that postural instability in PD leads to frequent unexpected falls^{66,85,86}

During everyday activities, balance is continuously challenged by external perturbations, different support surfaces and environment⁴⁹. The impaired balance and postural instability is more evident during transitioning from one position to another and walking in an attempt to maintain upright stance and stability. A fall is “an unexpected involuntary event that results in body coming to rest on the ground, and is not caused by any major intrinsic feedback⁸⁷”.

Another phenomenon, which has been described in several studies is “near falls”⁸⁸, which is the feeling that an individual senses that s/he is about to lose their balance but is not associated with a real fall.

1.9.1 Epidemiology of falls in PD

Falls in PD lead to serious injuries including fractures and head injuries⁸⁹. Bloem et al⁹⁰ suggested that individuals with PD are 9 times more susceptible to falls than the age matched

controls. Several prospective studies examined fall incidence rates⁹⁰⁻⁹³ in ambulatory individuals with PD, who had no other obvious causes of falls. The results showed that approximately 70% of individuals with PD reported at least one fall a year⁹⁴. Another study⁹⁵ that included a large sample (n=350) of PD patients reported that 46% of subjects fell once a week and 33% fell at least twice or more often in a week. A 20 year multicenter study⁹⁶ found that 87% of the PD patients experienced falls and about 35% sustained fall related injuries. Hip fractures caused by PD leads to high mortality and morbidity. Fall related injuries are the most common cause of hospital admissions in individuals with PD⁹².

1.9.2 Pathogenesis of falls in Parkinson's Disease:

It is well established that postural instability is one of the main causes of falls in PD. Walking and postural instability are not only regulated by higher subcortical mechanisms but also involve attentional mechanisms⁹⁷. Under particular conditions, gait and stability requires extra attentional resources. For instance during multi-tasking, individuals with PD demonstrate increased postural instability, which increases their risk of falls⁹⁸. When CoM is displaced out towards the limits of stability, which happens during everyday activities such as sit to stand transitions as well as walking, stepping strategies are used to prevent falls. Recently, studies in PD have shown that patients have difficulty in initiating compensatory stepping⁹⁹, more specifically towards lateral direction¹⁰⁰.

1.9.3 Biomechanical changes in CoP in Parkinson's Disease

Poor balance is one of the main risk factors associated with falling in PD^{60,91,101-103}. Force platform measurements have been used widely to assess changes in balance during quiet standing with eyes open (EO) and eyes closed (EC). The effects of normal aging superimpose the effects of disease pathology, as well as the treatment in PD. The effects of PD on postural sway appear unclear, with few studies reporting either increase⁷⁵, decrease⁴³, or no differences^{68,76}. To date, several studies incorporated measures to evaluate changes in CoP. Antero-posterior (AP) and medio-lateral (ML) CoP path lengths have been used to assess

differences in balance between PD individuals and healthy controls. Few studies have reported significant differences in the AP and ML path length in individuals with PD as compared to healthy controls^{74,104,105}.

In 1991, Schieppati and Nardone⁶⁸ evaluated CoP in individuals with PD using CoP position, sway area, and path length in quiet standing with EO and EC. They found that the mean CoP was significantly shifted toward forward directions in PD subjects as compared to healthy controls. Similarly, Blaszczyk in 2007 found that the shifted mean CoP was sensitive to visual conditions⁶⁸. These results support the argument related that stability is reduced in anterior direction in PD.

Recent studies provide some insight into the changes in sway measures and its relationship with the postural instability in PD patients. Although some studies examined these sway measures in PD as compared to healthy individuals, most failed to report definite conclusions. One study focused on the assessment of PI in the absence of visual feedback comparing 55 individuals with diagnosis of PD (Stages I – III of H& Y stage) and aged 64.6 ± 8.9 years to a group of age matched healthy control individuals with mean age of 64.3 ± 7.9 years⁷⁵. They tested the participants in 2 different conditions, EO and EC. The results of this study showed significant differences in the measures of sway area, sway range in AP and ML, and path length in both AP and ML directions between the PD group and the control group in eyes closed condition.

Excluding visual output showed greater impairment in the PD group as opposed to the control group; however, these changes might not reflect the severity of postural instability. This study⁷⁵ however, showed that mean CoP displacement is specifically greater in individuals with PD as compared to control group. These findings were different from the previous studies that reported no significant difference in the mean CoP displacement between the PD and control groups⁷⁶. Similarly, several other studies support the evidence that increased postural instability in PD is an indicator of increased fall risk^{106,107}. In light of the aforementioned information, it is important

to evaluate the effectiveness of exercise trials in individuals with PD to monitor the improvements in CoP parameters, which are directly related to postural instability in this population. Postural instability is a strong determinant of perceived disability in individuals with PD and is a leading cause of morbidity and mortality in this population. These studies suggest that balance and fear of falling measures are important factors for the efficacy of rehabilitation in this population.

1.10 Fear of falling:

The progression of PD is associated with fear of falling⁶⁵. Fear of falling can be more disabling than a fall¹⁰⁸ and is experienced during daily activities, which results in loss of mobility¹⁰⁹⁻¹¹² in addition to other negative consequences such as weakness, osteoporosis and cardiovascular problems⁹⁶. Limited studies in PD have examined fear of falling, despite the fact that increased fear of falling^{70,76} leads to decreased physical activity^{65,90,113-115} and poor quality of life. Few studies report that individuals with PD have decreased confidence in performing daily activities^{65,115-117}.

1.11 Other non-motor symptoms of Parkinson's Disease

Non-motor symptoms (NMS) are an integral part of the Parkinson's disease symptomatology, and in fact are present much earlier during the course of the disease. Despite the presence of and their impact, NMS are often overlooked in the presence of major motor symptoms. Depression, anxiety and fatigue were undiagnosed by the neurologists in more than 50% of the cases of PD¹¹⁸. Recent studies reported links between dopaminergic systems and the hippocampus, which could partly explain the pathophysiology of non-motor symptoms such as fatigue¹¹⁹. Several studies have reported the presence of fatigue in PD at higher rate than healthy individuals¹²⁰⁻¹²⁴. About 33 – 58% of individuals with PD report fatigue. One third of the individuals diagnosed with PD¹²⁵ recognize fatigue as one of the most disabling symptoms and about 67%¹²⁵ report that fatigue in PD is qualitatively different from the fatigue they experienced long before they were diagnosed. The pathophysiology of central fatigue in PD is largely

unknown; however the concept of primary and secondary fatigue hold true for individuals with PD. Fatigue has been associated with depression and other comorbidities. On the contrary, fatigue has also been reported in PD patients without depression. A feedback loop described by Convington et al.¹²⁶ suggested that presence of depression, fatigue, pain, inactivity and deconditioning act together resulting in disability. Research studies using transcranial magnetic stimulation demonstrated that physical fatigue causes cortico-motoneuron excitability in normal healthy individuals as well as individuals with PD^{127,128}. Additionally, a study by Lou et al¹²⁹ found that PD patients had increased motor evoked potential amplitudes and prominent post exercise facilitation as compared to controls following a fatiguing exercise. However, following administration of levodopa, these differences disappeared, which suggests that fatigue in PD may be caused by abnormal corticomotor neuron excitability.

Depression is widely reported in PD populations and has a large impact on the prognosis of the disease. The presence of depression is known to affect motor function, functional level and quality of life in this population¹³⁰, but sadly it still goes untreated and undiagnosed. The prevalence of depression varies between 4 - 90%¹³¹, with at least 30-50%^{132,133} reporting significant fatigue. PD affects limbic and cortical regions in addition to structures responsible for motor functions. The nor-adrenergic locus coeruleus and raphe neurons degenerate in PD. Additional dopaminergic neurons of substantia nigra as well as ventral tegmental area are affected¹³⁴. A study indicated increased loss of dopaminergic neurons and nor-adrenaline transporter in locus coeruleus and limbic system in individuals with depression as compared to non-depressed patients in PD¹³⁵. Additionally, serotonin transporters have been reported to be markedly decreased in brain in advanced stages of PD. Exercise has been reported to have beneficial effects on both motor and non-motor symptoms of PD. A few studies have reported either a decrease¹³⁶ or no change¹³⁷ in depression following an exercise training in individuals with PD.

Pain is one of the major NMS, which is reported by as many as 80% of patients with PD^{138,139}. A cause of disability and pain in PD is overlooked and underdiagnosed¹⁴⁰; a recent review study on practice guidelines from the American Academy of Neurology did not include pain in their report¹⁴¹. The various subtypes of pain reported in PD are musculoskeletal, dystonic, neuropathic and central pain. Although not well understood, clinical studies suggested that cortical-basal ganglia-thalamic circuit is involved in pain¹⁴². Data from an fMRI study showed increased cerebral blood flow indicates increased pain induced cortical activation in the “off” levodopa state as compared to “on” state in individuals with PD¹⁴³. Although exercise has been shown to be beneficial on many motor and NMS of PD, the effects of exercise on pain have not been reported. One study¹⁴⁴ reported improvement in pain following flexibility and relaxation, walking and Nordic walking training. Alternative therapies like massage therapy¹⁴⁵ and acupuncture^{146,147} reported significant reduction in pain and stiffness.

1.12 Motor function measures in Parkinson’s Disease:

In the last few decades, several biomechanical pieces of equipment like force plates, Gaitmat, and Biodex as well as clinical scales have been developed and validated to evaluate motor deficits in PD. Other scales have been designed to evaluate the impact of motor symptoms on the fear of falling, activities of daily living and quality of life. All these measures have been extensively used to evaluate the effectiveness of exercise on patients with PD.

1.12.1 Biomechanical instrumental methods

1.12.1a Posturography using force plates

One of the main and sensitive instrumental methods to measure postural sway is static posturography. The participants are instructed to stand on force plates and asked to stand upright with shoulders level, arms on the sides, eyes open looking straight ahead, with feet shoulder-width apart. The vertical ground reaction forces under each foot are used to calculate CoP for both left and right foot and the overall center pressure by combined measurements from both sides. The CoP is vertical representation of CoM, which reflects the postural sway. As

required by any particular protocol, the participants can be instructed to stand either with eyes open or closed, to help distinguish the effects of vision on postural sway. Additionally balance in steady standing can be evaluated by testing the participant's ability to maintain different positions. Patients can also be instructed to stand in a variety of standing positions such as feet shoulder-width apart, feet together, stride stance and tandem stance¹⁴⁸.

1.12.1b GaitMat II System:

GaitMat II is an instrumented walkway, which has been widely used to collect spatio-temporal gait data¹⁴⁹⁻¹⁵². Foot activated switches are embedded throughout the length of the walkway sending output to a computer that provides analyzed data on 9 different spatio-temporal parameters: walking speed, step length, step time, swing time, stance time, and double support time. The GaitMat II is 3.87 meter long, 0.75 meter wide and 0.03 meter thick. There are 40 rows and 256 columns of pressure sensitive switches arranged in a 2 dimensional (1 cm x 1 cm) grid. These pressure sensitive switches scan the pressure information every as the subject walks on the mat.

1.12.2 Functional Balance Tests

1.12.2a Berg Balance Scale

The BBS is a 14-item test, with each item scored from 0 to 4, developed to measure static and dynamic standing balance. A perfect score of 56 on the Berg Balance Scale (BBS) can be considered a reference standard for assessing balance in people with PD. BBS is one of the most commonly used balance assessment tools in the clinic and in research laboratories. The internal consistency of the BBS lies between moderate to high, ranging from .85 to .98. A score of 41-56 represents low, 21-40 represents medium and 0 - 20 represents high fall risk and a change of 5 points is considered clinically meaningful change. A standard procedure is used to administer this test. The equipment needed for this assessment includes a stopwatch, two chairs (one with and one without arms), a stepstool and a ruler or yardstick. This test takes no more than 15 minutes to complete.

1.12.2b Timed Up and Go Test (TUG):

The TUG is a quick measure of dynamic balance and mobility. The scores are reported in seconds. The test involves standing from a chair, walking 3 meters, and walking back to sit down. The equipment needed for the test is a chair, a bright colored cone, and a stopwatch. A clinically meaningful change between 2-5 second has been reported in individuals with PD¹⁵³.

1.12.2c Six Minute Walk Test (6MWT):

The 6MWT assesses endurance by measuring the distance walked in 6 minutes. The test is conducted in a long corridor usually 18 meters long, and the participants are asked to walk back and forth in the corridor continuously for 6 minutes. The equipment needed for the test is 4 chairs in case the participant wants to sit and rest during the test, one at the each end and one at 6 meters and one at 12 meters. A tape measure and two bright colored cones and movable measuring meter are required for the testing. The test usually takes 6-10 minutes^{154,155}

1.12.2d Survey of Activities and Fear of Falling in Elderly (SAFFE):

SAFFE is an 11 item scale¹¹⁴, which includes tasks of activities of daily living (ADL) and instrumental activities of daily living (IADL) (e.g., taking a tub bath or shower), mobility (such as in walking for exercise) and social life (such as visiting family or friends). Each question is followed by a series of questions such as (a) "Do you currently do an activity?" (b) "When you do the activity, how worried are you that you might fall?" (c) "If you don't do the activity, do you not do the activity because you are worried?" SAFFE indicates fear of falling and level of activity, which is measured on (0 – 4) Likert scale, with higher scores indicating increased fear of falling. An internal consistency of 0.7 has been reported for SAFFE¹⁵⁶.

1.12.2e Forward Reach Test (FRT):

FRT is a dynamic standing balance task¹⁵⁷, which measures the maximum distance that an individual can reach forward with a fully extended arm during a fixed base of support. The individuals are asked to stand with their dominant side close to the wall without touching the wall, with their feet 10 cm apart. The patient is required to raise the arm, with shoulder in 90

degrees of flexion with the outstretched hand. The patient is asked to reach as far as possible forward without bending the knees and without losing the balance. The difference between the starting and final position is measured using a tape measure. FRT has been shown to have good reliability and validity and has been used as an outcome measure for PD¹⁵⁸.

1.12.3 Clinical tests for Parkinson's Disease:

1.12.3a Unified Parkinson's Disease Rating Scale (UPDRS):

The UPDRS is a gold standard instrument used to measure disease severity in PD¹⁵⁹. It is a comprehensive, efficient and flexible scale to assess disability and impairment in PD. The scale has 4 components: Part I – motivation, behavior and mood, Part II – self-evaluation of the activities of daily living (ADL's), Part III – clinician scored motor evaluation, and Part IV – complications of therapy. The average time to administer the test is about 15 - 20 minutes. Sections I, II and IV are self-report whereas section III is administered by a trained clinician. Each question in sections I-III is based on a 0-4 scale, where 0 means minimal or no loss and 4 means severe loss.

1.12.4 Tests to assess non-motor symptoms of Parkinson's Disease

1.12.4a Geriatric Depression Scale (GDS):

The Geriatric Depression Scale is the most common self-rating depression scale in geriatric population. GDS comprises of 30 questions in yes/no format¹⁶⁰. GDS have been extensively used to assess the severity of depression in elderly individuals, as well as individuals with PD. In a large sample (n = 109) non-demented PD patients, it was established that GDS has high sensitivity (0.78), specificity (0.85) and validity¹⁶¹.

1.12.4b Fatigue Severity Scale (FSS):

FSS is a self-administered 9-item questionnaire¹⁶², which has been commonly used in geriatric population and more specifically in Parkinson's^{163,164}. All 9 questions on the FSS are rated on a 7 point Likert scale, where higher scores indicate higher levels of fatigue. High consistency, reliability and validity has been reported for FSS¹⁶⁵ in PD.

1.12.4c Numeric Rating Pain Scale (NRS):

Numeric Pain Scale is a scale to measure pain intensity at a numeric scale of 0 – 10, where 0 means no pain and 10 means unbearable pain. Numeric pain rating scale is sensitive, reliable and simple to use where higher scores mean greater pain¹⁶⁶. The NPS is administered verbally or graphically for self-completion.

1.12.4d Brief Pain Inventory – Short Form:

Brief Pain Inventory was originally developed to assess pain in cancer patients. It has been validated in non-cancer populations. There are 2 versions of BPI, a short form and a long form. BPI short form is the most commonly used clinical pain measure, which includes items to measure pain severity, interference of pain on activities of daily living, body diagrams to indicate location of pain, questions about pain medication and a visual analogue scale to assess the degree of pain over the last 24 hours. For 4 questions patient responds on 0 – 10 numeric scale, where 0 = “no pain” and 10 = “severe imaginable pain”. The pain interference scale assesses the interference of pain with everyday activities and again is answered on a 0 -10 rating scale, where 0 = “does not interfere” and 10 = “interfere completely”. Higher scores indicate higher levels of pain and impact on other activities.¹⁶⁷

1.12.4e Parkinson’s Disease Quality of Life (PDQ39):

Quality of life (QOL) is defined as an individual’s insight of their position in life in the context of culture, value systems and in relation to their standards, expectations, goals, beliefs and concerns¹⁶³. The health related QOL is an extension of the QOL, which accounts for physical well-being, emotional integrity and cognition. PD is a complex disorder, which significantly affects QOL. Previous research studies have identified several factors such as falls^{168,169}, functional ability¹⁷⁰⁻¹⁷², postural instability^{169,173}, gait abnormality^{169,172,174} pain¹⁷¹ and fatigue^{171,174} as the predictors of poor QOL in individuals with PD. Additionally, fear of falling, which is significantly higher in individuals with PD adds to the balance problem¹⁷⁵, which again adversely affects the QOL. A systematic review conducted by Goodwin et.al¹⁷⁶ identified that

exercise interventions including combined balance and strength, aerobic training, Qigong and physical therapy are likely to improve health-related QOL. Since only a few studies have investigated changes in QOL following exercise intervention and the detrimental effects of changes in balance, gait abnormality and functional status on the QOL, further investigation is warranted to determine whether the balance specific intervention affects the QOL in these individuals.

1.13 Rehabilitation of postural instability and gait problems in Parkinson's Disease

1.13.1 Introduction to Rehabilitation of Postural Instability

Despite the modern advances in medical and surgical management in PD, limited improvements in PI have been reported^{73,79}. Therefore, alternative treatment methods such as physical therapy is often recommended as an adjunct^{177,178} to medical and surgical management. Present literature revealed that there is a large disparity between the interventions used in PD. A Cochrane review^{92,93} on management of individuals with PD supported the fact that there is insufficient evidence to support the efficacy of one particular exercise intervention. In particular, few recent studies assessed the effects of specific exercise interventions on postural instability in PD. Many different rehabilitation interventions^{86,109,179-183} with varied dosage and outcome measures were utilized to treat motor as well as non-motor symptoms of PD. The various interventions that have been used include exercises to improve sensory integration, strength, and balance, either through regular physical therapy, home based exercises, yoga, tai-chi, qigong, or treadmill training. Several studies have reported promising results and demonstrated that exercise training specific to balance can help improve PI in individuals with PD (TABLE 1 and 2).

1.13.2 Exercise interventions in Parkinson's Disease: Literature review

Exercise has been shown to slow disease progression and improve the motor impairments caused by PD. Several exercise interventions have focused on balance impairment in PD.

