EFFECT OF AEROBIC EXERCISE ON COGNITION AND SEDENTARY BEHAVIOR IN PERSONS WITH PARKINSON DISEASE

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BY

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DEDICATION

To my wife, Teralynn, your selflessness and love both sustained me and provided the time necessary to complete this arduous journey.

To my children, Makaila and Cole, who ground me in the reality that this life is not my own.

Physical exercise has some value, but spiritual exercise is much more important, for it promises a reward in both this life and the next.

1 Timothy 4:8

ACKNOWLEDGEMENTS

This project, like many others, is in no way attained by the aspirations of one. Rather, it is a compilation of several individuals for whom I would like to express my gratitude. For Dr. Ann Medley, as my committee chair you helped me navigate the rough waters by rowing with me in a way only two novices could – to the finish line. For Dr. Mary Thompson, always the big picture person, you have continually challenged me to ask, "So what?" and that makes all the difference. For Dr. Elaine Jackson, your expertise in statistics and in physical activity has contributed greatly to the scope of this study. For Dr. Mark Barisa, your matter-of-factness has encouraged me to push through the minutiae that comes when trudging great distances. For Matrix Rehabilitation, without whom I would still be collecting data. For Texas Woman's University, School of Physical Therapy and Baylor Institute for Rehabilitation, you have been my home away from home to both serve and learn at the feet of masters.

ABSTRACT

CHAD SWANK

EFFECT OF AEROBIC EXERCISE ON COGNITION AND SEDENTARY BEHAVIOR IN PERSONS WITH PARKINSON DISEASE

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Parkinson disease (PD) progressively impairs individuals of physical function and cognitive capacity promoting sedentary behavior. Participation in regular exercise improves executive function in elderly persons. However, no studies have observed the impact of exercise on cognitive function or sedentary behavior in people with PD. The purposes of this study were to examine the effect of aerobic exercise on cognitive function and sedentary behavior in persons with PD. Both mode (self paced versus forced) and intensity (≤60 rpm versus >60 rpm) of exercise were investigated. We recruited 20 participants for our 12-week aerobic exercise intervention with 1-month follow-up. Executive function was measured by the Repeatable Battery for the Assessment of Neuropsychological Status™ (RBANS™) and dual tasks (TUG_{manual} and $TUG_{cognitive}$). Sedentary behavior was determined by physical activity level (volume and intensity) as gathered by the StepWatch™ Activity Monitor (SAM). Mann Whitney U tests were selected to analyze the difference between groups – both mode of exercise and intensity. Friedman's Analysis of Variance (ANOVA) test was used to analyze groups

across time to determine the impact of our intervention. Wilcoxon Signed Ranks test was used post-hoc. There were no differences between exercise modes for cognitive function or physical activity. Differences with TUG_{manual} were observed across time ($\mathbf{X^2}$=9.69, p=0.01) for all participants. Specifically, TUG_{manual} scores were different between post-test and 1-month follow-up (z=-2.38, p=0.017) and between baseline and 1-month follow-up (z=-2.83, p=0.005). RBANS™ had differences between post-test and 1-month follow-up (z=-2.876, p=0.004) with post-hoc analysis. No differences were observed for the low pedal rate group on cognition over time. For the high pedal rate group, $TUG_{cognitive}$ scores were significantly different over time (X^2=7.14, p=0.03) but not after post-hoc analysis. Our aerobic exercise intervention failed to minimize sedentary behavior. However, improvements were observed across time for all participants with executive function, specifically dual tasking during gait. While individuals with a high pedal rate may have benefitted from the intervention, the low pedal rate participants achieved clinically relevant improvement and reduced their fall risk. The exercise intervention may be a valuable adjunct for a multidimensional approach to maximize function in persons with PD.

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CHAPTER I

INTRODUCTION

Parkinson disease (PD) progressively impairs individuals of independent physical function and cognitive capacity. While physical function is suppressed by deterioration of the nigrostriatal system, commonly associated cognitive impairments include a wide array of extrastriatal systems including executive function and memory tasks. Therefore, both implicit and explicit memory may be impaired for persons with PD. Participation in regular exercise has been shown to improve working memory and executive function in elderly persons with and without known cognitive deficits. Though animal studies suggest aerobic exercise may benefit persons with neurologic diagnoses (Dishman, et al., 2006), a paucity of literature exists identifying the impact of exercise on cognition. Furthermore, while general exercise and task-specific training have been identified as possible approaches to improve physical performance in people with PD, no studies to date have examined the impact of fitness level on cognitive function.

PD is a common disorder with a conservatively estimated prevalence of 250 to 300 people per 100,000 yielding approximately 800,000 people with this diagnosis (Albin, 2006). However, with an aging population, the burden of PD will increase to an estimated 8.7 million cases worldwide in the next 25 years (Dorsey, et al., 2007). Currently, direct and indirect costs associated with PD exceed $20 billion annually in the United States (Weintraub, Comella, & Horn, 2008).

The well recognized cardinal features of PD are rigidity, tremor, postural instability and bradykinesia. Collectively, these impairments lead to a sedentary lifestyle which has been linked with risk for cognitive impairment (Singh-Manoux, Hillsdon, Brunner, & Marmot, 2005). Furthermore, cognitive impairment is now a well-recognized feature of PD. Between 10 to 20% of people with PD will develop frank dementia (Lewis, Dove, Robbins, Barker, & Owen, 2003) and 24 to 36% of newly diagnosed individuals display evidence of cognitive dysfunction (Muslimovic, Post, Speelman, & Schmand, 2005). The important role of cognition in persons with Parkinson disease was highlighted by Chodosh et al. (2004) who reported strong association between cognitive decline and hospitalization. Independent of medical comorbidities, high-functioning older persons who demonstrated cognitive decline were at greater risk of hospitalization. Similarly, poor cognition was associated with a steeper decline in muscle strength linking poor cognition with ADL disability (Raji, et al., 2005). Furthermore, cognitive impairment is a primary cause of nursing home placement (Goetz & Stebbins, 1993) and reduced quality of life (Schrag, A., Jahanshahi, M., & Quinn, N., 2000b).

Statement of Problem

Cognitive function progressively declines over the course of PD. Motor abilities similarly decline with advancing loss of function. Several studies have attempted to define joined but non-linear relationship between cognitive and motor loss (Burn, et al., 2006; Cooper, Sagar, Jordan, Harvey, & Sullivan, 1991; Goldman, Baty, Buckles, Sahrmann, & Morris, 1998; Locascio, Corkin, & Growdon, 2003). While some studies

have attempted to demonstrate improved gait and balance after aerobic exercise training (Cakit, Saracoglu, Genc, Erdem, & Inan, 2007; Goodwin, Richards, Taylor, Taylor, & Campbell, 2008; Herman, Giladi, Gruendlinger, & Hausdorff, 2007; Skidmore, Patterson, Shulman, Sorkin, & Macko, 2008), no studies have attempted to assess the impact of these interventions on cognition. Moreover, no study has examined the effect of aerobic exercise on sedentary behavior in individuals with PD.

Purposes of Study

Therefore, the primary purpose of this experimental study was to examine the effect of aerobic exercise on cognitive function in persons with PD. A secondary purpose was to determine if aerobic exercise also increases physical activity level. For both purposes, two aspects of aerobic exercise were investigated, a) mode of exercise (self paced versus forced) and b) intensity of exercise ($\leq$60 rpm versus >60 rpm).

Research Hypotheses

Within the scope of this experimental research study, the following research hypotheses were examined:

1. Aerobic exercise, both forced and self-paced, will improve cognitive function and increase physical activity levels.
2. Physical activity levels will be significantly higher immediately following forced aerobic exercise and at one-month followup when compared to self paced aerobic exercise.

3. Cognitive function will be significantly higher immediately following forced aerobic exercise and at one-month followup when compared to self paced aerobic exercise.

Operational Definitions

The following definitions were used throughout the course of this study:

1. *Aerobic capacity* is a state of optimal cardiovascular performance whereby an individual is able to carry out activities of daily living with a functional reserve to adapt to additional demands (Leaf, 1985).

2. *Functional mobility* is the execution of a task or action required for participation in life situations [American Physical Therapy Association (APTA), 2003]. An inability or limitation to perform a task at the level described results in diminished societal roles customary to the specific individual in his cultural and physical environment (APTA, 2003).

3. *Cognition or cognitive function* is the mental activity of acquisition, storage, transformation, and use of knowledge (Matlin, 2005).

4. *Cognitive Impairment* is a transitory or progressive decline of cognitive function without meeting Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM IV) diagnostic criteria for dementia. Using neuropsychological tests, cognitive impairment can be measured in multiple domains including: language, perception, thought, judgment, planning, memory, and attention (Paglieri, Bisbocci, Caserta, Canade, & Veglio, 2008).

5. *Executive function*, an amalgam of working memory and attention, will be measured by Repeatable Battery for the Assessment of Neuropsychological Status (RBANS™[1]) (Randolph, 1998).

6. *Quality of life* (QOL) is broadly interpreted as "happiness" including an assumption of needs, both well-being and health, being met and fulfilled (McKevitt, Redfern, La-Placa, & Wolfe, 2003). Quality of life was measured in this study by the Parkinson's Disease Questionnaire – 39 (PDQ-39[2]) which considers eight aspects of QOL including mobility, activities of daily living, emotions, stigma, social support, cognition, communication, and bodily discomfort (Jenkinson, Fitzpatrick, Peto, Greenhall, & Hyman, 1997).

7. *Aerobic Exercise* is the rhythmical contraction and relaxation of large muscle groups over a prolonged time (Dimeo, Rumberger, & Keul, 1998). Both exercise groups participated in an intervention of aerobic exercise.

8. *Forced Exercise* is an intervention, based upon animal studies, in which the participant is obliged to maintain an augmented rate of exercise compared to a preferred pace (Ridgel, Vitek, & Alberts, 2009). In this study, individuals in the MOTOmed exercise group performed the aerobic exercise intervention with their pace augmented up to 60 rpm via the MOTOmed motorized bicycle.

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[1] The RBANS™ is copyrighted by Pearson Education, Inc. in 2011. A product summary and purchase information are available at www.pearsonassessments.com.

[2] The PDQ-39 is copyrighted by Department of Public Health, University of Oxford. in 2011. A product summary and purchase information are available at www.publichealth.ox.ac.uk.

9. *Self Paced Exercise* is a voluntarily controlled exercise at a preferred pace (Ridgel et al., 2009). In this study, individuals in the self paced exercise group performed the aerobic exercise intervention using a recumbent bicycle.

Assumptions

For this study the following assumptions were:

1. Each participant was appropriately diagnosed with PD.
2. Categorization of participants on the Hoehn and Yahr (HY) scale was appropriate and representative within the population of PD. The primary investigator judged appropriately participants on the HY scale.
3. Participants in this study were representative of the population with PD in terms of aerobic capacity and cognitive function.
4. The participants exerted maximal effort to attain the most accurate results on each measurement tool.
5. The RBANS™ task effectively measured executive function and attention in people with PD.
6. The PDQ-39 accurately revealed subjective QOL for individuals with PD.
7. The Beck Depression Inventory® – II (BDI®-II[3]) accurately portrayed degree of depression for individuals with PD.

[3] The BDI®-II is copyrighted by Pearson Education, Inc. in 2011. A product summary and purchase information are available at www.pearsonassessments.com.

8. The Step Watch™ (Cymatech, Seattle, Washington, USA) step activity monitor (SAM) was able to correctly reflect physical activity during day-to-day life. Furthermore, a 3-day activity cycle accurately reflected participant activity variability.

9. The Timed Up and Go (TUG) test with dual tasks was able to sufficiently require attentional resources in persons with PD.

Limitations

The following limitations were anticipated for this study:

1. A sample of convenience may not be representative of the population of interest. However, analysis of participant demographics (age, gender, and ethnicity) was examined to determine relative similarity to the known population of PD.

2. PD is not uniform but presents with a varied onset and progression of signs and symptoms.

3. Persons with PD may not be able to adequately perform a submaximal cardiovascular assessment due to signs and symptoms consistent with disease progression. Each participant was asked to perform to the best of his ability.

4. No neuropsychological measure is able to detect performance of a specific neuroanatomical structure or region, but only indirectly measures cognitive performance.

Significance of Study

PD is a common disorder with motor and non-motor signs and symptoms including rigidity, tremor, postural instability and bradykinesia, and cognitive impairment. In fact, 24 to 36% of newly diagnosed individuals display evidence of cognitive dysfunction (Muslimovic, et al., 2005). Impaired cognition results in greater risk of hospitalization (Chodosh, et al., 2004), ADL disability (Raji, et al., 2005), is a primary cause of nursing home placement (Goetz & Stebbins, 1993), and reduces quality of life (Schrag et al., 2000b).

Researchers are exploring methods to mitigate cognitive demise. Aerobic exercise in healthy and aging populations has resulted in improvement of multiple cognitive domains (Colcombe, & Kramer,2003; Newson, & Kemps, 2006) and attenuation of cortical volume loss (Colcombe, et al., 2006; McAuley, Kramer, & Colcombe, 2004). However, scant evidence of aerobic exercise and its impact on cognition exists for clinical neurodegenerative populations. Moreover, no study has examined the influence of aerobic exercise on any cognitive domain in persons with PD. Therefore, examination of aerobic exercise and cognitive function in persons with PD lays a foundation for assisting in the potential treatment for cognitive and physical activity restriction.

CHAPTER II

LITERATURE REVIEW

Parkinson disease (PD) progressively impairs independent physical function and cognitive capacity. Though the cardinal features of PD are rigidity, tremor, postural instability and bradykinesia, cognitive impairment is now a well-recognized feature. Participation in regular exercise has been shown to improve working memory and executive function in elderly persons with and without known cognitive deficits. Though animal studies suggest exercise could benefit persons with neurologic diagnoses, a paucity of literature describing the impact of exercise on cognition exists particularly in degenerative diseases. Furthermore, while general exercise and task-specific training have been identified as possible approaches to improve physical performance in people with PD, no studies to date have examined the impact of aerobic exercise on cognitive function. Therefore, the primary purpose of this experimental study was to examine the effect of aerobic exercise on cognitive function in persons with PD. A secondary purpose was to determine if aerobic exercise also increases physical activity level. For both purposes, two aspects of aerobic exercise were investigated, a) mode of exercise (self paced versus forced) and b) intensity of exercise ($\leq$60 rpm versus >60 rpm).

This chapter contains the pertinent extant literature. The literature review begins with a discussion of the pathology and clinical presentation of PD, including motor and non-motor symptoms, followed by the role of physical therapy intervention. The review

will end with a rationale for incorporating physical activity through aerobic exercise to address the cognitive deficits of PD.

Pathology of Parkinson Disease

PD is the most common movement disorder associated with aging (Albin, 2006). Dopamine depletion and deficiency within the nigrostrial structures and projections result in a clinically observed constellation of signs and symptoms. Located in the rostral midbrain, the substantia nigra pars compacta projects to the striatum within the subcortical forebrain. From the striatum, neurons project downstream to other brain regions via dopaminergic pathways. The lack of dopamine results in characteristic clinical features of PD and similar disorders collectively known as parkinsonism.

