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Characterizing the Effects of High-intensity Exercise on Balance and Gait under Dual-task Conditions in Parkinson's Disease

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CHARACTERIZING THE EFFECTS OF HIGH-INTENSITY EXERCISE ON BALANCE AND GAIT UNDER DUAL-TASK CONDITIONS IN PARKINSON'S DISEASE

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CHARACTERIZING THE EFFECTS OF HIGH-INTENSITY EXERCISE ON BALANCE AND GAIT UNDER DUAL-TASK CONDITIONS IN PARKINSON'S DISEASE

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ABSTRACT

Parkinson's disease (PD) is a neurodegenerative disorder, characterized by four cardinal motor symptoms including bradykinesia, tremor, rigidity, and postural instability, and non-motor symptoms including cognitive impairment. Daily activities, such as walking and maintaining balance, are impacted due to impairments in motor function, and are further exacerbated with the addition of cognitive loading, or dual-tasking (DT). High-intensity exercise has demonstrated centrally-mediated improvements of PD symptoms, with additional positive effects on overall health.

The goal of this project was to identify changes in dynamic balance recovery and gait function under conditions with and without increased cognitive load after a high-intensity exercise intervention in a PD population. Participants included people with PD who completed an eight-week cycling intervention (PDE), people with Parkinson's disease who did not complete the intervention (PDC), and healthy age-matched controls (HC), with 14 subjects per group. In Aim 1, while participants underwent a series of destabilizing balance tests, the time taken to regain balance and the center of pressure movement during balance recovery were measured. The PDE group demonstrated greater improvement in balance recovery after exercise compared with the PDC group. In Aim 2, participants completed a series of gait and cognitive tasks, both separately and concurrently. Outcome measures included spatiotemporal and kinematic gait parameters

of the lower and upper extremities. The PDE group demonstrated significant improvement in gait measures and DT abilities compared to PDC, while no changes were found in cognitive function for any group.

The standard clinical methods of measuring motor function can be subjective, and may not capture subtle motor characteristics. Force plate and motion-capture technologies can provide detailed, objective outcome data, therefore improving the understanding of how exercise affects motor symptoms of Parkinson's disease. The Motek Computer Assisted Rehabilitation Environment (CAREN) system at the Cleveland Clinic was used to create the testing environment and for data collection.

These results of this project suggest global changes in motor function demonstrated by changes in balance recovery and lower and upper extremity gait function. Quantitative gait analysis has shown to be an important metric in assessing effectiveness of an exercise intervention in PD.

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INTRODUCTION

1.1 Parkinson's Disease

James Parkinson identified a movement disorder marked by flexed posture, resting tremor and shuffling gait. He termed this disorder "shaking palsy," and published his findings in 1817. This disorder was later named after him, and research on Parkinson's disease (PD) has continued since [3]. It was not until nearly a century later, in 1914 when Frederic Lewy discovered cytoplasmic inclusions in the brains of people with PD (now known as Lewy bodies) [4] and in 1919 when Konstantin Tretiakoff discovered lesions in the substantia nigra [5] that we began to understand the cause of Parkinsonian symptoms. In 1959, Arvid Carlsson published his findings that dopamine, not serotonin as previously thought, was deficient in the brains of Parkinson's patients [6]. These neurological discoveries are the foundation for what we know about Parkinson's disease today.

With the advancement of scientific discoveries, the description of Parkinson's disease has expanded to include additional symptoms and greater pathological detail (See Table 1). Symptoms are categorized as motor or non-motor, and patients exhibit some,

but not necessarily all of these symptoms. Parkinson's disease is unique to each diagnosed individual, and can vary greatly.

Table I – Parkinson's disease symptoms

Motor/Non-motor	Symptom	Description	Reference
Motor	Resting tremor	Tremor of a limb when not in action	[3]
Motor	Rigidity	Stiffness of movement	[3]
Motor	Bradykinesia	Slowness of movement	[3]
Motor	Stooped posture	Flexion of torso and/or limbs	[3]
Motor	Postural response issues	Improper balance reactions	[7]
Motor	Freezing of gait	Inability to step, usually at gait initiation	[3]
Motor	Festinating gait	Short, quick steps	[8]
Motor	Masked face	Lack of facial expression	[8]
Motor	Postural instability	Balance issues	[8]
Non-motor	Personality and behavior changes	Depression, fear, anxiety, passivity, dependence, apathy	[3]
Non-motor	Cognition and mental	Bradyphrenia (slowed thought process), dementia	[3]
Non-motor	Sensory	Olfactory loss, numbness, burning sensation, restless less syndrome, akathesia (restlessness)	[3], [9]
Non-motor	Autonomic function issues	Hypotension, bladder problems, constipation, sexual dysfunction, seborrhea, dermatitis, sweating	[3]
Non-motor	Sleep issues	REM sleep behavior disorder, excessive daytime sleepiness, altered sleep-wake cycle	[3]
Non-motor	Fatigue	Tiredness	[3]

The four cardinal symptoms of Parkinson's disease include resting tremor, bradykinesia, rigidity and postural instability [10]. Although disease presentation and progression is unique to every patient, these symptoms are typically the first to appear [3]. Unlike resting tremor - which dissipates during active movements - bradykinesia, rigidity, and postural stability deficits permeate daily activities, impacting quality of life. In Parkinsonian gait, for example, rigidity and bradykinesia often manifest as decreased walking speed [11]–[19], and postural abnormalities [10]. Deficits in postural stability

may induce compensatory tactics during gait such as increased double leg support time to increase stability during gait [12], [16], [17], [20].

As the disease progresses and symptoms worsen, the consequences of the disease increase. Indirect costs, such as productivity loss, or early retirement accounts for approximately $1.7 billion in reduced national productivity [21]. The estimated prevalence of PD in the /United States is 0.3% in the population overall, with an increased rate of 1-2% in those 65 years of age and older, and 4-5% for those 85 and older. The financial burden of this disease can be estimated at $14.0 billion a year in the United States [21]. The incidence rate increases with age, and most rapidly after 60 years of age [22]. As the number of people 65 and older continues to increase, costs can be expected to increase as well [23].

Although Parkinson's disease has no cure, treatments are available. Targeting brain function directly, dopamine replacement drugs and deep brain stimulation alleviate motor symptoms [3], [24]; however, side effects, such as dyskinesia (involuntary movements) [3], and risks of invasive surgery [24] accompany these treatment options. High-intensity aerobic exercise also aims to target changes in the brain, but is associated with lower risk and side effects. Animal models have shown significant symptom improvement from high-intensity exercise, and highlights several possible mechanisms for these results [25]–[27]. Human studies have also shown significant improvements in various measures, and are continuing to provide new information concerning the effects of different exercise parameters [28]–[31].

1.1.1 Parkinson's Disease Neuropathology

In a normal healthy brain, the basal ganglia, located at the base of the forebrain, are a collection of nuclei that are involved with various functions, voluntary movement control, procedural learning, cognition and routine behaviors [32]. The putamen, caudate nucleus, nucleus accumbens (collectively known as the striatum), globus pallidus (internal (GPi) and external (GPe)), subthalamic nucleus (STN) and substantia nigra comprise the basal ganglia. Excitatory and inhibitory signaling occurs between the nuclei in the basal ganglia, as well as to other areas of the brain (Figure 1). Dopamine - a key neurotransmitter involved in facilitating signal pathways - is produced by dopaminergic cells of the substantia nigra.

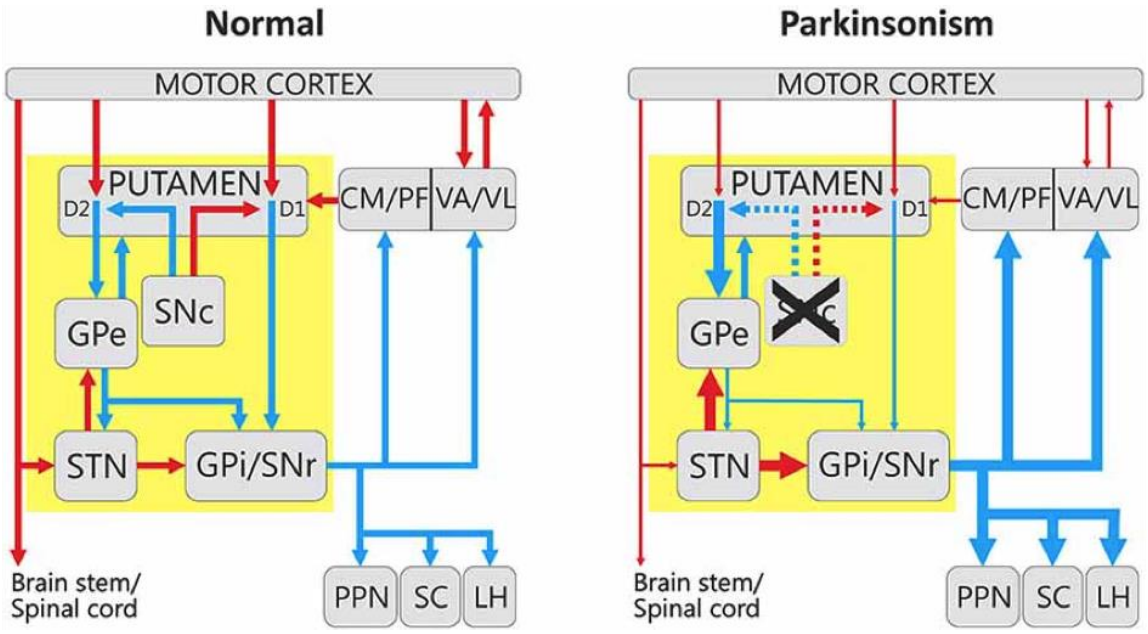

Figure 1 – Signaling pathways connecting the basal ganglia (yellow box) and surrounding cortical and thalamic areas. In the "Parkinsonism" diagram, thin lines represent a decrease in signaling, thick lines represent an increase in signaling. Blue represents inhibitory signaling, red represents excitatory signaling. SNc, substantia nigra compacta; SNr, substantia nigra reticular; GPe, globus pallidus external; GPi, globus pallidus internal; CM/PF,VA/VL, thalamus; STN, subthalamic nucleus; PPN, pedunculopontine nucleus; SC, superior colliculus; LH, lateral habenula [33].

The substantia nigra, located in the rostral midbrain, is comprised of two parts, compacta and reticular. The dopaminergic cells of interest are located in the substantia nigra compacta (SNc) which projects to the striatum. A simplified signaling pathway from the SNc to the motor cortex begins with dopamine produced in the SNc traveling to the striatum. From the striatum, inhibitory signals relay from the putamen to the GPe, inhibition from the GPe to the STN, excitation from the STN to the GPi, inhibition from the GPi to the thalamus, and excitation from the thalamus to the motor cortex. This activation modulates motor and cognitive functions. This entire process functions as a loop, with an signal originating in the cerebral cortex, modulated by the basal ganglia, and the appropriate commands sent back to the cortex for action initiation [34].

The destruction of dopaminergic cells that occurs with Parkinson's disease disturbs these pathways. The decrease in striatal dopamine leads to decreased inhibition from the GPe to the STN, therefore increasing excitation from the STN to the GPi, which leads to increased inhibition from the GPi to the thalamus, and decreased activation from the thalamus to the cerebral cortex [34], [35]. The dopaminergic signaling from to the striatum affects reward-seeking behavior and motor control functions [36], [37], which are markedly effected with PD. The symptoms manifesting from dopamine loss are listed above in Table 1.

In addition to altered signal magnitudes in the dopaminergic pathways, people with PD also experience changes in signal firing patterns. Animal and human studies have shown abnormal oscillations of frequency in the GPi and STN, as well as abnormal synchronization of neighboring neurons [38]. Additionally, structural connectivity in the cortical and subcortical regions and their projections to other brain regions of PD patients

with cognitive impairment has shown to be significantly decreased compared to healthy controls [39]. Although decreased dopaminergic signaling from cell death in the STN defines PD and can explain most motor dysfunction, Lewy body aggregates present in non-dopaminergic brain structures also contribute to PD symptoms. Areas involved with acetylcholine signaling and production in particular (such as the pedunculopontine nucleus and the nucleus basalis of Meynert), can be adversely affected by Lewy bodies and are related to postural control and compensatory motor strategies in dynamic balance control [40]. These different functional breakdowns illustrate the complexity of the neurobiology of PD and the challenges faced in developing disease treatments.

1.1.2 Motor Symptoms

Parkinson's disease symptoms vary greatly across individuals, and are often characterized by two main subtypes: tremor dominant, and postural instability and gait difficulty. As the name suggests, the severity of tremor symptoms is greater than postural instability and gait severity in tremor dominant, and vice versa. These classifications are general, and mixed symptomology is common as well [41]. These subtyped may also be expressed at tremor or akinesia-dominant, and have similar categorical criteria to tremor or postural instability and gait difficulty groupings [42].

1.1.2.1 Gait

Descriptions of Parkinson's disease gait includes stooped posture and shuffling gait [3], which is the culmination of slowness of speed, reduced arm swing, reduced stride length and decreases in joint ranges of motion [14]. Although normal slowed gait speed involves smaller, slower steps, hypokinesia, bradykinesia and rigidity are the sources of gait declines in PD. Bradykinesia is the overall slowness of muscle

movements, while hypokinesia limits step size, therefore decreasing stride length. Rigidity increases muscle tone inappropriately, inhibiting the full speed and extension of limbs [40].

Compared to healthy controls, PD specific gait declines, known as shuffle gait, typically include decreased speed [11]–[19] and decreased step length [11], [12], [14]–[19], yet no difference in cadence (steps per minute) [11], [13], [15], [16], [19]. These PD gait characteristics demonstrate a slowed walking speed attributed to shorter step length [12], [43], with increased double leg support time [12], [16], [17], [20] and increased stance phase [16], [44] representing gait stabilizing tactics. The kinematics of lower extremity joints often align with decreased step length and exhibit an overall decrease in range of motion (ROM) of the hip, knee, and ankle joints [11], [14]–[17], and typically inversely correlate with disease severity [11].

Biomechanical analysis of PD gait includes studies with participants both "on" [18], [45], [46] and "off" [11], [17], [47] medication, and significant gait declines exist for those with PD compared to healthy peers under both conditions. However, the type and degree of severity of outcome measures in which changes are seen differs between "on" and "off" medicated state. For example, "off" medication, subjects may exhibit significant declines in joint ROM for most of the lower extremity joints [11], [16], [17], while "on" medication they may show significant declines in the ankle joint only [46]. When the same cohort of subjects are tested both "on" and "off" Parkinsonian medication, some studies have indicated that levodopa has shown to elicit improvements in spatiotemporal, such as velocity and stride length, and kinematic outcome measures,

such as joint ROM, [11], [19], [47], [48], while other studies have shown a lack of levodopa induced change in temporal measures such as cadence [48].

Differing responses to levodopa as well as information from healthy adults and animal model studies contribute to the understanding of the underlying mechanisms of Parkinsonian gait disturbances. Healthy gait function involves a combination of cognitive and automatic processes to initiate, continue, and augment gait and posture. The cerebellum regulates and integrates feed-forward cognitive processes from the cerebral cortex and sensory feedback processes from the spinocerebellar tract. The continual basic gait pattern is engendered by central pattern generators, which are a spinal neural network influenced by sensory feedback. The basal ganglia can also contribute to modulating gait processes, with the midbrain dopaminergic neurons influencing this effect [49]. In PD, loss of dopaminergic cells, reduced connectivity in areas responsible for motor automaticity and reduced activation in cortical areas contribute to gait declines. Dopaminergic cell loss can lead to bradykinesia and rigidity, and impaired automatic motor functions necessitate compensatory neural recruitment, yet decreased neural activity in cortical regions limits ones ability to effectively compensate with these areas of the brain [42], [50]. Additionally, gait function has shown to predict cognitive decline, highlighting the dependency of gait function compensation on cognitive function in PD [51].

1.1.2.2 Arm Swing

Arm swing during gait is the pendulum motion of the arm traveling anteriorly/posteriorly in the sagittal plane. Patients with Parkinson's disease often show a decrease in arm swing function compared to healthy peers, with decreased ROM for both

the elbow and shoulder joints [15], [52] decreased acceleration and increased asymmetry between the right and left arms [52]–[54]. Decreases in arm swing excursion are to be expected with decreases in velocity. However, characteristics observed in PD suggest changes at a centrally mediated, subcortical level, independent of gait speed. Patients with Parkinson's disease who demonstrate decreased or loss of arm swing typically experience these declines before lower extremity declines [55], and exhibit abnormally timed muscle activations, both in a rhythmic pattern and randomly [56]. Parkinson's gait also experiences "phase shifting," where the phases of the repetitive swinging motion of the arms and the legs are not aligned as with healthy controls [57], [58]. In instances where patients have an affected and unaffected side, the affected side (greater symptom presentation) typically shows lesser arm swing motion, while the unaffected side might not reach a significant difference compared to healthy controls [54], [59]. Furthermore, dopaminergic modulation has shown the ability to alter impaired arm swing by decreasing arm-to-arm swing asymmetry and increasing velocity in the affected arm [47], [59], and subthalamic nucleus stimulation has shown the ability to decrease phase shift and increase ROM [58].

1.1.2.3 Balance

Postural stability is a key aspect of mobility and ambulation, and applies to static (such as stationary standing) and dynamic (such as walking, turning or responding to an external force) conditions. With PD, both static and dynamic balance is affected. Corrective muscular responses necessary to maintain an upright position under stationary or destabilizing conditions can become inaccurate in PD, resulting in declines in postural

stability and balance recovery [7], [60]–[62]. Poorly timed muscle activation driving bilateral coordination employed during walking, can also lead to instability [20], [63].

