Fall 10-4-2021

The Impact of High Intensity Interval Training on Neurogenesis and Angiogenesis in the Dentate Gyrus

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by

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This dissertation is submitted in partial fulfillment of the requirements for the

Doctor of Philosophy Degree

School of Health and Medical Sciences

Department of Interprofessional Health Sciences and Health Administration

Seton Hall University

Nutley, NJ

2021

APPROVAL FOR SUCCESSFUL DEFENSE

SETON HALL UNIVERSITY

School of Health and Medical Sciences

APPROVAL FOR SUCCESSFUL DEFENSE

Darrin A. Lenhart, has successfully defended and made the required modifications to the text of the doctoral dissertation for the Doctor of Philosophy in Health Sciences for the Fall, 2021.

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Acknowledgements

First and foremost, I would like to thank my committee members for their help and support throughout this entire journey. Were it not for their willingness to help me grow and develop, I would never have made it through. Especially to my chair, Dr. Zipp, your tireless efforts are immeasurable, and I cannot thank you enough for all you have done. To my family, without your love and support I could never have made it through and cannot express how much that means to me. To my brother, Brian, you were my first role model, and I appreciate all that you have done for me. To my children, Maura, Caelee and Daniel, each of you is growing into wonderful young adults. I love you all for challenging me to be a better person. I am so appreciative to each of you for showing me how to love in ways I never knew, and I am so proud of all three of you in so many different ways. Finally, to my wife, Clare. My partner, my best friend, and the love of my life. You have helped me grow into the man I always wanted to be and can't possibly put into words what that means to me. Thank you for being willing to walk this path together with me and being unwavering in your support.

Dedication

This dissertation is dedicated to my parents, Keith, and Linda. Everything I know and everything I am now, is a direct result of the lessons, guidance, love, and endless support you provided, and continue to provide. Through your examples, I was able to see very closely what work ethic, faith and love are and have been fortunate enough to be able to use them as a model for becoming the man I am now. None more so evident then when we lost dad on April 19th, 2021, during the final week of testing for this study. Were it not for those lessons of perseverance and faith, I would never have made it through that time. Thank you, mom, for all that you sacrificed for us and for all you've done, and, although no longer with us physically, dad, your legacy lives on in all of us. Until we meet again…and we will meet again.

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Abstract

BACKGROUND: Exercise is associated with improved neuronal health and longevity, synaptic plasticity, cerebral blood volume, overall brain volume, and neurogenesis which collectively may have the power to forestall neurodegenerative disease.

PURPOSE: This study aims to explore the impact of high intensity interval training on individuals with mild cognitive impairment using a range of cognitive, physiological, and biomechanical measures. Specifically, this study seeks to assess the impact of high intensity interval training on neurogenesis and angiogenesis in the dentate gyrus of individuals with mild cognitive impairment versus healthy age-matched controls, as assessed by urinalysis of BDNF levels, performance on the Rey Auditory Verbal Learning Test, and postural sway as measured by observing sway variability using force plates. **METHODS:** The indices of neurogenesis and angiogenesis were assessed using the surrogate measures of maximal oxygen uptake (VO_{2max}), cognitive function as assessed by the Rey auditory verbal learning test (RAVLT), urinalysis of brain-derived neurotrophic factor (BDNF), and medio-lateral sway jerk taken just prior to and just after a six-week training protocol. Fourteen adult males were randomized into either high intensity interval training group (HIIT) (N=7) or a control group (N=7) and were compared over the course of a six-week supervised training study.

RESULTS: Significant post-protocol changes were observed among experimental (e) versus control (c) group participants in VO_2 (e=3.16ml/kg/min, c=-1.16ml/kg/min; p=0.008), cognitive function as assessed by the RAVLT (e=2.29, c=.14, p<.001) and postural control (e=-.35, c=6.5; p<.001). Findings reflect a positive association between increased VO_2 and increased cognitive function (r=0.61 p=0.02), and negative associations between postural control and cognitive function (r=-.785, p=.001), and between postural control and VO_2 (r=-.58, p=.031).

CONCLUSION: High intensity interval training up-regulates neurogenesis and angiogenesis in the dentate gyrus. Therefore, high intensity interval training protocols, like the one used in this study, could forestall the onset of symptoms of neurodegenerative diseases that target the dentate gyrus.

Keywords: *High intensity interval training, cognitive function, neurogenesis*

CHAPTER I

Introduction

Cognitive functioning is vitally important in all stages of life. With an aging population and the associated increase in cognitive decline, opportunities to forestall age-related cognitive decline are needed. Exercise holds promise for maintaining cognitive function as one ages. Specifically, increases in the volume and intensity of exercise over time triggers increases in many critical growth and signaling proteins both peripherally and within the adult central nervous system (Yau et al., 2014). Two of these proteins are the vascular endothelial growth factor (VEGF) and the brain derived neurotrophic factor (BDNF). Expression of both proteins is known to increase with exercise and is corollary to neurogenesis and angiogenesis, the formation of new neurons and blood vessels, respectively (Pereira et al., 2007). Clinically, increased neurogenesis increases the volume of neurons in the brain. With a greater volume of neurons present at the onset of neurodegenerative diseases (i.e. diseases that decrease the volume of neurons), it will take a greater amount of time to breakdown the brain, therefore creating a prophylactic effect against neuron reduction seen in diseases like dementia, Parkinson's, and Alzheimer's, among others. In Parkinson's, and other diseases presenting with both cognitive and motor impairments, deficits in postural sway, measured against the concomitant advancement of the disease can collectively be used as an early indicator of the diseases. Therefore, given its neurogenetic effect and its potential impact on neuronal health and longevity, as well as synaptic plasticity, increased cerebral blood volume (CBV) and angiogenesis, overall brain volume, and neurogenesis, exercise could forestall the onset of symptoms of neurodegenerative diseases.

Previously, exercise studies showing increases in neurogenesis have included low volume, steady-state exercise protocols performed by human subjects (N=11 mean age=33) (Pereira et al., 2007). The subjects in these studies fell below the America Heart Association's criteria for below average aerobic fitness (VO_2 max<43 ml/kg/min for men and <37 ml/kg/min for women) (Pereira et al., 2007). Recently, investigators have begun to alter training protocols and have begun to investigate the impact on BDNF using combinations of high intensity interval (HIIT) and steady-state (SS) training protocols with college-aged, healthy adults (Marquez et al., 2015). While both training methodologies successfully achieved significant increases in BDNF acutely, interval training had more of an impact on the magnitude of change. In the same study, HIIT protocol subjects' BDNF concentration rose acutely 37.72% pre-to post, in comparison to a 23.77% increase in subjects of the steady-state protocol. This is consistent with the study by Angevaren et al. (2008) where the authors showed that aerobic exercise interventions resulted in an improvement in maximal oxygen uptake and increases in cardiorespiratory fitness of approximately 14% coincide with improved cognitive function (Angevaren et al., 2008). In summation, HIIT and steady-state training methodologies are linked with selective increases in BDNF (Marquez et al., 2015). What remains less clear in this body of research is the impact exercise induced BDNF changes may have on cognitive function and neurogenesis. Additionally, it is also unclear what the long-term impact is, and the impact that dosing strategies may have on these exercise-induced changes.

Previous researchers have shown BDNF concentration is a significant intermediary in the prevention of age-related decline and the decline in cognitive function that results from certain neurodegenerative diseases (Pereira et al., 2007; Yau et al., 2014). In theory, consistent training and physical activity could elicit a chronic, protective effect regarding cognitive decline. This

protective effect associated with exercise-induced neurogenesis would not only forestall the onset of the disease, but potentially insulate the individual from the diseased state entirely. Continued use of more prolonged and intensive HIIT and SS protocols among both trained and untrained individuals will benefit further understanding of this. The use of more intensive protocols is a novel idea and could possibly suggest that varying levels of activity could have a varied impact on neurogenesis and therefore a varied impact on forestalling certain neurodegenerative diseases. Additionally, if the onset of the disease is delayed, or eliminated entirely, the associated Medicare, Medicaid, private insurance, and out-of-pocket expenses would be at least partially alleviated.

In the early stages of neurodegenerative diseases associated with some type of cognitive decline, symptoms of mild cognitive impairment (MCI) are present in a vast majority of patients. Given that the symptoms of MCI can be identified, and this could also be indicative of the early stages of neurodegenerative disease, MCI has become a major factor for intervention. Studies have been conducted recently to document the frequency of MCI and the prevalence has been estimated to be between 15% and 20% in people 60 years and older (Petersen, 2016). Additionally, the rate in which MCI progresses to dementia varies between 8% and 15% per year and will not always result in the same disease (Ganguli et al.,2010). As such, MCI should also be a major factor for intervention studies of postural sway in neurodegenerative diseases, like Parkinson's that is not only associated with cognitive decline, but motor impairment as well.

Given that biomarkers, like BDNF, have begun to emerge in research they can be used to further direct future studies. Additionally, future study should aim to associate specific training modalities with the management of specific cognitive decline that is the result of specific diagnoses. It may also be advantageous to monitor the cumulative and chronic effects of

exercise-induced neurogenesis over a much longer period to gauge the impact different exercise protocols have on different diagnoses as well because, if varying the exercise protocol has a varying impact on cognitive function and BDNF, then it is likely that there is a specific chronic exercise blueprint associated with each neurodegenerative disease that in some way impacts cognitive function. Further, larger, and more representative samples are warranted to facilitate a better understanding of exercise's impact on cognitive function among a broader range of the population.

Statement of the Problem

To date, studies of this nature have generally included individuals with below average aerobic fitness utilizing low volume, steady-state exercise protocols and have not included individuals with lower cognitive function. Limiting studies to only these variables ignores the potential for differential changes in cognitive function, chronic changes in cognitive function, and the protective effect of BDNF. Additionally, observing only these variables in this way ignores the potential specific impact increased cardiorespiratory fitness has on cognitive function. This relationship could therefore be associated with the training intervention's effectiveness to impact the various pathways that are mediated by hippocampal BDNF and result in exercise-induced synaptic plasticity and improve cognitive function.

