THE INFLUENCE OF BDNF VAL66MET POLYMORPHISM ON COGNITION, DEPRESSION, QUALITY OF LIFE, AND MOTOR SYMPTOMS IN INDIVIDUALS WITH PARKINSON’S DISEASE AFTER DYNAMIC CYCLING

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BACKGROUND: Individuals with Parkinson’s disease (PD) tend to have high inter-individual variability in symptoms and in response to exercise. A genetic variation called brain derived neurotrophic factor (BDNF) Val66Met polymorphism may influence variability of attention and executive function domains, depression symptoms, quality of life, and motor symptoms after dynamic cycling. PURPOSE: The first aim was to determine if the prevalence of the Val66Met polymorphism influenced incidences of attention and executive dysfunction, depression symptoms, decreased quality of life, and motor symptoms. The second aim was to determine if Val66Met polymorphism influenced changes in attention and executive function, depression symptoms, quality of life, and motor symptoms after dynamic cycling. METHODS: Fourteen participants (n=10, 6M/4F Val-allele group, n=4, 2M/2F Met-allele group, 64±9 years old), diagnosed with PD performed WebNeuro® testing, Montreal Cognition Assessment (MoCA), Beck Depression Inventory (BDI-II), EuroQOL questionnaire, Kinesia ONE™ assessment, and Val66Met polymorphism genotyping. The intervention involved three, 40 minute dynamic cycling sessions. RESULTS: There was no influence of Val66Met polymorphism on the pre-intervention scores of attention, executive function, MoCA (cognition), depression symptoms, or motor symptoms. There were also no influences of
Val66Met polymorphism on changes in attention, executive function, MoCA, depression symptoms or motor symptom after dynamic cycling. However, Val66Met polymorphism did have a main effect of group for quality of life questionnaire regardless of the cycling intervention. **DISCUSSION:** This intervention did not promote overall improvements. However, there were some interesting trends in the data and a larger sample size will likely result in more conclusive results.
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CHAPTER I

INTRODUCTION

Parkinson’s disease (PD) is a progressive neurodegenerative disorder that affects approximately 4 million people worldwide (Dorsey et al., 2007). PD is characterized by motor and non-motor symptoms including bradykinesia, tremor, rigidity, postural instability, sleep, mood, and cognitive disturbances (van der Kolk et al., 2015). As the disease progresses, apoptosis of selective neurons in the substantia nigra of the midbrain decreases dopamine release, causing complications which affect the autonomic, limbic, and somatomotor systems (Braak, Ghebremedhin, Rub, Bratzke, & Del Tredici, 2004; Lev, Melamed, & Offen, 2003). In addition to motor symptoms, individuals with PD have non-motor symptoms, including a high incidence of depression (20–50%; Aarsland, Marsh, & Schrag, 2009), and cognitive deficits. The prevalence of depression has also been associated with decreased quality of life (Kuopio et al., 2001), which impacts the overall health of individuals with PD (Ishihara & Brayne, 2006). Ultimately, PD leads to higher healthcare costs (Kaltenboeck et al., 2012), and increased risk of death (Matsumoto et al., 2014). The cause of the disease is unknown but believed to be influenced by genetic variants (Le Couteur, Muller, Yang, Mellick, & McLean, 2002). One gene that has been of recent interest in PD is the brain derived neurotrophic factor (BDNF) gene that has a common single-nucleotide polymorphism. This polymorphism is an amino-acid substitution in the prodomain of valine (Val) to methionine (Met) at amino-acid codon 66 known as val66met (Bath & Lee, 2006). Approximately 20–30% of the population is a heterozygous carrier or met-carrier (Shimizu, Hashimoto, & Iyo,
When the Val66Met polymorphism is present it could cause altered BDNF distribution and decreased BDNF secretion (Hariri et al., 2003). The role of BDNF in neuron health involves regulation of synaptic transmission and neuronal growth (McAllister, Katz, & Lo, 1999), and the support of dopaminergic neurons in the substantia nigra (Hyman et al., 1991). Individuals with neurodegenerative diseases such as PD tend to have lower BDNF concentrations than healthy individuals and there is a positive correlation between low BDNF production and motor impairment in individuals with PD (Foltynie et al., 2009).

Both chronic and acute aerobic exercise has been shown to increase BDNF concentrations in animal models (Berchtold, Chinn, Chou, Kesslak, & Cotman, 2005), healthy individuals (S. W. Tsai, Chan, Liang, Hsu, & Lee, 2015) and individuals with neurodegenerative diseases (Aarsland et al., 2009; Scalzo, Kummer, Bretas, Cardoso, & Teixeira, 2010). It has been proposed that improvements in PD symptoms that result from aerobic exercise are associated with neuroplasticity changes in neurotrophins, such as BDNF (Rosenfeldt, Rasanow, Penko, Beall, & Alberts, 2015; Zigmond, Cameron, Hoffer, & Smeyne, 2012). However, there is a high amount of inter-individual variability in the neuroplasticity response to exercise (Roemmich et al., 2012). It is possible that this variability could be due to the BDNF Val66Met polymorphism.

Individuals with PD who have the BDNF Val66Met polymorphism reported a higher prevalence of depression (Hwang et al., 2006). It is also believed that the BDNF Val66Met polymorphism could also lead to cognition dysfunction (Bialecka et al., 2014; Guerini et al., 2009). Specifically, the polymorphism affects activity-dependent secretion
of BDNF, memory, and hippocampal function (Egan et al., 2003). In addition, the BDNF Val66Met polymorphism has been associated with problems in selective information processing in cognition (Schofield et al., 2009). There is evidence that aerobic exercise leads to increases in BDNF concentrations which could, in turn, decrease the prevalence of depression symptoms and cognitive dysfunction (Monteiro-Junior et al., 2015; Tuon et al., 2014).

Recently, there has been growing interest in high-cadence stationary cycling as an acute, aerobic exercise treatment for PD (Ridgel, Phillips, Walter, Discenzo, & Loparo, 2015; Ridgel, Walter, et al., 2015). Dynamic cycling, where a motor assists the rider in the pedaling motion at approximately 80 revolutions per minute (RPM), maintains a higher cadence cycling compare to other cycling modalities (Peacock et al., 2014; Ridgel, Abdar, Alberts, Discenzo, & Loparo, 2013; Ridgel, Kim, Fickes, Muller, & Alberts, 2011; Ridgel, Peacock, Fickes, & Kim, 2012; Ridgel, Phillips, et al., 2015; Ridgel, Vitek, & Alberts, 2009; Ridgel, Walter, et al., 2015; Rosenfeldt et al., 2015). Dynamic cycling has led to improvements in Unified Parkinson disease rating scale (UPDRS) scores and the timed up and go test (Ridgel, Phillips, et al., 2015). Despite these overall improvements, there was still a significant variability among individuals. It is possible that some of the variability in responses to dynamic cycling in individuals with PD may be associated with BDNF Val66Met polymorphism.

To better understand the effects of BDNF Val66Met polymorphism on symptoms of PD and responses to an acute, aerobic exercise intervention, this investigation examined the following aims. The first aim was to determine if the prevalence of BDNF
Val66Met polymorphism leads to incidences of attention and executive function cognitive dysfunction, greater prevalence and severity of depression symptoms, decreased quality of life, and greater motor impairments. The second aim was to determine if three sessions of dynamic cycling leads to improvements in attention and executive function, prevalence and severity of depression symptoms, improved quality of life, and improved motor symptoms over time (session 1, and session 4), and between the influence of BDNF Val66Met polymorphism presence (Val-allele group, and Met-allele group).

The following hypotheses were proposed: (a) Individuals with the BDNF Val66Met polymorphism (Met-allele group) will have worse baseline scores for attention and executive function cognitive function, increased prevalence and severity of depression symptoms, decreased quality of life, and greater motor symptoms compared to Val-allele group; (b) All individuals with PD will show improvements in attention and executive domains of cognition, reduced prevalence and severity of depression symptoms, improved quality of life, and reduced motor symptoms after three sessions of dynamic cycling with the Val-allele group having a greater overall improvement compared to the Met-allele group.
CHAPTER II
LITERATURE REVIEW

Idiopathic Parkinson’s disease (PD) is a chronic, neurodegenerative brain disorder that slowly progresses over time (Tanner & Goldman, 1996). PD is caused by degeneration or loss of dopamine-producing cells located in the substantia nigra in the midbrain. The loss of dopamine neurons leads to a dopamine deficiency. The degeneration of dopamine cells in the substantia nigra can be caused by an accumulation of protein alpha-synuclein (SNCA) and Lewy Bodies or neurites located in the midbrain, and brain stem, or dysfunctional mitochondrial activity (National Parkinsons’s Foundation, 2015; Goetz & Pal, 2014). Furthermore, PD has been associated with other chronic conditions such as loss of smell (Cavaco et al., 2015), dementia (Peppard et al., 1992), fatigue (Pavese, Metta, Bose, Chaudhuri, & Brooks, 2010), depression (Burn, 2002), compulsion (Claassen et al., 2011), and neuropsychiatric conditions (Aarsland et al., 2009; Chen et al., 2006). In addition, individuals with PD experience different characteristics and different severities of those characteristics.

Characteristics of PD

Individuals with PD have both motor and non-motor symptoms with varied symptoms due to progression and intensity of PD (Williams & Litvan, 2013). Motor symptoms include balance (Paul et al., 2014), rigidity (Williams & Litvan, 2013), tremor (Williams & Litvan, 2013), uncontrollable movements or dyskinesia (Rascol et al., 2000), slowness of movement or bradykinesia (Williams & Litvan, 2013), gait initiation difficulties (Roemmich et al., 2012), writing difficulties (Rabey et al., 1997), swallowing
difficulties or dysphagia (Bloem, de Vries, & Ebersbach, 2015), masked face or emotion-less (Mukherjee et al., 2011), and general loss of motor skills (National Parkinsons’s Foundation, 2015; Oung et al., 2015). Non-motor symptoms include anxiety (Aarsland et al., 2009), depression (Burn, 2002), mood disorders (Menza, Sage, Marshall, Cody, & Duvoisin, 1990), dementia (Goldman, Baty, Buckles, Sahrmann, & Morris, 1998), constipation (Rossi, Merello, & Perez-Lloret, 2015), pain (Lindholm, Hagell, Hansson, & Nilsson, 2014), genitourinary problems (Williams & Litvan, 2013), orthostatic hypotension (Wu & Hohler, 2015), sleep disturbances (Suzuki, Miyamoto, Miyamoto, & Hirata, 2015), loss of sense of smell (Takeda et al., 2014), vision (Bodis-Wollner, 2013), memory (Egan et al., 2003), hallucinations, and loss of energy (National Parkinsons’s Foundation, 2015). Individuals diagnosed with PD can experience a range of PD symptoms characterized at varied severities making a proper diagnosis challenging (Delenclos, Jones, McLean, & Uitti, 2015).

**Evaluation of PD Severity**

Throughout history new rating scales and diagnostic tools have been designed for evaluating the severity of PD (Nakano & Fujimoto, 2000). The first published diagnostic tool for PD that categorized the progression and severity of PD is called The Hoehn and Yahr Scale (HY) developed in 1967 (Hoehn & Yahr, 1998). HY is a clinical rating scale used to define motor function in PD. HY is simple to use and allows patterns of motor impairment to determine the stage. Stages range from 1–5 where 1 represents only unilateral involvement, usually with minimal or no functional disability and 5 represents confinement to a bed or wheelchair unless aided (Hoehn & Yahr, 1998). This rating
scale positively correlates with motor decline, lower quality of life (Kuopio et al., 2001) and neuroimaging confirming dopaminergic losses (Bhidayasiri & Tarsy, 2012).

Unfortunately, due to its simplicity, the scale therefore lacks essential details and does not account for non-motor symptoms diagnostics. Therefore, a modified version of HY that includes motor impairment in addition to non-motor symptoms was created. The stages range from 1–5 where 1.0 represents unilateral involvement only; 1.5 represents unilateral and axial involvement; 2.0 represents bilateral involvement without impairment of balance; 2.5 represents mild bilateral disease with recovery on pull test; 3.0 represents mild to moderate bilateral disease; some postural instability; physically independent; 4.0 represents severe disability; still able to walk or stand unassisted; 5.0 represents being wheelchair bound or bedridden unless aided (Goetz et al., 2004; Bhidayasiri & Tarsy, 2012).

Shortly after the development of HY scale, the Schwab and England Activities of Daily Living scoring system was developed in 1969. Ratings can be assessed by the rater or by the patient. It ranges from 0%–100% in 10% steps with descriptions such as 0% represents a vegetative functions such as swallowing, bladder, and bowel dysfunction; bedridden, and 100% represents completely independent and able to do all chores without slowness, difficulty, or impairment (Gillingham & Donaldson, 1969).

Today one of the more common, universal scales is the Unified Parkinson’s Disease Rating Scale (UPDRS) for evaluation of PD symptoms. Considered a more comprehensive screening tool, UPDRS factors in motor symptoms, activities of daily living, mental functioning, and behavior and mood categories (National Parkinsons’s
Foundation, 2015; Movement Disorder Society Task Force on Rating Scales for Parkinson’s, 2003). Individual elements in the UPDRS are scored on a scale from 0 normal–4 severe impairment. It is designed to follow the longitudinal development of PD and is assessed by a trained researcher (Eskandar, 2005; Movement Disorder Society Task Force on Rating Scales for Parkinson’s, 2003). Due to the subjectivity of the trained researcher performing the evaluation in comparison to others there is low inter-individual reliability. Specifically, one trained researcher may rate the same symptoms differently than another trained researcher.

Due to the low inter-rater reliability of UPDRS, the Short Parkinson Evaluation Scale (SPES) was developed (Rabey et al., 1997). The SPES uses a 0–3 scale to evaluate mental axis, activities of daily living, and motor symptoms. Complications of PD are also included as well as global scoring for motor fluctuations incorporated from the HY scale (Rabey et al., 1997). Raters in a previous research commented that SPES was easier to administer than UPDRS and is supported by strong mean inter-rater reliability (Rabey et al., 1997). In recent years, another rating scale has been developed called the scales for outcomes in Parkinson’s disease-psychosocial questionnaire (SCOPA-PS). SCOPA-PS was introduced as a new survey design for those with PD in 2003 (Marinus, Visser, Martinez-Martin, van Hilten, & Stiggelbout, 2003). These rating scales all inherently involve subjectivity by the rater or by the patient due to the lack of standardized, objective measures (Levine, 2003). Therefore, more objective measurements for evaluating PD symptoms have been developed.
Methods for PD Symptoms Assessment

Symptoms evaluation may assist in earlier detection of PD, therefore may be able to begin treatment in earlier-onset PD and allow for more time to determine if neuroprotective therapies are assisting individuals with PD (Loane & Politis, 2011). As previously outlined, several clinical evaluations of PD are available such as UPDRS, HY, and SPES. However these scales are inherently subjective with the clinician rating the severity of the symptoms observed. This causes a major limiting factor in the comparison of results among different studies (Levine, 2003). Current technology allows for more objective measures of motor function using accelerometers and gyroscopes. Kinesia ONE™ software is an objective tool that utilizes an application commonly installed on an iPad or tablet device that is then paired with a wireless accelerometer sensor to measure movement disorders such as PD (Heldman, Espay, LeWitt, & Giuffrida, 2014). This device allows individuals with PD to record symptoms and their severity any point in time. Kinesia ONE™ is a validated testing measurement for UPDRS and provides insight into PD symptom fluctuation (Pulliam, Burack, Heldman, Giuffrida, & Mera, 2014). The measurements include tremor, finger tapping, hand movements, rapid alternating movements, and dyskinesia.

Influential Genetic Factors in PD

Though the causes of PD are idiopathic, it is believed to be influenced by genetic factors (Kieburtz & Wunderle, 2013; Le Couteur et al., 2002; E. K. Tan, 2007). Genetic factors, or genes, refer to units of heredity that are made of DNA found in all cells. Genes produce proteins that control biological development and function (Health, 2015;
National Parkinson’s Foundation, 2015). Genome-wide association studies allow researchers to view entire genomes tested for association with a disease such as PD by examining case-control datasets compared to family based sets (Hindorff et al., 2009; M. S. Tan, Jiang, Tan, & Yu, 2014). However, family based sets can be useful. Approximately 15–25% of individuals diagnosed with PD have reported having a relative with PD (Sellbach, Boyle, Silburn, & Mellick, 2006). More specifically, individuals with PD who have a first-degree relative have a higher risk of developing PD compared to the general population.

Several gene mutations have been discovered that provide links to the potential cause of PD. Some genetic mutations are linked to a small number of individuals and families and it could also be inherited through Mendelian autosomal dominant or recessive genes in a small portion of families (Agrawal & Biswas, 2015; Movement Disorder Society Task Force on Rating Scales for Parkinson’s, 2003). Genetic mutations have been linked to dopamine cell functions. Individuals who have developed PD earlier in life often have known genetic mutations. Genetic mutations in ubiquitin carboxyl-terminal hydrolase Li (UCH-Li), putative kinase 1 (PINK1), and oncogene DJI (DJ1) are associated with early-onset PD (Agrawal & Biswas, 2015; National Parkinsons’s Foundation, 2015). UCH-Li encodes a protein that represents 1% of the protein and brain function. It is suggested that it may be modifying damaged proteins that would normally increase the toxic levels in the neuron. UCH-Li has been identified as a mutation in first degree relatives (Leroy et al., 1998). The mutation identified as Ile93Met in UCH-Li causes partial loss of catalytic activity of thiol protease which could...
lead to abnormalities in the proteolytic pathway and abnormalities of proteins (Agrawal & Biswas, 2015; Harhangi et al., 1999; Leroy et al., 1998). It is suggested that up to 50% of family-related cases of PD are associated with mutations on the parkin gene (Agrawal & Biswas, 2015). The genetic variation in the parkin gene on chromosome 2q36-37 may contribute to PD susceptibility. PINK1 has been identified in two families that links this particular genetic mutation to the mitochondria in PARK6 (Valente et al., 2004). Dekker and colleagues (Dekker et al., 2003) have characterized mutations in the DJ1 gene including the PARK7 mutation. The suggested role of DJ1 in oxidative stress and neurodegeneration could lead to a slow progression of PD related symptoms (Dekker et al., 2003).

Other genetic mutations such as SNCA, and leucine-rich repeat kinase2 (LRRK2) have been associated with late-onset PD. SNCA has been identified in some families with PD and accumulates in the brain (Agrawal & Biswas, 2015; Movement Disorder Society Task Force on Rating Scales for Parkinson’s, 2003). Mutations in LRRK2 are the most commonly known genetic cause of PD. An amino-acid substitution (G2019S) cause an enhancement in kinase function of the protein. Therefore, LRRK2 inhibitors have been a topic of interest by researchers (Kalia, Kalia, & Lang, 2015). Having a better understanding of the roles of these genes and genetic mutations could help understand the effects in PD (Agrawal & Biswas, 2015). More recently, the influence of mutations in genes that produce neurotrophic factors such as brain-derived neurotrophic factor (BDNF) have been associated with PD (Scalzo et al., 2010).
Brain-Derived Neurotrophic Factor

BDNF has a common genetic variation associated with PD and neuropsychiatric illnesses such as high anxiety, depression, and Schizophrenia (Chen et al., 2006; Egan et al., 2003; Elfving et al., 2012). BDNF has a single-nucleotide polymorphism (SNP) (c.196G<A and rs6265) with an amino-acid substitution in the prodomain of valine (Val) to methionine (Met; Egan et al., 2003; Gao et al., 2010; Knaepen, Goekint, Heyman, & Meeusen, 2010). BDNF is involved in phenotype survival and development of neurons in the central nervous system affecting the hippocampus and cortical neurons, cholinergic neurons, and nigral dopaminergic neurons (Binder & Scharfman, 2004; Chen, Bath, McEwen, Hempstead, & Lee, 2008). Moreover, the neurotrophic properties of BDNF could lead to treatment options for neurodegenerative diseases such as PD and neuropsychiatric disorders such as depression (Binder & Scharfman, 2004).

Since BDNF promotes neuron survival, it may have a therapeutic effect in individuals with neurodegenerative diseases (Vaynman & Gomez-Pinilla, 2005). This is due to the altered expression of BDNF that can result in abnormal functioning (Murer, Yan, & Raisman-Vozari, 2001). The reduced or abnormal expression may result from a substitution located at amino-acid codon 66 known as Val66Met polymorphism (Bath & Lee, 2006). Individuals who have one of two Met alleles present in substitution for one or two Vet allele have Val66Met polymorphism (Shimizu et al., 2004). Approximately 20–30% of the general population is a heterozygous carrier for the polymorphism (Shimizu et al., 2004). When the polymorphism is present, it could cause altered BDNF distribution and decreased BDNF secretion (Hariri et al., 2003). Abnormal expression of
BDNF concentration could lead to the development of cognitive dysfunction and neurodegenerative diseases such as PD (Bialecka et al., 2014; Scalzo et al., 2010; Schofield et al., 2009; Teixeira, Barbosa, Diniz, & Kummer, 2010; Zuccato & Cattaneo, 2009). Previous research has shown BDNF levels are reduced in the substantia nigra in individuals with PD (Murer et al., 2001). In animal models, Met allele carriers expressed normal BDNF serum levels but BDNF secretion from the neurons was found to be defective (Chen et al., 2006). In humans, Met allele carriers showed abnormal intracellular secretion of BDNF, and reduced hippocampal structure and function (Borroni et al., 2012; Hariri et al., 2003). The reduced hippocampal structure has a lower neuronal integrity that results in episodic memory deficits (Egan et al., 2003). Met allele carriers also have decreased motor task performances and a diminished capacity for motor cortex plasticity (Kleim et al., 2006). Furthermore, Met allele carriers also had reduced performance on executive function testing (Nagel et al., 2008). In contrast, those with PD who are Met allele carriers have demonstrated better delayed recall of information than individuals with PD who are Val allele carriers (Bialecka et al., 2014). BDNF is a complex genome that needs to be further investigated in those with PD and has been associated with other psychiatric illnesses such as depression (Taliaz, Stall, Dar, & Zangen, 2010). There is also evidence that in addition to genetic factors, environmental factors can increase the risk of PD (Campdelacreu, 2014; Kieburtz & Wunderle, 2013; Le Couteur et al., 2002).
In addition to genetic factors, environmental factors such as age, gender, history of traumatic brain injuries, area of residence, occupation, pesticide exposure, exposure to metals, exposure to chemicals have been suggested to increase risk of developing PD (Campdelacreu, 2014; Hubble, Cao, Hassanein, Neuberger, & Koller, 1993; Kieburtz & Wunderle, 2013; Le Couteur et al., 2002). In particular, certain chemicals have been associated with elevated risk of PD if exposed to chemical solvents, polychlorinated biphenyls (PCB), permethrin, beta-hexachlorocyclohexane (beta-HCH), herbicide parquet, 2, 4 dichlorophenoxyacetic acid (2, 4-D), Agent Orange, and 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyrididine (MPTP; National Parkinsons’ Foundation, 2015). Occupational exposure to chlorinated solvents can increase risk of developing PD (Gash et al., 2008). PCB exposure research is more consistent than research findings on other chemical associated with an increased risk of PD (Affairs, 2015). Exposure could have occurred during military occupations to individuals who repaired and maintained transformers prior to 1977 (Affairs, 2015). PCB has also reportedly found in excess in Greenland and meat consumption (Wermuth, Pakkenberg, & Jeune, 2002). Permethrin is an insecticide that blocks the mitochondria complex 1 and increases oxidative stress (Tanner et al., 2009). The herbicide paraquat was among the earliest chemicals investigated due to its association with rural environment living (Tanner & Goldman, 1996). Paraquat produces reactive oxygen species, then alpha-synuclein (SNCA) accumulates, and it can lead to nigral injury (Dinis-Oliveira et al., 2006). A component in Agent Orange, 2, 4-D, has also been associated with increasing
risk of developing PD specifically in military veterans of the Vietnam War (Tanner et al., 2009). MPTP is a synthetic neurotoxin agent known to cause immediate and permanent human parkinsonism that was first discovered in 1980s in a group of people who injected contaminated heroin (Langston, Ballard, Tetrud, & Irwin, 1983). Individuals were reporting injecting the compound in contaminated heroin (National Parkinsons’s Foundation, 2015). Previous research in animal models suggests that MPTP enters the brain through amino acid transporters and is then it metabolized into a reactive compound that blocks mitochondrial complex 1 (Tanner, Goldman, Ross, & Grate, 2014).