Balance is a combination of vestibular, visual and somatosensory inputs and regulation. The integration of modalities contributing to postural stability is impaired in PD, leading to instability [64]. Decreased connectivity networks in pathways to the occipital cortex [39] may impact visual processing, while disruption to the nigro-striato-collicular tracts in PD are believed to cause vestibular disturbances [65], potentially contributing to postural instabilities [66]. Somatosensory input remains intact [67], however, abnormal processing leads to inadequate recognition of the placement and forces required for proper movement [64], and inappropriate scaling of response movements under dynamic balance challenges [64], [67]. Neural synapses outside of the basal ganglia and its direct projections are also impacted by PD. Acetylcholinergic areas of the brain are adversely affected by Lewy bodies in PD, and may affect reactive balance control [40]. Decreased muscle force production and disproportionally smaller reactions may be attributed to bradykinesia, while rigidity contributes to increased background muscle tone, inhibiting quick, reactive muscle movements [68]. The consequences of poor postural stability often lead to falls and injury.

1.1.2.4 Fall Risk

As falls are common among older adults, they are more common amongst those with Parkinson's disease due to overall motor impairments. Recent studies report that on average, 60.5% of people with PD report at least one fall, and 39% on average report recurring falls [69]. The risk for falls increases with inadequate reactive postural responses, gait declines and increased difficulties in DT conditions [70]. Recurring falls

are common to about 50% of those who have previously sustained one fall [71]. Falls for older adults pose a greater risk than a younger population, often resulting in serious injuries such as hip fractures, which are accompanied by costly hospital and rehabilitation visits [72]. In addition to physical and financial consequences, past falls may invoke a fear of future falls, and is a strong predictor of future falls in PD [73]. This fear of falling may potentially facilitate negative life changes, such as isolation and reduced physical activity [74]. Furthermore, a reduction in physical activity can lead to poorer health outcomes, and isolation can lead to decreased mental well-being [75].

The relationship between falls and physical activity in Parkinson's disease is complex. An inverted U-shaped relationship between falls and disease severity is commonly seen in PD. At early disease onset with mild PD, falls tend to be infrequent; as the disease progresses to the moderate severity, falls increase; and towards the greatest disease severity falls return to infrequent. Ambulatory activity declines with age and disease severity, and has its own intricate relationship with fall risk [76], [77].

Characteristics of ambulation and motor function which decline in PD can be linked to increased fall risk, such as turning ability [78], retropulsion (loss of balance in the backward direction) [73], freezing of gait (inability to initiate walking, the feet seem "frozen" in place) [79], and poor balance recovery responses [7], [80]. Bradykinesia and rigidity pervasively alter motor tasks, and contribute to motor declines which increase fall risk [7], [68].

In addition to motor declines and their effects on fall risk, cognitive declines also show association with falls in PD. Increased incidence of falls has shown to correlate with increased cognitive decline [78], [81], and decreased brain volume in areas

associated with attention [81]. Falls and fall risk in people with PD remains complex and commands continued research in fall prevention.

1.1.3 Non-Motor Symptoms

In addition to motor function decline, people with PD experience a myriad of non-motor symptoms, specifically cognitive function decline. The basal ganglia-thalamo-cortical circuits responsible for motor function have parallel circuits responsible for associative/cognitive functions, which are also effected by impaired signaling in PD [33]. Executive function is mainly housed in the prefrontal cortex, and deficits in this area become apparent through cognitive decline [34]. Decreased dopamine in the striatum and its impaired connections to specific regions of the prefrontal cortex impact many of the executive functions that decline with PD [82]. The basal ganglia and prefrontal cortex in particular, play a role in allowing decidedly relevant information to be stored into working memory [83]. Decreased activity in the striatal and prefrontal regions leads to inappropriate signaling in the frontostriatal loop, resulting in declines in tasks measuring working memory, set-shifting, planning, attention and cognitive flexibility [82].

Executive function declines in PD are detectible in various neuropsychological tests [84]. For example, the N-Back test assesses working memory [85], serial-7 subtraction assesses attention and concentration, and the verbal fluency test assesses semantic memory [86]. These different cognitive functions are interwoven into daily tasks, and declines can significantly impair quality of life.

1.1.4 Current Treatment Methods

The conventional treatment methods for managing Parkinson's symptoms that directly target the brain include dopaminergic medication and deep brain stimulation.

Delivering dopamine to the brain is complicated by the fact that dopamine cannot cross the blood brain barrier; therefore, the precursor levodopa is administered orally. To inhibit conversion of levodopa peripherally, prior to delivery to the central nervous system, carbidopa or benserazide is combined with levodopa. This combination increases the bioavailability of levodopa (and ultimately, dopamine) to the brain, and decreases the side effects (nausea, vomiting) of increased peripheral dopamine [87], [88]. Overall, levodopa medications improve motor and non-motor symptoms [47], [87], [89], including gait function [47]. Although medications do improve symptoms, they do not eliminate them completely. Gait parameters do not necessarily reach the values of healthy controls, even during the peak of a dose cycle [19], [47]. Other drugs, such as bromocriptine, pramipexole and ropinirole mimic the actions of dopamine in the brain to provide similar affects [47].

In healthy individuals, dopaminergic neurons in the striatum metabolize, release and reuptake levodopa. With decreased dopaminergic neurons in PD, serotonergic neurons are recruited to convert and release levodopa. However, serotonergic neurons lack dopamine receptors and appropriate feedback, therefore leading to poorly timed dopamine release into the striatum contributing to motor side effects, such as dyskinesia (involuntary movements) [87]. Additionally, the risk for developing dyskinesia increases with earlier onset of the disease, as well as with higher cumulative levodopa medication doses [90].

Deep brain stimulation is another effective treatment for PD, involving an implanted device providing electrical stimulation to the brain [91]. Different target locations are used, with each location of the electrodes targeting slightly different

outcomes. Subthalamic nucleus stimulation primarily improves motor function and can reduce the need for medication, GPi stimulation show improvements in mood and cognition [91], the thalamic ventrointermedial nucleus is targeted for decreasing tremor [92], and stimulation in the pedunculopontine nucleus region (PPN) targets decreases gait freezing and postural instability [93]. Although some reviews have identified these locations with targeted symptomatic relief, there is certainly overlap due to neural connections and projections, such as tremor treated by both STN and GPi stimulation, and improvements in gait function with STN and PPN. The most ideal stimulation sites for maximum symptom relief are still being investigated, with increasing emphasis on non-motor symptom relief [94]. Although some research has shown improvements in cognition, sleep and attention with PPN stimulation [94], other studies have shown that STN and GPi stimulation can result in declines in attention, memory and executive functions [91] and further research is needed in this area.

Medication and deep brain stimulation are effective treatment methods for PD, targeting brain function directly; however, the side effects of dyskinesia [3], [90], [95], fluctuating effectiveness of the medications [96], and risks of surgery such as cost, device malfunction [97], infection [24], [97] and decreased cognitive function [91] accompany these treatments options..

1.2 Dynamic Balance - Perturbation Response

When an individual is destabilized by a sudden shift of balance, whether from an impact to the body, or a tilt or shift of the floor beneath them, the body responds in efforts to regain its balanced position. In addition to instinctual grasping reflex of the hands, the muscles and joints of the trunk and lower body react to shift the body to best support

itself. The muscular responses responsible for stabilization occur at different time points, typically characterized as short latency (occurring first), medium, then long latency (occurring last). It is believed that short latency responses are monosynaptic stretch reflexes occurring in the spinal cord, and medium and long latency responses involve muscle activations which induce balance recovery behaviors, such as grabbing for a stabilizing bar, and function under cortical influence [98], [99]. These responses usually involve flexion and extension of the ankle and hip joints to control anterior-posterior displacements, and lateral trunk flexion and weight shifting between the legs to regain control after lateral displacements [100]. One of two different strategies typically dominates at the ankle or the hip, each involving contraction of the surrounding muscles and motion at the joint [101]–[103], and is modifiable based on the most efficient option for the surrounding conditions [98]. The EMG muscle response pattern to a platform shift is typically a high EMG reading upon the initial movement, followed by tonic muscle contraction while the body is in motion with the moving platform [7], [60]. Both young and older healthy populations can appropriately scale their joint kinematics and kinetics to the magnitude of an induced perturbation to regain their balance [104], meaning muscle contractions and joint movements are directly correlated with the magnitude of the perturbation intensity.

Balance reactions for a PD population deviate from the healthy, normal patterns of balance recovery. Studies have shown differences in both muscle forces and activation timing. When analyzing muscle EMG's, the muscles of the lower limbs can be broken into groups via their reflex activation times – short and long latency. In a backwards tilt or shift for example, the tibialis anterior acts as the antagonist muscle, has a long latency

response, and contributes to postural stability [99]. While short latency muscles exhibit similar timing for PD and for controls, the tibialis anterior has a delayed onset [62], [105]. Since the long latency response likely utilizes cortical control [98], [99], decreases in postural stability in PD may reflect declines in cortical function. In situations with varying degrees of tilt or shift intensity, PD patients exhibit difficulty scaling their reactions appropriately. Studies have shown that PD patients do not exhibit significant changes in measures such as rate of center of pressure (COP) excursion [106], joint motion [104], and EMG response [62], [105] across varying perturbation intensities [104], whether the level of intensity is known or unknown [62], [105], [106]. Often, the active EMG response amplitudes are smaller than controls [7], [105], yet background and passive EMG activity is larger [7], [60]. Center of mass displacement is also typically greater than controls, while COP displacement is often smaller, indicating instability as the closeness of these two measures is necessary for proper stability [61], [107]. Bradykinesia and rigidity may be responsible for the inability to scale responses properly and inappropriate muscle activation [61], [68]. Dopaminergic medication alleviates rigidity; however, this results in decreased muscle tone and a worsening in perturbation response abilities [68].

1.3 Cognitive-Motor Dual-Task

Performing two simultaneous tasks requires a greater cognitive load than either task performed alone. Cognitive-motor dual-tasks (DT) can be effective in understanding task prioritization when mental resources are limited. Dual-task costs describe the effects of a DT paradigm compared to each task performed individually as a single-task (ST). Dual-task paradigms are sensitive enough to show both motor and cognitive dual-task

costs in healthy young adults [108], yet versatile enough that they have been used extensively with compromised populations.

Subjects with Parkinson's disease generally exhibit greater dual-task costs than healthy control subjects [109]–[112]. The manifestations of costs affecting gait include: increased gait asymmetry, slower, shorter steps, increased double support time [113], differences in gait profile, variability in torso and lower extremity joint rotations, [114], and decreased arm swing [115].

In dual-task tests, individuals tend to prioritize one task over the other. The "posture second" strategy – that individuals will allocate their attention primarily to the cognitive task in a dual task scenario and experience declines in motor or posture – is commonly observed in PD [20], [114], [116], [117]. However, other studies have shown conflicting results where prioritization varies, often depending on secondary task type [109], [118], [119].

Cognitive tests commonly utilized in dual-task paradigms include Stroop (both auditory and visual), serial subtractions, spontaneous speech, text comprehension and phoneme counting. Studies have shown variability in dual-task cost significance across different cognitive tests. For example, comparing the auditory Stroop test and the spontaneous speech test while walking in older adults, the spontaneous speech dual-task resulted in greater effects on gait parameters [120]; and comparing a serial seven subtraction test and the visual Stroop, the serial-7 subtraction test showed greater effects on trunk measurements [121]. Comparing tasks with phoneme counting, text comprehension and serial seven subtractions, only the serial subtractions test showed significance in dual-task costs [109]. Although the purpose of these tasks under DT

conditions is to provide excessive cognitive loading, they all address different aspects of cognitive function which likely contributes to differing results.

The exact changes in signaling pathways in PD under DT conditions are unknown; however, recent studies suggest activation extending beyond areas directly related to the tasks at hand. These misdirected signals may illustrate the decreased organization of neural signaling, impacting DT function [122], [123].

1.4 Technology

Detection of changes in motor function can be important in diseased populations for identifying disease progression and monitoring the impacts of intervention [124]–[126]. As technology has advanced, more objective measures have become available to analyze gait parameters, increasing the detailed understanding of gait and balance and how it is related to physical and neurological pathologies. Some of these technologies include force plates, inertial sensors and motion capture [127]–[129]. Integrated technology systems, such as the Motek Computer Assisted Rehabilitation Environment (CAREN) system [130] combines technologies to maximize objective data collection.

1.4.1 Basic Principles of Motion Capture

Motion capture can be broken down into two essential parts: determining the location of an object in space, and the changes in position of the object over time. The first step, determining object location, involves motion capture cameras, the objects in the space (often markers), and a series of equations. The process involves taking an object in 3-dimensional space, gathering information about its location in 2D space, and reconstructing it onto a virtual 3D coordinate system. This is accomplished by using a series of equations called projection equations. The point in space projects its image onto

the camera lens creating a 2D image, accounting for the focal length, location, and orientation of the camera relative to the space. Multiple cameras placed around the motion capture space each collect a different image to discern the third dimension, similarly to how stereopsis (binocular vision) of human eyes creates our perception of depth [131]. Although it is possible to determine a marker location with two cameras, three or more cameras are recommended for best results. To decrease the possibility of marker occlusion, a greater number of cameras are used. With limited views of the capture volume, markers can become out of sight (dropped), or incorrect markers can appear where there is actually no marker ("ghost"). For example, if two markers lay in the same horizontal plane, and their lines of sight to separate cameras cross, it may appear that there is only one marker in the crosshair instead of two separate markers (see Figure 2) [132]. Combining the information from the different camera views, a least squares method equation can solve for the three unknowns: the x, y, and z positions of the markers. These positions are calculated for every frame, and the changes in position over time translate to motion.

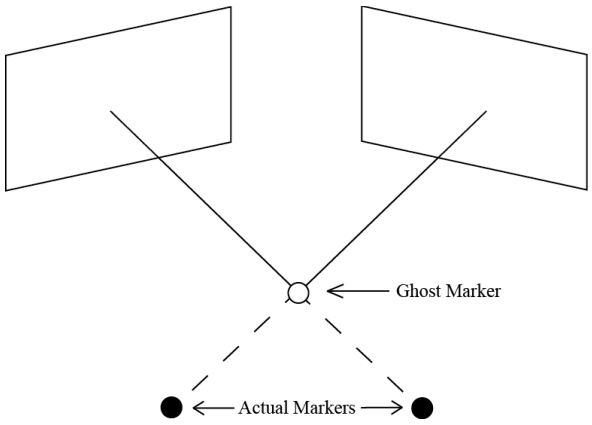

Figure 2 – Example of possible "ghost marker" configuration

When describing the location of objects in the capture volume space, two coordinate systems are used: global and local. The global coordinate system can be defined different ways, but it essentially describes the objects in the "original position". This may be defined in relation to the ground in the space volume, or as the marker location in the first recorded frame. The local coordinate system is defined as the new marker position after a rotation and/or translation in space, in relation to the new position. Detecting motion relies on a mathematical relationship between the global and local coordinate systems, see Figure 3.

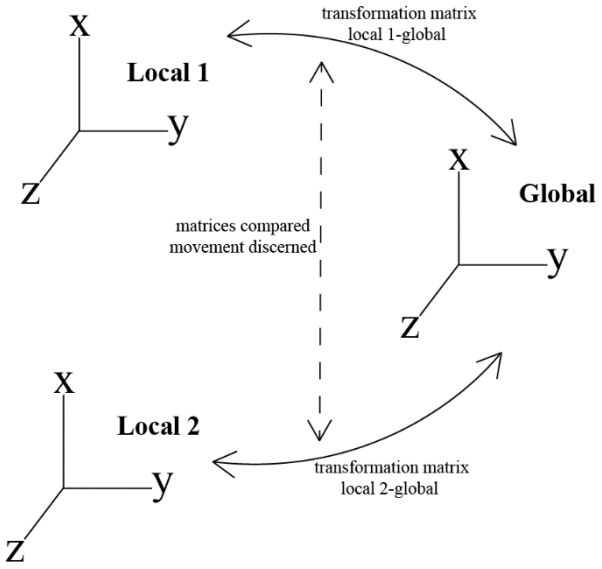

Figure 3 – Calculating the relationship between two joint segments. This involves comparing the relationship between the global-to-local transformation matrices of each segment.

With a motion capture system such as Vicon, the marker coordinates in the x, y, and z planes are provided per timestamp (the number of timestamps per second depends upon sampling frequency). Using this data, transformation matrices are created, containing the rotation and translation information of each object in 3-dimensional space from one timestamp to the next. To calculate relationships between body segments such as joint angles, the transformation matrix relating the local coordinate system of the first segment to the global coordinate system is created. Next, the transformation matrix relating the local coordinate system of the second segment to the global coordinate system in created. Finally, an equation describes the relationship between the two local-to-global transformation matrices of each frame (see figure 5) [133]. Motion capture for the human body often uses the coordinate system of the pelvis as the global coordinate system, and the coordinate system of the segment of interest as the local coordinate system [134].

To compute the angles between two objects such as the upper and lower arm segments, the rotation matrix (part of the transformation matrix) is decomposed into x, y, and z rotations, and the angles are extracted individually from matrix equations [135]. The order in which these rotation matrices' calculations are applied is significant. When measuring anatomical joints, this "joint angle sequence" will vary depending on which joint is being measured, following the individual joint rotation pattern of flexion/extension first, medial/lateral second, and interior/exterior rotation last [134].

1.4.2 Instrumentation (CAREN system)

Study assessment and data collection took place on the Motek CAREN system. Located on the Cleveland Clinic's main campus, CAREN is an integrative motion

capture system, consisting of a Vicon 10-camera real-time motion capture system, a Moog motion base platform with six degrees of freedom, a dual-belt treadmill with two Forcelink force plates (one located underneath each belt), a 180-degree cylindrical projection screen system, surround sound, and D-Flow software (see Figure 4).