Purpose of the Study

This study aims to explore the impact of high intensity interval training on individuals with mild cognitive impairment using a range of cognitive, physiological, and biomechanical measures. Specifically, this study seeks to assess the impact of high intensity interval training on

neurogenesis and angiogenesis in the dentate gyrus of individuals with mild cognitive impairment versus healthy age-matched controls, as assessed by urinalysis of BDNF levels, performance on the Rey Auditory Verbal Learning Test, and postural sway as measured by observing sway variability using force plates.

Research Questions

RQ1: What is the impact of HIIT on RAVLT score?

RQ2: What is the impact of HIIT on BDNF concentration as assessed via urinalysis?

RQ 3: What is the impact of HIIT on VO_{2max}?

RQ 4 What is the impact of HIIT on postural control as measured by detrended fluctuation analysis?

RQ 5: Is there an association between ΔVO_{2max} and changes in RAVLT, BDNF and postural control?

Hypotheses

$1H_o$: There will be no change in performance on the RAVLT between experimental and control groups, and therefore no change in the corollary measurement of neurogenesis in the hippocampus from pre- to post- test.

$1H_a$: There will be a change in performance on the RAVLT between experimental and control groups, and therefore a change in the corollary measurement of neurogenesis in the hippocampus from pre- to post- test.

$2H_o$: There will be no difference in the concentration of urinary BDNF between experimental and control groups from pre- to post- test.

$2H_a$: There will be a difference in the concentration of urinary BDNF between experimental and control groups from pre- to post- test.

$3H_o$: There will be no statistically significant change in the volume of maximal oxygen uptake (VO_2max_{diff}).

$3H_a$: There will be a significant change in the volume of maximal oxygen uptake (VO_2max_{diff}).

$4H_o$: There will be no change in postural control as measured by detrended fluctuation analysis and the coefficient of variability between experimental and control groups from pre- to post- test.

$4H_a$: There will be a change in postural control as measured by detrended fluctuation analysis between experimental and control groups from pre- to post- test.

$5H_o$: There will be no association between the change in the volume of maximal oxygen uptake (VO_2max_{diff}) and changes in the RAVLT, BDNF and postural control.

$5H_a$: There will be an association between change in the volume of maximal oxygen uptake (VO_2max_{diff}) and change in the RAVLT, BDNF and postural control.

CHAPTER II

Literature Review

Cognitive function is vitally important in all stages of life as it impacts one's functional independence. With an aging population and the associated increase in cognitive decline, opportunities to forestall age-related cognitive decline are needed (Radak et al., 2001). Exercise holds promise for maintaining cognitive function given its impact on neurogenesis and angiogenesis, the formation of new neurons and blood vessels, respectively (Pereira et al., 2007). By increasing the sheer volume of neurons or accelerating the rate of response to the exercise stimulus at the cellular level neurogenesis increases the volume of neurons in the brain (Pereira et al, 2007). With a greater volume of neurons at the onset of neurodegenerative diseases (i.e. diseases that decrease the volume of neurons), it will take a greater amount of time to breakdown the brain. Therefore, up-regulating neurogenesis can have a protective effect, building resistance to diseases like dementia, Parkinson's, and Alzheimer's, among others. As a result of a greater volume of neurons at the onset of neurodegenerative disease (i.e. diseases that will decrease brain and neuronal volume), the onset of symptoms impacting both cognitive and motor function could be delayed. If this protective effect, or delay in onset of neurodegenerative disease, surpasses the life expectancy of the individual, then the individual has been insulated from the neurodegenerative disease entirely.

Observing neurogenesis in live human models has been difficult to quantify in the absence of any surrogate measures. 5-Bromo-2'-Deoxyuridine (BrdU) was developed as a thymine analog that could be taken up by neurons and was used as a labelling technique. Unfortunately, the observing of BrdU-labeled neurons was only possible post-mortem which made studying human neuronal models in this way quite difficult. Then, in a study by Eriksson et

al. (1998), terminal cancer patients were injected with BrdU in life. Postmortem observation of various aspects of the brain later led to the discovery that on average, approximately seven hundred new neurons formed in the adult hippocampus. Specifically, this study revealed that neurogenesis primarily occurred in the sub-granular zone (SGZ), the sub-ventricular zone (SVZ), and the dentate gyrus (DG) (Eriksson et al., 1998). While this was observed in cancer patients, it still leaves unanswered questions given the difficulty in observing BrdU-labelled neurons in human models, and therefore the importance of finding a corollary biomarker is paramount for those attempting to elucidate the dynamics of neurogenesis. Lommatzsch et al. (1999) identified the importance of BDNF in the peripheral nervous system (PNS) as they observed deficiencies in visceroafferent neurons and a mere three-week life expectancy for mice bred without BDNF, thus reinforcing BDNF's critical role in nervous system functioning. Additionally, these authors demonstrated that BDNF concentration in the kidneys of mice was equal to levels in the brain and that BDNF concentration in the urinary bladder exceeded levels observed in the brain. These findings support the importance of quantifying BDNF via urinalysis as a viable tool for analysis.

Additional studies related to BDNF were performed by Vaynman et al. (2004), and Koven et al. (2014) which further illustrated the significant role the protein has in the hippocampal-dependent learning and cognitive flexibility. The former observed that BDNF mediates the efficacy of exercise on synaptic plasticity and cognitive function in the hippocampus such that exercised animals performed significantly better than sedentary controls on maze tests reflective of hippocampal-dependent learning (Vaynman et al., 2004). Furthermore, when treated with an immunoadhesin chimera to block the binding of BDNF in the brain, the advantages of the exercise on performances in the maze were lost with the exercised animals performing no better than their sedentary counterparts (Vaynman et al., 2004). Lastly,

these authors were able to demonstrate this study showed downstream effects specific to the cAMP response element binding protein (CREB), and on synaptic plasticity in the animals where BDNF function was blocked, further illustrating the significance of BDNF. Additionally, it was shown that the fastest learners with the quickest response times expressed the greatest BDNF and CREB mRNA levels (Vaynman et al., 2004). While this study by Vaynman et al, (2004) provided valuable data, the experimentation was carried out using animal models. More recently, Koevn et al. (2014) observed that urinary BDNF is a viable biomarker for executive function in healthy adults. In this study, fifty-two healthy young adults completed standardized executive function tests and BDNF levels were quantified with enzyme-linked immunosorbent assay of urine samples taken at the time of testing. It was shown that BDNF concentration was positively associated with cognitive flexibility and that urinary BDNF can be used as a peripheral biomarker of cognition in healthy adults (Koven, 2014). In summary, these findings related to BDNF serve to illustrate that the protein, which can be observed via urinalysis in humans, is also a significant corollary measure for neuronal function in the hippocampus as measured in animals. As a result, this corollary measure can be used to associate the extent of the impact various exercise modalities have on cognitive function and neurogenesis.

Following from the work of Lommatzsch et al. (1999) who identified BDNF as a significant biomarker, Radak et al. (2001) showed that regular exercise increases cognitive function, and that regular exercise decreases oxidative damage due to free radicals and peroxides in the rat brain. Additionally, Palmer et al. (2000) found that neurogenesis takes place in the hippocampus and that neurogenesis is linked to the vascularization of cells in the brain and therefore supports that is must be tightly linked to angiogenesis. To this point, increased BDNF concentration in the brain has been linked to improved cognitive function, increased cell

survival, as well as more intricate neuronal connections and synaptic plasticity, and that BDNF increases with exercise (Koven, 2014, Pereira et al., 2007). Collectively, this research points to a potential link between exercise and neurogenesis but finding a definitive, *in vivo* correlate, remained elusive until Pereira et al. (2007) exploited the neuronal circuitry of the dentate gyrus, the entorhinal cortex and the hippocampal CA3 region. The dentate gyrus of the hippocampus receives excitatory neuron input from the entorhinal cortex and relays excitatory output to the hippocampal CA3 region (Pereira et al., 2007). Imaging studies have also shown a direct correlation between performance on the Rey Auditory Verbal Learning Test (RAVLT) and increases in CBV within this hippocampal circuitry (Pereira et al., 2007).

The RAVLT is a cognitive test assessing learning and memory used by Pereira et al. (2007) simultaneously with imaging to observe CBV in human subjects (N=11, mean age=33). Pereira et al. (2007) adapted this test to include twenty non-semantically or phonemically related words presented over three learning trials and incorporated a distractor list. Immediate free-recall, delayed recall after five minutes and ninety minutes are then measured. The test protocol assessed in this way provides increased variability and therefore decreases the likelihood that performance improves due to familiarization, and is both valid and reliable (Pereira et al., 2007). Since increases in CBV result from angiogenesis, and angiogenesis is tightly linked with neurogenesis, we now have an in vivo correlate to neurogenesis (Pereira et al., 2007). Indeed, these same imaging studies have shown a positive correlation between neurogenesis in the DG, and performance on the RAVLT (Pereira et al., 2007).

Further research has illustrated a potential relationship between increased neurogenesis in the dentate gyrus and forestalled onset of neurodegenerative disease. For example, in a study by Wong-Goodrich et al. (2010), whole brain irradiation (WBI) in mice was shown to mimic the

memory and cognitive deficits of those seen in human cancer patients undergoing WBI. In this study, forty adult female C57Bl/6 mice were given a single dose of either whole brain irradiation (WBI) or a sham WBI, both groups were trained in a Barnes maze. Half of the mice in both groups received daily voluntary wheel access for running one month after WBI (Wong-Goodrich et al., 2010). Daily running following WBI was observed to prevent the decline in spatial memory that was noted months after irradiation. Additionally, partial rebirth of neurons in the dentate gyrus was also shown (Wong-Goodrich et al., 2010). These findings in mice show that voluntary running can alleviate memory decline and help recover hippocampal plasticity, illustrating exercise as a potential therapeutic intervention strategy (Wong-Goodrich et al., 2010).