Other environmental factors that may influence risk of developing PD include traumatic brain injuries (TBI), oxidative stress, and modifiable dietary intake. The onset of PD is associated with occurrences of TBI due to both environment and gene interactions (Jafari, Etminan, Aminzadeh, & Samii, 2013). TBI increase the risk of inflammation, SNCA accumulation among other changes that can lead to neurodegeneration (Povlishock & Katz, 2005). In addition, younger individuals diagnosed with PD that had high levels of oxidative stress had dopaminergic neuron death in the substantia nigra increasing their risk of PD (C. H. Tsai et al., 2002). Furthermore, dietary intake survey comparison of individuals with PD in comparison to healthy controls resulted in those with PD consuming more animal fats and had higher caloric diets than the control group. This is consistent with the development of oxidative stress and lipid peroxidation in individuals with PD (Logroscino et al., 1996). Both coffee and tea intake have also been associated with a lower risk of PD (Tanner et al., 2014; C. H. Tsai et al., 2002). In addition, higher amounts of uric acid and use of
anti-inflammatory drugs may also decrease risk of PD. Furthermore, a history of smoking and exercise has been associated with a lower risk of PD (National Parkinson’s Foundation, 2015; Kieburtz & Wunderle, 2013; Tanner et al., 2014). In addition, researchers have suggested that hyperuricemia and older individuals who regularly exercised reported a lower risk in developing PD (Campdelacreu, 2014; C. H. Tsai et al., 2002). Therefore, increasing preventable or positive risk factors for PD could help prevent PD, improve quality of life, and reduce healthcare costs associated with PD.

**Treatments for Symptoms of PD**

Previous research demonstrates that costs associated with PD are expensive for individuals and the healthcare system as whole. In 2000, quality of life costs were estimated at $25 billion per year for individuals with PD in the US (Kowal, Dall, Chakrabarti, Storm, & Jain, 2013; Scheife, Schumock, Burstein, Gottwald, & Luer, 2000). Those expenses increased when associated with indirect costs due to falls and fall-related injuries (Watts et al., 2008). Pharmacotherapy interventions such as levodopa have been associated with higher costs and increase subject discomfort related to side effects such as dyskinesia. In addition, dopamine agonists can lead to fewer delays in motor impairment due to the extended release of the drug. However, dopamine agonists are more expensive treatments (Eggert, Reese, Oertel, & Dodel, 2008). Currently, surgeries associated with PD such as deep brain simulation (DBS) are one of the most expensive treatments available today. Individuals with PD who have undergone surgery such as DBS in more severe cases are associated with medical cost information (Dodel, Berger, & Oertel, 2001). Therefore, to determine the total impact of PD, researchers
need to consider the economic outcomes in addition to clinical outcomes (Scheife et al., 2000).

**Drug Treatments for Symptoms of PD**

The primary treatment for individuals with PD includes pharmacologic therapy. Some common drug treatments include carbidopa-levodopa, dopamine agents, monoamine oxidase (MAO-B) inhibitors, catechol-O-methyltransferase (COMT) inhibitors, anticholinergics, and amantadine (Claassen et al., 2011; Dodel et al., 2001; LeWitt, 2015). The most common drug treatments are levodopa or carbidopa. Levodopa is the drug treatment in which most individuals with PD achieve long-term benefits with regular use. It is considered the gold standard drug treatment for those with PD (LeWitt, 2015). Levodopa results in the greatest improvement in UPDRS when compared to other PD medications and (Rascol et al., 2000) it has a 90% success rate in lessoning symptoms of PD (Nutt & Wooten, 2005). However, long-term use of levodopa increases dyskinesia (involuntary movements) in 33% of PD individuals within a two year period (Group, 2000). Levodopa also can cause acute side effects such as nausea, vomiting, and hypotension (Poewe, Antonini, Zijlmans, Burkhard, & Vingerhoets, 2010). Levodopa works by converting into an enzyme to help produce dopamine in the brain. When paired with carbidopa, it slows down the enzyme breakdown. This combination has been found to improve mobility in earlier stages of PD. However, there are complications with dopamine replacement therapies. Levodopa does not slow down the progression of PD. With chronic dopamine replacement use, symptoms of PD can return before the permitted time for another dose of the drug treatment. This could lead to an
uncomfortable period of time in-between doses. Furthermore, individuals on high proteins diets may limit the effectiveness of the therapy. Likewise, dopamine replacement therapy does not address PD symptoms such as posture, depression and cognitive problems (Levine, 2003).

Other common drug treatments include dopamine agents. Dopamine agents mimic the effect of dopamine in the brain and can be used in junction with dopamine release therapies (Brooks, 2000; Koller & Rueda, 1998). Dopamine agents are not affected by high protein diets and can be taken through a skin patch instead of oral administration. Though this may cause dyskinesia, it appears to be less severe dyskinesia than with dopamine replacement therapies (M. J. F. Foundation, 2015; Koller & Rueda, 1998). When paired with levodopa, acute side effects such as hallucinations, somnolence (sleepiness), and edema may occur (Poewe et al., 2010). In contrast to levodopa, dopamine agonists are not the most effective treatment for motor symptom in those with PD. Other side effects may also occur including daytime sleepiness, sudden unanticipated sleep, hallucinations, and risk-taking behavior (Goetz & Pal, 2014).

Similarity to dopamine release therapy, it does not reduce all symptoms of PD including posture, depression and cognitive problems (Brooks, 2000; M. J. F. Foundation, 2015).

A new drug treatment for individuals with PD involves MAO-B (monoamine oxidase-B) inhibitors. MAO-B inhibitors inhibit an enzyme that breaks down levodopa therefore prolonging the action of it by reducing the metabolic breakdown (Goetz & Pal, 2014). Generally, MAO-B inhibitors are used alone with or dopamine release therapy. Unfortunately, these drugs have little benefit for PD symptoms but prolong the
breakdown of dopamine (Goetz & Pal, 2014). These drugs may also have poor interactions with blood pressure medication, antidepressants, and could cause hallucinations (M. J. F. Foundation, 2015). In contrast, a systematic review revealed that MAO-B inhibitors may improve symptoms of PD and delay a need for prolonged use of levodopa (Goetz & Pal, 2014).

Catechol-O-methyl transferase (COMT) inhibitors are another drug treatment option for individuals with PD. They work by allowing more levodopa to reach the brain therefore increasing levodopa concentration (Ruottinen & Rinne, 1998). These drugs help maintain a stable amount of levodopa and are traditionally used with dopamine release therapy. Complications of COMT-inhibitors include increasing of the severity of side effects associated with levodopa such as dyskinesia. In addition, some COMT-inhibitors have been known to cause diarrhea and liver issues (Ruottinen & Rinne, 1998).

Other common drug treatments for individuals with PD include amantadine and anti-cholinergic. Amantadine may reduce dyskinesia in more advanced cases of PD and reduce symptoms of fatigue, tremor, and bradykinesia. However, it has side effects such as drowsiness, and hallucinations (Crosby, Deane, & Clarke, 2003; M. J. F. Foundation, 2015). In addition, amantadine is not metabolized well and is excreted in the urine. If excessive amounts of amantadine are found in blood, it could lead to psychosis, and hallucinations found in a small percentage of users (Goetz & Pal, 2014). Anti-cholinergic drug treatments also affect the muscarinic acetylcholine receptors that alter G protein activity (Katzenschlager, Sampaio, Costa, & Lees, 2003). These drug treatments try to
correct the imbalance of striatal dopamine and acetylcholine activity (Goetz & Pal, 2014). In addition, anti-cholinergic drugs may help individuals with PD younger than 70 years old with tremor symptoms. Its side effects include memory and cognition problems, hallucinations, constipation, dry mouth, and difficulty urinating (M. J. F. Foundation, 2015; Katzenschlager et al., 2003). Furthermore, autonomic and impaired neuropsychiatric functions are common side effects with anti-cholinergic drugs (Goetz & Pal, 2014). With many known side effects to common drug treatments, it is important to design a treatment that can reduce all symptoms of PD and improve quality of life.

Non-Drug Treatments for PD

Non-drug treatments can help target symptoms of PD include surgery, therapy, and exercise. Currently, no surgical treatments are available that slow down the progression of PD. However, surgical procedures such as DBS can provide PD symptomatic benefits such as reduced fluctuations caused by dyskinesia. This surgical technique involves implanting electrodes in the brain to target the globus pallidus or subthalamic nucleus to improve motor function. The electrodes are then connected to an electrical stimulator implanted in the chest wall. DBS is offered to individuals with severe PD diagnosis and those individuals that are unstable on traditional drug treatments (Heldman et al., 2014). Speech therapy can also help assist with reduced and/or fading volume, vocal clarity, or changed pace of speaking that may occur in individuals with PD. Furthermore, speech therapy has been shown to improve speech as well as quality of life. The Lee Silverman Voice Treatment is a common program recommend (El Sharkawi et al., 2002; Sapir, Spielman, Ramig, Story, & Fox, 2007). In addition,
occupational therapy can assist with tasks of daily living and improve quality of life (Deane, Ellis-Hill, Playford, Ben-Shlomo, & Clarke, 2001). Additionally, psychological therapy can assist with depression, and anxiety often experienced by those with PD (Charidimou, Seamons, Selai, & Schrag, 2011). Recently, there has been much interest in the value of exercise as a non-drug treatment for individuals with PD. Exercise can help target symptoms in those with PD that are not generally improved with standard drug treatments such as cognitive impairment, depression, and quality of life (Abbruzzese, Marchese, Avanzino, & Pelosin, 2015; M. J. F. Foundation, 2015).

Exercise as treatment for PD generally is in combination with drug treatments to decrease overall symptoms of PD and improve quality of life (Canning et al., 2009; Dowding, Shenton, & Salek, 2006; Teixeira-Machado et al., 2015) by increasing the ability for individuals to become more independent. Individuals with PD often report a lower quality of life compared to individuals who do not have PD. In addition, individuals with PD have an increased risk of depression (Teixeira-Machado et al., 2015). Moreover, quality of life is affected by factors such as depression, motor impairments, and experience with educational programs on PD (Dowding et al., 2006). Therefore, as motor impairments increase, quality of life decreases. In addition, individuals with PD who receive levodopa treatments are also more likely to have motor impairments occur increasing from 50% prevalence with 3–5 years of treatment to greater than 80% prevalence with more than 10 years of treatment (Dodel et al., 2001). Fortunately, exercise can help individuals with PD decrease motor impairments, and increase quality of life. Exercise can promote motor learning (Abbruzzese et al., 2015; Beall et al., 2013;
Dashtipour et al., 2015). This is critical since individuals with PD are associated with having altered motor function (Beall et al., 2013). Unfortunately, individuals with PD have reduced motor learning in comparison to control groups (Abbruzzese et al., 2015). Therefore, different modes of exercise may have different effects on motor and non-motor function.

**Comparison of Different Exercise Modalities**

In the neurodegenerative disease populations, modified aerobic exercises have led to more consistent motor symptom improvements than traditional, aerobic exercise (Knaepen et al., 2010). Specifically, individuals with PD may have difficulty with traditional, aerobic exercise. Therefore, researchers have designed modified, aerobic exercises for this population. Researchers have combined modified, body weight supported treadmill and limb exercise interventions that resulted in motor and non-motor symptom improvements (Dashtipour et al., 2015). In addition, another treadmill-based exercise intervention also used body weight supported treadmill training when comparing different intensities to determine which exhibited the greatest overall improvements (Fisher et al., 2008). Since individuals with PD experience a wide range of symptoms and at different severities therefore performing traditional, aerobic exercise can difficult. Thus, recumbent cycling interventions where individuals pedal sitting and supported would be more appropriate modality compared to other common modes of aerobic exercise.

Several recumbent bicycle designs are available to help provide a safe mode for aerobic exercise. The Theracycle tandem exercise bike (Franklin, MA) can maintain a
high 80–90 RPM that was used to examine the benefits of voluntary exercise (Alberts, Linder, Penko, Lowe, & Phillips, 2011). In addition, the Motomed exercise bike has a user friendly interface that allows for symmetry training with a smooth drive system recommended for neurological, neuromuscular and other orthopedic surgery conditions. Furthermore, the Motomed Viva 2 model has been heavily used in previous investigations (Peacock et al., 2014; Ridgel et al., 2013; Ridgel, Kim, et al., 2011; Ridgel, Muller, Kim, Fickes, & Mera, 2011; Ridgel et al., 2012; Ridgel, Walter, et al., 2015).

Novel cycling interventions have offered more insight into motor and non-motor symptom improvements in individuals with PD. In addition, several previous investigations have led to improvements in motor function with reduced symptoms in those with PD (Alberts et al., 2011; Ridgel et al., 2009). These newly introduced interventions include forced exercise, active-assisted cycling, and dynamic cycling interventions (Alberts et al., 2011; Peacock et al., 2014; Ridgel, Phillips, et al., 2015; Ridgel et al., 2009; Rosenfeldt et al., 2015). During forced exercise, individuals were actively participating through the revolution, which led to improvements in motor improvements potentially due to altered central nervous system functioning (Ridgel et al., 2009). The key mechanism behind the recumbent cycling interventions is high cadence cycling during a novel exercise mode called dynamic cycling (Ridgel, Phillips, et al., 2015). Dynamic cycling stems from forced exercise introduced earlier (Alberts et al., 2011; Ridgel et al., 2009). Forced exercise involved a high cadence (80 rpm) and required a stationary tandem bicycle with a human trainer to assist the individual with PD in the fast pedaling rate. Forced exercise resulted in both neuroprotective and improved
motor function (Alberts et al., 2011). Furthermore, forced exercise and medication may use the same pathways to produce symptomatic relief (Beall et al., 2013). Unfortunately, such a design may not be possible in standard rehabilitation centers having a human trainer present. Therefore, dynamic cycling was created. It involves a motorized stationary, recumbent bicycle that helps the participant pedal faster than they could on their own. The intervention is novel since the dynamic cycling motion involves some variation in the movement (Ridgel, Phillips, et al., 2015). Dynamic cycling was designed with a commercially available exercise bike called the Motomed Viva 2 (Reck, Germany). It was augmented with a motorized component that was integrated with commercially available programmable logic controller (PLC). Furthermore, dynamic cycling uses information from sensors to capture real-time data while an adaptive motor changes torque and speed (Abdar, 2014).

Interestingly, researchers found that individuals in the static cycling group performed higher intensity exercise in comparison to the dynamic cycling group. However, the dynamic cycling group had the greatest symptomatic improvement. Given these findings, Ridgel, Phillips, et al. suggested that these benefits are not due to cardiovascular or metabolically processes but potentially sensory or proprioceptive feedback (Ridgel, Phillips, et al., 2015). Specifically, the proprioceptive feedback refers to signals from the muscles, joints, and skin that regulate the pattern of muscle activation during movement. Due to these findings, the secondary measurements heart rate (HR), rating of perceived exertion (RPE), and RPM will be recorded to determine the intensity of exercise performed in the dynamic cycling group. If there is not a high cardiovascular
or metabolic demand determined by secondary measurements, then perhaps sensory feedback or increases of BDNF concentration are leading to changes in the primary measurements.

**Exercise and Neuroplasticity**

Exercise treatment for individuals with PD promotes neuroplasticity of the brain (Knaepen et al., 2010). The neuroplasticity changes refer to the ability of the brain to adapt to environmental change. Exercise may also have a neuroprotective mechanism in those with PD (Speelman et al., 2011). In addition, physical activity may induce increases in corticomotor excitability (Fisher et al., 2008), leading to increases in neurotrophic factors including BDNF, and angiogenesis, which helps to promote survival of dopamine neurons (Zigmond et al., 2012). Therefore, exercise is believed to stimulate neurotrophins such as BDNF synthesis (Adlard, Perreau, & Cotman, 2005; Monteiro-Junior et al., 2015), which could promote neuroplasticity decreasing cell death of dopaminergic neurons further reducing symptoms in those with PD.

Exercise may restore normal expressions of BDNF concentration (Knaepen et al., 2010; Loprinzi, Herod, Cardinal, & Noakes, 2013; Vaynman & Gomez-Pinilla, 2005). Neurotrophic factors such as BDNF are involved in changes in exercise metabolism and nervous system (Pedersen et al., 2009). In addition, previous research has shown that acute exercise elicits changes in neurotrophins that facilitate exercise metabolism (Cotman & Berchtold, 2002; van Praag, Shubert, Zhao, & Gage, 2005). Furthermore, research has examined the effects of BDNF and acute exercise focused in individuals
with neurodegenerative diseases to determine if exercise could reestablish appropriate levels of BDNF (Gold et al., 2003).

The exercise-induced BDNF response molecular origin is not entirely understood and needs to be further investigated. BDNF in the blood has been found to cross the blood-brain barrier (Poduslo & Curran, 1996). This enhanced permeability could be used for treatment of neurodegenerative diseases (Poduslo & Curran, 1996). The brain contributes to the majority of BDNF concentration however the exact brain regions from which its produced include the CNS, hippocampus, cerebral cortex, prosencephalon, cerebellum, and hypothalamus is not entirely known (Knaepen et al., 2010). Furthermore, older adults may have a reduction in BDNF resulting from reduced messenger RNA (Webster, Herman, Kleinman, & Shannon Weickert, 2006). The synthesis of BDNF in the bloodstream increases are activity-dependent. This suggests that BDNF is transported in the bloodstream to the brain crossing the blood-brain barrier (Berchtold et al., 2005).

These induced changes in BDNF concentration are associated with aerobic exercise (Goekint et al., 2010; Knaepen et al., 2010). In particular, acute, aerobic exercise interventions result in the greatest improvements in peripheral BDNF concentration (Knaepen et al., 2010). However, there is a mixed reports on whether anaerobic training influence BDNF concentration (Goekint et al., 2010; Yarrow, White, McCoy, & Borst, 2010). Regardless, previous findings are consistent that acute, aerobic exercise increases in BDNF concentrations in individuals with neurodegenerative diseases (Castellano & White, 2008; Schulz et al., 2004). Baseline values of BDNF
concentration for individuals with neurodegenerative diseases have been reported to be lower (Castellano & White, 2008), and the same as healthy subjects (Gold et al., 2003). One suggested reason for the lowered BDNF concentration in individuals with neurodegenerative disease is that the lower BDNF concentration due to tissue protection. More importantly, lower BDNF concentration could be resolved with exercise, which has been proposed to increase BDNF concentration (Vaynman & Gomez-Pinilla, 2005).

Sadly, the prevalence of depression in PD is approximately 50% (F. H. Costa, Rosso, Maultasch, Nicaretta, & Vincent, 2012; Reijnders, Ehrt, Weber, Aarsland, & Leentjens, 2008; Schrag et al., 2007). Individuals with PD who are clinically depressed may experience benefits from acute, aerobic exercise (Dashtipour et al., 2015; Doose et al., 2015; Goodwin, Richards, Taylor, Taylor, & Campbell, 2008; Ridgel, Walter, et al., 2015). If proper diagnostics were not conducted, then recommended treatment for individuals with PD could be altered. Individuals with depression and PD may have a faster progression of both cognition and motor symptoms (Burn, 2002). Fortunately, aerobic exercise can improve motor performance in individuals with PD and depression. However, as depression is reduced, so is the motivation to exercise (Ridgel, Walter, et al., 2015). It is important to develop an acute, aerobic exercise treatment to lesson symptoms of PD while keeping them engaged.

As previously discussed, depression in individuals with PD may overlap with cognitive impairment (Dobkin et al., 2014; Guerini et al., 2009). In addition, depression may influence changes in brain volume (van Mierlo, Chung, Foncke, Berendse, & van den Heuvel, 2015). Improvements in mood have been associated with improvements in
memory and executive function (Dobkin et al., 2014). Moreover, changes in brain volume occurred when BDI-II scores negatively correlates with bilateral hippocampus and the amygdala volume when it positively correlates with volume anterior cortex (Gerritsen et al., 2012; van Mierlo et al., 2015).

Individuals with PD and depression often have cognitive impairment and may experience benefits with acute, aerobic exercise (Dobkin et al., 2014; Fernandez et al., 2009). Specifically, individuals that participated in cognitive-behavioral treatment for depression also had improvements in executive function and verbal memory (Dobkin et al., 2014). In addition, depressive symptoms positively correlate with global cognition, naming, language, and verbal memory (Fernandez et al., 2009). Furthermore, lower peripheral BDNF concentration has been observed in depressed individuals (Karege, Perret, et al., 2002). Depressed animal models that performed aerobic exercise had a neuroprotective effect that led to an increased, normalized BDNF concentration (Tuon et al., 2014). Acute, aerobic exercise has also led to improvements in depression in three exercise sessions (Guszkowska, 2004).

Cognitive impairment has also associated with individuals with PD, unrelated to prevalence of depression (Higginson et al., 2003; Murray, Sacheli, Eng, & Stoessl, 2014). Previous research supports acute, aerobic exercise as a treatment to reduce cognitive impairment (Kramer, Colcombe, McAuley, Scalf, & Erickson, 2005). In particular, individuals with PD experience cognition impairments in task-set switching (Cools, Barker, Sahakian, & Robbins, 2001). Researchers have determined that animal models with PD have experienced exercise-related protection from dopaminergic neurotoxins
where a neuroplasticity effect has been linked to improvements in cognition (Ahlskog, 2011). In addition in review of aging, fitness and neurocognitive function indicated that individuals who were aerobic trained had improvements in executive control compared to those who were anaerobically trained (Kramer et al., 2005). Furthermore, older adults who performed moderate intensity cycling had improvements in reaction time (Kamijo et al., 2009). Acute, aerobic passive cycling has been found to improve Trail-Making Test-B occurred as well as the time to completion for both Trail-Making Tests-A & B (Ridgel, Kim, et al., 2011). In contrast, after acute exercise in healthy individuals there was a decrease in executive control (Labelle, Bosquet, Mekary, & Bherer, 2013).

**Role of BDNF in Exercise Related Cognitive Improvements**

Previous literature has supported exercise as treatment for cognition (Bloem et al., 2015). It has been determined that aerobic exercise can help increase BDNF improving cognition (Cools et al., 2001). Regular exercise and acute exercise prior to testing can lead to improved cognition in novel object recognition and had reduced perceived stress (Hopkins, Davis, Vantieghem, Whalen, & Bucci, 2012). A meta-analysis involving acute exercise and cognition revealed a small effect dependent on moderate intensity and arousal led to faster processing speeds (McMorris & Hale, 2012). A single bout of exercise was found to improve cognition in attentional processing (Pontifex, Parks, Henning, & Kamijo, 2015). In addition, of individuals with chronic diseases 86% of studies observed an increase in peripheral BDNF concentration after exercise (Knaepen et al., 2010). However, as previously discussed, it is suggested that individuals with BDNF Val66Met polymorphism (Met-carriers) have diminished activity-dependent
secretion (Chen et al., 2008; Egan et al., 2003). After three exercise sessions improvements in cognition were found (Chang, Labban, Gapin, & Etnier, 2012). Therefore, BDNF Val66Met polymorphism should be investigated in relation to neurocognitive function, depression, quality of life, and motor symptoms before and after a three-session aerobic exercise intervention. It is also suggested that moderate intensity, aerobic exercise will lead to improved cognition. Thus, it is proposed that dynamic cycling at moderate intensity would be appropriate for individuals with PD.

BDNF Val66Met polymorphism can effect cognition, depression, and quality of life (Hopkins et al., 2012). It is known that changes in BDNF concentration have been associated with neurodegenerative diseases such as PD and neuropsychiatric disorders such as depression (Chen et al., 2008). Understanding how BDNF Val66Met polymorphism affects depression, cognition, and quality of life can better explain neuron function in the brain (Bath & Lee, 2006). Interestingly, researchers determined that the BDNF Val66Met polymorphism does not have an increased expression in PD population (Svetel et al., 2013). In contrast, not-Met carriers were reported as over-represented in the PD population (Guerini et al., 2009).

