

ACUTE EFFECT OF INTENSE EXERCISE ON RHYTHMIC
GAIT IN PERSONS LIVING WITH EARLY PARKINSON'S DISEASE

A Thesis

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by

Megan Joanna Avilla

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Abstract
of
ACUTE EFFECT OF INTENSE EXERCISE ON RHYTHMIC
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Introduction

Parkinson's Disease (PD) is the second most common neurological disease following Alzheimer's Disease. It is progressive in nature involving neurodegeneration and neuronal death primarily in the basal ganglia. Among the many sequella of the disease, one of the most debilitating is the development of an Parkinsonian gait: hunched posture, muscular tremors, shuffling, increased gait velocity and a decrease or lack of arm swing. Current management of the disease involves the use of pharmaceuticals mimicking the neurotransmitter dopamine. Management of the disease may also come from other sources alongside pharmaceuticals in the form of exercise. Recent research on the effects of high intensity exercise training on the brain in both the normal aging population (Colcombe *et al*, 2003; Colcombe *et al*, 2006) and in Parkinson's patients (Fisher *et al*, 2008; Hirsch *et al*, 2003; Ridgel *et al*, 2009) have found that high intensity exercise increases brain plasticity, blood flow and brain volume. The purpose of this study was to determine whether intense exercise, at a predetermined target heart rate, on a stationary bicycle improves rhythmic gait immediately post activity in persons with early staged Parkinson's Disease. It was predicted that exercise will improve gait rhythmicity as evidenced by consistent stride length, gait velocity and increased toe clearance during the testing period.

Methodology

Testing protocol was approved by the Sacramento State University (CSUS) IRB department and the Kinesiology Graduate department. Three mild to moderate idiopathic Parkinson's diagnosed adults were recruited and cleared via a local primary care physician. Prior to participation subjects completed a Health History Questionnaire and a Mini-Mental Examination. Functional mobility was tested with a Timed Up and Go test. Gait Analysis was tested in the Biomechanics Laboratory at CSUS. Protocol involved riding a stationary Monarch bicycle with a 5 min warm-up, an exercise set of 20 minutes, and a 2 minute cool down. The heart rate reserve method was used to measure target heart rate was calculated based on prior stress test for clearance. Immediate post exercise, gait was once again tested motion capture cameras in the laboratory. A repeated measures test (dependent t-tests) was used to help determine the effect of intense exercise on comparing toe clearance, stride length, gait speed during level walking. Mean and standard deviation between pre and post trials are listed.

Results

Subjects were classified in stage 2.3 of the Hoehn and Yahr scale. Average years of diagnoses at 6.33 ± 1.6 years. All subjects reached target heart rate percent of 60-80% predetermined max heart rate (100.23 ± 11.77)% heart rate reserve. Average gait velocity pre exercise intervention was 0.802m/s, post average gait velocity was 0.798m/s. Average percent change in gait velocity - 5.488%. Average stride length pre exercise intervention 0.942m. Average stride length post exercise intervention was 0.959m. Stride length percent change was 1.655%. Mean toe clearance pre exercise intervention was 0.0853m. Post exercise intervention, mean toe clearance was 0.079m. Toe clearance percent change was -8.98%.

Conclusion

All subjects were able to meet the demands of the exercise intensity for the length of the exercise protocol. All subjects had an increase in stride length. Lack of access to MRI scanners leaves the conclusions for the changes seen in gait as hypothetical changes in the brain. Changes in gait from pre to post exercise have been proposed to be a result of a 'carry-over' of a smooth cyclical rhythm from movement to another. Changes gait strategy are also proposed as possible means of change. This research study is a pilot study and has opened the door to more questions to be answered.

_____, Committee Chair
David Mandeville, PhD.

Date

DEDICATION

Writing a thesis is a daunting task. I have realized it requires much courage, perseverance, frustrating moments of writers block, disappointment, inspiration and most importantly, integrity. I would like to thank:

Mom and dad for their love and support

Aunt Lani and Uncle Steve, without them I would not be where I am at today

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Chapter 1

INTRODUCTION

Parkinson's Disease (PD) is a progressive disease that is marked by neurodegeneration of the Central Nervous System and brain, causing hypokinesia. Parkinson's Disease is the second most common neurological disease following Alzheimer's Disease, affecting nearly 1 to 1.5 million Americans (~4% of the population over 65 years of age) with on average 50,000-60,000 new cases diagnosed each year (Alberts, 2011; McGovern Institute, 2012; Statistics on Parkinson's, 2012). It is estimated that these numbers will double by the year 2030 (Alberts, 2011; Gracies, 2011; McGovern Institute, 2012; O'Brien, 2009; Statistics on Parkinson's, 2012). As reported by the United States National Institute for Neurological Disorders and Stroke (NINDS) in 2006, the total number of cases in the United States is estimated to be at least 50,000; however, this number is inconclusive as the disease is not normally diagnosed until it reaches the more advanced stages (McGovern Institute, 2012). Parkinson's Disease is generally marked by a loss in dopamine neurons which eventually lead to loss in gait automaticity, with symptoms including muscle tremors, bradykinesia, spinal rigidity, postural instability, loss in bone integrity and muscular atrophy (Alberts, 2011; Hirsch, 2009; Sofuwa, 2005). As a result of these symptoms, the risks for falling in Parkinson's patient have disabling consequences such as hip fractures, head trauma, psychological fear of falling (causing a reduction in mobility), weakness, muscular atrophy and an increased risk of cardiovascular disease and osteoporosis. There is no known cure for the disease, yet it can be managed from other sources alongside pharmaceuticals, including but not limited to: exercise, physical therapy and nutrition.

Problem

The cost impact of those living with Parkinson's Disease is substantial. As the disease progresses, people living with Parkinson's are less able to take care of themselves and will require additional care from family and caregivers alike. PD patients are admitted to the hospital more frequently and for a longer duration than the general population (Gerlach, 2011). Various reports have been made on the economic cost of Parkinson's in the United States. According to the report by NINDS, the estimated US economic cost in 2006 exceeds \$6 billion (McGovern Institute, 2012). Alberts (2011) estimates the costs for annual treatment approaches close to \$25 billion. Huse DM (2005) estimates the direct cost to be about \$23,101 per patient (about \$23 billion cost to the US nation annually). O'Brien (2009) estimates the total cost to be \$21,626 per patient (about \$10.78 billion per year cost to the nation). In Europe, Gustavsson (2010) estimates the cost to be €13.9 billion.

A reduction in quality of life (QOL) is a consequence for persons living with PD. Falls are disabling, recurrent (up to 51% have been recorded to have more than one fall per year) and a common problem within PD (Tomlinson, 2012). Besides sustaining injury and death, other consequences of falling include disability, restriction of activity, fear of falling, reduced quality of life and independence, loss of confidence, hesitancy, tentativeness and resultant loss of mobility (Lord *et al*, 2001). Parkinson's patients are at an increased risk of falling due to the symptoms associated with the disease: spinal and gait rigidity, shuffling gait, muscular stiffness, freezing, stooped posture, balance impairment and sometimes side effects of medications (Fall prevention in Parkinson's Disease, 2012). Psychologically, falls tend to increase a PD patient's reluctance to perform activities of daily living (ADL). According to the Parkinson's Disease Foundation, research has found that PD are more prone to falling at home than elsewhere (Fall prevention in Parkinson's Disease, 2012). For many years, exercise has not been a recommended strategy for

person's living with Parkinson's Disease. Yet recent studies have shown that exercise may prove to be a new form of rehabilitative intervention alongside pharmaceuticals.

Research Solutions

An accidental discovery by Cleveland Clinic's Parkinson's researcher and biomedical engineer, Dr. Jay L. Alberts, has helped sparked interest in the link between exercise research and PD. In 2003, Dr. Alberts, rode a tandem bike across Iowa with a friend diagnosed with PD. According to Dr. Alberts, the purpose of the trip was to show that people diagnosed with PD can still live an active life (Reid, 2012). Following the first day of strenuous cycling, the PD patient was able to write her signature clearly (Reid, 2012). The conclusion and subsequent research has found that forced exercise in the form of pairing a PD patient with a healthy cyclist on a tandem bike resulted in improvement in motor function in both the upper and lower extremities, improved bilateral fine motor functioning in the fingers, and an increase in brain activation seen on functional magnetic resonance imaging (fMRI) data (Anderson, 2009). The increased brain activation yields similar results to that found with the drug Levodopa, used by many Parkinson's patients. Forced exercise (FE) in the form of augmented mechanically aerobic exercise, with the patient actively participating in the movement, have led to an alteration to the Central Nervous System (CNS) function, also known as neuroplasticity (Alberts, 2011; Hirsch, 2009). In the case of Parkinson's Disease plasticity can take place in the synapse, the space between neurons that allow for communication between nerves through neurotransmitters. Since the original discovery by Dr. Alberts, indoor cycling programs have become popular for persons living with Parkinson's; and non-profit organizations such as Pedaling for Parkinson's have become affiliated with the YMCA (Reid, 2012).

Other research studies have looked at the effects of intense exercise on brain plasticity in the Parkinsonian brain and multiple studies have shown that exercise, in Parkinson's animal

models, helped to maintain the stability and handling (use vs. storage) of dopamine in the synapse, as well as increase the number of dopamine D2 receptors which are associated with the initiation of signaling pathways controlling motor circuit connections within the basal ganglia, and thereby improving gait, motor movement, and mood (Petzinger *et al*, 2007).

It has been thought that medicine is required to be given or performed external to the body in order to treat and prevent disease. In 2008 the American College of Sports Medicine initiated a global approach for health care providers termed Exercise is Medicine, in the hopes that exercise will be promoted and monitored by providers. With the increase in knowledge on the benefits of physical activity, medicine may come from a more attractive source of applied science: exercise. It is well known that exercise elicits physiological changes on the body such as lower resting heart rate and blood pressure, decrease in body mass, better sense of well being, improved metabolism, decreased risk of depression and improved blood flow and capillary density. In the brain, exercise increases brain plasticity, blood flow, capillary density and promotes neurogenesis, angiogenesis and synaptic plasticity.

Purpose

The purpose of this study was to determine whether intense exercise, at a predetermined target heart rate, on a stationary bicycle improves rhythmic gait immediately post activity in persons with early staged Parkinson's Disease. It was predicted that exercise will increase stride length, gait velocity and toe clearance during the testing period as a result of plasticity in the brain.

Limitations

As a pilot study, there are multiple limitations impacting the results of this study including: stringent exclusion criteria, small sample size, lack of blood assay use, lack of MRI scanners, variability of the disease, prescreening protocol.

Definition of Terms

Dopamine - neurotransmitter

Gait velocity – speed of one gait cycle in meters per second

Heart Rate – number of ventricular beats per minute

Neuroplasticity – ‘brain remodeling’. Can be broken down into angioplasty, neuroplasticity and synaptic plasticity

Stride length – one full gait cycle measured in meters

Toe clearance – height of toe during swing phase of gait cycle, measured in meters

Chapter 2

REVIEW OF LITERATURE

Idiopathic disease, such as Parkinson's disease (PD) has no known etiology (cause). Several proposed methods of etiology include biochemistry, environment, medication reactions, drugs, excitotoxicity (excessive stimulation of neurotransmitters), oxidative stress, deficiency of neurotrophic factors, mitochondrial defects, genetic factors, and infections. With an unknown etiology, the cure is just as elusive. Therapy and management of the disease have become an immediate priority when working with patients: physiotherapy, medications, surgery, and recently, intense exercise for neuroprotection. Since the original publication on the "shaking palsy" in 1817 by Dr. James Parkinson, the progressive nature and the neurophysiology of the disease is now better understood. In essence, PD is a progressive neurodegenerative disease affecting the volitional mobility of the human body. Much research is attributed to identifying the biomarkers for the disease as well as finding ways for individuals living with the disease maintain an independent lifestyle for as long as possible.