Clinical Diagnosis and Presentation

Parkinsonism consists of a collection of neurodegenerative disorders that occur from neuron cell loss within different components of the basal ganglia of which PD is a part. Distinction between classic PD and other parkinsonism disorders is often difficult initially, due to a delayed onset of other extraneous clinical features. Though clinical clues such as symmetrical onset, absence of resting tremor, early autonomic dysfunction, dystonia, early significant cognitive impairment or frequent falls can be helpful in initial differentiation, a trial of dopamine often prognostically determines diagnosis. Individuals with PD have a significant positive response to dopamine while other syndromes will have little or no response. In fact, 10 to 15% of people seen initially for parkinsonism are later determined to have a separate parkinsonism syndrome from PD (Albin, 2006).

Diagnosis of PD requires presence of at least 2 cardinal features and a significant response to dopamine trials (Gelb, Oliver, & Gilman, 1999). Therefore, a neurologist specializing in movement disorders should be experienced in accurately differentiating between the subtleties of various clinical syndromes. Despite parceling out PD from other parkinsonism syndromes, the rate of progression of PD and decline of function over time follows a variable and unpredictable course. Though medical treatment is available, it is only symptomatic management while neurodegeneration continues.

Neuroimaging techniques can provide insights for diagnosing PD by revealing cortical and subcortical expressions of motor and non-motor dysfunction. Conventional imaging methods such as magnetic resonance imaging (MRI) have shown significant whole brain atrophy in people with PD when compared with age matched controls with rate of brain atrophy correlated to symptom presentation (Hu, et al., 2001). However, detection of cortical atrophy with MRI is not diagnostic of PD. Because early diagnosis of PD may allow for treatment to slow disease progression, the use of functional imaging techniques such as positron emission test (PET) and functional MRI (fMRI) to determine early neurochemical changes for differential diagnosis are more suitable. The ability to assess these changes is particularly appealing considering the delay of clinically observed symptoms of PD until 80% of striatal dopamine and 50% of nigral neurons have been lost (Nandhagopal, McKeown, & Jon Stoessl, 2008). The implication of this significant striatal neuron loss likely demonstrates compensatory cortical plasticity required to maintain daily function.

Due to progressive striatal neuronal loss, PD is characterized by four cardinal signs: tremor, rigidity, bradykinesia, and postural instability. Typical onset occurs asymmetrically. Tremor, though unclear in etiology and present in multiple pathologies, commonly distinguishes itself in early PD as a resting tremor occurring when the limb is relaxed. In PD, rigidity is abnormal muscle tone characterized by either "lead pipe" type, a uniform resistance throughout the passive joint range of motion, or cogwheel type, a ratcheting resistance throughout the passive joint range of motion. Bradykinesia, often considered a poverty of movement or hypokinesia, is the relative slowness or absence of movement and can be observed throughout the motor system. Postural instability reflects an impairment of systems necessary for maintaining upright postural control in sitting, standing, and walking. Each of these cardinal features are expressed in simple and complex daily tasks: getting dressed, holding a cup of coffee, brushing teeth, getting up from a chair, walking across the room, reading a book, talking with a spouse, and writing a letter.

Clinical and Functional Outcome Measures

The ability to perform simple and complex daily tasks can be assessed using a number of clinical and functional outcome measures. Common disease severity measures include the Hoehn and Yahr (HY) scale and Unified Parkinson's Disease Rating Scale (UPDRS). The HY scale is the original 5-stage PD severity classification system (Hoehn, & Yahr, 1967). The scale begins with stage one describing the early phase of one-sided symptoms and progresses through the bedridden condition of stage 5. The HY

continues to be utilized due to its ease of administration and practicality in clinical trials and clinical practice (Goetz, et al., 2004).

The Unified Parkinson's Disease Rating Scale (UPDRS), currently the most common PD rating scale, is comprised of six sections assessing mentation, motor impairment, activities of daily living, medical complications, a modified HY scale, and disability scale (Fahn, & Elton, 1987). Despite the complexity, the UPDRS has good interrater reliability ($r = 0.80$) and part III correlates well with the HY ($r = 0.80$). While the HY is still commonly used, the UPDRS adds a broader perspective to the progressive disorder.

Physical therapists often include functional disability measures such as Timed Up and Go test (TUG) (Podsiadlo, & Richardson, 1991) and the Gait and Balance Scale (GABS). The TUG examines functional mobility by requiring an individual to stand up, walk 3 meters, turn 180 degrees, walk 3 meters, and sit down. For people with PD, the TUG has an adequate test-retest reliability ($ICC = 0.85$) and a minimal detectable change of 11 seconds (Steffen & Seney, 2008). Motor and cognitive activities can be added to the TUG in order to functionally assess dual tasking (Lundin-Olsson, Nyberg, & Gustafson, 1998; Shumway-Cook, Brauer, & Woollacott, 2000). The GABS assesses its namesake by incorporating several of these tests (Thomas et al., 2004). The scale is comprised of historical data and 14 gait and balance parameters with items from the UPDRS, Tinetti (Tinetti, 1986), Functional Reach Test, and TUG. Though possessing high reliability ($k > .41$), it is clinically time consuming.

Quality of life is reduced in persons with PD and can be assessed by the Parkinson's Disease Questionnaire-39 (Jenkinson et al., 1997). The PDQ-39 is a 39 item questionnaire concerning 8 aspects of quality of life including mobility, activities of daily living, emotions, stigma, social support, cognition, communication, and bodily discomfort. The PDQ-39 has demonstrated good reliability (Cronbach's alpha 0.72 to 0.95 and test–retest 0.76 to 0.93) (Hagell & Nygren, 2007).

Cognitive Deficits in Parkinson Disease

In recent years, there is increasing recognition that motor signs are often accompanied by non-motor deficits in PD (Chaudhuri et al., 2006). While cognitive impairment is accepted as a significant contributor to disability in persons with PD, the mechanism of cognitive loss is not well understood. Though older age at the time of diagnosis worsens the cognitive prognosis, cognitive dysfunction has been difficult to quantify and qualify (Vingerhoets, Verleden, Santens, Miatton, & De Reuck, 2003). In early stages of PD, cognitive impairments include executive function, memory and spatial behavior indicating frontal lobe involvement that coincides with nigrostriatal dopamine deficiency (Vingerhoets et al., 2003). Specifically, dopaminergic dysfunction of the caudate nucleus is related to neurocognitive deficits (Rinne et al., 2000). However, in later stages, deficits in learning and memory implicate the temporal lobe (Vingerhoets et al., 2003) suggesting that cognitive deficits in PD are heterogeneous in neurotransmitter origins (Williams-Gray, Foltynie, Brayne, Robbins, & Barker, 2007). Noradrenergic, serotoninergic and cholinergic dysfunction may all play a role in

cognitive deficits in PD (Lewis, Dove, Robbins, Barker, & Owen, 2003) limiting the overall potential benefit of a singular pharmaceutical intervention.

Not surprisingly, individuals with PD have displayed cognitive deficits in a wide array of neuropsychological measures. However, core domains measured include memory, attention and executive function (Muslimovic et al., 2005). The Tower of London (TOL) task is a well-known neuropsychological measure used to assess planning performance requiring working memory (Shallice, 1982). A modified computerized version of the TOL (Beauchamp, Dagher, Aston, & Doyon, 2003) when utilized with neuroimaging reveals a compensatory shift of neural activation from the failing caudate nucleus to the hippocampus (Beauchamp, Dagher, Panisset, & Doyon, 2008; Carbon & Eidelberg, 2006; Nandhagopal et al., 2008). The hippocampus is important in forming new memories and retrieving old memories. Brain derived neurotrophic factor (BDNF) plays a fundamental role in this process. This neuroplastic functional neural network shift from striatum to hippocampus may allow exercise mediated BDNF to influence cognition in persons with PD.

Repeatable Battery for the Assessment of Neuropsychological Status™

A typical neuropsychological screening to assess deficits in PD includes measures for general function, attention and memory domains, language domain, visuospatial domain, and executive function (Okun et al., 2007). Though many specific measures may be suitable, a sample of tests for these areas could include the Mini-Mental State Exam (Folstein, Folstein, & McHugh, 1975), Paced Auditory Serial Addition Test

(Gronwall, 1977), Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983), Benton Judgement of Line Orientation (Benton, Hamsher, Varney, & Spreen, 1983), and Stroop Interference Procedure (Stroop, 1935). The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS™) (Randolph, 1998) attempts to combine these domains into a singular screening tool with individual domain scores and a total score. To this end, its advantages are brevity and tolerability compared to extensive neuropsychological batteries while offering more clinical information than a general screening tool (Randolph et al., 1998). Specifically, the RBANS™ is able to distinguish between various dementias (i.e. Alzheimer's disease and PD) and discriminating patterns of cognitive impairment in PD (Beatty et al., 2003).

Impact of Parkinson Disease on Cardiovascular Function

Two of the most commonly occurring complications associated with PD are cognitive impairment (24 to 36%) (Muslimovic et al., 2005) and autonomic dysfunction (20 to 50%) (Goldstein, 2003). Cardiac autonomic dysfunction, including orthostatic hypotension and cardiac sympathetic denervation (Goldstein, 2003) with increased risk of cardiac fibrosis (Fornai, Ruffoli, Soldani, Ruggieri, & Paparelli, 2007), contribute to cardiac disease. Cardiovascular conditions have emerged in nearly 30% of cases with PD (Martignoni et al., 2004) with heart failure twice as frequent compared to the normal population (Zesiewicz et al., 2004). Furthermore, an overall 2.3-fold increased risk of death in persons with PD has been associated with cardiac disease (Driver, Kurth, Buring, Gaziano, & Logroscino, 2008) and stroke. Indeed, co-morbidities in PD are twice as

common compared to the general population with hypertension as the third most frequently occurring comorbidity (Pohar & Jones, 2009). Pharmacological management of PD with levodopa has demonstrated no beneficial impact on managing either autonomic dysfunction (Martignoni et al., 2006) or cognitive impairment (Morrison, Borod, Brin, Halbig, & Olanow, 2004).

Impact of Parkinson Disease on Quality of Life

Not surprisingly, individuals with PD report lower quality of life (QOL) compared with the general population (Schrag, Jahanshahi, & Quinn, 2000a). In fact, depression (Behari, Srivastava, & Pandey, 2005; Muslimovic et al., 2005; Muslimovic et al., 2008; Schrag, Jahanshahi, & Quinn, 2000b) and axial impairment (Muslimovic et al., 2008; Schrag et al., 2000b) strongly influence a lower QOL in PD. Disability and cognitive impairment have also been shown to reduce QOL (Schrag et al., 2000b). An estimated that 11 to 44% of people with PD experience depression (Thanvi, Munshi, Vijaykumar, & Lo, 2003), whereby depression has been observed to be a co-habitator with cognitive impairment (Julian L, 2007). Interestingly, depression may also impair physical fitness performance (Hollenberg M, 2003) and functional activities in PD (Stella, Banzato, Barasnevicius Quagliato, & Aparecida Viana, 2008).

As cognitive function progressively declines over the course of PD, motor impairment similarly declines with advancing loss of function. Several studies have attempted to define this relationship (Burn, et al., 2006; Cooper, et al., 1991; Goldman, et al., 1998; Locascio, et al., 2003). Though current literature suggests benefits of physical therapy intervention, results are not conclusive (Deane et al., 2002). Exercise, treadmill training, balance training, and cued activities are probably effective to improve functional outcomes, but results are not lasting (Suchowersky et al., 2006). A review of current intervention strategies and suggested impact on people with PD follows revealing that while physical therapy is unlikely to influence the disease itself, it may improve daily functioning and influence secondary health problems (Keus, Bloem, Hendriks, Bredero-Cohen, & Munneke, 2007).

External versus Internal Cuing

Sensory cues, whether environmental or self-generated, are an attempt to facilitate automatic movements lost through basal ganglia degradation. Sensory cues are generally categorized into visual, auditory, somatosensory, and cognitive. Visual, auditory, and somatosensory cuing strategies employ external environments to aid mobility. However, cognitive strategies use explicit memory to replace implicitly learned tasks. While external cues are able to improve mobility by directing attention to the specific task (Thaut et al., 1996), cognitive strategies are equally effective (Morris, Iansek, Matyas, & Summers, 1996). However, task complexity appears to interfere with limited attentional

resources. When task requirements exceed the capacity of attentional resources, performance deteriorates (Rochester et al., 2004). When the basal ganglia are defective, control of automatic movements may be mediated by cortical mechanisms draining, otherwise available, attentional resources (Cunningham, Iansek, & Bradshaw, 1999). In addition to automatic behavior like ambulation, clinical symptoms such as executive dysfunction, depression, fatigue, and balance impairment, compete for limited attentional resources (Rochester et al., 2004). Consequently, task complexity common to daily functional tasks may result in observable impairment.

In this environment of competing influences, externally and internally driven cues may require different attentional system loads. Movement occurring through an internally generated initiative requires planning, feedback, and feedforward monitoring throughout the task demands attentional resources. However, an external cue, through selective frontal cortical control, may demand relatively less attentional resources most apparent on complex functional tasks (Rochester et al., 2005). External cues that focus on multiple parameters of movement (temporal and spatial) may be of greater benefit than cues on a single parameter (Rochester, Burn, Woods, Godwin, & Nieuwboer, 2009). In contrast however, levodopa appears to preferentially respond to internally generated cues (Kelly, Hyngstrom, Rundle, & Bastian, 2002).

In addition to limited attentional resources and degenerating automaticity, deficient executive functioning causes interference in performing dual tasks (Wu & Hallet, 2008). These deficits may contribute to a "posture second" strategy in the

presence of multiple or complex tasks to the detriment of balance and falls (Bloem, Grimbergen, van Dijk, & Munneke, 2006). Specifically, gait symmetry appears to be an automatic process. However, in the face of a degenerating basal ganglia, maintenance of gait symmetry becomes attention demanding. When presented with a dual task and declining executive function capabilities, gait symmetry becomes increasingly variable escalating fall risk *(Yogev* et al., 2005).