Previous research has demonstrated improvements in BDNF concentration in the brain are associated with non Met-allele carriers. Furthermore, the prevalence of BDNF Val66Met polymorphism suggests an altered activity-dependent release of BDNF in Met-allele carriers could reduce associated cognitive benefits of aerobic exercise (Hopkins et al., 2012). Met-allele carriers have also reported a lower hippocampus engagement of the brain, which accounted for 25% variance in recognition memory
(Hariri et al., 2003). Consistent with those findings, Met-allele carriers had poor medial temporal lobe memory performance suggesting that Met-allele carriers may have a role in visuospatial dysfunction (Ho et al., 2006). In addition, the presence of the BDNF Val66Met polymorphism also suggests poor episodic memory performance is likely to occur when executive demands are high (Li et al., 2010). Furthermore, previous research also supports that the presence of Met-alleles are associated with reduced cognitive functioning and a smaller hippocampus size (Miyajima et al., 2008). Additionally, Met-allele carriers have reported increased neural response from arousal which can alter facial emotions (Mukherjee et al., 2011).

In contrast to those findings, previous research has also suggested improvements in BDNF concentration and the brain are associated with Met-allele carriers. Met-allele carriers have also reported improved cognition. Met-allele carriers have reported better executive function in comparison to Val-allele carriers (Beste, Baune, Domschke, Falkenstein, & Konrad, 2010). In addition, Met-allele carriers performed better in the Tower of London, a planning test, compared to non Met-allele carriers (Foltynie et al., 2005). Furthermore, researchers concluded that Met-allele carriers had improved delayed recall of information compared to non Met-allele carriers (Bialecka et al., 2014). This suggests that acute, aerobic exercise could restore normal BDNF concentration however it is dependent on whether the BDNF Val66Met polymorphism is present. Likewise, the presence of BDNF Val66Met polymorphism may alter cognition, depression and quality of life in individuals with PD.
Effects of BDNF Val66Met Polymorphism on Cognitive Dysfunction, Depression, Quality of Life, and Motor Symptoms Individuals in PD

There are some inherent challenges in determining the effect of BDNF Val66Met polymorphism on cognition, depression, quality of life, motor symptoms in individuals with PD. Currently, no known literature has examined the influence of BDNF in individuals with PD during dynamic cycling as the aerobic exercise modality. In addition, it has been determined that aerobic exercise influences BDNF concentration. However, individuals with neurodegenerative diseases tend to have lower BDNF concentration at rest but may experience an increase with aerobic exercise. The activity-dependent response is likely affected by the presence of BDNF Val66Met polymorphism. Individuals who are non-Met carriers are suggested to have the greatest improvements in cognition, prevalence of depression, quality of life, and motor symptoms after the intervention. Therefore, the study will test for the influence of BDNF Val66Met polymorphism and the changes in neurocognitive function, depression, quality of life, and motor symptoms following three exercise sessions of dynamic cycling.

It is not understood how BDNF Val66Met polymorphism affects individuals with PD responses to dynamic cycling and the resulting affects in cognition, depression, quality of life, and motor symptoms. Therefore, the purpose of this study is to address the following aims. The first aim is to determine if the prevalence of BDNF Val66Met polymorphism leads to incidences of cognitive dysfunction (attention, executive function, and MoCA), greater prevalence and severity of depression, decreased quality of life, and greater motor impairments. The second aim is to determine if dynamic cycling leads to
improvements in attention, executive function and MoCA cognition, depression, quality of life, and motor symptoms after three sessions of dynamic cycling, time (session 1 and session 4), and BDNF Val66Met polymorphism presence (Val-allele and Met-allele carriers).
CHAPTER III

METHODOLOGY

All procedures were approved by Kent State University Institutional Review Board (IRB).

Sample Size Calculation

The G*Power 3.1.9.2 power analysis software was used to determine an approximate number of participants required for the study. Twenty four participants were recruited for this investigation. This was based on data from previous interventions which demonstrated that approximately 10 participants would be required based on executive function correct responses (Peacock et al., 2014). Power was set at 0.80, alpha = 0.05 performing paired samples t-tests with an a priori analysis. Data reported as mean±SD group 1 (2636±344), and group 2 (2011±162) determined a sample size of 10 participants per group. Therefore, a sample size of 12 participants was proposed accounting for participant drop-off and to strengthen the sample size of the design. In addition, more participants could have been required to recruit based on the unknown allele group classification. Furthermore, it may have allowed for more balanced BDNF Val66Met polymorphism allele grouping.

Inclusion/Exclusion Criteria

In order to qualify for the study, participants were pre-screened for the study and were between ages 50 to 85 years of age, diagnosed with idiopathic PD, and free of contraindications to exercise. This included cardiovascular disease (heart attack, heart surgery, angioplasty, pacemaker, rhythm disturbance, heart valve disease, heart failure,
heart transplantation, and congenital heart disease), stroke, and any surgical procedures for treatment of PD. All interested participants began the pre-screening process over the telephone using the telephone pre-screen protocol (Appendix A). Next, interested participants performed the AHA/ACSM pre-participation questionnaire and the Kent State University health history questionnaire (Appendices B & E; ACSM, 2014). Any interested individuals that identified as high risk were disqualified from participation in the study. Family history of cardiovascular disease did not constitute sufficient basis for disqualification. Following AHA/ACSM recommendations, potential participants with greater than two or more risk factors were at moderate risk for exercise. These participants needed to obtain physician clearance prior to participation (Appendix C). These risk factors included any known cardiovascular, pulmonary, and/or metabolic disease, cardiovascular disease risk factors such as age, family history, current cigarette smoking, sedentary lifestyle, obesity status, hypertension, hypercholesterolemia, or prediabetes (Appendix D) following ACSM standards. All interested participants with 1 or less cardiovascular risk factor were low risk and did not need to obtain physician consent to participate, unless 80 years of age or older. If 80 years of age or older, participants were required to obtain physician consent required by the Institutional Review Board.

**Protocol**

After arrival to the Applied Physiological laboratory, participants read and signed the informed consent to participate (Appendix F). The table overview of research (Appendix H) and research procedure (Appendix H) assist with outlining this research
investigation. Participants began visit 1 with the pre-intervention assessment, which took approximately 90 minutes–3 hours. Participants continued visit 1 by performing dynamic cycling. Visits 2 and 3 also involved dynamic cycling. Visit 4 included the post-intervention assessment, which concluded participation in the investigation. Figure 1 outlines the recruitment process.

![Recruitment process diagram](image)

*Figure 1. Recruitment process*

**Primary Outcome Measures**

The pre-intervention assessment consisted of the primary measurements WebNeuro® cognition testing (Silverstein et al., 2007), Montreal Cognitive Assessment (MoCA) test (Nasreddine et al., 2005), Beck Depression Inventory-II (BDI-II) test (Beck, Steer, Ball, & Ranieri, 1996), EQ-5D quality of life questionnaire (Schrag, Selai,
Jahanshahi, & Quinn, 2000), single nucleotide BDNF polymorphism genotyping (Genotek, 2015), and Kinesia ONE™ (Pulliam et al., 2014). Primary outcome measurements were obtained on visit 1 and visit 4 except for the BDNF Val66Met polymorphism was measured only during visit 1. The primary outcome measures involve the following variables (Table 1).

**Cognitive Dysfunction**

WebNeuro® computer software performed an assessment of neurocognitive function that utilizes different clinical tests to determine cognitive state that specifically measure attention, executive, emotional recognition and other cognitive domains (Silverstein et al., 2007). The attention domain involved digit span forward, choice reaction time, switching of attention while the executive function domain involved the maze task, switching of attention, and verbal interference (Silverstein et al., 2007; Stanek et al., 2013). The emotional recognition domain consisted of delayed recall of different emotions displayed which was an addition hypothesis developed during post-hoc theorizing (Clark, Neargarder, & Cronin-Golomb, 2008, 2010; Enrici et al., 2015).

**Digit span forward.** The forward digit span test procedure gave the participant a series of digits flashed on the computer screen separated by one second each. The participant was then asked to remember what they saw and then enter the digits on the number key pad in the same order as presented. In addition, not on the keyboard, the participant was required to recall the digits in the same order as they were given. These numbers increased gradually from 3 to 7 digits with two trials of the same number of
digits at each levels. The test would have terminated if two consecutive errors were made on a single string of digits.

**Choice reaction time.** The Choice reaction time test involved participants placing their left index finger on the left arrow key on the keyboard and their right index finger on the right arrow key on the keyboard. Next, participants needed to pay attention to the computer screen. There were two black circles on the computer screen. When the left circle turned the color green, they needed to use their left index finger to click the left arrow button on the keyboard. When the right circle turned the color green, they needed to use their right index finger to click the right arrow button on the keyboard. A total of 20 trials were administered with random delay of 2–4 seconds between each trial.

**Switching of attention.** During the switching of attention test the participant would have a pattern of 13 numbers (1–13) and 12 letters (A–L) on the computer screen. The participants were then required to use the mouse to click on each number and then each letter in a number-letter-number sequence until completed. The computer draws a fine line to connect each number, or letter to the preceding number, or letter in the sequence. This adds a visual element to the desired path.

**Verbal interference.** In this test each participant was presented with four colored words, one at a time. Each word was from the following set of four colors: red, yellow, green, and blue. Below each colored word was a response pad with four possible names of the colors displayed in black and in fixed format. The first part involved the participant reading the name of each word then as quickly as possible left-click on the appropriate matching tab. Therefore, if the word was “blue,” the participant should have
clicked on the key that is labeled in “blue.” Part two involved the participant naming the contrasting color of the ink in which the word is printed, as quickly as possible, and then clicking the appropriate tab. Therefore, if the participant saw the word “green” that is written in red ink, then the participant should click on the tab for “red” for the color of the ink of the screen. Each part or section took one minute each.

**Maze test.** This test was an electronic maze which presented with a grad matrix of circles on the computer screen. The object of the task was to identify the fixed, hidden path through the grid from the beginning point to the bottom of the grid in yellow to the end point at the top in blue. Each participant was able to navigate around the grid by using the arrow keys on the keyboard. A total of 24 correct moves was required to complete the maze.

**Emotional recognition.** In these tasks, participants were presented with a series of faces with different emotional expressions such as fear, anger, disgust, sadness, happiness, and a neutral expression. Each participant was required to use the mouse to click and identify the correct emotional expression presented by the face on the computer screen. This test analyzed the difficulty with negatively-associated faces deemed more challenging to properly identify (Clark et al., 2008). Once an emotional response has been identified, it should speed up the brain process in identifying. However, individuals with psychopathological illnesses tend to slow down on faces that may represent a threat (Clark et al., 2008). On delayed recall of emotions, some participants would be slower to identify a risk or negative facial expression. Healthy participants in comparison would process faster. For example, facial expressions such as happy, neutral, or disgust may be
slowed but not as much as fear, anxiety, or sadness facial expressions. The WebNeuro® testing took approximately 45–60 minutes total to complete (Silverstein et al., 2007).

In addition to WebNeuro®, MoCA was also determined as a primary measurement to determine cognitive dysfunction. MoCA has been deemed a valid instrument for measuring the cognition (Nasreddine et al., 2005) and is a common tool across other intervention studies for individuals with PD as well (Chou et al., 2010). For MoCA, a higher score represented better overall cognitive function performance and took 10–15 minutes to complete (Appendix H; Chou et al., 2010; Nasreddine et al., 2005). To prevent a learning effect, MoCA testing on visits 1 and 4 used alternative forms of MoCA (7.1 version, 7.2 version) in a counter-balance manner. Two participants indicated that they had previous experience and had memorized the delayed recall responses to MoCA 7.1 version. Therefore, MoCA 7.3 version was utilized once on visit 1 and once on visit 4 for the two participants, respectfully.

**Prevalence and Severity of Depression Symptoms**

BDI-II (Beck et al., 1996) was used to evaluate the prevalence and severity of depression symptoms in exercise interventions with healthy individuals (Dashtipour et al., 2015; Doose et al., 2015; Teixeira-Machado et al., 2015) and in individuals with PD (Teixeira-Machado et al., 2015). BDI-II test took approximately 10 minutes for participants to complete (Appendix H). The examination was self-administered by the participant and research personnel analyzed outcome measurements such as sadness, past failures, self-dislike, sleeping patterns, and changes in appetite (Beck et al., 1996). The raw scores were then converted into z-scores and averaged all BDI-II pre-intervention
and post-intervention results. Several past investigations have utilized BDI-II and it has been deemed a valid scale for screening the prevalence and severity of depression symptoms (F. H. Costa et al., 2012; Schrag et al., 2000; van Mierlo et al., 2015).

Standard operating procedures were in place due to the sensitive nature of question 9 regarding suicide in BDI-II. Research personnel reviewed responses to the questionnaire prior to the participants leaving the building for both visit 1 and visit 4. A sheet with hotline numbers for Psychological Services, DeWeese Health Center, and Medical Services at Robinson Memorial Hospital was created and ready to be provided if necessary. Participants would have been asked to call while still present during their visit if participants indicated a “2” or greater on the suicidal/self-harm item. Following the standard operating procedure, Dr. Angela Ridgel would have also been contacted. In addition, follow-up questions would have been asked to assess potential risk such as, “What did you mean by your answer on this item?” Afterwards, referral information would have been provided. Furthermore, counseling referrals would have been provided to all participants, not only those whom indicated elevated distress. Information from the following agencies listed below was prepared for Kent State Psychological Clinic located at 176 Kent Hall, Kent State University, Kent, OH, 44240 (330) 672-2372; DeWeese Health Center, Psychological Services located at 1500 Eastway Drive, Kent, OH, 44240 (330) 672-2487; as well as DeWeese Health Center located at 1500 Eastway Drive, Kent, OH, 44240 (330) 672-2322; and Robinson Memorial Hospital/University Hospitals located at 401 Devon Place, Kent, OH, 44240 (330) 297-0811. The participants would
have been told they were free to contact any of these agencies should they feel they
needed additional care following their participation.

**Quality of Life**

EuroQOL-5D-3L is a validated quality of life battery validated for those with PD
that strongly correlates with Hoehn and Yahr (HY) stage of illness, UPDRS and
depression symptom scores (Schrag et al., 2000). BDI-II and quality of life
measurements are often paired when determining the presence and severity of depression
symptoms in individuals with PD since the presence of depression would heavily
influenced an individuals’ quality of life (Teixeira-Machado et al., 2015). Individuals
with PD, who may have had depression symptoms, may also have a lower reported
quality of life than those who do not experience a higher prevalence and severity of
depression symptoms. The questionnaire consisted of descriptive and visual analog scale
designed for self-completion by the participant (EuroQOL, 2015). The EQ-5D quality of
life questionnaire took approximately 10 minutes to complete (Appendix 14). Though
previous studies have utilized other questionnaires such as PDQ39, SF36, and PDQL, and
EQ-5D questionnaires (Kusumi & Nakashima, 2000), the EQ-5D questionnaire was
determine easy to understand and a reliable questionnaire (Schrag et al., 2000). In
addition, the EQ-5D allowed for a health index across interventions for a range of health
illnesses including PD (Watts et al., 2008). EQ-5D results have been compared to the
BDI-II, Hoehn and Yahr scale, Schwab and England disability scale, UPDRS, and
PDQ-39 questionnaire. Furthermore, EQ-5D distinguished between individuals with and
without depression symptoms, history of falls, cognitive impairment and those with
overall deteriorating health in the past year. Therefore, EQ-5D was considered a valid instrument to measure quality of life in individuals with PD and (Schrag et al., 2000).

Measuring quality of life in exercise interventions was critical to demonstrate not only the physical benefits, but the potential psychological benefits as well (Baatile, Langbein, Weaver, Maloney, & Jost, 2000; Oguh, Eisenstein, Kwasny, & Simuni, 2014).

**Motor Symptoms**

Kinesia ONE™ was measured and recorded using an accelerometer device placed on the index finger that was validated with the UPDRS scale (Pulliam et al., 2014). Traditionally, as previous outlined in the diagnostic section earlier UPDRS was stated as a way to determine the severity of PD from a subjective measurement by a trained researcher. The subjective nature of the measurement introduces its own bias. Therefore utilizing Kinesia ONE™ was an objective approach by taking the participant through UPDRS upper-body movements wearing the wireless, accelerometer sensor on their dominant hand index finger allowed for an objective approach.

The sensor determined the swiftness of the motion, control of the motion, and categorized the results and rank accordingly. The measurements recorded from Kinesia ONE™ included resting tremor, postural tremor, kinetic tremor, finger tap speed, finger tap amplitude, finger tap rhythm, finger tap count, hand movement speed, hand movement amplitude, hand movement rhythm, rapid alternating movement speed, rapid alternating movement amplitude, rapid alternating movement rhythm and dyskinesia scores. All raw scores recorded were then converted in z-scores for analysis. All measurements strongly correlated with UPDRS scores and has been deemed a reliable
and valid measurement (Pulliam et al., 2014). Improvements in motor symptoms have occurred in a previous three visit, exercise session intervention (Kaski, Dominguez, Allum, Islam, & Bronstein, 2014; Ridgel, Phillips, et al., 2015).

**Brain Derived Neurotrophic Factor (BDNF)**

The BDNF Val66Met polymorphism was tested through a saliva measurement using a single nucleotide polymorphism genotype Oragene DNA collection kit (DNA Genotek, Inc., Ottawa, ON, Canada), which took approximately 5 minutes. This investigation measured the prevalence of the genetic variation BDNF Val66Met polymorphism in the participants. The presence of the polymorphism may have had influence leading towards attention, executive function, or emotion recognition cognitive dysfunction, increase in the prevalence and severity of depression symptoms, decreased quality of life, and greater motor impairments. Previous investigations have utilized Genotek’s products to determine BDNF allelic status for the Val66Met polymorphism (Hopkins et al., 2012).

Saliva testing was a good alternative to blood samples due to the ease of collection and storage. Compared to other non-invasive saliva collections, Oragene 500 Discover DNA collection kits have led to better quality DNA analyses (Bahlo et al., 2010; Hansen, Simonsen, Nielsen, & Hundrup, 2007; Rogers, Cole, Lan, Crossa, & Demerath, 2007). During data collection, participants refrained from eating or drinking for at least 60 minutes prior to collection. One saliva sample for each participant was collected following the manufacturer’s instructions. Participants were instructed to rub their tongues around the inside of their mouths and then deposit approximately 2
milliliters saliva into the collection cup. A cap was then placed over the vial and closed firmly. The collection cup was designed so the solution from the vial’s lower compartment releases and mixes with saliva when the cap is fastened (DNA Genotek, Inc., Ottawa, ON, Canada). Research personnel then held the tube upright, and shook the capped tube for 5 seconds and discarded the funnel. This phase of DNA isolation stabilized the saliva sample for long-term storage at room temperature in the Exercise Physiology Biochemistry laboratory (Appendix H).

**Secondary Outcome Measures**

Participants performed 40 minutes of dynamic cycling during visits 1, 2, and 3 with a day of rest between each visit outlined in Ridgel, Phillips, et al. (2015). Data such as heart rate (HR), revolutions per minute (RPM), torque (moment of force), and power (rate of doing work) were recorded by the computerized data collection system (Rockwell Automation, Twinsburg, OH) every second. Rating of perceived exertion (RPE) was recorded every 5 minutes by research personnel (Appendix H). These data were secondary outcome measurements and allowed research personnel to make comparisons of the exercise intensity performed during dynamic cycling and primary outcome measurements. In other words, it allowed researchers to compare if the intensity of the exercise influenced changes in primary outcome measurements over time.

**Heart Rate (HR)**

Physiological work was measured through a Polarlink® heart rate monitor that fits around the chest. Data were recorded utilizing Factory Talk Rockwell Automation software.
**Revolutions Per Minute (RPM)**

In addition to resistance or load, RPM was used to determine the participants’ intensity of work being performed. RPM during the dynamic cycling exercise had a pre-determined range; the warm-up and cool-down was set at 45 RPM while the main set was set at 80 RPM.

**Rating of Perceived Exertion (RPE)**

RPE was representative of how much physiological work was performed. The Borg scale was used which ranges from 6–20 (Borg, Ljunggren, & Ceci, 1985). Research personnel calculated a desired range of 13–17 for this population, for safety purposes.

**Power**

This was representative of how much physiological work the participant performed. Power outcome measurements are on a negative to positive range. A positive power output indicated the participant was actively pedaling in the dynamic cycling condition. A negative power output indicated the participant was likely in a passive state or not dynamically pedaling in the dynamic cycling condition.

**Torque**

This was the moment of force. Since the desired RPM was 80 RPM, the torque data represented 8/7 torque per second. All variables evaluated are listed in Table 1 (Appendix H).
### Table 1

*Variable Assessment*

<table>
<thead>
<tr>
<th>Task</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>Visit 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>WebNeuro®</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>MoCA</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>BDI-II</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>EuroQOL</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>SNP Genotyping</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kinesia ONE™</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Dynamic Cycling</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
</tbody>
</table>

### Statistical Analysis

Data from all visits for participants was presented as mean ± standard deviation (SD). WebNeuro® data scores were calculated through computerized algorithms based on previously established normative data (Silverstein et al., 2007). MoCA and EQ-5D both have scoring methods in which higher scores indicate better outcome using a number system to report scores and later converted to z-scores. BDI-II has a scoring system in which lower scores indicated lesser depression symptoms which was also converted to z-scores for analyses. All data were analyzed using Statistical Package for Social Sciences software (SPSS, Version 23.0 Armonk, NY).

The statistical analysis for hypothesis one involved Independent-Samples *t*-tests with all participants’ pre-intervention assessment data that created two groups based on
the Val66Met polymorphism presence. Once it was determined if Val66Met polymorphism was present, participants that were heterozygous for the Met-allele formed the Met-allele group. The Met-allele group was then compared with the homozygous Val-allele carriers for pre-intervention assessment analysis (Gerritsen et al., 2012). The statistical analysis for hypotheses two consisted of 2-way ANOVA comparing 2 allele groups (Met-allele and Val-allele) over time (session 1, pre-intervention and session 4, post-intervention) comparing WebNeuro®, MoCA, BDI-II, quality of life, and Kinesia ONE™ results converted to z-scores.
CHAPTER IV
THE INFLUENCE OF VAL66MET BDNF POLYMORPHISM ON COGNITIVE DYSFUNCTION IN INDIVIDUALS WITH PARKINSON’S DISEASE AFTER DYNAMIC CYCLING

Parkinson’s disease (PD) is a progressive neurodegenerative disorder that is characterized by non-motor symptoms and 20–50% incidences of cognitive dysfunction (Goldman et al., 1998; van der Kolk et al., 2015). Although cause of the PD is unknown, it is believed to be influenced by genetic variations (Le Couteur et al., 2002). One gene of interest in PD is one that encodes brain derived neurotrophic factor (BDNF). BDNF is involved with regulation of synaptic transmission, neuronal growth (McAllister et al., 1999), and supports dopaminergic neurons in the substantia nigra (Hyman et al., 1991). BDNF has a common single-nucleotide polymorphism, an amino-acid substitution in the prodomain of valine (Val) to methionine (Met) at amino-acid codon 66 known as Val66Met (Bath & Lee, 2006). When the Val66Met polymorphism is present, it could alter BDNF distribution and decrease BDNF secretion (Hariri et al., 2003). The Val66Met polymorphism incidence is approximately 20–50% in all individuals (18% in the United States; Shimizu et al., 2004). Individuals with neurodegenerative diseases such as PD tend to have lower BDNF concentrations than healthy individuals (Foltynie et al., 2009).