Neurophysiology and Neurodynamics

The phenomenon that sets human beings apart from other mammalian species is the ability to perform and complete single and sequential movements and patterns or thoughts of intellect. This is completed and orchestrated through the coordination of the nervous system and the brain (Brooks, Fahey & Baldwin, 2005; Petzinger *et al*, 2009). Electrophysiological imaging and dissections of the brain have allowed researchers and scientists insight into how the brain works. The human brain is composed of four major

areas: cerebrum, diencephalon, cerebellum and brainstem. When viewed superiorly, the cerebrum is divided into two halves (right and left cerebral hemispheres) and each hemisphere can be further divided into four superficial lobes: frontal lobe, parietal lobe, occipital lobe and the temporal lobe; there is an additional fifth lobe located inside the brain: the insula. The primary control of movement in the brain is found in the motor cortex, found on the posterior portion of the frontal lobe. Research on various types of hyperkinetic (excessive abnormal movements) and hypokinetic (recessive bodily movements) disorders; have shown that movement initiation and termination is known to be controlled by subcortical (below the <cerebral> cortex) nuclei in the midbrain (Coleman, 2012). A nuclei is a cluster of nerve and soma cells acting as a functional and cohesive unit.

Loss of the neurotransmitter (chemical messenger) dopamine (DA) and nigrostriatal dopaminergic (NDA) neurons is the main cause of Parkinson's Disease. Neurotransmitters are made up of proteins, their purpose is to relay information between nerves in the synapse. Neurotransmitters are classified into six groups based upon their chemical properties: (1) acetylcholine (2) biogenic amines (3) amino acids (4) neuropeptides (5) purines and (6) gases and lipids (Dow University of Health Sciences). Neurotransmitters are either excitatory (stimulators) or inhibitory (suppressants). Dopamine is a monoamine, a biogenic amine produced in the substantia nigra, and is both excitatory or inhibitory – depending on the receptor receiving the transmitter, which are D1 (stimulatory) or D2 (inhibitory) receptors. There are four major systems or pathways in the central nervous system containing dopamine: (1) mesolimbic pathway (reward and

reinforcement) (2) mesocortical pathway (regulates emotional response and motivation) (3) tuberoinfundibular pathway (regulates hormone prolactin) and (4) nigrostriatal pathway (produce muscle movement). Most Parkinson symptoms do not show until 80-90% of the dopamine function has been lost and in some dopaminergic systems, as little as 59% dopamine loss has been noted (Agid *et al*, 1989; Zigmond & Burke, 2008). The deficiency of dopamine in the nigrostriatal pathway in the basal ganglia prevents the brain cells from performing normal functions that are associated with motor control.

The basal ganglia are masses of gray matter which are of neuron cell bodies composing a component of the motor circuit at the base of the forebrain. It is involved in regulating the force, muscle tone and execution of movement sequences as well as allowing motor skills to move quickly and easily with little conscious attention (Albin, 1989; Guatteo, 2009). There are five nuclei that make up the basal ganglia circuit: (1 and 2) striatum, which consists of two parts: the (a) caudate and (b) putamen; (3) the globuspallidus; (4) the substantianigra (pars compacta and reticulata: abbreviated as SNc and SNr respectively); (5) and the subthalamic nucleus. The nuclei associated most with Parkinson's Disease are the substantianigra.

To produce smooth, rhythmic movement, dopamine works in conjunction with another neurotransmitter, acetylcholine. Like dopamine, acetylcholine is either an inhibitory or excitatory neurotransmitter, depending on the location in the body. In cardiac muscle it is inhibitory, lowering heart rate. In skeletal muscles it stimulates at the neuromuscular junction causing muscle movement and in the brain it acts as a neuromodulator affecting feelings of arousal and reward. In Parkinson's Disease, the loss

of dopamine blocks the auto inhibition of acetylcholine release, leading to an excessive amount of acetylcholine causing increase muscle tension, tremor and dysrhythmia (Aosaki *et al*, 2010). For further information the balance between acetylcholine and dopamine please reference Aosaki *et al* (2010).

Interactions between the dopaminergic and glutamatergic neurotransmission systems is important for normal basal ganglia function. Because the two systems are close in proximity (dopaminergic neurons on the substantia nigra and glutamatergic afferents on the cerebral cortex and thalamus synapse) with the spiny neurons on the striatum, they dictate the electrophysiology of the cells (Petzinger, *et al*, 2010). Loss in dopaminergic neurons causes an increase in glutamatergic corticostriatal drive on the spiny neurons – which also contribute to the motor dysfunction seen in Parkinson's Disease.

While the depletion of dopamine is not the *cause* of PD, it is a *mechanism*. This mechanism is not a simple dysfunction of the basal ganglia, but also includes other neuronal circuits and abnormalities (Niethammer *et al*, 2012). It is still unknown as to why the dopamine cells are degenerating, and the nerve cells do not grow back. To combat the disease medications have become the gold standard for management and to substitution of neurotransmitters. .

Pharmaceuticals and Current Treatment

When dopamine was discovered to be the mechanism behind the motor and movement complications in Parkinson's in 1957, the gold standard pharmaceutical drug – Levodopa (L-DOPA) -became the main therapeutic approach to manage PD in the late 1960's (Yeragani, Tancer, Chokka& Baker, 2010). In the brain, L-DOPA mimics dopamine in that it is converted into dopamine; yet only 1-5% of the L-DOPA given is able to cross the blood-brain barrier effectively, the remaining L-DOPA is metabolized into dopamine elsewhere (Coleman, 2012; Grace, 2008). The blood-brain barrier is a barrier composed of endothelial cells in brain capillaries that protect and prevent foreign particles from entering the brain (Scudellari, 2013). Gentech and Raptor pharmaceuticals, are one of many pharmaceutical companies researching ways to get antibodies to cross the blood-brain barrier more effectively while UCLA has a Blood-Brain Barrier Research Laboratory that is currently researching stroke treatment with neurotrophins, gene expression in vivo with antisense radiopharmaceuticals and genetic engineering of antibodies that can cross the BBB.

To prevent the L-DOPA from decarboxylating into dopamine before it needs to, it is combined with a peripheral decarboxylase inhibitor, Carbidopa, to prevent the Levodopa from decarboxylating outside the brain (Healthwise Incorporated, 2011). This allows more dopamine to be available to the brain, but does not slow the process of the disease or replace the neuronal machinery (Gracies, 2005; Healthwise Incorporated, 2011). Levodopa remains the gold standard for management due to its associations with increased quality of life and longevity (Gracies, 2015). There are complications and side

effects with *any* medication given to *any* patient with *any* disease. In Parkinson's Disease the complications associated with medications is the advancing difficulty to produce relief from symptoms without side effects or increasing dosage amounts. Side effects of Levodopa include motor fluctuations, dyskinesias, and neuropsychiatric problems, and a sudden discontinuation of the medication results in hyperthermia, psychological changes, agitation and dystonia (Friedman *et al*, 1985). As the disease progresses there is an increase in the narrowing of the therapeutic window. Without treatment given to those living with PD, the disease will progress over a period of 5 to 10 years into an akinetic and rigid state, in which patients are unable to care for themselves and they die from aspiration pneumonia, swallowing impairment, pulmonary embolism, cardiovascular disease (Grace, 2008). L-DOPA is also associated with Levodopa-induced dyskinesias – involuntary muscle movements. Dr. Anthony Grace (2008) classifies L-DOPA as a two-edged sword. The already fragile dopaminergic system goes through hyper activation of dopamine with the L-DOPA introduction, followed by depolarization and inactivation of dopamine firing leading to system disruption causing dyskinesias (Gracies, 2005). To date, there are now 6 classes of drugs for management of PD (research continues to develop other pharmaceuticals for potential cure), alongside therapies such as deep-brain stimulation, stereotaxic surgery, pallidotomy surgery, and recently physiotherapy. While the disease is better understood and medications are given for symptom relief, there is still no known cure. *To see a list of common pharmaceuticals provided to person's with Parkinson's Disease, please reference Appendices IV.*

Normal Gait

During normal movement, maintenance of an upright posture and the control of balance is a continuous task of the Central Nervous System and other peripheral systems such as the vestibular, visual and kinesthetic system. To keep from falling, the body maintains its dynamic stability by keeping its center of mass (COM) within the base of support, known as the center of pressure/position (COP) (Winter, 2009). The COM is the balance point of an object or body; it is not always located at the geometric center of a body. Because humans maintain an upright posture, the COM is relatively high (located at about the sacrum). During normal human walking, the body's COM will be displaced vertically as seen in the rocker feet model, and horizontally as seen in the inverted pendulum model (Gard *et al*, 2004). The rocker feet model involves a three-link segment model of the lower extremity illustrating limb motion on COM; with each single stance phase of the gait cycle, the COM rises in elevation and falls in double stance (Gard *et al*, 2004). The COP is the location of the vertical ground reaction force vector, located ventral the foot (Winters, 2009). As the foot cycles from dorsi flexion with heel strike to toe off in plantar flexion, the COP travels from heel to toe.

In the simplest form, the walking cycle can be broken into two phases: stance phase and swing phase. As the movement of the human body is propelled forward in a walk, one limb provides support as the other limb swings or advances forward in preparation to catch the body as a supporting limb (Bogey, 2012). The stance phase can be further subdivided into 3 segments as proposed by Bogey (2012) initial double stance, single limb stance and terminal limb stance; or into 5 segments as proposed in *Physical*

Medicine and Rehabilitation Board Review: initial contact, loading response, midstance, terminal stance and preswing. The swing phase can be subdivided into 3 segments: initial swing, midswing and terminal swing (Gait Analysis, 2004). These phases of walking are consistent for all humans walking bipedally.

Parkinsonian Gait

There are few studies on the kinematic analysis of the Parkinsonian gait. Gait disturbances can be continuous or episodic; continuous being constant alterations in gait and episodic being intermittent and occasional (Hausdorff, 2009). Continuous alterations of gait are associated with the four cardinal features. These features include: tremor, rigidity, hypokinesia (such as akinesia and bradykinesia) and postural instability. Episodic disturbances are unpredictable and detrimental. These include freezing of gait (FOG) and the inability to initiate and follow through a movement. All of these symptoms are correlated with the loss of dopaminergic innervations; however genetic predispositions such as an incline towards protein degradation may also play a role (Hausdorff, 2009; Shastry, 2001). As stated earlier in this paper, Parkinson's patients are admitted to the hospital more frequently and for a longer duration than the general population as a consequence of gait variability and dynamic instability.