Traditional physical therapy exercises have been used in various intervention studies, which include balance training, treadmill training, whole body vibrations and resistance training. Table 1 presents a summary of various exercise interventions including general physiotherapy exercises, treadmill training, cueing, dance, and martial arts in individuals with PD. The various outcome measures which were included in these trials included measures of balance and functional mobility such as Timed Up and Go Test, Functional Reach Test, Berg Balance Scale Test; activity specific balance confidence scales; fall measures like the number of falls and Falls Efficacy Scale; clinician rated impairment and disability scales such as Hoehn and Yahr scale, Unified Parkinson's Disease Rating Scale, Webster rating scale, and Columbia University Rating Scale, measures of gait like the 2 or 6 minute walk test, 10 or 20 meter walk test, cadence, stride length, step length, freezing of gait; and patient rated quality of life measures such as PD questionnaire (PDQ39) and PD specific health related quality of life questionnaire. The results of the interventions are also compiled in table 1. Most of these trials examined short term effects of the therapy. In general, the exercise interventions used in these research studies are widely varied in terms of intensity and duration and type of exercises used. The exercise sessions lasted anywhere between 30 - 60 minutes, 2-4 times a week for up to 4-24 weeks. Most of these studies reported significant improvements in measures of balance, measures of falls, clinician rated impairment and disability scales, and measures of gait and patient rated quality of life. Although, these studies provided first- hand evidence of the efficacy of these exercises in PD, none have used more sensitive objective biomechanical measures such as sway of CoP as assessed by sway area, CoP path length in ML or AP. Cross-sectional studies using biomechanical sway measures reported significant increase in sway area, path length in ML and AP in individuals with PD as compared to healthy controls. ML sway has been reported to be a better predictor of falls in PD. Additionally, it has been suggested that these biomechanical measures are more sensitive than the clinical measures of balance. Evidence from the literature review suggests that there is a scarcity of research studies which specifically

focused on balance and gait outcomes. Moreover, most of the exercise intervention where outcomes related to balance and gait were tested used a combination of exercise treatments, which makes it difficult to conclude which intervention would be more beneficial for individuals at risk of falls or the ones who experienced falls in PD. More research studies, which include more specific and feasible interventions using more sensitive biomechanical measures as outcomes would help clinicians design exercise programs, which could be tailored to the needs of individuals with PD.

One of the earlier studies analyzed the effects of balance intervention in individuals with PD with and without a tendency to fall¹⁸⁴. They enrolled 40 individuals with PD (stage III of H & Y scale) and 20 healthy controls. Physical therapy was provided for 30 days that included strategies for movement, fall prevention and education, regular physical activity, and strength and home based PT exercises. At initial testing before the intervention, they found no differences in standing with feet together, feet 10 cm apart and stride standing position between the PD patients and controls. However, they found significant differences in tandem standing and one foot standing between the PD and control individuals following the intervention, with greater difference in PD subject's tendency to fall. Additionally, PD patients were significantly improved in step test and external perturbation test scores as compared to controls, thereby decreasing the tendency of falls. Following the intervention, the group without the tendency to fall improved in tandem stance, single leg stance, step and external perturbation tests with values approaching that of the control group. The group without the tendency to fall also improved significantly in tandem stance, single leg standing, functional reach, step test and external perturbations. Although, this study had some limitations, it provides an important clue regarding the predictive tests of balance impairment in PD, as well as the importance of tandem stance and one legged standing outcomes for being sensitive measures to determine the effectiveness of balance training in individuals with PD.

Individuals with PD are often advised to perform home exercises considering the chronic

and progressive nature of the PD. Ashburn et. al.¹⁸⁴ found a consistent trend towards decreased at 8 weeks and 6 months fall rate following 8 weeks of 1 hour home based exercises, twice a week (n = 65) as compared to usual nursing care (n = 65) in individuals with PD. The exercise intervention included 6 levels of progression covering strength, range of motion, balance and walking. They observed a significant difference in only Functional Reach Test at 6 months. There were several limitations in the study, including failure to recruit the sample size required, self-report of falls and higher number of participants in the controlled group, who were also involved in additional exercises outside the study intervention. Similarly, Allen et. al. compared the effects of 6 months of minimally supervised exercise intervention on the fall risk in PD¹⁸⁵. They divided 48 PD patients into exercise and control group. The exercise group attended a monthly exercise class and exercised at home 3 times a week for 6 months. At the end of 6 months, there was a non-significant improvement in fall rate and a significant improvement in sit to stand task. This suggests that home based exercises completed over a period of 8 weeks up to 6 months may improve balance. However more aggressive exercises which target balance and postural instability may be needed to significantly improve the fall rates.

A pragmatic, parallel group randomized controlled study conducted by Goodwin et al¹⁸⁶ included 130 subjects (64 to intervention group and 66 to standard care group) between Hoehn and Yahr stages III-IV. The intervention group participated in 10 once weekly supervised exercise sessions and twice weekly home exercise sessions, which included 10 minutes of warm up, 10 minutes of cool down and 40 minutes of strength and balance training. The control group received standard care. The primary outcome measure was the number of falls during the 10 week intervention period and a 10 week follow-up period. They also prospectively recorded falls for 10 weeks before the beginning of the intervention. Additional, information collected included the falls efficacy scale (FES), European quality of life questionnaire (EuroQOL-5D), Phone-FITT (household and recreational physical activity), Berg Balance Scale (BBS) and Timed Up and Go test (TUG). The authors found non-significant improvements in the fall rate,

with the intervention group reporting 1507 falls and the control group reporting 3981 falls in the 20 weeks following baseline measurements. The authors found significant between group differences in BBS and FES at the post intervention assessment and significant between-group differences in BBS and Phone-FITT at the 10 week follow up. This was the first trial to include fall incidence as the primary outcome measure. Although, the study was unique in using fall incidence as the primary outcome, a 10 week follow up seems to be short. Adding the longer follow up such as at 6 months and 1 year would be particularly important in this population. Additionally, they reported an attrition rate of 15%. Moreover, the authors failed to recruit the desired number of participants (sample size of 248) and completed analysis with 130 subjects.

Although some studies investigated the balance interventions in PD, most of the studies lack well defined and specific balance interventions. Most of the studies, which fall under physical therapy realm did not use sensitive outcome measures such as CoP changes or sway measures before and after exercise intervention in PD. Qutubuddin et al¹⁸² used an advanced form of balance training using computerized dynamic posturography (CDP) to work sensory and voluntary motor control of balance on a movable surface and compared the training with standard balance therapy in 22 individuals with PD. . The pre testing included assessment of balance on Smart Balance Master and BBS. The participants were either randomized to CDP group or PT group. The CDP intervention included two 30-minute sessions per week for 4 weeks, and the PT intervention included two 30-minute sessions of usual upright exercises, theraball exercises and mat exercises for 4 weeks. Additionally, both groups were given 13 same specific home-based balance exercises. The authors found no between group differences, but did find significant differences between 9 CDP and 6 PT patients for reaction time, movement velocity, endpoint excursion and maximum excursion. Although, this study had several limitations such as small sample size, high attrition rate and all male subjects, the study provided evidence that an intervention using computerized platform is feasible in PD.

In a study by Nocera et al¹⁸⁷, 10 PD and 10 healthy age matched controls were compared using computerized dynamic posturography (CDP) with sensory organization testing pre and post intervention. The sensory organization testing (SOT) is sensory manipulations via visual surroundings and support surfaces during balance testing. The exercise intervention included abdominal crunches, wall squats, lunges, calf raise, knee flexion and extension and step ups. The participants in the home exercise group were given an exercise booklet for 10 week intervention following initial practice. The control group did not do any exercises however it was used to examine the learning effects from testing. The authors found that pre intervention differences between the PD and control no longer existed at the post intervention testing. Additionally, in PD group the composite score of NeuroCom SOT significantly improved after intervention. NeuroCom SOT requires participants to be tested under 6 conditions with eyes open and eyes closed. During the test, the participant's visual surround, force platform or combination of both are sway referenced. There was no difference in the static balance in this study, which signifies that either there was no improvement in static balance following the intervention or a different exercise intervention specific to the static balance is needed.

A recent study by Kara et al¹⁸⁸ indicates the usefulness of the Balance Master System in evaluating the improvement in static and dynamic balance following an exercise intervention. Seven subjects with stage III of H & Y scale completed a supervised 50-60 minutes of exercise intervention targeting motor skills, postural adjustments and coordination and motor dexterity in small groups per week for 12 weeks. Thereafter, the participants were asked to continue the exercises at home and record the time and date in a log book. The exercise was changed once a month starting with lying followed by sitting and then standing. The balance was assessed via balance master system once before and after the intervention completion. Static balance was assessed using a modified clinical test of sensory interaction on balance looking at the postural sway velocity. Dynamic balance tests included limits of stability (LOS), weight shift (WS), sit to stand (STS), tandem walk (TW), step/quick turn (SQT). The parameters tested were reaction

time (RT), movement velocity (sway), and endpoint excursion (EX). For static balance, only unilateral standing on right and left foot with eyes closed was significantly improved after treatment. In dynamic balance, maximum excursion of limits of stability improved and LOS was significantly improved before and after the intervention. However no differences in RT, movement velocity, end point excursion, and directional control, WS, SQT, TW and STS were noted following the intervention. Despite some promising results, there were some limitations such as small sample size, lack of control group and use of other clinical measures. These limitations reduced the reliability of results. In contrast to this, our study examined the training using BBS, for a short period and comparing it to a group that performed balance exercises from the booklet "Falls Prevention" without the use of BSS¹⁸⁸.

A rather improved study conducted by Smania et al.⁸⁶ evaluated the effects of balance specific training in 33 individuals with PD as compared to 31 controls with diagnosis of PD at stage III-IV of H & Y scale. Their balance intervention consisted of 50 minutes of exercises 3 times a week for 7 weeks. The training consisted of 3 different sets of exercises: self-destabilization of CoM, externally induced de-stabilization of CoM using foam and a movable platform, and coordination activities for arms and legs during different activities. The exercises for the control group included active joint mobilization, stretching and coordination. The primary outcome measures included BBS, activities specific balance confidence and time to execute different postural transitions. Additionally, the participants performed a target reaching task, while they stood barefoot on the force platform. Within-group comparisons showed significant improvement in BBS at post testing as well as at 1 month follow up, whereas no difference was observed for the control group. Between group changes were significant for all the primary outcome measures. This study provided evidence that a more specific balance intervention and sensitive outcome measures should be incorporated in the treatment of postural or balance problems in PD. Biodex Stability System (BSS) is a device containing a combination of a movable platform and a visual screen located in front to perform different challenging balance

tasks. Safety features on the device provide a better, yet challenging environment for balance training in these individuals. It is our expectation that training using such a device is more specific to balance and would yield better results than usual ground balance exercises.

Overall a common theme emerged out of all of the studies mentioned above. Exercise may result in improvements, but most studies used mixed methods of balance training in addition to some other form(s) of exercises. None of the exercise interventions were focused on balance specific training only and the lack of a control group in several studies questions generalizability of their results. Moreover, there is much variation in the duration of interventions and the outcome measures used. Specifically, balance interventions lack sensitive outcome measures such as CoP or limits of stability, which have been affected in individuals with PD.

Currently, the common practice to evaluate PI in clinic is to use clinical balance scales, which tend to have physician bias, do not detect mild impairments (have ceiling effects), and may not be sensitive enough to detect changes with progression of the disease¹⁸⁹⁻¹⁹¹ in diseases like PD where disease progression must be monitored¹⁹². CoP sway measures are shown to be sensitive measures for PI and detecting minor deficits. A study by Chasten et. al¹⁹³ found no differences in individuals with PD and healthy controls in performance of the clinical balance tasks; however PI was present in early stages of PD (H & Y – 1.22) as evidenced by force platform measurements of CoP. Additionally, use of sensitive sway measurements of CoP has been suggested to be better measurements for PI even in healthy elderly¹⁹⁴ as well as in individuals with stroke¹⁹⁵. Therefore, we suggest that sensitive outcome measures such as that of CoP sway may be more sensitive in evaluating improvements in postural control following balance interventions implemented herein. The CoP sway area and the CoP path length in medio-lateral (ML) and antero-posterior (AP) directions have been shown to be significantly increased in individuals with PD^{104,196}. Additionally, it has been suggested that CoP sway in ML direction is a better predictor of falls in PD¹⁹⁶. We hypothesize that challenging balance training

in individuals with PD will result in improvements in postural control as assessed by improvement in CoP sway area and CoP path length in ML and AP direction.

A meta-analysis conducted by Allen et al¹⁹⁷ investigated the effects of exercise and motor training on balance and falls in PD. The authors identified that falls are a major problem in individuals with PD, and compromised balance is one of the important risk factors for falls. Several outcome measures included the BBS, TUG, gait velocity/time, turning time, sit-to-stand; functional reach (FRT) and single leg stand time. The results indicated mean time period of most of the interventions to be 7 weeks, with almost 18 hours of exercise in total. The sample sizes ranged between 11-142. The meta-analysis concluded that the combination of exercise and motor training significantly improved balance related activity performance, and highly challenging and balance specific training improved outcome measures more than the usual exercises^{198,199}. The effect sizes were small to moderate (Hedges' g 0.2 – 0.5) but yielded meaningful improvement in the outcome measures (e.g. 0.05 m/s in gait velocity). The authors suggested that intervention studies should include highly challenging exercises such as movement of CoM, narrowing the base of support and minimizing the use of upper limbs for support. Such interventions may yield significant improvements in balance related outcome measures. Therefore, there is a pressing need to develop and evaluate balance challenging specific interventions in PD, as tested herein.

1.13.3 Other exercise interventions:

Alternative therapies: Several alternative therapies such as yoga, tai-chi, Qigong, vibration and dance therapies have shown promising results in improving postural instability in individuals with PD. Table 2 outlines some of the studies, which investigated balance outcomes following alternative therapies. Overall, alternative therapies listed in Table 2, have shown mixed benefits, with some reporting improvement and some reporting no change in balance outcomes. Although, the beneficial effects of these alternative therapies are moderate, most of these

interventions are considered safe and are encouraged in individuals with PD. However, due to scarcity of data, there is a need to explore alternative therapies in the future using large randomized control trials, as they provide additional treatment options for chronic neurological diseases such as PD.

1.13.4 Exercises focused on reducing falls

Fall frequency is reported to decrease in the elderly when individualized home exercise plans are provided. A large sample (n = 142) randomized controlled study by Pickering et al.²⁰⁰ evaluated the effects of 6 week home based exercise intervention in individuals with PD. The intervention group underwent home-based exercises which included muscle strengthening, range of motion exercises, balance training and walking. Balance training specifically included exercises focusing on static, dynamic and functional activities catering to the needs of individual patients. The control group had usual care, which was basically a meeting with a local PD nurse. A non-significant trend toward decreased incidence of falls was reported in the intervention group. Allen et al. reported similar findings, where the exercise group met with physical therapist once a month for an exercise session and completed 3 exercise sessions at home each week for 6 months. The exercise in this study consisted of balance and strength training. At the conclusion of the study, the exercise group showed greater decline in the fall risk score as compared to the control group. However, no significant changes were seen in fear of falling and static balance. Falling is a major problem in PD, which results in injuries and significantly impacts mobility and quality of life. As discussed earlier in this chapter, postural instability is the major cause of falls in PD, hence exercise studies focusing on improving postural instability in PD might help to improve balance leading to decreased incidence of falls.

1.14 Significance of present work:

Exercise has long been suggested as an adjunct to medical treatment of PD. However the efficacy of a short duration balance specific training with Biodex Stability System (BSS) and its effects on spatiotemporal gait, physical function and quality of life remain to be determined. This

limited understanding of the balance specific intervention response in individuals with PD has resulted in lack of standard exercise prescription; as it is unclear as to what extent balance specific training maximizes functional improvements in this population. By incorporating balance specific training into our protocol, we expect to elicit improvements in balance, gait, and their relative contributions to functional performance and QOL.

Additionally, the non-motor symptoms of PD have scarcely been evaluated in response to balance specific interventions. Research studies have described the potential interdependence of motor symptoms and non-motor symptoms in PD. Therefore, it is important to evaluate how changes in balance and gait parameters affect non-motor symptoms such as fatigue, pain and depression in PD. The results of this research will help characterize the balance specific exercise response in individuals with PD, and will enable medical professionals to appropriately design and prescribe exercise programs to maximize improvement in functional performance in this population. Since several studies used mostly subjective or less sensitive outcome measures to evaluate changes following balance interventions²⁰¹, there is a strong need to explore exercise interventions targeted to improve balance while using more sensitive, objective and functional tasks that are often impaired in PD. Challenging exercises have been suggested to increase production of dopamine and also help improve postural instability in individuals with PD. Since balance interventions in the past have used exercises with lower levels of challenge, the results of the present study may improve our understanding for the effects of challenging balance training on balance, gait and other non-motor symptoms of PD.

The underlying causes of postural instability have been related to abnormalities in postural sway and adjustments and dynamic postural control. Previous balance studies in individuals with PD have reported increased sway area and path length in medio-lateral and antero-posterior directions, resulting in postural instability²⁰². Appropriate balance responses require integration of visual, vestibular and somatosensory systems²⁰³, and patients with PD have abnormal processing of afferent input from vestibular, proprioceptive, and visual systems⁸⁶. However,

balance training alone and balance training with visual feedback have been shown to improve sway measures. Objective sway measures are more sensitive in detecting these changes in PD than clinical rating scales that are more comprehensive²⁰⁴.

Biodex stability system (BSS) is a commercially available device that can be used to significantly challenge balance by requiring the individual to maintain their stability as the base of the BSS become unstable and/or to perform visually guided dynamic balance tasks. BSS has been used for assessment of neuromuscular and somatosensory control and training of postural control and balance. The balance activities which can be carried out using BSS can be broadly divided into static and dynamic balance activities. Static balance activities include tasks such as standing and maintaining the CoM at one position as represented by a black dot on the screen. The dynamic balance tasks include activities such as AP or ML weight shift, limits of stability or maze control, where CoM as represented by a black dot on the screen is voluntarily moved away from the center towards the limits of stability. Balance training with Stability System (BSS) has yielded positive results in older frail individuals^{205,206} as well as individuals with diabetes²⁰⁵ and chronic ankle sprains²⁰⁷. However no studies have utilized BSS for training individuals with PD. On the other hand, studies that examined balance following use of exercises including general physical therapy exercises, balance and aerobic interventions¹⁷⁻²⁵ and/ or medications²⁰⁸⁻²¹⁰, showed inconclusive, insignificant or even negative results.

Therefore, we propose to conduct a quasi-randomized controlled study to compare two groups of individuals with PD undergoing supervised balance training using BSS versus supervised balance training without BSS, 3 times a week for 4 weeks. The results of the present study may help clinicians and researchers develop more efficient treatment strategies for improvement of postural instability, which has been a main concern for this population.