Both chronic and acute aerobic exercise have been shown to increase BDNF concentrations in animal models (Berchtold et al., 2005), healthy individuals (S. W. Tsai et al., 2015) and individuals with neurodegenerative diseases (Aarsland et al., 2009;
Scalzo et al., 2010). Maintenance and/or improvements in PD symptoms due to aerobic exercise may be associated with neoplastic changes in neurotrophin release, such as BDNF (Rosenfeldt et al., 2015; Zigmond et al., 2012). However, there is a high amount of inter-individual variability in the neuroplasticity response to exercise (Roemmich et al., 2012). The high inter-individual variability may have been influenced by the BDNF phenotype within this population known as Val66Met polymorphism. The presence of the BDNF Val66Met polymorphism could have influenced attention (A. Costa et al., 2015; Schofield et al., 2009), executive function (Enrici et al., 2015; McKinlay, Grace, Dalrymple-Alford, & Roger, 2010; Murray et al., 2014), and emotional recognition cognition dysfunction (Clark et al., 2008, 2010; Enrici et al., 2015; Mukherjee et al., 2011). In addition, the polymorphism could have influenced the activity-dependent secretion of BDNF (Chen et al., 2004; Egan et al., 2003; Hariri et al., 2003). If aerobic exercise increased BDNF concentrations, it could decrease the prevalence of attention, executive and emotion recognition cognitive dysfunction in individuals with PD (Monteiro-Junior et al., 2015; Tuon et al., 2014).

Recently, there has been growing interest in high-cadence cycling as an acute, aerobic exercise treatment for PD (Ridgel, Phillips, et al., 2015; Ridgel, Walter, et al., 2015). Dynamic cycling utilizes a motorized cycle to assist the rider to maintain a high pedaling cadence (80 Revolutions per minute, RPM; Peacock et al., 2014; Ridgel et al., 2013; Ridgel, Kim, et al., 2011; Ridgel et al., 2012; Ridgel, Phillips, et al., 2015; Ridgel et al., 2009; Ridgel, Walter, et al., 2015; Rosenfeldt et al., 2015). Dynamic cycling results in improvements in PD motor symptoms after just three sessions.
et al., 2015). However, it is not known if dynamic cycling improves aspects of cognitive function including attention and executive function. Individuals with PD tend to have high inter-individual variability in their symptom response to dynamic cycling (Ridgel, Phillips, et al., 2015), as well as other exercise interventions (Abbruzzese et al., 2015; Bloem et al., 2015; Dashtipour et al., 2015; Fisher et al., 2008). It could be possible that some of the variability may be associated with the presence of BDNF Val66Met polymorphism.

To better understand the influence of BDNF Val66Met polymorphism on cognition, PD and in response to dynamic cycling, this investigation focused on two aims: (a) to determine if the prevalence of the BDNF Val66Met polymorphism influenced attention, executive function, or MoCA (cognitive dysfunction), (b) to determine if BDNF Val66Met polymorphism influenced improvements in attention, executive function, or MoCA (cognition dysfunction) after three sessions of dynamic cycling. In order to address these aims we proposed several hypotheses: First, if individuals with PD have the BDNF Val66Met polymorphism (Met-allele group), then they would have decreased pre-intervention scores for attention, executive function, and MoCA. Second, if individuals with PD do not have the BDNF Val66Met polymorphism (Val-allele group), then they would have greater improvements in attention, executive function, and MoCA after three sessions of dynamic cycling compared to individuals who have the polymorphism (Met-allele group).
Methods

Protocol

Individuals between ages 50 to 85 years, who were diagnosed with idiopathic PD, and were free of contraindications to exercise including cardiovascular disease, stroke, and any surgical procedures for the treatment of PD, were recruited. All individuals who met the above criteria were pre-screened over the telephone using the American Heart Association/American College of Sports Medicine (AHA/ACSM) exercise pre-participation questionnaire (ACSM, 2014). Those identified as high risk were disqualified from participation in the study due to cardiovascular risk factors. Those with greater than two or more risk factors were designated as moderate risk and these participants were required to obtain physician clearance prior to participation. Individuals with one or less cardiovascular risk factor were designated as low risk and were not asked to obtain physician consent to participate, unless they were older than 80 years of age.

During the first session, participants read and signed the informed consent and completed the pre-intervention assessment that assessed attention, and executive function domains. WebNeuro® computer software provides an assessment of neurocognitive function that utilizes different clinical tests to determine the participant’s cognitive state (Silverstein et al., 2007).

Cognitive Dysfunction

WebNeuro® computer software performed an assessment of neurocognitive function that utilizes different clinical tests to determine cognitive state that specifically
measure attention and executive domains (Silverstein et al., 2007). The attention domain involved digit span forward, choice reaction time, switching of attention while the executive function domain involved the maze task, switching of attention, and verbal interference (Silverstein et al., 2007; Stanek et al., 2013).

**Digit span forward.** The forward digit span test procedure gave the participant a series of digits flashed on the computer screen separated by one second each. The participant was then asked to remember what they saw and then enter the digits on the number key pad in the same order as presented. In addition, not on the keyboard, the participant was required to recall the digits in the same order as they were given. These numbers increased gradually from 3 to 7 digits with two trials of the same number of digits at each levels. The test would have terminated if two consecutive errors were made on a single string of digits.

**Choice reaction time.** The Choice reaction time test involved participants placing their left index finger on the left arrow key on the keyboard and their right index finger on the right arrow key on the keyboard. Next, participants needed to pay attention to the computer screen. There were two black circles on the computer screen. When the left circle turned the color green, they needed use their left index finger to click the left arrow button on the keyboard. When the right circle turned the color green, they needed to use their right index finger to click the right arrow button on the keyboard. A total of 20 trials were administered with random delay of 2–4 seconds between each trial.

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**Maze test.** This test was an electronic maze, which presented with a grad matrix of circles on the computer screen. The object of the task was to identify the fixed, hidden path through the grid from the beginning point to the bottom of the grid in yellow to the end point at the top in blue. Each participant was able to navigate around the grid by using the arrow keys on the keyboard. A total of 24 correct moves was required to complete the maze.
In addition to WebNeuro®, MoCA was also determined as a primary measurement to determine cognitive dysfunction. MoCA has been deemed as a valid instrument for measuring cognition (Nasreddine et al., 2005) and is a common tool across other intervention studies for individuals with PD as well (Chou et al., 2010). For MoCA, a higher score represented better overall cognitive function performance and took 10–15 minutes to complete (Appendix H; Chou et al., 2010; Nasreddine et al., 2005). To prevent a learning effect, MoCA testing on visits 1 and 4 used alternative forms of MoCA (7.1 version, 7.2 version) in a counter-balanced manner. Two participants indicated that they had previous experience and had memorized the delayed recall responses to MoCA 7.1 version. Therefore, MoCA 7.3 version was utilized once on visit 1 and once on visit 4 for the two participants, respectfully.

**Genetic Testing**

The BDNF genotype was tested through saliva using an Oragene DNA collection kit (DNA Genotek, Inc., Ottawa, ON, Canada). DNA was extracted and analyzed for a single nucleotide polymorphism (SNPs) rs6262, or Val66Met by an outside lab facility (DNA Genotek, Inc., Ottawa, ON, Canada). Quality checks were performed including the PicoGreen analysis, Nanodrop absorbance readings and agarose gel electrophoresis for each of the samples. Previous investigations have utilized Genotek’s products to determine BDNF allelic status for Val66Met polymorphism and have been deemed valid and reliable (Hopkins et al., 2012).
**Intervention**

Following the pre-intervention assessment, participants performed 40 minutes of dynamic cycling as outlined in Ridgel, Phillips, et al. (2015). In short, this protocol consisted of a 5 minute warm-up at 45 RPM at low intensity, 30 minutes at 80 RPM at low-moderate intensity, and 5 minute cool-down at 45 RPM. Secondary variables were collected including heart rate (HR) through a Polarlink® monitor, RPM, power, and torque. These variables were measured every second during dynamic cycling visits 1, 2, and 3 through a computerized data collection system (Rockwell Automation, Twinsburg, OH). Rating of perceived exertion (RPE) was recorded with the Borg Scale every five minutes (Borg et al., 1985). Participants repeated the dynamic cycling protocol for visits 2 and 3 with a day of rest between each visit. The secondary measurements were used as covariates for examining how much physiological work (power) and what intensity of exercise (HR and RPE) was performed in relation to the cognitive function data. On visit four, all participants completed the post-intervention assessment including the primary measurements WebNeuro® battery test and MoCA.

**Data Analysis**

Data were recorded as mean ± standard deviation (SD). WebNeuro® battery test results were calculated through computerized algorithms based on previously established normative data (Silverstein et al., 2007). Z-scores were used from the analysis provided and calculated by Brain Resources compared to previous recorded data. Scores may range from -2.25 – +2.25. MoCA scoring methods were calculated with higher scores indicating better reported cognitive performance ranging from 0–30 point test. These
results were then converted to z-scores for analysis. All data were analyzed with parametric tests using Statistical Package for Social Sciences software (SPSS, Version 23.0 Armonk, NY). The statistical analyses involved Independent-Samples t-tests of attention, executive function, and MoCA (cognitive function) pre-intervention scores to determine if any allele group differences were present. Next a univariate analysis of variance (ANOVA) was performed comparing attention and executive function grouped by the presence of BDNF Val66Met polymorphism. Once it was determined if Val66Met polymorphism was present, participants that were heterozygous for the Met-allele formed the Met-allele group and were compared with homozygous Val-allele group (Gerritsen et al., 2012). Therefore, the attention, executive function were then compared with 2x2 mixed ANOVA.

Results

Fourteen individuals completed the study (see Figure 1). Ten individuals were classified into the Val-allele carrier group and four individuals were classified into the Met-allele carrier group. There were no significant differences between these groups in age, gender, height or weight (Table 2).
Table 2

**Descriptive Statistics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Val Allele ($n=10$)</th>
<th>Met Allele ($n=4$)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64 ± 9</td>
<td>68 ± 3</td>
<td>$P = 0.930$</td>
</tr>
<tr>
<td>Gender</td>
<td>6 M / 4 F</td>
<td>2 M / 2 F</td>
<td></td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.70 ± 0.12</td>
<td>1.73 ± 0.08</td>
<td>$P = 0.658$</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75.3 ± 22.2</td>
<td>83.8 ± 5.6</td>
<td>$P = 0.263$</td>
</tr>
</tbody>
</table>

*Note.* Values are represented as mean ± standard deviation.

**Dynamic Cycling Data**

Cycling power, torque, heart rate, and RPM were collected every second and then averaged across the total 30-minute main set (Table 3). There were no differences in any of these exercise outcomes over the three visits. RPE was reported, using the Borg Scale (6–20; Borg et al., 1985), approximately every 5 minutes and then averaged across the total 30-minute intervention and were similar across all three visits in Table 7 (Visit 1 10.57±2.28, visit 2 11.53±2.86, visit 3 11.03±2.49).

Table 3

**Dynamic Cycling Exercise Outcome Variables**

<table>
<thead>
<tr>
<th></th>
<th>Power</th>
<th>Torque</th>
<th>Heart Rate</th>
<th>RPM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Visit 1</strong></td>
<td>8.48 ± 23.72</td>
<td>6.70 ± 19.34</td>
<td>85 ± 7</td>
<td>81 ± 4</td>
</tr>
<tr>
<td><strong>Visit 2</strong></td>
<td>8.54 ± 23.78</td>
<td>6.92 ± 19.83</td>
<td>85 ± 10</td>
<td>81 ± 4</td>
</tr>
<tr>
<td><strong>Visit 3</strong></td>
<td>6.36 ± 20.10</td>
<td>12.96 ± 27.14</td>
<td>87 ± 14</td>
<td>80 ± 3</td>
</tr>
</tbody>
</table>

*Note.* Values are reported as mean ± standard deviation.
Although the Met-allele group had lower power values than the Val-allele group during every exercise session, these were not statistically different \((p = 0.280)\). For example, visit 2 power outcome (see Table 4) for the Val-allele group \((13.37\pm29.31)\) was greater than the Met-allele group \((0.09\pm4.16)\). There were also no statistical differences between allele groups for torque values \((Table 5, p = 0.316)\). However, there were some interesting differences. For example, during visit 3 torque values for the Val-allele group was \(2.30\pm21.20\) while the Met-allele group produced more torque \(22.55\pm37.46\). There were no significant differences between the two groups in average heart rate \((Table 6)\) across all three visits. Heart rate ranged from 80.44–90.03 beats per minute. Participants performed at approximately 51–58\% of their age-predicted maximal HR during the 30 minutes of high cadence cycling. Lastly, there were no differences in RPE between the two groups \((Table 7, p = 0.076)\).

Table 4

<table>
<thead>
<tr>
<th></th>
<th>Val-allele Power</th>
<th>Met-allele Power</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1</td>
<td>7.51±30.29</td>
<td>-1.74±5.27</td>
<td>(P = 0.567)</td>
</tr>
<tr>
<td>Visit 2</td>
<td>13.37±29.31</td>
<td>0.09±4.16</td>
<td>(P = 0.280)</td>
</tr>
<tr>
<td>Visit 3</td>
<td>3.61±24.55</td>
<td>1.10±7.21</td>
<td>(P = 0.847)</td>
</tr>
</tbody>
</table>

*Note.* Values are reported as mean ± standard deviation.
Table 5

**Torque Results Across Allele Groups**

<table>
<thead>
<tr>
<th>Visit</th>
<th>Val-allele Torque</th>
<th>Met-allele Torque</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.26±26.05</td>
<td>-1.55±54.87</td>
<td>( P = 0.623 )</td>
</tr>
<tr>
<td>2</td>
<td>10.82±24.48</td>
<td>0.08±3.72</td>
<td>( P = 0.295 )</td>
</tr>
<tr>
<td>3</td>
<td>2.30±21.20</td>
<td>22.55±37.46</td>
<td>( P = 0.216 )</td>
</tr>
</tbody>
</table>

*Note.* Values are reported as mean ± standard deviation.

Table 6

**Heart Rate Results Across Allele Groups**

<table>
<thead>
<tr>
<th>Visit</th>
<th>Val-allele HR</th>
<th>Met-allele HR</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80.44±9.81</td>
<td>86.92±6.32</td>
<td>( P = 0.256 )</td>
</tr>
<tr>
<td>2</td>
<td>84.34±10.60</td>
<td>87.48±14.54</td>
<td>( P = 0.677 )</td>
</tr>
<tr>
<td>3</td>
<td>88.53±16.32</td>
<td>90.03±10.05</td>
<td>( P = 0.871 )</td>
</tr>
</tbody>
</table>

Values are reported as mean ± standard deviation.

Table 7

**RPE Results Across Allele Groups**

<table>
<thead>
<tr>
<th>Visit</th>
<th>Val-allele RPE</th>
<th>Met-allele RPE</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11.13±2.07</td>
<td>9.16±2.44</td>
<td>( P = 0.150 )</td>
</tr>
<tr>
<td>2</td>
<td>11.53±2.86</td>
<td>8.59±1.30</td>
<td>( P = 0.076 )</td>
</tr>
<tr>
<td>3</td>
<td>11.50±9.85</td>
<td>9.85±1.98</td>
<td>( P = 0.280 )</td>
</tr>
</tbody>
</table>

*Note.* Values are reported as mean ± standard deviation.

**Cognitive Data – WebNeuro® Battery**

For each of the attention and executive function domains and MoCA, scores from individual’s tasks and analyses were averaged together to assess attention, executive
function, and MoCA. Though there were 10 participants in the Val-allele group and 4 participants in the Met-allele group, in some cases data points were removed when averaging together between six and 13 individual variables. This was due to either due the participant not fully comprehending the task and therefore no data points were calculated during WebNeuro®, or when reviewing assumptions, data points were considered outliers. This information is summarized in Table 8.

Table 8

*Summarized Removed Data Points*

<table>
<thead>
<tr>
<th>Data points removed</th>
<th>Attention Domain</th>
<th>Executive Function Domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recall accuracy</td>
<td>participants 1, 9</td>
<td>Completion time participants 5, 9</td>
</tr>
<tr>
<td>Correct trials</td>
<td>1, 9</td>
<td>Overall accuracy 5, 9</td>
</tr>
<tr>
<td>Processing reaction time</td>
<td>13</td>
<td>Overrun errors 5, 9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paths completed 5, 9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Path learning time 5, 9</td>
</tr>
</tbody>
</table>

The individual attention tasks that comprised the attention domain were processing speed for tapping, digit span, choice reaction time, and switching of attention were averaged together for assessment of the attention domain (Stanek et al., 2013). There was no significant difference in the average attention domain scores (Figure 2) between the allele groups at pre-intervention ($p = 0.695$). Furthermore, there were no significant interactions ($F_{(1,13)} = 0.118, \eta = 0.063, p = 0.734$) or main effect of time ($F_{(1,13)} = 0.190, \eta = 0.070, p = 0.667$), and no main effect of allele group.
There were no significant differences in the changes between the pre-intervention and after the dynamic cycling intervention between the Val-allele group (0.02 points) and Met-allele group (0.27 points).

Figure 2. Average attention domain z-score results between allele groups over time. Data were reported as mean ± standard deviation bars. Val-allele (pre -0.22 ± 0.93, n = 10, post -0.04 ± 1.19, n = 10). Met-allele (pre -0.75 ± 0.63, n = 4, post -0.13 ± 1.04, n = 4).

Individual executive function tasks such as controlled attention, switching of attention, and the maze data results were averaged together for assessment of the executive function domain (Stanek et al., 2013). There was no significant difference in the executive function domain scores (Figure 3) between the allele groups at
pre-intervention \((p = 0.351)\). Furthermore, there were no significant interactions \((F_{(1,13)}=0.107, \eta = 0.061, p = 0.746)\), no main effect of time \((F_{(1,13)}=0.001, \eta = 0.050, p = 0.746)\), and no main effect of allele group \((F_{(1,13)}=0.486, \eta = 0.103, p = 0.493)\). There were no significant differences in the changes between the pre-intervention and after the dynamic cycling intervention between the Val-allele group (-0.14 points) and the Met-allele group (0.12 points).

**Figure 3.** Average executive function domain z-score results between allele groups over time. Data were reported as mean ± standard deviation bars. Val-allele (pre -0.36 ± 0.91, \(n = 10\), post -0.54 ± 0.88, \(n = 10\)). Met-allele (pre -0.65 ± 0.63, \(n = 4\), post -0.63 ± 0.62, \(n = 4\)).
Cognitive Data: Montreal Cognitive Assessment (MoCA)

There was no significant difference in the overall MoCA scores between the allele groups at pre-intervention ($p = 0.934$; see Figure 4. Furthermore, there were no significant interactions ($F_{(1,13)}=0.817$, $\eta = 0.140$, $p = 0.375$), no main effect of time ($F_{(1,13)}=0.150$, $\eta = 0.066$, $p = 0.702$), and no main effect of allele group ($F_{(1,13)}=1.055$, $\eta = 0.167$, $p = 0.315$). There were no significant differences in the changes between the pre-intervention and after the dynamic cycling intervention between the Val-allele group (0.21 points) and the Met-allele group (-0.54 points). MoCA change scores from pre/post-intervention scores were also analyzed (Figure 5) demonstrated individual MoCA change scores for all participants.

![Figure 4](image)

**Figure 4.** Total MoCA score results between allele groups over time. Data were reported as z-score mean ± standard deviation bars. Val-allele (pre 0.02 ± 0.94, n = 10, post 0.23 ± 1.00, n = 10). Met-allele (pre -0.04 ± 1.30, n = 4, post -0.58 ± 0.84, n = 4).
Figure 5. MoCA change scores results were converted from the raw score to z-scores to calculate the pre/post-intervention difference. Data were reported as z-score mean difference for each participant.

**Discussion**

Our first aim was to evaluate if BDNF Val66Met polymorphism influenced the presence of attention domain, executive function domain, and MoCA scores (cognitive dysfunction) in individuals with PD. There were no statistical differences in pre-intervention for the polymorphism allele groups in attention domain, executive function domain, or total MoCA scores. Therefore, the null hypothesis was accepted for aim one.

Our second aim was to evaluate if BDNF Val66Met polymorphism influenced changes in attention domain, executive function domain, or MoCA scores (cognitive function) after the dynamic cycling intervention. Neither the WebNeuro® domains nor
MoCA had significant interactions, main effects of group nor time occur. Therefore, the null hypothesis was also accepted for aim two.

There are several reasons why we did not find any significant differences in these measures. We hypothesized that the Met-allele group would have greater cognitive dysfunction (worse attention, executive function, and MoCA scores) than the Val-allele group. When WebNeuro® and MoCA results were reviewed individually, the Met-allele group, in some cases, outperformed the Val-allele group. However, that initial analysis did not fully encompass the larger domains. Those observed differences however could be explained by the compensatory mechanism suggested by Scalzo and colleagues (2010). In early stages of PD, Met-allele carriers may have a lower BDNF serum level but as the disease progresses, more BDNF may be secreted in the serum (Scalzo et al., 2010). Furthermore, Met-allele carriers had better performance than Val-allele carriers in attention and executive function domains in individuals with cardiovascular disease that challenged many previous findings as well (Szabo et al., 2013). There was also evidence to support that Met-allele carriers had better delayed recall of information than Val-allele carriers (Bialecka et al., 2014). Furthermore, Met-allele carriers had shown a significantly smaller decline in set shifting compared to Val-allele carriers representing mental flexibility (van der Kolk et al., 2015). Val-allele carriers have also outperformed compared to Met-allele carriers in several previous studies (Guerini et al., 2009; Hariri et al., 2003). Met-allele carriers had significantly high correlations to cognitive impairment, age, and disease severity data (Guerini et al., 2009). Met-allele carriers were also found
to have lower hippocampal engagement compared to Val-allele carriers during memory-related tasks (Hariri et al., 2003).

In the attention domain, there were reasons to suspect that the Met-allele carriers would have great difficulty in attention, executive function domains, and MoCA than the Val-allele carriers. The attention domain is comprised of several elements including working memory deficits for digit span (Stanek et al., 2013). Researchers found that Met-allele carriers recorded more delayed recall errors during backward recall compared to Val-allele carriers (Li et al., 2010). In contrast, Foltynie and colleagues found that individuals with PD in the Met-allele group performed better in executive function domain than Val-allele group (Foltynie et al., 2005). In another study, Met-allele groups had higher verbal recall errors for executive function domain that supported the hypothesis that Val-allele carriers performed better in executive function than Met-allele carriers (Schofield et al., 2009). In addition, investigators concluded that Met-allele carriers had faster rates of cognitive delay (executive and memory function) than Val-allele carriers (Gajewski, Hengstler, Golka, Falkenstein, & Beste, 2012).

The total MoCA scores were not different at baseline between the two groups and did not change after the intervention. Previous studies have shown that Met-allele carriers had a significant, high correlation for cognitive impairment, using the Mini-Mental State Examination compared to Val-allele carriers which has similar aspects to MoCA (Guerini et al., 2009). For individuals with PD, the MoCA guidelines for mild cognitive impairment was less than 26 out of the 30 total points. Individuals with PD with dementia screening guidelines are less than 21 out of 30 total points.
(Dalrymple-Alford et al., 2010; McKinlay et al., 2010), whereas normal range score of 26.2/30 and 22.2 was reported for individuals with PD with mild cognitive impairment and dementia, respectively (Hoops et al., 2009). In this study, the Val-allele group scored 26.40 ± 2.72 at pre-intervention and 26.80 ± 3.16 at post-intervention so they were above the threshold of 26 out of 30 points at both time periods. In comparison, the Met-allele group scored 26.25 ± 3.78 at pre-intervention and then showed a decrease to below the threshold (24.25 ± 3.20) post-intervention. Whereas the MoCA scores were originally calculated out of 30 points, scores were converted to z-scores for consistency across the analysis of data. Although these data were not statistically different from one another over time or group, the two point drop in post-intervention MoCA is an interesting finding. Anecdotally, during the post-intervention assessment participants in the Met-allele group mentioned having other items in their life on their mind such as preparing to move a daughter across country and finding out that someone filing false tax claims in their name. Such items could have influenced post-intervention testing tremendously for the two of four participants in the Met-allele groups’ findings.