Treadmill Training

Locomotor treadmill training has evolved from an intervention for spinal cord injury to application for a wide range of neurologic diagnoses. Emerging from spinalized cats (Barbeau & Rossignol, 1987), treadmill training is currently promoted for spinal cord injury (Dobkin et al., 2006), stroke (Barbeau & Visintin, 2003), traumatic brain injury (Mossberg, Orlander, & Norcross, 2008), pediatric diagnoses of Down's syndrome (Ulrich, Ulrich, Angulo-Kinzler, & Yun, 2001) and cerebral palsy (Provost et al., 2007), and degenerative diseases including MS (Giesser, Beres-Jones, Budovitch, Herlihy, & Harkema, 2007) and PD (Herman et al., 2009). While Cochrane reports have reported insufficient evidence in favor of locomotor treadmill training (Mehrholz, Kugler, & Pohl, 2008; Moseley., Stark, Cameron, & Pollock, 2005), locomotor treadmill training has elicited benefits of advanced mobility (Behrman et al., 2005; Pohl et al., 2007), enhanced gait kinematics (McCain et al., 2008), improved activities of daily living (Pohl et al., 2007), improved cardiovascular fitness (Macko et al., 2005), and psychological well-being (Hicks & Martin Ginis, 2008). Additionally, treadmill training has demonstrated

improved subcortical neural network plasticity (Luft *et al.*, 2008). Specific parameters of locomotor treadmill training for optimal carryover to overground gait remain elusive. Parameters currently discussed to possibly influence potential therapeutic gain include timing, duration, and frequency of intervention, use of body weight support, treadmill speed, and cross-training with overground gait (Lamontagne & Fung, 2004; McCain et al., 2008; Nilsson et al., 2001; Pohl, Mehrholz, Ritschel, & Ruckriem, 2002; Sullivan, Knowlton, & Dobkin, 2002).

For application of locomotor treadmill training in PD, the ideal combination of parameters is unknown (Miyai et al., 2000). However, benefits appear to be speed-dependent (Miyai et al., 2002; Pohl, Rockstroh, Ruckriem, Mrass, & Mehrholz, 2003). While treadmill training in PD is a relatively new intervention, some benefits have been identified. Locomotor treadmill training in PD animal models has been shown to promote cardiorespiratory endurance (Al-Jarrah et al., 2007) while improving gait and reducing falls (Protas, et al., 2005) in persons with PD. Treadmill training may encourage a more stable gait pattern by increasing gait velocity, enhancing rhythmicity, and diminishing stride variability (Herman et al., 2009). This improved gait pattern after treadmill training boosts walking confidence and shrinks fear of falling (Cakit, Saracoglu, Genc, Erdem, & Inan, 2007). While some studies have attempted to demonstrate improved gait and balance after aerobic treadmill training (Cakit et al., 2007; Skidmore et al., 2008), no studies have attempted to observe the impact of locomotor treadmill training on cognition.

Exercise Training

One recent study suggests that a multimodal exercise program for people with PD may improve executive function (Tanaka, Carlos de Quadros, Santos, & Stella, 2009). Physical exercise impacts mortality by preventing deterioration from lack of activity (Kuroda, Tatara, Takatorige, & Shinsho, 1992). Moderate exercise for 8 weeks has resulted in improved QOL (Baatile, Langbein, Weaver, Maloney, & Jost, 2000) while intense exercise over 14 weeks improved motor performance (Reuter, Engelhardt, Stecker, & Bass, 1999b). Slower walking speeds are common in people with PD and likely results in progressive deconditioning (Canning, Ada, Johnson, & McWhirter, 2006). Additionally, respiratory muscle weakness may inhibit endurance exercise function in PD (Haas, Trew, & Castle, 2004). However, more frequent physical activity has been associated with greater exercise capacity (Canning, Alison, Allen, & Groeller, 1997). Indeed, individuals with mild to moderate PD have abnormal differences in peak power with elevated heart rate and oxygen consumption at submaximal levels compared with peers without PD (Protas, Stanley, Jankovic, & MacNeill, 1996). Nonetheless, cardiovascular training and testing can occur in people with PD (Canning et al., 1997; Protas et al., 1996; Reuter et al., 1999a) and may be more practical when done using a cycling protocol (Protas et al., 1996). While, the gold standard of aerobic assessment is VO_{2max} testing, peak VO_2 may also be a sensitive tool (Kramer, Colcombe, McAuley, Scalf, & Erickson, 2005). Defined as peak oxygen consumption during a specific task, VO_{2peak} has been comparable in persons with PD to maximal values of age-matched

normals reflecting maximal exercise performance on cycle ergometer tests (Protas et al., 1996).

While some studies have demonstrated improved gait, balance, economy of movement and quality of life after aerobic training (Cakit et al., 2007; Goodwin et al., 2008; Herman et al., 2007; Schenkman, Hall, Kumar, & Kohrt, 2008; Skidmore et al., 2008), no studies have attempted to observe the impact of aerobic exercise on cognition in humans. One study using a chronic severe mouse model reported autonomic and metabolic system adaptations to exercise, but no evidence of neurorestoration of nigrostriatal dopamine function (Al-Jarrah et al., 2007). However, non-motor symptoms of PD may be a result of impairment of non-dopaminergic pathways. As a result, though exercise did not restore nigrostriatal function in this chronic severe mouse model, aerobic exercise may still promote neurorestorative or enhance neuroconnective function of non-dopaminergic systems. Nevertheless, an increase in dopaminergic availability (Petzinger et al., 2007) and release into the dorsal striatum (Ouchi et al., 2002) has been demonstrated after regular exercise. Additionally, low levels of brain derived neurotrophic factor (BDNF) in the hippocampus of PD (Imamura et al., 2005) may be improved with intensive physical activity (Dishman et al., 2006). Basal levels of physical activity are necessary to maintain normal levels of BDNF and subsequent potential for neuroplasticity (Gomez-Pinilla F, Ying, Roy, Molteni, & Edgerton, 2002). Specifically, forced exercise is neuroprotective in parkinsonian animal models (Tillerson, Caudle, Reveron, & Miller, 2003) and may alter cortical excitability due to augmented quantity

and consistency of afferent information (Ridgel et al., 2009). Furthermore, despite ongoing degeneration of the nigrostriatal system, regular exercise through well devised physical therapy may prevent decline and enhance neural function of impaired motor systems in people with PD (Bergen et al., 2002; Schallert & Tillerson, 1999).

Aerobic Exercise and Cognition

Animal Studies

Regular physical activity, aside from health benefits of decreased risk of coronary heart disease, improved lung function, and improved lower-extremity function, may have neurogenerative, neuroprotective and neuroadaptive influences on the central nervous system. Growing evidence from the neurobiology of exercise shows favorable brain plasticity and health protective benefits (Dishman et al., 2006). Animal studies suggest several metabolic and oxidative responses to acute and chronic exercise. Though unclear as to specific mechanisms, regular physical activity improved brain health in depression and cognition, particularly executive functions. Exercise increases the stimulation of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) which modulates neuronal plasticity in the hippocampus while mitigating the consequences of stress by altering the serotonergic and norepinephrine systems. Mattson, Duan, Wan, and Guo (2004) report that enhancement of BDNF signaling by behavioral manipulations of cognitive stimulation, diet and exercise may help promote healthy brain aging. This may in part occur as exercise induced expression of BDNF is associated with increased expression of PI-3 kinase/Akt pathway which has a role in enhancing neuronal survival

(Chen & Russo-Neustadt, 2005). Additionally, the role of BDNF for synaptic plasticity in the hippocampal region aids learning and memory.

Essential for promoting survival of striatal neurons, BDNF exerts neuroprotective influence against excitotoxicity in the striatum (Perez-Navarro, Alberch, Neveu, & Arenas, 1999). Additionally, sufficient levels of BDNF are critical for cognitive function (Tsai, 2003) and may suggest potential for neuroplasticity (Kramer, Erickson, & Colcombe, 2006). BDNF protein expression is reduced in both the substantia nigra (Mogi et al., 1999) and hippocampus (Imamura et al., 2005) of individuals with PD. Serum BDNF levels elevate with intensity dependent exercise (Ferris, Williams, & Shen, 2007).

It appears basal levels of neuromuscular activity are necessary to maintain normal levels of BDNF and subsequent potential for neuroplasticity (Gomez-Pinilla et al., 2002). Vaynman, Ying, and Gomez-Pinella (2004) suggest short and moderate exercise periods may be sufficient to enhance cognitive function. Re-exposure to exercise after a "rest" period of weeks has also been shown to have benefit by rapidly reintroduce BDNF protein to levels normally requiring several weeks of exercise (Berchtold, Chinn, Chou, Kesslak, & Cotman, 2005). This may be important as degenerative disease states often preclude regular prolonged exercise but allows for intermittent bouts. The reduction of damage (neuroprotective) after brain injury and delay in onset (neuroplasticity) of Alzheimer's Disease by exercise increasing the availability of BDNF has not been duplicated by either pharmaceutical or other behavioral interventions (Cotman &

Engesser-Cesar, 2002). Additionally, chronic exercise increases cerebral blood flow and oxidative capacity (Dishman et al., 2006).

However, much of the research has been from animal subjects with scant information about the application to human populations. Suggestions for future research include determining the effect of dosage parameters of physical activity on brain function, identifying the impact of exercise on various disease models for cognition and motor recovery and using neuroimaging with human subjects to identify neural morphology with exercise (Dishman et al., 2006). As a caveat, exercise administered too soon after injury may delay recovery resulting in an optimal time-window for exercise interventions following injury (Griesbach, Gomez-Pinella, & Hovda, 2004; Griesbach, Hovda, Molteni, Wu, & Gomez-Pinella, 2004). Future research is necessary to determine if or when exercise may best be employed to lead to recovery.

Healthy Aging Human Studies

Prompted by basic science, healthy human subject studies have begun to examine the neuroprotective benefits of exercise on cognition. Exercise may result in higher brain or cognitive reserve hypothesis by increasing neural efficiency (Deary, Whalley, Batty, & Starr, 2006). In healthy normals, early life physical activity was significantly associated with information processing speed independent of later physical activity (Dik et al., 2003). Furthermore, Singh-Manoux et al. (2005) reported low levels of physical activity in middle age being a risk factor for cognitive functioning. Additionally, long term regular physical activity was associated with significantly better cognitive function and

less cognitive decline in older age (Weuve et al., 2004). Though, fluid intelligence associated with information processing and short term memory may be most susceptible to cognitive decline (Singh-Manoux et al., 2005), fitness may have a selective protective effect against cognitive decline particularly in measures of processing including attention, working memory and speed (Newson & Kemps, 2006). Furthermore, level of cardiorespiratory fitness has shown protection of global cognitive function and attention/executive function (Barnes, Yaffe, Satariano, & Tager, 2003). Vigorous physical activity may not be necessary; walking the equivalent of at least 90 minutes per week at a 21-30 min/mile pace was associated with higher cognitive performance (Ghisletta, Bickel, & Lovden, 2006). Leisure activity may also lessen the decline in perceptual speed (Ghisletta et al., 2006). Neurocognitive benefits from moderate cardiovascular fitness begin to accrue in as short as 6 months (Colcombe et al., 2004).

Despite the non-human and growing number of human subject studies strongly supporting the link between chronic physical activity and cognitive benefits across the human lifespan, the neurorestorative ability of exercise to induce cognitive change in an aging or clinical human population has been less clear. Colcombe and Kramer (2003) performed a meta-analysis to examine the effects of fitness on cognitive function. Examining 18 articles from 1966 to 2001, the authors concluded that exercise had the greatest effect on executive processes but also improved spatial and speed processes. The meta-analysis also suggested that exercise interventions may be equally beneficial for clinical and non-clinical populations.

Studies with Clinical Populations

As provocative as the above human studies appear, it is unclear whether or not similar neurostructural and neurocognitive will accrue in persons with pathologically impaired central nervous systems. In response, the scientific community has begun to examine the benefits of physical activity from neurotrophic and cerebral morphological viewpoints in various clinical populations including Alzheimer's disease and Multiple Sclerosis. In a large scale prospective study, Laurin, Verreault, Lindsay, MacPherson, and Rockwood (2001) showed a significant protective effect of regular exercise on the risk of cognitive impairment in Alzheimer's dementia. Though these effects were observed throughout the cohort, the greatest associations were with women where a greater exercise frequency yielded the most protective effect in a dose-response relationship. These results were corroborated in a meta-analysis of the effect of exercise on cognition in persons with cognitive impairment (Heyn, Abreu, & Ottenbacher, 2004). A medium treatment effect was observed for the combined outcomes of physical, cognitive, functional, and behavioral components in persons with dementia and other related cognitive impairments. However, the largest effect sizes were observed in those individuals who were most impaired and those who accrued a higher number of training sessions per week. Furthermore, increased activity may improve cognition in individuals with cerebral palsy (Damiano, 2006). To date, no study has examined the impact of cardiovascular fitness on cognition in PD.

Corroboration of Neuropsychological Measures and Neuroimaging

Neuroimaging technology has corroborated the neuropsychological findings that exercise influences cognitive function. McAuley et al. (2004) indicated that cardiovascular fitness levels significantly tempered the trajectory of age-related tissue loss by using MRI scans. In particular, significantly less grey matter loss was observed in the frontal, temporal and parietal lobes and in the anterior and posterior white matter tracts. Highly fit individuals exhibited significantly greater activity in cortical regions associated with attentional control: right middle frontal gyrus, superior frontal gyrus, superior parietal lobules with significantly less activation in the anterior cingulated cortex as identified using fMRI (Colcombe et al., 2004). Indeed, the cortical regions most predominately affected by aging show the greatest influence aerobic exercise (Colcombe et al., 2003). Moreover, fitness moderated the age related decline in tissue density. Furthermore, an increased volume in both gray and white matter, primarily of prefrontal and temporal cortices, was found in the elderly fitness trained group (Colcombe et al., 2006). Neuroimaging has also corroborated cortical plasticity after aerobic exercise in neurodegenerative populations(Prakash et al., 2007). Though exercise participation may be remediative to the functional integrity of the brain, the dose response relationship among mode, duration and intensity between exercise and cognition remains unclear (Kramer et al., 2005).

Cardiovascular Performance with Aging

While exercise has shown benefit for motor signs and quality of life, aerobic fitness may promote cognitive function as well. In isolation from disease-related deficits, Fleg et al. (2005) determined a longitudinal decline of VO_{2peak} in healthy adults. Interestingly, the rate of decline was not linear but accelerated with advancing age. This finding was independent of level of physical activity as demonstrated by a similar relative decline in peak VO_2 in endurance trained versus sedentary women. The important clinical ramifications are older persons ability to function independently in the community often depends on cardiovascular endurance and muscular strength to perform basic activities of daily living. This accelerated loss of aerobic function contributes to low levels of physical activity. Though rate of decline in VO_{2peak} is not fully restored by increased physical activity, habitual aerobic activity was accompanied by higher peak VO_2 levels at all ages and was maintained over the lifespan. Riebe et al. (2005) corroborated the role of physical activity and function in older adults observing age to be a "significant moderator variable affecting stage of change, physical activity, and physical function".

Effect of Lifestyle on Cognition

Impaired cognition may also be a result of contributing lifestyle influences. Obesity, stress and lack of sleep may be confounding factors in this study. Previous studies have indicated that 60% of Americans are overweight with nearly half of these obese (Ogden et al., 2006). The deleterious effects of being overweight or obese are numerous and include reduced life expectancy, coronary heart disease, type 2 diabetes

mellitus, sleep apnea and stroke (Olshansky, et al., 2005). Additionally, there is increasing evidence associating obesity with adverse neurocognitive outcomes. Longitudinal studies have linked obesity to temporal lobe atrophy (Gustafson, Lissner, Bengtsson, Bjorkelund, & Skoog, 2004) and dementia (Gustafson, Rothenberg, Blennow, Steen, & Skoog, 2003) in older adults. Additionally, middle-aged obese adults may experience greater brain atrophy (Ward, Carlsson, Trivedi, Sager, & Johnson, 2005) with memory deficits (Gunstad, Paul, Cohen, Tate, & Gordon, 2006) including executive function performance (Gunstad et al., 2007).