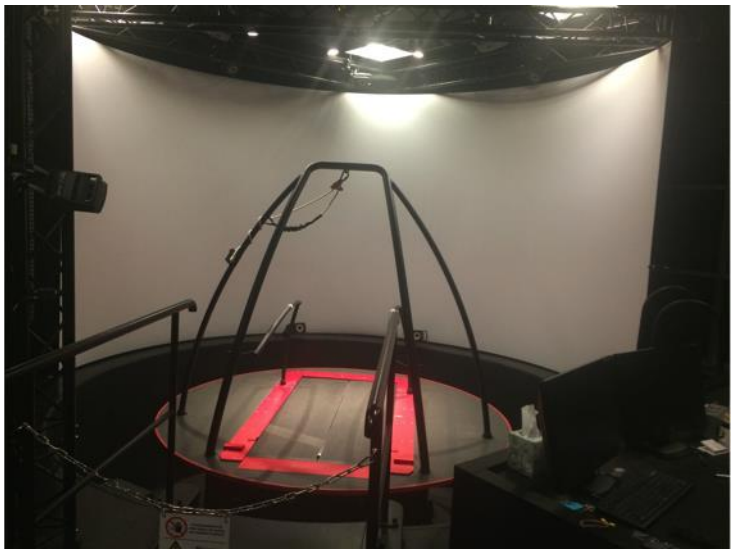

Figure 4 – The Computer Assisted Rehabilitation Environment (CAREN) system at the Cleveland Clinic, Cleveland Ohio.

Various data are collected from the system and are sent to D-Flow for processing. These inputs are processed within module-based applications and allows for real-time feedback. D-Flow provides a library of modules, each possessing unique qualities and functions. Data streams into these modules and different connections between modules process the data for output functions, calculations, changes to the system, etc (see Figure 5).

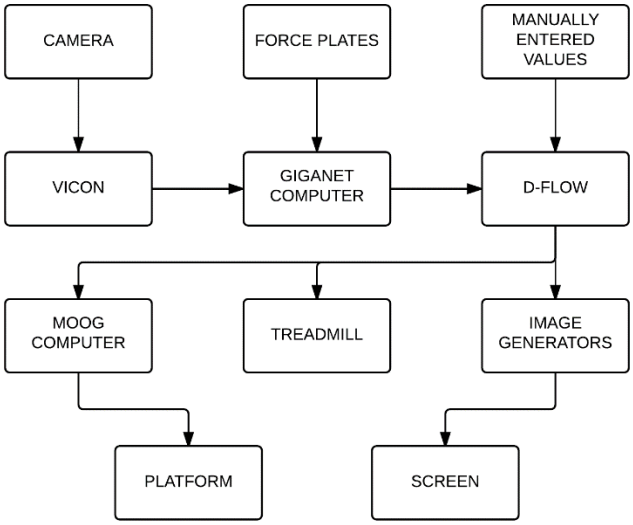

Figure 5 – The flow of information through the CAREN system. The marker data from the cameras is processed through Vicon and sent to the *giganet* computer to combine with force data from the force plates. This information is processed in D-flow according to programmed specifications. The outputs from the D-flow application can program platform movement, treadmill speeds, and images on the screen.

The motion capture aspect of the CAREN system includes a passive marker system and force plates. The motion capture system includes Vicon MX-T cameras, which consist of a digital video camera, a strobe head unit, a lens, and optic filter. The strobe unit consists of LED's (Light Emitting Diodes) that shine infrared light on the retroreflective spherical markers, which then reflect the light beam back to the cameras. The force plates have six load cell sensors per plate - three in the Y direction (vertical), two in the X direction (horizontal left-right), and one in the Z direction (horizontal forward-backward). Two video cameras are also located on the rear-left and right of the treadmill to capture live video. The video does not affect the data flow of the system, and therefore was not included in the diagram (Figure 5).

1.5 Exercise and Parkinson's Disease

Exercise results in various positive effects on people with Parkinson's disease, including improvements in motor and non-motor functions [136]–[139]. Changes in functions not directly related to the exercise task are of particular interest, as they suggest centrally mediated changes at the cortical and subcortical areas of the brain. In gaining understanding of the effects of exercise on the brain, animal studies provide valuable insight, and have set a foundation for this area of research.

1.5.1 Animal Models

To induce Parkinson's-like physiology in mice for animal models, 6-hydroxydopamine (6-OHDA) is commonly injected to facilitate nigrostriatal neuronal loss. Tillerson et al. discovered that increased use of limbs impaired by 6-OHDA injection results in decreased loss of function as well as decreased loss of dopamine located in striatal tissue [140]. Additionally, decreased used of the affected limb resulted in the opposite: increased loss of function and increased loss of striatal dopamine [141]. These studies contributed to the foundation for investigating the neuroprotective role of physical activity on PD. Subsequent animal studies have shown that high-intensity exercise (typically treadmill running) in PD mice results in neuroprotective effects, changes in neurotransmitter transport, and increases in neurotrophins [25]–[27], [142]–[147]. The neuroprotective effects include increased defense from oxidative stress and support of angiogenesis and synaptogenesis [25]. In addition to symptom improvement, exercise in PD mice results in increases in dopamine D2 receptor mRNA, and significant decreases in dopamine transporter [26], [27], decreasing dopamine reuptake into presynaptic vesicles. With increased dopamine receptors and increased postsynaptic

dopamine signaling, dopaminergic effects increase despite no differences in striatal dopamine levels in PD + exercise mice compared to PD control mice [142]. These results suggest that high-intensity exercise causes compensatory changes in the brain concerning dopamine processing. Studies have also found increases in neurotrophins such as brain-derived neurotrophic factor (BDNF), glial cell-derived neurotrophic factor (GDNF) and insulin-like growth factors as a result of exercise [25], [143]. Furthermore, Gomez-Pinilla et al. demonstrated a positive correlation between BDNF and proteins involved in cellular metabolic processes [147]. The proteins include: AMPK which monitors energy levels in cellular metabolism [145], uMtCK which is involved with energy maintenance and transduction [144], and UCP-2 which regulates energy metabolism by uncoupling mitochondrial electron transport during ATP synthesis [146].

1.5.2 Human Exercise Research

Methods of neuropathological data collection used in animal model studies are often invasive and result in subject sacrifice; therefore, alternative testing methods are employed for human studies investigating neurophysiological effects of exercise. Peripheral neurotrophic factors have been shown to increase from exercise interventions; however, this is not an exact measure of the neurotrophic factors in the brain [148]. Other methods to study brain activity, such as non-invasive fMRI tests have been used in human studies with cycling interventions [28], [149]. Physical outcome measures representing symptom improvement are also used to assess changes in a PD population due to an exercise intervention, such as the UPDRS assessment or accelerometers measuring tremor. Exercise programs with mixed tasks (such as cardiovascular, strength, balance, stretching, etc.) have shown improvements in motor function measured by the

UPDRS, improvements in walking [136], [137], and balance ability [136]. Forced exercise cycling studies have shown improvements post-intervention in UPDRS scores [29], [30], [149], tremor [150], manual dexterity and force [28], [30], and shoulder ROM [151]. Improvements in upper extremity function (a part of the body not actively involved in the exercise) and changes in brain activation following forced exercise resulting in excitation in the basal ganglia (specifically the putamen, globus pallidus, thalamus, subthalamic nucleus) [28], [149], and the cortical and subcortical areas [28] suggest centrally mediated changes. Improvements in overall motor function can have profound effects on daily activities.

The effect of exercise interventions on motor function as it applies to dynamic postural control is particularly important in PD as improvements in balance can lead to a decreased risk of falls [152]. Most studies using an exercise intervention assessing postural stability show significant improvements in balance measures from balance training when the training targets the specific movements tested in the outcome measures [153], [154]. Additionally, task-specific balance training improvements have shown to sustain up to six months post intervention [155]. Although it is encouraging that people with PD can improve dynamic postural stability with interventional training, these results demonstrate that motor skill learning abilities are still present in people with PD [152]. Less is known about the effects of exercise on centrally mediated changes in balance in PD. A few studies show improvements in postural stability with training not specifically targeting outcome measures, such as weighted treadmill walking, with improvements in the Berg Balance Scale [156] and improvements in the pull test portion of the UPDRS [157], while cycling training has shown improvements on the Berg Balance Scale [158].

Improvements in balance measures resulting from cardiovascular exercise are promising; however, more objective outcome measures will strengthen the knowledge of how exercise impacts dynamic postural control.

Exercise interventions investigating changes in gait parameters range from treadmill training [158], [159], to dancing [160], [161]. Overall, most exercise interventions elicit some improvements in gait [160], [162]. Similar to balance training targeting improvements in postural stability measures, many interventions targeting improvements in gait measures are treadmill or walking based [162]–[164]. Other studies focusing on strength training experienced improvements in gait parameters [165], [166], which may be due to improvements in muscular function [167], [168]. High-intensity cycling training has shown improvements in gait measured by the Timed Up and Go test and increased gait speed [158], and although common gait measures have objective quantifiable results, such as time, distance, etc., tests like the Timed Up and Go test and 6-minute walk test fail to describe quality of gait. A study by Mirek et al. used motion capture technology to characterize changes in gait in greater detail, such as joint ROM, due to exercise intervention [169]. Understanding methods to improve PD gait is crucial for decreasing fall risk; however, walking while mentally occupied further decreases gait function and poses a greater risk. Although there is a growing understanding of how exercise can improve gait in PD, there is little known of how exercise can affect gait under DT conditions.

People with PD experience increased gait deficits when performed simultaneously with a cognitive task [109]–[112], and efforts are being made to uncover interventions to improve DT abilities in PD [170]–[172]. Improvements in DT performance are often

elicited through DT training [173]; however, less is known on how interventions dissimilar from DT training affect gait under DT conditions. A study by Altmann et al. investigated how aerobic cycling exercise affects DT performance; however the motor portion of the DT test was cycling as well [171].

In addition to effects on physical outcomes, exercise can also result in positive effects on cognitive function. A meta-analysis by Colcombe and Kramer concluded that aerobic exercise increases cognitive test performance across different cognitive tests, exercise programs, and participant characteristics. Of these results, executive control processes demonstrated the greatest improvements [174]. Additionally, studies have shown increases in brain mass in the prefrontal, temporal, and cortical regions as a response to aerobic exercise [175]. Following this trend, exercise interventions with a PD population involving moderate- to high-intensity aerobic exercise also exhibit cognitive improvements. Similar to Colcombe's findings, the greatest improvements occurred in executive function tasks [139], [176], [177].

CHAPTER II

SPECIFIC AIMS, STUDY DESIGN AND PARTICIPANTS

2.1 Specific Aims

Aim 1: To determine the effects of an intensive aerobic cycling intervention on postural responses following an induced platform perturbation. *This assessment was an application developed by Motek as part of a battery of assessments for patients with Parkinson's disease. The "Time to Stability" application quantifies postural responses by measuring time and body mass excursion. The test begins with the participant standing in the center of the force plate with both feet firmly planted in a comfortable, narrow stance. The center of pressure is recorded by the system and stored. A series of platform shifts occur in four directions, at varying time intervals, and different accelerations. The direction and time interval are randomly programmed, and the acceleration remains constant for each test (three tests will be performed, one at each acceleration). Before each shift, the platform returns to center and a visual cue lets the participant know that the next platform shift is approaching.*

Subjects completed this assessment once before beginning the exercise regimen to establish their "baseline" values, and once after completion. Baseline scores were compared to the post-exercise scores of each individual participant.

Aim 2: To determine the effect of an intensive aerobic cycling exercise on biomechanical gait parameters and cognition in ST and DT conditions. *Three tasks were performed to evaluate ST and DT changes: a self-paced walking ST, three cognitive ST's, and three walking/cognitive DT's. Biomechanical gait parameters were quantified as walking speed, cadence, step length, joint angles, marker movement, and gait regularity. The verbal fluency test, the serial subtractions test, and the N-back test served to assess executive function, attention and working memory in the single tasks, as well as to increase cognitive loading in the DT conditions. All tests proceeded for 60 seconds.*

Subjects completed the gait assessments once before beginning the exercise regimen to establish their baseline values, and once at the end of the intervention. Comparisons were made between baseline and post-exercise for ST and DT conditions to assess changes due to the exercise intervention, as well as between ST and DT conditions to assess changes due to DT cognitive loading.

2.2 Subjects

Forty-five participants were recruited for this study, comprising three subject groups: PD intervention (PDE), PD non-intervention control (PDC), and healthy age-matched control (HC). Forty-two subjects participated, 14 per group; one participant in the PDE dropped out due to physical inability to complete study tasks, one participant in the PDC group dropped out due to a broken shoulder, and one age-matched participant in the HC group was removed to equalize the groups. Participants were recruited from the CYCLE clinical trial (R01NS673717) in the Neural Motor Lab [178], and those who participated in past studies and indicated willingness to be contacted in the future. The intervention group included exercisers in both the forced and voluntary cycling groups,

and the PD non-intervention group included some individuals who have already completed the CYCLE Trial. Recruitment involved asking participants: if they were willing to be contacted about a concurrent additional study, a phone call follow-up involving educating the participant about this study, review of the consent form, and the researcher answering any and all questions. Age-matched healthy control subjects were recruited from the subjects with Parkinson's. The Parkinson's subjects (both intervention and non-intervention groups) were asked if they have a spouse, friend, family member, etc. in the same age range who may be interested in participating. The inclusion criteria for the healthy control participants are that they are within three years of age of the subject with whom they are matching, and must be able to stand unassisted. The exclusion criteria include: known neurological or balance disorders. The primary inclusion criteria included: clinical diagnosis of idiopathic Parkinson's disease; between ages 30-75 Hoehn and Yahr stage II-III when on antiparkinsonian medication; not currently involved in formal exercise intervention or clinical study; ability to stand unassisted. The primary exclusion criteria included: existing cardiopulmonary disease or stroke; dementia; and any medical or musculoskeletal contraindications. The subject consort diagram is illustrated below (Figure 6), as well as baseline demographics (Table 2) and a sample of outcome measures from the exercise intervention for the PDE group (Table 3).

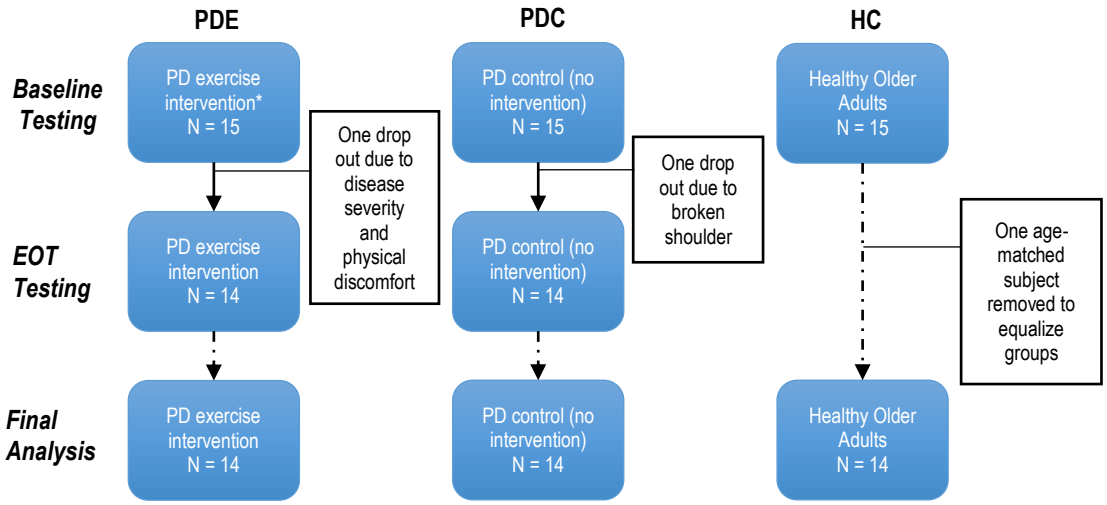

Figure 6 – Subject consort diagram. PD, Parkinson's disease; EOT, end of treatment.

Table II – Subject baseline demographics

Mean (SD)	**PDE**	**PDC**	**HC**
Number of subjects	14	14	14
Gender (male)	8	9	4
Age (yrs)	64.9 (5.4)	62.2 (7.1)	64.0 (5.0)
Leg Length (m)	0.83 (0.06)	0.83 (0.04)	0.80 (0.04)
Weight (kg)	76.80 (20.89)	88.46 (20.01)	74.17 (15.04)
Hoehn and Yahr stage	2.2 (0.4)	2.2 (0.4)	

PDE, Parkinson's disease exercise group; PDC, Parkinson's disease control group; HC, healthy control group.

Table III – Exercise intervention mean outcomes of PDE group

Outcome variable	**Mean (SD)**
# of sessions attended	23.71 (0.82)
Heart rate during session (beats/min)	115.10 (14.63)
HHR during exercise sessions (%)	69.50 (11.79)
Cadence (revolutions per minute)	75.97 (13.01)

HHR, % heart rate reserve.

Participants were off antiparkinsonian medication for this study. In addition to physical improvements due to medication, dyskinesia caused by levadopa has shown to result in decreased postural stability, exaggerated arm swing, and increased sway during stance phase [47]. Eliminating factors that alter the subjects physically increases the integrity of the measurements.