It is also possible that familiarity with the MoCA test skewed our results. Upon delivery of the MoCA assessment to three participants, two had notified me that they were familiar with 7.1 version of MoCA. However, the pre-determined, counter-balanced order was adjusted on these two counts and replaced with 7.2 version; 7.3 version was introduced for their post-intervention assessment. The MoCA results were similar to the other cognition domains in that the Val66Met polymorphism was not associated with cognitive dysfunction in this small experimental population.
The Influence of Intensity and Duration of Exercise

The exercise prescription guidelines were calculated to monitor the safety of participants using HR and RPE. Adjustments were made from Ridgel, Phillips, et al. (2015) with regards to heart rate reserve (HRR) to match RPE Borg scale recommendations. HRR was calculated using the Karvonen formula. On average, participants maintained approximately 12% HRR during the dynamic cycling high cadence protocol. In addition, RPE was fairly light according to the average reported response over 30 minutes of high-cadence cycling. Compared to previous findings, this investigation had lower HR (86±2) and lower RPE (11±0.0). Specifically in Ridgel, Phillips, et al. (2015), the dynamic cycling group reported higher HR (91±3) and higher RPE (13±1) in comparison. Improvements that occurred during the dynamic cycling intervention happened at a low intensity of exercise that was compared to a static cycling condition (Ridgel, Phillips, et al., 2015). If improvements in motor symptoms occurred during the same protocol, it offers support that it may influence other outcome variables as well at the lower intensity. However, our findings are still lower than the intensity reported utilizing the same protocol design which may be influenced results. Though the protocol was not manipulated from previous work, the intensity and duration differs from other research designs. Previous researchers that evaluated the role of physical activity, Val66Met polymorphism, and cognition concluded that Met-allele carriers had greater cognitive impairment (Kim et al., 2011). It is also important to note that intensity reported in our investigation and Ridgel, Phillips, et al. had low exercise intensities similar to other previous findings (Ridgel, Phillips, et al., 2015; Ridgel et al., 2009;
Shulman et al., 2013) and contradictory to other exercise intensity research suggesting that higher intensities led to improvements or better improvements compared to low intensity exercise (Ahlskog, 2011). In addition, previous work has documented improvements in executive function with passive (low-intensity) cycling in individuals with PD (Ridgel, Muller, et al., 2011). However, Ridgel and colleagues measured cognitive function immediately after the cycling session while this study re-assessed 48 hours after the last cycling session (Ridgel, Muller, et al., 2011). Furthermore, cognition performance changes have been primarily reported with moderate or high intensity fitness (Chang et al., 2012; Murray et al., 2014). Precisely, reaction time of a cognition test was shorten or improved during moderate intensity cycling compared in low intensity cycling in older adults (Kamijo et al., 2009). Progressive 12 weeks of aerobic exercise led to improvements in executive function (Cruise et al., 2011). In individuals with PD have also reported that reported improvements in cognition with longer durations and higher exercise intensities. Others found that six months of physical training improved executive function (Tanaka et al., 2009). Another investigation observed that two, 90 minute dance sessions for twelve weeks resulted in spatial cognition and executive function (McKee & Hackney, 2013). BDNF also led to improvements in executive function after an exercise intervention (Leckie et al., 2014). Cognitive improvements have also been observed in research designs that utilized low-intensity exercise but had longer intervention durations (dos Santos Mendes et al., 2012). Therefore, the low-intensity high-cadence cycling may not have been of sufficient intensity and/or the duration may not have been long enough to induce cognitive changes.
**Post-Hoc Theorizing**

After data collection and initially proposed data analysis, a third hypothesis was proposed that involved emotional recognition and the prevalence of depression symptoms. During emotional recognition domain tasks, participants were presented with a series of faces with different emotional expressions that had negative bias and the reaction time was recorded for fear, anger, disgust, sadness expression. Each participant was required to use the mouse to click and identify the correct emotional expression presented by the face on the computer screen. This test analyzed the difficulty with negatively-associated faces deemed more challenging to properly identify (Clark et al., 2008). Once an emotional response has been identified, it should have sped up the brain process in identifying. However, individuals with psychopathological illnesses tend to slow down on faces that may represent a threat (Clark et al., 2008). If individuals with depression symptoms improved from pre-intervention to post-intervention, then those individuals would also have an improvement in their emotional recognition.

There was support that improvements in emotional recognition in individuals could occur in individuals with PD that also experienced a decrease in the prevalence and severity of depression symptoms after dynamic cycling. Individuals with PD who experience depression symptoms or distress may have further difficulty recognizing negatively bias emotions such as fear, anger, disgust, and sadness (Clark et al., 2008). Therefore if the dynamic cycling intervention did improve depression symptoms, it may have had resulted in improvement in emotional recognition in those individuals. Previous research has indicated that Met-allele carriers had worse fear recognition
compared to Val-allele carriers (Mukherjee et al., 2011). This is an interesting finding because individuals with PD often experience a symptom known as mask face and they often have difficulty expressing and identifying facial expressions (Sapir et al., 2007). Typically, individuals with PD have reported delays in emotional recognition (Clark et al., 2008; Enrici et al., 2015). Though the participants in our research investigation had below average scores in emotional recognition, our results were not significantly different between the two allele groups. Previous research has noted that individuals with neurodegenerative and depression symptoms would have differences in negative emotion bias such as sad, fear, anger and disgust accuracy (Clark et al., 2008, 2010; Enrici et al., 2015). The emotion bias reaction times for both allele groups had lower than normal range z-scores for both pre-intervention and post-intervention, similar to other cognitive domains. These results however did not observe an interaction or main effects of group or time and the null hypothesis was accepted.

**Limitations and Future Directions**

Although this study yielded some interesting findings, future work should build upon this work by increasing the sample size to account for unknown BDNF genotyping, evaluate BDNF serum levels and consider lengthening the exercise intervention. The sample size for this investigation was 14 participants. Mechanical issues with the dynamic cycle ergometer led to an unexpected end to the current data collection period. Originally, 24 individuals were proposed for recruitment. At the time of the mechanical issue, two participants began the four visit protocol while two other individuals were scheduled for 18 potential participants. Throughout the research recruitment process,
approaches for recruitment were re-evaluated and improved. An existing list of previous contacts unfortunately was not assisting with recruitment to the extent previously thought. Many of the individuals with PD on the contact list did not qualify for this investigation for various reasons health reasons including cardiovascular diseases, stroke, mobility impairment, being older than 85 years old, and death. Therefore, alternate approaches were taken to contact local PD support groups in the Northeast Ohio area, local PD specialists, PD exercise specialists, and other sources such as Michael J. Fox Trial Finder. In addition, the BDNF allele classification was unknown until the analysis was completed which took five weeks to process. Although the researchers were able to identify individuals with the BDNF Val66Met polymorphism after the intervention was completed, the Val66Met presence of the gene indicated in salivary BDNF, it does not reflect systemic BDNF levels which could further assist in understanding the role of BDNF (Terracciano et al., 2013).

Lastly, it is possible that three exercise sessions were not sufficient to elicit changes in attention, executive function, emotional recognition, or MoCA (cognitive function). The current literature is mixed on whether acute changes in cognitive function can occur after single sessions of exercise (Hopkins et al., 2012; Loy & O’Connor, 2016; Ridget, Kim, et al., 2011; Weng, Pierce, Darling, & Voss, 2015). Thirty minutes of light cycling resulted in no differences in cognitive tasks (Loy & O’Connor, 2016). However, improvements in executive function have previously been documented after one bout of passive cycling (Ridget, Kim, et al., 2011). In other findings, the intensity of the exercise had a greater role. Moderate intensity cycling led to improvements on executive function
and working memory compared to low intensity cycling (Weng et al., 2015). Future studies should also utilize longer exercise interventions and should analyzing BDNF serum levels and other BDNF polymorphisms to better understand the potential role of BDNF polymorphism on cognitive function and cognitive responses to exercise interventions. If these genetic markers were better understood, then it could assist in individualizing treatment interventions.
CHAPTER V
THE INFLUENCE OF VAL66MET POLYMORPHISM ON DEPRESSION AND ANXIETY IN INDIVIDUALS WITH PARKINSON’S DISEASE AFTER DYNAMIC CYCLING

Parkinson’s disease (PD) is a progressive neurodegenerative disorder that affects approximately 4 million people worldwide (Dorsey et al., 2007). PD is characterized by non-motor symptoms including depression and anxiety (van der Kolk et al., 2015). Individuals with PD have a high incidence of depression at 20–50% (Aarsland et al., 2009). The prevalence of depression is also associated with decreased quality of life (Kuopio et al., 2001), which impacts the overall health of individuals with PD (Ishihara & Brayne, 2006). Ultimately, PD leads to higher healthcare costs (Kaltenboeck et al., 2012), and increased risk of death (Matsumoto et al., 2014). The cause of the disease is unknown but believed to be influenced by genetic variations (Le Couteur et al., 2002). One gene that has been of recent interest in PD is the brain derived neurotrophic factor (BDNF) gene. A common single-nucleotide polymorphism where an amino-acid substitution in the prodomain of valine (Val) to methionine (met) at codon 66 known as BDNF Val66Met polymorphism (Bath & Lee, 2006). Approximately 20–30% of the general population is a heterozygous carrier or Met-allele carrier (Shimizu et al., 2004). When the Val66Met polymorphism is present it could lead to altered BDNF distribution and decreased BDNF secretion (Hariri et al., 2003). BDNF is involved in regulation of synaptic transmission and neuronal growth (McAllister et al., 1999) and supports dopaminergic neurons in the substantia nigra (Hyman et al., 1991). Individuals with
neurodegenerative diseases such as PD tend to have lower BDNF concentrations than healthy individuals (Foltynie et al., 2009).

It has been proposed that improvements in PD symptoms resulting from aerobic exercise are associated with neuroplasticity changes in neurotrophins, such as BDNF (Rosenfeldt et al., 2015; Zigmond et al., 2012). However, there is a high amount of inter-individual variability in the neuroplasticity response to exercise (Roemmich et al., 2012). That may be due to the high inter-individual variability influence of BDNF Val66Met polymorphism. Individuals with PD who have the BDNF Val66Met polymorphism have reported a higher prevalence of depression symptoms (Hwang et al., 2006). There is evidence that aerobic exercise may lead to increases in BDNF concentrations which could, in turn, decrease the prevalence of depression (Monteiro-Junior et al., 2015; Tuon et al., 2014).

Recently, there has been growing interest in high-cadence stationary cycling as an acute, aerobic exercise treatment for PD (Ridgel, Phillips, et al., 2015; Ridgel, Walter, et al., 2015). During dynamic cycling involves a motor that assists the participant in maintain a high pedaling cadence (80 revolutions per minute, RPM; Peacock et al., 2014; Ridgel et al., 2013; Ridgel, Kim, et al., 2011; Ridgel et al., 2012; Ridgel, Phillips, et al., 2015; Ridgel et al., 2009; Ridgel, Walter, et al., 2015; Rosenfeldt et al., 2015). However, it is unknown how dynamic cycling affects non-motor symptoms such as depression, anxiety, and quality of life. To better understand the influence of BDNF Val66Met polymorphism on symptoms of PD and responses to an acute, aerobic exercise intervention, this investigation focused on two aims: (a) to determine if the prevalence of
BDNF Val66Met polymorphism influences greater prevalence and severity of depression symptoms and decreased quality of life, (b) to determine if BDNF Val66Met polymorphism presence influenced improvements in prevalence and severity of depression symptoms, quality of life over after three sessions of dynamic cycling. The following hypotheses were proposed: (a) If individuals with PD have the BDNF Val66Met polymorphism (Met-allele carriers), then they will have a greater prevalence and severity of depression symptoms and lower quality of life compared to Val-allele carriers, (b) If individuals with PD do not have the BDNF Val66Met polymorphism (Val-allele carriers), then they have greater improvements in the prevalence and severity of depression symptoms and improvements in quality of life after three sessions of dynamic cycling then those with the polymorphism (Met-allele carriers).

**Methods**

Recruited individuals were between ages 50 to 85 years, diagnosed with idiopathic PD, and free of contraindications to exercise including cardiovascular disease, stroke, and any surgical procedures for treatment of PD. Recruitment of participants was outlined previously in Chapter 4 (Figure 1). During the first session, participants read and signed the informed consent and completed the pre-intervention assessment which consisted of the primary variables Beck Depression Inventory-II (BDI-II) depression test (Beck et al., 1996), EQ-5D quality of life questionnaire (Schrag et al., 2000), and single nucleotide polymorphism genotyping measurement (Genotek, 2015).

The BDI-II (Beck et al., 1996) has been used to evaluate the prevalence and severity of depression symptoms during exercise interventions in healthy individuals over
a two week period (Dashtipour et al., 2015; Doose et al., 2015; Teixeira-Machado et al., 2015), and in individuals with PD (Teixeira-Machado et al., 2015). Previous investigations have utilized BDI-II with responses ranging on a 0–3 scale (F. H. Costa et al., 2012; Schrag et al., 2000; van Mierlo et al., 2015). The Beck Depression Inventory-II outcome variables assessed include sadness, pessimism loss of pleasure, guilty feelings, punishment feelings, self-dislike, self-criticalness, suicidal thoughts or wishes, crying, restlessness, loss of interest, worthlessness, loss in energy, changes in sleep patterns, appetite, irritability, difficulty concentrating, tiredness or fatigue, and loss of interest in sex. The score from each question was summed for a total score BDI-II. Twenty-one questions equaled a total range of 0–63. The prevalence and severity of depression symptoms were classified with the following ranges: 0–13: minimal depression, 14–19: mild depression, 20–28: moderate depression, 29–63: severe depression. These scores were then converted into z-scores for data analysis consistency.

EQ-5D-3L is a validated quality of life battery test for PD that strongly correlates with Hoehn and Yahr (HY) stage of illness, UPDRS and depression scores (Schrag et al., 2000). Both the BDI-II and quality of life measurements are often paired when determining the presence of depression symptoms in individuals with PD since it is heavily influenced by an individual’s quality of life (Teixeira-Machado et al., 2015). Individuals with PD, who may be clinically depressed, often report a lower quality of life than those who are not clinically depressed. The quality of life questionnaire consists of descriptive and visual analog scale designed for self-completion by the participant (EuroQOL, 2015). Previous research has established that the EQ-5D questionnaire is
easy to understand and is reliable for individuals for PD (Aarsland et al., 2009; Kusumi & Nakashima, 2000; Schrag et al., 2000). In addition, the EQ-5D allows for a health index across interventions for a range of health illnesses including PD for a one-day assessment indicating statements of mobility, self-care, usual activities, pain/discomfort and anxiety/depression (Watts et al., 2008).

Furthermore, EQ-5D can help identify individuals with and without depression, history of falls, cognitive impairment and those with overall deteriorating health in the past year. Measuring quality of life in exercise interventions is critical to demonstrate not only the physical benefits, but the psychological benefits as well (Baatile et al., 2000; Oguh et al., 2014). Specifically, EuroQol measures mobility, self-care, usual activities, pain/discomfort, anxiety/depression summed and then performed a visual analog log rating their overall health state.

The BDNF Val66Met polymorphism was tested through saliva test using an Oragene DNA collection kit (DNA Genotek, Inc., Ottawa, ON, Canada) and outsourced to GenoFind (Salt Lake City, Utah). The saliva sampled first had DNA extracted and then were genotyped for a single nucleotide polymorphism (SNPs) rs6262, or Val66Met. Quality checks were performed including the PicoGreen analysis, Nanodrop absorbance readings and agarose gel electrophoresis for each of the samples. Previous investigations have utilized Genotek’s products to determine BDNF allelic status for Val66Met polymorphism (Hopkins et al., 2012).

Following the pre-intervention assessment, participants performed 40 minutes of dynamic cycling outlined in Ridgel, Phillips, et al. (2015). These were secondary
measurements to evaluate intensity and the physiology work performed. These measurements were used as covariates when examining changes in depression and quality of life. Heart rate (HR) through a PolarLink® monitor, revolution per minute (RPM), power, and torque were measured during dynamic cycling sessions 1, 2, and 3 through a computerized data collection system (Rockwell Automation, Twinsburg, OH) every second. Rating of perceived exertion (RPE) was recorded by research personnel every five minutes. Participants repeated the dynamic cycling protocol for sessions 2 and 3 with a day of rest between each session. On session four, all participants completed the post-intervention assessment including the depression and quality of life primary measurements

Data are represented as mean ± standard deviation (SD). BDI-II and the quality of life questionnaire have scoring methods in which lower scores indicate better reported performance. The quality of life visual analog scale scoring method indicated that a higher score represents a poorer reported performance. Both BDI-II and quality of life scores were then converted into z-scores for data analysis for consistency. The statistical analysis involved Independent-Samples T-tests and univariate analysis of variance (ANOVA) with all participants’ results creating two groups based on the Val66Met polymorphism presence. Once it was determined if Val66Met polymorphism was present, participants that were had a Met-allele formed the Met-allele group which was compared with homozygous Val-allele carriers for pre-intervention assessment analysis (Gerritsen et al., 2012). The Met-allele and Val-allele groups then compared results from BDI-II and EQ-5D questionnaire with a 2x2 ANOVA (group x time).
Results

Fourteen individuals completed the study. Ten individuals were classified into the Val-allele group and four individuals were classified into the Met-allele group. There were no significant differences between these groups in age, gender, height, weight, BDI scores, and QOL scores (Table 9). In addition, there were no statistical differences in the dynamic cycling data for power, torque, heart rate, RPM, or RPE previously discussed in Chapter 4 results.

Table 9

Descriptive Statistics of Participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Val-Allele (n=10)</th>
<th>Met-Allele (n=4)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64 ± 9</td>
<td>68 ± 3</td>
<td>P = 0.930</td>
</tr>
<tr>
<td>Gender</td>
<td>6 M / 4 F</td>
<td>2 M / 2 F</td>
<td></td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.70 ± 0.12</td>
<td>1.73 ± 0.08</td>
<td>P = 0.658</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75.3 ± 22.2</td>
<td>83.8 ± 5.6</td>
<td>P = 0.263</td>
</tr>
<tr>
<td>Pre-intervention BDI scores</td>
<td>11 ± 12</td>
<td>6 ± 6</td>
<td>P = 0.468</td>
</tr>
<tr>
<td>Pre-intervention QOL VAS scores</td>
<td>69 ± 20</td>
<td>82 ± 7</td>
<td>P = 0.236</td>
</tr>
</tbody>
</table>

Note. Values are represented as mean ± standard deviation.

There were no significant differences between allele groups at pre-intervention in the total BDI-II scores (Figure 6, p = 0.468). In addition, there were no significant interaction (F(1,13)=0.0001, η = 0.050, p = 0.976), main effect of group (F(1,13)=1.191, η = 0.182, p = 0.286), or main effect of time (F(1,13)=0.001, η = 0.050, p = 0.990). There were no significant differences in the changes between the pre-intervention and after the
dynamic cycling intervention between the Val-allele group (-0.01 points) and the Met-allele group (-0.02 points).

![Graph showing BDI-II results between pre-intervention and post-intervention assessments.](image)

**Figure 6.** BDI-II results between pre-intervention and post-intervention assessments. The data were reported as z-score mean ± standard deviation bars. Val-allele (pre 0.13 ± 1.13, n = 10, post 0.14 ± 1.15, n = 10). Met-allele (pre -0.32 ± 0.54, n = 4, post -0.34 ± 0.41, n = 4).

Of the 14 participants, 10 experienced minimal depression symptoms, 1 had mild depression symptoms, 2 had moderate depression symptoms, and 1 had severe depression symptoms. In order to examine individual changes in BDI-II scores, the pre-intervention to the post-intervention differences were calculated (Figure 7). Positive scores represented an increase in BDI-II score or increased depression symptoms after the intervention and negative scores represented a decrease in depression symptoms.
Figure 8 shows the individual participant data changes from pre-intervention to post-intervention for those who had indicated greater than minimal depression symptoms on BDI-II.

Participants 3, 7, 9, and 11 had greater depression symptoms with scores 13 or higher out of the 0–63 range. These participants also had large decreases in BDI-II scores after the dynamic cycling intervention (Figure 8).

*Figure 7.* Pre-intervention BDI scores for all 14 participants. The solid black line represented the cut-off for minimal depression 0–13. The small dashed line represented the cut-off for mild depression 14–19. The large dashed line represented the cut-off for moderate depression 20–28. Participants’ scores above 28, represented severe depression 29–63.
Figure 8. BDI-II change score results between pre-intervention and post-intervention assessments. The data were reported as the change score difference for all 14 participants.

The four participants had greater depression symptoms. The data were then averaged for both pre-intervention (24.50±9.68) and post-intervention (5.75±6.24) in Figure 9. These participants had a statistically significant decline in depressive symptoms into the minimal depression symptom range ($p = 0.017$) after the intervention.
Figure 9. Data from participants 3, 7, 9, and 11 that reported mild – severe depression symptoms during the pre-intervention are reported as average ± standard deviation for pre-intervention and post-intervention. The black line represents the cut-off for minimal depression symptoms 0–13. The small dashed line represent the cut-off for mild depression symptoms 14–19. The large dashed line represents the cut-off for moderate depression 20–28. Participants’ scores above 28, represent severe depression symptoms 29–63. \(* p \geq 0.05.\)

There was a significant difference observed between the Val-allele and Met-allele groups at pre-intervention (Figure 10, \(p = 0.020\)) for the overall quality of life today’s health state questionnaire results. There was no significant group by time interaction \((F_{(1,13)}=0.113, \eta = 0.062, p = 0.740)\) and no main effect of time \((F_{(1,13)}=0.021, \eta = 0.052, p = 0.887)\), but there was a main effect of group \((F_{(1,13)}=4.468, \eta = 0.527, p = 0.045)\).

There was a difference in quality of life for allele groups. Specifically, the Val-allele
group reported more concern for their health state on pre/post-intervention than the Met-allele group.

![Quality of life results between pre-intervention and post-intervention assessments. The data were reported as z-scores mean ± standard deviation bars. Val-allele (pre 0.28 ± 1.06, n = 10, post -0.6 ± 1.48, n = 10). Met-allele (pre -0.70 ± 0.27, n = 4, post -0.65 ± 0.30, n = 4). *p ≥ 0.05, allele group.](image)

Figure 10. Quality of life results between pre-intervention and post-intervention assessments. The data were reported as z-scores mean ± standard deviation bars. Val-allele (pre 0.28 ± 1.06, n = 10, post -0.6 ± 1.48, n = 10). Met-allele (pre -0.70 ± 0.27, n = 4, post -0.65 ± 0.30, n = 4). *p ≥ 0.05, allele group.

There was no significant difference observed in quality of life visual analog scale between the Val-allele and Met-allele groups at pre-intervention (Figure 11, p = 0.236). There was no significant group by time interaction ($F_{(1,13)}=0.131$, $\eta = 0.064$, $p = 0.721$), no main effect of group ($F_{(1,13)}=1.863$, $\eta = 0.259$, $p = 0.185$), and no main effect of time ($F_{(1,13)}=0.024$, $\eta = 0.053$, $p = 0.878$).
Figure 1. Visual analog scale quality of life results between pre-intervention and post-intervention assessments. The data were reported as mean ± standard deviation bars. Val-allele (pre -0.21± 1.11, n = 10, post -0.12 ± 1.13, n = 10). Met-allele (pre 0.52 ± 0.38, n = 4, post 0.30 ± 0.58, n = 4).

The quality of life results were then compared pre/post-intervention for the individuals who expressed greater than minimal depression symptoms on BDI-II. There was no significant difference observed in quality of life visual analog scale between the Val-allele and Met-allele groups at pre-intervention (Figure 12). There was no difference in quality of life for those individuals over time (F(1,13)=0.012, η = 0.051, p = 0.916).
Figure 12. Quality of life results for participants who had greater depression symptoms (BDI-II) between pre-intervention and post-intervention assessments. The data were reported as z-score mean ± standard deviation bars. Pre-intervention (-0.60 ± 1.48, n = 4), post-intervention (-0.72 ± 1.57, n = 4).

Discussion

Our first goal was to evaluate the BDNF Val66Met polymorphism influenced pre-intervention BDI-II scores, which examined the prevalence and severity of depression symptoms and EuroQol which examined quality of life. Although it was hypothesized that the presence of the BDNF Val66Met polymorphism would increase the
prevalence and severity of depression symptoms and decrease quality of life, it did not. Therefore, the null hypothesis was accepted.

Our second goal was to examine if BDNF Val66Met polymorphism would influence the prevalence and severity of depression symptoms and quality of life after three sessions of dynamic cycling. There were no differences in BDI-II scores after dynamic cycling. There were however allele group differences in EuroQol assessment where the Val-allele group had a higher or greater concern for their health state assessment of quality of life compared to the Met-allele group. No differences occurred for visual analog scale quality of life assessment. The null hypothesis was accepted for depression symptoms and quality of life assessments.