However, increasing physical activity and moderating food intake can have beneficial effects of preventing obesity which contribute to maintenance of functional performance and cognitive health later in life (Hendrickx, McEwen, & van der Ouderaa, 2005). Dietary restriction consisting of caloric restriction and intermittent fasting affects gene expression and various levels of proteins to activate stress response pathways (Mattson et al., 2004b). Exercise may also counteract the deleterious effects of stress (Sarbadhikari & Saha, 2006). Together, dietary restriction, mental exercise, and physical fitness may induce the genetic expression encoding proteins to promote synaptic plasticity and neurogenesis (Mattson et al., 2004a) reducing the incidence and severity of neurodegenerative disorders (Mattson, 2000). This may be possible because diet and exercise target the hippocampus influencing activation of synaptic plasticity molecules (Molteni et al., 2004).

Sleep disorders, in particular REM sleep behavior disorder (RBD), is characterized by the presence of complex motor behaviors during REM sleep and abnormalities of cognition (Ferini-Strambi *et al.*, 2004). Sleep disturbances are common in PD (Chaudhuri et al., 2006) with RBD estimated in one-third of persons with PD without dementia (Gagnon et al., 2002). Specific cognitive impairments in verbal memory, visuospatial processing and executive functions have been identified in persons with PD and RBD (Vendette et al., 2007). Clearly, the presence of sleep disorders could confound any relationship identified between cognition and cardiovascular fitness.

A sedentary lifestyle, linked with risk for both cardiovascular disease (Lloyd-Jones et al., 2009) and cognitive impairment (Singh-Manoux et al., 2005), is common in persons with PD where less time is spent standing and more time is spent lying down than peers (Dunnewold, Hoff, & van Pelt, 1998). Locomotor dysfunction due to decreased and variable stride length, freezing and postural instability (Morris, 2006) is likely to contribute to this sedentary lifestyle. Gait deficits are more pronounced during dual-task events suggesting frontal executive dysfunction (Sniijders, Verstappen, Munneke, & Bloem, 2007). As a result, people with PD are nine times more likely to fall than peers and 25% of people with PD will experience a fractured hip (Bloem, Hausdorff, Visser, & Giladi, 2004). Activity restriction due to fear of falling further predicts declining function and reinforces sedentary behavior (Deshpande et al., 2008). Decreased physical activity may contribute to neurochemical loss in the nigrostrial system (Tillerson, Cohen, Caudle, Zigmond, Schallert, & Miller, 2002). While slower

walking speeds, common in people with PD, likely results in progressive deconditioning (Canning et al., 2006), more frequent physical activity has been associated with greater exercise capacity (Canning et al., 1997).

Summary

PD progressively impairs physical and cognitive function while degrading quality of life. Physical therapy and exercise have demonstrated assistance to improve motor performance. Additionally, aerobic exercise has been shown to improve cognitive performance in healthy individuals and in animal disease models in both neuropsychological measures and neuroimagry. However, after thorough review, a gap in the literature exists between cognition and exercise in persons with PD. Specifically, no study to date has examined the relationship between cognitive function and cardiovascular fitness in PD.

CHAPTER III

METHODOLOGY

Parkinson disease (PD) progressively impairs independent physical function and cognitive capacity. Though the cardinal features of PD are rigidity, tremor, postural instability and bradykinesia, cognitive impairment is now a well-recognized feature. While general exercise and task-specific training have been identified as possible approaches to improve physical performance in people with PD, no studies to date have examined the effect of aerobic exercise on cognitive function. Therefore, the primary purpose of this experimental study was to examine the effect of aerobic exercise on cognitive function in persons with PD. A secondary purpose was to determine if aerobic exercise also increases physical activity level. For both purposes, two aspects of aerobic exercise were investigated, a) mode of exercise (self paced versus forced) and b) intensity of exercise ($\leq$60 rpm versus >60 rpm). This chapter describes the study design, associated variables, instrumentation, procedures and statistical analysis.

Design

This study was an experimental, two group pretest-posttest design with 12 week intervention and 1 month follow-up (Appendix A). Two groups received an aerobic exercise intervention; the experimental group performed forced-use aerobic exercise and the comparison group performed a self-paced aerobic exercise program. Both groups were encouraged to exercise at an aerobic level of 60-80% of maximal heart rate.

Concerning the impact of aerobic exercise training, we hypothesized an improved activity level. However, we anticipated greater improvement within the forced exercise group for both activity level and cognitive function.

Target Population and Variables

Individuals diagnosed with PD were recruited for participation in this study. Each individual diagnosed with Parkinson's disease was classified on disease severity by the Hoehn and Yahr (HY) scale (Appendix B). Additionally, the United Parkinson Disease Rating Scale (UPDRS) was ascribed to each participant (Appendix C). Using six subscales, the UPDRS describes the mentation, motor impairment, activities of daily living, and medical complications while incorporating a modified HY scale, and Schwab & England disability scale. The HY and UPDRS are often used in tandem to describe disease severity. Sublevels of disease severity were identified to perform a modified random assignment to groups blocked on disease severity.

Independent Variable

Aerobic exercise group membership was the independent variable with two levels: forced exercise and self-paced exercise. The forced exercise group performed an individualized aerobic exercise program using the MOTOmed® lower extremity cycle. The self-paced exercise group performed an individualized aerobic exercise program using a stationary recumbent cycle. Each group was asked to perform aerobic exercise for similar duration and intensity.

Dependent Variables

This study consisted of a two groups tested on multiple dependent variables before and after a 12 week intervention and a 1 month follow-up period. Dependent variables included measures of activity level, cognitive function, and QOL. Activity level was assessed by Step Watch™ (Cymatech, Seattle, Washington, USA) step activity monitor (SAM) over a three day, 24 hours/day wearing schedule. QOL was assessed on the Parkinson's Disease Questionnaire -39 (PDQ-39).

Cognition is a complex concept consisting of multiple domains. While global measures exist, specific cognitive domains are more sensitive to both progression of PD and aerobic fitness. Therefore, the specific cognitive domains of executive function and attention were assessed during this study. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS™) (Randolph, 1998) is a screening instrument composed of subsets to examine immediate memory, delayed memory, visuospatial construction, language, and attention. These subsets examined several facets comprising executive function. Divided attention was functionally assessed in dual task scenarios through the TUG under two conditions: TUG_{manual} and $TUG_{cognitive}$ (Shumway-Cook, Brauer, & Woollacott, 2000).

Attribute and Confounding Variables

Potential remaining variables were divided into two categories: attribute and confounding. A common stereotype is that PD affects aged Caucasian males. However, PD affects individuals from both genders, many ethnic groups and a wide range of age. Typical onset occurs between ages 50-80 years, but young onset PD can affect people in their third decade of life. Gender, age, and ethnicity are attribute variables and, while unlikely, may influence potential outcomes. Therefore, we collected these data.

Confounding variables included length of diagnosis and medication. While PD is progressive and degenerative, the relative disease progression and course of treatment are variable amongst individuals. Additionally, the onset of symptoms and diagnosis of PD will vary amongst participants. Consequently, the length of diagnosis may not be reflective of disease severity.

Medication has significant benefits and limitations. Specifically, commonly prescribed dopaminergic medications, such as carbidopa-levodopa, are beneficial for some physical symptoms of PD, but ineffective for mitigating cognitive loss (Morrison, Borod, Brin, Halbig, & Olanow, 2004). Clearly, this confounding variable may impact one or more dependent variables. However, in an effort to maintain ecological validity in this study, individuals were asked to continue antiparkinsonism medications both during cardiovascular and cognitive assessments and training periods. Medications were monitored with particular attention to physician prescribed pharmacological changes, if

any, during the study period in an attempt to allay the influence of medication on outcomes.

A third confounding variable potentially impacting both physical activity and cognition is depression. We measured depression in this study with the BDI®-II.

Participants

Twenty individuals diagnosed with PD were recruited from a sample of convenience through advertisement to local PD support groups from the Dallas-Fort Worth Metropolitan. Participants were assigned, through a modified random assignment blocked on disease severity, to either a forced exercise (MOTOmed®) group or self-paced exercise (stationary bicycle) group to participate in this prospective study. Men and women of any race or ethnic group participanted in this study if they were between the ages of 50-80 years and diagnosed PD stages 1-4 on the HY scale. Persons with acute or uncontrolled co-existing diagnoses of cardiac or respiratory disease, co-existing neurological disease beyond PD, acute orthopedic condition that would limit participation in an aerobic exercise program, gross cognitive impairment as defined by a score of <24 on the MMSE, or inability to complete the cardiovascular fitness assessment in order to determine VO_{2peak} were excluded. A failed cardiovascular fitness assessment is defined as 1) an inability to attain 50-60 revolutions/minute or 2) an inability to demonstrate an increase in heart rate, oxygen consumption or rate of perceived exertion. Persons who met the inclusion criteria and possessed none of the exclusion criteria were asked to

participate in the study. Those who volunteered to participate were asked to read (or be read) the rights to human subjects and asked to sign a consent form.

Instrumentation

Each participant completed a standardized assessment on measures of cardiovascular endurance, activity level, QOL, and cognitive performance. Activity level was assessed using the Step Watch^{TM} (Cymatech, Seattle, Washington, USA) step activity monitor (SAM): The SAM is a research-grade accelerometer for long-term assessment of ambulatory activity during day-to-day life. It is a small (70 x 50 x 20 mm; 38 g), waterproof, self-contained device that is worn on the ankle and records the number of strides taken every minute over a 3-day period. The activity monitor is programmed and downloaded with a standard computer via a USB port docking station. The SAM and dock communicate through an infrared link which allows the SAM to be completely sealed, waterproof and impervious to tampering. The SAM is able to generate information concerning: average steps/day, activity level percentage (inactive, low moderate, high), and peak activity index. SAM, as an accelerometer, is more accurate than pedometers in persons with asymmetrical gait (Pearson, Busse, Van Deursen, & Wiles, 2004). Reliability of the SAM for individuals with PD among other neurological populations has been reported to be ICC = 0.86 (Busse, Pearson, Van Deursen, & Wiles, 2004).

Cardiorespiratory fitness was assessed by peak heart rate and ratings of perceived exertion (RPE). Peak heart rate was monitored by a heart rate monitor during

electronically braked cycle ergometry. Using a progressive and incremental test to measure VO_{2peak}, exercise testing began at a power output of 20 watts with equal increments of 20 watts every minute in order to achieve peak exercise capacity between 6 and 12 minutes (Canning et al., 1997). Participants were instructed to maintain a pedal rate of 50-60 revolutions per minute and continue cycling until no longer able to maintain or increase the work level. RPE (Borg, 1970), a subjective exercise intensity rating, was assessed by the participant using intensity values from 6-20 during and after the assessment (Appendix D).

Cognitive function was assessed by a neuropsychological battery, the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS™) (Randolph, 1998). The RBANS™ is a screening instrument composed of subsets to examine immediate memory, delayed memory, visuospatial construction, language, and attention. This tool is commonly utilized in determining subcortical dementia characteristics and is 78% accurate in classifying dementia in people with PD (Beatty et al., 2003). Divided attention was functionally assessed in dual task scenarios through the TUG under two conditions: TUG_{manual} (Lundin-Olsson *et al.*, 1998) and $TUG_{cognitive}$ (Shumway-Cook et al., 2000). To accomplish familiarity with the task, each participant completed the TUG_{alone} (a non-divided attention task) where the participant was required to stand up at a normal safe pace, walk 3 meters, turn 180 degrees, walk back, and sit down (Podsiadlo & Richardson, 1991). During the TUG_{manual}, the participant carried a full cup of water throughout the task. During the $TUG_{cognitive}$, the participant counted aloud backwards by

three from a randomly selected number between 50 to 100 during the task. Additionally, the participant counted aloud backwards by three as a cognitive alone task to serve as comparison to $TUG_{cognitive}$. The time required to complete each task was recorded. One practice trial of the TUG_{alone} was allowed to familiarize the participant with the task. The sensitivity and specificity of both TUG_{manual} and $TUG_{cognitive}$ were 80% and 93% respectively with an interrater reliability of 0.99 for community dwelling elderly (Shumway-Cook et al., 2000). Interrater reliability of the TUG_{alone} in people with PD was 0.87-0.99 (Morris, Morris, & Iansek, 2001)

QOL was assessed by the PDQ-39. The PDQ-39 is a 39-item disease specific self-assessment questionnaire concerning 8 aspects of quality of life including mobility, activities of daily living, emotions, stigma, social support, cognition, communication, and bodily discomfort (Jenkinson et al., 1997). The PDQ-39 has demonstrated good reliability (Cronbach's alpha 0.72–0.95 and test–retest 0.76–0.93) (Hagell & Nygren, 2007).

Depression was assessed by the Beck Depression Inventory – II (BDI®-II). The BDI®-II (Beck, 1993) is a 21-item questionnaire measuring depression with an internal scale reliability for older adults of 0.86 (Segal, Coolidge, Cahill, & O'Riley, 2008). In people with PD, test-retest reliability was 0.89 (Visser, Leentjens, Marinus, Stiggelbout, & van Hilten, 2006).

Disease severity was assessed using the Hoehn & Yahr (HY) and the Unified Parkinson's Disease Rating Scale (UPDRS). HY is the most common original

classification system for grading severity of PD into 5 stages (Hoehn & Yahr, 1967). The HY continues to be utilized due to its ease of administration and practicality applied in both clinical trials and clinical practice, 89% and 70% respectively (Goetz et al., 2004). The UPDRS is the most common PD rating scale and is comprised of 6 sections assessing mentation, motor impairment, activities of daily living, medical complications, a modified HY scale, and disability scale (Fahn & Elton, 1987). Despite the complexity, the UPDRS has good interrater reliability ($r = 0.8$) and part III correlates well with the HY ($r = 0.8$).

Procedure

Each participant signed an informed consent form approved by Baylor Research Institute and Texas Woman's University (TWU) Institutional Review Board. After giving written consent, each individual participated in pre-intervention assessment using a standardized battery of tests to determine activity level, QOL, and cognitive function. The order of testing was standardized so as to minimize potential variance in performance based upon either mental or physical fatigue. Each testing session required 2 distinct parts in order to blind testers. However, both parts occurred on the same day at the same location. Testing part 1 consisted of cardiovascular fitness assessment followed by part 2 consisting of cognitive function assessment. The testers of part 1 and part 2 were blinded to scores from the other tester.