2.3 Study Design

Data collection for both Aim 1 and Aim 2 occurred during the same testing session. The order of data collection is illustrated below. Testing proceeded from top to bottom, tests aligned horizontally occurred in random order (see Figure 7)

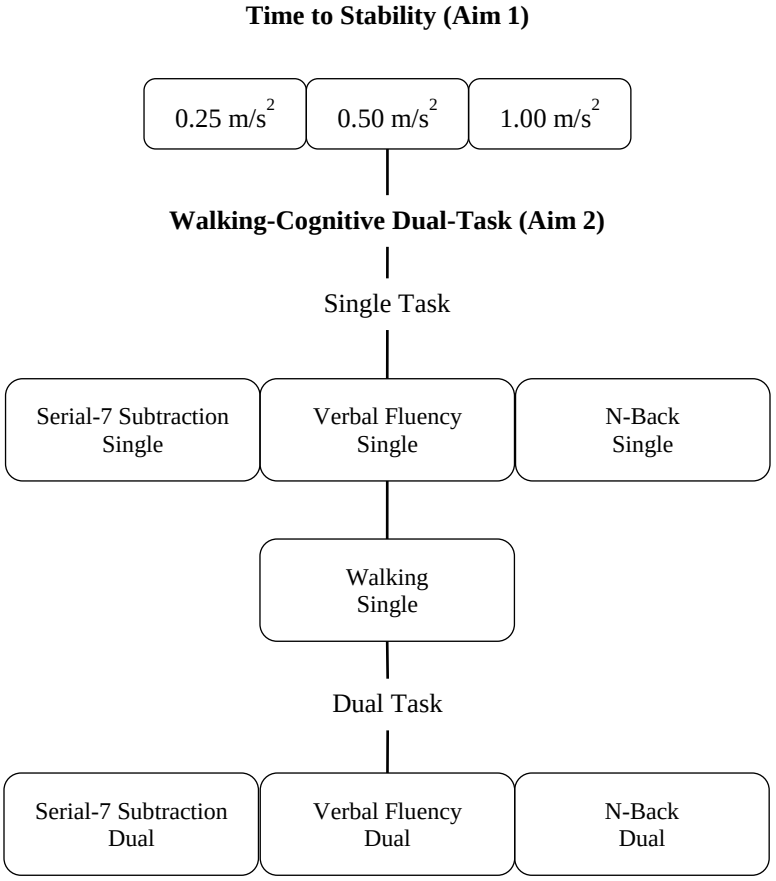

Figure 7 – Order of testing session. Tasks listed vertically are in chronological order (beginning at top), tasks listed horizontally are randomized.

The CYCLE trial intervention duration was eight weeks, with three exercise sessions per week (totally 24 exercise sessions). Participants completed a cardiovascular stress test prior to the start of their intervention to determine maximum heart rate reserve. Exercise sessions included a five-minute warm up, a 40-minute high-intensity exercise session, and a five-minute cool down. Subjects in the PDE group were comprised of exercisers in both the voluntary (self-paced cadence) and forced (bike-set cadence) exercise groups from the CYCLE trial. Despite differences in group assignment, all

exercisers were either programmed or encouraged to exercise at resistance and cadence to keep their heart rate in 60-80% of their heart rate reserve [178].

CHAPTER III

DYNAMIC BALANCE RECOVERY

3.1 Introduction

Postural instability is one of the cardinal motor symptoms of PD [10]. Poor balance can increase fall risk, decrease balance confidence and lead to decreased physical activity [74]. Dynamic stability, particularly motor responses to perturbations, can be important in navigating daily balance challenges. Specifically, medium and long latency muscle responses, which participate in feedback loops associated with the cerebellum and basal ganglia [179], are impaired with PD, and take longer to initiate and process under balance destabilizations [62].

Physical training interventions aimed at improving postural stability in older adults can improve reactive recovery responses and reduce incidence of falls [180]. Various types of exercise and physical training have also proven beneficial in those with mild to moderate PD [136], [181]. Animal models have demonstrated changes in neurotropic factors post exercise along with PD symptom improvement [26], [27], [142], while human studies have shown improvements in UPDRS scores as a result of high-intensity cycling [29], [30], [149]. The findings that dopaminergic therapy does not improve postural control [47] suggest that non-dopaminergic regions of the brain impact

dynamic postural stability [40] and support the exploration of treatments alternative to medication. This study aims to investigate if a high-intensity cycling intervention can elicit centrally mediated changes in the areas that affect improvements in dynamic balance.

Healthy individuals possess the ability to central-set, or prepare sensory and motor systems to react appropriately to an anticipated change in physical surroundings, such as a platform perturbation. This, in turn, can decrease the time spent in regaining balance [182]. This central-set ability is decreased in PD, and patients often lack the ability to appropriately scale their muscular responses to changing stimulation [68], [182]. This study aims to investigate how individuals with PD differ from healthy peers in their ability to scale motor responses, how quickly and accurately the responses are at regaining balance, and if exercise can improve these balance measures in people with PD. The time taken to regain balance and the center of pressure excursion represent the resultant physical movements of compensatory postural adjustments necessary to regain postural stability after a balance destabilization.

3.2 Methods

3.2.1 Testing Procedure

The “Time to Stability” application, developed by Motek Medical, functions by destabilizing the subject, and measuring their postural response performance. Destabilization occurs via unexpected, horizontal displacement of the platform. The test measures the time taken to regain balance after destabilization, and center of mass displacement.

Prior to test initiation, the system calibrated the subject by estimating center of pressure (COP). Once successfully calibrated, the platform underwent a series of shifts, inducing a temporary loss of balance. After the subject reestablished postural stability and returned to their original, balanced position, the platform slowly returned to the center, neutral position and prepared for the next shift.

Studies have demonstrated significant impairments with perturbation response scaling in Parkinson's disease [62], [102], [183]. To assess differences among various difficulty levels, a total of three tests were performed (in random order), one at each acceleration level: 0.25 m/s^2, 0.5 m/s^2, and 1.0 m/s^2. At each level, eight shifts occurred, two in each direction: forward, backward, left and right. The platform displacement was the same for all shifts, at 0.081 meters. Upon the start of each shift, an orange circle appeared on the screen, warning the subject of the impending platform shift. After the appearance of the orange circle, the platform shifted after a random time delay between one and four seconds. The unknown direction and timing of the shifts intended to reduce anticipatory postural adjustments. The subject's feet were separated by 5.0 cm to standardize the base of support between trials. A narrow base was chosen based on previous findings that a narrow stance results in a significant difference in center of mass displacement between people with Parkinson's and controls, where no significant difference was seen in a wider stance [61].

Friedman's ANOVA's revealed no significant difference between shift directions within an acceleration level for any subject groups ($p > 0.05$), therefore all eight shifts were collapsed per acceleration level.

3.2.2 Instrumentation

The Time to Stability application utilized various components of the CAREN system to provide testing conditions and for data collection. The forces exerted through the feet, measured from the force plate are used to estimate the center of pressure (COP). The platform, controlled by hydraulic motors, induced the perturbation shifts. Images projected on the surround screen provided a visual testing environment, and minimal visual cues. The D-Flow software orchestrated the functionality of the test, as well as collected and completed preliminary processing of the data.

3.3 Data Analysis

The "Time to Stable" (TTS) outcome is the time in seconds from when the platform has reached its maximum displacement to when the estimated COP has reached "balanced". During calibration, the average COP and standard deviation of the average COP is calculated. The subject is considered balanced when the standard deviation of the COP (measured in both the medial-lateral and anterior-posterior directions for 100 ms) is lower than the initially recorded measurement. The COP outcome measure is provided by the application in both the anterior/posterior and left/right directions as a coordinate value. The COP excursion (COPex) outcome measure is obtained from the COP data along both the anterior/posterior and left/right axes, and is collected over the same time frame as the TTS measure. Both TTS and COPex are reported as the average of the eight shifts performed within the same acceleration magnitude.

The COPex is the 2-dimensional path of the COP during a perturbation shift, calculated using the 'arclength' Matlab function [184]. Prior to computing the path length of the 2-dimensional COP, noisy data was processed using a threshold and interpolation

method. The D-Flow software calculates the COP from each force plate individually, (left and right) and takes the weighted average of the two. Instances where one foot lifts off of the platform are not properly accounted for, and the lack of consistent contact force between the two standing feet could lead to mathematical calculations resulting in distances outside of the reasonable limits of stability. This process involves removing noise point by point based on the theoretical speed that the point is traveling. Based on previous studies measuring speed of COP [185]–[187], a maximum threshold of COP speed was set at 0.50 m/s. First, the 2-dimensional speed of each COP point is calculated by two data points in chronological order from the first point to the end of the trial. Upon each comparison, the second time point of a pair is removed if the speed is above the threshold, and replaced with the coordinates of the previous point. This process handles noise based on physical properties, while leaving the "true" COP data signal untouched. On average, < 10% of the data was removed/replaced using this method.

Shapiro-Wilk normality testing revealed non-normally distributed data for over 50% of the TTS data; therefore, nonparametric measures were used for all TTS data analysis. For baseline comparisons between groups, a Kruskal-Wallis ANOVA was performed. A Friedman's ANOVA was used to determine the difference between shift levels (0.25 m/s, 0.5 m/s, 1.0 m/s) for baseline and, if applicable, EOT testing sessions of all subject groups. If significant differences were found, Wilcoxon Signed Ranks tests were used for pairwise comparison. Wilcoxon Signed Ranks tests were also used to compare baseline to EOT of outcome measures. To test for differences due to the exercise intervention, the ΔTTS was calculated (EOT – baseline) and compared between the PDE and PDC groups for each acceleration level using Mann-Whitney U tests.

The results of Shapiro-Wilk normality testing of the COPex data revealed normal distribution; therefore, one-way, two-way, and two-way repeated measures ANVOA's were used for COPex analysis. Where significance was found, pairwise comparisons with Bonferroni corrections were completed. For baseline comparisons between groups a two-way ANOVA comparing factors of group (PDE, PDC, HC) and acceleration level was used. A two-way repeated measures ANOVA investigating the factors of session (baseline and EOT) and acceleration level was completed for both PDE and PDC groups. Due to unforeseen loss of data, COPex data analysis included the PDE group: N = 12, the PDC group: N = 6, and the HC group: N = 7.

3.4 Results

3.4.1 Time Taken to Regain Balance

Comparing baseline measures between the PDE, PDC and HC groups, no significant differences were found for time taken to regain balance for all three levels of acceleration. Differences in TTS across the three acceleration levels were compared for each group, as well as each testing session (baseline and EOT for PDE and PDC, baseline only for HC). The PDE group at baseline showed significant differences between accelerations: the median TTS during the 0.5 m/s acceleration was 50.7% longer than the 0.25 m/s acceleration ($Z = -2.57$, $p < 0.05$); and the median TTS during the 1.0 m/s acceleration was 41.4% longer than the 0.25 m/s acceleration ($Z = -2.76$, $p < 0.01$); and at EOT the 1.0 m/s median acceleration experienced a 26.0% longer TTS than the 0.25 m/s acceleration ($Z = -2.57$, $p < 0.05$). The PDC group at baseline showed that the median TTS at the 1.0 m/s acceleration was 40.5% longer than the 0.25 m/s acceleration level (Z

= -2.39, p <0.05), and there were no significant differences between acceleration levels at EOT. For the HC group, the 3 accelerations levels were not significantly different.

Significant differences in TTS comparing baseline to EOT testing sessions are seen in the PDE group with the 0.5 m/s median acceleration decreasing by 22.1% (Z = 2.76, p < 0.01). The PDC group did not show any significant difference in TTS from baseline to EOT for any acceleration level. In comparing the ΔTTS between the PDE and PDC groups, no significant differences were found at any acceleration level (see Figure 8). Results listed in Appendix A.

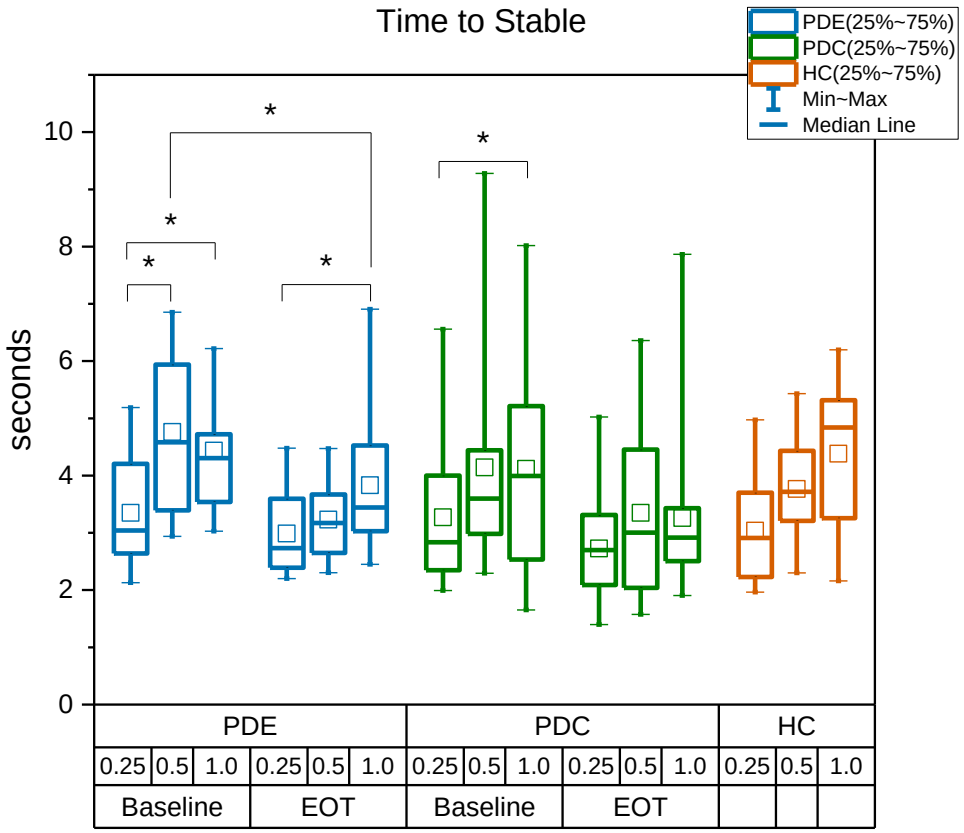

Figure 8 – Time to Stable median results in seconds for all three subject groups. PDE, Parkinson's disease exercise group; PDC, Parkinson's disease control group; HC, healthy control group; EOT, end of treatment. Square inside 25%-75% box indicates mean.

3.4.2 Center of Pressure Excursion

At baseline, there was a significant main effect of group; the mean COPex for the HC group was 16.6% larger than the PDC group ($t = 2.86$, $p < 0.05$). There was no effect of level or interaction at baseline. The two-way repeated measures ANOVA for the PDE group revealed a significant main effect for the testing session, $F(1, 11) = 7.91$, $p < 0.05$, such that the average COPex during EOT testing decreased significantly from baseline testing by 0.17 meters (SD = 0.05). The main effect of acceleration level was non-significant, nor was the interaction effect. The two-way repeated measures ANOVA for the PDC group yielded no significant main effects for testing session, acceleration level, or their interaction effect (see Figure 9). Results listed in Appendix B.

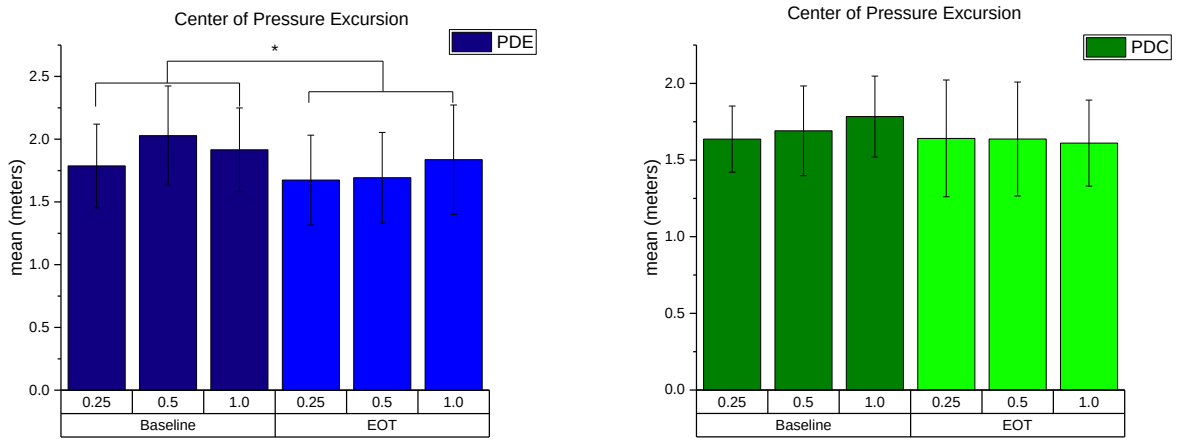

Figure 9 – Center of Pressure Excursion mean results in meters, for each acceleration level (m/s^2). PDE, Parkinson's disease exercise group; PDC, Parkinson's disease control group; EOT, end of treatment.

3.5 Discussion

Both PD groups did not differ from the HC group on time taken to regain balance for any of the three acceleration levels. Contrary to previous studies [104], [188], there was not a clear difference between the PD groups and the HC group in terms of ability to

modify perturbation recovery time to different acceleration levels. The PDE and PDE groups had significant differences in TTS in one or two levels at baseline, which differs from the hypothesis that the PD groups would be less able to scale their recovery time responses than the HC group, and would take similar amounts of time for all three different accelerations. The results of this study did not demonstrate a lack of scaling of postural responses in a PD population as anticipated; however, these results are similar to other studies which have shown intact or partial gain scaling, but decreased amplitude [104], [107]. Studies that have demonstrated significantly slower perturbation responses and decreased ability to scale postural responses compared to controls had PD patient populations with greater disease severity, suggesting that disease severity may contribute to degree of dynamic stability deficits [61], [105]. Additionally, Schieppati and Nardone have found that PD patients with mild impairment show similar muscle activation patterns compared with age-matched healthy controls [62], and Dimitrova, Horak and Nutt found that muscle coactivation in response to a perturbation significantly correlated with disease severity (subjects ranging from 1-4 on Hoehn and Yahr scale) [60].

The time taken to regain a balanced position, measured here as TTS, represents the time taken for motor responses to adequately stabilize the body. This process involves muscle responses from both cortical and subcortical activation with variable activation latencies, [60], [68], [98], [99], [182], and may not be well characterized by time alone. The movement of the COP may provide additional information on how the body responds to perturbations.

Although numerous balance deficits in PD are well established, center of pressure excursion specifically has not been well studied in the PD population. The results of this

study indicate no significant differences between the COPex of mild to moderately impaired individuals with PD (for the PDE group) and healthy older adults, which mirrors the findings of a similar study [189]. Although there was a significant difference between the PDC group and HC at baseline, there was no significant difference between the PDE and PDC groups. Therefore, further analysis proceeded as intended.