In a recent study by Yau et al. (2014) exercise-induced neurogenesis was shown to uniformly slow the cognitive decline associated with neurodegenerative disease in animal models. However, due to the constraints of studying these parameters in live human models, there exists some inconsistencies in the literature likely due to inherent anatomical and physiological differences in the diseased state of the rat brain versus the human brain. What is consistent is that neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) all result in the progressive loss of structure and function of neurons, and these neurodegenerative diseases are all accompanied by loss of cognitive function, including learning and memory, despite impacting different neural circuitry (Yau et al., 2014). These shared characteristics of neurodegenerative diseases in humans suggests a shared anatomical link in the circuitry of the brain. Given their shared impact on learning and memory, as well as the accompanied loss of cognitive function, the hippocampus is likely this anatomical link. Specifically, in the adult hippocampus, neurogenesis in the DG has been shown to potentially impact this loss of cognitive function, and physical activity has been shown to improve cognitive

function as well as prevent age-related cognitive decline (Yau et al., 2014). Additionally, Smith et al. (2010) performed a meta-analysis of exercise and neurocognition and reported that quantifiable changes in processing speed, memory, attention, and executive function can be observed in as little as one month of exercise in healthy adult individuals. Aerobic exercise over this minimum timeframe has also been linked to improved cognitive ability of non-demented adults and has shown that this physical activity may enhance memory performance among individuals with mild cognitive impairment (MCI) (Larrieu et al., 2002).

Although the underlying mechanism responsible for the impact of this exercise-induced hippocampal neurogenesis in adults is unclear, there is evidence that supports BDNF, VEGF, and insulin-like growth factor 1 (IGF-1) as primary intermediaries in this process (Yau et al., 2014). In a study performed by Marquez et al. (2015), serum was taken from subjects and BDNF concentration was measured acutely, after individual training sessions and demonstrated that BDNF concentration acutely rose immediately following both high-intensity interval training (HIIT) and steady-state (SS) training sessions. Not only did this study show that BDNF concentration rose after both types of training protocols, but it also showed BDNF concentration rose higher after HIIT training. While, Marquez et al. (2015) did not specifically link exercise and cognitive function, the findings demonstrated that BDNF concentration rose following both HIIT and SS training thus leaving us to attempt to link these specific training modalities not only to BDNF concentration, but also to cognitive function.

Neurodegenerative Disease and Motor Function

When the cognitive decline associated with neurodegenerative diseases is accompanied by impaired motor function as in Parkinson's, aspects of postural control (sway) can be useful as a

tool for early prediction of the disease. Postural control is the foundation of our ability to stand and to walk independently. Deterioration in postural control due to normal aging or neurodegenerative disease such as Parkinson's disease (PD) is illustrated by more pronounced sway in either the medio-lateral or antero-posterior directions. Deterioration in this control measure predisposes 68% of people with PD to fall at least once each year (Mancini et al., 2012). Although subjects with PD show postural instability in advanced stages of the disease, very few studies have investigated whether it is possible to identify abnormal balance in early stages of the disease, prior to starting antiparkinsonian medication (Mancini et al., 2012). In the study by Mancini et al. (2012), it was demonstrated that sway deteriorates significantly (as measured by inertial sensors) during two minutes of quiet standing, with only minimal changes in unified Parkinson's disease rating scale (UPDRS) motor scores being observed. Specifically, sway measures in the medio-lateral (ML) plane were more pronounced than sway measures in the antero-posterior plane in detecting progression of the disease (Mancini et al., 2012). Additionally, the ML jerk (i.e. the derivative of linear acceleration of the trunk with respect to time) was observed to be larger, and the ML sway excursion and velocity were also significantly higher in PD when compared to control subjects (Mancini et al., 2012). Therefore, it is reasonable to hypothesize that the progression of PD can be tracked by observing the structure of the sway variability using detrended fluctuation analysis (DFA), the coefficient of variability (CV), or accelerometers to measure quiet standing(Mancini et al. 2012; Ota et al. 2012). Although it is reasonable to measure postural sway using accelerometer-based measurement tools as in the study by Mancini et al. (2012), further research is needed to assess the validity and reliability of its use as a surrogate for kinetic measures taken from force plates (Raper et al., 2018). Therefore, even though accelerometer-based measurement systems are a reasonable option for measuring PD

progression and could benefit from further testing of validity and reliability, force plates are the preferred apparatus, and DFA and CV the preferred metrics (Ota et al. 2012).

Whether via kinetic (measures) of force plate analysis, immunosorbent protein assays measuring BDNF protein concentration, or imaging and cognitive studies, the present evidence involving both human and animal models all support the effect exercise has on cognitive function and neurogenesis in the hippocampus, and specifically the dentate gyrus. Given that neurogenesis is mediated by proteins such as BDNF, with increased BDNF concentration and increased neurogenesis, increased cognitive function is observed. Although the exact mechanism underlying the improved neurocognition that results from these variables, and the ability to identify the exercise interventions that are the most appropriate are still unclear, what is clear is the positive impact exercise-induced neurogenesis has on the impact of neurodegenerative disease, and age-related cognitive decline.

Impact on Disease Burden

Nearly three-quarters of all healthcare cost stem from chronic disease. Health behaviors can have a substantial impact on chronic disease via the disease course and health outcomes. Whether it be avoiding tobacco use, eating a healthy diet, or adhering to exercise and physical activity guidelines, living a healthy lifestyle has health benefits (Patrick et al., 2012). For those that adhere to a healthy lifestyle, there exists both cardiovascular and neurological benefits, as exercise has been shown to up-regulate neurogenesis. According to Miller and Hen (2015), the framework of neurogenic theory has five pillars: 1) Adult hippocampal neurogenesis (AHN) is significantly altered in neurological disorder; 2) Impaired AHN is enough to induce symptoms of neurological disorders; 3) Treatments of depression, anxiety and other neurological disorders alter

AHN; 4) In order for antidepressants and other medication to be effective in treating neurological disorders, AHN is required; and 5) Increased AHN is enough to treat certain neurological disorders.

In an aging population, the social and financial impact of age-related cognitive and motoric decline and the prevalence of neurodegenerative disease is of paramount importance. For example, in the study by Kelley et al. (2015), the social costs of neurodegenerative disease, specifically dementia, and the associated components of Medicare, Medicaid, private insurance, out-of-pocket spending, and informal care of those afflicted with dementia and their families was observed and compared to that of people who died of heart disease, cancer or other causes. These authors measured these components over the last 5 years of life and out-of-pocket spending as a proportion of household wealth. Kelley et al. (2015) showed the average total cost per patient with dementia was significantly greater than that of those who died of heart disease, cancer, or other causes. These authors also showed that although the Medicare expenditures of each group was similar, as a result of the overwhelming logistical burden associated with the disease, the average out-of-pocket spending for patients with dementia was 81% higher than that for patients without dementia.

Additionally, out-of-pocket spending for those with dementia represented 32% of wealth measured 5 years before death compared with 11% for those without dementia. Finally, health care expenditures among those with dementia were larger than those for other diseases and a substantial amount of these expenses were not covered (i.e. uninsured). The result of this is not only a large financial burden, but one that falls on those groups least prepared to manage it, i.e. those who lack health insurance (Kelley et al., 2015). Clinically, increased neurogenesis can increase resistance to dementia and other neurodegenerative diseases by increasing neuronal

volume and synaptic plasticity (Bartsch, 2012). Increasing the volume of neurons could increase the amount of time it takes a neurodegenerative disease to deplete brain volume to the point of expressing symptoms. Concomitantly, increasing synaptic plasticity allows for greater variability in neuronal pathways and circuitry that could allow more pliability before the circuitry is broken down with the progression of neurodegenerative diseases. This protective effect of exercise on cognitive decline could serve as a low-cost means to alleviate the financial burden on those afflicted by the disease, and that of the caregiver for those afflicted by these diseases.

Improving cardiovascular health by engaging in regular exercise has long been a supported idea in the literature. However, exercise being implicated in neuronal health and longevity, as well as synaptic plasticity, increased cerebral blood volume (CBV) and angiogenesis, overall brain volume, and neurogenesis is a more novel idea. Both high-intensity interval training (HIIT) strategies and steady state (SS) exercise protocols have been shown to increase levels of VEGF (Morland et al., 2017). VEGF is a signaling protein that is crucial for angiogenesis; therefore, the presence of VEGF in higher concentrations indicates an increase in capillarization (Kraus et al., 2004). When the increase in VEGF occurs in the brain, it is indicative of an increase in CBV (Fabel et al., 2003). CBV has long been an accepted means by which brain function can be assessed (Maia et al., 2005). Although change in cerebral blood flow is an accepted indicator of brain activity, VEGF is also a biomarker for angiogenesis in the periphery (Kraus et al., 2004). Therefore, while angiogenesis and increased cerebral blood flow is a significant physiological outcome of exercise, the ambiguity of VEGF as a biomarker decreases the effectiveness of this protein as an investigative tool. Fortunately, exercise has also been shown to selectively increase DG CBV, neurogenesis, plasma and serum levels of BDNF in humans (Pereira et al. 2007; Marquez et al., 2015). DG CBV correlates with aerobic fitness and

cognitive function as assessed by the RAVLT. Additionally, only the DG shows increased CBV during the RAVLT and CBV is a corollary measure for brain function. Therefore, RAVLT performance and BDNF can be used as surrogate measures for the DG (Pereira et al., 2007; Marquez et al., 2015).