One of the primary reasons these results are different than predicted was due to the BDI-II pre-intervention results. Four of the 14 participants experienced moderate-severe depression symptoms. These results are equal to 29% prevalence, which is within the 20–50% range found in previous findings (F. H. Costa et al., 2012). The participants experiencing moderate-severe depression symptoms did have a significant improvement in the prevalence and severity of their depression symptoms after dynamic cycling sessions. If all participants involved in the research investigation experienced equal to or greater than moderate depression symptoms, then there would have been the potential for a greater spread of results and potential improvement in the prevalence and severity of depression symptoms after the dynamic cycling intervention. Specifically, only four participants had depression symptoms of the 14 participants and were classified as: 1-mild depression symptoms, 2-moderate depression symptoms, and
1-severe depression symptoms. Those participants’ average BDI-II scores significantly improved from pre-intervention to post-intervention on the 63 point scale. Depression and quality of life have also been often associated (Menon et al., 2015; Quelhas & Costa, 2009; Schrag, 2006). Interestingly, when reviewing the participants’ depression moderate-severe symptoms and comparing their quality of life scores, there was no changes observed in quality of life from pre/post-intervention. The findings from our investigation are also different from previous work which has focused on BDNF serum levels in addition to the Val66Met polymorphism as a determinant. There was evidence to support that there could have been pre-intervention differences (Elfving et al., 2012). Furthermore, differences could have occurred since reduced BDNF levels may be associated with depressive behavior (Taliaz et al., 2010). Since our current research focus was the Val66Met polymorphism, rather than BDNF levels in serum, it was not known how the Val66Met polymorphism affected BDNF levels in this population.

Our hypothesis was that the BDNF Val66Met polymorphism would influence the prevalence and severity of depression symptoms was supported by previous findings (Erickson, Miller, & Roecklein, 2012; Hwang et al., 2006). Others have shown that decreased BDNF may be associated with hippocampal dysfunction and could lead to an increased risk of depression. If BDNF serum concentration could be increased through aerobic exercise, then it could improve hippocampal reduction leading to a reduction in the severity of depression (Erickson et al., 2012). Previous research had suggested that Met-allele carriers had a greater prevalence for depression (Hwang et al., 2006). Met-allele carriers have also been associated with lower activity dependent BDNF
secretion (Karege, Schwald, & Cisse, 2002; Kim et al., 2011). Therefore, individuals with the BDNF Val66Met polymorphism could have been at greater risk for geriatric depression in otherwise healthy older adults (Hwang et al., 2006).

These findings were different than expected for the quality of life questionnaire. The Val-allele group was expected to report a greater quality of life on the pre/post-intervention health state assessment as well as the visual analog scale for pre/post-intervention. Exercise interventions had improved quality of life using the EuroQOL in individuals with Parkinson’s disease (Schrag, 2006; Schrag et al., 2007; Schrag et al., 2000). Depression is often associated with an individual’s quality of life (Kuopio et al., 2001). Therefore, it was interesting that the individuals who experienced moderate or greater depression symptoms, did not report a change in their quality of life health state or the quality of life visual analog scale. Furthermore, the Met-allele group had less concerns of their current health state than the Val-allele group. Presence of the BDNF Val66Met polymorphism (Met-allele group) had been associated with negative emotionality (Lehto, Maestu, Kiive, Veidebaum, & Harro, 2016). Other researchers concluded that stressed individuals, who may have had greater concern for the anxiety or depression within the pre/post-intervention health state questionnaire, trend towards decreased BDNF serum levels which are often associated with Met-allele group (Chui et al., 2014). When reviewing coping strategies to stress, Met-allele groups were more anxious than Val-allele groups in individuals with advanced gastric cancer (Koh, Jeung, Namkoong, Chung, & Kang, 2014).
Our findings are similar to other studies that have shown that the presence of Met-allele does not influence the prevalence or severity of depression symptoms in those with PD (Gao et al., 2010; Svetel et al., 2013). Previous research found evidence that BDNF influenced depression in PD after longer exercise interventions. Tuon et al. (2014) showed, in a mouse model, that exercise can possibly have an antidepressant effect by increasing levels of BDNF. Therefore, two different types of exercise (running and strength training) were examined for 60 days and then compared to depressive-like behavior. PD was induced 1 day after the last exercise session and 7 days later depressive-like behavior was induced. Both types of exercise prevented depressive-like behavior and restored BDNF levels in the pro-domain (Tuon et al., 2014).

**Limitations and Future Directions**

There are several limitations in this study including the prevalence and severity of depression symptoms experiences, smaller sample size, inability to correlate BDNF polymorphism to production of BDNF, short duration of the intervention and the exercise intensity that have been previously discussed in Chapter 4. More specific limitations include the number of depressed PD individuals, the length of the intervention specific to depression and quality of life, and surveys given. Only four out of the 14 participants were experiencing moderate-severe depression symptoms using BDI-II at pre-intervention. Those four participants did have a significant reduction in depression symptoms after the dynamic cycling intervention which also represented of the reported depressed range 20–50% (F. H. Costa et al., 2012). A larger sample size would also assist in comparing the severity of depression symptoms grouped by the presence of the Val66Met
polymorphism to determine the influence of the polymorphism. Lastly, it is likely that a longer intervention would promote greater changes in depression symptoms and quality of life. In addition, Depression, Anxiety, Stress Scales-21 (DASS 21) and Parkinson’s disease Quality of Life Questionnaire (PDQL) would be welcomed additions to the current protocol questionnaires to fully assess depression, anxiety, stress and quality of life. The PDQL covers 37 items compared to 6 with EuroQol. In addition, the PDQL and DASS 21 may have been easier to evaluate for potential change with more scoring points and longer time-frames. The EuroQol time-frame only measures the day given while DASS 21 focuses on the past week.

The next steps for future research will involve targeting those individuals with PD and depression symptoms, through pre-screening, since the four out of 14 participants had moderate-severe depressed symptoms and those participants significantly improved after the three session of dynamic cycling. Since both the prevalence of depression in PD and BDNF Val66Met polymorphism in the general population are 20–50%, a larger sample size of the same design would allow for proper analysis of how BDNF Val66Met polymorphism influences the prevalence and severity of depression and the influence of the dynamic cycling in those participants. One proposed addition to the current design would be collecting pre-intervention and post-intervention BDNF serum samples to not only compare the BDNF Val66Met polymorphism but also the concentration which is often compared in previous investigations.

Furthermore as discussed in Chapter 4, post-hoc theorizing had led to the development of an additional hypothesis. If individuals with depression symptoms
improved from pre-intervention to post-intervention, then those individuals would also have an improvement in their emotional recognition. The emotional recognition domain power was set at 0.80, alpha = 0.05, and based on the Val-allele group pre/post-intervention data. Emotional recognition domain for the Val-allele group at pre-intervention was (-1.24±1.10) and post-intervention (-0.67±1.34) which calculated a 0.46 effect size. A new total sample size was projected at 31 participants. Moving forward with analysis, this domain will be re-evaluated. Therefore moving forward, the estimated sample size for the Val-allele group is 31 participants. Given the current 71% Val-allele present rate of the participants, a new participant sample size with this given information of the unknown BDNF Val66Met polymorphism would now be approximately 44 Val-allele participants. From the current data sample, data on an estimated 30 more participants would need to be collected given all of the information. It should be noted that the prevalence of the BDNF Val66Met polymorphism varies from 20–50% with 29% based off of the initial findings.
CHAPTER VI
THE INFLUENCE OF VAL66MET POLYMORPHISM ON MOTOR
SYMPTOMS IN INDIVIDUALS WITH PARKINSON’S DISEASE AFTER
DYNAMIC CYCLING

PD is characterized by motor symptoms such as tremor, bradykinesia, rigidity, and postural instability (Dashtipour et al., 2015; Movement Disorder Society Task Force on Rating Scales for Parkinson’s, 2003). The cause of the disease is unknown but believed to be influenced by genetic variations (Le Couteur et al., 2002). One gene that has been of recent interest in PD is the brain derived neurotrophic factor (BDNF) gene. Approximately 20–30% of the population is a heterozygous carrier or Met-allele carrier (Shimizu et al., 2004). When the Val66Met polymorphism is present it could lead to altered BDNF distribution and decreased BDNF secretion (Hariri et al., 2003). BDNF is involved in regulation of synaptic transmission and neuronal growth (McAllister et al., 1999) and supports dopaminergic neurons in the substantia nigra (Hyman et al., 1991). Individuals with neurodegenerative diseases such as PD tend to have lower BDNF concentrations than healthy individuals (Foltynie et al., 2009).

Both chronic and acute aerobic exercise has been shown to increase in BDNF concentrations in animal models (Berchtold et al., 2005), healthy individuals (S. W. Tsai et al., 2015), and individuals with neurodegenerative diseases (Aarsland et al., 2009; Scalzo et al., 2010). It has been proposed that improvements in PD symptoms resulting from aerobic exercise are associated with neuroplasticity changes in neurotrophins, such as BDNF (Rosenfeldt et al., 2015; Zigmond et al., 2012). However, there is a high

95
amount of inter-individual variability in the neuroplasticity response to exercise (Roemmich et al., 2012). That may be due to the high inter-individual variability influenced by the BDNF Val66Met polymorphism.

Individuals with PD who have the BDNF Val66Met polymorphism often have higher BDNF serum levels (Bus et al., 2012; Lang, Hellweg, Sander, & Gallinat, 2009). In contrast, previous research also concluded that higher BDNF serum levels were associated with longer PD disease onset. Furthermore, the higher BDNF serum values had also correlated with poor motor symptoms in tasks such as Berg Balance Scale, TUG test, and six-minute walk test (Scalzo et al., 2010). Though previous research in conflicting, it is believed that individuals with the Val66Met polymorphism (Met-allele carriers) may result in worse motor symptoms than the Val-allele carriers.

Increasing BDNF serum levels is believed to be beneficial for neurodegenerative diseases such as PD. Therefore aerobic exercise interventions have been of interest (Ridgel, Phillips, et al., 2015; Ridgel, Walter, et al., 2015). In particular, dynamic cycling is a mode of exercise that most individuals with PD, regardless of the severity, may be able to perform. It involves a motor that assists the participant in maintain the desired cadence or 80 revolutions per minute (RPM) that results in greater improvements in motor function. However, its effects on motor symptoms require more review on potential influences (Peacock et al., 2014; Ridgel et al., 2013; Ridgel, Kim, et al., 2011; Ridgel et al., 2012; Ridgel, Phillips, et al., 2015; Ridgel et al., 2009; Ridgel, Walter, et al., 2015; Rosenfeldt et al., 2015). Despite these past motor symptom improvements,
there is high inter-individual variability responses. BDNF Val66Met polymorphism may influence and help explain the variability in those responses.

To better understand the effects of BDNF Val66Met polymorphism on motor symptoms of PD and responses to an acute, aerobic exercise interventions, this investigation focused on two aims. The first aim was to determine if the prevalence of BDNF Val66Met polymorphism influenced the severity of motor symptoms at pre-intervention. The second aim was to determine if BDNF Val66Met polymorphism influences improvements in motor symptoms after three sessions of dynamic cycling. In this study two hypotheses were tested.

1. Individuals with the BDNF Val66Met polymorphism (Met-allele carries) will have less severe motor symptoms compared to Val-allele carriers at pre-intervention.

2. Individuals will show improvements in motor symptoms after three sessions of dynamic cycling with the Val-allele carriers having greater improvement than the Met-allele carriers.

**Methods**

Recruitment of participants with PD was outlined in Chapter 4 (Figure 2). All participants completed the pre-intervention assessment which consisted of the primary variables including Kinesia ONE™ (Pulliam et al., 2014), and single nucleotide polymorphism genotyping measurement (Genotek, 2015). Kinesia ONE™ involves an accelerometer device placed on the index finger on the self-selected dominant hand of the participant and took them through a series of tasks which included: finger to nose, rotated
palms, resting condition, hand grasping, finger touching and holding arms out, all of which are utilized in the Unified Parkinson’s Disease Rating Scale (UPDRS) upper-body assessment (Movement Disorder Society Task Force on Rating Scales for Parkinson’s, 2003).

Data are represented as mean ± standard deviation (SD). Kinesia ONE™ ranges from 0–4 scale in which lower scores indicated lower motor-based symptoms. The raw data were then converted into z-scores. All data were analyzed using Statistical Package for Social Sciences software (SPSS, Version 23.0 Chicago, IL). The statistical analysis involved Independent-Samples T-tests at pre-intervention and created two groups based on the Val66Met polymorphism presence. Once it was determined if Val66Met polymorphism was present, Met-allele carriers were merged into a group and compared with homozygous Val-allele carriers (Gerritsen et al., 2012). Next, the statistical analyses involved 2-way Analysis of Variance (ANOVA) comparing two allele groups (Val-allele and Met-allele groups), and two time periods (pre-intervention and post-intervention) for Kinesia ONE™ results.

Results

Descriptive data were presented in Chapter 4. Kinesia ONE™ scores were organized and categorized into average tremor, speed, rhythm, and amplitude scores for all participants. This approach was used to compare Kinesia ONE™ results to UPDRS in previous research and allows for a better summary of motor symptom results (Heldman et al., 2014; Heldman et al., 2011).
There were no differences between the allele groups at pre-intervention in Table 10 ($p = 0.231$). In addition, there were no significant differences in the average speed scores (Table 11). Furthermore, there were no significant interactions in Figure 13 ($F(1,13)=0.080$, $\eta=0.059$, $p = 0.779$), no main effect of time ($F(1,13)=0.015$, $\eta=0.052$, $p = 0.904$). There was a main effect of allele group ($F(1,13)=4.461$, $\eta=0.527$, $p = 0.045$). Val-allele group (0.05 points) and Met-allele group (-0.16 points) had non-significant changes.

Table 10

*Pre-Intervention Group Differences*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-Intervention Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Speed Scores</td>
<td>$P = 0.837$</td>
</tr>
<tr>
<td>Average Tremor Scores</td>
<td>$P = 0.231$</td>
</tr>
<tr>
<td>Average Rhythm Scores</td>
<td>$P = 0.158$</td>
</tr>
<tr>
<td>Average Amplitude Scores</td>
<td>$P = 0.535$</td>
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</tbody>
</table>
Table 11

*Averaged Kinesia ONE™ scores*

<table>
<thead>
<tr>
<th>Variable</th>
<th>BDNF</th>
<th>Pre-Intervention</th>
<th>Post-Intervention</th>
<th>Interaction</th>
<th>Main Effect of Group</th>
<th>Main Effect of Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Speed</td>
<td>Val</td>
<td>-0.66 ± 1.96</td>
<td>-0.02 ± 1.06</td>
<td>$P = 0.908$, $F = 0.031$, Power = 0.051</td>
<td>$P = 0.805$, $F = 0.062$, Power = 0.057</td>
<td>$P = 0.960$, $F = 0.003$, Power = 0.050</td>
</tr>
<tr>
<td></td>
<td>Met</td>
<td>0.16 ± 1.42</td>
<td>0.06 ± 0.97</td>
<td></td>
<td></td>
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<tr>
<td>Average Tremor</td>
<td>Val</td>
<td>0.21 ± 1.12</td>
<td>0.27 ± 1.07</td>
<td>$P = 0.779$, $F = 0.080$, Power = 0.059</td>
<td>$P = 0.045^*$, $F = 4.461$, Power = 0.527</td>
<td>$P = 0.904$, $F = 0.015$, Power = 0.052</td>
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<tr>
<td></td>
<td>Met</td>
<td>-0.52 ± 0.19</td>
<td>-0.68 ± 0.20</td>
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<td></td>
</tr>
<tr>
<td>Average Rhythm</td>
<td>Val</td>
<td>0.18 ± 1.11</td>
<td>1.83 ± 0.24</td>
<td>$P = 0.686$, $F = 0.171$, Power = 0.067</td>
<td>$P = 0.680$, $F = 0.322$, Power = 0.082</td>
<td>$P = 0.011^*$, $F = 8.686$, Power = 0.778</td>
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<tr>
<td></td>
<td>Met</td>
<td>-0.46 ± 0.47</td>
<td>1.73 ± 0.00</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Average Amplitude</td>
<td>Val</td>
<td>0.11 ± 1.30</td>
<td>-0.23 ± 1.18</td>
<td>$P = 0.593$, $F = 0.293$, Power = 0.081</td>
<td>$P = 0.726$, $F = 0.125$, Power = 0.063</td>
<td>$P = 0.819$, $F = 0.054$, Power = 0.056</td>
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<tr>
<td></td>
<td>Met</td>
<td>-0.28 ± 0.61</td>
<td>0.06 ± 0.35</td>
<td></td>
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</table>

*Note.* Values are reported as $z$-scores mean ± standard deviation. *$p \leq 0.05$*
Figure 13. Average tremor results between pre-intervention and post-intervention assessments. The data were reported as z-score mean ± standard deviation bars. Val-allele (pre 0.21 ± 1.12, n = 10, post 0.27 ± 1.07, n = 10). Met-allele (pre -0.52 ± 0.19, n = 4, post -0.68 ± 0.20, n = 4). *p ≤ 0.05, main effect of group.

There was no significant difference in the average speed scores (Table 11) between the allele groups at pre-intervention (p = 0.158). Furthermore, there were no significant interactions in Figure 14 (F(1,13)=0.171, η=0.067, p = 0.686), and no main effect of allele group (F(1,13)=0.322, η=0.082, p = 0.580). There was a main effect of time (F(1,13)=8.686, η=0.778, p = 0.011). There were significant changes in Val-allele group (1.65 points) and Met-allele group (2.19 points).
Figure 14. Average rhythm results between pre-intervention and post-intervention assessments. The data were reported as z-score mean ± standard deviation bars. Val-allele (pre 0.18 ± 1.11, n = 10, post 1.83 ± 0.24, n = 10). Met-allele (pre -0.46 ± 0.47, n = 4, post 1.73 ± 0.00, n = 4). *p ≤ 0.05, main effect of time.

Discussion

The focus of the first aim was to evaluate the BDNF Val66Met polymorphism influence on incidences of motor symptoms in individuals with PD. Kinesia ONE™ was used to test upper body motor symptoms through an accelerometer device, which has been validated with UPDRS Motor III clinical score (Pulliam et al., 2014). Participants were grouped based on BDNF Val66Met polymorphism presence to evaluate for
potential differences. There were no significant differences pre-intervention. The null hypothesis was accepted.

The second aim was to evaluate whether the presence of the BDNF Val66Met polymorphism influenced motor symptoms after the dynamic cycling exercise intervention. Data were averaged for speed, tremor, rhythm, and amplitude and then converted to z-scores for analysis. There was a main effect of group for average tremor and main effect of time for average rhythm. The Val-allele group had a higher average tremor compared to the Met-allele, not in support of the hypothesis. In addition, the main effect of time for average rhythm observed a decrease in performance from pre/post-intervention. These results confirm that the null hypothesis was accepted.

These results could have occurred based on several factors. First, the participants in this investigation were primarily interested in being involved due to the primary focus on non-motor symptoms. These participants more commonly reporting cognitive dysfunction, depression, and other non-motor related issues. Therefore, if motor symptoms were not the primary focus during recruitment, there may not necessarily be a large change to record (deficit and then improvement). Second, compared to Heldman et al., Kinesia ONE™ resulted in higher ratings for “finger-tapping speed, amplitude, and rhythm but were not different from [either] resting or postural tremor” (Heldman et al., 2014, p. 1862). From this position, the participants’ average tremor scores would have had no statistical difference from UPDRS if it had been performed during our investigation. Third, Kinesia ONE™ would have been able to capture whether these participants had notable bradykinesia and if changes occurred after dynamic cycling by
evaluating the speed, rhythm, and amplitude recorded (Heldman et al., 2011). In addition, participants were instructed to perform the Kinesia ONE\textsuperscript{TM} task with their dominant hand index finger in contrast to most-affected side. It was noted for two participants, their most-affected side was the left side but the right dominant side was tested. Kinesia ONE\textsuperscript{TM} was used before exercise on visit one and visit four similar to previous studies (Ridgel, Phillips, et al., 2015). However, this aspect of the study design is different than unpublished work observing Kinesia ONE\textsuperscript{TM} score changes immediately after exercise through 20 hours post exercise (Ault, 2016; Phillips, 2014). Furthermore, BDNF serum level concentration would have been beneficial to observe in addition to the presence of the polymorphism. Previous research had suggested that individuals who were in early stages of PD may have had lower BDNF serum levels, then it increased over time as compensatory effect (Scalzo et al., 2010) and BDNF may change with aerobic exercise (Knaepen et al., 2010).

It is not understood why the average motor symptom rhythm increased over time. When physician-rated motor symptoms (UPDRS) are compared to Kinesia ONE\textsuperscript{TM} scores, there is usually a greater emphasis on amplitude compared to rhythm (Heldman et al., 2011) compared to UPDRS. Kinesia ONE\textsuperscript{TM} results had great reliability ($p \leq 0.05$). It has been significantly higher intra-class correlation for rhythm compared to clinician ratings of symptoms (Heldman et al., 2014). It is possible that participants were fatigued and unmotivated from their participation in the study. This was the final assessment in the four visit protocol. In addition, some participants noted other outside distractions on visit four which may have influenced their focus on the task at hand.
Though our results do not reflect past investigations, previous research has utilized the same three session dynamic cycling protocol and found a 14% improvement in motor symptoms as measured with the UPDRS Motor III score (Ridgel, Phillips, et al., 2015). A recent study utilizing a longer motor rehabilitation intervention (20 sessions) found improvements in UPDRS and motor symptoms (6 minute walk test) as well as increases in BDNF levels from pre-intervention to day 7 (Angelucci et al., 2016). Frazzitta and colleagues showed that BDNF serum levels significantly increased from pre-intervention to day 10 in the exercise group (3 hours daily) compared to control group (no therapy). In addition, exercise continued through day 28. BDNF serum levels were maintained throughout. Furthermore, UPDRS Motor III scores improved from day 28 compared to pre-intervention (Frazzitta et al., 2014).

**Limitations and Future Directions**

There were specific limitations to the motor symptoms aspect of the study design. The Kinesia ONE™ measurements were taken only on the reported dominant hand index finger. This was also the hand chosen for the computerized cognition test to allow for comparisons between the cognition and motor symptom evaluation. Another limitation was collecting Kinesia ONE™ results without a comparison such as Unified Parkinson’s Disease Rating Scale (UPDRS). UPDRS evaluates the severity of PD through a subjective scale reviewing mentation, behavior and mood, activities of daily living, motor examination, and complications of therapy (Movement Disorder Society Task Force on Rating Scales for Parkinson’s, 2003). Kinesia ONE™ is an objective, task-based assessment of motor symptoms by using the accelerometer sensor device which adds an
objectiveness to the evaluation. Kinesia ONE$_{TM}$ offers a unique insight due to the objective nature; however UPDRS is a more predominate measurement at this point in time because it is well-established (Movement Disorder Society Task Force on Rating Scales for Parkinson’s, 2003). Therefore, UPDRS should also be added to the protocol for a better representation of motor symptoms. Although UPDRS motor scores are used readily in previous studies, the value of the Kinesia ONE$_{TM}$ measurements are that they are unbiased and not subjective. Furthermore, Kinesia ONE$_{TM}$ provides information on motor performance such as speed, amplitude, and rhythm. A second limitation was that post-intervention results were collected two days after the previous dynamic cycling visit. Most recent improvements in motor symptoms had shown immediately after and up to 24 hours post exercise improvements (Ault, 2016; Phillips, 2014). Therefore, it would have been beneficial to test participants immediately after the third cycling session as well.