1.15 Specific Aims and Hypothesis

The **primary goal** of this study is to evaluate whether a balance training intervention with BSS can improve balance in individuals with PD. A secondary goal of the study is to evaluate if

changes in balance also translate to improving gait, physical function and quality of life. Our central hypothesis was that the balance exercise group using the BSS system will show greater improvement in balance. We also hypothesized that improvement in balance will result in better gait and physical function in individuals with PD. Our rationale for this project was to understand if challenging exercises result in better outcomes as compared to simple over ground exercise, which is often prescribed in PD. To achieve this, we followed the underwritten specific aims and their respective hypotheses:

AIM 1: To determine if balance training with BSS can improve specific balance parameters in individuals with PD compared to Non-BSS group

Hypothesis 1a: Berg balance score will be significantly increased in the BSS group as compared to the Non-BSS group

Hypothesis 1b: CoP path length in the antero-posterior direction and the medio-lateral direction will be significantly decreased in the BSS group as compared to the Non-BSS group

Hypothesis 1c: Sway area will significantly decrease in the BSS group as compared to the Non-BSS group

AIM 2: To determine if balance training with BSS can improve specific gait parameters in individuals with PD compared to Non-BSS group

Hypothesis 2a: Gait velocity will be significantly improved in BSS group as compared to the Non-BSS group

Hypothesis 2b: Step length will be significantly improved in BSS group as compared to the Non-BSS group

AIM 3: To determine if balance training with BSS can improve functional outcomes in individuals with PD as compared to Non-BSS group

Hypothesis 3a: Timed Up and Go Test score will be significantly decreased in BSS group as compared to Non-BSS group

Hypothesis 3b: 6 Minute Walk Test distance will be significantly increased in BSS group as compared to Non-BSS group

Hypothesis 3c: fear of falling will be significantly decreased in BSS group as compared to Non-BSS group

Hypothesis 3d: quality of life in individuals with PD will be significantly improved in BSS group as compared to Non-BSS group

AIM 4: To determine if balance training with BSS can improve non-motor symptoms in individuals with PD as compared to Non-BSS group

Hypothesis 4a: Fatigue will be significantly decreased in BSS group as compared to Non-BSS group

Hypothesis 4b: Depression will be significantly decreased in BSS group as compared to Non-BSS group

Hypothesis 4c: Pain will be significantly decreased in BSS group as compared to Non-BSS group

To achieve the purpose of above mentioned aims, we proposed a 4 week quasi randomized controlled study (Table 3) of a balance training program in individuals with PD using Biodex Stability System (BSS). BSS is a commercially available device, which consists of a circular platform that provides up to 20° of surface tilt and is capable of moving in 360° range of motion. The platform is interfaced with computer software (Biodex, Version 3.1, Biodex Medical Systems) that enables the subject to visually track the CoP. In static stance position, the CoP is used to measure the movement or sway of center of gravity. The BSS has an inbuilt feature to vary the stability of the platform by changing the resistance underneath the platform. Most Individuals with PD experience balance problems at some point during the course of the disease and the balance worsens with the progression of the disease. BSS is a device, which can be used to train individuals with PD, to control the movement of CoP, which ultimately helps to improve balance impairment.

Subjects with a diagnosis of PD were invited to participate in the study and presented with a choice of either the balance exercise group using BSS or without BSS. Each group had 10 subjects. A part of testing and full training took place at Clinical Orthopedic Rehabilitation and Research laboratory, Department of Physical Therapy and Rehabilitation Science and some part of the testing and patient recruitment was completed at Parkinson's Disease & Movement Disorders Center at the University of Kansas Medical Center.

This study will be the first study to attempt to compare the changes in balance and gait following 4 weeks of balance training using either BSS or supervised exercises without BSS.

This study will also examine the effects of the balance training on the non-motor symptoms of Parkinson's disease including fatigue, pain and depression in individuals with PD.

Figure 1: Basal Ganglia: caudate and putamen comprises largest nuclear complex of basal ganglia (<http://new.vechnayamolodost.ru/pages/biomedicin/genboparaus7f.htm>)

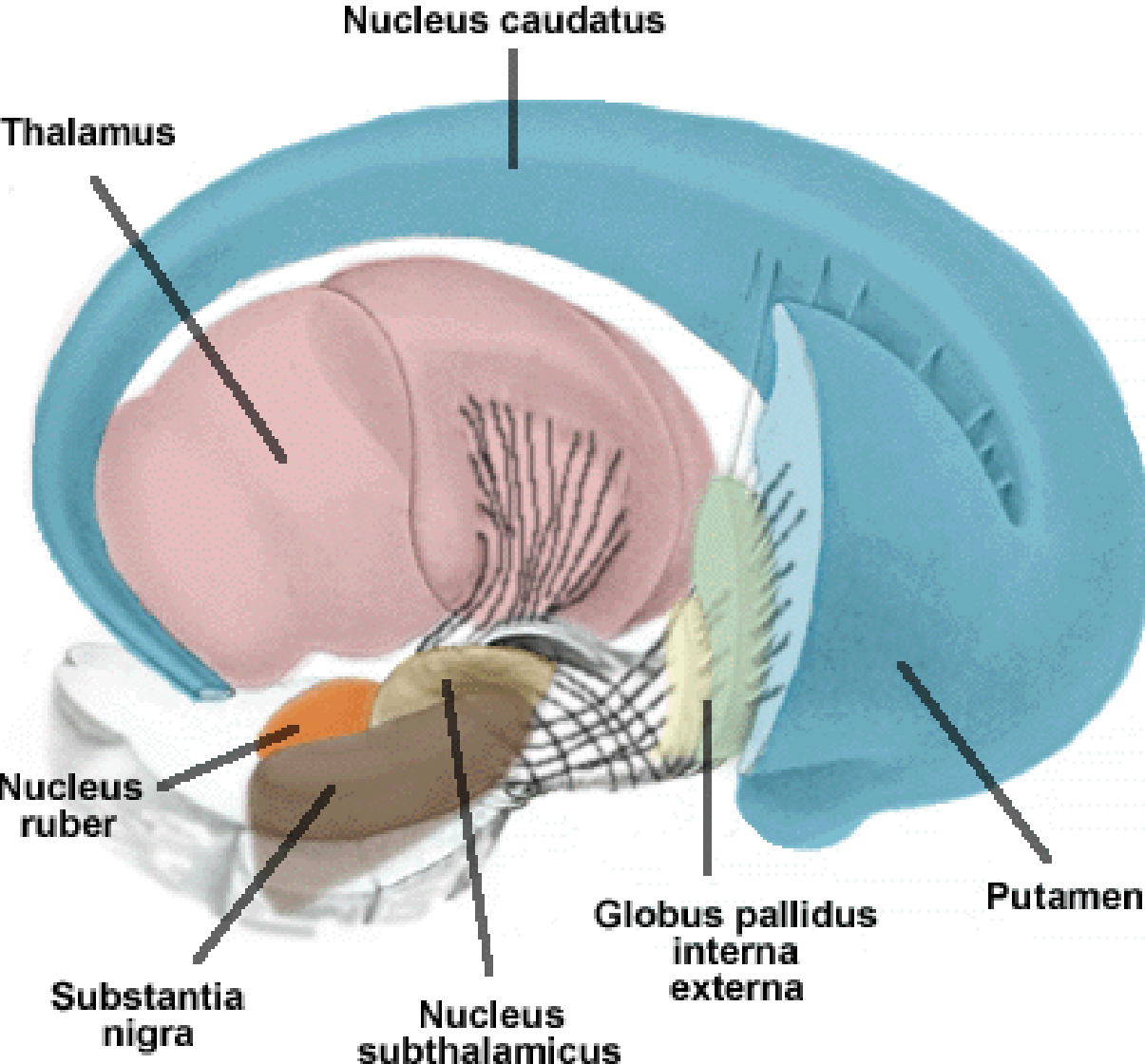
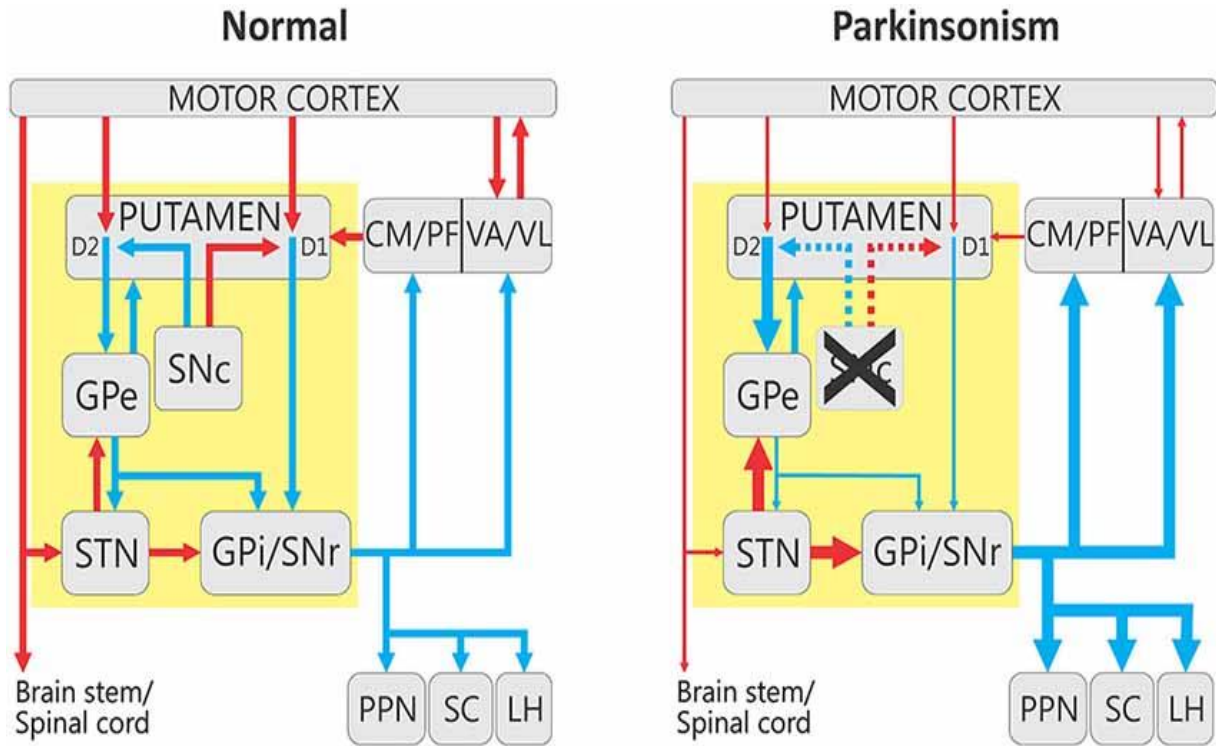


Figure 2: Neuronal activity in basal ganglia – thalamocortical circuits in the parkinsonian state²¹¹



GPe – Globus pallidus externus
 SNc – Substantia nigra compacta
 STN – Sub thalamic nucleus
 GPi – Globus pallidus internus
 SNr – Substantia nigra reticulata

Red arrow represents inhibition
 Blue arrow represents facilitation
 Thick arrow represents increased inhibition/facilitation
 Thin arrow represents decreased inhibition/facilitation

Table 1: Exercise studies in Parkinson's disease

Author/ Year	Interventions			Outcome measures	Results
	Group 1	Group 2	Group 3		
Almeida ² ¹² 2012	Visual cueing on the ground (OG) (n=14;30 minutes,3 times per week, 6 weeks)	Visual cueing on Treadmill (TG) (n=14;30 minutes,3 times Per week, 6 weeks)	Control (CG) (n = 14) no exercise	Primary: Step length Secondary: UPDRS III, TUG Gait speed, Cadence, Double support time, Step time, Step to-step variability, Step time variability, 30 second chair stand	There was no difference between treatment arms in any of the outcome measures. Both groups improved in step length. The OG improved in TUG.
Braun ²¹³ 2011	Physiotherapy with Mental practice (n=25; 1 hour (or 2 x 30 min) weekly, 6 weeks)	Control group (n =22) relaxation according to Dutch guidelines, 1 hour weekly for 6 weeks		Visual analogue scale, TUG 10 m walk test	There was no difference between treatment arms. The results showed non-significant trend of improvement in the mental practice group.
Burini ²¹⁴ 2006	Aerobic training (n=13; 45 minutes, 3 times per week, 7 weeks)	Qigong group (n=13; 45 minutes, 3 times per week, 7 weeks)		Primary: UPDRS III,II, Brown's disability scale 6 minute walk test, Borg scale for breathlessness, Beck depression inventory PDQ- 39 Secondary: Spirometry test, Max. cardiopulmonary Exercise test	There was no difference between treatment arms for the primary outcomes. Significant changes were observed in 6MWT and Borg Score for only aerobic group. Significant interaction effect between group and time was observed for 6MWT and Borg scale. Additionally, significant interaction effect between group and time was seen in double product peak, and VO ₂ .

Chaiwani chsiri 2011	Treadmill walking with music cue (n=10; 30 minutes, 3 times Per week, 4 weeks) and home walking 3 days/week	Treadmill training (n=10; 30 minutes, 3 times per week, 4 weeks)	Home walking only, 6 days a week	TUG, Walking speed, Step length, Cadence, Stride length, 6- minute walk test, 6 meter walk time, Single leg stance, UPDRS I, II, III	There was no difference between treatment arms. Step length and stride length at both 4 and 8 weeks in treadmill plus walking group, 6MWT time was significantly improved in both treadmill plus walking and treadmill groups both at 4 and 8 weeks. 6MWT distance improved at 4 and 8 weeks in treadmill group. TUG score improved in the treadmill group only at 4 weeks but TUG scores improved in all 3 arms at 8 weeks.
Dias 2005	Physiotherapy And cardiovascular exercise with visual cues (n=8; total 20 sessions)	Conventional physiotherapy (n=8; total 20 sessions)		UPDRS, FIM, BBS H&Y scale	Physiotherapy and cardiovascular exercise with visual cues significantly improved functional independent measure, step length, velocity (gait speed) and cadence compared to the conventional physiotherapy
Diehl ²¹⁵ 2011	Group Box training (n=unknown , total n= 20) 90 minutes for 12 weeks			BBS ABC Functional reach test, PDQ39 TUG 6MWT Gait speed Cadence Stride length Step Width UPDRS PDQ39	There was no significant difference between baseline and post intervention testing
Eberbach ²¹⁶	LSVTBIG training (n=20; 1 hour,	Nordic Walking (n=20; 1 hour, twice a week, 8 weeks)	Home exercise (n=20; 1	Primary: UPDRS III. Secondary: PDQ-39	Significant improvement of UPDRS, Timed up and go and timed

2010	4 times per week, 4 weeks)		session)	Time to walk 10 m	10m walking in LSVT BIG group compared to Nordic walking and home exercise. There was no difference between treatment arms for PDQ-39
Fisher ²¹⁷ 2008	Treadmill group (n=10; 1 hour, 3 times per week, 8 weeks)	Physiotherapy group (n=10; 1 hour, 3 times Per week, 8 weeks)	Control group – 6 one hour education (n=10; 1 hour, total of 6 sessions over 8 weeks)	UPDRS (Total, I, II and III), Hoehn and Yahr, Functional assessments, Gait velocity Step length, Stride length, Cadence, Double limb support time, Ankle, knee, hip rotation Sit-to stand test, Transcranial magnetic stimulation	There was no difference between treatment arms. All the 3 groups showed non-significant improvements at the post testing for all the outcome measures.
Frazzitta ²¹⁸ 2009	Treadmill with auditory and visual cues (n= 20; 20 minutes daily, 4 weeks)	Auditory and Visual cues (n= 20; 20 Minutes daily, 4 weeks)		UPDRS III, Gait speed, Freezing of gait questionnaire Stride length, 6 minute walking test	The treadmill with auditory and visual cues had significant improvement in gait speed, freezing of gait questionnaire, stride length and 6 minute walking test when compared to the auditory and visual cues group. There were no differences between treatment arms for UPDRS III
Hackney ²¹⁹ 2007	Tango (n=9; 1 hour, 20 sessions within 13 weeks)	Exercise (structured strength/flexibility) (n=10; 1 hour, 20 sessions within 13 weeks)		UPDRS III, BBS Freezing of gait, TUG, Velocity of walking And dual task walking	There was no difference between treatment arms. Only tango group showed significant improvement in BBS. There was a trend of improvement in TUG for tango group only. Both groups showed non-

					significant improvement in velocity of walking and dual task.
Hackney ¹ 98 2009	Tango group (n=19; 1 hour, twice weekly, total 20 sessions in 13 week)	Waltz/ foxtrot Group (n=19; 1 hour, twice weekly, total 20 sessions in 13 weeks)	Control group – no exercise (n=20; 13 weeks)	PDQ-39, UPDRS III, BBS Tandem stance test, TUG One leg stance test 6 minute walk test, Gait	PDQ- 39 significantly improved in the Tango arm compared to the waltz/ foxtrot and control arms. Timed up and go test was significantly improved in the tango arm compared to the waltz/ foxtrot and control. There was no difference between treatment arms in UPDRS III
Hackney ² 20 2010	Partnered tango (n=19; 1 hour, twice weekly, 10 weeks)	Non partnered tango (n=20; 1 hour, twice weekly, 10 weeks)		Tandem stance, One leg stance, TUG 6 minute walk test, Gait velocity, Cadence, Stride length, Swing percentage, Double support percentage	There was no difference between treatment arms. However both groups significantly improved at post testing as well as follow up for BSS, OLS, Comfortable cadence, fast cadence, fast swing percent and fast double support percent
Hass ²²¹ 2006	Tai Chi (n=unknown, Total n=23; 1 hour, twice weekly, 16 weeks)	Qi-gong (n=unknown, total n=23; 1 hour twice weekly, 16 weeks)		Gait initiation, Gait velocity, Stride length, Stance, Double limb support, Step duration	There was no difference between Treatment arms. Participant reported feeling good and more confident in their balance in tai chi group.
Hirsch ¹⁸⁰ 1996	Combined balance and resistance training (n=6; 45 minutes, 3 times per week, 10 weeks)	Balance training group (n=9; 30 minutes, 3 times per week, 10 weeks)		Balance, Muscle strength: Knee extensors, Knee flexors, Ankle plantar flexors Latency to fall, %of trials resulting in falls	Combined balance and resistance training showed improved balance scores significantly more than the the balance training group. There were no differences between treatment arms for the falls outcomes