Of the cardinal features, tremors are usually the one of the first noticeable signs. It occurs in at least 70% of patients at rest (Zigmond & Burke, 2008). Tremors normally range from 4-6 Hz, though there are fluctuations in frequency that are maximal when the limb is at rest and decreased with voluntary movement (Coleman, 2012). Tremors are managed medically in the beginning stages of the disease, however with progression of

neurodegeneration and lack of communication between the axon terminals, the symptom will eventually outgrow the medication.

Rigidity is an increase in muscle stiffness. The stiffness in the spine causes a postural hunch, and movements of balance such as trunk rotation and arm swing during a walk become difficult to execute. Alongside the increase in stiffness, resistance to passive motion and limited full range of motion will be noted. The major muscles are not the only ones affected, the muscles in the face become hypomimic - masked face; and smooth muscles such as those of the esophagus become despondent (Coleman, 2012). Rigidity may be asymmetric at first, however it will eventually progress to the entire body.

Hypokinesia is a slowing of movement. It is characterized by a reduction in gait speed, step amplitude and a slight increase in cadence (Grabli, 2012). There are two forms of movement subsequent to hypokinesia: akinesia and bradykinesia which are the absence or freezing gait, and slowing of movement, respectively. Like rigidity, these may initially be asymmetric before progressing to the whole body and like rigidity it will decrease with medical therapy but only temporarily. Also like rigidity, the kinesia is not limited to gross musculature or gross movement. When muscles such as those in the oropharynx are affected, the patient will have difficulty in swallowing - eventually causing aspiration pneumonia (Zigmond & Burke, 2008). Freezing gait is when the patient is unable to follow through a movement sequence or initiate a movement – typically seen in walking or changing direction. These forms of dyskinesia are correlated with falls and hospitalization.

Behind the cardinal features, Parkinsonism gait is much like the gait of the elderly. Changes in gait with age include decreased walking speed, a longer double stance phase, smaller base of support and shorter stride lengths. However there are debates as to this being a self-selected reason for fall prevention or due to physiological bases, or even a contribution of both? Physiologically, muscle strength and flexibility are decreased, reaction times are slower, the sensory systems (vestibular system <ears>, visual system <eyes> and proprioceptive system <touch>) closely related to balance are compromised. Parkinson's patients subsequently acquire a decrease in foot clearance in the swing phase of the walk cycle (Coleman, 2012). The decrease in foot clearance, increase in cadence and reduction in stride length causes a "shuffle". As a result of the reduced stride length, gait will be slower and the double-stance phase of the gait cycle will last longer (Sofuwa *et al*, 2005). Due to the unequal ratio of dopamine to adenosine, PD patients are unable to maintain a steady rhythmic gait, have a higher probability of falling, and may develop a fear or anxiety to perform motor movements.

Physical therapy, balance and gait training alongside external cues, have proven to be beneficial in the PD gait – leaving a possible explanation that the PD gait variability is not intrinsic to the disease (Frenkel-Toledo *et al*, 2005). Those living with PD no longer have the ability to compute and follow through the normal gait cycle, and many therapies involve balance and gait training in the hopes of maintaining independent quality of life in PD patients. Medication therapy is helpful in the early stages of PD, but eventually the disease outgrows the medications and patients are reduced to being dependent on aids and other human beings.

Hoehn and Yahr Staging

Symptomatic progression of the disease was not classified until 1967 by Margaret Hoehn, MD, and Melvin Yahr, MD, who studied 856 patients: mean age of men in the study being 55.6 years and in women 54.8 years, for 15 years in order to stage the diversity of the disease in signs, symptoms and rate of progression. The scale diagnoses the disease based on symptoms as progressing from unilateral to bilateral involvement of muscle, decrease in righting reflexes, balance and rigidity; it should be noted that the progression of the disease is not always uniform and may not be reflective of the pathophysiology correlation (Hoehn & Yahr, 1967). Mortality is caused by the increasing disability of the disease, and in Hoehn and Yahr's study, there was a wide range of age in death (mean age 65.9 years) and in duration of disease prior to death. At the time of the study, only 15% of the obtained death certificates listed Parkinsonism as underlying cause and 46.2% as contributing cause of death. The leading cause of death in study being diseases of the heart, bronchopneumonia, malignant neoplasm's (unregulated cell growth) and cerebrovascular accidents (Hoehn & Yahr, 1967). Please see Table below for Hoehn & Yahr's scale of PD.

Table 1 Adapted from Hoehn & Yahr’s scale of stages and symptoms associated with Parkinson’s Disease across a 30 year life span.

STAGES	SYMPTOMS
<u>I</u>	Unilateral involvement only - usually with minimal or no functional impairment
<u>II</u>	Bilateral or midline involvement, no impairment of balance; minimum disability
<u>III</u>	First sign of impaired righting reflexes, may have some work capacity, mild to moderate, generalized disability
IV	Fully developed, severely disabling disease; able to walk and stand without assistance
V	Confinement to bed or wheelchair

Exercise and Parkinson’s Disease

In 1982 at the first Parkinson Foundation of Canada Educational meeting, a PD patient asked the panel if exercise and physical therapy were beneficial to the disease. The answer given by one of the physicians was exercise “is a waste of time” (Hirsch, 2009). For many years, exercise has not been the recommended form of rehabilitation or treatment for persons living with PD. Instead, physical therapy has been used in conjunction with medications to help enhance daily function beyond what surgery and medicine can do alone. The goal of physical therapy is rehabilitation. Clinically exercise can be used in rehabilitation in both in-patient and out-patient setting and to measure fitness level or improvement, graded exercise stress tests are also useful measurements. Despite the positive effects of physical therapy on the disease, as of 1999 only less than 30% of those diagnosed with Parkinson’s disease were recorded to have participated in physical therapy programs (Deane, 2009).

PD patients tend to develop muscular atrophy, cardiovascular disease, pulmonary diseases, mobility issues, decreased muscular strength, balance disorders and osteoporosis. To improve upon these clinical characteristics, physical therapy is designed to improve these characteristics by: mobility exercises, cueing strategies for gait improvement, training for daily activities, balance exercises, relaxation, stretching, walking, swimming, breathing exercise and light weights – vigorous exercise has not been deemed necessary (de Goede, 2001; Hirsch, 2009). Dr. Katherine Deane from the Colchrane society compiled and summarized research in the 1980's and 1990's to find what form of physical therapy is most beneficial to PD patients (Deane *et al*, 2009). According to her findings, she concluded that there “is insufficient evidence for the effect of physical therapy versus no physical therapy...no conclusive evidence” that physical therapy is beneficial (Hirsh & Farley, 2009). Partially her conclusions resulted from the flaws of the studies themselves: documentation by researchers, methodological flaws, research design, and randomization of subjects and lack of follow-up (Deane *et al*, 2009; Hirsh & Faley, 2009). In 1994, a change in paradigm was pushed by the American Academy of Neurology as they started recommending physical therapy *with exercise* as an adjunctive therapy with early diagnoses (Hirsch, 2009). The term exercise umbrellas all intensity levels. To be consistent in this research, intensity levels will be divided into three categories: low grade moderate and high intensity. Physical therapy usually consists of low grade to moderate intensity levels and represents the traditional form of therapy for those living with Parkinson's Disease. In 2008, American Medical Association and American College of Sports Medicine launched a program called

“Exercise is Medicine” in an effort to encourage physicians and health care professionals in education and encouragement on the importance of exercise. While this program is greatly stressed in the cardiology, pulmonary and weight loss programs and rehabilitation, this also applies to neurology.

Exercise and Neuroplasticity

Exercise can essentially help the brain *maintain* old connections, reform new ones, and restore lost ones (Petzinger *et al*, 2009). Parkinson’s disease is caused by neurodegeneration of the dopamine transmitter and neuron. Unfortunately these components cannot be recovered. Contrary to old beliefs, research in neuroscience has revealed that the brain is not a static organ, but evolves and changes in accordance to the demands placed on it. Exercise causes a phenomenon termed as plasticity and depending on the location, brain-plasticity, neuroplasticity or synaptic plasticity.

Plasticity, also called experience-dependent neuroplasticity or neuroplasticity, is the brain’s ability to essentially adapt and reorganize the neural pathways as a result of new or intense experiences. Neuroplasticity can occur at a variety of levels from cellular changes, synaptic changes, increases in capillary density and cortical remapping. There are two different types of situations that cause plasticity: an enriching environment and exercise. About three decades into the lifespan, the physiology and structure of the brain deteriorates, especially in the frontal, parietal and temporal lobes – which are also associated with a decline in cognition, memory and higher order thinking (Colcombe *et al*, 2003; Colcombe *et al*, 2006). Cardiovascular exercise has been shown to improve memory and cognition, increase brain volume, increase the number and length of

dendritic neurons, improve brain metabolism, increase capillary density, increase cell production, and increase neurotransmitter receptors in synapses (Colcombe *et al*, 2003; Colcombe *et al*, 2006; Lovinger, D. 2010). These results are indirectly seen in cognition and mental exams and surveys, visually seen through use of MRI scanners, and seen in increases in certain biomarkers from plasma draws.

Research on plasticity has shown there are two different types of situations that cause plasticity: an enriching environment and exercise. These situations cause a cascade of various types of brain plasticity: angiogenesis, neurogenesis, synaptic growth, astrocyte and neutrophil plasticity. In accordance to the demands placed on the brain there is an increase in vasculature (angiogenesis) bringing nutrients and oxygen to the brain tissue. The increase in vasculature increases synaptic plasticity (changes in strength and number of connections between neurons) an important factor for the brain in its adaptation.

The brain produces protein molecules in order to ensure health, development, survival and nourishment of neurons called neurotrophins (Cotman and Engesser-Cesar, 2002). Neurotrophins are a type of secretory protein that includes growth factors such as brain derived neurotrophin (BDNF), glia-derived neurotrophin (GDNF), nerve growth factor (NGF), and insulin-like growth factor (IGF) (Colcombe *et al*, 2003; Hirsh *et al*, 2009). The most widely researched of the neurotrophic factors and it's connection with brain plasticity is the BDNF, which can be measured and obtained through platelet samples. Increases in the blood BDNF have been recorded with both acute and longitudinal studies on exercise. Research has linked the BDNF with “neuronal protection and survival, axonal and dendritic growth and remodeling, neuronal

differentiation and synaptogenesis” as well as enhancing neuronal function via promotion of both synaptogenesis and neurogenesis (Alberts et al, 2011; Fisher et al, 2008).

Exercise has not only proven to increase levels of BDNF in the motor-sensory portions of the brain, but also in the hippocampus (associated with cognition), the lumbar spinal cord, cerebellum and cortex (Cotman, 2002). The main importance of neurotrophins and neurotrophic factors is the increase in brain health and promotion for plasticity. With exercise as a stimulus for brain plasticity, new therapeutics are developed for treatment of neurological diseases such as Parkinson’s Disease.