Both healthy aging and diseased states have also been associated with the loss of complexity in some aspects of the kinetic, and kinematic properties associated with locomotion. For example, deterioration in balance control is lower in healthy older adults as compared to their younger counterparts (Hausdorff et al., 1997; Scafetta et al., 2009). In patients with Parkinson's disease, this is further diminished, to the extent that these changes closely resemble uncorrelated white noise (Herman et al., 2005). Therefore, it is reasonable to measure progression of PD by observing the structure of the variability using detrended fluctuation analysis and the coefficient of variability (CV) associated with postural sway (Vieira et al. 2017). There could also exist a continuum between white noise (i.e. slope of zero), pink noise (i.e. a slope of one), and brown noise (i.e. a slope of two) in the associated frequency versus power graphs that could be helpful in gauging the advancement of degeneration (Van Orden et al., 2009). Although, this has been the subject of some conjecture in the literature. As shown in Van Orden et al., (2009), the introduction of task constraints and dual task parameters, tends to "whiten" the noise of a healthy individual, in the same way disease constraints could. These changes being associated with the diseased state are at times so subtle, they could be considered an aspect of some minute constraint, and therefore could be considered somewhat subjective.

Since increased CBV is a result of angiogenesis, and angiogenesis is coupled with neurogenesis, we postulate that performance on cognitive tests previously linked specifically to these regions in imaging studies can be used to quantitatively assess the associated brain regions.

Thus, performance on these cognitive tests can be used as an analytical tool to assess anatomical and physiological changes within the brain. Additionally, imaging studies have isolated the dentate gyrus (DG) of the hippocampus as an area of the brain particularly impacted by exercise. These same imaging studies have shown a positive relationship between increased neurogenesis in the DG, and increased performance on the RAVLT (Pereira et al., 2007). Increases in angiogenesis, neurogenesis, cognitive function and BDNF concentration could therefore be associated with specific postural sway metrics and the correlation could become a useful tool in analyzing the severity and progression of degeneration.

Gaps in the Literature

Previously, exercise studies showing increases in neurogenesis have included low volume, steady-state exercise protocols performed by human subjects (N=11 mean age=33) (Pereira et al., 2007). The subjects in these studies fell below the America Heart Association's criteria for below average aerobic fitness (VO_2 max<43 ml/kg/min for men and <37 ml/kg/min for women) (Pereira et al., 2007). Recently, investigators have begun to alter training protocols and investigate the impact on BDNF using combinations of high intensity interval (HIIT) and steady-state (SS) training protocols with college-aged, healthy adults (Marquez et al., 2015). While both training methodologies successfully achieved significant increases in BDNF acutely, interval training had more of an impact on the magnitude of change. In the same study, HIIT protocol subjects' BDNF concentration rose acutely 37.72% pre-to post, in comparison to a 23.77% increase in subjects of the steady-state protocol. This is consistent with the study by Angevaren et al. (2008) where it was shown that aerobic exercise interventions result in an improvement in maximal oxygen uptake and increases in cardiorespiratory fitness of approximately 14% coincide with improved cognitive function (Angevaren et al., 2008). In

summation, HIIT and steady-state training methodologies are linked with selective increases in BDNF (Marquez et al., 2015). What remains less clear in this body of research is the impact exercise induced BDNF changes may have on cognitive function and neurogenesis. Additionally, it is also unclear what the long-term impact is, and the impact of the dosing strategies may have on these exercise-induced changes.

Previous study has also shown BDNF concentration is a significant intermediary in the prevention of age-related decline and the decline in cognitive function that results from certain neurodegenerative diseases (Pereira et al., 2007; Yau et al., 2014). Theoretically speaking, consistent training and physical activity could elicit a chronic, protective effect regarding cognitive decline. This protective effect associated with exercise-induced neurogenesis would not only forestall the onset of the disease, but potentially insulate the individual from the diseased state entirely. Additionally, if the onset of the disease is delayed, or eliminated entirely, the associated Medicare, Medicaid, private insurance, and out-of-pocket expenses would be at least partially alleviated. Continued use of more prolonged and intensive HIIT and SS protocols among both trained and untrained individuals will benefit further understanding of this. The use of more intensive protocols is a novel idea and could possibly suggest that varying levels of activity could have a varied impact on neurogenesis and therefore a varied impact on forestalling certain neurodegenerative diseases.

In the early stages of neurodegenerative diseases associated with some type of cognitive decline, symptoms of mild cognitive impairment (MCI) present in a vast majority of patients. Given that the symptoms of MCI can be identified, and this could also be indicative of the early stages of neurodegenerative disease, MCI has become the target for intervention. Studies have been conducted recently to document the frequency of MCI and the prevalence has been

estimated to be between 15% and 20% in people 60 years and older (Pearson, 2016). Additionally, the rate in which MCI progresses to dementia varies between 8% and 15% per year and will not always result in the same disease (Ganguli et al.,2010). As a result, MCI should also be the factor to explore for intervention studies of postural sway in neurodegenerative diseases, like Parkinson's that is not only associated with cognitive decline, but motor impairment as well.

Biomarkers should therefore be the aim of future study. Future study should also aim to associate specific training modalities with associative cognitive decline of specific diagnoses. It may also be advantageous to monitor the cumulative and chronic effects of exercise-induced neurogenesis over a much longer period to gauge the impact different exercise protocols have on different diagnoses as well because, if varying the exercise protocol has a varying impact on cognitive function and BDNF, then it is likely that there is a specific chronic exercise blueprint associated with each neurodegenerative disease that in some way impacts cognitive function. Further, larger and more representative samples are warranted to facilitate understanding of exercise's impact on cognitive function among a broader range of the population.

Future Study

To date, most research involving exercise and cognitive function has been primarily focused on steady-state training protocols in individuals with below average cardiorespiratory fitness as in the study by Pereira et al. (2007). Future study should attempt to show a difference in increased cognitive function as assessed by the RAVLT between participants of both HIIT and SS protocols and include a more expansive population. The findings of Pereira et al. (2007) show that SS training resulted in improved RAVLT score and this was associated with a significant increase in neurogenesis in the dentate gyrus by observing BrdU labeled images of the brain in untrained individuals. Additionally, the findings of Marquez et al. (2015) show an

increase in BDNF after bouts of both SS and HIIT training, with a greater increase observed after the HIIT protocol. Therefore, in trained individuals, we should expect that cognitive function as assessed by RAVLT score would be positively impacted after both HIIT and SS training. Additionally, if we use RAVLT score as a surrogate measure, neurogenesis would also be positively impacted.

Whereas previous research has focused on untrained individuals where any exercise is likely to exert a positive effect when compared to none, future study should attempt to provide evidence to support the notion that one can achieve both recommended levels of fitness per ACSM guidelines (Haskell et al., 2007), and enjoy improved cognitive function. Given that there are studies that show a greater acute rise in BDNF concentration as the result of HIIT when compared to SS training protocols (Marquez et al., 2015), it stands to reason that there could be other variables at work that impact this effect. This could then suggest that in trained individuals, there exists a chronic effect as well as a differentiated effect of exercise on cognitive function, neurogenesis and neuronal health in the adult dentate gyrus that is dependent upon the incorporated training modality. Previous study has shown BDNF concentration is a significant intermediary in the prevention of age-related decline and the decline in cognitive function that results from certain neurodegenerative diseases (Pereira et al., 2007; Yau et al., 2014). It follows then that chronic training and physical activity could elicit a chronic, protective effect regarding cognitive decline. Continued use of more intensive training protocols will benefit further understanding of this, and the use of more intensive protocols would be novel to future study and could possibly show that varying levels of activity could have a varied impact on neurogenesis and therefore a varied impact on forestalling certain neurodegenerative diseases, however that remains to be seen.

A positive association exists between aerobic exercise interventions and cognitive function if the intervention results in an improvement in maximal oxygen uptake and increases in cardiorespiratory fitness (Angevaren et al., 2008). Therefore, future training studies of both HIIT and SS training protocols can elicit an improvement in cognitive function and neurogenesis if the training results in an increase in maximal oxygen uptake. However, different protocols could be associated with different magnitudes of change given varied nature of genetic predispositions and previous training history. This varied effect could then be associated with the training intervention's effectiveness at impacting the various pathways that are mediated by hippocampal BDNF. These being the pathways that result in exercised-induced synaptic plasticity and cognitive function as shown by Vaynman et al. (2004). However, baseline differences between groups would also likely exist, so in future study, larger groups could help to alleviate these baseline differences

Future study should aim to associate specific training modalities with specific cognitive decline and impaired motor function that is the result of specific diagnoses. It may also be advantageous to monitor the cumulative and chronic effects of exercise-induced neurogenesis over a much longer period to gauge the impact different exercise protocols have on different diagnoses as well. If varied exercise has a varied impact on BDNF and cognitive function, there is likely a specific, chronic, exercise blueprint associated with each neurodegenerative disease. RAVLT, BDNF, and postural sway can be collectively used to observe altered progression of PD as the result of exercise intervention and this could provide an early predictive tool for PD. Further, larger, and more representative samples are warranted to facilitate understanding of exercise's impact on cognitive function among a broader range of the population.

Summary

Neurogenesis occurs in the dentate gyrus but is difficult to observe in human models, therefore a biomarker is needed as a surrogate. BDNF, which can be analyzed using urinalysis, can serve as a surrogate biomarker for neurogenesis. Additionally, RAVLT performance and BDNF can be used as surrogate measures for angiogenesis and neurogenesis in the DG. Postural sway can also be used to track the associated degeneration in certain neurodegenerative diseases. Therefore, RAVLT, BDNF, and postural sway can collectively be used to observe and document the progression of PD as the result of exercise intervention.

CHAPTER III

Methodology

The purpose of this chapter is to outline and explain the methodologies related to the experimental design of this study. The following sections will be explained in further detail: operational definitions, dependent variables, limitations, delimitations, subjects, experimental procedures, and study design.

Operational Definitions

1. HIIT cycling protocol: 3-minute warm-up at 60W followed by 1-minute intervals at 90% maximum workload with active rest at 60 watts (W).
2. Recreationally active: Intense exercise 20 minutes per day 3 days per week, or exercise of moderate intensity for 30-60 minutes per day for 5 days per week (Haskell et al., 2007).
3. Inactive: Physically active less than the ACSM guidelines for physical activity.
4. Compliance: Compliance with exercise protocols was defined as attendance at 80% of training days, and no more than one absence per week.