It would be helpful if future studies examined motor symptoms in individuals with PD on both participants’ hands and test motor symptoms immediately after dynamic cycling sessions. By testing both participants’ hands, comparison could be made between hand dominance, the most affected hand, and observe whether changes occurred more specifically. It would be helpful to also perform Kinesia ONE$_{TM}$ immediately after each dynamic cycling session to capture potential changes in addition to pre-intervention and 48 hours post-intervention.
CHAPTER VII

SUMMARY

Individuals with PD often experience both motor and non-motor symptoms. Exercise interventions are beneficial and may decrease the rate progression of the disease. To help address the high inter-individual variability in responses to exercise based interventions, brain-derived neurotrophic factor (BDNF) has been suggested as a potential factor in exercise-related responses. Several modes of exercise have been shown to promote improvements in motor and cognitive function in PD, but there has been recent interest in stationary cycling due to its non-weight bearing nature and ease of use. Furthermore, high cadence or dynamic cycling allows for an individualized approached with motor assisting the rider to maintain the desired high cadence.

In this study, our results indicate the BDNF Val66Met polymorphism does not influence incidences of attention, executive function cognitive dysfunction, MoCA, prevalence or severity of depression symptoms, quality of life, or motor symptoms. Furthermore, BDNF Val66Met polymorphism does not influence attention, executive function, MoCA, prevalence or severity of depression symptoms, quality of life, or motor symptoms after dynamic cycling. However, there were some interesting trends in the data and a larger sample size will likely result in more conclusive results.

It is important to note that only four participants had moderate to severe depression symptoms of the 14 participants and classified as: 1–mild depression symptoms, 2–moderate depression symptoms, 1–severe depression symptoms. The participants with depression symptoms average BDI-II scores significantly improved
from pre-intervention and post-intervention on the 63 point scale where 0–13 was considered minimal depression. If more participants involved had depression symptoms, this offers support that the dynamic cycling intervention may have had an effect on the prevalence and severity of depression symptoms.

Future research should build upon this investigation by increasing the sample size focusing on attention and emotional recognition given the power analyses results and evaluate BDNF serum levels in addition to BDNF Val66Met polymorphism. Lastly, it is possible that three exercise sessions may not have been intense or long enough to elicit changes. Future studies should review the optimal intensity and duration of dynamic cycling interventions to optimize cognitive improvement, decrease depression symptoms and increase motor function in Parkinson’s disease.
APPENDIX A

PRE-PARTICIPATION TELEPHONE SCRIPT/SCREENING PROTOCOL
Appendix A

Pre-Participation Telephone Script/Screening Protocol

Prospective participants that have expressed interest in participating in a Parkinson’s disease study will receive a telephone call from the researcher. The following telephone script will be used:

“Hello, I received your name because you have expressed interest in participating in the Parkinson’s disease study. This study will be taking place at Kent State University in Kent, Ohio and is evaluating BDNF Val66Met polymorphism effects during dynamic cycling in individuals with Parkinson’s disease. If you choose to participate in this study, you will be asked to visit the exercise laboratory at Kent State University for 4 sessions. Are you interested in hearing more about the study?”

- At this point, if the individual does not have an interest in participating in the study then the prospective participant will be thanked for their time and the researcher will provide their contact information in case the individual has a change in mind. The telephone call will then be ended.
- If the participant has an interest in participating in the study then the telephone call will continue as follows:

“On your first visit you can expect to have cognition, depression, quality of life tested. Brain derived neurotrophic factor (BDNF) will be tested through a saliva sample. All techniques that are performed are non-invasive. When all assessments have been completed you will begin dynamic cycling and static stretching. Session 1 will take approximately 120 minutes. Sessions 2–3 will approximately take 40 minutes to complete. Session 4 will consist of cognition, depression, quality of life testing taking approximately 70 minutes. When this visit has been completed you will have finished this research study. Are you interested in seeing if you are a candidate for this study?”

- If the prospective individual is not interested in this study then they will be thanked for their time and the telephone call will be ended.
- If the prospective individual is interested in the study then these additional questions will be asked:

_________________ Have you been diagnosed with Idiopathic Parkinson’s disease?
_________________ Are you between the age of 50 and 79 years old?
_________________ Do you have physician approval to participate in this study?
_________________ Do you have a history of non-Parkinson’s disease related neurological disorder or brain injury such as stroke?
_________________ Do you have an orthopedic injury that would limit your ability to exercise?
_________________ Do you have a history of non-Parkinson’s disease related cardiovascular disease such as recent heart surgery or pacemaker?
Are you able to move around without, or minimal use, of ambulatory equipment?

Do you have unpredicted motor fluctuations?

- If the individual does not meet the inclusion/exclusion criteria then they will be thanked for their time and the telephone call will end.
- If the individual meets the inclusion/exclusion criteria then research personnel will go through the AHA/ACSM Health/Fitness Pre-participation Screening Questionnaire. Interested individuals are eligible to participate in the study with physician approval, and the telephone conversation will continue as follows:

  “Would you like to schedule an appointment for the first session?”
  - If no, then the researcher would thank the individual for their time.
  - If yes, an appointment will be scheduled, and a timeline to schedule.

  “You will be required to sign an informed consent form prior to participating in this study. Also, please bring your physician approval to participate in this study with you to your first appointment. You should wear comfortable clothing that allows you to exercise and wear tennis shoes to all your sessions.”
  - If the individual does not have physician approval yet, then the participant will be informed the following:

    “In order to participate in this study you will be required to get clearance from your physician. Please have your physician write their approval on documented paper.”
APPENDIX B

PRE-PARTICIPATION QUESTIONNAIRE
Appendix B

Pre-Participation Questionnaire

Assess your health status by checking all true statements:

History: You have had:

- [ ] a heart attack
- [ ] Heart surgery
- [ ] Cardiac catheterization
- [ ] Angioplasty or stent
- [ ] Pacemaker/implantable cardiac defibrillator
- [ ] Rhythm disturbance
- [ ] Heart valve disease
- [ ] Heart failure
- [ ] Heart transplantation
- [ ] Congenital heart disease

Symptoms:

- [ ] You experience chest discomfort with exertion.
- [ ] You experience unreasonable breathlessness
- [ ] You experience dizziness, fainting, or blackouts
- [ ] You take heart medications
- [ ] Other health issues
- [ ] You have diabetes
- [ ] You have asthma or other lung disease
- [ ] You have burning or cramping sensation in your legs when walking short distances.
- [ ] You have musculoskeletal problems that limit your physical activity.
- [ ] You have concerns about the safety of exercise
- [ ] You take prescription medication(s).
- [ ] You are pregnant.

Cardiovascular risk factors:

- [ ] You are a man older than 45 years.
- [ ] You are a woman older than 55 years, have had a hysterectomy, or are postmenopausal
- [ ] You smoke, or quit smoking within the previous 6 months.
- [ ] Your blood pressure is greater than 140/90 mm Hg (Last date checked: __________)
- [ ] You do not know your blood pressure.
- [ ] You take blood pressure medication.
Your blood cholesterol level is greater than 200 mg/dl (Last date checked: ______)

You do not know your cholesterol level.

You have a close blood relative who had a heart attack or heart surgery before age 55 (father or brother) or age 65 (mother or sister).

You are physically inactive (i.e., you get <30 minutes of physical activity on at least 3 days per week).

You are greater than 20 pounds overweight.
APPENDIX C

PHYSICIAN CLEARANCE FORM
Appendix C

Physician Clearance Form

Kent State University—Dept. of Exercise Physiology

Patient’s name:
Address:
Telephone number:

Dear Doctor-

Your patient, ____________, has expressed an interest in participating in a cycling exercise study in individuals with Parkinson’s disease (KSU IRB approval #15-605). The object of this project is to compare cycling and seated stretching while testing BDNF Val66Met polymorphism and changes in neuropsychological measurements. The participant will complete either 3 sessions of dynamic cycling or static stretching over a week period. Each session include 5 minutes of warm up, 30 minutes of moderate intensity cycling or seated static stretching and 5 minutes cool down. The exercise sessions will last 40 minutes. We will examine changes in cognition, depression, quality of life, Kinesia One measurements in these individuals before and after the exercise sessions.

Exclusion Criteria:

- Age below 50 or above 79
- No diagnosis of idiopathic Parkinson’s disease (PD)
- Cardiovascular disease (heart attack, heart surgery, angioplasty, pacemaker, rhythm disturbance, heart valve disease, heart failure, heart transplantation and congenital heart disease), stroke, and any surgical procedures for treatment of PD.

Below is a clearance form to be filled out and signed by you and returned via fax: 330-672-2250.

Physician’s recommendation (check the appropriate line)

a. There is no contraindication for participation in this exercise research project.
b. Participation in this exercise research program is inadvisable.

Physician’s name: ____________________________
Signature: ______________________________________
Date: __________________________________________
Address: _______________________________________
Telephone: _____________________________________
Fax: ___________________________________________

Please return completed form to:
Angela Ridgel, Ph.D., Principal Investigator & Associate Professor
Dept. of Exercise Science, Kent State University
Fax: 330-672-2250, Phone: 330-672-7495
APPENDIX D

RISK STRATIFICATION
Appendix D

Risk Stratification

- **Low Risk:** Asymptomatic men and women who have \(< 1\) CVD risk factor
- **Moderate Risk:** Asymptomatic men and women who have \(\geq 2\) CVD risk factor
- **High Risk:** Individual who have known cardiovascular, pulmonary, or metabolic disease or one or more signs and symptoms

**Positive Risk Factors**

1. **Age:** Men \(\geq 45\) years, women \(\geq 55\) years
2. **Family History:** Myocardial infarction (heart attack), coronary revascularization (heart bypass or angioplasty) or sudden death before 55 years of age (men) in father or other first degree relative or before 65 (women) in mother or other first degree relative
3. **Smoking:** Current smoking or those who quit within the previous six months
4. **Hypertension:** Systolic blood pressure \(\geq 140\)mm or diastolic blood pressure \(\geq 90\)mm, confirmed by measurements on at least two separate occasions or on antihypertensive medications
5. **Dyslipidemia:** LDL \(\geq 130\) mg/dL, HDL <40 mg/dL or on lipid-lowering medication, if serum cholesterol is all that is available, use serum cholesterol \(\geq 200\)mg/dL
6. **Pre-diabetes:** Fasting blood sugar \(\geq 100\) mg/dl, confirmed on at least two separate occasions
7. **Obesity:** BMI \(\geq 30\) kg/m2 or Waist girth >102 cm (40”) for men and >88 cm (35”) for women
8. **Sedentary Lifestyle:** Persons not participating in at least 30 mins of physical activity on or at least three days of the week for 3 months.

**Negative Risk Factors**

1. **HDL:** HDL \(\geq 60\) mg/dL

Assign a positive numerical score of one (1) to each positive risk factor category that the client possesses. This implies a maximal score of seven if the client demonstrates all seven positive risk factors.

Assign a negative numerical score of one (1) to the negative risk factor if applicable.

Sum the total of all numbers for a final score.
APPENDIX E

HEALTH HISTORY QUESTIONNAIRE
Appendix E

Health History Questionnaire

Kent State University

Thank you for volunteering to be a participant for a study to be conducted in the Applied Physiology Research Laboratory. Some of the tests used in our experiments require that you perform strenuous exercise. Consequently, it is important that we have an accurate assessment of your past and present health status to assure that you have no medical conditions that would make the tests especially dangerous for you. Please complete the health history as accurately as you can.

THIS MEDICAL HISTORY IS CONFIDENTIAL AND WILL BE SEEN ONLY BY THE INVESTIGATORS AND KENT STATE UNIVERSITY HEALTH CENTER PERSONNEL

Name__________________________________________ Date___/___/___

Date of Birth___/___/___ Current Age____years

Ethnic Group: ___ White
___ African American
___ Hispanic
___ Asian
___ Pacific Islands
___ American Indian
___ Other______________

HOSPITALIZATIONS AND SURGERIES
If you have ever been hospitalized for an illness or operation, please complete the chart below. Do not include normal pregnancies, childhood tonsillectomy, or broken bones. YEAR______________

OPERATIONS OR ILLNESS

YEAR______________

OPERATIONS OR ILLNESS

YEAR______________

OPERATIONS OR ILLNESS

121
Are you under long-term treatment for a protracted disease other than Parkinson’s disease, even if presently not taking medication?  [ ] Yes  [ ] No
If Yes, explain:
_______________________________________________________________________

MEDICATION
Please list all medications that you have taken within the past 8 weeks: (Include prescriptions, vitamins, over-the-counter drugs, nasal sprays, aspirins, birth control pills, etc.)
Check this box [ ] if you have not taken any medication.
MEDICATION________________________
DOSE________________________
REASON FOR TAKING THIS
_______________________________________________________________________
MEDICATION________________________
DOSE________________________
REASON FOR TAKING THIS
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REASON FOR TAKING THIS
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ALLERGIES
Please list all allergies you have (include pollen, drugs, alcohol, food, animals, etc.)
Check this box [ ] if you have no allergies.
1.______________________________________________________________________
2.______________________________________________________________________
3.______________________________________________________________________
4.______________________________________________________________________
When was the last time you were “sick”? (e.g. common cold, flu, fever, etc.)
**PROBLEMS AND SYMPTOMS**

Place an X in the box next to any of the following problems or symptoms that you have had:

**General**

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<tr>
<td></td>
<td>Mononucleosis</td>
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<td>Excessive fatigue</td>
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<td>Recent weight loss while not on a diet</td>
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<td>Recent weight gain</td>
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<td></td>
<td>Thyroid disease</td>
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<td></td>
<td>Fever, chills, night sweats</td>
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<td></td>
<td>Diabetes</td>
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<td>Arthritis</td>
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<td>Sickle Cell Anemia</td>
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<td>Heat exhaustion or heat stroke</td>
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<td>Recent sunburn</td>
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**Heart and Lungs**

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<tr>
<td></td>
<td>Abnormal chest x-ray</td>
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<tr>
<td></td>
<td>Pain in chest (persistent and/or exercise related)</td>
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<tr>
<td></td>
<td>Heart attack</td>
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<td>Coronary artery disease</td>
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<td></td>
<td>High blood pressure</td>
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<td>Rheumatic fever</td>
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<td>Peripheral vascular disease</td>
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<td>Blood clots, inflammation of veins (phlebitis)</td>
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<td></td>
<td>Asthma, emphysema, bronchitis</td>
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<td>Shortness of breath</td>
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<td>At rest</td>
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<td>On mild exertion</td>
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<td></td>
<td>Discomfort in chest on exertion</td>
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<td></td>
<td>Palpitation of the heart; skipped or extra beats</td>
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<td>Heart murmur, click</td>
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<td>Other heart trouble</td>
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<td></td>
<td>Lightheadedness or fainting</td>
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<td>Pain in legs when walking</td>
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<td></td>
<td>Swelling of the ankles</td>
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<td>Need to sleep in an elevated position with several pillows</td>
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**G-U SYSTEM**

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<td></td>
<td>Get up at night to urinate frequently</td>
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<td></td>
<td>Frequent thirst</td>
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<td>History of kidney stones, kidney disease</td>
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**G.I. TRACT**

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<tr>
<td></td>
<td>Eating disorder (e.g. anorexia, bulimia)</td>
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</table>
[ ] Yellow jaundice
  If yes, when____________________________________________

[ ] Hepatitis
  If yes, when____________________________________________

[ ] Poor appetite
[ ] Frequent indigestion or heartburn
[ ] Tarry (black) stool
[ ] Frequent nausea or vomiting
[ ] Intolerance of fatty foods
[ ] Changes in bowel habits
[ ] Persistent constipation
[ ] Frequent diarrhea
[ ] Rectal bleeding
[ ] Unusually foul smelling or floating stools
[ ] Pancreatitis

Nervous System
[ ] Alcohol problem
[ ] Alcohol use
  If yes, how many drinks ingested per week? _________________

[ ] Frequent or severe headaches
[ ] Stroke
[ ] Attacks of staggering, loss of balance, dizziness
[ ] Persistent or recurrent numbness or tingling of hands or feet
[ ] Episode of difficulty in talking
[ ] Prolonged periods of feeling depressed or “blue”
[ ] Difficulty in concentrating
[ ] Suicidal thoughts
[ ] Have had psychiatric help

Have you ever passed out during or after exertion? YES NO
Do you have a family history of coronary artery disease YES NO
If yes, who? (grandparents, parents, siblings, uncles, and aunts)

Are there any other reasons not mentioned above that you feel you should not participate in this research study? YES NO

Do you currently smoke cigarettes? YES NO
Do you currently use any smokeless tobacco products? YES NO
APPENDIX F

INFORMED CONSENT
Appendix F

Informed Consent

Informed Consent to Participate in a Research Study

Study Title: BDNF Val66Met polymorphism effects during dynamic cycling in individuals with Parkinson’s disease

Principal Investigator: Angela Ridgel, PhD
Co-Investigators: Sara Harper, MS; Brandon Pollock, PhD; Dana Ault, MS

You are being invited to participate in a research study. This consent form will provide you with information on the research project, what you will need to do, and the associated risks and benefits of the research. Your participation is voluntary. Please read this form carefully. It is important that you ask questions and fully understand the research in order to make an informed decision. You will receive a copy of this document to take with you.

Purpose:
There are two purposes of this study. First, determine if a gene affects cognition, depression, quality of life, and motor symptoms in individuals with Parkinson’s disease. Second, determine if a gene variation affects cycling performance. People who participate in this study will be randomly assigned into 4 sessions of cycling or 4 sessions of seated stretching. During this study, information will be collected on cognition, depression, quality of life, motor symptoms, and a gene. This information will help with future exercise treatments for individuals with Parkinson’s disease.

Procedures:
If you choose to participate in this study then you will be asked to visit Kent State University’s Exercise Science lab for 4 sessions of cycling or seated stretching. On the first day, you will visit with the researcher. During this time, the researcher will further explain the study, show you the equipment and explain how to use it, and record it. The recorded information will include a few assessments. Below is a description of the information and tests that will be recorded.

WebNeuro® Cognition Test: Values of cognition will be recorded. This will take about 30 minutes.

Montreal Cognitive Assessment (MoCA): Values of global cognitive function and will be recorded. This will take about 10 minutes.

Beck Depression Inventory-II (BDI-II): Values of depression will be measured in a 21-item questionnaire. This will take about 10 minutes.

EQ-5D-3L QOL: A questionnaire will ask about health status and quality of life in individuals with Parkinson’s disease. This will take about 10 minutes.
SNP Genotyping: A gene will be measured through a saliva test. This will require you to spit in a tube and will take about 5 minutes.

Kinesia One: Motor symptoms of Parkinson's disease will be measured with a small finger device. This will take about 10 minutes.

If you are assigned to the cycling group you will be asked to visit Exercise Science lab for 4 sessions. Each visit will be between by a day of rest. On your first visit, you will meet with the researcher to record cognition, depression, quality of life, and motor symptoms. Next, you will be asked to complete 40 minutes of cycling. Cycling will include a 5 minute warm-up pedaling at 40-50 revolutions per minute (rpm), 30 minutes of cycling at 75-85 rpm, and a 5 minute cool down at 40-50 rpm. On sessions 2-3 you will perform the same cycling task. On session 4, researchers will record cognition, depression, quality of life, and motor symptoms. There will be no cycling on session 4. Session 4 completes the study and you will no longer need to come to the Exercise Science lab.

If you are assigned to the seated stretching group you will be asked to Exercise Science lab for 4 sessions. Each visit will be between by a day of rest. On your first visit, you will meet with the researcher to record cognition, depression, quality of life, and motor symptoms. Then you will be asked to complete 40 minutes of seated stretching. On sessions 2-3 you will perform the same seated stretching task. On session 4, researchers will record cognition, depression, quality of life, and motor symptoms. Session 4 completes the study and you will no longer need to come to Exercise Science lab.

Criteria for Inclusion/Exclusion:
Inclusion: To be included in this study you must be diagnosed with Idiopathic Parkinson's disease and be between the ages of 50-79 years. Also, you may not have any medical conditions such as cardiovascular disease or stroke, and you need to be able to follow simple instructions.

Exclusion: You will not be eligible to participate in this study if you have, uncontrolled movement, and any history of brain (stroke, multiple sclerosis), heart (recent heart surgery, pacemaker), or bone condition (broken bone, bone fracture) that limits your ability to participate in exercise.

Benefits
Both groups can benefit from information given to them regarding their cognition, depression, quality of life, and genes. Both groups may have better cognition, less depression, better quality of life, and less motor symptoms. The results of this study will provide important information on the effect of a gene during cycling and seated stretching in individuals with Parkinson's disease.
Risks and Discomforts
There are risks and discomforts associated with exercising, such as heart attack, stroke, muscle injury, and muscle soreness. Every effort will be made to minimize these risks by using the information you provide in your pre-exercise medical screening. The research personnel are trained in basic cardiac life support and there is an Automatic External Defibrillator (AED) in the lab. If the exercise intensity is too hard you may rest at any time. Your exercise intensity will be monitored by a device called a heart rate monitor and you will be asked on a regular basis while at the lab. If at any time you are uncomfortable please inform the research personnel and they will stop the session. Emergency services can be called for injuries or any other circumstances. Your medical insurance will be billed for any emergency services that are performed by medical staff.

Privacy and Confidentiality
All results will be kept private. Any identifying information will be kept in a secure location and only the researchers will have access to this information. Individuals who participate in this study will not be identified in any publication or presentation of research results. Your personal information, such as your name and date of birth, will be removed as soon as possible. Only information you have disclosed to the researchers will be collected, such as your health history. Your research information may, in certain circumstances, be disclosed to the Institutional Review Board (IRB), which oversees research at Kent State University, or to certain federal agencies. Privacy may not be maintained if you indicate that you may do harm to yourself or others.

Your research information may, in certain circumstances, be disclosed to the Institutional Review Board (IRB), which oversees research at Kent State University, or to certain federal agencies. Specifically, the questionnaires include questions about thoughts of suicide and harming self or others. If you indicate that you might harm yourself or others, confidentiality may be broken.

Compensation
If you take part in this research study, you will be compensated with a $10.00 gift card for each session. Both groups will receive a total of $40.00 for 4 sessions.

Medical treatment by the University Health Center is provided only to currently registered students. Please be advised that for all other injuries, emergency services will be called for those occurring on the Kent State University campus. You or your medical insurance will be billed for this service. No other medical treatment or financial compensation for injury from participation in this research project is available.

Voluntary Participation

BDNF Val66Met polymorphism effects during dynamic cycling in individuals with Parkinson’s disease

Page 3 of 4
Taking part in this research study is entirely up to you. You may choose not to participate or you may discontinue your participation at any time without penalty or loss of benefits to which you are otherwise entitled. You will be informed of any new, relevant information that may affect your health, welfare, or willingness to continue your study participation.

**Contact Information**
If you have any questions or concerns about this research, you may contact Dr. Angela Ridgel at 330.672.7495 or Sara Harper at 440.227.3722. This project has been approved by the Kent State University Institutional Review Board. If you have any questions about your rights as a research participant or complaints about the research, you may call the IRB at 330.672.2704.

**Consent Statement and Signature**
I have read this consent form and have had the opportunity to have my questions answered to my satisfaction. I voluntarily agree to participate in this study. I understand that a copy of this consent will be provided to me for future reference.

Participant Signature

Date

---

BDNF Val66Met polymorphism effects during dynamic cycling in individuals with Parkinson’s disease

Page 4 of 4
APPENDIX G

RESEARCH FLYER
Appendix G

Advertising Flyer

Dynamic cycling & static stretching effects in individuals with Parkinson’s disease

Purpose:
1) Determine if BDNF Val66Met polymorphism predicts cognition, depression and quality of life.

2) Determine if presence of Val66Met polymorphism predicts the dynamic cycling or static stretching response.