In a series of studies by Petzinger *et al* of University of Southern California (years 2004-2010), the effects of intense exercise on the brain was the object of study. One of these studies published in *The Journal of Neuroscience* in 2007, looked at mouse models with basal ganglia injury. The mice were divided into 4 groups, 2 control (saline and saline plus exercise) and 2 lesioned (striatal dopamine lesioned mice – 1 lesion only, 1 lesion and exercise). 5 days after being lesioned, the mice were exercised 5 days a week for a total of 28 exercise days. Post total exercise session, the mice showed an increase latency or delay to falls – improved balance (Petzinger *et al*, 2007). Exercise did not increase the amounts of dopamine in the brain, yet it did increase the *handling* of the dopamine. The authors describe handling as the features of how the dopamine is released from the nerve terminals and how long it is made available for the body to use (Petzinger *et al*, 2009). Exercise improved the handling of dopamine from ‘storage mode’ to a ‘use mode’, which allows dopamine to maintain its stability outside the synapse and to work as is should in transmitting messages or initiating signals within the motor circuit

(Petzinger, 2007). Exercise also increased the dopamine D2 receptors needed to receive the messages from the dopamine transmission. PET imaging's on exercise groups performed at the beginning and the end (pre and post total exercise session) of the studies showed an 80-90% increase in the dopamine D2 receptor in the PD subject, two healthy controls had only an increase of <10% (Petzinger, 2007). The dopamine transmitter cannot be replaced with medicine, and cannot be regenerated through exercise; however the handling of the transmitter and the increase in the D2 receptor as a result of exercise is a novel finding and can have significant impact on exercise prescription for Parkinson's patients.

The effects of Parkinsonian medications turning to dopamine in the brain and expressing gait improvement exemplify the importance of dopamine in maintaining gait rhythm. While dopamine plays an important role modulating the connection and communication between neurons in the synapse, exercise has shown to cause brain connections to form despite the loss in dopamine.

It is the belief of the author of this paper that exercise will cause synaptic plasticity in the Parkinsonian brain. With the depletion of dopamine transmitters, it is the hope that an acute bout of exercise will improve the handling of dopamine. While MRI scanners are not available for the use of this study, the researchers believe that a result of an acute bout of exercise will be improved motor function as seen in the walking gait with an increase in stride length, increase in toe clearance and a reduction in gait velocity. As in the case of the 'accidental discovery' by Dr. Jay Alberts, the importance of exercise

in relation to intensity, specificity, difficulty and complexity, can have significant implications in designing exercise prescriptions for PD patients.

Effect of Exercise on Dopamine Neurotransmission

The phenomenon that exercise has on the brain is termed ‘activity-dependent neuroplasticity, which are changes in brain and central nervous system in response to exercise. Scientists are just beginning to understand the effects of exercise on the brain. In regards to Parkinson’s Disease, exercise elicits fine and gross motor improvement. To look at the effects of exercise on neurotransmitters and enhancing neuroplasticity Petzinger *et al* of University of Southern California, from 2004-2010, did a series of studies on the effects of intense exercise on the brain.

One of these studies published in *The Journal of Neuroscience* in 2007, looked at mouse models with basal ganglia injury. The mice were divided into 4 groups, 2 control (saline and saline plus exercise) and 2 lesioned (striatal dopamine lesioned mice – 1 lesion only, 1 lesion and exercise). 5 days after being lesioned, the mice were exercised 5 days a week for a total of 28 exercise days. Post total exercise session, the mice showed an increase latency or delay to falls – improved balance (Petzinger *et al*, 2007). Exercise did not increase the amounts of dopamine in the brain, yet it did increase the *handling* of the dopamine. Exercise improved the handling of dopamine from ‘storage mode’ to a ‘use mode’, which allows dopamine to maintain its stability outside the synapse and to work as is should in transmitting messages or initiating signals within the motor circuit (Petzinger, 2007). Exercise also increased the dopamine D2 receptors needed to receive the messages from the dopamine transmission. PET imaging’s on exercise groups

performed at the beginning and the end (pre and post total exercise session) of the studies showed an 80-90% increase in the dopamine D2 receptor in the PD subject, two healthy controls had only an increase of <10% (Petzinger, 2007). The dopamine transmitter cannot be replaced with medicine, and cannot be regenerated through exercise; however the handling of the transmitter and the increase in the D2 receptor as a result of exercise is a novel finding and can have significant impact on exercise prescription for Parkinson's patients.

A review by Petzinger et al (2010) on the current research in the laboratories at UCLA, highlights important findings and understanding of how exercise and neuroplasticity in the basal ganglia work. They hypothesize that neuroplasticity may be driven through alleviating corticostriatal hyperexcitability via controlling dopaminergic signaling and/or diminishing glutamatergic neurotransmission.

It is the belief of the author of this paper that exercise will cause synaptic plasticity in the Parkinsonian brain. With the depletion of dopamine transmitters, it is the hope that an acute bout of exercise will improve the handling of dopamine. While MRI scanners are not available for the use of this study, the researchers believe that a result of an acute bout of exercise will be improved motor function as seen in the walking gait with an increase in stride length, increase in toe clearance and a reduction in gait velocity.

Intense Exercise and Gait

In 2003, Dr. Jay Alberts rode a tandem bike across the country with a friend whom had Parkinson's disease. Dr. Alberts was the pace setter on the bike, and kept a revolution of 60-90 rpm for two weeks – 40% faster than what his Parkinson's friend had

been training at prior to the ride. Two days into the ride, his Parkinson's friend noted improvements in her symptoms and handwriting. As a result of this discovery, several studies have been conducted involving Parkinson's patients and cycling. These studies have looked at 'forced' exercise (as opposed to voluntary exercise) and intense exercise on the effects of global motor movement, fine motor movement and gait (Fisher *et al*, 2008; Pohl *et al*, 2003; Ridgel *et al*, 2009). As opposed to physical therapy where low to mid intensity levels are recommended for therapy and rehabilitation, the effects of high intensity exercises may prove to be more beneficial for overall health in those who live with Parkinson's Disease.

Based on the experiences in 2003, Dr. Alberts with Ridgel *et al* (2009) did further research on the effects of 'forced' exercise on motor movement in Parkinson's subjects. Subjects were required to exercise at 60-85% of their predicted max heart rate based on the Karvonen formula for 5 days a week, 8 weeks in duration. The subjects were imaged under functional connectivity magnetic resonance imaging (fMRI) pre 8 week exercise protocol, and post 8 week exercise protocol. Functional connectivity MRI's measures blood oxygenation levels in the brain and allows for the study of functional connectivity between different portions of the brain. The results expressed neuroplasticity in the brain, a phenomenon formally observed in stroke patients and in musicians. Correlating with the expressed neuroplasticity there was an increase in task-related connectivity (increase in strength) between the primary cortex and the posterior portion of the thalamus and there was a 35% increase in motor scores as rated in the Unified Parkinson's Disease Rating scale (UPDRS) – a scale used mostly in clinical studies and by neurologists to

evaluate the progression of the disease (Lowry, 2012; Ramaker *et al*, 2002). The increases in the neural network connections and the 35% improvement as seen in the UPDRS hint that ‘forced’ exercise may be a key element to treatment and management of the disease aside from medications.

In 2008, Fisher *et al* of the University of Southern California obtained preliminary data on the effects of high intensity exercise on walking gait compared with low and zero intensity exercise in Parkinson’s patients. Early stage Parkinson’s disease patients were recruited and randomly assigned into the three exercise intensities. All intensities consisted of 24 sessions over the course of 8 weeks. The high intensity exercise was body weight supported via a harness attached to the ceiling and the exercise was performed on a treadmill. The intensity level was based on heart rate level and metabolic equivalent (MET) level of greater than 75% age appropriate max heart rate and 3.0 MET’s or greater, respectively. The low intensity group consisted of physical therapy sessions targeting strength training, range of motion, balance and gait training and had to maintain a heart rate of 50% or less of the age appropriate max heart rate and less than 3.0 MET’s. The zero intensity group consisted of educational classes on the benefits of exercise, stress coping, improving memory, and improving quality of life. Before and after all training protocols, subjects had their gait analyzed at the Musculoskeletal Biomechanics Research Laboratory by the motion capture system consisting of an 8-camera motional analyses for 3-dimensional coordinates of the lower extremity (pelvis, thigh, shank and foot) and ground reaction forces were picked up via force plates (Fisher *et al*, 2008). The high intensity group maintained an average of 4.3 METs with a range

of 2.5-13.3 METs and only 7 individuals obtained >8 METs. The high intensity individuals had a heart rate 70-75% of their predicted max with speeds ranging from 8.0-12.8 km/h (5.0-8.0mph). The low intensity individuals had a heart rate range of 60-65% of predicted max with treadmill speeds being less than 8.0km/hr (Fisher *et al*, 2008). All groups had an improvement in gait performance, with the most consistent improvements seen in the high intensity group. Interestingly, the zero intensity group had a increase in stride length in comparison to the low intensity group. This may be possible do to the fact that the low intensity group was allowed to maintain their normal exercise routine outside of the research protocol. The results of this preliminary study all express the importance of high intensity aerobic training on a clinical brain such as Parkinson's disease, and how brain plasticity can be tangibly seen in improvements of gait performance.

In 2003, Pohl *et al* from Landesarzttekammer Sachsen, Germany looked at immediate effects of speed from treadmill training on gait in person's with early Parkinson's Disease. The subjects were early staged as defined by Hoehn and Yahr scale, stages I-III and were cleared as healthy enough for vigorous exercise and scored <26 on the Mini-Mental State Exam (see Chapter 3 and Appendices II and Appendices V for further reference). The methodology consisted of 3 gait training interventions and 1 control intervention over the course of 4 consecutive days. As opposed to BWS treadmill training as described in Fisher *et al* (2008), Pohl *et al* (2003) neglected to use overhead body support so as to minimize the positive effects of supported weight on the results. The three gait training groups were (1) structured speed-dependent treadmill training, (2)

limited progressive treadmill training, (3) conventional gait therapy and (4) the control intervention. In structured speed-dependent treadmill training the goal was to increase walking speed at 0% incline with each training session lasting 30 minutes. In limited progressive treadmill training, speed was not increased over the initial self-adapted over ground walking speed but walking distance varied. This training session was also 30 minutes in length. Conventional gait therapy consisted of physiotherapeutic gait therapy based on the proprioceptive neuromuscular fasciculation concept, this training session was also 30 minutes in length. The control intervention consisted of the subjects resting for 30 minutes. Gait was assessed as a blind test by those unfamiliar with the intervention. Walking speed and stride length were recorded. Gait analyses took into consideration ground reaction forces, peak vertical ground reaction force at heel strike, toe-off, loading and deloading rates, duration of the double stance phase and ration of single stance phase between right and left legs. The highlighted results expressed significant increases of self-adapted walking speeds in m/s, stride length in self-adapted walking speed and double stance duration (% of gait cycle) $P < 0.001$ in structured speed dependent treadmill training and progressive treadmill training with no significance in conventional gait therapy or the control group.

Met's and Neuroplasticity

At how many metabolic equivalents (METs) is neuroplasticity induced? METs are useful in describing and measuring the intensity of an activity and are used heavily in cardiac rehabilitation and pulmonary rehabilitation programs. The American College of Sports Medicine classifies and calculates METs based on $VO_2\%$ max in relative values

of ml/kg/min and are organized into categories: light intensity being <3METs, moderate 3-6METs and vigorous >6 METS (~6-20METs). Only one study noted the MET's achieved and averaged throughout the course of the exercise protocol/program. Petzinger *et al*, 2008 noted on a treadmill run at 0% grade, an average of 4.3 METs were obtained. The range was 2.5-13.3 METs and only 7 individuals obtained >8 METs. The high intensity individuals had a heart rate 70-75% of their predicted max with speeds ranging from 8.0-12.8 km/h (5.0-8.0mph). The low intensity individuals had a heart rate range of 60-65% of predicted max with treadmill speeds being less than 8.0km/hr (Fisher *et al*, 2008). To date, no research has been done on the MET intensity level and the initiation of neuroplasticity. This would be helpful information in a clinical rehabilitation setting and help those diagnosed with neurological disease set goals for their intensity of exercise.