Limitations

For the present study, the following limitations apply:

1. Subjects were required to maintain their "normal" level of physical activity throughout the study; non-study physical activity was recorded via MyFitnessPal but was not quantitatively analyzed in this study.
2. Neurogenesis and angiogenesis are not being directly studied, they are being studied through surrogate measures.

3. Subjects maintained their “normal” kilo-caloric intake throughout the duration of the study; non-study dietary intake was recorded via MyFitnessPal in weeks 1 and 6 but was not quantitatively analyzed in this study.
4. The control group was instructed to maintain their “normal” physical activity/inactivity for the duration of the study however full accounting of non-study physical activity was beyond the scope of this study.
5. The control group’s level of inactivity was assessed using verbal confirmation.
6. The impact of cognitive gains achieved outside this study, could not be disentangled from any physical activity-related cognitive gains.
7. The extent to which subjects become familiarized with the learning trials on the RAVLT is controlled for, but difficult to assess.

Delimitations

This study has been delimited to the following:

1. Adults from the East Stroudsburg University of Pennsylvania College of Health Sciences and Lehigh Valley Health Network-Pocono.
2. Adult males, ages 18-55
3. A sample size of 14 subjects
4. Subjects who are currently free from musculoskeletal injury in the lower extremities
5. Subjects who are free from diseases that may impact their ability to complete the exercise protocol safely and correctly
6. Subjects who have completed the informed consent and PAR-Q form
7. Subjects are recreationally active per ACSM guidelines.

8. Subjects who are apparently healthy, able to exercise, and maintain their normal level of activity (exercise) or inactivity (control).

Study Design, Protocols, and Instrumentation

Study Design-Fourteen adult men participated in this study. Seven individuals comprised the experimental group (EXP), and seven individuals comprised the control group (CON). Testing was done in the Human Performance, Biomechanics, and Research Labs of East Stroudsburg University of Pennsylvania's department of exercise science. All subjects were instructed to maintain their normal exercise, physical activity, and dietary habits throughout. To be compliant with the training portion of the study, all participants participated in at least 80% of the training sessions and did not miss more than one session per week. During week one of the study, all participants' cognitive function was assessed using the Montreal Cognitive Assessment (MOCA). Participants who scored between twenty and twenty-six on the MOCA were included in this study. The Physical Activity Readiness Questionnaire (PAR-Q) was then used to assess all participants' exercise readiness. In the first active session of week 1, all participants completed the maximal exercise test to determine VO_2 max, and maximal work rate. Afterward, participants were randomly assigned to either the EXP group (N=7), or a CON group (N=7). During weeks one and eight, both CON and EXP participants' performance on the RAVLT was assessed, and their BDNF concentration was measured as well. Participants in the CON group were instructed to maintain their normal exercise, physical activity, and dietary habits throughout the study. All participants in the EXP group were trained via the High Intensity Interval Training (HIIT) protocol three days per week for six weeks. Participants were fully informed about the exercise protocol during an orientation session. Prior approval by the East Stroudsburg University of Pennsylvania and Seton Hall University of New Jersey Institutional Review Board

was obtained for this study. All participants were informed of any risks associated with participation in the study, signed an informed consent document and PAR-Q questionnaire before participating, and all exercise training was performed on a stationary cycle ergometer (Ergomedic 828 E, Monark, Vansbro, Sweden). Work rate and heart rate was monitored continuously as was perceived exertion using the RPE 20-point scale.

Maximal Exercise Test-The following maximal exercise test was used to determine maximal work rate and VO_2 (Mancini et al., 2012). Participants were instructed to avoid intense exercise on the day of, and the day prior, to their maximal exercise test. Participants were also instructed to be three to four hours post absorptive at their scheduled time for the maximal exercise test. The maximal exercise test started with a three-minute warm-up period of unloaded pedaling on an electromagnetically braked cycle ergometer (Lode Excalibur Sport, Groningen, The Netherlands). The maximal work test involved a ramp protocol whereby the resistance of the cycle ergometer started at 100W and was increased by 10W every minute until volitional exhaustion. VO_2 and respiratory exchange ratio (RER) was monitored continuously via an online metabolic analysis system (TrueOne 2400, Parvomedics, Sandy, UT). Heart rate (HR) (Polar, Bethpage, NY) was also monitored continuously, and rating of perceived exertion (RPE) was assessed in the last 30 seconds of each stage. Maximum work rate was determined as the workload corresponding to the last stage that participants fully completed. VO_2 was averaged every five seconds and VO_{2max} was determined utilizing achievement of three of the following four criteria: HR $\geq$ age-predicted maximum $\pm$ 10 bpm, RER $\geq$ 1.15, VO_2 increase of $\leq$ 2.1 ml/kg/min with increased workload and RPE $\geq$ 18

HIIT Cycling Protocol: The following protocols have been shown to increase BDNF levels (Mancini et al. 2012). Training sessions took place three times per week for six weeks and participants were instructed not to exercise prior to the session as well as being 3-4 hours post absorptive. Participation was required for 80% of the total sessions and a minimum of two sessions per week to comply. All training sessions were performed on cycle ergometers (Monark 828E, Monark, Vansbro, Sweden). Seat height was adjusted per manufacturers guidelines. After mounting the cycle ergometers, the protocol started with a rest period of two minutes (no pedaling) and a warm-up period of three minutes at 60W. The HIIT protocol included intervals of one minute at 90% of maximal work rate, alternating with one minute of active rest at 60W for a duration of 20 minutes. Participants were provided their resistances based on their maximum workload and were instructed to change the resistance at the appropriate time (i.e., work or recovery interval) as well as pedaling at a minimum 60RPM. Participants were instructed to cool down at 60W for 5 minutes, and then unloaded pedaling until heart rate returns to 120bpm.

Biochemical Analysis: Urine samples were taken both pre and post in both EXP and CON groups to determine $[BDNF]_{uri}$ and the BDNF E_{max}® ImmunoAssay System from Promega (Madison, WI, USA) was used to analyze the samples. Procedures were conducted according to the manufacturer's guidelines and the accompanied protocol as follows: Prepare coating antibody (per plate): Mix 10µl Anti-BDNF mAb + 9.99ml carbonate coating buffer (pH 9.7). Add 100µl/well. Cover and incubate without shaking overnight at 4˚C. Empty the coating buffer from the wells and wash once. Prepare Block & Sample 1X Buffer: For each 96-well plate, mix 42.4ml deionized water + 10.6ml Block & Sample 5X Buffer. Add 200µl/well. Incubate without shaking for 1 hour at room temperature. Wash once. Prepare standard curve:

Dilute BDNF Standard 1:2,000 with Block & Sample 1X Buffer; add 200µl to row A of columns 11 and 12 of a 96-well plate. Add 100µl of Block & Sample 1X Buffer to rows B-H of columns 11 and 12. Perform six, 1:2 serial dilutions. Do not add BDNF Standard to row H. Prepare sample dilutions: Each well should contain 100µl. Incubate with shaking for 2 hours at room temperature; wash 5 times. Prepare Anti-Human BDNF pAb: For each 96-well plate, mix 20µl BDNF pAb + 9.98ml Block & Sample 1X Buffer. Add 100µl/well. Incubate with shaking for 2 hours at room temperature; wash 5 times. Prepare Anti-IgY HRP Conjugate: For each plate, mix 50µl Anti-IgY HRP Conjugate + 9.95ml Block & Sample 1X Buffer. Add 100µl/well. Incubate with shaking for 1 hour at room temperature; wash 5 times. Equilibrate TMB One Solution to room temperature during incubation. Per plate: Add 100µl/well room temperature TMB One Solution. Incubate with shaking for 10 minutes at room temperature. Stop reaction with 100µl/well 1N hydrochloric acid. Measure A450 BDNF: Read plate within 30 minutes. The absorbance spectrum at 450nm was observed using the Absorbance 96 microplate reader from Byonoy (Hillsborough, NJ).

Rey Auditory Verbal Learning Test: The Rey Auditory Verbal Learning Test was used at baseline and after six weeks of training. The test protocol assessed in this way provided increased variability and therefore decreased the likelihood that performance improved due to familiarization. The procedure for carrying out the cognitive test was as follows (Pereira et al., 2007): Twenty non-semantically or phonemically related words were presented over three learning trials. Test administrator read the word list and the subject free recalled as many words as possible. Three learning trials were immediately followed by one learning trial of a distracter list and then a short delayed free recall of the initial list. After 90-min delay period, subjects were asked to freely recall words from the initial list and then to freely recall items from the

distracter list (subjects contacted by phone). After a 24-hr delay period, subjects were contacted by telephone and asked to freely recall items from the initial list and then from the distracter list. A forced-choice recognition trial in which participants were required to identify the 20 words from the initial learning trial among semantically and phonemically related words, as well as words from the distracter trial was administered. A source memory trial was administered in which participants were read a list containing only words from the initial learning list and from the distracter list and were asked to identify from which list each word came. We measured: words correctly recalled on the first trial of the initial learning trials, the average number of words recalled across the three learning trials, and the number of words from the initial learning trial that were correctly recalled after a short delay (5 min). The number of words from the initial learning trial that were correctly recalled after a 90-min delay and the number of items correctly identified on the recognition trial, and the correct number of items identified on the source memory trial may be used to observe aspects of different aspects of brain function not associated with this study (Palmer et al., 2000).

Montreal Cognitive Assessment: 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, visuoconstructional skills, conceptual thinking, calculations, and orientation. Time to administer the MoCA was approximately 10 minutes. The total possible score was 30 points; a score greater than 26 was considered normal. See appendix A.