Joudoux 2011	Asymmetric motor training program (n=unknown , Total n=50; 1 hour, 3 times Per week, 8 weeks)	Broad program (n=unknown, total n=50; 1 hour, 3 times per week, 8 weeks)		UPDRS III, GMT score, Rapid alternating mts, Handwriting and spiralography, PDQ-39, Depression (GDS15), Video recording of 8 activities of daily living And biomechanical evaluations	Abstract describing methodology. No result data
Juncos 2006	Aerobic exercise (n=unknown , total n= 56; 6 months)	Tai Chi (n=unknown, total n=56; 6 months)	Qi-gong (n=unkno wn, total n= 56; 6 months)	UPDRS total, UPDRS motor, UPDRS ADL, PDQ-39, Clinical global impression, Walking speed, Falls	UPDRS ADL scores improved significantly more with Qigong than aerobic exercise. There was no difference between treatment arms for PDQ- 39 and UPDRS total and motor subscores. There was insufficient information on clinical Global impression, walking speed and falls
Khallaf 2011	Physiothera py and treadmill (n= 15)	Physiotherapy (n=15)		UPDRS II & III, Hamilton rating scale of depression, Walking speed, Walking distance	Both treatment arms showed significant improvement in walking distance, speed and ADL. A significant improvement in depression observed in physiotherapy and treadmill group only. It was unclear if there were any differences between treatment arms
Li ²²² 2012	Tai Chi (n=65; 1 hour, twice weekly, 24 weeks)	Resistance training (n=65; 1 hour, twice weekly, 24 weeks)	Control, stretchin g group (n=65; 1 hour, twice weekly, 24	Primary: Two indicators of postural stability: maximum excursion and directional control Secondary: Stride length,	The Tai Chi group performed significantly better than those in the resistance training And stretching groups on the primary outcomes. The Tai Chi group

			weeks)	Walking velocity, Strength of bilateral knee Extensors and flexors, Functional reach test, TUG UPDRS III, Number of falls	had significantly better performance/scores in many outcomes compared to the stretching group. The Tai Chi group out-performed the resistance training group on the stride length and functional reach task
Mak ²²³ 2008	Audiovisual cued task specific Training (n=19; 20 minutes, 3 times Per week, 4 weeks)	Conventional exercise (mobility and strength) (n=19; 45 minutes, twice weekly, 4 weeks)	Control group (n = 14) no exercise	Peak horizontal velocity, Peak vertical velocity, Movement time, 3D Kinematics data of sit-to- stand	The audiovisual cued task specific training group increased both peak horizontal and vertical velocities and reduced time taken to complete sit-to stand. These improvements were greater than those of the conventional exercise group
McGinley ²²⁴ 2012	Movement strategy training (n=69; 2 hours + 2 hours home practice program, once a week, 8 weeks)	Progressive strength training (n=70; 2 hours + 2 hours home practice program, Once a week, 8 weeks)	Life skills control (n=71; 2 hours + 2 hours home practice program, once a week, 8 weeks)	Primary: Falls: no. of fallers per group, no. of multiple fallers falls rate over 12 months in each group Secondary: Number of falls, Walking speed, 6 minute walk test, TUG UPDRS II and III, PDQ- 39, EuroQol-5D	Time to first fall during the intervention phase did not differ across groups. Full trial results not yet published
Miyai ²²⁵ 2000	Body weight supported treadmill Training (n=5; 45 minutes, three times per week, 4 weeks)	Physical therapy (n=5; 45 minutes, three Times per week, 4 weeks)		UPDRS, UPDRS subscales (mental, ADL, motor and complications) Over ground ambulation endurance, Gait speed, No. steps taken for 10 Meter walk	Crossover trial, combined data presented. Body weight supported treadmill training showed greater improvement in UPDRS total, ambulation speed and number of steps than physical therapy arm. Additional data supplied by author

					allowed data to be separated and there was no difference between arms
Miyai ²²⁶ 2002	Body weight supported treadmill training (n=11; 45 minutes, three times per week, 4 weeks)	Physical therapy (n=9; 45 minutes, three times per week, 4 weeks)		Primary: UPDRS, Gait speed, Steps for 10 meter walk Secondary: UPDRS subscales (mental, ADL, motor and complications)	Body weight supported treadmill training had significantly greater improvement than the physical therapy group in gait speed at 1 month and in the number of steps at 1, 3 and 4 months
Morris ²²⁷ 2009	Movement strategy training (n=14; 45 minutes, max 16 sessions over 2 weeks)	Musculoskeletal Exercise (n=14; 45 minutes, max 16 sessions over 2 weeks)		Primary: UPDRS Motor and ADL (combined). Secondary: 10 m walk test, TUG 2 min walk test, Balance shoulder TUG PDQ- 39	The movement strategy training group had a significant improvement in balance compared to the musculoskeletal arm. There were no other differences between treatment arms
Piceli ²²⁸ 2012	Robot assisted gait training group (n=21; 45 minutes, three times per week, 4 weeks)	Physiotherapy group (n=20; 45 minutes, three times per week, 4 weeks)		Primary: 10m walk test, 6 min walk test. Secondary: Spatiotemporal gait: Stride length, Parkinson's fatigue scale, UPDRS Total	Robot assisted gait training significantly improved in 10 m walk test, 6 min walk test, Parkinson's fatigue scale, and UPDRS Total compared to the physiotherapy group
Reuter ¹⁴⁴ 2011	Nordic walking group (n=30; 70 minutes, three times per week, 6 months)	Walking group (n=30; 70 minutes, three times per week, 6 months)	Flexibility and relaxation group (n=30; 70 minutes, three Times per week, 6 months)	Max walking speed on treadmill, 12 m and 24 m walking test, Stride length, Gait variability, UPDRS, PDQ- 39, Physical activity in everyday Adverse effects	Main reported differences were that the Nordic walking group was superior to the Walking and flexibility and relaxation program in improving postural stability, Stride length, gait pattern, and gait variability
Ridgel ²²⁹ 2009	Forced exercise group (n=5; 1 hour, 3 times per week, 8 weeks)	Voluntary exercise group (n=5; 1 hour, 3 times per week, 8 weeks)		UPDRS part III Manual functional dexterity, Bimanual dexterity, Centre of pressure (CoP)	UPDRS motor scores showed a significantly greater improvement in the forced exercise arm compared to the voluntary exercise

					arm. Only forced exercise resulted in significant improvements in bimanual dexterity
Robichaud ²³⁰ 2012	Progressive resistance exercise (n=unknown (total n= 48 at 6 month time point); 1 hour, twice per week, 24 months)	Fitness counts (n=unknown (total n= 48 at 6 month time point); 1 hour, twice per week, 24 months)		UPDRS motor, TUG BBS Modified physical performance test	There was no difference between treatment arms physiotherapy. All the outcomes measures showed significant effects of time in both the groups.
Schenkman ²³¹ 2012	Flexibility/ balance/ function exercise group (n=39; 1 hour, 3 times per week for the first 4 months then tapered for 1 month to once monthly sessions out to 16months)	Aerobic exercise group (n=41; 1 hour, 3 times per week for the first 4 months then tapered for 1 month to once monthly sessions out to 16 months)	Home exercise National Parkinson Foundation Fitness Counts program group (n= 41; once monthly supervised sessions)	Primary: Overall physical function, Balance Functional reach, Walking economy VO2 Secondary: UPDRS, ADL, UPDRS Motor, PDQ- 39	Overall physical function: improvement at 4 months was greater in the flexibility/ balance/ function exercise group than the aerobic and home exercise groups. Functional reach was not different between groups. Walking economy:aerobic exercise improved compared to flexibility/ balance/ function exercise group. The only secondary outcome that showed significant differences was UPDRS ADL: flexibility / balance/ function exercise group performed better than home exercise group at 4 months
Shankar 2009	Treadmill with cueing group (n=10; 30 minutes, twice a week, 8 weeks)	Treadmill without cueing (n=9; 30 minutes, twice A week, 8 weeks)	Cueing only group (n=10; 30 minutes, twice a week, 8 weeks)	Gait and Balance Scale, UPDRS III, PDQ- 39	There was no difference between treatment arms

Shen 2011	Balance group (n=23; treatment delivered over 12 weeks)	Strength training (n=22; treatment delivered over 12 weeks)		Limit of stability, Walking speed, One leg stance time, ABC, UPDRS III	The balance group improved significantly more than the strength group in movement velocity and one leg stance
Sigurgeirsson 2009	Walking with visual cues (n=unknown, Total n=26; 30 minutes, 4 sessions per week, 4 weeks)	Walking without cues (n= unknown, total n=26; 30 minutes, 4 sessions per week, 4 weeks)		TUG PDQ-39	There was no difference between treatment arms for Timed up and go
Smania ⁸⁶ 2010	Balance training (n=33; 50 minutes, 3 times per week, 7 weeks)	General physical exercise (n= 31; 50 minutes, 3 times per week, 7 weeks)		Primary: BBS, ABC, Postural transfer test, Self-destabilization of the Centre of foot pressure test, Falls diary Secondary: UPDRS Total, Hoehn and Yahr, Geriatric depression scale	There was a significant difference in favor of the balance training arm in the Berg Balance Scale and the self-destabilization of the center of foot pressure test when compared to the general physical exercise group
Werner ²³ 2010	Verbal instruction With augmented feedback group(n=6; 90 minutes, 2 times per week, 2 weeks)	Verbal instruction only group (n=6; 90 minutes, 2 times per week, 2 weeks)		Stride length, Cadence, Gait velocity, Shoulder excursion	There was no difference between treatment arms. Both groups significantly improved in stride length, gait velocity and shoulder excursion.

Table 2: Alternative therapies focused on balance

Study (year)	Design	H & Y Stage	Training/ Intervention	Frequency/ Duration	Outcomes measures and assessment	Results
Lie et al. (2012) (n = 195) ²²²	RCT	I - IV	Tai-chi	2x/wk for 60 min (24 weeks)	Limits of stability (maximum excursion and directional control), functional reach, no. of falls	Improved balance
Nocera et al. (2013) ²²¹	RCT	II - III	Tai-chi	2-3x/wk for 60 min (16 weeks)	CoP path length AP and ML, CoP velocity AP and ML, Gait	No improvements
Colgrove et al. (2012) ²³³	RCT	I –II	Yoga	2 x/ wk for 60 min (12 min)	Muscle strength, Range of motion, Balance	Trend of improvement was seen
Turbanski et al. (2005) ²³⁴	RCT	N/A	Vibration	5 bouts of 1 min each		
Ebersbach et al.(2008) ¹⁷⁹	RCT	N/A	Vibration	5 x/ wk for 30 min (4 weeks)	Posturography Tinnetti balance	Improved balance
Hackney et al (2009) ^{198,220,235}	RCT	I -III	Tango dance	2 x/wk for 60 min (13 weeks)	Balance Gait Functional mobility	Improved balance
Duncan et al	RCT	I - IV	Tango	2 x/ wk for 60 min (1 year)	Balance Gait UPDRS	No improvement in balance

Table 3: Overview of the study design

Visit 1		Visit 2 – 13	Visit 14
Baseline testing (one week before intervention)	Familiarization session	Intervention	Post-intervention testing (one week after intervention)
Demographics BBS TUG 6 Min walk test MOCA PDQ-39 GDS UPDRS GaitRite Assessment Force Plate assessment	Balance exercise with Biodex Stability System (15 minutes) Balance exercise without Biodex Stability System (15 minutes)	Balance exercise with Biodex Stability System, 55 minutes at KUMC, 3 times a week for 4 weeks Over ground balance exercises from the falls prevention booklet at National Parkinson Foundation , 55 minutes at KUMC, 3 times a week for 4 weeks.	Demographics BBS TUG 6 Min walk test MOCA PDQ-39 GDS UPDRS GaitRite Assessment Force Plate assessment

CHAPTER 2

Balance Training in Individuals with Parkinson's Disease

Balance Training in Individuals with Parkinson's Disease

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Submitted to Journal of "Parkinsonism and Related Disorders" – In review

Date of submission: August 12th, 2015

2.1 Abstract

Introduction: Postural Instability is a common feature of Parkinson's Disease, which results in frequent falls. Exercise is known to improve motor functions in PD, however there is scarcity of studies which evaluated effects of balance specific training in this population, specifically using Biodex Stability System (BSS). The purpose of this study was to evaluate the effect of balance

training, using the BSS or supervised exercises, on balance and gait in adults with Parkinson's disease (PD).

Methods: This study was a prospective, non-randomized pilot study. 20 PD subjects at Hoehn and Yahr stages I – III were recruited (10 in the BSS group and 10 subjects in Non-BSS group i.e. supervised balance exercise training without Biodex Stability System) participated in exercise sessions 3 times a week for 4 weeks for 55 minutes per session. Postural sway measures were collected at baseline and post intervention. Secondary measures of Berg Balance Scale, spatio-temporal gait measures, Timed Up and Go (TUG) and 6 minute walk test data were also collected at baseline and post exercise intervention for both groups.

Results: Improvements in postural sway were seen in the BSS group post intervention (sway area mean change = - 435.3 mm²; 95% CI = - 818.5, -52.2). Postural sway data from the Non-BSS group were unavailable, due to a technical failure. All secondary measures improved for both groups independently; however we did not find any significant between group differences for any of the secondary measures.

Conclusions: 4 week exercise training using BSS improved measures of balance and gait in adults with PD. However, improvements were also seen after an exercise program that did not use BSS. This suggests that for the measures used in this study, there were no differences between BSS training and general exercise balance training.

Key Words: Parkinson's disease, balance, exercise, Biodex Stability System, gait

2.2 Introduction

Postural instability (PI) is one of the most disabling symptoms of Parkinson's disease (PD), which increases with the progression of the disease and leads to balance difficulties and falls²³⁶. Decreased balance confidence also leads to decreased mobility and increased number of falls. About 68% of people with PD fall at least once in a year¹⁸⁶, leading to injuries and further gait impairments^{110,116,237}. Hip fractures caused by PD cost about \$192 million every year¹⁹⁹. These injuries cause significant impact on physical function and quality of life in these individuals. Medical and surgical treatment provide limited improvement for balance and postural problems.

Biomechanical postural sway measures of balance are altered in PD. The center of pressure (CoP) sway area, path length in anterior-posterior (AP) and medial-lateral (ML) directions and root mean square (RMS) velocity of mean CoP in AP and ML directions are increased in individuals with PD^{75,196,238,239}. Blaszczyk et al⁷⁵ found significant increases in sway area, sway range and path length in people with PD as compared to healthy controls. Similar findings were reported by several other authors^{105,240}

Despite the fact that an increase in postural sway has been reported in individuals with PD, very few studies have examined specific interventions to improve postural instability. Even fewer studies have examined the efficacy of specific balance training equipment on biomechanical measures that are more sensitive in determining treatment efficacy. The Biodex Stability System (BSS) (Biodex, Version 3.1, Biodex Medical Systems) is a commercially available device, which consists of a circular platform that provides up to 20° of surface tilt and is capable of moving in 360° range of motion. The platform is interfaced with computer software (Biodex, Version 3.1, Biodex Medical Systems) that enables the subject to visually track the movement of CoP. BSS challenges static and dynamic balance by either moving the platform or guiding subjects to move in AP or ML directions well beyond the person's limits of stability.

Studies indicate individuals with diabetic neuropathy have significant improvements in overall stability index, AP and ML stability index using the BSS for balance training with a total of 10 training sessions in 3 weeks.^{241,205,242} A randomized, controlled trial by Gusi et.al²⁴³ examined the effects of a 12 week BSS balance training program on institutionalized older individuals. Significant reduction in fear of falling and improvement in dynamic balance and knee strength was found following BSS training. BSS has been extensively used to challenge²⁴⁴ and train^{245,246} dynamic balance following ankle and knee injuries, but has not been used in PD. The primary aim of the present study was to evaluate if balance specific training using the BSS improves postural instability in individuals with PD to a greater degree than standard balance exercises and to determine if improvement in balance translates into improvements in measures of gait.

2.3 Methods

All participants signed written informed consent for participation approved by the University of Kansas Medical Center's (KUMC) Institutional Review Board. Subjects between 40 -70 years of age with a diagnosis of PD were recruited from the Parkinson's Disease and Movement Disorder Center at KUMC. Subjects were diagnosed using the United Kingdom Parkinson's Disease Society Brain Bank Criteria by the team neurologist. Further inclusion criteria included Hoehn & Yahr stage I – III, Berg Balance Scale score of at least 50 out of 56, and ambulation with or without an assistive device. Participants were excluded if they 1) had neurological disorders other than PD or significant head trauma, 2) received neurosurgical intervention for PD such as deep brain stimulation, 3) reported substance abuse, 4) reported any cardiovascular or medical dysfunction which could preclude participation a challenging balance training program, 6) had a history of any major injuries to the lower extremities such as replacements of hip, knee or ankle or 7) had a score of less than 20 on the Montreal Cognitive Assessment (MOCA), indicating significant cognitive impairment^{247,248}.

Participants completed a series of tests, which included force plate measures, GaitMat (CIR Systems Inc. / GaitRite, Sparta, NJ, USA) and other tests of balance and endurance such as Timed up and Go test (TUG) and 6 minute walk test (6MWT), 2-3 days prior to the beginning of the intervention. During the study, the participants were instructed to take their usual anti-parkinsonian medications. All participants were tested and trained during the medication “ON” phase, (1 - 2 hours after taking PD medications). None of the participants had any change in their activity level, exercise participation and medications during the 4 week study period.

Primary Outcomes:

Participants were evaluated before and immediately after the completion of 4 weeks of training. CoP measures were collected using two force platforms (AMTI Measurements Group, Watertown, MA, USA). The signals were sampled at a frequency of 100 Hz^{249,250}. The participants were asked to stand on the force plates once with eyes open (EO) and then with eyes closed (EC) for the following four conditions: 1) feet shoulder width apart; 2) feet together, but on separate force plates; 3) one foot ahead of the other as in stepping; 4) tandem standing. A total of 5 trials of 20 seconds each were collected under each condition, with a 10 second rest between each trial. A gait belt and overhead harness were used for safety measures. In addition, a research assistant always stood behind the participants during testing. The parameters included in the CoP measures were sway area, CoP path length in AP and ML directions, and root mean square velocity in AP and ML directions.

Secondary outcome measures:

The Berg Balance Scale¹⁵³ is a 14-item gold standard clinical scale for balance. A score below 56 suggests a fall risk. TUG and 6 minute walk were obtained to examine effects on gait.

Spatiotemporal gait parameters:

The GaitRite system (CIR Systems Inc. / GAITRite, Sparta, NJ, USA) is a computerized instrument consisting of a 4.6 meter electronic walkway with embedded sensors to identify foot contacts and the spatio-temporal gait components during walking. Participants walked 1 meter before the walkway and continued 1 meter beyond the walkway. A total of 3 trials were collected, and the average of the 3 trials was used for analysis. A clinically meaningful change of 0.19 m/sec in walking velocity has been reported for PD^{153,251}.

Intervention:

Participants were assigned to either the BSS group or the Non-BSS group for 12 treatment sessions, 55 minutes each, 3 days a week (Monday, Wednesday, and Friday) for 4 consecutive weeks. The training was conducted in the Clinical Orthopedic Rehabilitation Research (CORR) laboratory at KUMC.

Biodex stability system (BSS) balances exercise:

The participants in the BSS group performed voluntary movements utilizing static or dynamic tasks (Table 1). Under the static task, participants were required to maintain the CoP (shown as a small black dot on the front screen: Image 1) in the smallest circle during 4 different standing conditions: standing with feet shoulder width apart, standing on left foot alone, standing on right foot alone, and standing with feet together. During the dynamic task in the second set of exercises, the training included moving the CoP in AP and ML directions, tracking the random dot on the screen in different directions and finally moving the CoP in clockwise and counterclockwise directions.

The tasks required the participants to keep their CoP within the limits of stability to avoid possible falls. The training started at a low level (L1) and progressively challenged participants' balance as described in Table 1. All the participants performed 3 sets of 6 repetitions, which

took 6 minutes for each exercise on average to complete the task. Limits of stability (where the participants tried to reach points on the screen, which challenged their balance) and maze control (where the participants tried to maintain the black dot within the boundaries of the maze while moving the dot clockwise and counterclockwise) exercises included 4-6 repetitions on average, which also took approximately 6 minutes (Table 1). During the fourth week of training period, the level of challenge was randomly selected (Level 1, 2 or 3). The participants were given verbal instructions and provided the required assistance in carrying out the activities. The total training time was about 55 minutes, excluding warm up and cool down exercises of stretching and walking in the hallway. Although, participants were allowed to break a fall by holding on to the side grab bars (handrails), they were suggested to take the hands off from the handrails during the balance training tasks. Continuous use of handrails would have lessened the amount of challenge applied and thus influenced the resulting outcomes; thus, none of the participants held on to the handrails, other than momentarily (under 10 seconds) to regain their balance, during each training session. Approximately each participant held on to the handrails 2-3 times/task level/session as they transitioned from one challenging task to the next or until they become familiar with the task.