Ideal Exercise Intensity

An editorial on a recently published cohort study by DeFina *et al* (2013) notes the ideal metabolic equivalent ideals for the best benefits on improving cognition as seen in previous studies: >8 maximal metabolic equivalents (Sano, 2013). In the study by DeFina *et al* (2013), it was found that higher levels of physical fitness in middle age lowered the diagnoses of Alzheimer's and Dementia later in life (pushing diagnoses back by about 5-10 years) (Sano, 2013). DeFina *et al* (2013) looked at a population of clients at the Cooper Clinic in Dallas, Texas in the Cooper Center Longitudinal Study observational database. The database analyses suggested that higher fitness levels demonstrate protection against all-cause mortality and illness (stroke, diabetes etc). All study subjects gave a comprehensive medical history, educational history and exercise/fitness history. It

was found that lower fitness levels at midlife examination were associated with higher prevalence of cardiovascular disease, increased body mass, hypertension, diabetes, hyperlipidemia and smoking (DeFina *et al*, 2013). Higher fitness levels were associated with lower incidents of dementia (DeFina *et al*, 2013). DeFina *et al* (2013) notes that fitness levels are not possible to give as generalizations of physical activity to any one person due to previous physical fitness, habitual physical activity, gene-environment interactions and are modifiable. With this being said, previous reports have shown that moderate intensity of physical activity at a minimum of 150 min per week for 5-6 months improves V02 max (by 3-5 ml/kg/min) and/or 1-2 MET's in fitness levels (DeFina *et al*, 2013; Sano, 2013). While this is ideal, only about 10% of the population reaches this recommendation of 150 min per week (Sano, 2013). Intensity can be based on an individual's rate of perceived exertion, and age predicted max heart rate. On the Borg scale of Rate of Perceived Exertion, the intensity would be a target of 11-13 (light-somewhat hard) out of 20.

For the Parkinson's patient an ideal exercise intensity has not yet been defined. Published research has included in methodology intense exercise sessions of individualized 60-80% heart rate reserve, a MET level of greater than 3.0, or exercising at 30% greater than normally comfortable with (Ridgel *et al*, 2009; Fisher *et al*, 2008). This research study will look at an individualized 60-80% target heart rate reserve method, to be explained in Chapter 3.

A gap in the Literature

Most, if not all the literature to date has looked at the effects of exercise on neural plasticity in both the normal and Parkinsonian brain. However, the studies focus more on the long term effects of exercise on the injured and damaged brain. There are few studies on acute exercise sessions and immediate effects on Parkinsonian gait (Pohl *et al*, 2003), and none on the immediate effects of stationary bicycle training on gait parameters.

Chapter 3

METHODOLOGY

Participants:

Three mild to moderate idiopathic Parkinson's diagnosed adults, classified into stages I-III of the V stages of Hoehn and Yahr's Staging (cite) for Parkinson's Disease (3 men, 0 women; 70 ± 2 years mean age; 6.33 ± 2.33 years mean illness) were recruited for this study. Subjects were recruited via a local medical clinic (Sacramento Heart and Vascular Associates) and were contacted by both phone and an in-office visit with the supervising physician. Subjects were referred to their neurologist for staging diagnoses and physician clearance was given after successfully completing the Bruce Protocol Treadmill Test or after a chemically induced exercise stress test.

Participants were excluded from the study if any health history included any other neurological problems; acute medical problems that could affect gait (such as visual impairments, vertigo, head trauma, musculoskeletal disease or injury, and unpredictable off-periods). Participants completed a Health History Questionnaire (Appendix IV) and a Mini-Mental Examination (Appendix V); they were excluded if they scored below a 23. Participants were also excluded if they cannot complete the Timed Up and Go test prior to the protocol. All participants were tested in the Biomechanics Laboratory, California State University Sacramento. All participants signed a voluntary informed consent as approved by Sacramento State Human Subjects Review Board.

In an effort to minimize effects of medications impacting patient's ability to exercise, participants took part in the protocol on the "on" phase of their medication cycle, equating to about 1 hour after mid-day Levodopa is administered (Morris, 2001). Prior to the forced exercise (FE) testing session, subjects completed Health History questionnaire and TUG. Subjects then walked at their self-selected pace for 3-5 trials of gait analysis. Subjects were next asked to complete a FE stationary cycling protocol for 30 minutes, after which their self-selected walking was immediately retested. The total testing protocol lasted 90 minutes.

Timed Up and Go Test (TUG)

To assess patients' mobility and balance, three attempts of the TUG test were performed. Subject were barefoot during ambulation. Subject were not assisted during TUG test, however a researcher stood nearby to assist in fall prevention, and subjects were allowed to sit in a stable chair as long as was required if they grew tired.

Protocol:

- (1) Subject were asked to sit in a stable chair on a stable surface
- (2) On the word "go", subjects walked 10 meters, before returning to a seated position in chair. Efficiency was monitored and speed was recorded.

If subjects were to stumble or fall, they would have been immediately excluded from the participation in the research study. Speed of the TUG test helped in determination of time needed to measure capture volume during walking protocol.

Gait Analysis

Instrumentation and Procedure

The Vicon Motion Capture System utilized contains an array of 8 cameras placed around a 10 meter walkway. Three-dimensional kinematic data will be collected at 100 Hz and low-pass filtered (4th order Butterworth 6 Hz cutoff frequency). Kinematic data was received and integrated by the Nexus Operating System (Vicon Oxford, UK) on the host computer. Thirty four reflective markers were placed on the following bony landmarks: right and left forehead and rearhead, C7, T10, xyphoid process, clavicle, right scapulae, right and left acromial process on clavicle, right and left lateral epicondyle of the humerus, styloid processes on ulna and radius, posterior portion of the hand between the second and third meta-carpals, right and left anterior superior iliac spine, right and left mid thigh between the greater trochanter and lateral epicondyle of the femur, right and left lateral epicondyle of tibia, mid shank of fibula, right and left ankle, right and left heel, right and left superior portion between the second and third metatarsals.

The markers placed upon these bony landmarks allowed the Nexis operating system to obtain a 13 link segment model of the whole body (Dynamic Plug-in-Gait Model, Vicon Oxford, UK). Anthropometric reference data was adapted from the initial work by Demster in 1955 for both sexes.

Participants were asked to wear shorts and a tank top. Subjects were measured for body height and weight before being instrumented with 34 reflective markers. A researcher stood nearby subject for fall prevention. Subjects were instructed to walk barefoot at their usual self-selected pace for three to five trials both pre and post exercise.

The motion capture data including stride length, gait velocity and toe clearance were obtained and used for statistical analysis.

Forced Exercise Bicycle Protocol

A Monarch Stationary bicycle placed strategically next to a wall to allow for subject balance by hand, was used as the forced exercise device for this study.

Participants sat astride the bike with a researcher standing next to the participant to assist in fall prevention. To control for any difference in aerobic fitness between patients, the exercise intensity was based on heart rate percentage calculated by the heart rate reserve method, also known as the Karvonen formula:

Target Heart Rate = ((max HR – resting HR) × %Intensity) + resting HR; target percent intensity was 60-80% of heart rate reserve as modeled previously on Ridgel et al, 2009 target heart rate intensity.

The exercise session consisted of a 5-minute warm up at a self-selected pace, but kept at less than 50% of heart rate reserve; a 20-minute main exercise set in at 60-80% of predicted heart rate reserve, and a 2 minute cool down at a self-selected pace. Following exercise, participants were then to repeat 3-5 walking trials through the Motion Capture array.

Processing the Data

All marker accuracy was double-checked on the Nexus system software. Heel strike and toe of were identified unilaterally (right foot) for all gait cycles. The heel marker was identified as the lateral heel marker of a selected foot and was selected in Nexus to allow for viewing of 3D trajectories. Minimum vertical peak of the heel was identified as the

heel strike and marked on the gait event bar. The toe marker was identified as the marker on the superior portion between the second and third metatarsals of the same foot as the heel marker, and toe-off was identified and marked as the toe-marker left the floor. The gait trails were cropped from the first heel strike to a full three gait cycles before ending at toe-off. The cropped model was checked via Polygon and foot trajectory data was sent to Microsoft Excel for computing. All raw data from Microsoft Excel, trial numbers and condition (pre or post exercise), sacrum marker, right heel, right toe, gait velocity (meters/second), stride length (meters/second), toe clearance (height in meters) were compiled. Stride length was computed as the horizontal displacement of the heel marker between successive heel strikes. Gait velocity was calculated as the time it took for one cycle of stride length to be complete. Toe clearance was the vertical displacement of the toe marker from toe-off to the highest vertical point in swing phase. Mean gait velocity, mean stride length and mean toe clearance were taken of all gait events per subject pre and post exercise trial. The raw data was transferred to a separate data set and averages on gait velocity, stride length and toe clearance pre and post exercise trials were taken for all subjects. From these averages, graphs and tables were made.

Statistical Analyses

This study is a preliminary repeated measures design used to assess the responsiveness of gait to an acute high intensity exercise bout. Dependent variables included: toe clearance, stride length, gait speed. Allowing for a sufficient sample, a repeated measures t-test will be used to determine the effect of intensive exercise on gait. In lieu of a sufficient sample, further analyses will include percentage change (mean and

standard deviation) in stride length, gait velocity and toe clearance, calculated as the post value-pre value x 100 for each subject.

Chapter 4

RESULTS

Three persons living with Parkinson's Disease (Table 1) were recruited for the purpose of this study and this sample was deemed inadequate for statistical analysis. Two of the three subjects were classified in stage II of the Hoehn and Yahr scale, and one subject was classified in stage III. Average years of living with disease was 6.33 ± 1.6 years. All subjects reached a Mini Mental State Exam Score > 24 , with an average of $28.66 (\pm 1.34)$ making them qualified to participate in the study. All subjects completed the Timed Up and Go test, average $12.55 (\pm 2.14)$ seconds. All subjects are on pharmaceutical management and the medications directly related to the disease are listed in Table 2. All three subjects were on a form of Levodopa (Stevello and Sinemet), the gold standard medication for Parkinson's. Azilect and Eldepryl both are taken as an adjunct to Levodopa, and are usually taken in the early stages the disease in order to relieve the side effects of Levodopa.

Table 2. Subject demographics for three Parkinson's patients undergoing forced exercise testing.

Subject	1	2	3
Age (years)	68	70	72
Sex (male/female)	M	M	M
Hoehn and Yahr stage	II	III	II
Duration of disease	8	7	4
MMSE score	29	29	28
TUG test average	14.69 seconds	11.95 seconds	11.006 seconds

Table 3. List of Parkinsonian pharmaceuticals taken by research participants undergoing forced exercise protocol.