Prior to baseline testing session, each participant was diagnosed with PD by a neurologist. Baseline testing took place at the School of Physical Therapy, Texas

Woman's University (TWU-PT), Dallas Presbyterian campus and consisted of two parts. During part 1, disease severity rating with the HY and United Parkinson Disease Rating Scale (UPDRS) measures and a cognitive screen with the Mini Mental State Examination (MMSE) were conducted to determine eligibility for the study. Once eligibility was determined, the participant underwent a cardiovascular fitness assessment. Each participant was fitted appropriately to the electronically braked cycle ergometer. Cardiovascular fitness was measured during a progressive and incremental cycle exercise test lasting an anticipated 6-12 minutes. Participants were instructed to maintain a pedal rate of 50-60 revolutions per minute and continue cycling until no longer able to maintain or increase the work level while resistance increased by 20 watts every minute. Each participant reported their rating of perceived exertion (RPE) scale (Borg, 1970) each minute throughout the fitness test. Additionally, heart rate and blood pressure were closely monitored and recorded each minute to ensure participant tolerance and safety. Time requirement to complete part 1 was 90 minutes.

During part 2, each participant underwent a neuropsychological assessment consisting of RBANS™, BDI®-II, and PDQ-39 measures. Additionally, both conditions of the divided attention task (TUG variations) were performed in random order. Anticipated time required to complete part 2 was 60 minutes. At the conclusion of baseline testing, the participant was provided with the StepWatch™ step activity monitor (SAM). The individual was asked to wear the SAM for 3 consecutive days allowing for

removal of the device only for bathing. The participant was scheduled for the exercise intervention.

Exercise sessions took place at Baylor Institute for Rehabilitation (BIR), Dallas, Texas, TWU-PT, and Matrix Rehabilitation, Richardson, Texas. The 12-week aerobic exercise intervention was initiated within one week of completion of baseline testing. Each participant were randomly assigned to either a forced exercise (MOTOmed®) group or a self-paced exercise (stationary bicycle) group. The forced exercise group performed the aerobic intervention at BIR using the MOTOmed®. The MOTOmed® is a computer driven, motorized bicycle with ability to provide passive, active-assistive movement, and active-resistive training. The MOTOmed® provides feedback during and after the workout concerning leg activity symmetry, distance covered with and without assistance, power generation, duration, and energy consumption. The MOTOmed® has improved mobility and cardiovascular endurance in geriatric individuals (Diehl *et al.*, 2008). The self-paced exercise group performed the aerobic exercise intervention at TWU-PT and Matrix Rehabilitation using a stationary recumbent bicycle with manually adjustable resistance.

Participants in each group completed a 12-week aerobic exercise program with 3 exercise sessions per week. Exercise sessions lasted up to 60 minutes consisting of a 10-minute warm-up, 40-minute exercise set, and a 10-minute cool down. A 2-5 minute break was afforded, if needed, every 10 minutes during the 40-minute exercise set. Consistent with Ridgel et al. (2009), participants were asked to sustain aerobic intensity

at 60-80% of individualized target heart rate or 12-14 on the RPE. Individuals in both groups were encouraged to exercise at an increased average heart rate every 4 weeks (i.e. 60%, 65%, 70%, 75% target heart rate). During the exercise sessions, each participant was monitored with a heart rate monitor. Blood pressure was taken at the beginning and end of each session.

At the conclusion of the exercise intervention, each participant performed post-testing in a similar format to baseline testing. All post testing occurred on the same day at TWU-PT and took place within one week after completion of the intervention. Part 1 consisted of a cardiovascular fitness assessment and part 2 consisted of the cognitive assessments. Total post-intervention test time was 2 hours with 60 minutes allotted for each session. At the conclusion of post-intervention testing, the participant was provided with the StepWatch^{TM} step activity monitor (SAM). The individual was asked to wear the SAM for 3 consecutive days allowing for removal of the device only for bathing. The participant was also scheduled for the follow-up testing.

Follow-up testing occurred one month after the completion of the intervention. Participants completed part 1 and 2 in the same manner as the post-intervention test format. Activity monitoring took place for 3 days after completing follow-up testing parts 1 and 2 (Appendix E).

Data Analysis

Power analysis conducted to determine number of participants per group was performed using alpha level of .05, effect size of the RBANS™ (0.55). Anticipated power of 0.6 to 0.7 yielded two groups of 10 participants. Our independent variable of exercise group had two levels: forced exercise and self-paced exercise. A second analysis divided participants into two groups based upon revolutions/minute (rpm) performance of the exercise intervention.

All data collected was entered into a database for analysis by SPSS version 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Demographic and clinical data were compared between groups for descriptive purposes. Descriptive statistics and independent t-tests were utilized for this analysis. Nonparametric analysis of the intervention effect was performed due to limited sample size and failure to meet the assumptions necessary for more robust parametric measures. Mann Whitney U test was selected to analyze the difference between groups – both mode of exercise and intensity. Friedman's Analysis of Variance (ANOVA) test analyzed related groups across time to determine the impact of our intervention. Wilcoxon Signed Ranks test was used post-hoc as necessary. Dependent variables examined separately were physical activity level and cognitive function. Alpha level of .05 was set for all statistical tests. Bonferroni's correction was applied to post-hoc analyses.

CHAPTER IV

RESULTS

Parkinson disease (PD) progressively impairs independent physical function and cognitive capacity. Though the cardinal features of PD are rigidity, tremor, postural instability and bradykinesia, cognitive impairment is now a well-recognized feature. While general exercise and task-specific training have been identified as possible approaches to improve physical performance in people with PD, no studies to date have examined the effect of aerobic exercise on cognitive function. Therefore, the primary purpose of this experimental study is to examine the effect of aerobic exercise on cognitive function in persons with PD. A secondary purpose is to determine if aerobic exercise also increases physical activity level. For both purposes, two aspects of aerobic exercise were investigated, a) mode of exercise (self paced versus forced) and b) intensity of exercise ($\leq$60 rpm versus >60 rpm). This chapter provides a description of the study participants in total and group characteristics. Next, descriptive and inferential statistical data are provided comparing measures in the two groups before and after the exercise intervention. Lastly, determination of a responder group is provided for appropriate variables.

Subjects

Twenty participants who met the inclusion criteria were enrolled in this study. Participants were recruited from a sample of convenience in the Dallas-Fort Worth Metroplex including local hospitals and support groups. Fourteen participants completed the 12-week exercise training program and post-intervention assessment. Thirteen participants returned for 1-month follow-up assessment. The 7 participants who dropped out of the study represent an overall 35% dropout rate. The Forced Exercise group had an attrition rate of 44.4% while the Self Paced exercise group had an attrition rate of 27.3%. A flow diagram summarizing participant recruitment, participation, and attrition is presented in Figure 1.

The 20 participants who were enrolled in the study consisted of 15 men and 5 women. While 15 participants did not use an assistive device for mobility, 1 individual used a wheelchair, 2 used walkers, and 2 used canes. Of the 7 participants who dropped out, 6 were men. The 13 participants who completed all phases of the study consisted of 9 men and 4 women. In the remaining 13 participants, only 1 person used a walker and 1 person used a cane. Participants were initially assigned to their exercise group based upon a modified random assignment blocked on disease severity. A t-test determined there were no differences between groups at baseline ($p = 0.23 - 0.95$). A summary of characteristics of participants who completed the study is located in Table 1.

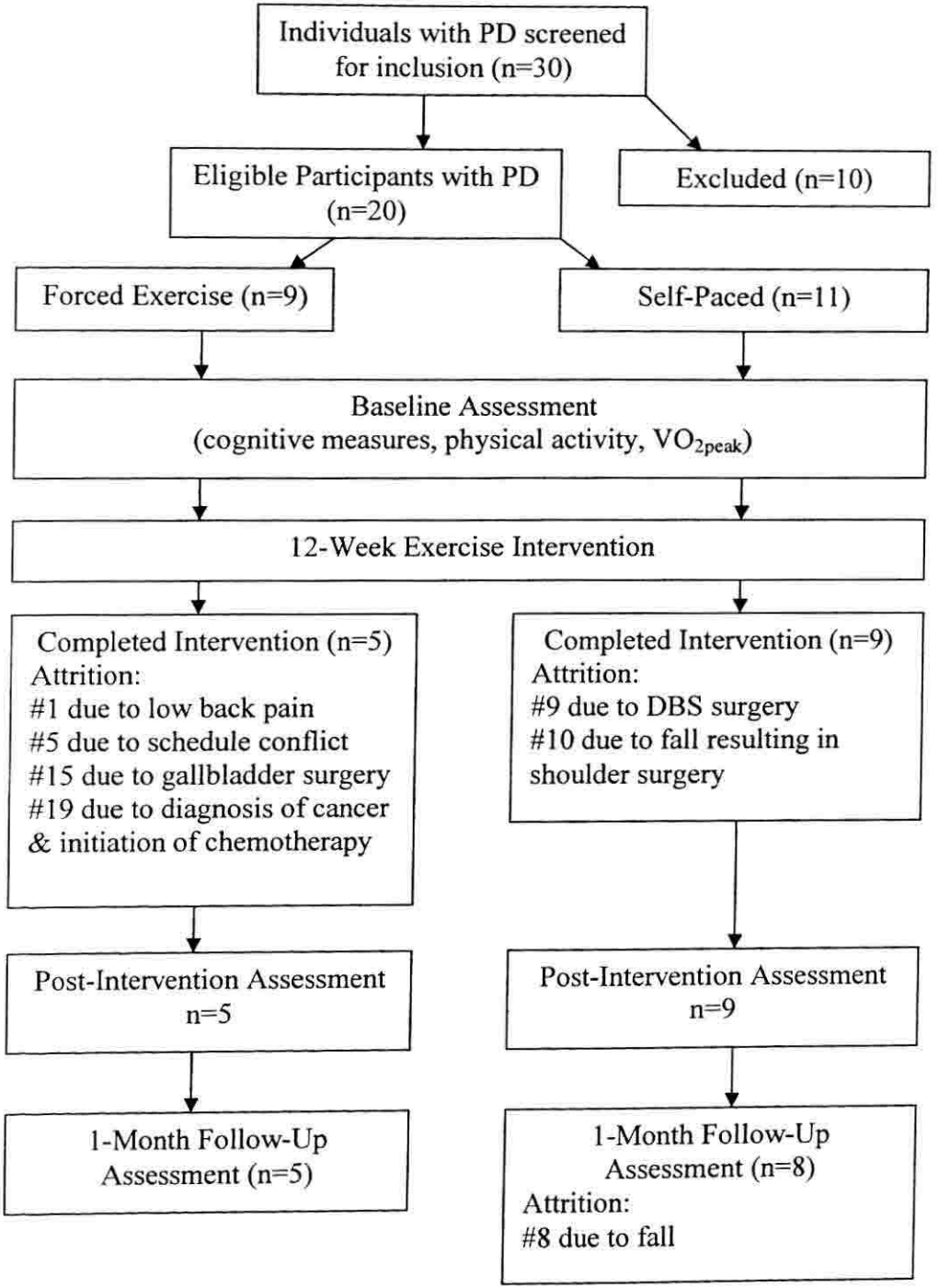

Figure 1. Flow diagram of participant experience

Table 1

Participant Characteristics

	Forced-use Group[a] *M* (*SD*)	Self-paced Group[b] *M* (*SD*)	Total[c]
Age	66.5 (8.76)	70.4 (4.79)	68.45 (7.16)
Length of PD (years)	7.0 (4.5)	9.9 (6.6)	8.5 (5.7)
HY	2.3 (0.8)	2.5 (0.7)	2.4 (0.8)
UPDRS	39.5 (22.3)	43.9 (16.7)	41.7 (19.3)
UPDRS part III	27.2 (17.2)	27.6 (10.1)	27.4 (13.7)

Note. PD = Parkinson disease; HY = Hoehn & Yahr scale; UPDRS = Unified Parkinson Disease Rating Scale; UPDRS part III = Unified Parkinson Disease Rating Scale, motor subscale

[a]$n = 9$. [b]$n = 11$. [c]n=20.

Completion of the study was determined by participation in all phases: baseline assessment, exercise intervention, post-intervention assessment, and follow-up assessment. Each participant who completed the study was also judged according to compliance with the exercise program. Compliance with the exercise program was determined by attendance and the amount of time spent performing aerobic exercise. Participants were determined to have 100% attendance if they completed all 36 exercise sessions within 12 weeks at a frequency of 3 times per week. Participants were considered 100% compliant if they completed 40 minutes of aerobic exercise and attended each session. Beyond attendance and compliance, the progression of the exercise intervention was determined by performance. Table 2 reveals exercise intervention attendance, compliance, and performance.

Table 2

Group Means for Intervention Attendance, Compliance, and Performance

	Forced Use[a]	Self-paced[b]	Total[c]
Attendance (%)	71.75	86.73	80.74
Compliance (%)	62.87	71.96	68.47
Time per session (minutes)	35.02	33.19	33.92
Pedal rate (rpm)	62.34	58.17	59.84

Note. rpm = revolutions per minute
[a]$n = 5$. [b]$n = 8$. [c]$n = 13$.

Nonparametric Statistics Examining the Effect of Aerobic Exercise on Cognitive Function

The primary purpose of this study was to examine the effect of aerobic exercise on cognitive function in persons with PD. Cognitive function was determined by two primary methods: RBANS™ for executive function and dual task variations of the TUG. Initially, forced use and self-paced groups were formed with the expectation that the forced use group would perform at a higher overall intensity. Mann-Whitney U tests were used to analyze the differences between the two groups for both cognitive variables at baseline, post-test, and follow-up intervals. There were no significant differences between the groups at baseline, at post-intervention testing, or at the 1-month follow-up for any of the cognitive function variables. Table 3 has the analysis.

Table 3

Differences Between Forced Use and Self-Paced Exercise Groups on Cognitive Performance

	Forced-use *M* (*SD*)	Self-paced *M* (*SD*)	*p*-value
TUG_{manual} (sec)			
Baseline[a]	13.77 (8.03)	16.39 (18.28)	0.91
Post-test[b]	10.74 (5.14)	14.84 (15.34)	1.00
Follow-up[c]	9.61 (4.53)	8.74 (2.65)	0.94
$TUG_{cognitive}$ (sec)			
Baseline[a]	16.22 (11.81)	17.04 (16.06)	0.91
Post-test[b]	12.33 (7.87)	18.48 (20.41)	0.70
Follow-up[c]	10.78 (5.26)	10.66 (5.93)	0.72
RBANS™ (score)			
Baseline[a]	88.20 (14.17)	89.50 (24.25)	0.97
Post-test[b]	92.40 (9.71)	87.00 (18.31)	0.44
Follow-up[c]	100.40 (9.81)	91.63 (20.69)	0.52

Note. Mann-Whitney U tests were used to analyze the differences between groups; TUG = Timed Up and Go; RBANS™ = Repeatable Battery for Assessment of Neuropsychological Status
[a]$n = 20$. [b]$n = 14$. [c]$n = 13$.