Comparing the results of the PDE and PDC groups of this study, the PDE group shows a significant decrease in COPex, whereas the PDC group has no significant change. Previous studies demonstrate that higher COP excursion indicates worse functional balance [187], [190], [191], therefore suggesting improvement in the PDE group. Although interventions employing physical activities which practice a balance component have shown efficacy in improving postural stability in a PD population [180], [181], anti-Parkinson's medications have not shown consistent improvements in balance deficits [47], [68]. Impaired acetylcholine signaling pathways related to postural control can be damaged by Lewy body aggregation, adding to the complexity of PD balance impairment, and perhaps explaining the lack of improvement from medication [40]. Furthermore, potential improvements in dynamic balance resulting from an exercise intervention not only demonstrates the ability of people with PD to improve their balance from a task that does not practice balance, but it also suggests that exercise may elicit changes differently than the levodopa-replacing mechanism of medication.

CHAPTER IV

GAIT AND DUAL-TASK

4.1 Introduction

In healthy individuals, neural coupling controls the cyclical movement of arm swing and leg movements during walking gait, and is likely controlled by central pattern generators [192]. The integration of spinal cord output and higher level executive processes results in successful gait performance [192]. These neural circuits are disrupted in PD [33], resulting in gait impairments such as stooped posture, decreased speed, reduced arm swing, reduced stride length, decreases in joint ROM, [14], yet no difference in cadence (steps per minute) [11], [13], [15], [16], [19]. Gait stabilizing tactics also common to PD gait include increased double leg support time [12], [16], [17], [20] and decreased swing phase [16], [44]. The magnitude of gait impairment is typically inversely correlated with disease severity [11].

Gait deficits present in PD are further exacerbated under DT conditions. Decreases in task performance occur when two tasks are performed simultaneously in a healthy population; however, those with PD generally exhibit greater dual-task costs than healthy peers [109]–[112]. Under DT conditions people with PD may experience the following: increased gait asymmetry; slower; shorter steps; increased double support time

[113], differences in gait profile and variability in pelvic tilt, pelvic obliquity, pelvic rotation, hip flexion/extension, hip abduction/adduction, knee flexion/extension, and ankle dorsi/planar flexion [114].

People with PD also experience non-motor symptoms, such as cognitive decline. The basal ganglia-thalamo-cortical circuits that cause motor declines when affected by PD have parallel associative/cognitive functions [33]. The impact of PD on executive function results in declines that are detectible in neuropsychological tests such as logical memory and associative learning [84]. Cognitive and motor declines are exacerbated under DT conditions when attentional demands are increased and adequate neural compensation is not available [119].

Disease modifying treatments are not yet available for PD, but dopaminergic medication and deep brain stimulation provide symptom relief [3], [24]. Unfortunately, side effects such as dyskinesia (involuntary movements) [3], and risks of invasive surgery [24] are associated with these treatment options. High-intensity aerobic exercise targets neurological modifications to alleviate symptoms as well; however, it is associated with lower risk and potentially positive side effects.

Parkinson's disease patients with relatively more severe gait declines show higher prefrontal activation during gait tasks than PD patients with relatively milder gait declines. This suggests compensatory neural activation to improve gait performance [193]. Exercise studies have shown increases in volume in the prefrontal, temporal, and cortex regions as a response to aerobic exercise, [175], suggesting that exercise may have a direct effect on areas of the brain that affect gait function in PD. Studies investigating cycling exercise and PD measured motor symptom outcomes [28]–[30], [150], and brain

activation [28], with key findings related to motor function including 35% UPDRS improvement at end of trial and improvements in upper extremity function (measured as grasping forces and tremor). Exercising the lower extremity, while experiencing improvements in symptoms of limbs not involved in the exercise suggest that the cycling intervention facilitates neurophysiological changes directly impacting PD symptoms [28]–[30], [150].

Exercise studies have also shown improvements in cognitive function, with the greatest improvements in executive control processes [174]. These improvements have also been found in PD with moderate to high-intensity aerobic exercise, and similar to Colcombe and Kramer's findings, the greatest improvements occurred in tasks involving executive function [139], [176], [177].

Studies have shown significant improvement in gait function after an exercise intervention [158], [159], [194]; however, individuals frequently encounter walking conditions that are more complicated than the ST conditions commonly tested in clinical environments. When an individual is walking while talking on the phone, answering a question, recalling the directions to their desired location, etc., they are effectively completing a cognitive-motor DT. Studies targeting DT performance improvement often employ physical interventions based on DT movements and exercises [195]. Whether the neurological effects of high-intensity exercise can affect DT performance in PD remains unclear. In addition to lower extremity outcome measures illustrating changes in gait, it has been suggested that arm swing may also serve as a proxy for gait function [115]. Research has shown that dopaminergic treatment has the ability to improve gait function,

specifically arm swing [59]. However, it is unclear how a high-intensity exercise intervention can improve gait function illustrated by arm swing.

This study aims to investigate the effect of a high-intensity cycling exercise intervention with a PD population on gait parameters under ST and DT conditions. The various biomechanical outcomes measured with a motion capture system will provide an objective summary of changes in PD gait under different task conditions, and after intervention.

4.2 Methods

4.2.1 Testing Procedure

Participants completed ST and DT testing on the platform in the CAREN environment. The ST tests were completed first, with the participant seated on a chair with the test prompts delivered visually on the screen. After all three cognitive ST tests were complete, the participants walked on the treadmill for 60 seconds for the motor ST test. Next, the DT tasks were performed, where the participant completed both the cognitive and motor tasks simultaneously. The versions of the cognitive tasks were different for each testing presentation to minimize learning effect.

Walking speed was self-selected by the participants using the self-paced feature of the CAREN system. The “self-paced” speed algorithm uses the four anterior/posterior iliac crest markers of the pelvis to adjust the treadmill speed to the pace of the individual relative to their positon on the treadmill. Once the participants audibly declared their speed “comfortable” and “constant”, that speed was recorded and manually entered for all walking trials in that testing session. The speed was held constant for the ST and DT

trials in the same session to minimize the confounding effect of speed on other gait parameters that may change due to DT effects.

4.2.2 Instrumentation

The application used for providing testing conditions as well as collecting and completing preliminary data processing was custom built in the D-Flow software. In addition to the hardware of the CAREN system used to create the testing environment and data collection, the HBM with its specific marker model and the Gait Offline Analysis Tool were used for initial data processing.

4.2.2.1 Software - Human Body Model

The Human Body Model (HBM) developed by Motek Medical uses marker and force plate data to estimate subjects' kinematics. The model has 18 body segments and 46 degrees of freedom, with the pelvis serving as the root segment. Although complex, this process computes with sufficient speed to function in real-time, while the subject is on the system (Figure 10). The first step involves calibrating the model to the subject. The initialization uses the marker coordinates, marker diameter, and knee and ankle width to calculate joint centers, bone lengths and joint axes. The subject weight and gender are used to calculate the mass properties of the model. Data extraction and body segment compilation use reference frames, defined during the initialization pose, illustrated below (Figure 11). Generally, the origin of each segment lies at the proximal joint, and the Z axis is oriented to go through the distal joint, in accordance with de Leva [1].

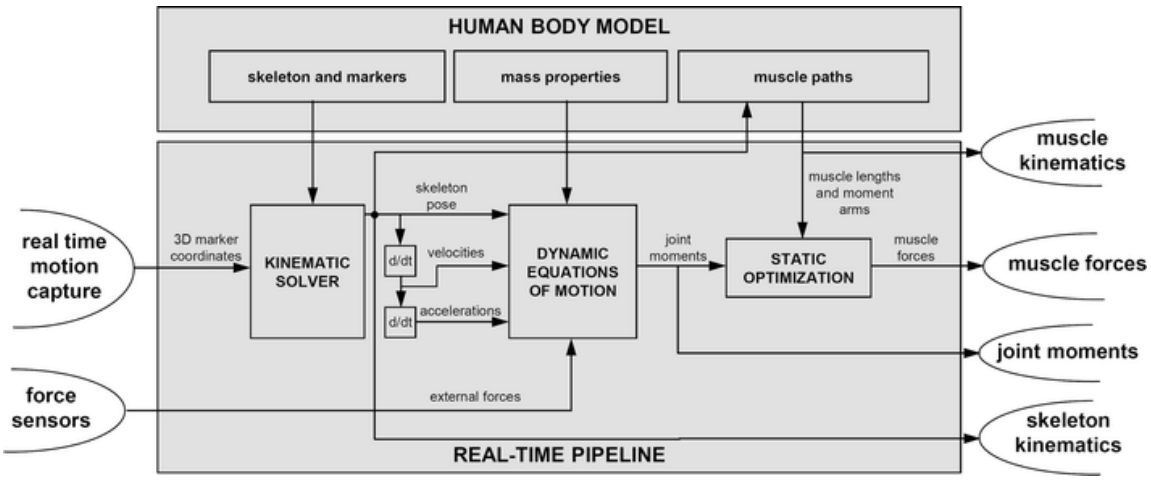

Figure 10 – Data processing through the Human Body Model (HBM) [1].

Formulas unique to each joint, and anatomical information available from surrounding markers are used to calculate the joint centers. The coordinate system for HBM is: X=anterior; Y=left; Z=up. The hip joint center, for example, uses an algorithm presented by Bell at al. [196]:

- X of hip joint center is X of greater trochanter marker
- D is distance between LASIS and RASIS
- Y of right hip joint center is Y of RASIS + 0.14D (- 0.14D for left) in the local Y direction
- Z of hip joint center is Z of ASIS – 0.3D

Mass properties of body segments are calculated using anatomical information from de Leva's anthropometry model, which provides segment mass as a percentage of total body mass, segment center of mass as a percentage of segment length, and radii of gyration for frontal plane, sagittal plane, and longitudinal axis [197].

The joint axes and degrees of freedom are based on International Society of Biomechanics standards [134], [198], [199]. The joint rotation sequence, (described earlier) follows the pattern of the axis with major muscle movement first, then the lesser two axes. For example, with the pelvis coordinate system as Z=yaw, Y=pitch, X=roll, the knee rotation sequence follows: Y (flexion), X (abduction), Z (internal rotation).

Once the program acquires all of the necessary input information, the HBM is fit to the subject. The model is scaled to the size of the subject, and forward kinematic equations are used to calculate the coordinates of the markers. The skeleton pose is then found by a process known as global optimization [200], where the entire model as a whole is best fit to the markers. This function is a nonlinear least-squares equation, which essentially minimizes the difference between the measured marker pose and the desired pose of the model. This is an iterative solution process, where the function runs repeatedly until the solution with the smallest difference is found. Since this process occurs for each frame, the computation occurs quickly, at the speed of 1.0ms to run in real-time [130].

An important factor in every calculation is filtering. Since the raw data undergoes many calculations, unfiltered noise will become amplified through the process. A second-order Butterworth filter, for both force plate and marker data is used. Since filtering causes a time delay, choosing the appropriate filter was a balance between power and speed to allow for continual real time processing [130].

4.2.2.2 Marker Model

This study used the full-body marker model, which uses 47 markers to discern the body segments and the kinematic degrees of freedom (see Figure 11 and Table IV). The

goal for a good marker model is to use the least amount of markers while providing the cameras with enough information to accurately assign the location of each body segment. Three markers are the minimum for each body segment to properly discern the x, y, and z coordinates. This eliminates the possibility of two markers rotating about an axis that produces no translation, therefore appearing to have no motion. It is also advantageous to have markers that may apply to more than one segment to minimize the total number of markers. For example, the lateral epicondyle is part of both the femur and shank segments [1].

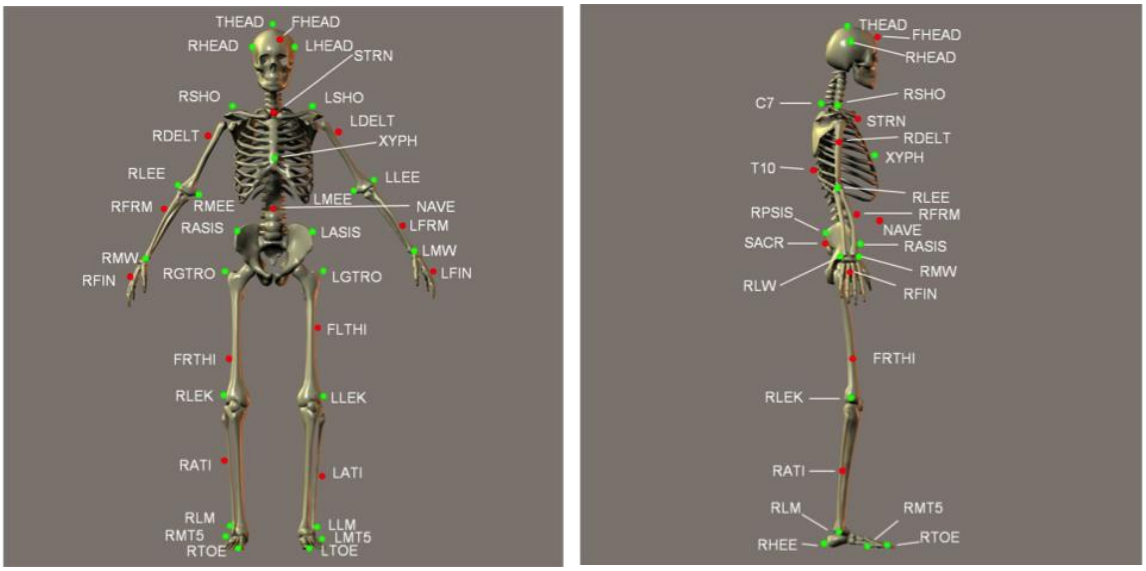

Figure 11 – Full-body marker model [1].

Table IV – Anatomical marker placement key [1]

Marker Name	Anatomical Marker Location	Marker Name	Anatomical Marker Location
LASIS	Left anterior superior iliac spine	THEAD	Top of head
RASIS	Right anterior superior iliac spine	RHEAD	Right side of head
LPSIS	Left posterior superior iliac spine	LHEAD	Left side of head
RPSIS	Right posterior superior iliac spine	SACR	Sacrum
LGTRO	Left greater trochanter	T10	Vertebra T10
RGTRO	Right greater trochanter	NAVE	Navel
LLEK	Left lateral epicondyle of knee	STRN	Sternum
RLEK	Right lateral epicondyle of knee	LDELT	Left deltoid of the humerus
LLM	Left lateral malleolus	RDELT	Right deltoid of the humerus
RLM	Right lateral malleolus	LFIN	Left 3rd metacarpal
LTOE	Left head of first toe	RFIN	Right 3rd metacarpal
RTOE	Right head of first toe	BBAC	Center of right scapula
LSHO	Left acromion process of shoulder	FLTHI	Left mid-thigh
RSHO	Right acromion process of shoulder	FRTHI	Right lateral mid-thigh
LLEE	Left lateral epicondyle of elbow	LATI	Left lateral tibialis anterior
RLEE	Right lateral epicondyle of elbow	RATI	Right lateral tibialis anterior
LMEE	Left medial epicondyle of elbow	LHEE	Left posterior of heel
RMEE	Right medial epicondyle of elbow	RHEE	Right posterior of heel
LLW	Left lateral epicondyle of wrist	LMT5	Left head of 5th metatarsal
RLW	Right lateral epicondyle of wrist	RMT5	Right head of 5th metatarsal
LMW	Left medial wrist	LFRM	Left mid forearm
RMW	Right medial wrist	RFRM	Right mid forearm
XYPH	Xyphoid process	FHEAD	Forehead
C7	Vertebra C7		

4.2.2.3 Outcome Variables

The CAREN lab provides vast amounts of data from its different integrated systems. The Vicon motion capture system yields marker coordinates in an x, y, z coordinate system, the forces and moments in the x, y, and z directions, and the video cameras record video from two different angles. These inputs are all integrated into the D-Flow software, which can take the raw data and compile more meaningful metrics for various applications. In addition to D-Flow, the CAREN system is equipped with the Gait Offline Analysis Tool, which manipulates saved data from an HBM session for further

analysis. The metrics exported from the Gait Offline Analysis Tool include: marker coordinates, joint angles, stance phase, stride length and treadmill speed. This data was further processed, if necessary, and organized with a custom Matlab program to yield the biomechanical outcome variables listed below in Table V.

Table V – Biomechanical outcome measures

Variable	Description
Speed	Measured by self-selected speed algorithm
Cadence	Number of heel strikes per minute (both left and right)
Step Length	Meters from heel strike to subsequent heel strike on each leg separately
Stance Phase	Percent of gait cycle (defined as heel strike to subsequent heel strike on same leg) in which the foot makes contact with the ground. The remainder of the cycle is considered swing phase
Ankle ROM	Ankle flexion/extension (plantar flexion/dorsiflexion) along the X axis in the sagittal plane, measured as maximum flexion minus minimum flexion per gait cycle
Knee ROM	Knee flexion/extension, along the X axis in the sagittal plane, measured as maximum flexion minus minimum flexion per gait cycle
Hip ROM	Hip flexion/extension, along the X axis in the sagittal plane, measured as maximum flexion minus minimum flexion per gait cycle
Arm swing path length	The 3-dimensional path length per arm swing cycle, which is measured from the maximum anterior position in the –Z direction to the subsequent maximum anterior position of the finger marker, which is placed approximately in the center of the back of the hand
Normalized Jerk	Jerk is calculated from the arm swing path length per arm swing cycle (defined above), normalized by time and distance
Trunk Rotation ROM	Rotation about the Y axis in the transverse plane, left twist is a positive value, right twist is negative, measured as maximum rotation value minus the minimum rotation value per gait cycle
Pelvic Tilt ROM	Rotation about the X axis in the sagittal plane, anterior tilt (ASIS markers lower than PSIS markers) is a positive value, posterior tilt (PSIS markers lower than ASIS markers) is a negative value, measured as maximum rotation value minus the minimum rotation value per gait cycle
Pelvic Obliquity ROM	Rotation about the Z axis, in the frontal plane. Left drop/right lift is a positive value, left lift/right drop is negative. Measured as maximum angle minus minimum angle per gait cycle
Pelvic rotation ROM	Measured similarly to trunk rotation

4.2.3 Cognitive Tasks

4.2.3.1 N-Back

The N-back task is a working memory test where a list of stimuli is presented at regular intervals, and the participant is asked to recall the stimulus presented N times prior in the list [201]. This test has been used in various populations, for various purposes [201]–[204]. Commonly seen versions include a string of numbers, shapes, or an object placement in space [205]. For this study, the 2-back version of the test was used, which entails the subject to recall whether the letter currently presented is the same ("yes") or different ("no") from the letter presented two prior in the string. The score is calculated as number of correct responses.