Azilect 1mg (Rasagiline Mesylate)
Stevello 100 25-100-200 (Carbidopa-Levodopa-Entacapone)
Sinemet 25/100mg (Carbidopa-Levodopa)
Eldepryl 5mg (Selegline HCL)

Heart rate:

All subjects completed the acute exercise session with no adverse events. All subjects were able to reach their target heart rate percent of 60-80% heart rate reserve for the duration of the 20min exercise (See Table 4).

Table 4. Calculated and average heart rate of Parkinson's subjects during forced exercise bicycle protocol.

	Subject: 1	2	3
Calculated 60% heart rate reserve (bpm)	91	78	76
Calculated 80% heart rate reserve (bpm)	122	100	90
Heart rate average (bpm)	114	101	103
Heart rate max during bike protocol (bpm)	119	103	106
Heart rate percent of heart rate reserve reached (%)	91.5	97.2	112

The average max hart rate (bpm) during the bike protocol of all three subjects was 106bpm, at an average heart rate reserve of 100.23%.

Gait velocity:

Two of the three subjects had a decrease in gait velocity from pre to post exercise intervention. Only one subject showed an increase in gait velocity from pre to post exercise intervention (see Table 4 and Figure 1).

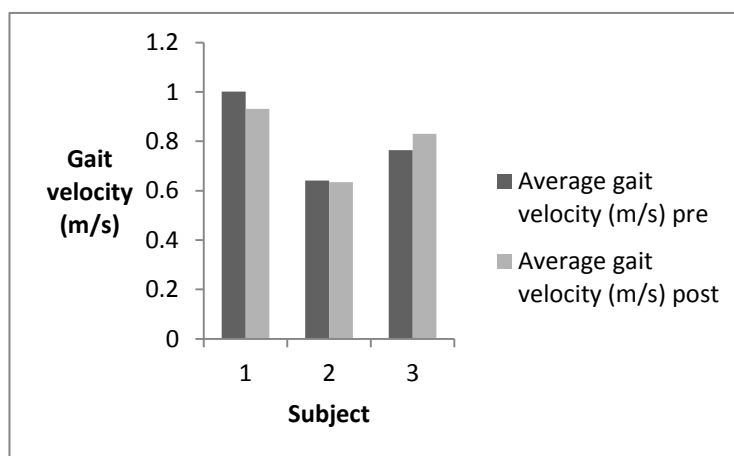


Figure 1. Average gait velocity of Parkinson's patients from pre to post exercise protocol.

Stride length:

Stride length increased on all subjects on average of 1.655% (See Table 4 and Figure 2)

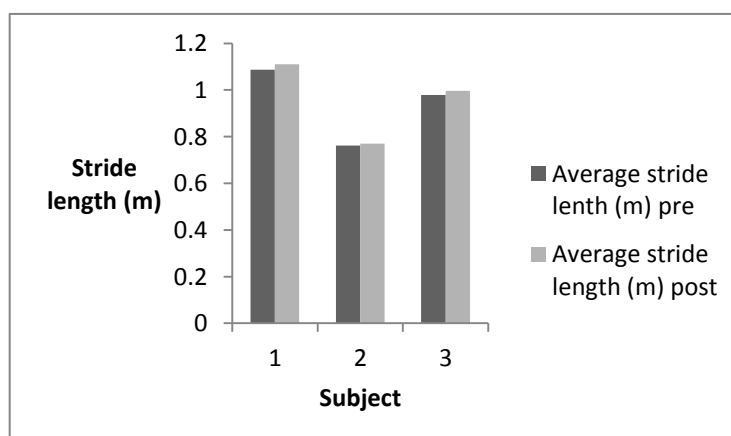


Figure 2. Average stride length of Parkinson's research patients from pre to post exercise trial.

Toe clearance:

Subject 1 had an increase in toe clearance from pre to post exercise intervention (See Table 5 and Figure 3). Subjects 2 and 3 had a negative change in toe clearance meters.

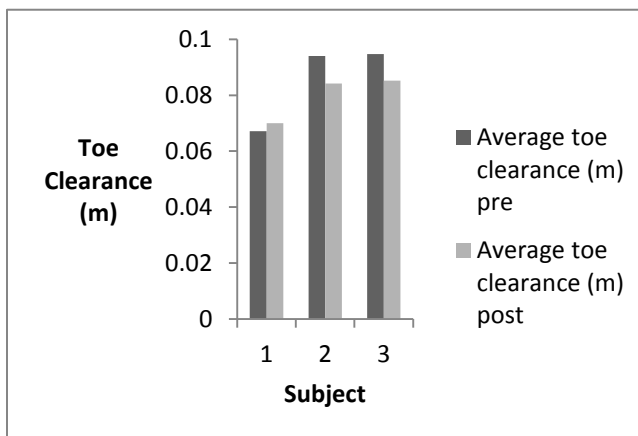


Figure 3. Toe clearance of Parkinson's subjects foot during walking gait before and after exercise.

Table 5. Mean (\pm standard deviation) gait characteristics (gait velocity, stride length and toe clearance) of all Parkinson's participants during testing protocol before and after exercise protocol.

Participant:	1	2	3
Mean (\pm SD) gait velocity (m/s) pre	1.001(0.038)	0.641(0.067)	0.764(0.136)
Mean (\pm SD) gait velocity (m/s) post	0.931(0.167)	0.634(0.157)	0.830(0.199)
Percent change (%) in gait velocity	-7.534	-1.078	7.852
Mean (\pm SD) stride length (m) pre	1.086(0.010)	0.762(0.040)	0.979(0.036)
Mean (\pm SD) stride length (m) post	1.110(0.013)	0.770(0.046)	0.997(0.099)
Percent change (%) of stride length	2.158	1.018	1.789
Mean (\pm SD) toe clearance (m) pre	0.067(0.006)	0.094(0.007)	0.095(0.004)
Mean (\pm SD) toe clearance (m) post	0.070(0.026)	0.084(0.031)	0.085(0.017)
Percent change (%) in toe clearance	4.188	-11.682	-11.066

Chapter 5

DISCUSSION

The problem for person's living with Parkinson's Disease is the diminished motor cortical activity. Additionally, the pharmaceutical management carry adverse side effects such as motor complications and increased risk of falls. Physical therapy programs have been designed to work on increasing muscular strength and improving walking characteristics in Parkinson's patients. The disease eventually becomes costly to the patient and family as a result of hospital charges, office visits with a physician, testing, physical therapy, medications and a daily living changes; therefore there is a need to identify alternative low cost interventions. Recent research suggests that those living with Parkinson's Disease can exercise at higher intensities than previously thought. Intense exercise training for 6-8 weeks has been shown to relieve symptoms associated with the Disease (Alberts *et al*, 2011; Anderson, 2009; Fisher *et al*, 2008; Hirsche *et al*, 2003; Petzinger *et al*, 2007; Ridgel *et al*, 2009). With past research looking at the effects of long-term intense exercise on motor control, gait and the brain, or same day finger exercises on brain activation, the purpose of this study was to see if any of the effects seen in these exercise programs would be present after an acute, single session of intense exercise. This research took into consideration the physiology and biomechanics of the human body during exercise. This includes heart rate, intensity, stride length, gait velocity and toe clearance. The purpose of this study was to look at the effects of a 'forced' intense cycling exercise on the walking gait in Parkinson's patients. The goal was to note any changes in gait (stride length gait velocity or toe clearance) from pre to

post exercise. An unintended result of this study was the participants increase in confidence level in the ability to exercise at a higher intensity than they were comfortable with.

Heart rate

In the role of an exercise physiologist, there are two popular ways to prescribe exercise intensity in relation with heart rate: the percentage of maximal heart rate method and the percentage of heart rate reserve method (Swain & Leutholtz, 2007). The heart rate max method is a rough estimation of max heart rate based on simple method that calculates a target heart rate

$$\text{Target heart rate} = \text{intensity fraction} \times \text{heart rate max}$$

based on age and intensity fraction – it does not take into account resting heart rate. The

$$\text{Target heart rate} = (\text{intensity fraction})(\text{heart rate max} - \text{heart rate rest}) + \text{heart rate rest}$$

heart rate reserve method takes into account resting heart rate, maximal heart rate and intensity – regardless of age and fitness level (Swain & Leautholz, 2007). It is a reliable method in targeting and calculating heart rate based on how the individual is feeling on a particular day.

For the purpose of this study a range of intensity (60-80%) was used to calculate the target heart rate range, as was also used in Ridgel *et al*'s study in 2009. As per ACSM guidelines, exercise is termed moderate to hard with deconditioned subjects at 74-84% maximal heart rate reserve. Because there is no set recommendations for those

living with Parkinson's in terms of exercise intensity, the intensity level was based on a previous study. Max heart rate was obtained from the stress test required prior to participation in the research study, and resting heart rate was taken on the day of the testing protocol. All subjects were able to reach their target individualized heart rate percent of 60-80%, reaching $100.23(\pm 11.77)\%$ heart rate for the duration of the 20min exercise (See Table 3), much higher than expected by researchers. However the high percent reached by the subjects may also be reflective of the exercise testing protocol that was used to clear subjects for research participation, as will be explained in *limitations*.

Intensity

Once diagnosed with Parkinson's Disease, patients start treatment with pharmaceuticals, typically Levodopa for disease management. Long term use of the medication has motor complications and involuntary motor movement. Combined with the progressive nature of the disease and decrease in mobility and function, physical therapy is suggested for disease management. While physical therapy is highly beneficial for disease management, it is restricted to low grade and low intensity exercise sessions that does not promote plastic changes seen in the brain at higher intensities. The protocol and purpose of this research was based on the research by Ridgel *et al* (2009) who looked at the effects of forced exercise on motor improvement and neuroplasticity in the brain. The concept of intensity was based on the research by Fisher *et al* (2008) who looked at different exercise intensities of treadmill walking on gait. This concept replaced the idea of 'forced exercise' in the current research and subjects were asked to exercise at a higher intensity on a stationary bike. Subjects were encouraged to exercise at a higher heart rate

than what was comfortable and for a longer period of time than what was comfortable. Our subjects were able to meet the demands of the exercise intensity for the length of the exercise protocol. All subjects verbally stated that they felt more confident in their exercise capability as a result of this research.

Gait

Gait disorders are an observable hallmark feature in those living with Parkinson's Disease. It is believed that gait disorders occur as a result of damaged central nervous system involving locomotor synergies and automaticity due to the degeneration of dopamine and loss in dopaminergic producing neurons (Frenkel-Toledo, 2005; Sofuwa *et al*, 2005). Observable gait disorders in Parkinsonian patients include rigidity, hypokinesia, freezing of gait, reduced toe clearance, shuffle, decreased walking speed, longer double stance phase and shorter stride lengths.

As the disease progresses, walking gait worsens as stride length reduces, walking speed becomes slower and there is a longer double stance phase in Parkinsonian patients (Sofuwa *et al*, 2005). Fisher *et al* (2008) looked at the effects of high intensity exercise in motor performance in person's with Parkinson's Disease looked at various exercise intensities on walking gait, and Ridgel *et al* (2009) looked at the effects of 'forced' exercise on motor function. Both studies noticed improvements in gait and motor function following intense and 'forced' exercise. In the current study average stride length pre exercise intervention 0.942m. Average stride length post exercise intervention was 0.959m. Stride length increased on all subjects on average of 1.655%. Similar results were seen in another study which looked at the immediate effects of speed on gait

in person's with early Parkinson's Disease. Pohl *et al* (2003) developed three speed treadmill training protocols and one control protocol: structured speed-dependent treadmill training, limited progressive treadmill training and conventional gait training. Their results expressed increases in stride length and speed after structured speed dependent and limited progressive treadmill training – the conventional gait training and control protocol had no changes.