Postural Control (PC): Medial-lateral (ML) sway measures are more sensitive than antero-posterior sway measures in detecting progression in Parkinson's disease (PD) (Saucedo Marquez et al. 2015). Specifically, ML JERK (i.e. the first derivative of acceleration) is larger in PD than

in control (Saucedo Marquez et al. 2015)). Therefore, this study used the Neurocom Balance Master System (Natus Medical Incorporated, Pleasanton, CA) to analyze ML JERK in participants during quiet standing. Participants stood quietly on both feet, on the left foot alone, and on the right foot alone while the velocity of sway in the medial-lateral direction was recorded for ten seconds, and the second derivative of the velocity (i.e. ML JERK) was calculated. After ML JERK was calculated, the following procedure for detrended fluctuation analysis (DFA) from Arsac et al. (2018) was used to interpret the data in Excel:

Regular numbering that will serve to identify the position of each sample in the analyzed series was placed in the first column. This was made long enough to match the physiological time series (i.e. ML JERK). The ML JERK time series was imported in the adjacent column. In DFA, the analyzed time series is first integrated; the resulting series was called $y(k)$. This was done in two steps:

- First, the difference between each sample value and the mean value of the series was computed.
- Second, the cumulated sum was calculated.

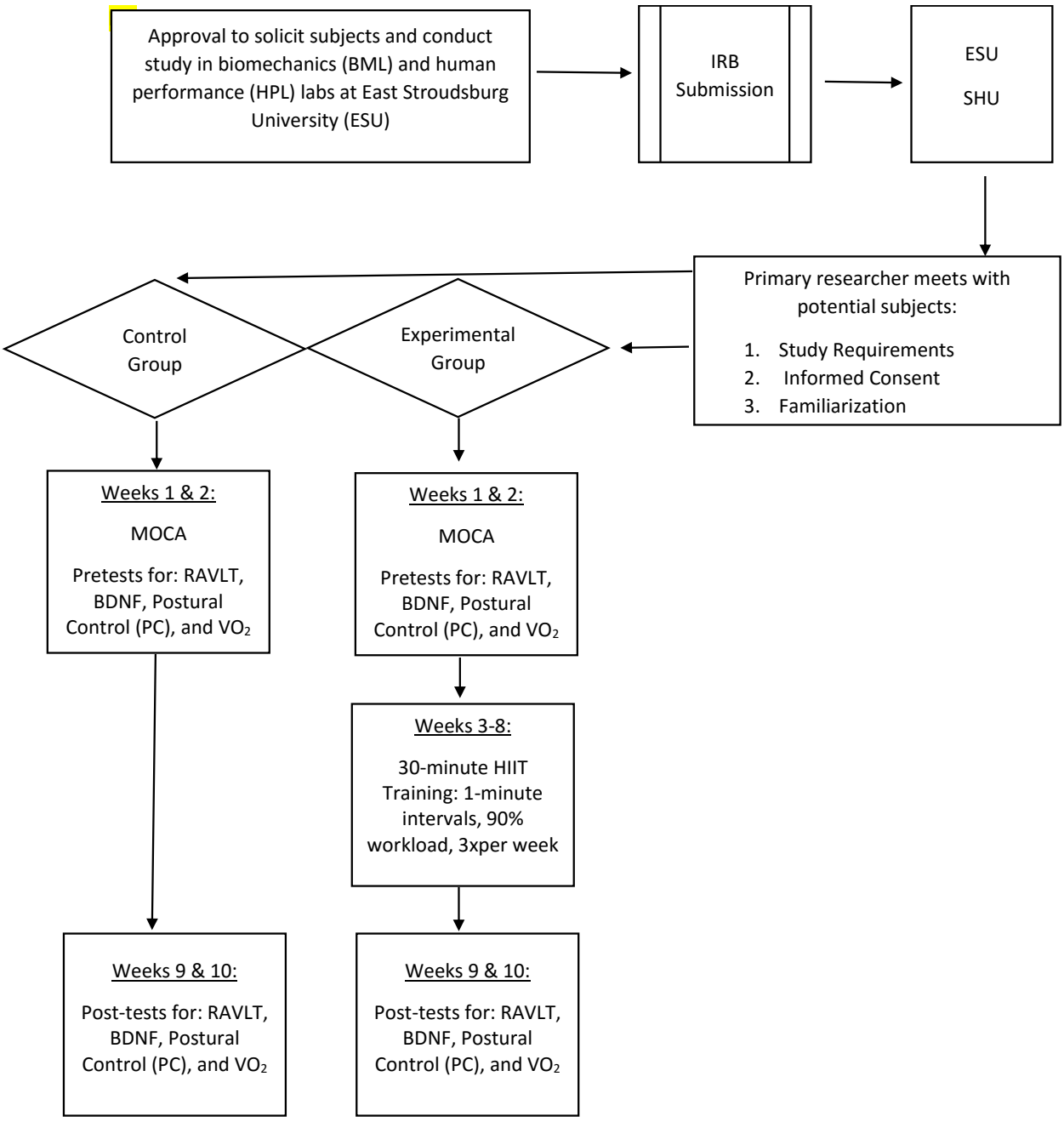
The integrated series $y(k)$ was then divided into boxes of equal size, $n=10$. In each box of size n, a least squares line was fitted to the samples, thus representing the trend in that box. In the next two adjacent columns, the slope and the y-intercept of the linear trend fit in each box was calculated. To assess local fluctuations, the y-coordinate of the straight line (trend) in each box was calculated. This series of y-values was called $y_n(k)$ and was calculated after repeating the slopes and y-intercepts in each row. The data were then checked to see how long it is necessary to repeat the value of slope and intercept, or if a new value of slope or intercept is returned. At

this stage, the $\log_{10}n$ and $\log_{10}F(n)$ were calculated, and served to identify the fluctuation function. Once this DFA was implemented in the spreadsheet, n was changed iteratively and evenly spaced to return more coordinates and to account for a nonlinear increase of n, respectively.

Statistical Analysis: Measures of central tendency and spread of the data were reported as means ± standard deviation for VO_2, RAVLT, BDNF and PC for pre and post measures of both EXP and CON groups. Independent samples t-test using SPSS version 25.0 was run to assess ΔBDNF, ΔRAVLT, ΔPC, and ΔVO_2 between CON and EXP groups. With an N<20, independent samples t-test comparisons of effect size were interpreted using Hedges' g. Hedges g in this case is preferred over Cohen's d because Hedges' uses a pooled weighted standard deviation instead of the pooled standard deviation of Cohen. Therefore, with an N<20, Hedges' tends to out-perform Cohen. Operationally, g-values less than .2 were considered to have a small effect, values of .5-.8 were considered to have a medium effect, and values greater than .8 were considered to have a large effect (Durlack et al., 2009). A Pearson correlation was then run to observe any significant correlation between ΔVO_2, ΔBDNF, ΔPC, and ΔRAVLT. R-values of .1-.3 were considered small associations, .3-.5 were considered medium associations, and .5-1 were considered large associations (Schober et al. 2018). P-values of 0.05 or less were considered statistically significant.

Figure 1

Visual Overview of Study Design



Note. Study protocol spans a ten-week period including pre-, post- and familiarization sessions.

Chapter IV

Results

This study aimed to explore the impact of high intensity interval training (HIIT) on individuals with mild cognitive impairment using a range of cognitive, physiological, and biomechanical measures. Specifically, this study assessed the impact of HIIT on neurogenesis and angiogenesis in the dentate gyrus of individuals with mild cognitive impairment versus healthy age-matched controls, as assessed by urinalysis of brain-derived neurotrophic factor (BDNF) levels, performance on the Rey Auditory Verbal Learning Test (RAVLT), and postural control (PC) as measured by observing sway variability using force plates. Fourteen adult males participated in this study. The overall mean age of the study participants was 37.5 years of age. Prior to beginning the study, participants' MOCA scores were assessed and the mean MOCA score among all study participants was found to be 24.86. Also prior to participating in the study, participants' workload capability was assessed on the cycle ergometer to correctly establish appropriate training metrics. Participants' overall mean workload capability was found to be 245 Watts. Participant baseline data for each of the groups can be found in Table 1 (Table 1).

Table 1

Baseline subject data prior to study.

	Experimental	Control	Total
	N=7	N=7	N=14
Age (years)	36.86	38.14	37.50
MOCA	25.00	24.70	24.86
Workload (watts)	235.70	254.30	245.00

Note. Values are mean age, MOCA, and workload. MOCA=Montreal Cognitive Assessment.

Workload is recorded from last completed stage on the cycle ergometer.

Changes in Dependent Variables After Protocol

Table 2 illustrates the magnitude of change in subjects' VO_2 between those in the HIIT protocol (3.16ml/kg/min) and those in the control group (-1.16ml/kg/min) as well as the results demonstrating change in the magnitude of urine BDNF concentration between HIIT (.11ng/ml), and control (.04ng/ml) groups. Finally, changes in cognitive function as assessed by the RAVLT and postural control was compared between HIIT (2.29 and -.35, respectively) and control (.14 and 6.5, respectively) groups.

Table 2

The Impact of high intensity interval training on oxygen uptake, brain-derived neurotrophic factor, postural control, and the Rey auditory verbal learning test.

	Experimental			Control		
	Pre	Post	Δ	Pre	Post	Δ
VO2 (ml/kg/min)	31.59±5.41	34.74±5.99	3.16±1.75*	27.95±5.47	26.79±4.52	-1.16±3.11
BDNF (ng/ml)	0.25±.07	0.36±0.10	0.11±0.099	0.25±0.006	0.29±0.05	0.04±0.09
RAVLT	9.00±0.76	11.29±0.88	2.29±.76*	9.72±1.28	9.86±0.99	.14±.69
Postural Control	1.49±2.25	1.14±2.16	-.35±2.77*	0.41±0.17	6.91±0.12	6.50±0.09

Note. BDNF=Brain-Derived Neurotrophic Factor. VO_2=Oxygen uptake during exercise. RAVLT= Rey Auditory Verbal Learning Test. *=change is significant with respect to the change in control values.