4.2.3.2 Serial Subtractions

The serial sevens subtractions test was first developed in 1942 by Dr. Max Hayman M.D. as a time efficient and cost effective cognitive test to assess mental capacity of cognitively challenged populations. The original design of the test consists of starting with the number 100, subtracting seven, subtracting seven from the calculated difference, and continually repeating these subtractions until the number two is reached. The score is the completion time, as well as the number of correct answers over the number of total answers [206]. This test uses working memory and information processing, which are both related to executive functioning [11]. Modifications are often made to the test, such as using a different starting number [108], different subtrahend [108], [116], allowing a limited time for test completion [108], or scoring by counting total number correct [109]. This study used a version of this test where a random starting

number between 200 and 400 was used, and calculations subtracting seven occurred for 60 seconds. The number of correct responses only was used to calculate the score.

4.2.3.3 Verbal Fluency

The verbal fluency test entails producing as many words as one can think of in a specific category in a set time frame. Versions of the test vary by category, such as "animals", "colors", or "words that begin with the letter F", and response, written or oral. The test is scored as number of correct, unique answers in one minute (oral) or five minutes (written) [86]. The verbal fluency test examines the executive function of selective attention, internal response generation and self-monitoring [207]. The Controlled Word Association Test (COWAT) is a common, standardized version of verbal fluency. Three letters are given to the participant, allowed 60 seconds of response time per letter, and the score is combined from all three letter responses. Currently, there are two sets of letters that are considered equivalent and utilized in the COWAT [86]. Borkowski et al. have studied each letter of the alphabet individually to find equivalency in terms of possible answers [208], which broadens testing options. The letters S, T, F, and P were used for this study.

4.3 Data Analysis

The spatiotemporal gait parameters compared between the PDE and PDC groups include: walking speed (m/s), cadence (steps/min), normalized step length (% of leg length) and stance phase (% of gait cycle). The kinematic gait parameters include: ankle, knee and hip ROM (degrees), ROM of trunk rotation in the transverse plane (trunk rotation) (degrees) and ROM of the pelvis in the sagittal, frontal, transverse and planes (pelvic tilt, pelvic obliquity, pelvic rotation) (degrees). The upper extremity gait

parameters include: normalized arm swing path length (PL) (% of arm length), and normalized jerk (NJ). Walking speed was selected at the beginning of each testing session, and remained constant for the remainder of the session across all walking and DT conditions. Cadence, step length, stance phase, and joint ROM were all calculated and reported through the Gait Offline Analysis Tool. A custom-built Matlab program provided additional data processing. Cadence was calculated by total number of steps taken for both feet combined, divided by the total time. Step length and stance phase were calculated per gait cycle, then the average was taken over all gait cycles completed per trial. Joint ROM was calculated from the joint angles reported per time stamp by finding the maximum and minimum angles per gait cycle to calculate the total ROM, and taking the average ROM over all gait cycles per trial. Further description of biomechanical outcome measures can be found in Table K.

Arm swing outcomes (PL and NJ) used 3-dimensional coordinate position data. First, the arm swing was calculated relative to the pelvis to account for body displacement within the motion capture volume. The pelvis center was found by taking the average of the 3-dimensional coordinates of the four iliac crest markers, which was then subtracted from the lateral wrist markers. The arm swing metrics were reported as average per arm swing cycle (one cycle defined as the maximum anterior position to the subsequent maximum anterior position). Path length computed from the left and right wrist markers using the ‘arclength’ Matlab function [184], describes the 3-dimensional distance traveled per arm swing. Path length was also used to calculate jerk, a measure to describe smoothness of movement.

Jerk, or smoothness of movement, is defined as the rate of change in acceleration. The methods for calculating arm swing jerk have been publish in previous work [115]. Using position data, the third derivative was taken to obtain jerk. Mathematical noise increases with each derivative calculation [209]; therefore, a jerk measurement derived from position data would be noisier from a jerk measurement derived from accelerometer data. To assess this discrepancy, trials were completed on the CAREN system to compare accelerometer-derived jerk and position-data-derived jerk. An individual walked at a constant speed with an iPod attached to the wrist, with a marker attached to the iPod itself. The jerk calculated from the position data was compared to the jerk calculated from the acceleration data from the iPod.

Before comparison, the appropriate filtration was found for both the accelerometer and position data. The accelerometer data from the iPod was filtered using a second-order Butterworth filter. The cutoff frequency was found using residual analysis [2]. This process involves comparing the difference between the raw and filtered signal, called the residual, across a range of cutoff frequencies. The residual is calculated as follows (N = number of sample points in time, x_i = raw data at *i*th sample, $\hat{x_i}$ = filtered data at *i*th sample, see Figure 12):

$$R(f_c) = \sqrt{\frac{1}{N}\sum_{i=1}^{N}(x_i - \hat{x_i})^2} \quad [2]$$

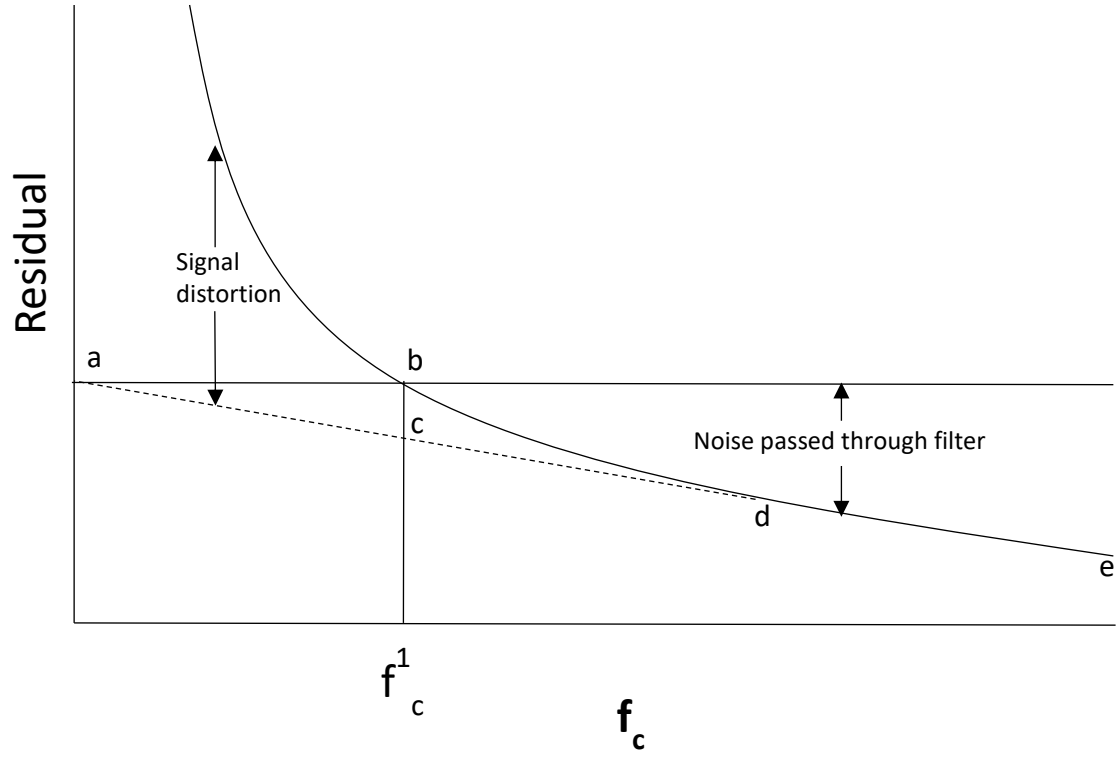

Figure 12 – Residual analysis [Winter 1990], along the y-axis is the residual $R(f_c)$ calculated from increasing cutoff values (f_c, along the x-axis), line de = estimate of noise residual, line bc = estimate of noise distortion and allowed noise, point a = projection of tangent line from line de at 0Hz , horizontal projection from point a to the residual curve creates point b, vertical projection of point b lands at the desired cutoff frequency, f^1_c.

Once the appropriate filter was applied to the accelerometer data, the derivative was taken to obtain the jerk measure from the accelerometer data (accelerometer-to-jerk). Next, second-order Butterworth filters with a range of cutoff frequencies were applied to the position data, then the third derivative was taken (position-to-jerk):

$$f_i''' \approx \frac{f_{1+2} - 2f_{i+1} + 2f_{i-1} - f_{i-2}}{2h^3}$$

The results of varying cutoff frequencies of the position-to-jerk data were then compared to the accelerometer-to-jerk data. Jerk by time plots were visually inspected, as

well as resulting values (see Figure 13). Keeping to the closest multiple of 0.05 Hz, a frequency cutoff value of 1.25 Hz was selected.

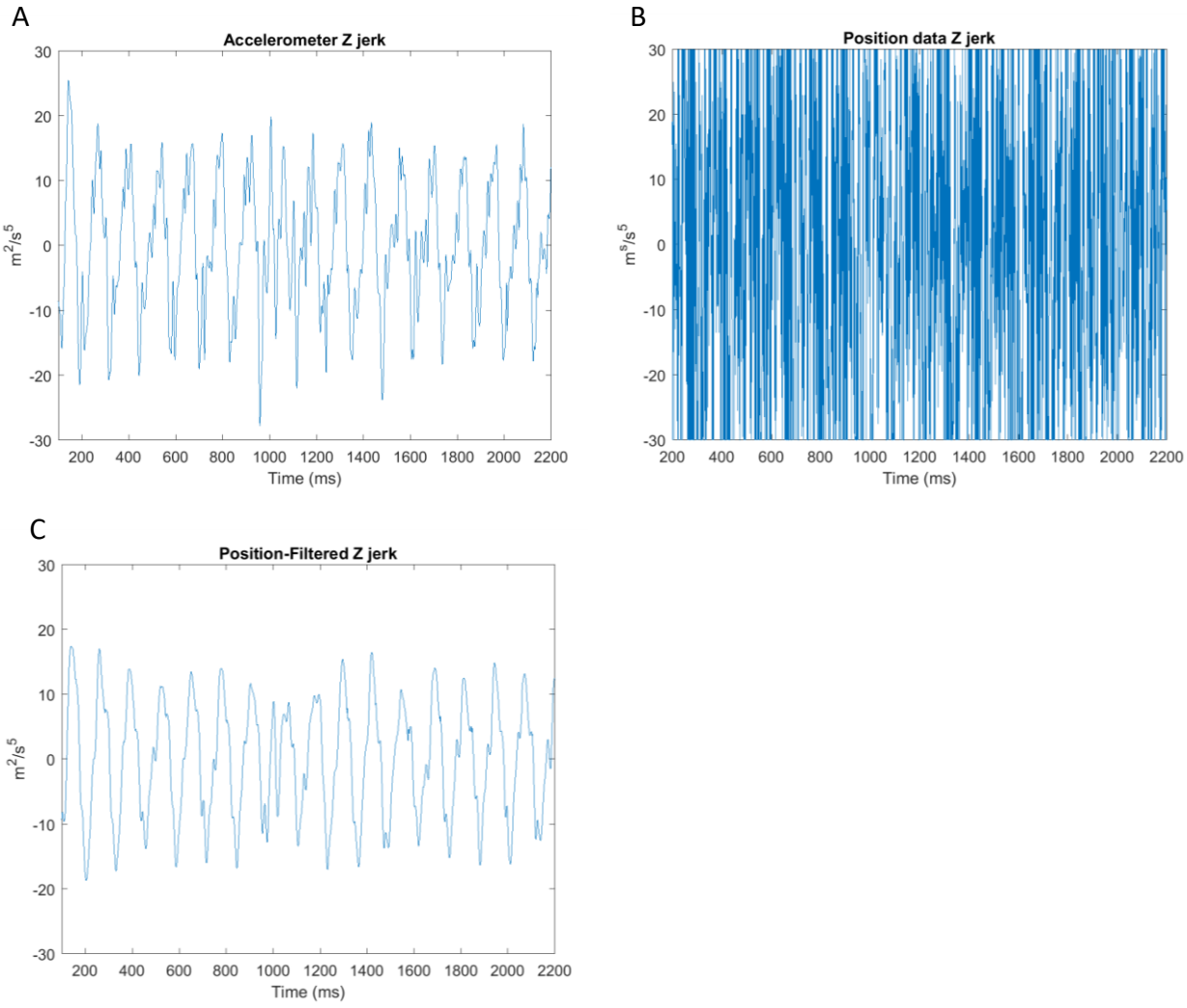

Figure 13 – Comparing arm swing jerk plots between accelerometer derived and position derived data in anterior-posterior (z) direction. A: accelerometer derived jerk plot, B: position data derived jerk without additional filter, C: position data derived jerk with 2nd order Butterworth filter using 1.25 Hz cutoff frequency.

Jerk can be employed and reported in a variety of ways [210], depending on the application. For this study, normalized jerk (NJ) was chosen [211] to account for the variability between subjects' arm movements (T = total time, L = total length).

$$NJ = 0.5 \int_{t_1}^{t_2} [\dddot{x}(t)^2 + \dddot{y}(t)^2 + \dddot{z}(t)^2]\, dt(\frac{T^5}{L^2})$$

All outcome measures were calculated for the left and right side separately, and further categorized into the more and less affected side based on severity of symptom presentation determined by UPDRS scores or self-report. Due to the lack of significant differences between the more and less affected sides, results were collapsed across sides. To test group differences at baseline, each outcome measure during the ST condition was compared between the PDE, PDC and HC groups. Kruskal-Wallis ANOVA was performed between the three subject groups, and Mann-Whitney U tests were performed between the PDE and PDC groups, and the PDE and HC groups.

To assess differences in change over time/intervention, the delta (Δ = EOT – baseline) was computed for all outcome measures (PDE and PDC groups only), and compared between the PDE and PDC groups to assess changes due to the exercise intervention. Shapiro-Wilk normality tests revealed non-normality for over 50% of Δ outcome data, therefore Mann-Whitney tests were conducted for each Δ outcome measure, for each task condition (ST, BACK, SUB, VERB) between the PDE and PDC groups. Comparison between the PDE group at baseline and the HC group, and the PDE group at EOT and the HC group were completed using Mann-Whitney tests.

Cognitive test scores were analyzed for changes in cognition (Δ under ST conditions) and changes due to dual-tasking. In efforts to use cognitive test scores in the manner that clinicians do to assess cognitive changes [212], dual-task difference (DTD) was used. Dual-task difference is simply the raw change in score from ST to DT conditions. Changes due to dual-tasking were also analyzed for all gait outcome measures

for both the PDE and PDC groups. Friedman's ANOVA's were performed first between all four tasks (ST and DT's) in a testing session, and if significance was found, subsequent pairwise Wilcoxon Signed Rank Tests were performed between the ST and each DT condition. The significance level was set at $\alpha=0.05$. All statistical analysis was performed using OriginPro 2017 statistical software (OriginLab Corporation, Northampton, Massachusetts). Due to data integrity standards, some outcome measures have a decreased sample size. Particular outcomes that were deemed inaccurate and unrecoverable were omitted. Sample size for each outcome measure is listed in Appendix C.

4.4 Results

Comparing the PDE and PDC groups at baseline and the HC group, there were significant differences in speed, stance phase, step length, hip ROM, PL, and pelvic obliquity ROM under ST conditions.

Subsequent comparisons of the PDE and PDC groups showed no significant differences at baseline in any outcome measure under ST conditions.

4.4.1 Change from baseline to EOT (Δ)

Of the spatiotemporal measures, significant differences in the change from baseline to EOT between the PDE and PDC groups existed for all measures. Results are listed in Appendix D. The change in self-selected walking speed from baseline to EOT in the PDE group (median = 0.11 m/s) was significantly greater than the Δ walking speed for the PDC group (median = -0.05 m/s), $U = 146.5$, $p < 0.05$ (See Figure 14). The Δ cadence was only significant for the ST condition, with a significantly larger increase for the PDE group (median = 4.52 steps/min) compared to the PDC group (median = -3.00

steps/min), U = 142, $p < 0.05$. The Δ stance phase was significant for the ST, SUB and VERB conditions, with the PDE group showing significant decreases compared to the PDC, and Δ step length showed significant increases for the PDE group compared to the PDC group for all task conditions. Of the lower extremity kinematic measures, there were significant differences in the change from baseline to EOT between the PDE and PDC groups for the ankle, knee and hip joint ROM (See Figure 15). The Δ ankle ROM for the BACK condition was significantly larger for the PDE group (median = 1.52) compared to the PDC group (median = -2.13), U = 153, $p < 0.05$. The Δ knee ROM was significantly larger than the PDC group for both the BACK and SUB conditions, and the Δ hip was significantly larger than the PDC group for all task conditions. Of the trunk and pelvis ROM measures, only Δ trunk rotation ROM showed significance, with the PDE group (median = 1.35) resulting in a significantly larger increase than the PDC group (median = -0.16), U = 135, $p < 0.05$. Of the arm swing measures, no significant differences were observed in changes in PL; however, the Δ NJ was significantly larger for the PDE group compared to the PDC group for the ST, BACK and SUB conditions (See Figure 15).