Since this study looked at single exercise session at a high intensity, many hypothesis can be debatable as to the positive increases in stride length and future research may be done to prove the exact cause of stride increase. This research did not focus on psychology of participant and whether gait improvements were a result of increased confidence. Without the access of brain scanners to assess neuroplasticity and changes in brain function or volume, it is unknown whether the stride length increase is due to an immediate rewiring of the brain in response to the demands of a stimulus or consistency of afferent feedback.

A proposed hypothesis for the increase in stride length is the idea of a 'carry-over' or transient cross of the cyclical rhythmic movement forced on a subject by a stationary bike to a normal walking gait. Ridgel *et al* (2008) hypothesized that forced exercise may lead to changes in the central nervous system and will be seen in motor improvement. It is proposed that activities such as this cause an increase in quality and consistency of afferent nerve output and therefore altering the neural patterns in the basal ganglia, allowing for quicker and smoother movements. The global motor improvements seen in the current research study may also be a transient improvement as a result of improved

motor learning. Currently, there is no known research on the concept of a ‘carry-over’ from the cyclical movement on a bike to a walking gait. Yet, in Ridgel *et al*’s study (2008), Dr. Jay Alberts of the Cleveland Clinic designed a new ergometer named Theracycle. Theracycle is a stationary bike that is designed to create high cadences (replicating 80-90 RPM) via a “smart motor” in the hopes of facilitating intense exercise and improving motor function in those living with Parkinson’s Disease.

Kinematically gait velocity was used to measure the effects of intense exercise on gait. Research on gait velocity have shown there is an increase in gait and stride variability in the disease which contribute to falls. Frankel-Toledo *et al* (2005) note that the increase gait variability is related to an increased risk of falls, while gait speed is a relation to fear of falling. In 2008, Fisher *et al* of the University of Southern California obtained preliminary data on the effects of high intensity exercise on walking gait compared with low and zero intensity exercise in Parkinson’s patients. All groups had an improvement in gait performance, with the most consistent improvements seen in the high intensity group, however arguments have been made that changes in gait performance may be due to changes in gait strategy (Fisher et al, 2008). In our research, gait velocity average pre exercise intervention was 0.802m/s, post average gait velocity was 0.798m/s. Average percent change in gait velocity -5.488%. The changes seen could be a result of the transient cyclical movement and speed however more research needs to be done to determine this. The improvement in walking speed can also be a result of improved confidence as a result of exercise and familiarity of the exercise

protocol. Again further research needs to be done to assess the accuracy of the proposed conclusion.

Coupled with a decrease in stride length, a decrease in toe clearance contributes to what is known as the 'Parkinson's shuffle' which contributes heavily to falls. Normal foot strike is a heel-to-toe motion. As the severity of Parkinson's Disease increases, the foot strike becomes a simultaneous strike of the heel and forefoot, causing a flat-foot strike. Based on research on abnormalities in the heel strike of Parkinson's patients, a study by Kimmeskamp & Henning (2000) looked at the heel-to-toe motion characteristics during free walking. The results of the study found that there is a reduced impact on heel strike and depending on the severity of the disease, a higher load in the forefoot area. The researchers also hypothesize that in the beginnings of the double stance phase (heel-strike and toe-off) Parkinson's patients are most unstable and may produce an adaptive mechanism via a flat foot strike (Kimmeskamp & Henning, 2000). Another study by Nieuwboer et al (1999) who looked at the plantar force distribution in Parkinsonian gait reconurred a less pronounced heel strike and an increase in force at the mid-foot in Parkinson's subjects versus normal controls. These studies did not look at toe clearance relationship with forefoot strike, yet it may be possible that there is a possible relationship.

Mean toe clearance for the present study is not exact toe clearance as the marker was on the second and third metatarsal, however with pre exercise intervention the toe marker clearance was 0.0853m. Post exercise intervention, mean toe clearance was 0.079m. Toe clearance percent change was -8.98%. The decrease in toe clearance may

subconsciously reflect a change in gait strategy to accommodate the increase in stride length or it may be related with an increase in forefoot strike force. To obtain a higher toe clearance, a shorter stride length would be a more feasible approach for those without gait training. As hip angle and knee angle the measurements were not calculated and as force production was not obtained, we cannot conclude that the decrease in toe clearance is a result of a change in gait strategy.

Limitations

As a pilot study, there are multiple limitations impacting the results of this study. One such limitation was the stringent exclusion criteria: under the age of 80 years old, no prior history of cardiovascular disease and contraindications such as stroke, aneurism, pulmonary disease, or diabetes. Subjects were also excluded if they presented with any other neurological problems that can affect gait and balance, acute medical problems that could affect gait or balance (such as visual impairments, vertigo, head trauma, musculoskeletal disease or injury, and unpredictable off-periods) were also be excluded.

For ease of accessibility and physicians interested in the purpose of this study, Sacramento Heart & Vascular Associates provided the facility for a means of research clearance given that the subjects qualified and were interested in participation. All participants were required to undergo a graded exercise stress test with EKG for clearance to participate in the study. If apprehensive about walking fast on a treadmill, a Lexiscan Myoview stress test or a Positron Emission Tomography (PET scan) was used. The injection Regadenoson (Lexiscan) a pharmaceutical agent used to vasodilate the coronary vessels and to increase blood flow to the heart muscle during these chemical

stress tests increases heart rate by only by 20-24bpm from rest (Akinpelu and Gonazles, 2012; Lee, 2009). The problem with pharmaceutical stress tests is that a true heart rate max is not reached due to the need for subject safety. As a result, the heart rate “max” achieved from a pharmaceutical stress test for this research are an approximation of true heart rate max, and thus not a good indication for computing target heart rate intensity. The pharmaceutical stress protocol was available to two of the Parkinson’s patients who were not comfortable walking at high speeds on a treadmill without external support such as an overhead harness. The pharmaceutical stress protocol is designed to increase heart rate for those who are unable to walk on a treadmill as a result of mobile impairment or obesity. For future research, a better indication of maximal heart rate under stress should not include a pharmaceutical stress test, or if it does, obtain a true heart rate max after clearance on a bicycle ergometer or treadmill and monitored by a physician and/or registered exercise physiologist.

No accessibility to brain scanner leads only to the conclusions based on observations seen in motor movement. We are unable to determine if the effects seen are a result of neuroplasticity or improved motor learning. The results of this study are on the biomechanical observations seen in gait analyses.

Future Research and Conclusion

While the direct cause of the disease is unknown, the management and treatment has improved based on the research performed at the Cleveland Clinic with intense cycling, its effects on motor improvement and neuroplasticity. Additionally, studies by University of California Los Angeles have looked at the effects of various exercise

intensities on motor function, walking and neuroplasticity. The use of stationary, tandem and motorized-bikes for ‘force’ or intense exercise in research can be transferred to developing therapy models for Parkinson’s patients. There are alternative methods for exercise on a bike if the above bikes are not available, such as recumbent and/or upright tricycle .

The novelty of the current research is the assessment of the immediate effects of intense exercise on walking gait. The idea of a ‘carry-over’ within cyclical movements to walking gait is an interesting idea to further explore at a deeper level.

Past research have demonstrated that the human brain is altered through experience, an enriching environment or “activity-dependent neuroplasticity” such as cultural changes, playing and/or listening to music, and learning a new language (Colcombe *et al*, 2003; Colcombe *et al*, 2006; Petzinger *et al*, 2010). If person’s living with Parkinson’s were to be free to ride safely on a recliner bike or tandem bike, the external cues of other people on the bike trail and wildlife may do more for the person and their disease than riding on a stationary bike at home.

Most research is done within hours of Parkinson’s subjects taking their medications. This is for comfort and liability with research. To improve upon past research exercise interventions on and off pharmaceuticals can be compared and contrasted. Further research on any changes take place without medication interaction on Parkinson’s Disease will help in treatment and management of the disease. Is motor dysfunction reversible without interception of pharmaceuticals? If so, can the duration between patients taking their medication be extended?

As this thesis research looked at the immediate effects of exercise on gait, the true question is when does neuroplasticity first happen in the brain? Other studies (Thomas *et al*, 2010) have shown that after 30 days of intense exercise in rats, angiogenesis took place in the brain, however capillary density levels may return to normal after 4 days if intervention ceases. A lifetime of moderate to intense exercise helps in prevention of Alzheimer's and dementia (DeFina *et al*, 2013). What is the ideal exercise intensity? Can it be based on heart rate, perception or type?

Once diagnosed with the disease in order to cope and live with the disease, those living with Parkinson's Disease undergo a lifestyle change. Medication is the front line defense treatment against the disease. After diagnoses, physical therapy and life interventions take place. Exercise should be incorporated into both physical therapy and life interventions in order to improve the quality of life.

APPENDICIES

Appendix I

**California State University Sacramento
Consent to Participate in a Research Study**

**Acute Effect of Intensive Exercise on Rhythmic Gait in Persons Living with
Parkinson's Disease**

You are being asked to participate in a research study. The purpose of this document is to provide you with information to consider in deciding whether to participate in this research study. Your consent should be made based on your understanding of the nature and risks of the procedures. Please ask questions if there is anything you do not understand. Your participation is voluntary and will have no effect on the quality of your medical care if you choose not to participate.

Investigators:

- | | |
|--------------------------|--|
| 1) Megan Avilla, B.Sc. | xxxx Solano Hall
Sacramento State
University
Ph. No: xxx-xxx-xxxx |
| 2) David Mandeville, PhD | xxxx Solano Hall
Sacramento, CA xxxx
Ph no: xxx-xxx-xxxx |

Source of support:**Site of research study:**

The Biomechanics Laboratory, Solano 1030, Kinesiology and Health Science Department, California State University Sacramento.

Purpose of research study:

The purpose of this study is to determine whether intensive exercise on a stationary bicycle improves gait immediate post activity in persons living with Parkinson's Disease.

Eligibility:

You are being asked to participate because you have been diagnosed with Parkinson's Disease and fall into the stages I-III phase as determined by your physician and neurologist.

Procedures:

If you decide to take part in this research study, you will undergo the following procedures:

- 1) First, you will need clearance by your physician. Your physician will order graded exercise stress test with EKG.
- 2) Second, please complete the provided health history questionnaire and a the Mini State Mental Exam.
- 3) Third, your basic functional mobility will be tested with a Timed Up and Go test.
- 4) Fourth, you will have your walking motion tested in the Biomechanics Laboratory, California State University Sacramento. This testing will last 40 minutes -most of that time you'll be seated, or standing.
- 5) Fifth, you will ride a stationary Monarch bicycle for a total of about 30 minutes: 5 min warm-up, an exercise set of 25 minutes, and a 3 minute cool down. The exercise set of 25 minutes will be based on your heart rate at a predetermined calculation of 60-80% max heart rate.
- 6) Sixth, 3-5 minutes following the exercise protocol, you're walking motion will be tested once again. This testing will last 30 minutes and most of that time you'll be seated or standing.