Independent samples t-test comparisons of mean delta values reflect significant post-protocol changes among experimental (e) versus control (c) group participants in VO_2 (e=3.16, c=-1.16; p=0.08), cognitive function as assessed by the RAVLT (e=2.29, c=.14, p<.001) and postural control (e=-.35, c=6.5; p<.001) (Table 3).

Table 3.

Impact of training on measures of cognitive function, postural control and Neurogenesis. Values are means ± standard deviations.

	Experimental	Control		
	Δ	Δ	P	t
VO_2 (ml/kg/min)	3.16±1.75	-1.16±3.11	.008*	3.194
BDNF (ng/ml)	0.11±0.099	0.04±0.09	.15	1.537
RAVLT	2.29±.76	.14±.69	<.001*	5.539
Postural Control	-.35±2.77	6.5±0.09	<.001*	-6.535

Note. Training= mean values following HIIT protocol. BDNF=Brain-Derived Neurotrophic Factor. Measured in ng/ml. VO_2=Oxygen uptake. RAVLT= Rey Auditory Verbal Learning Test. *=changes are significant with respect to changes in control group.

Hedges' g effect size values reflect large post-protocol effect among experimental versus control group participants' VO_2 (g=1.60), cognitive function as assessed by the RAVLT (g=2.77)) and postural control (g=-3.27), and a medium post-protocol effect for participants' BDNF concentration (g=0.77) (Table 4).

Table 4

Impact of training on measures of cognitive function, postural control, and Neurogenesis. Values are effect sizes using Hedges' g, with the upper and lower 95% confidence interval.

	Hedges'	95% CI	
	g	Lower	Upper
VO_2 (ml/kg/min)	1.60	0.41	2.72
BDNF (ng/ml)	0.77	-0.27	1.78
RAVLT	2.77	1.28	4.22
Postural Control	-3.27	-4.87	-1.62

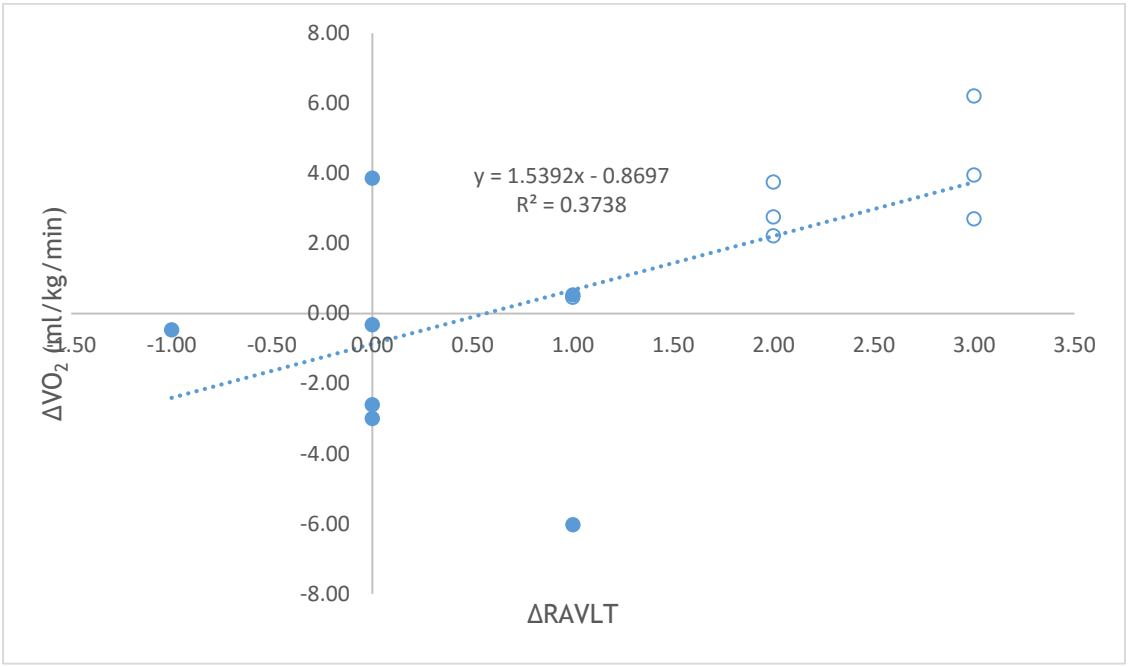
Note. BDNF=Brain-Derived Neurotrophic Factor. Measured in ng/ml. VO_2=Oxygen uptake. RAVLT= Rey Auditory Verbal Learning Test CI=Confidence Interval.

Relationship Among Variables

Pearson correlation shows a medium positive association between increased VO_2 resulting from the HIIT protocol and increased cognitive function as assessed by the RAVLT ($r=0.61$ $p=0.020$) (Figure 2).

Figure 2

Change in VO_2 versus change in RAVLT.

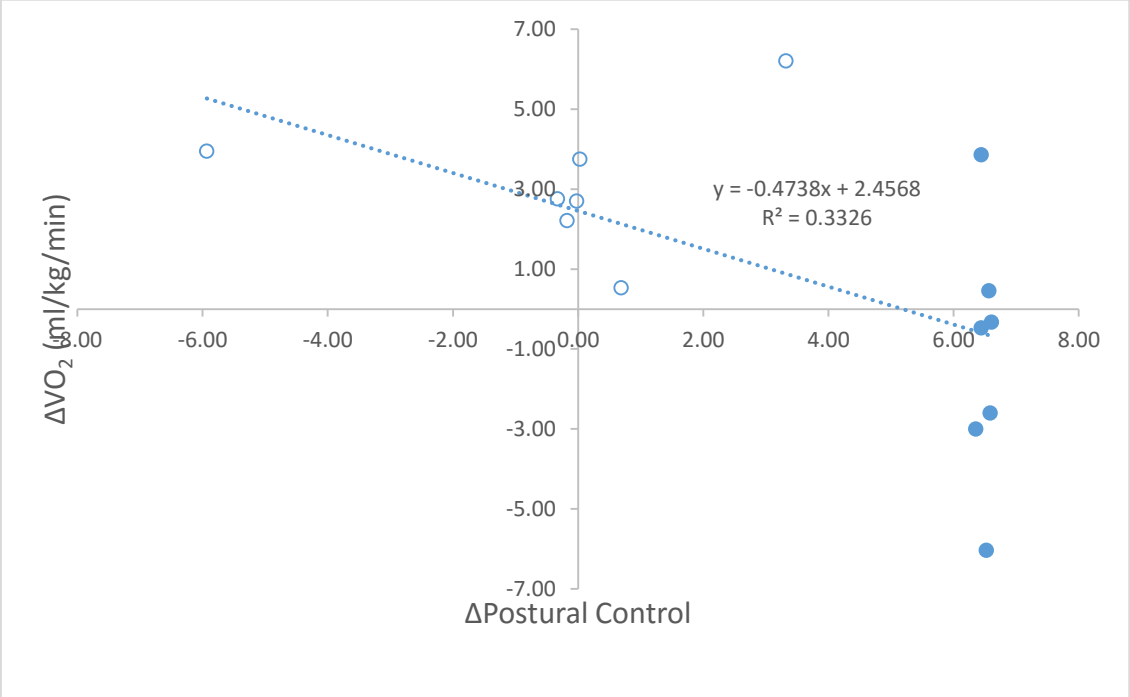


Note. Pearson correlation of ΔVO_2 vs ΔRAVLT shows a positive association between increased VO_2 resulting from the HIIT protocol and increased cognitive function as assessed by the RAVLT (r=0.61 p=0.02). Filled circles=control group; Open circles=experimental group.

Negative associations exist between the change in postural control to the changes in VO_2, cognitive function and BDNF respectively. A medium negative association was observed between both Postural control and VO_2 (r=-.58, p=.031) (Figure 3), and postural control and BDNF concentration although the latter was not found to be a significant association (r=-.504, p=.066).

Figure 3

Change in VO_2 versus change in postural control.

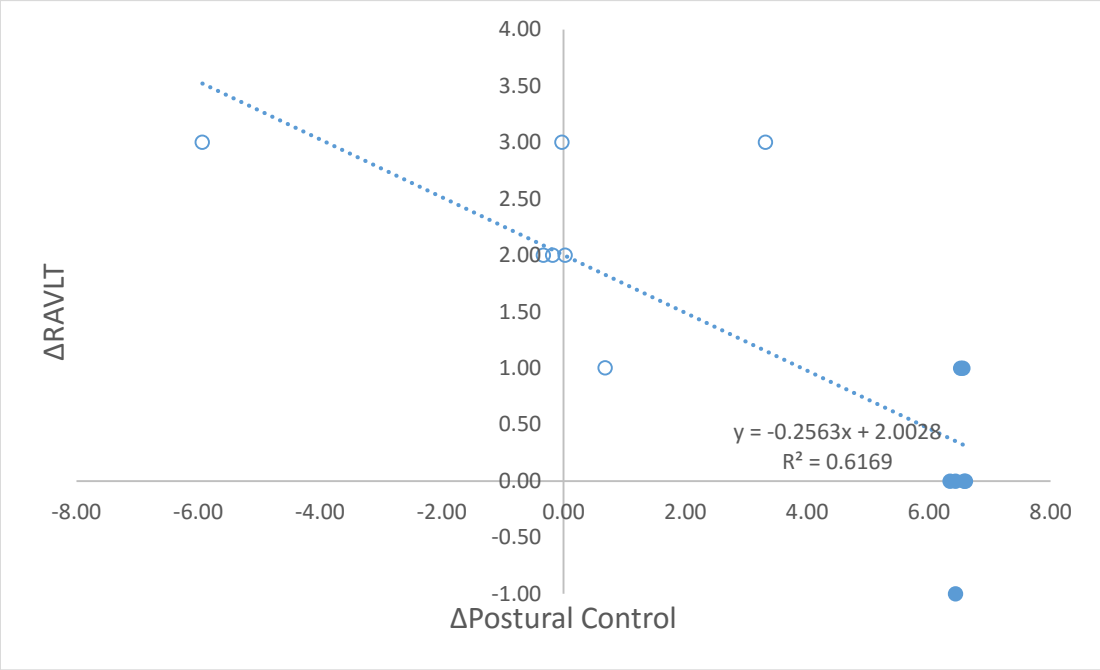


Note. Pearson correlation of ΔVO_2 vs ΔPostural control shows a negative association between VO_2 resulting from the HIIT protocol and postural control (r=-0.58 p=0.031). Filled circles=control group; Open circles=experimental group.