Since there were no differences between the groups on any of the cognitive variables, the decision was made to combine the two groups into one. Both groups performed aerobic exercise because they utilized large muscle groups and worked for a duration of 40 minutes per session. Subsequent analyses, assessed the effect of aerobic activity (regardless of mode used), on cognitive function.

To assess the effect of aerobic exercise on cognitive function in all participants over time, Friedman's analysis of variance (ANOVA) tests were used. Three separate Friedman's ANOVAs were conducted to test differences in each of the dependent variables (TUG_{manual}, $TUG_{cognitive}$ and RBANS™). TUG_{manual} was found to have significant differences across time (χ^2=9.69, p=0.01). Post hoc multiple comparison tests (Wilcoxon Signed Ranks tests) with Bonferroni's correction were then performed on the TUG_{manual} to determine where the significant differences in TUG_{manual} existed. The Wilcoxon Signed-Ranks test revealed significant differences in TUG_{manual} scores between the post-intervention test and 1-month follow-up (z=-2.38, p=0.017) and between the baseline and 1-month follow-up (z=-2.83, p=0.005). RBANS™ was found to have significant differences across time (χ^2=5.92, p=0.05). Post hoc multiple comparison tests (Wilcoxon Signed Ranks tests) with Bonferroni's correction (alpha level / number of tests = 0.05 / 3 = 0.017) were then performed on the RBANS™ to determine where the significant differences in RBANS™ existed. The Wilcoxon Signed-Ranks test revealed significant differences in RBANS™ scores between the post-test and 1-month follow-up (z=-2.876, p=0.004). Table 4 reflects the data analysis.

Table 4

Cognitive Function Over Time for All Participants

	Baseline *M* (*SD*)	Post-test *M* (*SD*)	Follow-up *M* (*SD*)	*p*-value
TUG_{manual}	11.84 (7.54)	10.20 (4.17)	9.07 (3.34)	.01
$TUG_{cognitive}$	13.39 (9.56)	12.23 (7.68)	10.70 (5.45)	.06
RBANS™	94.92 (20.65)	89.62 (15.99)	95.00 (17.37)	.05

Note. Friedman's ANOVA tests were used to analyze differences; TUG = Timed Up and Go; RBANS™ = Repeatable Battery for the Assessment of Neuropsychological Status
[a]$n = 13$.

The second aspect of aerobic exercise that we investigated was intensity. The maximum intensity for the forced use bicycle was only 60 rpm but we realized some participants might pedal at a higher rate. So, we also looked at the differences between participants who pedaled slower than 60 rpm and those who pedaled faster than 60 rpm. Therefore, participants were divided into two groups based on intensity (pedal rate) achieved during the training sessions. Seven individuals pedaled the bicycle or exercised at less than or equal to 60 rpm while the remaining seven individuals pedaled at greater than 60 rpm. Mann-Whitney U tests were used to analyze the differences between the two groups for cognitive variables at baseline, post-test, and follow-up intervals. Differences between pedal rate groups were observed at all time points for both TUG_{manual} and $TUG_{cognitive}$, but no differences were observed at any time point for RBANS™. Table 5 shows the result of this data analysis.

Table 5

Differences Between High Intensity and Low Intensity Exercise Groups on Cognitive Performance

	≤ 60 rpm *M* (*SD*)	>60 rpm *M* (*SD*)	*p*-value
TUG_{manual}			
Baseline[a]	21.83 (18.99)	7.81 (1.18)	<0.01
Post-test[b]	18.66 (16.47)	8.09 (1.97)	0.03
Follow-up[c]	11.37 (3.66)	7.11 (1.14)	0.02
$TUG_{cognitive}$			
Baseline[a]	23.36 (16.77)	8.05 (1.80)	<0.01
Post-test[b]	23.86 (21.85)	8.71 (2.29)	0.04
Follow-up[c]	14.62 (5.66)	7.35 (2.09)	0.01
RBANS™			
Baseline[a]	89.00 (17.28)	96.14 (24.51)	0.46
Post-test[b]	87.43 (11.24)	90.43 (19.86)	0.62
Follow-up[c]	94.67 (13.49)	95.29 (21.25)	0.73

Note. Mann-Whitney U tests were used to analyze the differences between groups; TUG = Timed Up and Go; RBANS™ = Repeatable Battery for Assessment of Neuropsychological Status.
[a]$n = 15$; [b]$n = 14$; [c]$n = 13$

Having established that significant differences exist between the high pedal rate group and the low pedal rate group, a Friedman's ANOVA analysis was utilized to determine if either pedal rate reflected a significant change over time. Wilcoxon Signed Ranks test was used for post-hoc analysis with Bonferroni's correction (alpha level / number of tests = 0.05 / 3 = 0.017) when the Friedman's ANOVA was found to be

significant. No differences over time were identified for the low pedal rate group on TUG_{manual} (χ^2=5.33, p=0.07), $TUG_{cognitive}$ (χ^2=2.33, p=0.31), or RBANS™ (χ^2=4.33, p=0.12). For the high pedal rate group, no differences were observed for TUG_{manual} (χ^2=5.43, p=0.07) or RBANS™ (χ^2=2.15, p=0.34), but $TUG_{cognitive}$ scores were significantly different over time (χ^2=7.14, p=0.03). Post-hoc analysis for $TUG_{cognitive}$ using Wilcoxon Signed Ranks test was not significant after Bonferroni's correction.

Nonparametric Statistics Examining the Effect of Aerobic Exercise on Sedentary Behavior

The secondary purpose of this study was to determine if aerobic exercise improves sedentary behavior. Sedentary behavior was determined by physical activity measures and tracked by the SAM worn over three consecutive days. The SAM was able to record both volume and intensity of physical activity for each participant. Volume of physical activity was defined as the average number of steps per day. Intensity of physical activity, defined as the average step rate of the highest 30 minutes during the day, was labeled peak activity index. Initially, forced use and self-paced groups were formed with the expectation that the forced use group would perform at a higher overall intensity. Mann-Whitney U tests were used to analyze the differences between the two groups for physical activity variables at baseline, post-test, and follow-up intervals. There were no significant differences between the groups at baseline, at post-intervention testing, or at the 1-month follow-up for any of the physical activity variables. Refer to table 6 for analysis.

Table 6

Differences Between Forced Use and Self-Paced Exercise Groups in Physical Activity Participation

	Forced Use *M* (*SD*)	Self-paced *M* (*SD*)	*p*-value
Steps/day			
Baseline[a]	4078.30 (2389.57)	3304.30 (1866.21)	0.48
Post-test[b]	4344 (1570.05)	3418.11 (2036.05)	0.30
Follow-up[c]	4462.00 (2195.69)	3866.29 (2155.69)	0.64
Peak Activity Index			
Baseline[a]	34.88 (11.42)	34.05 (10.68)	0.85
Post-test[b]	40.16 (5.69)	35.52 (12.81)	0.36
Follow-up[c]	37.20 (7.22)	36.79 (10.91)	0.88

Note: Peak Activity Index = step rate at highest 30 minutes of activity; Mann-Whitney U tests were used to analyze the differences.
[a]$n = 20$. [b]$n = 14$. [c]$n = 13$

Since there were no differences between the groups on any of the physical activity variables, the decision was made to combine the two groups into one. Both groups performed aerobic exercise because they utilized large muscle groups and worked for a maximum duration of 40 minutes per session. Subsequent analyses, assessed the effect of aerobic activity (regardless of mode used), on physical activity. Friedman's ANOVA test analyzed the effect of aerobic exercise on all participants over time. No difference was observed across time for physical activity variables. Table 7 reveals the data analysis.

Table 7

Physical Activity Participation Over Time for All Participants

	Baseline[a] *M* (*SD*)	Post-test[a] *M* (*SD*)	Follow-up[a] *M* (*SD*)	*p*-value
Steps/day	3941.00 (2254.19)	4154.92 (1699.61)	4114.50 (2093.31)	0.72
Peak Activity Index	36.23 (9.14)	40.02 (8.58)	36.96 (9.16)	0.47

Note: Peak Activity Index = step rate at highest 30 minutes of activity; Friedman's ANOVA tests analyzed the effect of aerobic exercise on all participants over time.
[a]$n = 12$

Similar to the primary purpose, the second aspect of aerobic exercise that we investigated for the secondary purpose was intensity. Participants were divided into two groups based on intensity (pedal rate) achieved during the training sessions. Seven individuals pedaled the bicycle at less than or equal to 60 rpm while the remaining seven individuals pedaled at greater than 60 rpm. Mann-Whitney U tests were used to analyze the differences between the two groups for physical activity variables at baseline, post-test, and follow-up intervals. Differences were identified for volume (steps/day) at post-test and for intensity (peak activity index) at baseline. Table 8 shows the result of this data analysis.

Table 8

Differences Between High Intensity and Low Intensity Exercise Groups in Physical Activity Participation

	≤60 rpm *M* (*SD*)	>60 rpm *M* (*SD*)	*p*-value
Steps/day			0.09
Baseline[a]	2851.00 (1891.07)	4951.57 (2062.29)	0.03
Post-test[b]	2597.14 (1414.88)	4900.43 (1591.67)	
Follow-up[c]	2856.60 (768.33)	5013.00 (2319.39)	0.07
Peak Activity Index			0.03
Baseline[a]	29.56 (10.22)	40.79 (6.04)	0.07
Post-test[b]	32.70 (10.68)	41.66 (9.54)	
Follow-up[c]	32.62 (2.33)	40.06 (11.11)	0.15

Note: Peak Activity Index = step rate at highest 30 minutes of activity; Mann-Whitney U tests were used to analyze the differences between groups.
[a]$n = 15$. [b]$n = 14$. [c]$n = 13$.

Having established that significant differences exist between the high pedal rate group and the low pedal rate group, a Friedman's ANOVA was utilized to determine if either pedal rate group reflected a significant change over time. No differences were observed on the variables over time for either the low or high pedal rate groups.

Determination of a Responder Group to Aerobic Exercise on Cognition and Sedentary Behavior

Given our small sample size and to get further clarity of the results, a secondary analysis was conducted to see if it was possible to identify participants as responders or non-responders to the exercise intervention. The intention of this secondary analysis was to identify, if possible, a responder group. Plots for each participant's performance on all variables were developed. Visual inspection was utilized to identify responders. A responder was defined as a participant who demonstrated improvement greater than minimal detectable change on the TUG variations, greater than half the standard deviation on the RBANS™, or greater than half the standard deviation on the baseline physical activity variables (steps/day and peak activity index). At least two participants were identified as a responder for each dependent variable. Steps/day had the largest number of responders with four. However, only three participants (#3, #7, and #16) were responders on multiple variables. Participant 16 responded favorably on all dependent variables except for the RBANS™. Five additional participants (#8, #13, #17, #18, and #20) were responders to a single dependent variable. Unfortunately, no trends for a "typical responder" were overtly apparent. Table 9 depicts the responders and associated characteristics.

Table 9

Depiction of Responder Group

Characteristics of Responders															***Variable of Response***				
Participant	Age	Gender	Length of PD (years)	Assistive device	HY	MMSE	UPDRS	UPDRS part III	S & E	BDI®-II	PDQ	% attendance	% Compliance	Pedal Rate Group	TUG_{manual}	$TUG_{cognitive}$	RBANS™	Steps/day	Peak Activity Index
16	75	m	10	RW	2	29	61	35	30	24	51.04	69.44	68.75	Low	•	•		•	•
7	74	m	6	none	3	27	54	33	70	6	12.08	97.22	93.99	Low	•	•			•
3	71	f	7	none	2	30	27	19	90	11	14.9	77.78	76.17	High				•	•
17	72	m	24	none	2	29	28	19	90	6	14.1	61.11	47.51	High				•	
18	74	m	11	none	3	28	60	38	60	6	22.1	88.89	55.82	Low				•	
13	64	m	4	none	2	29	36	20	90	9	39.29	100	91.5	High			•		
20	73	f	7	none	1	28	15	9	100	0	7.29	50	39.3	Low			•		
8	76	m	12	RW	4	30	67	43	60	9	34.01	97.22	65.87	Low	•				

PD = Parkinson disease; HY = Hoehn & Yahr scale; MMSE = Mini-mental Status Examination; UPDRS = Unified Parkinson's Disease Rating Scale; UPDRS part III = Unified Parkinson's Disease Rating Scale, motor subscale; S & E = Schwab & England Scale; BDI®-II = Beck Depression Inventory® – II; PDQ = Parkinson Disease Questionnaire – 39; TUG = Timed Up-n-Go; RBANS™ = Repeatable Battery for the Assessment of Neuropsychological Status; RW = Rolling Walker.

In summary, the intervention did not have an effect on sedentary behavior. However, a difference was observed on all participants for cognitive function on dual tasks across time. While no differences were observed between the assigned groups on any dependent variable, the groups based upon exercise intervention performance were different across time on all variables. The participants who exhibited the faster pedal rate during the intervention did positively improve cognitive dual tasking during gait. Lastly, a responder group was identified for each dependent variable. Only three participants were responders on multiple variables. Five additional participants were responders to a single dependent variable.

CHAPTER V

DISCUSSION

Parkinson disease (PD) progressively impairs independent physical function and cognitive capacity. Though the cardinal features of PD are rigidity, tremor, postural instability and bradykinesia, cognitive impairment is now a well-recognized feature. While general exercise and task-specific training have been identified as possible approaches to improve physical performance in people with PD, no studies to date have examined the effect of aerobic exercise on cognitive function. Therefore, the purposes of this experimental study were to examine the effect of aerobic exercise on cognitive function in persons with PD and to determine if aerobic exercise improves sedentary behavior. For both purposes, two aspects of aerobic exercise were investigated, a) mode of exercise (self paced versus forced) and b) intensity of exercise ($\leq$60 rpm versus >60 rpm). This chapter provides a discussion of the study results, their relevancy to community dwelling individuals with PD, and reflection on study limitations and future recommendations.

Exercise as physical activity served as the inspiration and formed the backbone of this study. Physical activity is touted as beneficial for increased survival, independent living, and improved QOL in healthy individuals (Hirvensalo, Rantanen, & Heikkinen, 2000). Additionally, exercise may be useful in delaying decline in PD (Tillerson et al., 2001). Specifically, forced aerobic exercise shows promise for regaining motor function,

if only temporarily (Ridgel et al., 2009). Furthermore, exercise is increasingly recognized as neuroprotective in animal models and human studies of persons with Alzheimer's disease and mild cognitive impairment (Cotman & Engesser-Cesar, 2002; Heyn et al., 2004). Only recently has the potential benefit of exercise on cognition been investigated in people with PD (Tanaka et al., 2009).