Potential Risks:

- 1) The risks associated with the gait analysis testing are minimal. You may experience minor skin irritation from the adhesive tape; however this is highly unlikely as the testing period is relatively short. If you have a known allergy to adhesive materials you may choose not to participate. A gait belt will be provided for fall prevention. This is a belt worn about the waist with handles for the researcher in the event of a fall.
- 2) The risks associated with the Monarch bicycle are greater than minimal. This will be a physically demanding exercise requiring at least 60-80% max heart rate for 25 minutes. This form of exercise will result in labored breathing and possibly muscle soreness of the lower limbs. Similar research protocols have been done on Parkinson's patients during stationary cycling and all necessary precautions will be made to ensure your safety from falling off the bicycle. To minimize your risk, you will be required to complete your Health History Questionnaire as accurate as possible; you will be required to be cleared by your primary care physician as well as perform a graded exercise stress test with EKG; and your awareness of physical and mental status will be monitored throughout the course of the study.
- 3) An external defibrillator will be on site in case of a cardiac event, your researchers are CPR and AED certified.

Benefits:

Your participation in this study is completely voluntary. The benefits of this study will be a better understanding of the effects of bicycle exercise on gait in Parkinson's patients. This information will improve our knowledge about alternative ways of improving quality of life for those diagnosed with Parkinson's disease, aside from medications.

Professional Applications:

It is possible that a report may be written and presented at a professional conference as a result of this research project. Your identity will be kept confidential and your data will be coded.

Alternatives to participating in the study:

The procedures performed during the study are solely to increase the existing body of information available for understanding exercise as medicine. As an alternative to participating in this study, you may choose not to participate if wish so.

Cost associated with research study:

Neither you nor your insurance provider will be charged for the costs of any of the special procedures (gait analysis) performed for the purpose of this research study as described above. You will be charged, in the standard manner, for any procedures performed in your routine medical care (Office visit).

Reimbursement for medical treatment:

California State University Sacramento, its agents, or its employees do not compensate for, or provide free medical care for participants in the event that any injury results from participation in a human research project. In the unlikely event that you become ill or injured as a direct result of participating in this study you may receive medical care but it will not be free of charge even if the injury is a direct result of your participation.

Confidentiality:

Information related to you will be treated in strict confidence to the extent provided by law. Your identity will be coded and your personal identify or likeness will not be associated with any published results. Your code number and identity will be kept in a locked file of the principal investigator. In order to monitor this research study, representatives from health sciences institutional review board may inspect the research records which may reveal your identity.

Medical records:

Any records provided to the researchers will be filed and kept in an office that is locked when unoccupied. These records will be returned to you when the research is completed. All records obtained during the course of this study regarding evaluation and treatment will be kept on a password protected computer kept in the locked office.

Freedom to withdraw:

Your participation in this study is voluntary and you may stop your participation at any time and you may stop participation at any time without penalty or loss of rights to which you are otherwise entitled. If you withdraw from the study, your data will be removed from the data set.

Removal from the study:

It is possible that you may be removed from the research study by the researchers if, for example, you are injured between the time of subject screening and your scheduled appointment for data collection or if you undergo other conservative or surgical treatment after the initial data collection.

Authorization for the Use and Disclosure of Identifiable Health Information for Research Purposes:

The following information is provided to you as part of the Health Insurance Portability and Accountability Act (HIPAA), requiring that additional safeguards be put into place to protect the privacy and security of an individual's health information, including persons enrolled as research subjects.

1. What individually identifiable health information will be collected about you as part of this research study?

Individually identifiable health information created from the health history questionnaire will include whether or not you have had any of the following conditions in the last 6 months: head injury, heart disease, other neurological disorders, vision impairment, lower limb injury, or vertigo.

2. Who will provide or collect this information?

The research team or the qualified designee of the principal investigator will be collecting the required information at California State University Sacramento, Sacramento, CA.

3. With whom will the research team share this information?

Your information may be shared with individuals responsible for general oversight and compliance of research activities. Examples of this include the institution's Privacy and Security Officers. All reasonable efforts will be used to protect the confidentiality of your individually identifiable health information that may be shared with others as described above.

4. How long will this information be kept by the research group?

The health history information will be used for approximately 12 months following data collection.

5. What are your rights after signing this authorization?

You have the right to revoke this authorization at any time. If you withdraw your authorization, no additional efforts to collect individually identifiable health information about you will be made. If you chose to withdraw this authorization, you have the right to remove your data from the data set. If you chose to withdraw this authorization, you must do so in writing to the following individual:

David Mandeville, Ph.D.
 Kinesiology and Health Science Department
 xxxx Solano Hall
 Sacramento, CA 95819-6073
 Ph no: xxx-xxx-xxxx

6. What will happen if you decide not to sign this authorization?

Refusing to sign this authorization will not cause any penalty or loss of benefits to which you are otherwise entitled. If you decide not to sign this authorization, you will not be able to participate in the research study.

Voluntary Consent
 (signature page)

All of the above has been explained to me and all of my current questions have been answered. I am encouraged to ask questions about any aspects of this research study, and that future questions will be answered by the researchers listed on the front page of this form.

Any questions I have about my rights as a research participant will be answered by the staff at the Office of the Health Sciences Institutional Review Board, California State University Sacramento (916-278-7565).

By signing this form I do not waive any of my legal rights. By signing this form, I agree to participate in this research study. A signed copy of this consent form will be given to me.

_____	_____	_____
Signature of participant	Name of participant	Date

I certify that the nature and purpose, the potential benefits and possible risks associated with participation in this research study have been explained to the above individual and that any questions about this information have been answered.

_____	_____	_____
Signature of the person obtaining consent	Name of person obtaining consent	Date

I certify that the individuals named above as “participant” and “person obtaining consent” signed this document in my presence.

_____	_____	_____
Signature of witness	Name of witness	Date

Appendix II

Health History Questionnaire

This brief questionnaire is to verify some health information. If you answer yes to any question, and if you're current daily function is moderately or significantly impaired due to that condition, physician approval will be required for participation in the study.

Have you been under recent medical care (last 6 months) for any of the following conditions? (if yes, please explain)

- 1) Have you been hospitalized within the last 6 months for any fall related injuries?
 Yes No
- 2) Have you been hospitalized within the last 6 months for any neurological diseases?
 Yes No
- 3) Have you ever been diagnosed with heart disease?
 Yes No
- 4) Have you been diagnosed with any visual impairments, persistent vertigo, light headedness, unsteadiness or other neurological diseases?
 Yes No
- 5) Do you have lower limb muscle, joint or other orthopedic disorder
 Yes No
- 6) Do you participate in any exercise regimens or engage in any form of physical activity?
 Yes No
- 7) Please provide a list of current medications you are taking:

Print Name: _____

Signature _____

Date: _____

Appendix III

Mini-Mental Examination

Participant: _____ Examiner: _____

Date: _____

Orientation:

What is the:

Time?

Date?

Day?

Month?

Year?

(_____) / 5

points

What is the name of this:

Country?

State?

City?

College?

(_____) / 5

points

Registration:

Name three objects. Score up to 3 points if, at the first attempt, the patient repeats, in order, the 3 objects you have randomly named. Score 2 or one if this is the number of objects he repeats correctly. Endeavour, by further attempts and prompting, to have all 3 repeated, so as to test recall later.

(_____) / 3

points

Attention and calculation:

Ask the patient to subtract 7 from 100, and then 7 from the result – repeat this 5 times, scoring one for each time a correct subtraction is performed.

(_____) / 5

points

Recall:

Ask for the 3 objects repeated in the registration test, scoring each one correctly recalled.

(_____) / 3

points

Language:

Name a pencil and a watch.

(_____) / 2
points

Repeat the following “No ifs, ands or buts”

(_____) / 1

points

Score a 3 if a 3-stage command is correctly executed: “with the index finger of your right hand, touch the tip of your nose and then your left ear”

(_____) / 3

points

On a blank piece of paper write, “CLOSE YOUR EYES” and ask the patient to obey what is written. Score one point if he closes his eyes.

(_____) / 1

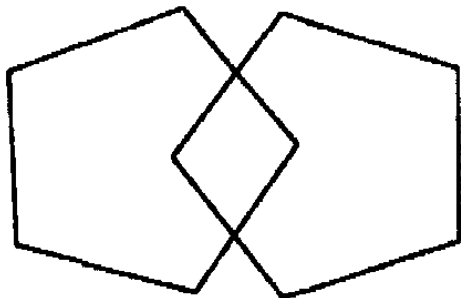
point

Ask the patient to write a sentence. Score one if the sentence is sensible and has a verb and a subject.

(_____) / 1

point

Correctly copy a pair of intersecting pentagons, each side one inch long. Score one if this is correctly copied.



(_____) / 3

points

Total Score: _____ / 30

Dick, J., Guiloff, R., Stewart, A., Blackstock, J., Bielawska, C., Paul, E., Marsden, C. (1984). Mini-mental state examination in neurological patients. *Journal of Neurology, Neurosurgery, and Psychiatry*. 47:496-499.

Appendix IV

Common Pharmaceuticals Prescribed to Parkinson's Patients

Indications	Generic Name	Brand Name	Common Short-Term Side Effects
Bradykinesia, tremor & rigidity	levadopa-carbidopa	Sinemet, Atamet	Dizziness, nausea, psychiatric symptoms, dyskinesia
Bradykinesia, tremor, rigidity, & high levadopa dose	dopamine receptor agonists – ropinirole	Requip	Nausea, drowsiness, sleepiness
	pramipexole	Mirapex	Dizziness, lightheadedness, fainting, nausea
Indications	Generic Name	Brand Name	Common Short-Term Side Effects

Bradykinesia, tremor, rigidity, & high levadopa dose (Cont)	enzymatic inhibitors – monoamine oxidase type B (MAOB) inhibitors; selegiline hydrochloride	Eldepryl	Dizziness, lightheadednes, fainting, dry mouth, nausea
	Catechol-O-methyl transterase (COMT) inhibitors tolcapone	Tasmar	Dizziness, orthostasis, diarrhea, dyskinesai
	entacapone	Comtan	Dizziness, Dizziness, orthostasis, diarrhea, dyskinesai
	levadopa + carbidopa + entacapone	Stalevo	Dizziness, nausea, irregular HR, orthostasis
Indications	Generic Name	Brand Name	Common Short-Term Side Effects
Bradykinesia, tremor, & rigidity	amantadine	Symmetrel	Confusion, nausea, hallucinations
	Anticholinergic drugs – trihexyphenidyl	Artane	Confusion, dry mouth, nausea

	biperiden	Akineton	Confusion, dry mouth, nausea
	procyclidine	Kemadrin	Confusion, dry mouth, nausea
Indications	Generic Name	Brand Name	Common Short-Term Side Effects
Cell death	MAOB inhibitors – selegiline hydrochloride	Selegiline, Eldepryl	Dizziness, lightheadedness, fainting, blurred vision, headache
	rasagiline	Axilect	Mild headache, joint pain, heartburn, constipation
	dopamine receptor agonists – ropinirole	Requip	Nausea, drowsiness, sleepiness
	pramipexole	Mirapex	Dizziness, lightheadedness, fainting, nausea
	bromocriptine	Pariodel	Nausea, constipation, orthostasi

Adapted from Parkinson's Disease powerpoint presentation by Dr. Bryan Coleman of Sacramento State University in 2012

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