What is involved?
Participants will be randomized into either:
1) Static stretching group visiting the lab for 4 sessions
2) Dynamic cycling group visiting the lab for 4 sessions

You may qualify for this research study if you:
✓ Are between the ages of 50–79 years old
✓ Diagnosed with idiopathic PD
✓ Free of contraindications to exercise
✓ Receive physician approval to participate
✓ Had no surgical procedures related to PD

For more information please contact:
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330-422-8014

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APPENDIX H
DATA SHEETS AND PROTOCOLS
## Research Overview

<table>
<thead>
<tr>
<th>Task (time)</th>
<th>Session 1</th>
<th>Session 2</th>
<th>Session 3</th>
<th>Session 4</th>
</tr>
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<tbody>
<tr>
<td>WebNeuro ® Battery (30 minutes)</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
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<tr>
<td>MoCA (10 minutes)</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>BDI-II (10 minutes)</td>
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<td>X</td>
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<tr>
<td>ED-5Q Quality of life (10 minutes)</td>
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<td>X</td>
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<tr>
<td>Genotyping (5 minutes)</td>
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<tr>
<td>Kinesia One (10 minutes)</td>
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<tr>
<td>Dynamic Cycling (40 minutes)</td>
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<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>
Research Procedure

Participant recruitment: telephone pre-screening of participants: AHA/ACSM Questionnaire

Session 1
a. Greet participant in parking lot and escort into the 165 Gym Annex Applied Physiology Lab (5 minutes)
b. Review the informed consent with participant (10 minutes)
c. Participants are randomized into groups (draw from envelope)
d. Anthropometric Measures (5 minutes)
   - Weight
   - Height
   - Years Old
e. Collect functional assessment data
   - WebNeuro® Battery (30 minutes)
   - MoCA (10 minutes)
   - BDI-II (5 minutes)
   - QUALITY OF LIFE (5 minutes)
   - SNP Genotyping (5 minutes)
   - Kinesia One (10 minutes)
f. Groups perform either dynamic cycling or stretching protocol
   - Dynamic Cycling Protocol (40)
   - Static Stretching Protocol (40)

Session 2
g. Group Sessions
   - Dynamic Cycling Protocol (40)
   - Static Stretching Protocol (40)

Session 3
h. Group Sessions
   - Dynamic Cycling Protocol (40)
   - Static Stretching Protocol (40)

Session 4
i. Functional Assessments
   - WebNeuro (30)
   - MoCA (10)
   - BDI (5)
   - QUALITY OF LIFE (5)
   - Kinesia One (10)
WebNeuro® Protocol

Subject Number: _______________________ Date: _______________________

Researcher: WebNeuro is an objective assessment of cognitive strengths and weaknesses. Use the participant’s assigned research code to log-in the participant. The participant will complete the testing battery that includes sensorimotor, attention, executive function, memory and social cognition domains. The protocol should take approximately 30 minutes to complete. The WebNeuro® report is given shortly after completion of the assessment.

Login Username: _______________

Login Password: _______________

Researcher: Once the participant has completed the WebNeuro® protocol log-out of the laboratory computer.

Researcher: Initial once the participants has successfully completed the WebNeuro® protocol.

Researcher’s Initials: ____________
Montreal Cognitive Assessment (MoCA) Protocol

Subject Number:_________________________ Date:_________________________

Researchers: MoCA will be scored by two independent research personnel to ensure reliability of results.

Researcher: The Montreal Cognitive Assessment (MoCA) was designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuocostructional skills, conceptual thinking, calculations, and orientation. Time to administer the MoCA is approximately 10 minutes. The total possible score is 30 points; a score of 26 or above is considered normal.

1. Alternating Trail Making:
   **Administration:** The examiner instructs the subject: “Please draw a line, going from a number to a letter in ascending order. Begin here [point to (1)] and draw a line from 1 then to A then to 2 and so on. End here [point to (E)].”
   **Scoring:** Allocate one point if the subject successfully draws the following pattern: 1 –A- 2- B- 3- C- 4- D- 5- E, without drawing any lines that cross. Any error that is not immediately self-corrected earns a score of 0.

2. Visuocostructional Skills (Cube):
   **Administration:** The examiner gives the following instructions, pointing to the cube: “Copy this drawing as accurately as you can, in the space below.”
   **Scoring:** One point is allocated for a correctly executed drawing. • Drawing must be three-dimensional • All lines are drawn • No line is added • Lines are relatively parallel and their length is similar (rectangular prisms are accepted) A point is not assigned if any of the above-criteria are not met.

3. Visuocostructional Skills (Clock):
   **Administration:** Indicate the right third of the space and give the following instructions: “Draw a clock. Put in all the numbers and set the time to 10 past 11.”
   **Scoring:** One point is allocated for each of the following three criteria: • Contour (1 pt.): the clock face must be a circle with only minor distortion acceptable (e.g., slight imperfection on closing the circle); • Numbers (1 pt.): all clock numbers must be present with no additional numbers; numbers must be in the correct order and placed in the approximate quadrants on the clock face; Roman numerals are acceptable; numbers can be placed outside the circle contour; • Hands (1 pt.): there must be two hands jointly indicating the correct time; the hour hand must be clearly shorter than the minute hand; hands must be centered within the clock face with their junction close to the clock center. A point is not assigned for a given element if any of the above-criteria are not met.
4. Naming:
Administration: Beginning on the left, point to each figure and say: “Tell me the name of this animal.”
Scoring: One point each is given for the following responses: (1) lion (2) rhinoceros or rhino (3) camel or dromedary.

5. Memory:
Administration: The examiner reads a list of 5 words at a rate of one per second, giving the following instructions: “This is a memory test. I am going to read a list of words that you will have to remember now and later on. Listen carefully. When I am through, tell me as many words as you can remember. It doesn’t matter in what order you say them.” Mark a check in the allocated space for each word the subject produces on this first trial. When the subject indicates that (s)he has finished (has recalled all words), or can recall no more words, read the list a second time with the following instructions: “I am going to read the same list for a second time. Try to remember and tell me as many words as you can, including words you said the first time.” Put a check in the allocated space for each word the subject recalls after the second trial. At the end of the second trial, inform the subject that (s)he will be asked to recall these words again by saying, “I will ask you to recall those words again at the end of the test.”
Scoring: No points are given for Trials One and Two.

6. Attention:
Forward Digit Span:
Administration: Give the following instruction: “I am going to say some numbers and when I am through, repeat them to me exactly as I said them.”
Read the five number sequence at a rate of one digit per second.
Backward Digit Span:
Administration: Give the following instruction: “Now I am going to say some more numbers, but when I am through you must repeat them to me in the backwards order.”
Read the three number sequence at a rate of one digit per second. Scoring: Allocate one point for each sequence correctly repeated, (N.B.: the correct response for the backwards trial is 2-4-7).
Vigilance:
Administration: The examiner reads the list of letters at a rate of one per second, after giving the following instruction: “I am going to read a sequence of letters. Every time I say the letter A, tap your hand once. If I say a different letter, do not tap your hand.”
Scoring: Give one point if there is zero to one errors (an error is a tap on a wrong letter or a failure to tap on letter A).
Serial 7s:
Administration: The examiner gives the following instruction: “Now, I will ask you to count by subtracting seven from 100, and then, keep subtracting seven from your answer until I tell you to stop.” Give this instruction twice if necessary.

Scoring: This item is scored out of 3 points. Give no (0) points for no correct subtractions, 1 point for one correction subtraction, 2 points for two-to-three correct subtractions, and 3 points if the participant successfully makes four or five correct subtractions. Count each correct subtraction of 7 beginning at 100. Each subtraction is evaluated independently; that is, if the participant responds with an incorrect number but continues to correctly subtract 7 from it, give a point for each correct subtraction. For example, a participant may respond “92 – 85 – 78 – 71 – 64” where the “92” is incorrect, but all subsequent numbers are subtracted correctly. This is one error and the item would be given a score of 3.

7. Sentence repetition:
Administration: The examiner gives the following instructions: “I am going to read you a sentence. Repeat it after me, exactly as I say it [pause]: I only know that John is the one to help today.” Following the response, say: “Now I am going to read you another sentence. Repeat it after me, exactly as I say it [pause]: The cat always hid under the couch when dogs were in the room.”

Scoring: Allocate 1 point for each sentence correctly repeated. Repetition must be exact. Be alert for errors that are omissions (e.g., omitting “only,” “always”) and substitutions/additions (e.g., “John is the one who helped today;” substituting “hides” for “hid,” altering plurals, etc.).

8. Verbal fluency:
Administration: The examiner gives the following instruction: “Tell me as many words as you can think of that begin with a certain letter of the alphabet that I will tell you in a moment. You can say any kind of word you want, except for proper nouns (like Bob or Boston), numbers, or words that begin with the same sound but have a different suffix, for example, love, lover, loving. I will tell you to stop after one minute. Are you ready? [Pause] Now, tell me as many words as you can think of that begin with the letter F. [time for 60 sec]. Stop.”

Scoring: Allocate one point if the subject generates 11 words or more in 60 sec. Record the subject’s response in the bottom or side margins.

9. Abstraction:
Administration: The examiner asks the subject to explain what each pair of words has in common, starting with the example: “Tell me how an orange and a banana are alike.” If the subject answers in a concrete manner, then say only one additional time: “Tell me another way in which those items are alike.” If the subject does not give the appropriate response (fruit), say, “Yes, and they are also both fruit.” Do not give any additional instructions or clarification. After the practice trial, say: “Now, tell me how a train and a bicycle are alike.” Following the response, administer the second trial,
saying: “Now tell me how a ruler and a watch are alike.” Do not give any additional instructions or prompts.
Scoring: Only the last two item pairs are scored. Give 1 point to each item pair correctly answered. The following responses are acceptable: Train-bicycle = means of transportation, means of travelling, you take trips in both; Ruler-watch = measuring instruments, used to measure. The following responses are not acceptable: Train-bicycle = they have wheels; Ruler watch = they have numbers.

10. Delayed recall:
Administration: The examiner gives the following instruction: “I read some words to you earlier, which I asked you to remember. Tell me as many of those words as you can remember.” Make a check mark (✓) for each of the words correctly recalled spontaneously without any cues, in the allocated space.
Scoring: Allocate 1 point for each word recalled freely without any cues.

11. Orientation:
Administration: The examiner gives the following instructions: “Tell me the date today.” If the subject does not give a complete answer, then prompt accordingly by saying: “Tell me the [year, month, exact date, and day of the week].” Then say: “Now, tell me the name of this place, and which city it is in.”
Scoring: Give one point for each item correctly answered. The subject must tell the exact date and the exact place (name of hospital, clinic, and office). No points are allocated if subject makes an error of one day for the day and date.
TOTAL SCORE: Sum all sub scores listed on the right-hand side. Add one point for an individual who has 12 years or fewer of formal education, for a possible maximum of 30 points. A final total score of 26 and above is considered normal. Data Collection:
Researcher 1 total raw score count: __ Researcher 2 total raw score count:
MONTREAL COGNITIVE ASSESSMENT (MOCA®)  
Version 7.2 Alternative Version

NAME:  
Education:  
Sex:  
Date of birth:  
DATE:  

VISUOSPATIAL / EXECUTIVE

Copy rectangle

Draw CLOCK (Five past four)  
(3 points)

NAMING

MEMORY

Read list of words, subject must
repeat them. Do 2 trials, even if 1st trial is successful.
Do a recall after 5 minutes.

TRUCK  BANANA  VIOLIN  DESK  GREEN

1st trial

2nd trial

ATTENTION

Read list of digits (1 digit/sec.). Subject has to repeat them in the forward order
Subject has to repeat them in the backward order

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥2 errors


[ ] 3 2 9 6 5

[ ] 8 5 2

Serial 7 subtraction starting at 90

[ ] 83

[ ] 78

[ ] 89

[ ] 62

[ ] 55

4 or 5 correct subtractions: 3 pts. 2 or 3 correct: 2 pts. 1 correct: 1 pt. 0 correct: 0 pt

LANGUAGE

Repeat: A bird can fly into closed windows when it’s dark and windy. [ ]
The caring grandmother sent groceries over a week ago. [ ]

Fluency / Name maximum number of words in one minute that begin with the letter S

[ ] ______ (N ≥ 11 words)

ABSTRACTION

Similarity between e.g. carrot - potato = vegetable [ ] diamond - ruby [ ] cannon - rifle

DELAYED RECALL

Has to recall words

WITH NO CUE

TRUCK  BANANA  VIOLIN  DESK  GREEN

Points for UNCUESD recall only

Optional

Category cue

Multiple choice cue

ORIENTATION

[ ] Date  [ ] Month  [ ] Year  [ ] Day  [ ] Place  [ ] City

Adapted by: Z. Nasreddine MD, N. Phillips PhD, H. Chertkow MD
© Z. Nasreddine MD  www.mocatest.org

Normal: ≥26 / 30

TOTAL: ______ / 30

Add 1 point if ≤12 yr edu
Beck Depression Inventory-II Protocol

Subject Number: ____________________  Date: ____________________

The Beck Depression Inventory–II (BDI-II) was revised in 1996 and consists of a 21-item self-report multiple-choice inventory. The questionnaire takes approximately 10 minutes to complete.

BDI-II is scored on a 4-point scale ranging from 0 to 3 based on severity of each item. The maximum total score is 63.

<table>
<thead>
<tr>
<th>Raw Scores</th>
<th>Depression Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-13</td>
<td>Indicates minimal depression</td>
</tr>
<tr>
<td>14-19</td>
<td>Indicates mild depression</td>
</tr>
<tr>
<td>20-28</td>
<td>Indicates moderate depression</td>
</tr>
<tr>
<td>29-63</td>
<td>Indicates severe depression</td>
</tr>
</tbody>
</table>

Researcher:
- Read to participants: “This questionnaire consists of 21 groups of statements. Please read each group of statements carefully then pick out the one statement in each group that best describes the way you have been feeling during the past two weeks, including today. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including items 16 and 18.
- Distribute BDI-II.
- Collect BDI-II.

Data Collection:
Researcher 1 total raw score count: _______ Researcher 2 total raw score count: _______
Name: ___________________________ Marital Status: ________ Age: ________ Sex: ________
Occupation: _________________________ Education: _________________________

**Instructions:** This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including today**. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. **Sadness**
   0. I do not feel sad.
   1. I feel sad much of the time.
   2. I am sad all the time.
   3. I am so sad or unhappy that I can’t stand it.

2. **Pessimism**
   0. I am not discouraged about my future.
   1. I feel more discouraged about my future than I used to be.
   2. I do not expect things to work out for me.
   3. I feel my future is hopeless and will only get worse.

3. **Past Failure**
   0. I do not feel like a failure.
   1. I have failed more than I should have.
   2. As I look back, I see a lot of failures.
   3. I feel I am a total failure as a person.

4. **Loss of Pleasure**
   0. I get as much pleasure as I ever did from the things I enjoy.
   1. I do not enjoy things as much as I used to.
   2. I get very little pleasure from the things I used to enjoy.
   3. I can’t get any pleasure from the things I used to enjoy.

5. **Guilty Feelings**
   0. I don’t feel particularly guilty.
   1. I feel guilty over many things I have done or should have done.
   2. I feel quite guilty most of the time.
   3. I feel guilty all of the time.

6. **Punishment Feelings**
   0. I don’t feel I am being punished.
   1. I feel I may be punished.
   2. I expect to be punished.
   3. I feel I am being punished.

7. **Self-Dislike**
   0. I feel the same about myself as ever.
   1. I have lost confidence in myself.
   2. I am disappointed in myself.
   3. I dislike myself.

8. **Self-Criticalness**
   0. I don’t criticize or blame myself more than usual.
   1. I am more critical of myself than I used to be.
   2. I criticize myself for all of my faults.
   3. I blame myself for everything bad that happens.

9. **Suicidal Thoughts or Wishes**
   0. I don’t have any thoughts of killing myself.
   1. I have thoughts of killing myself, but I would not carry them out.
   2. I would like to kill myself.
   3. I would kill myself if I had the chance.

10. **Crying**
    0. I don’t cry any more than I used to.
    1. I cry more than I used to.
    2. I cry over every little thing.
    3. I feel like crying, but I can’t.
11. Agitation
0  I am no more restless or wound up than usual.
1  I feel more restless or wound up than usual.
2  I am so restless or agitated that it’s hard to stay still.
3  I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest
0  I have not lost interest in other people or activities.
1  I am less interested in other people or things than before.
2  I have lost most of my interest in other people or things.
3  It’s hard to get interested in anything.

13. Indecisiveness
0  I make decisions as well as ever.
1  I find it more difficult to make decisions than usual.
2  I have much greater difficulty in making decisions than I used to.
3  I have trouble making any decisions.

14. Worthlessness
0  I do not feel I am worthless.
1  I don’t consider myself as worthwhile and useful as I used to.
2  I feel more worthless as compared to other people.
3  I feel utterly worthless.

15. Loss of Energy
0  I have as much energy as ever.
1  I have less energy than I used to have.
2  I don’t have enough energy to do very much.
3  I don’t have enough energy to do anything.

16. Changes in Sleeping Pattern
0  I have not experienced any change in my sleeping pattern.
1a  I sleep somewhat more than usual.
1b  I sleep somewhat less than usual.
2a  I sleep a lot more than usual.
2b  I sleep a lot less than usual.
3a  I sleep most of the day.
3b  I wake up 1-2 hours early and can’t get back to sleep.

17. Irritability
0  I am no more irritable than usual.
1  I am much more irritable than usual.
2  I am irritable all the time.

18. Changes in Appetite
0  I have not experienced any change in my appetite.
1a  My appetite is somewhat less than usual.
1b  My appetite is somewhat greater than usual.
2a  My appetite is much less than before.
2b  My appetite is much greater than usual.
3a  I have no appetite at all.
3b  I crave food all the time.

19. Concentration Difficulty
0  I can concentrate as well as ever.
1  I can’t concentrate as well as usual.
2  It’s hard to keep my mind on anything for very long.
3  I find I can’t concentrate on anything.

20. Tiredness or Fatigue
0  I am no more tired or fatigued than usual.
1  I get more tired or fatigued more easily than usual.
2  I am too tired or fatigued to do a lot of the things I used to do.
3  I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex
0  I have not noticed any recent change in my interest in sex.
1  I am less interested in sex than I used to be.
2  I am much less interested in sex now.
3  I have lost interest in sex completely.
Quality of Life EQ-5D-3L Protocol

Subject Number:_________________________ Date:_________________________

Researcher: The Euro EQ-5D-3L paper questionnaire is a self-reported health status and should take approximately 10 minutes to complete. The EQ-5D is a valid instrument to measure quality of life in Parkinson’s disease and reflects the severity and complications of the disease. It assesses mobility, self-care, usual activities, pain, psychological functioning, and visual analog scale.

Researcher: Initial once the participants has successfully completed the battery.

Researcher’s Initials:___________
Health Questionnaire

English version for the USA
By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

**Mobility**
- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

**Self-Care**
- I have no problems with self-care
- I have some problems washing or dressing myself
- I am unable to wash or dress myself

**Usual Activities (e.g. work, study, housework, family or leisure activities)**
- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

**Pain / Discomfort**
- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

**Anxiety / Depression**
- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed
To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today

---

USA (English) © 1998 EuroQol Group EQ-5D® is a trade mark of the EuroQol Group
Single Nucleotide Polymorphism (SNP) Protocol

Genetics SNP Protocol

Subject Number: ______________________  Date: ______________________

Researcher: Participants can choose whether they want to know their results from BDNF Val66Met Polymorphism

Prior to collection participants will be instructed to refrain from eating or drinking for at least 60 minutes.

Testing for BDNF Val66Met Polymorphism will occur during session 1 pre-intervention assessment.

**SNP Genotyping:** The BDNF Val66Met polymorphism will be tested through saliva using an Oragene DNA collection kit (DNA Genotek, Inc., Ottawa, ON, Canada) for DNA extraction taking approximately 5 minutes.

One saliva sample for each participant will be collected following the manufacturer’s instructions.

- Participants will be instructed to rub their tongues around the inside of their mouths for about 15 seconds.
- Participants will then deposit approximately 2 milliliters saliva into the collection cup.
- The cap will be placed over the vial and closed firmly.
- Researchers will then hold the tube upright, unscrewing the funnel from the tube.
- The collection cup will then be shaked for 5 seconds and discard the funnel.
- Researchers will then label the tube with the participant’s research code.
- This phase of DNA isolation stabilizes the saliva sample for long-term storage at room temperature in the Exercise Physiology Biochemistry laboratory.

Participants:

1) Do you want to know your results for BDNF Val66Met Polymorphism?

   YES______________  NO______________

Researchers: **Label participant’s tube with the participant’s research code**
**Dynamic Cycling Protocol**

The dynamic cycling protocol takes place at the end of session 1 – session 6. Participants will wear a Polar Wearlink+ Coded Transmitter to collect heart rate (HR). A programmable logic controller (PLC) will determine the appropriate motor speed and load values and send this information back to the motor drive.

Each dynamic cycling session will begin with a 5 minute warm-up (40-50 rpm). Next the participants will complete 30 minutes of dynamic cycling (75-85 rpm) and finish with a 5 minute cool-down (40-50 rpm). During the dynamic cycling rating of perceived exertion (RPE) and HR will be recorded by a researcher. Participants will be encouraged to maintain 50-80% HR reserve.

**Researcher:**
- Adjust seat height (place bolt in 1st hole behind seat)
- Mount participant’s feet on pedals before motor is turned “ON”
- Secure the feet straps
- Ensure that loose clothing and shoe laces are secured

**Smart Bike Data Computer Collection Instructions:**
- Open KSU Bike Final on the desktop (Bike Project folder)
- Click “Yes”
- KSU Bike Final.mer run application
- Dynamic load active button then hit control
  - The time of day including second must be recorded. For example 4:15:10pm.
  - Note the time of day at the completion of the dynamic cycling protocol. See above.
- Run RS View Enterprise File to view with log file
  - File is loaded into c:\logs\data_log
  - Change file types visible
  - Open – change file type to .csv
  - Save file as CSV – change name of the file. For example PD_DC_Session_1.csv
- Next delete data_log file before starting next subject data collection.
  - Note the data log file will automatically be overwritten when another participant begins their session.
<table>
<thead>
<tr>
<th>Time</th>
<th>HR</th>
<th>RPE</th>
<th>Torque</th>
<th>Cadence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-warm-up</td>
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<td>5 minutes</td>
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<td>30 minutes</td>
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<tr>
<td>Cool-down finish</td>
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</tbody>
</table>

Subject Number: ______________________

Session 1: Date:

<table>
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<tr>
<th>Time</th>
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<th>Torque</th>
<th>Cadence</th>
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<tr>
<td>Cool-down finish</td>
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</tbody>
</table>

Subject Number: ______________________

Session 2: Date:

<table>
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<th>Torque</th>
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</thead>
<tbody>
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<tr>
<td>Cool-down finish</td>
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Session 3: Date:

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<thead>
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<th>Torque</th>
<th>Cadence</th>
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<td>30 minutes</td>
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<tr>
<td>Cool-down finish</td>
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Borg Scale

<table>
<thead>
<tr>
<th>Rating</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>6</td>
<td>No exertion at all</td>
</tr>
<tr>
<td>7</td>
<td>Extremely light</td>
</tr>
<tr>
<td>8</td>
<td>Very light</td>
</tr>
<tr>
<td>9</td>
<td>Light</td>
</tr>
<tr>
<td>10</td>
<td>Somewhat hard</td>
</tr>
<tr>
<td>11</td>
<td>Hard (heavy)</td>
</tr>
<tr>
<td>12</td>
<td>Very hard</td>
</tr>
<tr>
<td>13</td>
<td>Extremely hard</td>
</tr>
<tr>
<td>14</td>
<td>Maximal exertion</td>
</tr>
</tbody>
</table>
RPR-1

Research Participant Receipt 1 (RPR-1)

Kent State University (KSU) is required to maintain the confidentiality of information about research study participants while still complying with record keeping requirements of the State of Ohio, the Internal Revenue Service (IRS), and funding agencies. This form serves as documentation of receipt of compensation by individuals participating in research studies conducted by KSU personnel and is used to obtain information to comply with IRS reporting requirements.

1. I, [Participant's Name], have received or am requesting compensation in the form and amount indicated below:

- [ ] Cash $__________
- [ ] Check $__________
- [ ] Gift Certificate/Card $__________

[Signature]  Date

TO KSU PERSONNEL:
This form is to be used for research participants receiving $575 and the total of payments received for participation in the entire project = $500. If a research participant chooses not to provide their name, address, and taxpayer identification number they can choose to participate in the research without receiving compensation.

If a KSU check needs to be issued for payment, complete a Check Request form and submit to Accounts Payable, Schwartz Center Room 227. Do not attach a copy of this form to the request.

RPR-1 (revision 1.0)
For use when a research participant receives $575 and total payment for participation in research = $500
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