For these reasons, the primary purpose of this study was to examine the effect of aerobic exercise on cognitive function in persons with PD. We hypothesized that cognitive function will be significantly higher with forced aerobic exercise compared with self-paced aerobic exercise. Two analyses were utilized to assess the veracity of our hypothesis. While no differences were observed between the forced exercise group and the self-paced group, improvement on the motor dual task and RBANS™ was identified across time when all participants were analyzed. Gait, once learned, moves from a task requiring attention to one of automaticity (Paul, Ada, & Canning, 2005). However, in people with PD, gait becomes attention demanding due to motor and cognitive dysfunction (Yogev et al., 2005). This increased attention demand is compounded by insufficient reserves of motor and cognitive capacities resulting in a deteriorating gait (Plotnik, Dagan, Gurevich, Giladi, & Hausdorff, 2011). Because the decline in executive function exacerbates gait variability during dual tasking (Yogev et al., 2005), the paired improvement observed in executive function and dual task gait seems plausible. It may be that the inherent reciprocal rhythmicity of riding a stationary bike promoted automaticity during gait. Concurrently, the aerobic exercise intervention may have built

up motor or cognitive reserves to more effectively navigate the attention demanding dual task.

Furthermore, two potential reasons for the lack of difference between forced exercise and self-paced groups must be considered. First, our intervention lasted only 3 months. Colcombe and Kramer (2003) suggest a minimum of 6 months is necessary to affect a positive change in cognition in healthy elderly. Our sample consisted of individuals with PD, a neurodegenerative disease. The duration of exercise intervention necessary to accomplish cognitive improvement in neurologically compromised populations is unknown. However, our study supports the notion of the needed duration to be longer than 3 months. A second reason for the lack of exercise mode differences, may be due to insufficient exercise intensity to yield positive cognitive change. Frequent moderate intensity exercise has shown to be effective in promoting cognitive benefits in older adults (Colcombe & Kramer, 2003). Though our intervention was frequent (3 times/week), the moderate intensity requested through the protocol (12 to 14 on the RPE scale), may not have been attained due to motor impairments associated with PD. Indeed, for this reason the forced exercise paradigm was included in our study. However, the forced exercise group pedaled at a minimum of 60 rpm and this speed may not have been of sufficient speed for moderate intensity for each participant. Furthermore, members of the self-paced group often pedaled at rates from 30 to 40 rpm which may not have been sufficient for moderate intensity. In our study, neither exercise group as a whole may have attained the intensity necessary to induce positive cognitive change.

Nonetheless, some members of both the forced use group and the self-paced group did exceed the 60 rpm threshold. We had anticipated the forced use group to have a significantly higher pedal rate and intensity. However, since members of both groups, regardless of forced use or self-paced designation, pedaled at rates in excess of 60 rpm, a true difference in intensity of exercise was likely not obtained between the groups. As a result, we performed an additional intensity biased analysis based upon pedal rate performance during the intervention. In this analysis, the low pedal rate group did not show improvement on any cognitive variable. The high pedal rate group improved only on the cognitive dual task, but this difference did not hold up under a post-hoc Bonferroni correction. A small initial sample size compounded with attrition limited the power in this study and may have negated any potentially observable differences. While the high pedal rate group came nearest to an intensity necessary for inducing cognitive change, it is possible that for our sample, either a sufficient intensity was not obtained or a sufficient duration was not sustained. It is also plausible that moderate intensity of aerobic exercise may have no effect on cognition in a person with PD.

Beyond research statistics, the difference in performance across time can be applied to the clinical setting by determining responsiveness of a measure. More specifically, does a statistical difference also reflect a clinically important difference? Comparison to normal values, comparison to cut-off scores, and change scores can help determine clinical impact. Table 10 reflects the responsiveness of the TUG (single and dual tasks) for healthy populations and for individuals with PD. Table 11 reveals the average scores for our participants.

Table 10

Responsiveness for the Timed Up-n-Go

	Normal	Parkinson Disease		
		Fall Cut-off	**MDC**	**MCID**
TUG_{alone}	9.4 seconds[1]	7.95 seconds[3]	3.5 seconds[4]	Not established
TUG_{manual}	11.6 seconds[2]	Not established	Not established	Not established
$TUG_{cognitive}$	9.8 seconds[2]	8.50 seconds[3]	Not established	Not established

Note. TUG = Timed Up and Go; MDC = Minimal Detectable Change; MCID = Minimal Clinically Important Difference; [1](Bohannon, 2006); [2](Hofheinz & Schusterschitz, 2010); [3](Dibble & Lange, 2006); [4](Huang et al., 2011)

Table 11
Timed Up and Go Mean Values for Study Participants who Completed the Study

	Baseline (seconds)	Post-test (seconds)	Follow-up (seconds)	Difference (seconds)
TUG_{alone} (≤60 rpm)	10.16	9.93	**9.55**	0.61
TUG_{alone} (>60 rpm)	6.44	6.70	6.22*	0.22
TUG_{manual} (≤60 rpm)	16.53	12.67	11.37*	<u>5.16</u>
TUG_{manual} (>60 rpm)	7.81	8.09	7.11*	0.70
$TUG_{cognitive}$ (≤60 rpm)	19.64	16.34	**14.62**	<u>5.02</u>
$TUG_{cognitive}$ (>60 rpm)	8.05	8.71	7.35*	0.70

Note. TUG = Timed Up and Go; <u>Underline</u> = hypothetical MDC exceeded; **Bold** = exceeded cut-off for fallers; *= at or below fall cut-off

While statistical analysis only showed an improvement across time for $TUG_{cognitive}$ in the high pedal rate group; our intervention accomplished two goals for functional mobility under single and dual task gait when viewed from a clinical application perspective. First, the slower pedaling group may have exceeded the minimal detectable change (MDC) for both dual task conditions reflecting improvement beyond measurement error. Second, four of the six scores at the time of follow-up assessment were below the fall cut-off values associated with all TUG conditions.

Though seemingly paradoxical, this clinically relevant improvement for dual-task gait across time occurred only in the group pedaling less than 60 rpm. While literature typically supports the notion of higher intensity exercise yielding greater improvements (Lee & Skerrett, 2001), this study observed the opposite effect where a lower pedaling velocity had greater improvement. On the other hand, literature also supports the notion that the most limited individuals have the greatest potential for improvement (Bean et al., 2004). It appears as though our study confirms this notion. Those persons who pedaled at the slower rate (less than 60 rpm) were more advanced in PD symptoms, and demonstrated the most improvement. Conversely, those who pedaled at the faster rate (greater than 60 rpm) had less overall PD symptoms, and demonstrated no improvement in dual tasks.

Nonetheless, despite our intervention two mean scores remained in the fallers category. Importantly, though exceeding MDC, slower pedaling individuals scored in the fallers category for two of three conditions after our intervention. Our intervention of aerobic exercise may provide benefit to individuals with PD; however, it should not be viewed as a panacea but rather an important ingredient toward effectiveness. In this instance, a falls prevention program or balance intervention would likely benefit these more symptomatically progressed individuals of the slower pedaling group. A future study incorporating a balance program with our aerobic intervention may shed light on this matter. Until that time, it would behoove clinicians to create a broad intervention approach with aerobic exercise components, balance activities, and fall prevention education for their clients with PD, particularly those with a slower pedal rate.

Alternatively, or perhaps concurrently, physical therapists may select an intervention strategy specifically targeting dual tasking. We know that walking in "real world" is complex and requires cognitive flexibility to attend to environment (Rochester et al., 2008). Specifically, motor function, attention, and executive function explain 66% of gait variance under complex conditions (Lord, Rochester, Hetherington, Allcock, & Burn, 2010a). Dual tasking requires executive function which is impaired in people with PD (Rochester et al., 2004). Currently, debate exists concerning whether people with PD can improve dual tasking and whether training dual tasking should be advocated for people with PD. Brauer et al. (2011) have proposed the first comparison study to help answer this question. The results of our study suggest that dual tasking can improve even with an intervention targeting cognition through aerobic exercise. However, a direct intervention in either single or dual task training may be helpful.

Interestingly, an intervention that specifically targets dual tasking may indirectly contribute to improving physical activity. Multiple regression analysis of the data for a future presentation indicated that performance on the $TUG_{cognitive}$ accounted for 54% of the variance in volume of physical activity (average steps/day). Furthermore, physical therapists must consider how to remove barriers to participation in physical activity. While Elsworth et al., (2009) identified perceived functional, environmental, and psychological barriers and facilitators of physical activity in individuals with neurological conditions, practical behaviors for optimizing function have been suggested by caregivers and individuals with PD (Pretzer-Aboff, Galik, & Resnick, 2009).

However, targeting behavior change for multidimensional, complex tasks is challenging. Self-monitoring, risk communication, and social support have been identified as effective strategies to implement healthy behaviors (Van Achterberg et al., 2010). Additionally, self-efficacy may contribute more to community ambulation than executive function (Lord, Weatherall, & Rochester, 2010b). Our responder group demonstrated no common themes during our analysis other than the ability to respond to our intervention. Perhaps, these individuals, though burdened with motor and non-motor symptoms of PD, carried a great deal of self-efficacy with social support. These traits were not measured in our study but may explain the elusive quality exhibited by our responders.

Four participants in our responder group demonstrated improvement in physical activity volume and three individuals showed increased intensity of physical activity. However, our study group average of around 4,000 steps/day is indicative of sedentary behavior according to Tudor-Locke and Bassett, Jr. (2004). Sedentary behavior typifies individuals with PD in part because of motor and non-motor symptoms (van Nimwegen, van Rossum, Deeg, Bloem, & Borm, 2008). Physical inactivity is undesirable because it is a risk factor for cardiovascular disease, diabetes, cognitive impairment and depression [World Health Organization (WHO), 2010]. By contrast, regular physical activity is promoted as neuroprotective (Kramer et al., 2006). Furthermore, regular physical activity may ameliorate symptoms of PD (Tillerson et al., 2001). Therefore, the second purpose of this study was to determine if aerobic exercise improves sedentary behavior. Our corresponding hypotheses were that our intervention of aerobic exercise, both forced

and self-paced, would increase physical activity levels and that physical activity levels would be higher following forced aerobic exercise compared with self-paced aerobic exercise.

For our sample in this study, neither the forced use nor self-paced aerobic exercise intervention improved sedentary behavior in either volume or intensity of physical activity. In our estimation, the attempt to use aerobic exercise to affect a positive behavioral change on sedentary behavior in people with PD is unique. No other study has been identified to attempt using aerobic exercise for this purpose in people with PD or any other neurologic condition. The rationale employed in this study was that aerobic exercise would improve motor function and subsequently, if not indirectly, increase physical activity. Justification for aerobic exercise to improve motor function in people with PD comes from Ridgel et al. (2009) who reported 35% reduction of motor impairment after forced exercise on a bicycle at 90 rpm. However, in contrast to Ridgel et al., our participants did not demonstrate improved motor function as measured by the UPDRS. The lack of improved motor function may be due to our motorized bicycle, the MOTOmed, topping out at a speed of 60 rpm. Ridgel et al. has recommended a minimum of 90 rpm necessary to improve motor function. To rectify this issue, MOTOmed has released a newer version of the viva2 model, the MOTOmed viva2 Parkinson. Unfortunately, this model was not available at the time of our study. Future research in this area may benefit from this newer model. Furthermore, while forced exercise at less than 90 rpm in this study may account for the lack of motor improvement,

it remains to be determined if an improvement in motor function alone would be sufficient to modify sedentary behavior and increase physical activity.

Interestingly, members of both exercise groups exceeded 60 rpm volitionally, potentially minimizing or nullifying any potential difference between groups or benefit of the forced exercise. Due to the inability to accomplish a true forced use paradigm, we analyzed the difference between high (>60 rpm) and low (≤60 rpm) pedal rate groups. Our analysis demonstrated no difference between pedal rate groups on sedentary behavior. Though overall lack of intensity of exercise, as discussed in the preceding paragraph, was postulated as one potential reason for a lack of change in sedentary behavior, a second possibility emerges in light of this analysis. Sedentary behavior is pervasive throughout our culture across age groups, socioeconomic factors, and health status (WHO, 2010). Motor dysfunction is not required for physical inactivity. Moreover, physical disability is not an exclusive determinant of physical inactivity. Sedentary behavior is a complex, multi-factorial construct (Lord et al., 2011). More, specifically, the factors of sedentary behavior in PD remain elusive and poorly understood (van Nimwegen et al., 2011). Due to the complexity of sedentary behavior, it may have been overly ambitious to attempt to increase physical activity simply by addressing physical disability in persons with PD. It may be necessary to include a multi-focal approach (physical, environmental, and behavioral) to address this multi-factorial problem (Ebers et al., 2009). Of note, a Dutch program entitled ParkFit Program is hoping to discover behavioral interventions for physical activity promotion in people with PD (van Nimwegen et al., 2010). Toward this end, an encouraging footnote to our

project was the expressed concerted desire to continue exercising and/or cycling from most of the participants. Exploration of a community based outlet and opportunity for encouraging actual ongoing behavioral modification was beyond the scope of this study, but appeared to be a desired commodity for a subset of our sample.

Potentially, a study design error could contribute a third reason to the lack of impact on sedentary behavior. Physical activity in our study was measured by wearing the SAM for three consecutive days. Though measuring physical activity for three days has a reliability coefficient of 0.70 and a power of greater than 90% to detect a difference at 0.07 standard deviations (Mattocks et al., 2008), three days may not have been representative of an individual's average physical activity. For instance, some participants wore the device over weekdays and others wore the device over weekends. Additionally, the same participant may have encountered both scenarios during the various testing phases. While many participants were retired, some continued to perform vocational activities during weekdays. Both the type of vocation and health status have been identified as moderators to physical activity behavior (Chastin & Granat, 2010). As a result, a seven day monitoring of physical activity employed by other studies (Chastin & Granat, 2010; Ford et al., 2010) may been a more suitable selection for determining sedentary behavior.

Our study had several limitations. Most notably, our small sample size decreased the power of our analyses and limited the generalizability of our conclusions. Though mentioned earlier, our inability to "force" an exercise tempo beyond volitional tempo achieved by several participants mitigated any potential observations between our

original exercise groups of forced use and self-paced. Furthermore, our three day collection period for physical activity may have been inadequate to accurately represent physical activity levels in our participants. Based upon these limitations and our findings, we suggest future studies include a true forced use paradigm at 90 rpm. We also recommend including a broader multifocal behavioral intervention to reduce sedentary behaviors.

In summary, the aerobic exercise intervention for our participants with PD failed to minimize sedentary behavior. However, improvements were observed across time for all participants with executive function, specifically dual tasking during gait. While individuals with a high pedal rate may have benefitted from the intervention, the low pedal rate participants achieved clinically relevant improvement. Nonetheless, our exercise intervention may be a valuable adjunct in the context of a multidimensional approach to maximize function in persons with PD.