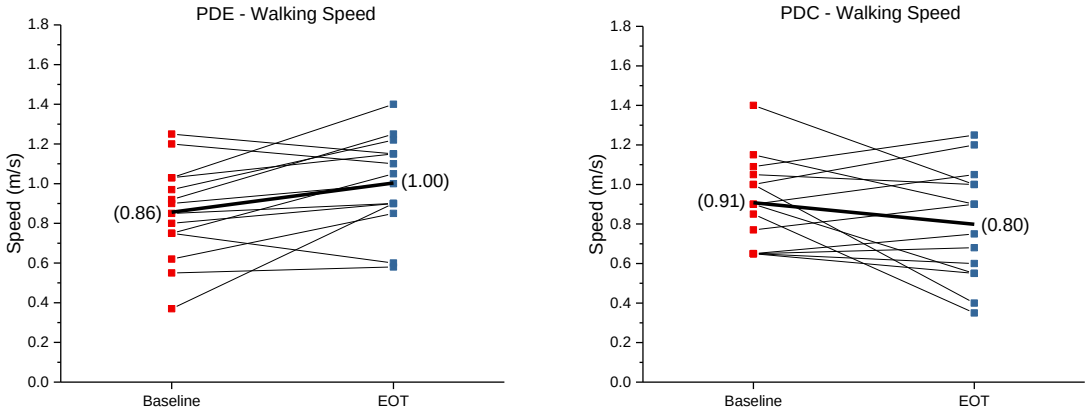

Figure 14 – Average speed for Parkinson's disease exercise (PDE) and Parkinson's disease control (PDC) groups at baseline and EOT.

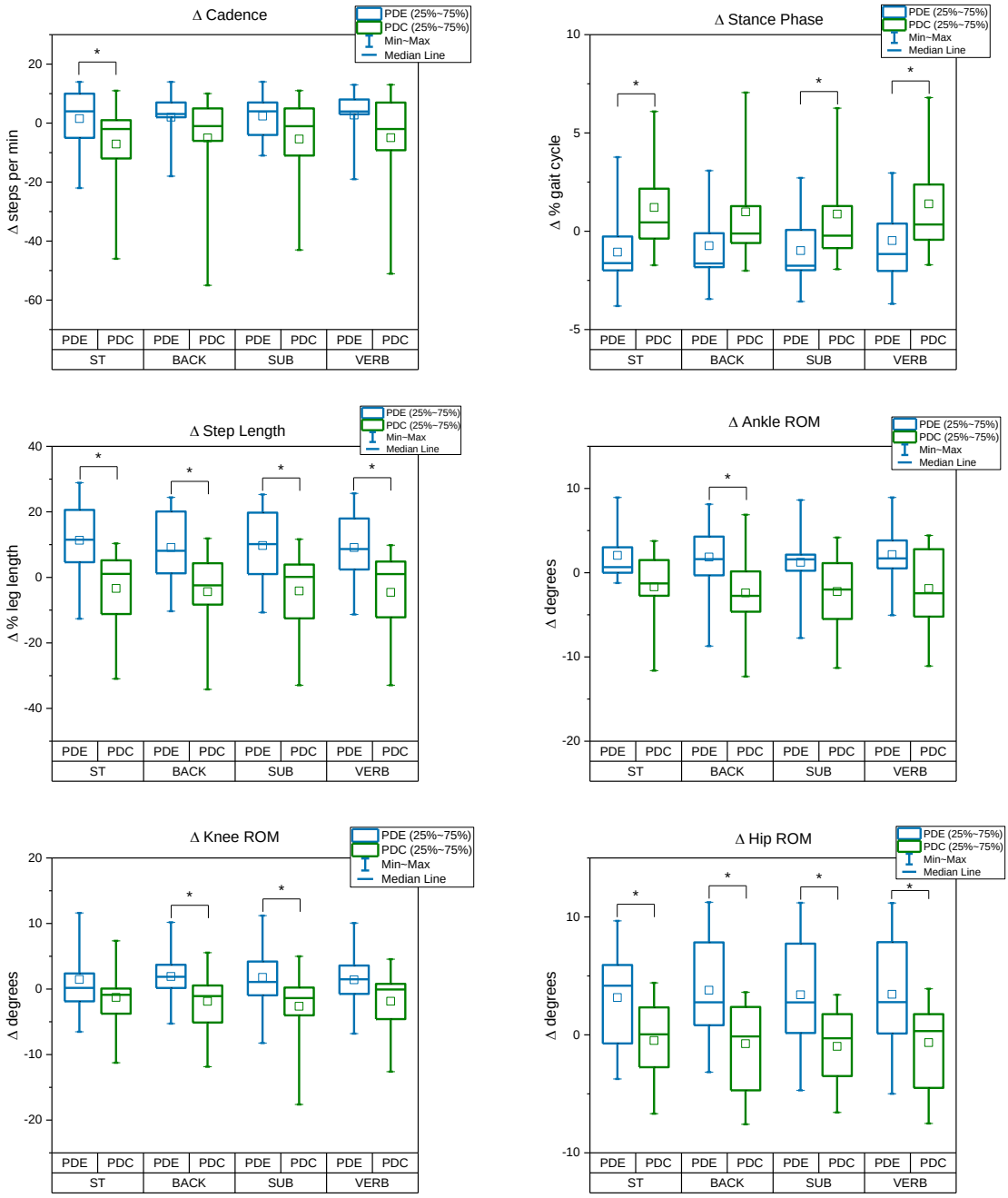

Figure 15 – Median results of change from baseline to end of trial (Δ) for lower extremity measures comparing Parkinson's disease exercise (PDE) and Parkinson's disease control (PDC) groups. ST, single-task; BACK, N-back dual-task; SUB, serial-7 subtraction dual-task; VERB, verbal fluency dual-task; *, significant difference between PDE and PDC groups at $p < 0.05$ level.

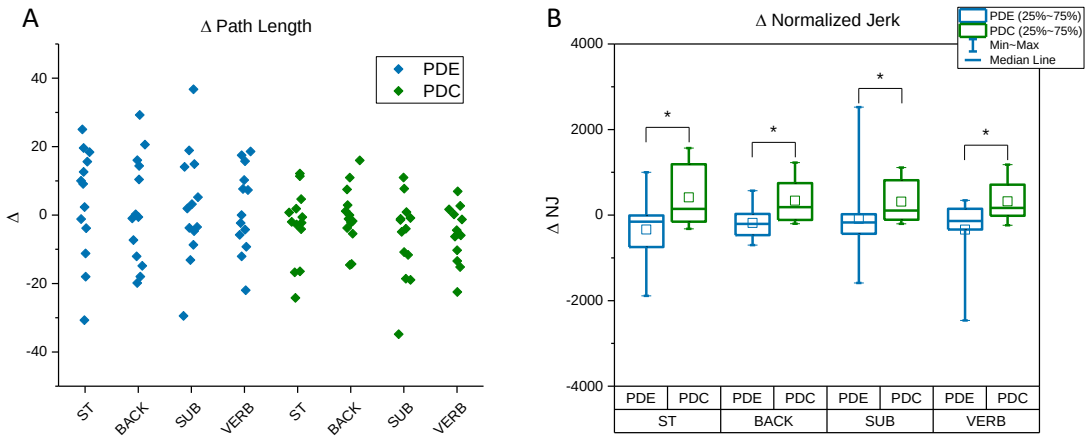

Figure 16 – A) Results of change from baseline to end of trial (Δ) for normalized path length (PL), B) median results of change from baseline to end of trial (Δ) for normalized jerk (NJ). PDE, Parkinson's disease exercise group; PDC, Parkinson's disease control group; ST, single-task; BACK, N-back dual-task; SUB, serial-7 subtraction dual-task; VERB, verbal fluency dual-task; *, significant difference between PDE and PDC groups at $p < 0.05$ level.

4.4.2 Comparison between PDE and HC

Comparison between PDE at baseline and the HC group showed that the PDE group displayed significant gait deficits in speed, cadence, stance phase, step length, knee ROM, pelvic obliquity ROM, pelvic rotation ROM, PL and NJ. When comparing the PDE group at EOT with the HC group, the PDE group maintained gait deficits in pelvic obliquity ROM, PL and NJ, but was no longer significantly different in speed, cadence, stance phase, step length, knee ROM and pelvic rotation ROM (see Figure 17). Results listed in Appendix E.

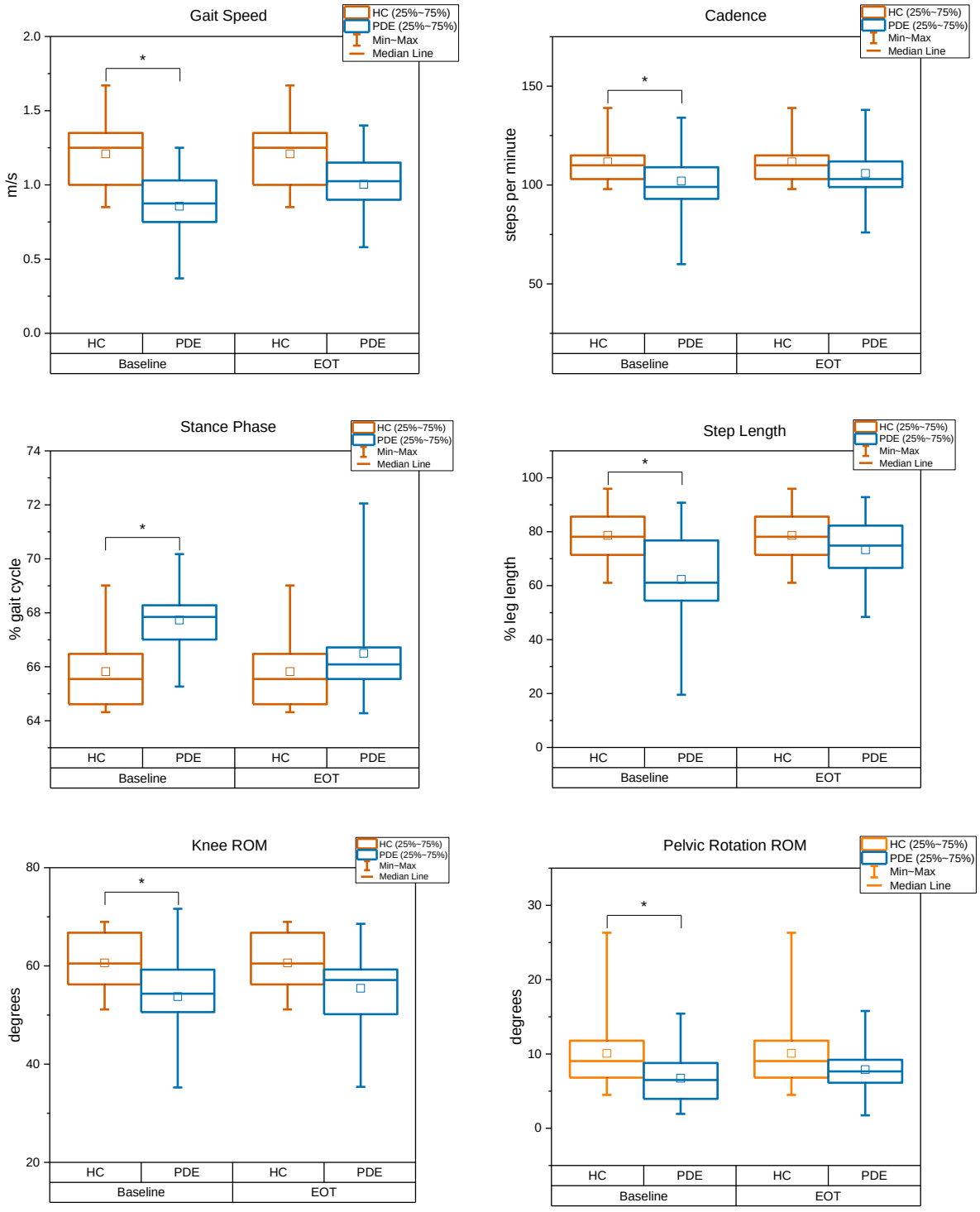

Figure 17 – Median results for comparison between the Parkinson's disease exercise group (PDE) and healthy control (HC) group. ST, single-task; BACK, N-back dual-task; SUB, serial-7 subtraction dual-task; VERB, verbal fluency dual-task; *, significant difference between PDE and HC groups at $p < 0.05$ level.

4.4.3 Change in Variability

There were no significant differences between the PDE and PDC groups in Δ variability for any outcome measure.

4.4.4 Cognitive Test Scores

There were no significant differences between the PDE and PDC groups in Δ under ST conditions for any of the cognitive tasks.

4.4.5 Changes from ST to DT

Differences in outcome measures between ST and DT conditions were present for both the PDE and PDC groups. The PDE group experienced DT declines in cadence, knee ROM and pelvic tilt ROM. The PDC group experienced DT changes in cadence, hip ROM, PL, trunk rotation ROM, pelvic tilt ROM, and pelvic obliquity ROM, results listed in Appendix F.

4.5 Discussion

As anticipated, significant differences were observed between all three subject groups. Subsequent group comparisons between the PDE and PDC groups resulted in an overall lack of significance between the two groups, and comparisons between the PDE and HC groups resulted in significant differences, with the PDE group showing gait declines across most outcome measures. These results are consistent with previous studies [17], [46], [213].

To investigate changes in gait parameters in PD due to a high-intensity cycling intervention compared to changes observed in PD over the same time frame without a prescribed intervention, the Δ was compared between the PDE and PDC groups. The

comparison of the Δ for PDE and PDC groups was intended to account for inter-subject variability and possible improvements due to learning effects. However, in this particular sample group, the PDC group showed no significant change from baseline to EOT.

Not only did the self-selected speed increase significantly for the PDE group compared to the PDC group, but the 0.11 m/s median increase also falls in the minimal clinically important difference range (0.10 – 0.20 m/s) [214]. Under the ST condition, significant improvements were seen in seven out of 13 biomechanical outcome measures. All spatiotemporal measures showed significant improvement, as well as hip and trunk rotation ROM, and NJ. Improvement in lower extremity gait function in those with PD due to an exercise intervention is consistent with previous studies [125], [136], [158], [159], [194], [215]. Although upper extremity gait function is less critical for a successful walking motion and rarely investigated in interventional studies, it can be an indicator of global deficit [54], [124]. Similar to different biomechanical measures describing the quality of walking gait for the lower extremities, PL and NJ demonstrate differences in arm swing function.

Although differences in PL did not reach statistical significance, there was a significant decrease in NJ in the PDE group compared to the PDC group, indicating an increase in smoothness of movement. It has been suggested that declines in arm swing are related to rigidity [216], a symptom affecting all aspects of gait. Therefore, positive changes observed in arm swing may be linked to changes in gait. Furthermore, these changes may be centrally mediated, suggested by the lack of participation of the upper extremity in the intervention [28]–[30], [150]. Crenna et al. suggest that projections from the basal ganglia to the cervical spinal cord are regarded as less evolutionarily crucial as

compared to projections to lumbo-sacral segments, explaining the early appearance of arm swing deficits in PD, as well as its limited improvements due to dopaminergic therapy or deep brain stimulation [58]. Since prioritization of gait function lies with the lower limb first, changes seen in the upper limb may signify a more robust change. Interestingly, the PDE group in Figure 16a shows a collection of individuals reaching higher levels of improvement in PL than what is seen in the PDC group. These results in addition to improvements in NJ, suggest further investigation of the mechanics of arm swing as a result of exercise intervention and its role on overall motor function.

Improvements in gait function due to high-intensity exercise are encouraging in terms of supplementing current treatment methods for PD symptom relief. Understanding how exercise effects gait in objective detail will contribute to the understanding of specific aspects of gait improvement, and how it impacts movements of daily activities. Successful walking is important for individuals to carry out daily tasks safely and effectively. It is well understood that individuals with PD experience increased gait declines under DT conditions, which poses another obstacle for successful walking. Therefore, the presence of significant improvements in gait measures under DT conditions suggests sustained motor improvement, and results that are clinically and practically relevant to the everyday lives of those struggling with PD. All DT conditions showed improvements in spatiotemporal and lower extremity joint kinematics, demonstrating the ability to sustain benefits from exercise across additional cognitive loading across various aspects of executive function.

Changes in arm swing not only manifest with the presence of PD [54], [55], but it can also change under conditions of increased cognitive load [115], [124]. This

connection of a relatively passive movement during gait to neurological function might serve as a marker for centrally mediated changes [28]–[30], [150]. Declines in smoothness of arm swing movement in PD has been shown to worsen under DT conditions, suggesting cognitive loading impacts movement quality [115] as well as magnitude. Similar to lower extremity measures, NJ has shown improvement across ST and two of the DT conditions, suggesting that centrally mediated improvements remain under cognitively taxing conditions.

Due to the significant findings comparing the PDE and PDC group, the results were expanded to compare the PDE group to the HC group. Changes in walking speed typically includes proportional changes in overall biomechanics, such as joint angles and step length [217]. Therefore, increases in biomechanical measures are to be expected as walking speed increases. With PD however, the gait patterns are not simply characteristic of slowed gait. The combination of decreased speed with little to no change in cadence, decreased joint ROM, increased stance phase and decreased step length indicate a trademark pattern of walking known as “shuffle gait” [213]. Compared to the HC group, the PDE group at baseline walked significantly slower, spent a larger portion of the gait cycle with both feet on the ground in stance phase, and had smaller step lengths. This indicates that the PDE group took smaller, quicker steps than healthy peers, and had less overall knee ROM.