Non- BSS Group:

Supervised balance exercises taken from the National Parkinson Foundation's "Falls Prevention" booklet were used as intervention training in this group (www.parkinson.org)²⁵². The booklet contained 6 different balance exercises (Table 2). Training was supervised by a team member and lasted 55 minutes/exercise session, 3 days a week for 4 weeks.

All the participants from both the groups were instructed to take breaks as needed.

Additionally, participants were instructed to sit down or stop exercising if they experienced undue fatigue, light headedness or dizziness.

Statistical Analysis

SPSS 22.0 (SPSS Inc, Chicago, IL) was used for the statistical analysis. Mann Whitney U tests were conducted to test the homogeneity of the samples. Wilcoxon signed rank test was used to assess within group differences and Mann-Whitney U test was used to assess between group differences from the baseline and post-intervention scores. An alpha level for significance was set up at 0.05.

2.4 Results:

Eighteen participants completed the study. One participant from each group withdrew from the study due to time commitment and transportation problems. Demographic data and baseline measures are presented in table 3. There were no differences between the groups at baseline.

Primary Outcomes: BSS intervention resulted in a significant decrease in total sway area (mean change = -435 ± 535 mm²; 95% CI = -818.5, -52.25), path length in AP direction, (mean change = -12.6 ± 14.5 mm; 95% CI = -23.1, -2.2), path length in ML direction (mean change = -9.15 ± 15 mm; 95% CI = -20.4, 2.11), RMS velocity in AP direction (mean change = -2.7 ± 3 ; 95% CI = -4.9, -0.5) and RMS velocity in ML direction (mean change = -1.8 ± 3.16 , 95% CI = -4.09, 0.43) (Fig. 1). These measures were obtained with a force plate during quiet standing with eyes open. We did not find any significant changes with eyes closed.

Due to technical failure of the force plates, we were not able to capture the force plate data from the Non-BSS group. The data on the BSS group was collected first. The data on the Non-BSS group was collected later. In between this data collection, the lab equipment was moved including the force plates. Later, it was found that the data for the Non-BSS group was never collected on the force plates. Thus, we were not able to determine changes within this group or evaluate between group differences for force plate measures.

Secondary outcome measures:

Berg Balance Scale scores improved significantly in both the BSS and Non-BSS groups following training. However, no significant between group difference was noted following the interventions. Significant improvements were also found for gait velocity, step length and stride length following BSS and Non-BSS training (within group, pre - post); however no significant between group differences were found in any of the gait parameters (Table 4). Within group differences were found for TUG and 6MWT measures for both BSS and Non-BSS groups respectively. There were no significant between group differences.

2.5 Discussion:

Balance training using the BSS over a relatively short period of time (4 weeks) improved balance and gait. Similar improvements were also seen in the Non-BSS group. These results suggest that both exercise training programs are equally beneficial for people with PD. The 4 week intervention with BSS was found to be safe and feasible for individuals with PD in Hoehn and Yahr stages I – III. All the participants expressed verbal satisfaction with the exercise program in both groups, which included the dosage of exercise (55 minutes, 3 times a week) and the participants were able to complete all the exercises without any adverse events.

Sway measures such as sway area, AP and ML CoP path length, and RMS velocity have been shown to be affected in individuals with PD as compared to healthy age matched controls^{75,253}. In general these values are higher in PD patients, however since we did not use a healthy control group, we don't know if our group of patients had higher values than the healthy individuals, however both groups were not different at baseline, and we saw significant improvement in BSS group following training. The sway measures significantly improved following the BSS training in our study. The CoP displacement decreased in both AP and ML directions. These results are consistent with previous studies^{137,30,37}.

Crizzle et al²⁵⁴ suggested that challenging balance exercises can result in better improvement in balance as compared to simple home exercise. A recent study¹³⁷ found significant differences in postural sway in a cohort of stage 2.5 - 3 PD patients following 8 weeks of training (3 times a week for 30 minutes) on a Wii balance board, using challenging balance exercise. Another study²⁵⁵ found significant improvement in the CoP RMS velocity following 6 weeks of balance exercises (40 minute sessions, 3 days a week) using Wii fit games at home. These studies suggest that challenging balance exercises can potentially improve postural instability and help reduce falls better than other types of exercise sessions³⁸. These challenging exercises often involve exercises in standing with a smaller base of support, decreased assistance from upper extremities and controlled movements of CoM. Our study utilized similar exercises, which challenged balance statically and dynamically in both AP and ML directions, and resulted in significant improvements in the sway area, CoP path length and CoP RMS velocity in both AP and ML directions. Unfortunately we failed to compare postural instability data between the BSS and Non-BSS groups. Otherwise, we could examine whether the use of BSS can further improve postural stability compared to the standard balance training in PD. Furthermore, the BSS provides 20 degrees of tilt in every direction, we did not utilize the maximum tilt in our intervention considering the ability and safety of the participants, which limited the movement in either direction. Future exercise programs focusing on even more challenging exercises by using maximum tilt of the BSS may result in better improvement in the overall balance in these individuals.

The Berg Balance Scale is a valuable tool to assess responsiveness to change in patients with neurological diseases²¹. A clinically meaningful change of 5 points on the Berg Balance Scale has been suggested to be a useful functional gain¹⁵³. We found an average improvement of 5.9 points in the BSS group and 6.7 points in the Non-BSS group. These results are similar to previous work by Smania et al⁸⁶ who found significant improvements in the Berg

Balance Scale (5.3 points) following 50 minutes of balance specific exercises 3 times a week for 7 weeks. Other forms of exercise interventions such as Yoga²⁵⁶ and Tai chi¹⁹⁹, which incorporate balance training including challenging balance exercises improve balance in PD. Our study shows that even short-term balance training of 4 weeks can result in improvements in balance.

Although several exercise studies have examined the benefits of exercise training in PD, the effects of balance specific exercises on gait parameters have not been fully investigated. Gait directed exercise interventions such as treadmill training or aerobic exercises have shown to improve gait velocity, step and stride length^{228,257}. Our results suggest that balance specific exercises, with or without BSS, can also improve gait speed, stride length and step length, even after a short period of training. Studies that utilized balance directed interventions such as Tai chi⁶ and Wii fit balance board¹⁴ report similar findings. Collectively, these results suggest that improvement in balance translates to improvement in gait.

Postural instability and impaired gait in PD result in an increased risk of falls³⁵. We expected that improvement in balance and gait would result in enhanced mobility. Both groups showed improvement in TUG, which is a similar finding to previous studies¹²⁻¹⁴; although with our small sample size, the improvement in TUG was less than the clinical meaningful change range (2-5 seconds)²¹. Training aimed at improving balance and reducing fall risk have also shown improvement in the 6MWT¹⁵⁴. The 6MWT is considered a mobility endurance test for individuals with PD. A change of 82 meters is considered a clinical meaningful change in the 6MWT performance following intervention²⁴. Our study is the first to examine the effects of balance training on 6MWT, which although is below the clinical meaningful change, resulted in 57.3 m change in the BSS group and 40.2 m in Non- BSS group, again suggesting that both forms of challenging balance exercises may have been effective in improving walking endurance.

One of the major limitations of this study was a non-randomized design. The second major limitation was non availability of force plate data from the Non-BSS group. The availability of the force plate data would have helped to understand the potential usefulness of the BSS training as opposed to balance exercises without the BSS. Follow up assessment to evaluate long term effects of training was not included. Additionally, our sample size was small, which may not adequately represent this population and results should be interpreted with caution. Future studies on balance rehabilitation in PD should also take into account the use of more challenging exercises using the full tilt of the BSS. Furthermore, future studies should also determine the adequate frequency, duration of treatment and the long term effects of such interventions.

Conclusion:

Our study suggests that regardless of the type of training methods, targeted balance training in individuals with PD results in improvements in balance, gait and mobility. Patients at all stages of PD should be encouraged to engage in regular exercise in order to maintain good balance and to reduce decline in physical function. In conclusion, the results of this pilot trial show that short duration balance training with BSS in individuals with PD is feasible and can improve postural instability and gait function.

Table 1: Biodex Stability System (BSS) Intervention

Balance Component	Activity	No. of Repetitions	Time spent
Static	Normal standing	6	6 minutes
	Standing on both feet tightly together	6	6 minutes
	Standing on left foot	18	6 minutes
	Standing on right foot	18	6 minutes
Dynamic	Antero-posterior weight shift	n/a	6 minutes
	Medio-lateral weight shift	n/a	6 minutes
	Percentage weight shift	n/a	6 minutes
	Limits of stability	n/a	6 minutes
	Maze Control	n/a	6 minutes

Table 2: Non- Biodex Stability System (BSS) group exercises

Exercise	No. of Repetitions	Time spent
Single leg stance (Left and Right)	40 (20 on each side)	6 minutes* 2
Standing eyes closed	6	6 minutes* 2
Toe taps on book	10	4 minutes* 2
Step ups on a book	24	4 minutes* 2
Standing foot on a step with head movements	12	4 minutes* 2
Side stepping at counter	10	4 minutes* 2

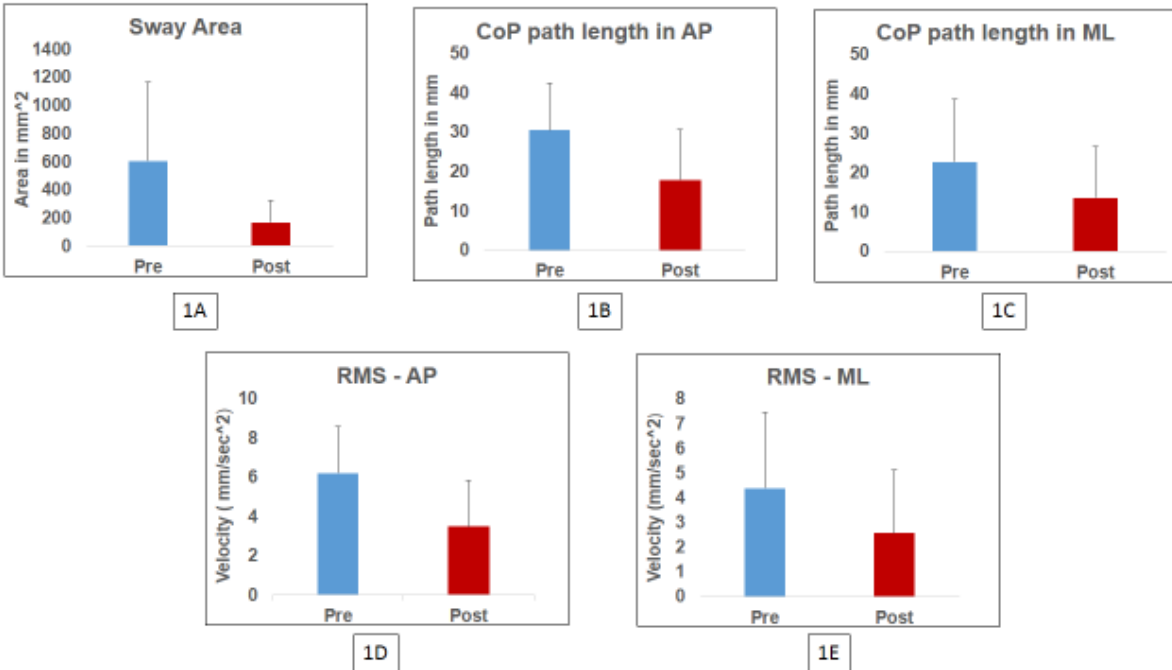
Table 3: Baseline Demographics and Clinical Measures

	Group 1 (BSS Group)	Group 2 (Non-BSS Group)	<i>p</i> - value
Gender (Male/Female)	6/4	5/5	
Age (yrs)	63.9 ± 3.84	66.33 ± 7.97	0.46
Weight (lbs)	164.24 ± 24.5	176.66 ± 52.82	0.67
Height (inches)	66.47 ± 4.3	68.611 ± 5.4	0.45
Disease severity (H & Y)	2.7 ± 0.42	2.6 ± 0.83	0.40
Cognitive Status (MOCA)	27.8 ± 1.81	26.6 ± 2.36	0.18
Berg balance scale	46.8 ± 2.5	46.4 ± 3.3	0.85
Step length	0.55 ± 0.1	0.55 ± 0.07	0.85
Velocity	0.98 ± 0.23	1.02 ± 0.10	0.24
Functional reach test	9.3 ± 2.1	10.3 ± 1.2	0.21
6 minute walk test	427.1 ± 67	428.8 ± 73	0.79

Table 4: Secondary balance and gait outcomes

Outcome measure	BSS Group		Mean difference	95% CI	Non-BSS Group		Mean difference	95% CI
	Pre	Post			Pre	Post		
Berg Balance Scale	46.8 ± 2.5	52.7 ± 3.4	5.9	4.49, 7.3	46.4 ± 3.3	53.1 ± 1.9	6.7	5.3, 8.09
Gait Velocity (m/sec)	0.98 ± 0.2	1.12 ± 0.1	0.13	0.04, 0.23	1.02 ± 0.1	1.16 ± 0.1	0.14	0.04, 0.23
Step Length (meters)	0.55 ± 0.1	0.61 ± 0.08	0.05	0.02, 0.08	0.55 ± 0.07	0.62 ± 0.08	0.07	0.03, 0.11
Stride Length (meters)	1.12 ± 0.2	1.23 ± 0.16	0.10	0.03, 0.17	1.10 ± 0.15	1.26 ± 0.17	0.15	0.07, 0.24
TUG (Sec)	10.3 ± 1.9	8.44 ± 1.09	- 1.87	-3.12 , - 0.6	10.2 ± 1.33	8.07 ± 1.67	-2.14	-2.6, - 1.6
6MWT (meters)	427.7 ± 6	485 ± 56	57.73	21.76, 93.6	428.8 ± 73	469 ± 56	43.93	8.4, 79.3

Figure 1: Changes in force plate measures in Biodex Stability System (BSS) group



CoP: Center of pressure

AP: Antero-posterior

ML: Medio-Lateral

RMS: Root mean square velocity

Image 1: Image taken from the Biodex stability system device showing one type of exercise completed by our participants. The green line represents the movement of CoM, while the participant was asked to stand quietly with eyes open.



Chapter 3

Effects of Balance Training on Non-Motor Symptoms in Parkinson's Disease

Effects of Balance Training on Non-Motor Symptoms in Parkinson's Disease

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Manuscript in preparation; to be submitted to "Journal of Parkinson's disease"

3.1 Abstract

Background: More than 50% of individuals diagnosed with Parkinson's disease (PD) present with non-motor symptoms; however, these symptoms are often unrecognized and consequently untreated. Only a few studies have examined the effect of exercise training on the non-motor symptoms of PD and the results have been inconsistent. It is suggested that highly challenging balance exercises should be included in the rehabilitation programs for improvement in non-motor symptoms, however, their efficacy has not been fully tested.

Objective: To evaluate the effects of balance training using the Biodex Stability System (BSS) on non-motor symptoms of fatigue, depression and pain and the relationship of the impact on non-motor symptoms to other measures such as functional reach, fear of falling and quality of life in PD.

Methods: Twenty individuals with PD (Hoehn & Yahr (H&Y) Stage 1-3) were assigned to either the BSS group (mean age = 63.9 ± 3.8 years) or the Non-BSS group (mean age = 66.3 ± 7.9 years); mean severity based on H&Y was 2.7 ± 0.42 and 2.6 ± 0.83 respectively. Each participant in the BSS group underwent 4 weeks on training on the BSS, which included static and dynamic exercises. The Non-BSS group underwent 4 weeks of balance exercise training using exercises from the National Parkinson Foundation's Fall Prevention booklet. Changes in fatigue using fatigue severity scale, depression using geriatric depression scale, pain using numeric pain rating scale, function using survey of activities and fear of falling scale and functional reach test and quality of life using parkinson's disease quality of life 39 questionnaire.

Results: There were significant improvements in fatigue after BSS training (mean difference from Baseline: -4.6 ± 5.6 points, 95% CI = -0.27, 0.45) and the BSS group had significantly greater improvement than the non-BSS group (mean difference between groups: -12.6 ± 12.3

points, 95% CI = - 20, - 4). There were no significant improvements for any of the other non-motor symptoms.

Conclusion: Balance training using the Biodex Stability System improves fatigue in PD patients and this improvement was significantly greater than with standard balance exercises. This improvement in fatigue may have valuable implications on fear of falling and QoL in individuals with PD.

Key words: Parkinson's disease, Balance exercises, Biodex Stability System, non-motor symptoms, fatigue

3.2 Introduction

More than 50% of individuals diagnosed with Parkinson's disease (PD) present with non-motor (NM) symptoms²⁵⁸. Some of the common NM symptoms in PD include depression, fatigue, and pain and sleep disorders. Shulman et al.²⁵⁹ reported depression in 44%, anxiety in 39%, fatigue in 42% and sleep disorders in 43% of individuals with PD (disease duration = 7.7 ± 5.5 years). Garcia Ruiz et al.²⁶⁰ reported pain is experienced by as many as 85% of PD patients.²⁶¹ The presence of NM symptoms may intensify motor dysfunction and further deteriorate quality of life (QoL)^{262,263} and physical function in individuals with PD^{264,265}. Early recognition and treatment of these NM symptoms can have a profound effect on the management of PD¹¹⁸. Although NM symptoms are can be early symptoms of PD, they are often unrecognized and consequently not treated, as the focus of PD treatment has traditionally been on the motor symptoms²⁵⁹.

A limited number of studies have examined the effects of various forms of exercise on NM symptoms in PD with a lack of consistent findings. Exercise training has resulted in mixed effects on NM symptoms of PD, with a few studies reporting positive effects and a few reporting no effects²⁶⁶⁻²⁶⁸. Recently Abrantes et al.²⁶⁹ reported a higher level of physical activity to be associated with less depression, fatigue and apathy in individuals with PD. Exercises focusing on endurance²⁷⁰, resistance²⁷⁰ and balance²⁷¹ interventions were reported to be helpful in managing NM symptoms such as depression²⁷⁰, pain²⁷¹ and fatigue²⁷⁰. A recent meta-analysis¹⁹⁷ suggested that highly challenging balance exercises should be included in the rehabilitation programs for improvement in PD NM symptoms. In contrast, other exercise studies of aerobics²⁷², qigong²¹⁴, Wii balance¹³⁷ training, combined aerobic and strength training²⁷³ and treadmill²⁷⁴ did not have any effect on depression^{137,214,272,273} or fatigue¹³⁷. Reuter et al.¹⁴⁴ reported improvement in general pain following flexibility, walking and Nordic walking training in persons with PD. The impact of exercise training on fear of falling in PD has not been investigated.

Overall there is a scarcity of studies reporting changes in NM symptoms following exercise training targeted specifically to improve balance and posture. The Biodex Stability System (BSS) is a commercially available device (Biodex, Version 3.1, Biodex Medical Systems) frequently used for rehabilitation of musculoskeletal injuries (i.e. ankle sprain). BSS enables participants to challenge their balance outside of their limits of stability. We have recently shown the feasibility of BSS in PD for balance and gait training (manuscript in review). However, the usefulness of BSS-based challenging balance exercises on NM symptoms of PD has not yet been tested.