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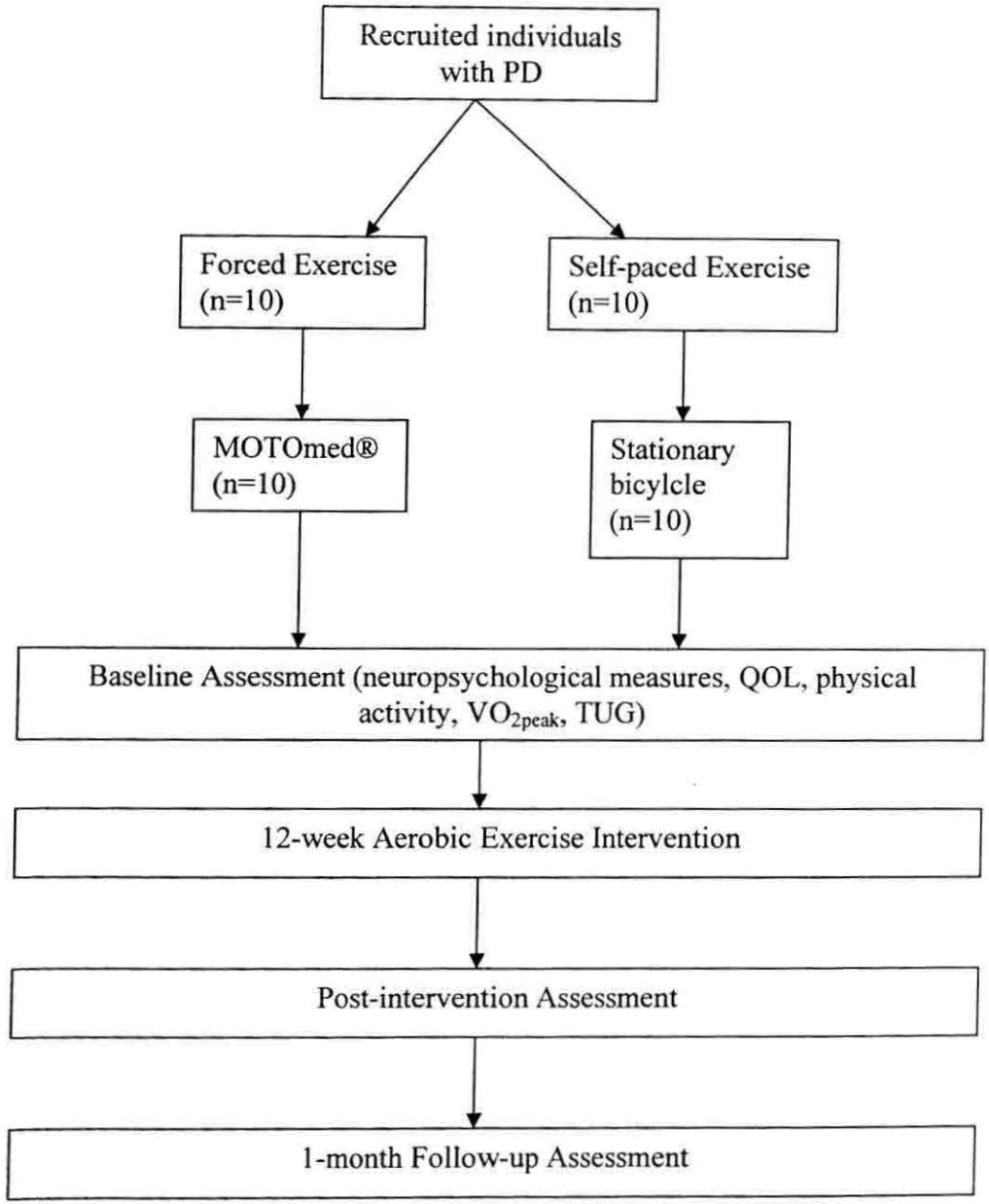
APPENDIX A
RANDOM ASSIGNMENT CHART

Random Assignment Chart



APPENDIX B
HOEHN AND YAHR SCALE

Hoehn and Yahr Staging of Parkinson's Disease

1. Stage One
    1. Signs and symptoms on one side only
    2. Symptoms mild
    3. Symptoms inconvenient but not disabling
    4. Usually presents with tremor of one limb
    5. Friends have noticed changes in posture, locomotion and facial expression

2. Stage Two
    1. Symptoms are bilateral
    2. Minimal disability
    3. Posture and gait affected

3. Stage Three
    1. Significant slowing of body movements
    2. Early impairment of equilibrium on walking or standing
    3. Generalized dysfunction that is moderately severe

5. Stage Four
    1. Severe symptoms
    2. Can still walk to a limited extent
    3. Rigidity and bradykinesia
    4. No longer able to live alone
    5. Tremor may be less than earlier stages

5. Stage Five
    1. Cachectic stage
    2. Invalidism complete
    3. Cannot stand or walk
    4. Requires constant nursing care

APPENDIX C
UNITED PARKINSONISM DISEASE RATING SCALE

Unified Parkinson's Disease Rating Scale (UPDRS)

The UPDRS is a rating tool to follow the longitudinal course of Parkinson's Disease. It is made up of the 1) Mentation, Behavior, and Mood, 2) ADL and 3) Motor sections. These are evaluated by interview. Some sections require multiple grades assigned to each extremity. A total of 199 points are possible. 199 represents the worst (total) disability, 0--no disability.

I. Mentation, Behavior, Mood

A. Intellectual Impairment

0-none
1-mild (consistent forgetfulness with partial recollection of events with no other difficulties)
2-moderate memory loss with disorientation and moderate difficulty handling complex problems
3-severe memory loss with disorientation to time and often place, severe impairment with problems
4-severe memory loss with orientation only to person, unable to make judgments or solve problems

B. Thought Disorder

0-none
1-vivid dreaming
2-"benign" hallucination with insight retained
3-occasional to frequent hallucination or delusions without insight, could interfere with daily activities
4-persistent hallucination, delusions, or florid psychosis.

C. Depression

0-not present
1-periods of sadness or guilt greater than normal, never sustained for more than a few days or a week
2-sustained depression for >1 week
3-vegetative symptoms (insomnia, anorexia, abulia, weight loss)
4-vegetative symptoms with suicidality

D. Motivation/Initiative

0-normal
1-less of assertive, more passive
2-loss of initiative or disinterest in elective activities
3-loss of initiative or disinterest in day to say (routine) activities
4-withdrawn, complete loss of motivation

II. Activities of Daily Living

Speech
0-normal
1-mildly affected, no difficulty being understood
2-moderately affected, may be asked to repeat
3-severely affected, frequently asked to repeat
4-unintelligible most of time

Salivation
0-normal
1-slight but noticeable increase, may have nighttime drooling
2-moderately excessive saliva, have minimal drooling
3-marked drooling

Swallowing
0-normal
1-rare choking
2-occasional choking
3-requires soft food
4-requires NG tube or G-tube

Handwriting
0-normal
1-slightly small or slow
2-all words small but legible
3-severely affected, not all words legible
4-majority illegible

Cutting Food/Handing Utensils
0-normal
1-somewhat slow and clumsy but no help needed
2-can cut most foods, some help needed
3-food must be cut, but can feed self
4-needs to be fed

Dressing
0-normal
1-somewhat slow, no help needed
2-occasional help with buttons or arms in sleeves
3-considerable help required but can do something alone
4-helpless

Hygiene
0-normal
1-somewhat slow but no help needed
2-needs help with shower or bath or very slow in hygienic care
3-requires assistance for washing, brushing teeth, going to bathroom
4-helpless

Turning in Bed/ Adjusting Bed Clothes
0-normal
1-somewhat slow no help needed
2-can turn alone or adjust sheets but with great difficulty
3-san initiate but not turn or adjust alone
4-helpless

Falling-Unrelated to Freezing
0-none
1-rare falls
2-occasional, less than one per day
3-average of once per day
4->1 per day

Freezing When Walking
0-normal
1-rare, may have start hesitation
2-occasional falls from freezing
3-frequent freezing, occasional falls
4-frequent falls from freezing

Walking
0-normal
1-mild difficulty, day drag legs or decrease arm swing
2-moderate difficultly requires no assist
3-severe disturbance requires assistance
4-cannot walk at all even with assist

Tremor
0-absent
1-slight and infrequent, not bothersome to patient
2-moderate, bothersome to patient
3-severe, interfere with many activities
4-marked, interferes with many activities

Sensory Complaints Related to Parkinsonism
0-none
1-occasionally has numbness, tingling, and mild aching
2-frequent, but not distressing
3-frequent painful sensation
4-excruciating pain

III. Motor Exam
Speech
0-normal
1-slight loss of expression, diction,volume
2-monotone, slurred but understandable, mod. impaired
3-marked impairment, difficult to understand
4-unintelligible

Facial Expression
0-Normal
1-slight hypomymia, could be poker face
2-slight but definite abnormal diminution in expression
3-mod. hypomimia, lips parted some of time
4-masked or fixed face, lips parted 1/4 of inch or more with complete loss of expression

***Tremor at Rest**
Face
0-absent
1-slight and infrequent
2-mild and present most of time
3-moderate and present most of time
4-marked and present most of time

Right Upper Extremity (RUE)
0-absent
1-slight and infrequent
2-mild and present most of time
3-moderate and present most of time
4-marked and present most of time

LUE
0-absent
1-slight and infrequent
2-mild and present most of time
3-moderate and present most of time
4-marked and present most of time

RLE
0-absent
1-slight and infrequent
2-mild and present most of time
3-moderate and present most of time
4-marked and present most of time

LLE
0-absent
1-slight and infrequent
2-mild and present most of time
3-moderate and present most of time
4-marked and present most of time

***Action or Postural Tremor**
RUE
0-absent
1-slight, present with action
2-moderate, present with action
3-moderate present with action and posture holding
4-marked, interferes with feeding

LUE
0-absent
1-slight, present with action
2-moderate, present with action
3-moderate present with action and posture holding
4-marked, interferes with feeding

***Rigidity**
Neck
0-absent
1-slight or only with activation
2-mild/moderate
3-marked, full range of motion
4-severe

RUE
0-absent
1-slight or only with activation
2-mild/moderate
3-marked, full range of motion
4-severe

LUE
0-absent
1-slight or only with activation
2-mild/moderate
3-marked, full range of motion
4-severe

RLE
0-absent
1-slight or only with activation
2-mild/moderate
3-marked, full range of motion
4-severe

LLE
0-absent
1-slight or only with activation
2-mild/moderate
3-marked, full range of motion
4-severe

***Finger taps**
Right
0-normal
1-mild slowing, and/or reduction in amp.
2-moderate impaired. Definite and early fatiguing, may have occasional arrests
3-severely impaired. Frequent hesitations and arrests.
4-can barely perform

Left
0-normal
1-mild slowing, and/or reduction in amp.
2-moderate impaired. Definite and early fatiguing, may have occasional arrests
3-severely impaired. Frequent hesitations and arrests.
4-can barely perform

***Hand Movements (open and close hands in rapid succession)**
Right
0-normal
1-mild slowing, and/or reduction in amp.
2-moderate impaired. Definite and early fatiguing, may have occasional arrests
3-severely impaired. Frequent hesitations and arrests.
4-can barely perform

Left
0-normal
1-mild slowing, and/or reduction in amp.
2-moderate impaired. Definite and early fatiguing, may have occasional arrests
3-severely impaired. Frequent hesitations and arrests.
4-can barely perform

***Rapid Alternating Movements (pronate and supinate hands)**
Right
0-normal
1-mild slowing, and/or reduction in amp.
2-moderate impaired. Definite and early fatiguing, may have occasional arrests
3-severely impaired. Frequent hesitations and arrests.
4-can barely perform

Left
0-normal
1-mild slowing, and/or reduction in amp.
2-moderate impaired. Definite and early fatiguing, may have occasional arrests
3-severely impaired. Frequent hesitations and arrests.
4-can barely perform

***Leg Agility (tap heel on ground, amp should be 3 inches)**
Right
0-normal
1-mild slowing, and/or reduction in amp.
2-moderate impaired. Definite and early fatiguing, may have occasional arrests
3-severely impaired. Frequent hesitations and arrests.
4-can barely perform

Left
0-normal
1-mild slowing, and/or reduction in amp.
2-moderate impaired. Definite and early fatiguing, may have occasional arrests
3-severely impaired. Frequent hesitations and arrests.
4-can barely perform

***Arising From Chair (pt. arises with arms folded across chest)**
0-normal
1-slow, may need more than one attempt
2-pushes self up from arms or seat
3-tends to fall back, may need multiple tries but can arise without assistance
4-unable to arise without help

***Posture**
0-normal erect
1-slightly stooped, could be normal for older person
2-definitely abnormal, mod. stooped, may lean to one side
3-severely stooped with kyphosis
4-marked flexion with extreme abnormality of posture

***Gait**
0-normal
1-walks slowly, may shuffle with short steps, no festination or propulsion
2-walks with difficulty, little or no assistance, some festination, short steps or propulsion
3-severe disturbance, frequent assistance
4-cannot walk

***Postural Stability (retropulsion test)**
0-normal
1-recovers unaided
2-would fall if not caught
3-falls spontaneously
4-unable to stand

***Body Bradykinesia/ Hypokinesia**
0-none
1-minimal slowness, could be normal, deliberate character
2-mild slowness and poverty of movement, definitely abnormal, or dec. amp. of movement
3-moderate slowness, poverty, or small amplitude
4-marked slowness, poverty, or amplitude

IV. Schwab and England Activities of Daily Living

* **100%**-Completely independent. Able to do all chores w/o slowness, difficulty, or impairment.
* **90%**-Completely independent. Able to do all chores with some slowness, difficulty, or impairment. May take twice as long.
* **80%**-Independent in most chores. Takes twice as long. Conscious of difficulty and slowing
* **70%**-Not completely independent. More difficulty with chores. 3 to 4X along on chores for some. May take large part of day for chores.
* **60%**-Some dependency. Can do most chores, but very slowly and with much effort. Errors, some impossible
* **50%**-More dependant. Help with 1/2 of chores. Difficulty with everything
* **40%**-Very dependant. Can assist with all chores but few alone

* **30%**-With effort, now and then does a few chores alone of begins alone. Much help needed
* **20%**-Nothing alone. Can do some slight help with some chores. Severe invalid
* **10%**-Totally dependant, helpless
* **0%**-Vegetative functions such as swallowing, bladder and bowel function are not functioning. Bedridden.

APPENDIX D
RATING OF PERCEIVED EXERTION SCALE

The Rating of Perceived Exertion (RPE) was developed by Borg to describe a person's perception of exertion during exercise.

Exertion	**RPE**
no exertion at all	6
extremely light	7
	8
very light	9
	10
Light	11
	12
somewhat hard	13
	14
hard (heavy)	15
	16
very hard	17
	18
extremely hard	19
maximal exertion	20

APPENDIX E
TABLE OF EVENTS

Table of Events

Event	Screen	Baseline		12 week Intervention	Post-Intevention		1 month follow-up	Post-Follow-up	
		Session	Session		Session	Session		Session	Session
Inclusion/Exclusion Criteria	X								
Disease Severity (HY & UPDRS)		X							
Activity level (StepWatch™)		X			X			X	
Cardiovascular assessment (VO_{2peak})		X			X			X	
Divided Attention (TUG)		X			X			X	
Neuropsychological Test			X			X			X
Quality of Life (PDQ-39)			X			X			X
Depression (BDI®-II)			X			X			X