The change in gait characteristics exhibited by the PDE group were not only significant compared to the PDC group, but they were also particularly interesting when compared to healthy older adults. As mentioned, the PDE group demonstrated typical PD related gait deficits compared to the HC group. At EOT, the PDE groups not only

improved, but they also were no longer significantly different from the HC group in gait speed, cadence, stance phase, step length and knee ROM. This is similar to the effects of dopaminergic therapy for some studies [11], [12], and shows greater improvement than others [46], [47]. Exercise studies with animal models have shown increased neurotrophic factors, such as brain- and glial-derived neurotrophic factors (BDNF and GDNF), contributing to neuroprotection of existing nigrostriatal pathways, and regeneration of dopaminergic axons [218]. Detailed structural and chemical neural changes due to exercise are difficult to obtain and corroborate with animal model results; however, peripheral BDNF has been shown in increase in human exercise studies [218]. The results of this study mimicking the effects of dopaminergic medication while "off" medication may be explained by these previous findings. Arm swing function, however, remains significantly worse in PD than HC, even after intervention. Further studies are warranted to investigate arm swing as it relates to alternative treatments for PD.

The results of this study coincide with previous studies regarding decreased motor function under DT conditions in PD [109]–[111], [119]. Despite the regularity of the speed of the treadmill potentially providing external cuing and regulating walking patterns [219], significant changes occurred. Interestingly, cadence increased significantly in all three DT conditions for the PDE group at baseline and EOT, even though the speed maintained the same from ST to DT. The PDC group also experienced significant increases in cadence at EOT testing. Step length and stance phase also followed patterns of decline under DT conditions, however these measures did not reach significance. In previous studies, gait declines under DT conditions include changes in speed [111], [114], [220]–[222], which cannot decipher whether the declines are due to

general slowed walking speed, or gait characteristics are actually changing. The results found in this study suggest that changes in gait performance from ST to DT conditions signifies a change in gait pattern, independent of gait speed. Changes in upper extremity independent of speed, under DT conditions has been found in previous studies [115], [124], and now the decoupling of lower extremity measures adds greater understanding to the breakdown of the interconnected rhythmic nature of walking when cognitive loading in increased.

The CV outcome measures did not result in any significant differences. The predicted cause of this finding is similar to the DTC findings. The constant speed of the treadmill may have regulated gait movements, therefore altering any potential changes in variability [219].

The results of the cognitive test scores were contradictory to the hypothesis predicting increases in cognitive function, as well as changes in dual-tasking strategies. A "posture second" DT strategy is common with PD, where individuals prioritize the cognitive task over the motor task. The safety features of the CAREN system may have contributed to a feeling of security, therefore allowing subjects to adhere to a posture second strategy.

CHAPTER V: Conclusion

Gait and balance measures have shown improvements after a high-intensity cycling exercise intervention in PD. Balance recovery after a perturbation has shown a decrease in COPex, suggesting less compensatory movements and, potentially, improved balance control. Walking also showed marked improvements in speed and quality of gait movement under both ST and DT conditions.

The ability to recover from destabilization is essential for avoiding falls and injury. People with PD have an increased fall risk compared to healthy older adults [77], therefore efforts to decrease the risk of falling and resultant injuries are particularly important in the PD population. Since dopaminergic therapy cannot be relied upon to aid in balance improvement [47], [68], other therapies and interventions need to be investigated for their potentials in improving dynamic postural stability. The results from this study point towards positive effects from exercise intervention, suggesting that the neural effects of exercise impact non-dopaminergic pathways. The effects of Lewy bodies on PD symptoms is not as prominently studied as the effects from basal ganglia dysfunction, yet it may point to discrepancies between dopaminergic therapies and remaining symptoms [40]. Brain-derived neurotrophic factor increases in the central nervous system after aerobic exercise, and has a positive effect on synaptic plasticity [223]. Although research investigating the effects of exercise on Lewy bodies in the brain is sparse [224], the results from this study suggest further investigation.

Spatiotemporal outcome measures are common to describe biomechanical data; however, jerk has shown to provide additional information about movement quality, especially in PD [115], [225]. Jerk has shown to differentiate PD patients from healthy controls in static balance studies [226]–[228], and with the addition of marker data to a perturbation study on the CAREN system, this knowledge could be expanded to include jerk under dynamic balance conditions.

In addition to balance recovery, healthy gait function is also important for fall avoidance. Safe, successful gait not only minimizes injury, it can increase self-efficacy for physical activity in older adults and encourages continual physical activity [229].

Conscious gait strategies have proven successful in improving gait in PD such as external cueing and thoughtful stepping [230]; however, everyday situations do not always lend themselves to gait focused thoughts while traversing. The ability to complete a cognitive task while walking is crucial to daily activities, even tasks as simple as remembering a room number while walking through a large building. Compensatory gait strategies that require additional cognitive resources risk competing with the cognitive tasks commonly encountered in real world situations, leaving either the cognitive task or gait function to suffer. Parkinson's disease medications provide symptom relief and help deter gait declines; however, these declines may still be present with dopaminergic medication [11], [46], [47]. The abstract nature of stationary cycling translating to balance and upper extremity improvements suggests neural changes worth further exploration. The ease of execution and positive side effects of high-intensity cycling make for an attractive supplemental PD treatment option.

High-intensity exercise interventions that demonstrate improved function in "off" medication conditions may potentially have an additive affect to levodopa/carbidopa medications, as suggested from increases in motor functions while "on" medication, seen in previous studies [158], [159], [194]. The potential structural improvements in nigrostriatal projections from an exercise intervention [218] may increase motor function improvements when coupled with additional dopamine via medication. To better understand the effects of intervention on specific balance recovery and gait parameters, future studies are needed that include analysis under both "off" and "on" conditions.

The resources necessary for detailed motion capture analysis are not attainable nor feasible for a wide population of individuals. Efforts are being made to enable small,

portable technology to provide specific measures that can infer gait function [231]–[233] which can expand the usage of gait function as a clinical tool. As the understanding of the implications of arm swing develops, it has the potential to provide valuable information for gait analysis [115], [124] in a concise manner. The results from this study suggest that further investigation of arm swing as it relates to gait, cognition, and interventions is warranted.

Limitations exist within this project. The PD population for both exercise and control groups were comprised of mild to moderately affected individuals, and it is unclear if a more severe population would demonstrate different results from an exercise intervention. Information concerning the presence of clinical cognitive impairment was not collected, which may have shown a relationship in different cognitive test abilities. During balance data collection with the Time to Stable application, some participants took a step to catch their balance, or grabbed onto the handrails. It was instructed to avoid these movements and return to their original position as quickly as possible if this does occur; however, suppressing these automatic responses was difficult for some individuals. Steps or handrail grabs were recorded manually, however no correction or data segregation was made based on these actions. Future studies could investigate potential differences in trials with catching actions versus those without. Marker occlusion of some degree was present in most gait trials. Much of this was corrected within the HBM, or was fixed manually via post processing; however, some data was lost. Most of the marker occlusion was a result of clothing coverage. Future studies should provide motion capture suits to ensure the best methods of data collection.

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APPENDICES

APPENDIX A

Time to Stable outcome data

	Baseline Acceleration Level (m/s^2)			EOT Acceleration Level (m/s^2)		
Group	**0.25**	**0.5**	**1.0**	**0.25**	**0.5**	**1.0**
PDE	3.04	4.58 [a]	4.30 [a]	2.73	3.17 [c]	3.44 [a]
PDC	4.30	5.98	5.05 [a]	3.65	3.71	4.61
HC	2.91	3.72	4.84			

	PDE Acceleration Level (m/s^2)			PDC Acceleration Level (m/s^2)		
Outcome	**0.25**	**0.5**	**1.0**	**0.25**	**0.5**	**1.0**
ΔTTS	-0.15	-1.61	-0.64	-0.70	-1.03	-0.43

Median results in seconds. PDE, Parkinson's disease exercise group; PDC, Parkinson's disease control group; HC, healthy control group; ΔTTS, change in Time to Stable from baseline to end of treatment; x^a, significant difference compared to 0.25 of same session; x^b, significant difference compared to 0.5 of same session; x^c, significant difference compared to baseline, significant at 0.05 level.

APPENDIX B

Center of pressure excursion data

Acceleration Level	PDE Baseline	PDE EOT	PDC Baseline	PDC EOT	HC
0.25 m/s^2	1.79 (0.33)	1.67 (0.36)	1.63 (0.22)	1.64 (0.38)	1.88 (0.29)
0.5 m/s^2	2.03 (0.40)	1.69 (0.36)	1.69 (0.29)	1.64 (0.37)	1.95 (0.25)
1.0 m/s^2	1.92 (0.33)	1.84 (0.44)	1.78 (0.26)	1.61 (0.28)	2.13 (0.17)

Mean (SD) results in meters. PDE, Parkinson's disease exercise group; PDC, Parkinson's disease control group; HC, healthy control group; EOT, end of treatment.

APPENDIX C

Sample size of biomechanical outcome measures

	PDE				PDC				HC			
Δ	**ST**	**BACK**	**SUB**	**VERB**	**ST**	**BACK**	**SUB**	**VERB**	**ST**	**BACK**	**SUB**	**VERB**
Gait speed (m/s)	14				14				14			
Cadence (steps/min)	14	14	14	14	14	14	14	14	14	14	14	14
Stance Phase (% gait cycle)	14	14	14	14	14	14	14	14	14	14	14	14
Normalized step length (step/leg length)	12	13	13	13	14	14	14	14	14	14	14	14
Ankle ROM (degrees)	14	14	14	14	14	14	14	14	14	14	14	14
Knee ROM (degrees)	14	14	14	14	14	14	14	14	14	14	14	14
Hip ROM (degrees)	14	14	14	14	14	14	14	14	14	14	14	14
Trunk rotation ROM (degrees)	13	13	13	13	14	14	14	14	14	14	14	14
Pelvic tilt ROM (degrees)	14	14	14	14	14	14	14	14	14	14	14	14
Pelvic obliquity ROM (degrees)	14	14	14	14	14	14	14	14	14	14	14	14
Pelvic rotation ROM (degrees)	14	14	14	14	14	14	14	14	14	14	14	14
Normalized PL (PL/arm length)	13	13	13	13	13	13	13	13	14	14	14	14
Normalized jerk	13	13	13	13	13	13	13	13	14	14	14	14

Right and left sides were collapsed when applicable, out of 14 participants maximum. PDE, Parkinson's disease exercise group; PDC, Parkinson's disease control group; HC, healthy control group; PL, normalized path length; NJ, normalized jerk; ROM, range of motion; CV, coefficient of variation; ST, single-task; BACK, N-back dual-task; SUB, serial-7 subtraction dual-task; VERB, verbal fluency dual-task.

APPENDIX D

Change from baseline to EOT outcome measures

	PDE				PDC			
Δ	**ST**	**BACK**	**SUB**	**VERB**	**ST**	**BACK**	**SUB**	**VERB**
Gait speed (m/s)	0.11				-0.05 *			
Cadence (steps/min)	4.52	3.05	3.00	3.64	-3.00 *	-0.51	-0.52	-2.01
Stance Phase (% gait cycle)	-1.69	-1.27	-1.58	-1.43	0.46 *	0.04	-0.10 *	0.36 *
Step length (% leg length)	11.49	7.73	7.13	8.50	-0.19 *	-3.24 *	-2.01 *	-1.31 *
Ankle ROM (degrees)	0.65	1.52	1.36	1.87	-0.52	-2.13 *	-1.94	-2.26
Knee ROM (degrees)	1.19	1.93	1.94	2.09	-1.05	-1.80 *	-1.51 *	-0.77
Hip ROM (degrees)	3.04	2.03	2.56	2.56	-0.44 *	-0.23 *	-0.51 *	-0.02 *
Trunk rotation ROM (degrees)	1.35	2.15	1.66	1.79	-0.16 *	-0.23	-0.73	0.25
Pelvic tilt ROM (degrees)	-0.27	-0.60	-0.24	-0.17	2.07	2.65	1.99	2.61
Pelvic obliquity ROM (degrees)	-0.37	-0.20	-0.01	-0.03	-0.12	-0.81	-1.02	-0.55
Pelvic rotation ROM (degrees)	0.79	0.61	0.36	0.46	1.06	0.11	0.44	0.96
PL (% arm length)	9.12	-0.56	1.92	-0.01	-1.97	-1.11	-4.00	-5.43
NJ	-144.98	-83.23	-151.91	-128.00	297.33 *	214.81 *	157.84 *	206.94
CV Stance phase	0.02	-0.47	-0.42	-0.51	-0.21	-3.60	-0.50	-0.18
CV Step length	-0.07	-1.41	-1.60	-1.30	-0.10	-0.23	0.32	0.18
CV Ankle ROM	-0.80	-0.75	-0.42	0.44	0.68	-0.99	-0.01	0.26
CV Knee ROM	-0.16	-0.40	-0.26	-0.29	0.64	-0.45	0.09	0.32
CV Hip Rom	-1.21	-0.96	-0.93	-0.36	0.23	-1.04	-0.46	0.15
CV PL	-2.07	0.28	1.88	-1.13	-1.04	1.28	-2.60	-0.21

Median results. PDE, Parkinson's disease exercise group; PDC, Parkinson's disease control group; HC, healthy control group; PL, normalized path length; NJ, normalized jerk; ROM, range of motion; CV, coefficient of variation; ST, single-task; BACK, N-back dual-task; SUB, serial-7 subtraction dual-task; VERB, verbal fluency dual-task; *, significant difference between PDE and PDC groups at $p < 0.05$ level.

APPENDIX E

Comparison between Parkinson's disease exercise and healthy control groups

Outcome measure	PDE - baseline	PDE - EOT	HC
Speed (m/s)	0.875	1.03	1.25 [a]
Cadence (steps/min)	99.01	103.00	109.99 [a]
Stance Phase (% gait cycle)	67.85	66.09	65.54 [a]
Step length (% leg length)	61.10	74.90	78.12 [a]
Ankle ROM (degrees)	28.46	28.73	31.37
Knee ROM (degrees)	54.35	57.13	60.49 [a]
Hip ROM (degrees)	37.45	39.98	42.38
Trunk rotation ROM (degrees)	12.02	13.24	17.23
Pelvic tilt ROM (degrees)	4.09	4.08	4.95
Pelvic obliquity ROM (degrees)	6.46	6.65	9.11 [a,b]
Pelvic rotation ROM (degrees)	6.50	7.65	9.05 [a]
PL (% arm length)	43.50	54.39	91.62 [a,b]
NJ	1815.81	1786.51	1402.74 [a,b]

PDE, Parkinson's disease exercise group, PDC, Parkinson's disease control group; HC, healthy control group; PL, normalized path length; NJ, normalized jerk; ROM, range of motion; x^a, significant difference compared to PDE at baseline; x^b, indicates significant difference compared to PDE at EOT, significance at $p < 0.05$ level.

APPENDIX F

Dual-task effects, PDE and PDC groups

PDE

	Baseline				EOT			
	ST	**BACK**	**SUB**	**VERB**	**ST**	**BACK**	**SUB**	**VERB**
Cadence (steps/min)	99.01	104.48 *	101.51 *	104.01 *	103.00	108.50 *	105.00 *	109.00 *
Stance Phase (% gait cycle)	67.85	67.23	67.32	67.35	66.09	66.16	65.79	65.96
Step length (% leg length)	61.10	58.81	59.66	58.09	74.86	70.00	72.87	70.90
Ankle ROM (degrees)	28.46	27.46	27.59	28.11	28.73	29.17	28.48	28.80
Knee ROM (degrees)	54.35	53.14 *	53.06	52.30	57.13	56.10 *	57.45	55.84 *
Hip ROM (degrees)	37.45	36.82	38.26	37.42	39.98	38.48	39.06	38.13
Trunk rotation ROM (degrees)	11.20	9.78 *	10.53	10.17 *	13.24	12.50	12.21	12.25
Pelvic tilt ROM (degrees)	4.09	4.27	4.45	4.12	4.08	3.59	3.89	3.96
Pelvic obliquity ROM (degrees)	6.46	5.89	6.43	5.83	6.65	6.57	7.13	6.70
Pelvic rotation ROM (degrees)	6.50	5.95	6.29	5.66	7.65	7.18	7.51	7.33
PL (% arm length)	43.50	29.94	30.45	28.25	54.39	43.82	41.43	38.62
NJ	1815.81	1816.62	1975.04	2045.72	1786.51	1739.88	1945.70	1849.99

PDC

	Baseline				EOT			
	ST	**BACK**	**SUB**	**VERB**	**ST**	**BACK**	**SUB**	**VERB**
Cadence (steps/min)	106.98	107.49	105.48	106.98	98.46	104.48 *	100.49	102.49
Stance Phase (% gait cycle)	65.97	65.98	66.68	65.98	66.30	66.14	66.21	66.03
Step length (% leg length)	60.55	61.86	61.00	63.02	53.49	50.90	52.08	54.96
Ankle ROM (degrees)	28.17	28.00	29.15	28.50	26.94	24.70	26.22	25.75
Knee ROM (degrees)	55.51	55.96	55.80	55.97	55.11	53.81	54.63	54.21
Hip ROM (degrees)	35.66	34.59	33.84	34.13	34.80	33.75 *	32.75 *	33.27 *
Trunk rotation ROM (degrees)	11.70	9.98	9.67	10.79	10.68	8.61	10.26	10.04 *
Pelvic tilt ROM (degrees)	4.89	4.89	5.06	4.89	4.64	4.38	4.38	4.35
Pelvic obliquity ROM (degrees)	5.48	5.58	6.20	5.72	5.07	4.82 *	4.92 *	4.96
Pelvic rotation ROM (degrees)	5.75	5.50	6.71	6.13	6.95	6.39	6.58	6.52
PL (% arm length)	45.40	35.46 *	33.71	37.87	42.03	26.91 *	26.66	26.82 *
NJ	1559.58	2089.28	2303.49	2366.72	1744.00	2870.67	2618.71	2914.70

Median results. PDE, Parkinson's disease exercise group; PDC, Parkinson's disease control group; HC, healthy control group; PL, normalized path length; NJ, normalized jerk; ROM, range of motion; ST, single-task; BACK, N-back dual-task; SUB, serial-7 subtraction dual-task; VERB, verbal fluency dual-task; *, significant difference between task and ST condition of same session at $p < 0.05$ level.