Therefore, the aim of this study was to examine the effects of balance specific exercise programs (with and without use of the BSS) on NM symptoms including fatigue, pain and depression in PD. A secondary aim was to determine the relationship between the changes in NM symptoms to fear of falling and QoL.

3.3 Methods:

Participants:

Individuals with a diagnosis of PD, aged 40 - 70 years and stage I-III (Hoehn & Yahr) were included in the study. A score of less than 50 out of 56 on the Berg Balance Scale (BBS) was selected as an indication of balance problems. Additional inclusion criterion was participants' capacity to independently ambulate with or without the use of an assistive device.

Individuals were excluded from this study if they had any of the following conditions: 1) neurological disorder other than PD, 2) head trauma, 3) neurosurgical intervention for PD such as deep brain stimulation, 4) substance abuse, or 5) self-reported cardiovascular or medical dysfunction which would preclude participation in a challenging balance training program. Additionally individuals with a history of any major injuries or replacements to hip, knee or ankle

were excluded from the study. A score of 20 or below on Montreal Cognitive Assessment (MoCA) was also used as an exclusion to rule out any significant cognitive deficit.

Recruitment was achieved through the Parkinson's Disease and Movement Disorder Center at the University of Kansas Medical Center (KUMC). Individuals were given the option to either be a part of the BSS group or the Non-BSS group. The study was approved by the KUMC Institutional Review Board and all participants gave written consent prior to participation in the study.

The participants were asked to visit KUMC at least 2-3 days prior to the beginning of the exercise training. The participants were instructed to continue their usual anti-parkinsonian medications. Each participant was in the "ON" phase of medication (within 1 – 2 hours of taking medications) during the testing (pre and post intervention) as well as during the exercise sessions.

Testing:

All participants were evaluated before and immediately after the completion of 4 weeks of balance exercise training using a battery of tests, including non-motor outcome measures, fear of falling and quality of life as described below. Two different PhD candidates blinded to the assignments, who were also PT's completed the outcome assessments pre and post completion of the study. 2 other examiners, who were blinded to the study participants carried out UPDRS assessments.

Outcome Measures:

Depression was assessed with the Geriatric Depression Scale (GDS). The GDS has high discriminant validity, internal consistency and clean cut off scores, which can be utilized for

individuals with PD^{161,275}. The GDS includes 30 self-completed questions with a yes or no response and takes approximately 10 minutes to complete.

Fatigue was assessed with the Fatigue Severity Scale (FSS), which can be used for both diagnosis and severity of fatigue in PD²⁷⁶. The FSS is a nine-item self-completed questionnaire, measuring the effect of fatigue on daily functioning. The items are rated on a scale of 1 to 7 (1 = completely disagree; 7 = completely agree). Higher scores indicate a higher level of fatigue. Herlofsan et al¹⁶³ reported that a score of 4 or higher in individuals with PD is indicative of fatigue. The FSS has excellent reliability with Cronbach's alpha of 0.94 and split half reliability of 0.86 and 0.91^{277,278} in other neurological conditions and it has been suggested for use in patients with PD²⁷⁶.

The Numeric Pain Rating Scale (NRS-pain) was used to record pain level. NRS-pain is an 11 point scale (0 -10), where "0" represents no pain and "10" represents worst possible pain. The NRS-pain has never been validated or used in individuals with PD, however it has been extensively used to assess pain severity in other medical conditions such as diabetic peripheral neuropathy²⁷⁹, cancer²⁸⁰ and amputations²⁸¹. Due to ease of use, we utilized the NRS to assess pain.

The Survey of Activities and Fear of Falling in Elderly (SAFFE) was developed by Lachman et al¹¹⁴ to assess the role of fear of falling on activity restriction in elderly individuals. It is an 11-item questionnaire with good internal consistency, reliability and convergent validity^{108,115} for fear of falling measures. SAFFE was used to assess the effects of exercise training on activities and fear of falling.

Quality of life was assessed using the Parkinson's Disease Questionnaire-39 (PDQ39)²⁸², which is a 39 item questionnaire addressing 8 different domains: mobility (10 items); emotional well-being (6 items); stigma (4 items); social support (3 items); cognition (4 items);

communication (3 items); and bodily discomfort (3 items). All questions are scored from 0 (never) to 4 (always). Domain and total scores are translated into a percentage such that 0 would equal the best and 100 would equal the worst QoL.

Intervention:

Participants received 12 supervised treatment sessions of 55 minutes of either the BSS exercises or standard balance exercises (Non-BSS) from the National Parkinson Foundation's Fall Prevention booklet, 3 days a week for 4 consecutive weeks.

BSS group intervention:

Each participant in this group underwent a balance training protocol using BSS. Intervention included static and dynamic exercises where participants were asked to either keep or move their CoP in order to challenge their balance. Under the static condition, the participants maintained static position by sustaining the center of balance. The center of balance was represented on the device's screen by a small black dot in the smallest circle (the screen showed 4 circles, with higher radius representing the movement away from the CoM). Under the static position, participants are asked to maintain their balance over the dot, while standing on both feet, shoulder width apart and close together, as well as standing on the left and the right foot. Under the dynamic condition, the participants moved their center of balance in antero-posterior and medio-lateral directions and in a circular pattern (clockwise and counter clockwise), tracking a small dot presented in random directions. For all the tasks, participants started at Level 1 (easy) in the first week and moved to Level 3 (difficult) by the 3rd week. During the 4th week, the levels were chosen randomly between Levels 1-3. The participants were given instructions and were provided assistance during training sessions, as needed. A total of 55 minutes were spent in every session excluding warm up and cool down exercises. Participants were instructed to take breaks as they wish in order to minimize undue fatigue or other

symptoms such as light headedness or dizziness. A warm up and cool down session was added to the beginning and the end of the training session lasting 5 minutes each. Participants were allowed to hold on to the side grab bars to break a fall but were instructed to perform the balance tasks without continuously holding on to the sidebars. Thus, participants momentarily (under 10 seconds) held the sidebars to regain their balance as necessary during each training session. On average each participant held on to the handrails 2-3 times during transition between tasks or until they become familiar with the task.

Non-BSS group: The participants in the balance exercise group performed balanced exercises from the National Parkinson Foundation (NPF)²⁸³ (www.parkinson.org, Fall Prevention booklet, pages 117-125; appendix 1) under the supervision of a research assistant. The intervention contained 6 different balance exercises. The participants were asked to visit KUMC to perform all exercises (Table 1). A total of 55 minutes were spent on each exercise session excluding the rest breaks, and exercises were conducted 3 days a week for 4 weeks. Participants were instructed to take breaks as they wish in order to minimize undue fatigue or other symptoms such as light headedness or dizziness. Similar to the BSS group, individuals in Non-BSS group completed 5 minutes of warm up session and 5 minutes of cool down session in the beginning and at the conclusion of each exercise session. The description of the exercises are listed in table 1.

Statistical Analysis:

Statistics software (IBM SPSS v20, IBM Corp, Armonk, NY) was used to analyze the data, and the alpha level was set at 0.05 for all statistical analyses. For each of the outcome measures, descriptive statistics (mean and standard deviation) were calculated. Normal distribution was checked using the Kolmogorov-Smirnov z statistic. No power analysis was calculated for this study because it was an exploratory preliminary study. Outcome measures were tested both

within and between groups using the Wilcoxon sum rank test and Mann Whitney U test respectively. For the significant findings, the 95% confidence interval (CI) of the difference was calculated. A Spearman correlation analysis was performed between change in score (post-pre intervention) for depression, fatigue and pain to change in scores of fear of falling and QoL for both groups separately.

3.4 Results:

After screening for the inclusion and exclusion criteria, out of 31 subjects initially identified, 20 were recruited for the study. The groups were not statistically different at baseline in age (BSS group = 63.9 ± 3.8 , Non-BSS group = 66.3 ± 7.9 years, $p = 0.46$), weight (164.2 ± 24.5 , 176.6 ± 52.8 lbs., $p = 0.67$), disease severity as assessed by Hoehn & Yahr scale (2.7 ± 0.4 , 2.6 ± 0.8 , $p = 0.40$) or cognitive status as assessed by Montreal Cognitive Assessment test (27.8 ± 1.8 , 26.6 ± 2.36 , $p = 0.18$) (table 2). The groups were also not statistically different with non-motor outcomes at the baseline (table 1).

We found significant improvements in fatigue as measured by the FSS for the BSS group (Table 4) only (mean change = 8 points, 95% CI = - 0.27, 16) following 4 weeks of the training. Additionally, we found significant differences for FSS (mean difference = 12.6 pts., 95% CI = 23.4, 1.7) between the 2 groups (Fig 1 and Table 4). However, we did not find significant within group or between group differences following the intervention for depression, QoL, pain, or fear of falling.

3.5 Discussion:

The purpose of this pilot study was to evaluate the effects of challenging balance exercise training using either BSS or Non-BSS on NM features of PD and the relationship of changes in the NM symptoms to fear of falling and QoL. Our results indicate that balance exercises, with BSS, resulted in significant improvement in fatigue. . These results suggest that fatigue can be

improved with balance training and that BSS should be utilized, when available, to maximize these effects.

Fatigue is defined as “an overwhelming sense of tiredness”, “lack of energy”, or “a feeling of exhaustion”. Fatigue is a major NM symptom affecting mobility and function in people with PD. Fatigue in PD can be classified primarily into peripheral fatigue and central fatigue. Several studies have reported increased fatigue in individuals with PD^{120,122,125}. Although the cause of fatigue is unclear in PD, several mechanisms have been proposed such as altered activation of hypothalamic-pituitary-adrenal system due to stress, dysfunction of basal ganglia and striato-thalamus-cortical loop²⁸⁴. This impairment of central sensory organization has been linked to fatigue²⁸⁵.

In the present study, fatigue improved after 4 weeks of balance training using the BSS. A study by Abrantes et al²⁶⁹ found that higher levels of physical activity were associated with less fatigue, which is in accordance with the results of our study, where the increased activity in the form of challenging balance exercises resulted in decreased fatigue. A study by Rochester²⁸⁶ identified that better balance is correlated with walking speed, depression and fatigue; however, we saw no changes in depression after either form of balance training. Improvement in balance and gait may decrease the unwanted loading of the cognitive system and allow better attention for the physical tasks²⁸⁷.

BSS group showed greater improvement in fatigue compared to non-BSS training. we infer that improvement may be attributed to greater input from the central nervous system. BSS training requires greater engagement of the visual system and cognitive input. The training improved individual's ability to stand upright to view the screen panel and continuously correct their balance, which may have resulted in improved upright posture and decreased fatigue²⁸⁸. These results are in accordance with previous studies, which indicated that poor posture

resulted in increased fatigue in individuals with low back pain²⁸⁹ as well as healthy individuals²⁹⁰. In contrast, several previous exercise trials reported either no effect^{266,273} or even an increase in fatigue²⁹¹ following exercise interventions in PD.

The neurophysiology of pain perception in PD is not well understood²⁹² but recently pain in PD has been classified into several categories i.e. musculoskeletal, radicular or neuropathic, dystonia related pain, akathitic discomfort and primary, central parkinsonian pain, suggesting multifactorial involvement. Basal ganglia are responsible for modulation and sensory control of nociceptive information to higher motor areas, which may impact several dimensions of pain¹⁴⁰. Although exercise has been repeatedly shown to decrease pain in various conditions²⁹³⁻²⁹⁶, its effect in PD has not been well studied. Only a few studies reported effects of exercise training on pain in PD¹⁴⁴⁻¹⁴⁷. One study evaluated the effects of a 12-week of exercise program consisting of flexibility, strength and aerobic training and reported a non-significant (8%) reduction in pain. Another study investigated the effects of flexibility and relaxation programs, walking and Nordic walking in PD and reported improvement in pain with all forms of exercise¹⁴⁴. Contrary to the previous studies, our study resulted in no change in pain for either of the 2 groups. Pain has been associated with fear of falling²⁹⁷ and poor QoL²⁹⁸ in PD, but we did not find any significant correlations between improvement in pain with fear of falling and QoL following the balance exercises for any group.

Although, the pathophysiological mechanism underlying depression is unknown, it is well understood that PD pathological changes extend beyond midbrain and involve loss of non-adrenergic and serotonergic neurons. These neuronal systems are associated with regulation of mood and reward systems as well as mood disturbances in PD. One model suggests that disruption of serotonergic neurons lead to dysfunction of orbitofrontal –basal ganglia-thalamic circuits, which are related to depression²⁹⁹. This is further confirmed by reduced dopamine transport activity, frontal blood flow and caudate frontal glucose metabolism in depressed PD

patients^{300,301}. Exercise studies have reported mixed results on depression, with some reporting no change²¹⁴, and some reporting significant reduction^{86,302} in individuals with PD. Studies reporting significant reduction in depression can be attributed to the type of exercises, which mainly included aerobic interventions. In our study we found a non-significant reduction in depression, which could be attributed to short duration and specificity of exercises or small sample size. High intensity and longer duration exercises addressing more aerobic fitness, which may influence the neural structures responsible for depression in PD, may result in better improvement in depression. In addition, the socialization of group exercise sessions may help improve depression in this population; however this was not the case in this present study.

Presence of NM symptoms can significantly increase fear of falling²⁹⁷ and impact QoL in individuals with PD. In the present study, neither form of balance training had a significant impact on fear of falling or QoL outcomes. However, non-significant improvement in both fear of falling (14% change) and QoL (9.6% change) was noted in the BSS group and non-significant improvement in QoL (12.9%) in Non-BSS group. Although, these changes were non-significant, they may have significant implications for exercise interventions for individuals with PD.

Previous exercise studies have either reported no change or improvement in QoL, however it is important to understand that those studies reporting a significant change in QoL either used dynamic physical therapy exercises or aerobic training protocols¹⁷⁶. On the contrary, our intervention focused more on static and simple dynamic exercises, which could have led to lower non-significant changes in QoL. More challenging exercises which include more difficult balance exercise trials may further improve fear of falling and QoL in these individuals.

We did not find any significant correlation of fatigue, depression or pain with either fear of falling or QoL, which is to be expected as no significant changes were observed for any of the variables following the intervention, except for fatigue in the BSS group. Previous studies that reported improvements in these variables either used different training strategies (aerobic and

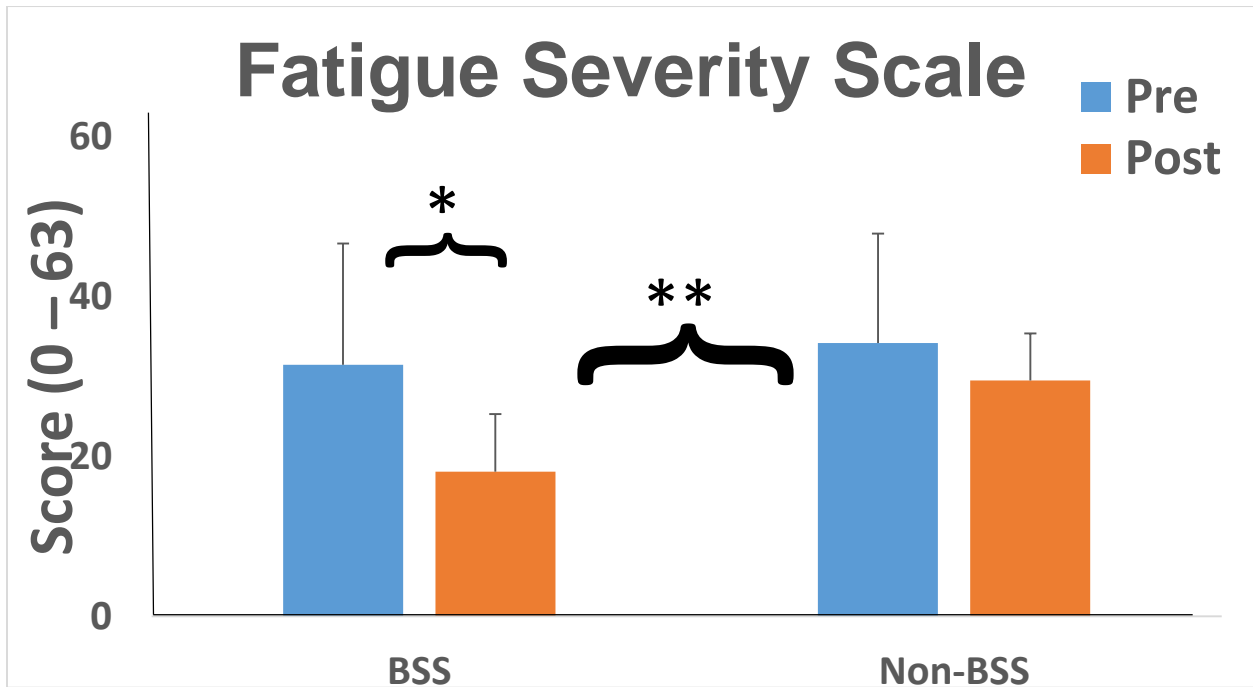
endurance training^{303,304} or interventions over longer periods of time¹⁷⁶. Since strong evidence related to presence of fatigue²⁸⁴, depression³⁰⁵, pain¹⁴⁰, poor QoL³⁰⁶, and fear of falling²⁹⁷ exists in the PD literature, the effects of various interventions on these variables should be examined.

This pilot study has a number of limitations including the small sample size and lack of randomization. However, the results provide initial evidence that balance specific exercise can have some effect on fatigue in PD, but these results should be confirmed with a larger sample size and random allocation of treatments. Additionally, future studies should undertake interventions with components of both balance and aerobic exercises and interventions of longer duration.

Conclusion

The results of our balance training intervention using BSS indicates that challenging balance exercises may result in a decrease in fatigue in individuals with PD. Further research is necessary to determine the effects of the BSS specifically and exercise in general on the non-motor symptoms of PD.

Graph 1: Fatigue severity score for BSS and Non-BSS groups



FSS: Fatigue severity scale

BSS: Biodex stability system group

Non-BSS: Balance exercises recommended by National Parkinson Foundation (fall prevention booklet)

P – Value represents significant difference between groups for change in fatigue

Table 1: Baseline demographics and clinical outcomes for both BSS and Non-BSS groups

	Group 1 (BSS Group)	Group 2 (Non-BSS Group)	<i>p</i> - value
Gender (Male/Female)	6/4	5/5	
Age (yrs)	63.9 ± 3.84	66.33 ± 7.97	0.46
Weight (lbs)	164.24 ± 24.5	176.66 ± 52.82	0.67
Height (inches)	66.47 ± 4.3	68.611 ± 5.4	0.45
Disease severity (H & Y)	2.7 ± 0.42	2.6 ± 0.83	0.40
Cognitive Status (MOCA)	27.8 ± 1.81	26.6 ± 2.36	0.18
Geriatric depression scale	5.1 ± 5.5	4.4 ± 4.7	0.85
Numeric pain rating scale	1.9 ± 1.45	2.16 ± 2.7	0.43
Parkinson's disease quality of life -39	41.5 ± 29	34.3 ± 17.9	0.73
Survey of activities and fear of falling in elderly	0.91 ± 0.53	0.88 ± 0.68	0.52
Fatigue severity scale	31.5 ± 15	34.2 ± 13.7	0.57
Timed up and go test	10.3 ± 1.9	10.2 ± 1.33	0.79

Table 2: Exercises for Non-BSS group:

Exercise	No. of Repetitions	Time spent
Single leg Stance	40	6 minutes * 2
Standing eyes closed	6	6 minutes* 2
Toe taps on book	10	4 minutes* 2
Step ups on a book	24	4 minutes* 2
Standing foot on step with head movements	12	4 minutes* 2
Side stepping at counter	10	4 minutes* 2

Table 3: Means and Standard Deviation of Outcomes at Baseline and Post intervention for BSS and Non-BSS groups

	BSS		Non-BSS	
	Baseline	Post – Intervention	Baseline	Post – Intervention
Fatigue Severity Scale FSS	34 ± 13	29.4 ± 12	31.5 ± 15	39.5 ± 13
Geriatric Depression Scale (GDS)	5.1 ± 5.5	3.4 ± 2.9	4.1 ± 4.7	3.2 ± 3.5
Numeric Pain Scale (NPS)	1.9 ± 1.4	2.2 ± 2.0	2 ± 2.75	1.2 ± 1.8
Parkinson Disease Quality of Life (PDQ39)	41.5 ± 29	37.5 ± 30	33.8 ± 17.9	27.9 ± 13
Visual analog scale (VAS)	6.2 ± 2.4	5.8 ± 2.4	6.05 ± 2.2	6.7 ± 1.6

Table 4: 95% Confidence Interval for within and between groups for BSS and Non-BSS groups:

	BSS			Non-BSS			Between groups		
	Mean change Post - pre	95% CI of change	p – value	Mean change Post - pre	95% CI of change	p – value	Mean difference Between groups	95% CI of change	p – value
Fatigue Severity Scale FSS	-4.6	- 8.74, -0.45	0.05*	8	- 0.27, 16.2	0.20	12.6	- 21.4, - 3.78	0.005*
Geriatric Depression Scale (GDS)	- 1.7	- 4.1, 0.7	0.07	-1.2	- 2.3, 0.13	0.11	-0.6	- 2.1, 3.3	0.79
Numeric Pain Scale (NPS)	0.3	- 0.82, 1.4	0.24	-0.8	- 2.22, 0.62	0.46	1.1	2.8, - 0.69	0.39
Parkinson Disease Quality of Life (PDQ39)	-4	-12.9, 4.9	0.26	- 4.4	- 14.7, 2.96	0.44	1.9	15.2, - 11.4	0.73
Visual analog scale (VAS)	- 0.4	- 1, 0.20	0.30	0.72	- 0.74, 2.0	0.15	-1.05	0.62, - 2.7	0.28

CHAPTER 4

Conclusion

4.1 Overview

Although postural instability is a major problem in individuals with PD leading to frequent falls, few research studies have examined balance specific training interventions to evaluate changes in postural/motor, and non-motor symptoms. Recent studies indicate that challenging balance exercises may be more beneficial as compared to simple over ground balance or other strengthening exercises and aerobic training, which do not necessarily challenge balance for individuals with PD. We examined the effectiveness of progressively challenging balance exercise training using the Biodex Stability System (BSS) on postural/motor and non-motor symptoms of PD. The BSS device has a movable platform with 20 degrees of tilt to challenge balance with and without an option of visual feedback; it has not been utilized as a training modality in PD, despite the fact that its efficacy to improve balance in musculoskeletal and other neurological disorders has been reported. The purpose of this dissertation was to determine the effects of 4 weeks of supervised balance training using BSS as compared to supervised standard balance exercises without the BSS on balance, gait, and non-motor symptoms of pain, fatigue and depression.

Four weeks of exercise training using the BSS improved measures of balance and gait in adults with PD. However, similar improvements were also seen after an exercise program that did not use BSS. This suggests that for the measures used in this study, there were no differences between BSS training and general balance exercises (Chapter 2). Additionally, significant within group and significant between group improvements (BSS and Non-BSS groups) was seen in fatigue following 4 weeks of training. There were no significant within or between group improvements noted for any of the other non-motor symptoms Chapter 3).

4.2 Summary of Findings

4.2.1 Effects of 4 weeks of balance training in individuals with Parkinson's Disease (chapter 2)

This study was a prospective, non-randomized (self-selected) pilot study. PD subjects at Hoehn and Yahr stages I – III (BSS group; n=10 and Non-BSS group, n=10) participated in 55 minute exercise sessions 3 times a week for 4 weeks. The training required voluntary movements during static or dynamic balance tasks. The BSS group performed progressively challenging tasks with visual feedback over the course of 4 weeks whereas the control group (Non-BSS) performed supervised non-progressive balance exercises taken from the National Parkinson Foundation “Falls Prevention” booklet for the same session duration and frequency as the BSS group. Both groups completed 5 minutes of warm up and 5 minutes of cool down session before beginning and completion of each exercise session respectively. Postural sway measures and secondary measures of Berg Balance Scale, spatio-temporal gait measures, Timed Up and Go (TUG) and 6 Minute Walk test data were collected at baseline and post exercise intervention for both groups.

We found significant within group improvements for sway area, CoP path length in ML as well as AP direction and Berg Balance Scale scores in the BSS group. Postural instability in PD has a complex pathophysiology, which results in inability to perform tasks of transfers and gait, frequent falls, and problems with independent living. Recent studies recommended the use of CoP sway measures as better indicators of postural instability as opposed to traditional clinical measures. Our exercise intervention for the BSS group involved exercises that employed 1) dynamic destabilization of CoP pushing the limits of stability, yet maintaining the base of support and 2) static balance exercise that required participants to maintain the control of CoP within their base of support. During the training the participants needed to rely both on feedback and feed forward mechanisms to control their balance. In addition to employing appropriate postural control strategies, the participants were using a visual exploration activity that challenged the visual and dual task cognitive control. Thus, we believe our BSS intervention trained participants to control their CoP within the base of control during static as well as dynamic balancing tasks.

In addition to improvement in the BSS group in Berg Balance Scale scores, we also found significant within group improvement for the non-BSS group as well. The exercises in the non-BSS group were taken from the fall prevention booklet available at National Parkinson Foundation website. These exercises involved activities such as toe taps on a book and toe taps with head movements and side-stepping; these exercises likely challenged the dynamic control of CoP within the limits of stability. Additional tasks included single leg stance and standing in one position with eyes closed which challenged the static balance, requiring the maintenance of CoP at single point with the base of support. However, the subjects in this group were not adjusting and pushing their balance outside of their limits of stability with any visual feedbacks; nor were they changing the amount of challenge with balance exercises.

We were not able to compare sway measures as measured by CoP sway and CoP path length in ML and AP directions between the BSS and non-BSS groups. Failure to complete between group comparisons was caused by technical failure of the force plates to record the CoP sway data during the testing of participants in the non-BSS group. Future studies using force plates for outcome assessments should clearly verify if the data are collected after every trial. On the other hand, we did not find any significant between group differences for clinical outcome measure of balance from the Berg Balance Scale score. Research studies have shown significant correlation between sway measures such as ML sway and Berg Balance Scale³⁰⁷. Considering very few studies examined the correlation between sway measures and clinical measures of balance with the berg balance scale, it is difficult to conclude whether significant changes in Berg Balance Scale score for non-BSS group would have translated into significant improvement in sway measures. A future study is needed to directly compare the force plate outcomes following BSS training to a control training to gain a better understanding of the effects of BSS-based balance exercises on balance.

The results of our study are similar to previous studies which used similar exercises to challenge balance; however previous studies neither compared balance exercise training to

other exercise interventions nor used sensitive outcome measures such as sway area or path lengths of CoP. We did not find significant between group differences in balance scores measured by Berg Balance Scale. There are several possible reasons for this: 1) both exercise interventions were similar in intensity and duration, 2) we did not utilize all possibilities available in BSS to further challenge participants' balance; the level of resistance of the platform of BSS can be increased to destabilize it further, and 3) a more homogenous group of participants at the similar level of disease would reduce variability and result in group difference from the intervention.

We also found significant within group improvements in measures of spatiotemporal gait that is gait velocity and step length for both BSS and non-BSS groups. Gait deficits are commonly reported in PD and associated with impaired balance. Dopamine deficiency in PD has been associated with increased neuronal activity in the basal ganglia⁸⁰. Increased activity in basal ganglia with increased output from globus pallidus pars interna via indirect loop that inhibits thalamo-cortical circuitry, leads to movement deficiency or hypokinesia. Decreased leg extensor muscle activity and poor balance due to impaired proprioception and deficits in neuronal coordination of upper and lower limbs have been linked to gait problems⁸¹. The major contributor to gait problems in PD is the reduced amplitude of movement leading to decreased stride length³⁰⁸. A shortened stride length can be linked to other gait abnormalities such as decreased walking speed and increased cadence and double limb support time. All of these gait problems lead to increased fall risk in PD⁸⁴. A study by Rochester²⁸⁶ identified that better balance is correlated with walking speed and other gait related outcomes such as stride length and step length. Walking and postural instability are not only regulated by higher subcortical mechanisms but also involve attentional mechanisms⁹⁷. Under particular conditions, gait and stability requires extra attentional resources. For instance during multi-tasking, individuals with PD demonstrate increased postural instability, which increases their risk of falls⁹⁸. When CoM is displaced out towards the limits of stability, which happens during everyday activities such as sit

to stand transitions as well as walking, stepping strategies are used to prevent falls. Recently, studies in PD have shown that patients have difficulty in initiating compensatory stepping⁹⁹, more specifically towards lateral direction¹⁰⁰.

Our intervention was targeted to improve the control of CoP sway and path lengths in both AP and ML directions, and we tested the hypothesis that improvement in postural control would translate to improvement in gait. We believe that better control of CoP within the base of support not only improved the postural instability in these individuals but also took away the use of extra attentional resources required in activities of daily living such as walking. This may have helped to improve gait related outcomes such as gait velocity and step length in the BSS group. Additionally, we found that our non-BSS group also improved significantly in gait speed and step length. The reason for this significant improvement may be that even though ground-based exercises did not challenge the participants' balance at the same level as the BSS, they were still challenging enough to cause static or dynamic perturbation. The improvement in clinical measures of balance in both groups suggest that both exercise interventions were sufficient enough to improve balance, and it strengthens the fact that improvement in balance led to better control of CoP (although measured only in BSS group) and improved ability to multitask such as those required in walking.

We did not find any significant differences between the 2 groups for any of the spatiotemporal gait measures that is gait velocity and step length. As explained earlier and is also evidenced from the description that many exercises in both groups were not significantly different in the level of challenge. Additionally, we found that even though the results of our study were significantly different at post intervention for both groups, we failed to achieve the clinically meaningful change in any measures except for the balance measures which may have better implications such as higher intensity and highly challenging exercises may be needed for this population. Unfortunately at present there is no data on clinically meaningful changes for the

sway measures. Future studies should focus on intervention which employs challenging activities and causes the CoP to work on timing and speed of movement in order to reach the clinically meaningful difference.

Furthermore, we found significant within group improvements for dynamic functional tasks as assessed by Timed Up and Go (TUG) test and functional endurance as assessed by 6 Minute Walk Test (6MWT). Previous research has shown conflicting results with some studies reporting significant correlation^{153,309,310} and some reporting no association³¹¹ between the measures of CoP or measures of balance and functional dynamic tasks such as TUG or 6MWT. We believe that the significant differences seen in our study was due to better control of CoP within the base of support. Better control of CoP would have resulted in improved ability to carry out the parts of the tasks such as sit to stand, turning etc. owing to decreased sway. Additionally, improvement in balance might have resulted in improved confidence in carrying out the task associated with movement of CoP towards the limits of stability. One of the other important factors that may have played a crucial role in improved timing of TUG and distance covered in 6MWT could be the improvement in gait velocity as explained above. Gait velocity is a major determinant of the results of both TUG and 6MWT. Additionally, our non-BSS group also improved significantly following the intervention. As stated above, the non-BSS exercises were very similar to the BSS exercises in terms of challenge. These exercises were completed over ground, which resembles the natural environment of the participants and might have improved their confidence level in performing these activities.

We did not find significant between group differences for TUG or 6MWT partly due to the fact that both exercise interventions were very similar in terms of challenge. We recommend that future studies should employ more challenging exercises, which may results in significant and clinically meaningful changes in the functional and endurance outcome measures. In our study, we did not explore other options available on the BSS such as moving the platform to the

maximum available tilt, which could have significantly changed the dynamics of the training. Considering this as the first study looking at the efficacy of BSS in individuals with PD, we decided to use less challenging environment considering participants' safety. However the device appears to be safe and has inherent capability to significantly challenge balance by decreasing the resistance of the platform, thereby allowing greater movement in all planes.

Limitations of the training:

The result of this work provides the first evidence that individuals with PD demonstrate improved balance using BSS system after 4 weeks of balance training assessed by sway measures on the force plates. We failed to record the force plate data for the non-BSS group due to technical failure. Force plate results from the non-BSS group would have helped us tremendously in delineating whether training specifically focused on only improving sway measures was in fact better than the general balance exercises, which are being prescribed to individuals with PD. However, it should be noted that we found significant within group improvements in other balance outcome measures as well such as Berg Balance Scale for both groups. Previous studies have reported significant improvement in Berg Balance Scale scores following similar training strategies, which employed manipulation of CoP^{86,182}. Both types of trainings improved balance significantly following the training. One of the major reasons for not being able to see any between group differences in our study is the fact that even though BSS was used, we did not explore other options such as using the full tilt of BSS system. The platform can be made to tilt up to 12 degrees in any direction which would have increased the challenge significantly; however considering the vulnerability of this population and also considering the fact that this was the first study using BSS, we decided not to go below the resistance level of 9 degrees regardless of the patient's ability. It is possible that some of the individuals who were at lower severity level that stage I or II of H& Y scale might have reached a ceiling effect. Training beyond the resistance level 9 would have significantly challenged these individuals and might have resulted in statistically as well as clinically meaningful changes. Future studies should

definitely try to have more uniform sample size in terms of severity level and also should use more challenging protocol by decreasing the platform resistance, thereby significantly challenging these individuals.

Both types of balance training that is either using BSS or the one without BSS resulted in improved gait variables as assessed by GaitMat. Again, higher level of challenge and equality of groups in terms of severity of the disease may have resulted in better outcomes in terms of statistical significance as well as clinically meaningful changes. We recommend that future studies should employ more challenging training by using the full available tilt (1 -12 degrees, where 12 is maximum resistance, platform is practically stationary).

The results from this study suggest that adding challenging balance exercises using devices such as BSS, to the rehabilitation of individuals with balance problems more specifically those with PD can help improve balance and spatiotemporal gait. This improvement in balance and gait may reduce the number of falls and improve quality of life in individuals with PD. However, the results of our study should be considered with caution as the sample size is very small (n =10 in each group) and results may not represent the real change. Additionally, the participants were between stages I – III of the H &Y stage, where stage I represents minimal unilateral symptoms and stage III represents bilateral changes with mild postural instability. It is possible that individuals with stage I or II might have reached the ceiling effect in terms of the task difficulty and the training was not intense enough to cause any further changes in their balance, whereas the individuals at Stage III may have significant difficulty in the task completion. A more homogenous group in terms of severity would have helped us in determining the efficacy of our intervention. We suggest that future research studies should conduct large sample sized, randomized control trial with more challenging balance exercises by using the full tilt available on the BSS. Additionally, the CoP sway measures should be compared between groups to identify the better treatment options for postural instability in these individuals.

4.2.2 Effects of balance training on non-motor symptoms of Parkinson's Disease (chapter 3).

The objective of this study was to evaluate the effects of balance training using the BSS on non-motor symptoms of fatigue, depression and pain in individuals with PD. This study was a prospective, non-randomized pilot study. PD subjects with Hoehn and Yahr stages I – III (BSS group; n=10 and Non-BSS group, n=10) participated in the exercise sessions 3 times a week for 4 weeks as described above. The control group (Non-BSS) performed supervised balance exercises taken from the National Parkinson Foundation “Falls Prevention” booklet, as described above. The outcome measures included fatigue, depression, pain, function, and quality of life. There were significant within group improvements in fatigue after BSS training and significant between group (BSS and Non-BSS groups) improvements in fatigue. There were no significant improvements for any of the other non-motor symptoms.

Non-motor problems coexist with the motor symptoms in PD and are easily overlooked and untreated for long time after the diagnosis is made³¹². Several studies using different interventions such as physical activity^{136,313}, endurance²⁷⁰, dance³¹⁴ and qigong³¹⁵ exercises have reported mixed results, with some reporting no improvement and some reporting modest improvements in non-motor symptoms of PD. Studies in elderly³¹⁶ as well as young³¹⁷ healthy individuals have reported association of balance deficits/problems with fatigue, pain³¹⁸ and depression. Individuals with greater fatigue and more symptoms of depression had more falling incidences as compared to those without these symptoms³¹⁹. Despite the clear evidence of a relationship of balance with non-motor symptoms, none of the balance specific intervention studies reported in literature examined changes in non-motor symptoms of the PD following balance training. Our study is the first study to examine changes in the non-motor symptoms of fatigue, depression, pain, and fear of falling following 4 weeks of balance training.

Although the cause of fatigue is unclear in PD, several mechanisms have been proposed such as altered activation of hypothalamic-pituitary-adrenal system due to stress and dysfunction of basal ganglia and striato-thalamus-cortical loop²⁸⁴. This impairment of central sensory organization has been linked to fatigue²⁸⁵. Research studies using transcranial magnetic stimulation demonstrated that physical fatigue causes cortico-motor neurons excitability in normal healthy individuals as well as in individuals with PD^{127,128}. Exercises focusing on endurance²⁷⁰, resistance²⁷⁰ and balance²⁷¹ interventions were reported to be helpful in managing non-motor symptoms such as depression²⁷⁰, pain²⁷¹ and fatigue²⁷⁰. A recent meta-analysis¹⁹⁷ suggested that highly challenging balance exercises should be included in the rehabilitation programs for improvement in non-motor symptoms of PD.

The BSS group showed greater improvement in fatigue compared to non-BSS training. We infer that improvement may be attributed to greater input from the central nervous system. BSS training requires greater engagement of the vision, proprioception, and cognitive input in order to complete the tasks of static and dynamic balance exercises. The participants were required to control the movement and speed of the CoP sway in BSS group in order to complete the tasks. Improved balance has been related to improvement in fatigue¹⁸⁰. Additionally, BSS training may have improved individual's ability to stand upright in order to view the screen panel and continuously correct their balance, which may have resulted in improved posture and decreased fatigue²⁸⁸ as suggested by few previous research studies in low back pain²⁸⁹ as well as in healthy individuals²⁹⁰. Holding an upright posture during the entire 60 minutes of training may have strengthened postural muscles leading to decline in fatigue in this group. Conversely, fatigue was not significantly decreased in the non-BSS group. Participants in the non-BSS group did not receive visual input and thus may have not been able to sense and adjust their posture, causing less stress on postural muscles and thus less change in fatigue. Fatigue declined in both the groups, although greater in the BSS group, signifies that balance training

with a capability to improve the control of CoP sway may improve fatigue or perception of fatigue in individuals with PD. In addition, increase in general activity by participation in the balance exercises would have also contributed to improvement in fatigue. Recently Abrantes et al²⁶⁹ reported a higher level of physical activity to be associated with lower levels of depression, fatigue, and apathy in individuals with PD. Future studies should employ greater challenging balance activities, which may indirectly improve fatigue. Additionally future studies could use sensitive measures to delineate any central changes in the form of neuroplasticity via functional resonance imaging studies of the brain following challenging balance exercise interventions.

Depression is a commonly reported non-motor feature in PD. Increased loss of dopaminergic neurons and nor-adrenaline transporter in locus coeruleus and limbic system was reported in individuals with depression as compared to non-depressed patients in PD¹³⁵. Additionally, animal studies have shown that physical activity causes restoration of brain derived neurotrophic factor (BDNF) and proBDNF, which are decreased in rats with experimentally induced PD³²⁰. Our results did not show any significant improvement in depression in either group. Exercise has been reported to have beneficial effects on both motor and non-motor symptoms of PD. A few studies have reported either a decrease¹³⁶ or no change¹³⁷ in depression following an exercise training in individuals with PD. Treadmill training has shown improvements in depression in PD induced animals^{321,322}, however this has not been repeated in any human studies. Other studies which used components of balance training i.e. yoga^{323,324} tai chi or dance interventions^{325,326} in addition to strength, aerobic, or gait training reported either a trend of decline³²⁴ or significant decline^{313,323} in depression scores. Although our balance specific training did not show any significant improvement in depression, there was a trend in decline in the depression scores of both groups. Additionally, score between 0 - 9 represents no depression on the GDS scale. The mean scores for the depression scores for both groups (BSS – 5.1 and Non-BSS – 4.1) were well below the cut off score for depression. The fact that none of

the participants in either group had significant depression at the baseline it is not surprising that depression was not significantly changed. Future studies should include individuals with and without the depression to identify the efficacy of balance training on depression. Additionally, as reported previously, balance exercises combined with other forms of training such as gait and mobility offered in a group setting such as in yoga and dance may have better positive impact on the patients and thus result in better improvement in depression.

Over 80% of the individuals with PD report some form of pain¹⁴⁰. Expert opinion recommends exercise should be included as one component of pain management in Parkinson. Recent research studies indicate the presence of diffuse pathology in both dopaminergic as well as non-dopaminergic pathways resulting in numerous motor as well as non-motor symptoms. Participants in both of the groups had minimal pain to begin with mostly of musculoskeletal origin. Our results indicated no change in pain in either of the groups. A research study¹⁴⁴ indicated improvement in pain following all three interventions, flexibility and relaxation, walking and Nordic walking. They attributed these changes to increased physical activity. A higher proportion of their sample (36%) had osteoarthritic pain, which may have improved due to increased physical activity itself. Emerging evidence suggests that exercise may promote neuroplasticity and neuro restoration in individuals with PD via impact of nociceptive signals. Research studies have indicated that people with PD lose dendritic spines from striatal neurons^{327,328}, however treadmill training reverse this loss of dendritic spine³²⁹. Loss of dendritic spine has been related to neuropathic pain in diabetes³³⁰. This reversal of loss of dendritic spines following exercise provides some evidence of neuroplastic changes in PD following exercise. Neuroplasticity has also been reported following walking³³¹ and balance exercises³³² in brain imaging studies. Recent literature suggests high intensity exercises in animals resulted in pain inhibition. This pain inhibition following high intensity exercise is caused by adenosine expression in addition to opioid regulation. Another neurotransmitter which may have been

involved in pain inhibition is adenosine. Adenosine is released following the breakdown of adenosine triphosphate during exercise, causing increased extracellular adenosine³³³. Adenosine in turn plays important role in suppression of inflammation and inhibition of cytokines; therefore adenosine may have important role in pain inhibition following exercise in PD. The only one study which examined pain as an outcome¹⁴⁴ assessed the efficacy of 3 different exercise programs, flexibility and relaxation, walking, or Nordic walking in individuals with PD. Exercises completed 3 times a week for 6 months results in improvements in pain in all 3 groups. However, this study lacked no exercise control group as well as no description of pain was provided. Our study was targeted to improve balance and gait outcomes with pain being a secondary outcome. We did not find any significant improvement in pain both groups. Overall, this information suggests that future studies of high intensity exercises should also include aerobic interventions or other form of training (i.e. behavioral training) that may have implications for improvement in pain in PD. Additionally, the severity and description of pain should be taken into consideration along with pain intensity.

4.2.3 Exercise related neuroplasticity as a possible mechanism for changes in improved balance, gait and non-motor symptoms reported herein

Neuroplasticity is the process by which brain translates experiences and learns new behaviors by creating new or by modifying current neural pathways. Neuroplasticity strengthens neuronal circuitry via several processes such as synaptogenesis (addition or modification of synapses), neurogenesis (creation of new neurons) and neuronal sprouting (modification of neurons)³³⁴ in response to changes in behavior or environment, including exercise training. Exercise induced benefits such as increased or altered use of cognition and increased blood flow provide optimal environment required for neuroplasticity.

Exercise training for neuro-rehabilitation in PD incorporates goal directed motor skill tasks. The improvement of motor performance depends on many components of the training such as the number of repetitions, level of intensity, degree of challenge, and execution of skillful tasks. The fact that individuals with PD show retention of task benefits (especially gait and balance) after a period of time is consistent with principles of motor learning and underlying neuroplasticity³³⁵. Another important component widely used in exercise training for PD is cognition. Cognitive involvement can be expedited by (I) feedback (e.g. verbal or proprioceptive), (II) cueing (i.e. attention), (III) dual tasking (i.e. attention), and (IV) motivation.

Individuals with PD experience increasing difficulty with balance and gait. Research studies that focused on challenging static and dynamic balance training have reported positive results. Training using challenging tasks, which require repetitive control of dynamic balance, proprioceptive feedback from moving platform, and verbal feedback/cues that include attention and facilitate cognitive engagement during the task, may be the cause for improvement in balance and gait seen in PD. Exercise modalities targeting balance and gait include goal-oriented skill training while increasing cognitive demand.

Balance exercise studies in the form of balance training^{336,337}, Tai Chi^{222,338}, Argentinian Tango^{198,235} and boxing²¹⁵ share common elements, which include **goal-based practices** under supervision to facilitate **learning through feedback**. Feedback helps in (i) **challenging** patients beyond their perceived level of comfort, (ii) **motivation to perform tasks**, and (iii) facilitating patient's **engagement** to control the previously learned automatic and unconscious movements.

Automatic control of movements without conscious attention or executive control³³⁹ of balance and gait are impaired in PD. Early pathological changes are marked by depletion of dopamine within the basal ganglia that result in impaired circuitry responsible for automatic control.

Depletion of dopamine causes inhibition of indirect pathway in the striatal-thalamic-cortical

circuit due to reduced dopamine receptor activation. This inhibition of the indirect pathway results in bradykinesia³⁴⁰. The loss of automaticity remains a difficult problem in individuals with PD.

Exercise interventions using both intense and challenging goal based training in combination with aerobic training have shown some evidence of neuroplasticity in the striatal thalamic cortical circuit responsible for automatic control²¹⁷. Fisher et al. reported improved gait and balance along with exercise-induced decrease in cortico-motor excitability via increase in duration of cortical silent period²¹⁷ following 8 weeks of (24 sessions) of gait training at faster speeds using treadmill. In another study, 8 weeks of treadmill training was associated with increase in dopamine receptor (DA-D₂R) binding potential³³¹. Both changes in cortico-motor excitability and DA-D₂ receptor availability may be responsible for moderating inhibitory drive of the automatic circuitry. Albert et al. ³⁴¹showed possible effects of exercise on neuroplasticity and the circuitry responsible for automatic control using forced cycling. The participants were forced to pedal at 30% greater rate than their preferred rate thereby adding cognitive component required to keep up with the higher pace in addition to the effects of aerobic training³⁴². This caused central changes as evidenced by improved automatic manual dexterity in addition to improved connectivity between the cortical and the subcortical regions involved in automaticity. This data supports that exercise that involve both goal-directed practices and aerobic training may work collectively to facilitate neuroplasticity within the basal ganglia.

Our study included exercises that utilized challenging goal-based practice of the balance tasks. Additionally, the challenges posed increased level of difficulty every week, which maintained subjects' motivation and interest in the exercise intervention. This increasing challenge with exercise may have been responsible for the better results in the BSS group. However, the group that performed supervised over-ground exercises also showed positive results in terms of balance and gait. One of the reasons for this could be that the exercises were

new to the patients, which would have provided a challenging environment and kept subjects' motivation throughout the intervention period. Additionally, most of the tasks completed in BSS group involved movement of the CoM outside the base of support, which challenged these individuals. We did not find significant between group differences in our study. One of the major reasons could be the relative equality of the exercise interventions (i.e. exercise duration and possibly exercise intensity) and lack of clear distinction of the level of challenge between both groups. It has been suggested that highly challenging exercises are more beneficial for individuals with PD. Increasing the difficulty level of the task or using the time constraint may challenge these individuals even more, which can further improve their balance and other gait-related dynamic functions.

4.3 Clinical Implications

Past studies have suggested that exercise in the form of balance training has the potential to improve postural instability in individuals with PD. Postural instability, which is one of the cardinal and most disabling features of PD, results in frequent falls. Recently, studies have suggested that more challenging balance training, especially one which forces the individuals to move out of their limits of stability, may help to improve postural instability. There is scarcity of studies focused on balance specific training in PD. The results of this study may lead to a better understanding about the role of specific and challenging balance exercise on postural instability in individuals with PD. From past studies it is unclear whether improvements in postural instability results in improvement of gait in PD. The results of this study further suggest that improvements in balance are translated into the gait.

Although non-motor features of PD such as depression, pain, fatigue and fear of falling are reported in several studies, these non-motor symptoms begin much earlier in the disease progression than motor symptoms and they can have profound effects on mobility and quality of life. However, none of the balance training studies have reported any changes in non-motor

symptoms of PD. Our results indicated that balance specific training with BSS may help to alleviate fatigue in PD but have no effects on depression, pain and fear of falling.

We failed to find any between group differences for BSS and Non-BSS groups. This indicates that balance exercises regardless of the modality used might help in improvements in balance and gait, which is indicated by significant changes in the BSS as well as Non-BSS groups.

However considering the fact that both exercise interventions with and without using BSS resulted in similar improvements in both groups, we acknowledge that it was possible to further challenge balance significantly in the BSS group by decreasing resistance of the platform beyond 9 degrees. A further decline in the resistance of the platform, would have enabled us to challenge the participants more, however considering the balance issues in our group, a potential to lose balance and the fact that this was the first study utilizing BSS for training these individuals, we did not decrease the resistance level below 9 degrees.

The findings of this study suggest that clinicians could effectively use challenging balance exercises either individually or in conjunction with other exercises to improve postural instability in PD. Additionally, specific challenging balance training can help with improvements in gait and other non-motor symptoms such as fatigue. Clinicians should consider using specific balance training while designing exercise programs for individuals with postural instability in PD. Further research should be conducted using a large sample size in a randomized control design and using full range of resistance to the platform in order to understand the effects of highly challenging balance training on balance, gait, functional tasks and other non-motor issues in PD. It is difficult to conclude whether challenging the balance further below 9 degrees of movement of the platform would result in significant improvements. Additionally, it is difficult to conclude whether training using BSS is better than non-BSS or not. Having the sensitive biomechanical data from the force plates from both groups would be beneficial in making a better conclusion.

4.4 Limitations

The results of this study should be viewed with caution due to several limitations:

- A. Study Design: One of the major limitations of the current study was the design of the study where subjects were not randomly assigned to either the BSS or non-BSS groups. The BSS group selected to participate in the balance exercise and then the non-BSS exercise group was recruited with age, gender and severity matched to complete balance exercises without BSS. A properly randomized control trial would have helped to better assess the differences between the 2 groups.
- B. Data collection error: The initial intention was to compare the groups using more sensitive biomechanical measures of sway such as sway area, path length or root mean square velocity. Due to technical failure of equipment to save the data from the Non-BSS group discovered after the completion of the data collection period of the study, we were unable to compare BSS and Non-BSS groups on more sensitive biomechanical measures, which may have answered our initial research question more precisely (hypothesis 1a).
- C. Small sample size: Another major limitation of this study was the limited sample size. Sample size was calculated based on the confidence intervals determined from the preliminary investigations completed in our lab. Since our study utilized multiple outcome measures, the meaningful clinical difference from all the measures would have helped in better sample size calculation. However following the preliminary study, we added many new outcome measures; therefore a larger sample size might have helped to justify the efficacy of our treatment.
- D. Intervention: Our intervention used balance training using the BSS system for 4 weeks. Previous studies with longer duration (6 -10 weeks) of training have shown significant improvements in balance and gait related outcomes. During the training, we did not utilize the whole 20 degrees of tilt available on the BSS due to feasibility and subjects'

safety concerns. Decreasing the resistance of the platform could have triggered more postural reactions, which in turn might have improved postural instability even more. Considering this was the first study using BSS system and the severity of postural instability in these individuals; we decided to use highest resistance possible on the device for movement of the platform. Using the entire range of tilt during training may improve balance more as compared to the Non-BSS group.

- E. Although, we tried to control for the time of exercise and testing, some of our participants may have come at a time when their medications were not working at their peak. Dosages of medication in individuals with PD vary, which may have influenced treatment outcomes. Although pharmacological studies have shown significant improvement in patients' general mobility, dopaminergic treatment has shown no effects on balance and postural instability^{90,343}. However, to fully investigate and understand the effects of exercise/balance training only, it is imperative to have a more homogeneous group of participants with similar medications. Future studies should include participants who are at similar severity level of the disease, intake similar medications with a specific range of medication dosage as an inclusion criterion.

4.4 Future Directions

Our results showed that challenging balance specific exercises can help improve sway measures, gait variables and other non-motor symptoms of PD. However, due to several limitations in the study, future studies using similar training methods are warranted to evaluate the full effects of such training in individuals with PD. We propose several extensions and remediation to the present work to address motor as well as non-motor symptoms of PD.

- a) Large sample size and randomized control trial

The results of the present study are promising; however the limited sample size and non-randomized design weakens the generalizability of the results. Our results from the preliminary

data provided an effect size of 0.38 and 0.60 for the CoP path length in medio-lateral direction and sway area respectively. These effect sizes and use of multiple outcome measures warrants a large sample size for studies like this. Based on the effect sizes obtained, it is estimated that a sample size of 90 would be required. Additionally, using randomized design will help in evaluating the differences between the balance training using BSS system as compared to the true control groups like usual care or only education. .

a) Challenging exercises:

Several studies have indicated that highly challenging exercises may yield better outcomes in PD. In our study, we used challenging exercises, where individuals stood on the BSS platform. Considering this as the first exercise trial using BSS system and balance problems of these individuals, we used maximum resistance for the platform during exercises of static and dynamic balance. The platform has the inbuilt capacity to move 20° in every direction, which can make the tasks of balancing even more challenging. The future exercise trials should focus on using more challenging exercises by utilizing the whole tilt available on the BSS system which may result in further improvement eventually leading to clinically meaningful changes. Additionally, we also found significant improvements in the non-BSS group, but none of the gait and functional outcomes reached the clinically meaningful difference. Adding more challenges to the non-BSS group may also result in clinically meaningful changes such as increasing the length of time for one legged standing or including the tasks with activities such as forward reaching, turning etc.

b) Mixed exercise options:

It has been reported that muscle weakness is not only due to inactivity but also from disease process, as muscle weakness is present during the early stages of PD when patients are active^{176,183}. Several studies in elderly (age ≥ 65 years) have indicated that weakness of lower extremities result in postural instability³⁴⁴. A recent review study by Orr et al³⁴⁵ indicated significant association between strength and balance. Toole et al¹⁸³ evaluated whether the

effects of strength and balance training can improve postural instability in individuals with PD. They found that individuals, who received both strength and balance training combined demonstrated improvement in both strength and balance, whereas the group that received only balance training did not show any improvements in any outcome measures. Similar results were reported by Hirsch et al.¹⁸⁰, which found higher rate of improvement following 10 weeks of combined balance and strength training as compared to only balance training in individuals with PD. Trunk strengthening have been related improved postural stability in individuals with PD³⁴⁶. Strength training could have improved the functioning of sensorimotor systems (visual, vestibular and proprioceptive), which might have helped with better postural stability. Additionally, better muscle strength might have provided additional strength to counteract the effects of destabilization forces resulting in better balance. Therefore, the future studies using BSS should also include strength training including strengthening for trunk and lower extremities to evaluate whether such training is better than just balance training.

- c) Considering the progressive course of PD, it is important to evaluate whether the exercise training has any effects on the symptoms beyond the time period of the intervention. Our study examined the effects of balance training immediately following the 4 weeks of training. A long term follow up of balance training and control group at 6 months and one year following training will help clinicians decide, whether balance training using BSS system is a better option as compared to other forms of balance training. Additionally, since the changes did not reached clinically meaningful changes, we suggest that effects of longer training duration should be examined in future.

4.5 Conclusions:

The body of work presented in this dissertation extends the current literature related to the effects of a balance specific training in individuals with PD. The limited work on balance interventions and more specifically challenging exercises using BSS system led us to develop this intervention. The findings of this study are an extension of preliminary work completed in

our lab and add to the body of knowledge about balance exercise training in PD. This is the first study, which utilized the BSS system for the training and also included biomechanical measures of sway to evaluate changes following such an intervention. Furthermore, the results of this study indicate that the changes in sway measures are translated into spatio-temporal measures of gait. Finally, this work indicated that participation in exercise in general and specific balance training may lead to improvement in fatigue, which is one of the leading non-motor symptoms reported in PD. However considering the small sample size, short duration of the study and co-morbidities present in this population, it is difficult to make any definite conclusions. Overall, the present body of work provides concurrent evidence that balance training using BSS system is feasible and effective in individuals with PD. However a further study with larger sample size, randomized control trial and long term follow up is required to better understand the mechanism of balance training in these individuals. The findings of this work have implications for research and rehabilitation of not only individuals with PD but also in individuals with other neurological disorders, which affect gait and balance.

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Appendix 1: Biodex stability system

Biodex stability system (BSS)



Full

Limits of Stability Testing

Test Time: 00:00

Trial: 3

Score: 0

Posture Stability: Static

Press START to Release Platform

START

Home

Back

Full

Limits of Stability Testing

Test Time: 00:28

Trial: 3/3

Score: 94%

Posture Stability: 11

Test Complete!

Results

Home

Back

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Appendix 2: Biodex stability system training

Balance component	Activity	# sets	Duration	# reps
Static	Normal standing	3	6 min	6
	Standing on both feet tightly together	3	6 min	6
	Standing on left foot	3	6 min	18
	Standing on right foot	3	6 min	18
Dynamic	Antero-posterior weight shift	3	6 min	N/A
	Medio-lateral weight shift	3	6 min	N/A
	Percentage weight shift	3	6 min	N/A
	Limits of stability	n/a	6 min	N/A
	Maze control	n/a	6 min	N/A

Appendix 3: Balance exercise from “Falls prevention” booklet from National Parkinson’s Foundation

Exercise	#of reps	Time spent
Single leg stance	40 (20 each on side)	6 minutes* 2
Standing eyes closed	6	6 minutes* 2
Toe taps on book	10	4 minutes* 2
Step ups on a book	24	4 minutes* 2
Standing foot on step with head movements	12	4 minutes* 2
Side stepping at counter	10	4 minutes* 2