A very strong negative association was also observed between postural control and cognitive function (r=-.785, p=.001) (Figure 4). Finally, only weak and negligible associations were observed between the change in BDNF concentration and the changes in both VO_2,(r=.248, p=.393) and RAVLT (r=.363, p=.202) respectively.

Figure 4

Change in RAVLT versus change in postural control.



Note. Pearson correlation of ΔRAVLT vs Δpostural control shows a negative association resulting from the HIIT protocol (r=-0.785 p=0.001). Filled circles=control group; Open circles=experimental group.

In summation, significant post-protocol changes were observed among EXP versus CON group participants in VO_2 (e=3.16, c=-1.16; p=0.008), cognitive function as assessed by the RAVLT (e=2.29, c=.14, p<.001) and postural control (e=-.35, c=6.5; p<.001). Findings reflect a positive association between increased VO_2 and increased cognitive function (r=0.61 p=0.02), and negative associations between postural control and cognitive function (r=-.785, p=.001), and between postural control and VO_2 (r=-.58, p=.031).

CHAPTER V

Discussion

The aim of the present study was to investigate the effects that a HIIT exercise protocol has on indices of neurogenesis and angiogenesis in the dentate gyrus of the hippocampus. This was assessed using the corollary measures of VO_2 to assess cardiovascular fitness from exercise, cognitive function as assessed by the RAVLT, urine BDNF concentration, and postural control reflecting survival, growth, and maturation of nerves just prior to and just after a six-week training protocol.

To date, most research involving exercise and cognitive function has been primarily focused on steady-state training protocols in individuals with below average VO_2max as in the study by Pereira et al., (2007). The current study has shown high intensity interval training had a large effect on RAVLT score from pre- to post-protocol (Hedges' $g=2.77$, $p<.001$). This is consistent with the findings of Pereira et al., (2007) where training resulted in improved RAVLT score and this was associated with a significant increase in neurogenesis in the dentate gyrus by observing BrdU labeled images of the brain. Therefore, it has been shown that in trained individuals, after HIIT training, cognitive function as assessed by RAVLT score has been positively impacted. Additionally, if we use RAVLT score as a surrogate measure, neurogenesis could also be positively impacted.

Previous research has focused on untrained individuals where any exercise is likely to exert a positive effect when compared to none. This study has provided preliminary evidence to support the notion that one can achieve both recommended levels of fitness per ACSM guidelines (Haskell et al., 2007) and enjoy improved cognitive function. The present finding that significant change in BDNF concentration was not observed after six weeks of HIIT training

(p=0.151) is not consistent with the findings of Marquez et al. (2015) where it was shown that HIIT protocols elicit a greater acute rise in BDNF concentration when compared to other training protocols. However, this could suggest that in trained individuals, there exists a differentiated effect of exercise on cognitive function, neurogenesis and neuronal health in the adult dentate gyrus that is dependent upon the incorporated training modality. Previous investigators have shown BDNF concentration is a significant intermediary in the prevention of age-related decline and the decline in cognitive function that results from certain neurodegenerative diseases (Pereira et al., 2007, Yau et al., 2014). Continued use of more intensive training protocols will benefit further understanding of this. The use of more intensive protocols is novel to this study and could possibly suggest that varying levels of activity could have a varied impact on neurogenesis and therefore a varied impact on forestalling certain neurodegenerative diseases, however that falls outside the scope of this study.

A positive association was observed between increased VO_2 resulting from the HIIT and increased cognitive function as assessed by the RAVLT (r=0.611, p=0.02). This is consistent with the study by Angevaren et al., (2008) where it was shown that aerobic exercise interventions result in an improvement in maximal oxygen uptake and increases in cardiorespiratory fitness coincide with improved cognitive function. As a result of the HIIT protocol in this study, subjects' maximal oxygen uptake improved significantly and therefore lends itself to improved cognitive function.

Mancini et al. (2012) previously showed ML sway increases with minimal changes in Unified Parkinson's Disease Rating Scale. These authors also reported ML sway measures to be more sensitive than antero-posterior sway measures in detecting disease progression. Additionally, Mancini et al. (2012) showed that ML JERK is larger in PD than in control. In the

current study, the HIIT protocol had a large effect on ML sway (g=-3.27), cognitive function (g=2.77) and VO_2 (g=1.60). The current study also found that large, negative associations exist between ML sway and both VO_2 and cognitive function (r=-.577 p=.031; r=-.785 p=.001). Therefore, since subjects' ML sway decreased in association with increased VO_2 and cognitive function, this training protocol could be an intervention when working with person for whom cognitive and motoric diseases have impacted the dentate gyrus.

Practical Application

Given that the magnitude of change was significantly greater among the intervention group when compared to the control group, support for the protocol's potential for varying the impact on neurogenesis in the adult dentate gyrus is present. These findings lend further support for the protocols ability to potentially stave off symptoms of neurodegenerative diseases related to cognitive decline. Therefore, we can infer that high intensity interval training protocols, like the one used in this study, could forestall the onset of symptoms of neurodegenerative diseases that target the dentate gyrus

Future Study

The use of a more intensive protocol is novel to this study and could possibly suggest that varying levels of activity could have a varied impact on neurogenesis and therefore a varied impact on forestalling certain neurodegenerative diseases. If varying the exercise protocol has a varying impact on RAVLT and BDNF, then it could be likely that there are specific chronic exercise blueprints associated with each neurodegenerative disease that in some way impacts cognitive function.

In this regard, future study should aim to associate specific training modalities with specific cognitive decline that is the result of specific diagnoses. Also, it may be advantageous to monitor the cumulative and chronic effects of exercise-induced neurogenesis over a much longer period to gauge the impact different exercise protocols have on different diagnoses as well. Larger and more representative samples are warranted to facilitate understanding of exercise's impact on BDNF and cognitive function among a broader range of the population. Any varied effect could be associated with the training intervention's effectiveness at impacting the various pathways that are mediated by hippocampal BDNF or could be the result of the varied nature of genetic predispositions and previous training history of subjects in the study. Given that these baseline differences between groups could exist, future study should incorporate larger groups thereby helping to alleviate the impact of these baseline differences.

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Appendix A

IRB Approval

SETON HALL UNIVERSITY
1 8 5 6

November 19, 2020

Darrin Lenhart
Seton Hall University

Re: Study ID#2021-152

Dear Darrin:

The Research Ethics Committee of the Seton Hall University Institutional Review Board reviewed and approved your research proposal entitled, "The Impact of High Intensity Interval Training on Neurogenesis and Angiogenesis in the Dentate Gyrus" as resubmitted. This memo serves as official notice of the aforementioned study's approval as exempt. If your study has a consent form or letter of solicitation, they are included in this mailing for your use.

The Institutional Review Board approval of your research is valid for a one-year period from the date of this letter. During this time, any changes to the research protocol, informed consent form or study team must be reviewed and approved by the IRB prior to their implementation.

You will receive a communication from the Institutional Review Board at least 1 month prior to your expiration date requesting that you submit an Annual Progress Report to keep the study active, or a Final Review of Human Subjects Research form to close the study. In all future correspondence with the Institutional Review Board, please reference the ID# listed above.

Sincerely,

Mara C. Podvey, PhD, OTR
Associate Professor
Co-Chair, Institutional Review Board

Phyllis Hansell, EdD, RN, DNAP, FAAN
Professor
Co-Chair, Institutional Review Board

Office of the Institutional Review Board
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EAST STROUDSBURG UNIVERSITY

East Stroudsburg University Institutional Review Board
Human Research Review
Protocol # **ESU-IRB-011-2021**

Date: **September 17, 2020**
To: **Darrin Lenhart and Gavin Moir**
From: **Shala E. Davis, Ph.D., IRB Chair**
Proposal Title: **"The Impact of High-Intensity Interval Training on Neurogenesis and Angiogenesis in the Dentate Gyrus"**

Review Requested:	Exempted	Expedited	Full Review **X**
Review Approved:	Exempted	Expedited	Full Review **X**

FULL RESEARCH

__X__ Your full review research proposal has been approved by the University IRB (12 months). Please provide the University IRB a copy of your Final Report at the completion of your research.

____ Your full review research proposal has been approved with recommendations by the University IRB. Please review recommendations provided by the reviewers and **submit necessary documentation for full approval.**

____ Your full review research proposal has not been approved by the University IRB. Please review recommendations provided by the reviewers and resubmit.

EXEMPTED RESEARCH

____ Your exempted review research proposal has been approved by the University IRB (12 months). Please provide the University IRB a copy of your Final Report at the completion of your research.

____ Your exempted review research proposal has been approved with recommendations by the University IRB. Please review recommendations provided by the reviewers and **submit necessary documentation for full approval.**

____ Your exempted review research proposal has not been approved by the University IRB. Please review recommendations provided by the reviewers and resubmit, if appropriate.

EXPEDITED RESEARCH

____ Your expedited review research proposal has been approved by the University IRB (12months). Please provide the University IRB a copy of your Final Report at the completion of your research.

____ Your expedited review research proposal has been approved with recommendations by the University IRB. Please review recommendations provided by the reviewers and **submit necessary documentation for full approval.**

____ Your expedited review research proposal has not been approved by the University IRB. Please review recommendations provided by the reviewers and resubmit, if appropriate.

Please revise or submit the following: