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Long-term Aerobic Exercise Can Enhance Cognition and Delay the Onset of Alzheimer's Disease

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Long-term aerobic exercise can enhance cognition and delay the onset of Alzheimer’s disease

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Introduction

Alzheimer’s disease (AD) is the most common type of dementia, accounting for 60 to 80% of all dementia cases in the United States (Alzheimer's Association 2019). According to the Alzheimer’s Association (2019), there were roughly 5.7 million Americans suffering from AD in 2018 and it has become the 6th leading cause of death in the US. Emerging evidence from the last decade has introduced a promising alternative therapeutic strategy to combat AD. Studies have shown that aerobic exercise could potentially be linked to preventing cognitive dysfunction, hippocampal volume loss, and enhancing neurogenesis (Phillips et al. 2015; Tyndall et al. 2018; Karssemeijer et al. 2019; Etnier et al. 2016; Baird et al. 2018; Intlekofer and Cotman 2013; Mora 2013; Colzato et al. 2018; Song et al. 2014; Cotman et al. 2007; Beckett et al. 2015; Wang and Holsinger 2018; Ma et al. 2017; Brasure et al. 2018; Dougherty et al. 2017; Szuhany et al. 2015; Morris et al. 2017; Peven et al. 2018). Studies conducted on humans and animals have found that aerobic exercise can alter synaptic function, restore neurogenesis, and increase neurotrophin levels (especially that of Brain-Derived Neurotrophic Factor).

Synaptic functioning plays an important role in proper brain function. Synapses are the site where neurons communicate with each other; therefore, proper synaptic functioning is crucial for maintaining cognitive ability (Phillips et al. 2015; Tyndall et al. 2018). One hallmark of AD is a major loss of synaptic functioning, especially in areas of the hippocampus (Phillips et al. 2015; Tyndall et al. 2018; Ma et al. 2017; Dougherty et al. 2017; Morris et al. 2017). Because of this loss of synaptic functioning in the hippocampus, AD patients show declines in learning and memory formation. Daily aerobic exercise has been shown to counteract this loss in AD patients by improving the synaptic properties in
Evidence has also revealed that exercise is capable of restoring neurogenesis (Phillips et al. 2015; Ma et al. 2017). Certain cells in the hippocampus, called dentate granule cells, contribute to important tasks, such as learning and memory, and it is these cells in the hippocampus that are most vulnerable to the crippling effects of AD (Ma et al. 2017; Phillips et al. 2015). The hippocampus loses approximately 1 to 2% of its volume annually after the age of 60, but aerobic exercise has been shown to counteract this loss (Fjell et al. 2014; Erickson et al. 2010). This is because aerobic exercise induces neurogenesis in the dentate gyrus of the hippocampus (Phillips et al. 2015).

Along with increases in synaptic functioning and neurogenesis, several studies have provided evidence that aerobic exercise can increase neurotrophic levels in the brain, which can aid in preventing or delaying the onset of AD (Phillips et al. 2015; Karssemeijer et al. 2019; Etnier et al. 2016; Baird et al. 2018; Intlekofer and Cotman 2013; Song et al. 2014; Mora 2013; Colzato et al. 2018; Dougherty et al. 2017; Szuhany et al. 2015). Neurotrophins are important types of proteins located in the brain that aid in the survival, growth, and maintenance of neurons, which allow them to perform a variety of specific functions such as learning and memory (Phillips et al. 2015). Patients with AD demonstrate a failure in binding, releasing, and action of certain neurotrophins (Phillips et al. 2015). One particular neurotrophin, called Brain-Derived Neurtrophic Factor, has become closely linked with the beneficial effects of exercise on the brain. Brain-Derived
Neurotrophic Factor (BDNF) is part of the Central Nervous System and is important in the consolidation of memory and learning (Etnier et al. 2016; Song et al. 2014).

Exercise is beneficial for cognitive enhancement, because exercise rapidly induces BDNF mRNA and protein into the hippocampus immediately after exercising, which allows for more memory consolidation, learning, and synaptic plasticity (Intlekofer and Cotman 2013; Mora 2013; Baird et al. 2018; Phillips et al. 2015; Etnier et al. 2016; Song et al. 2014; Wang and Holsinger 2018). BDNF has this effect because increased levels of this neurotrophin in the brain supports the survival of new neurons and provides a favorable environment for neural plasticity (Intlekofer and Cotman 2013; Mora 2013; Song et al. 2014; Baird et al. 2018). Recent evidence from earlier this year has found that a specific protein in the blood, called neurofilament light chain (Nfl), can determine whether a patient will develop Alzheimer’s disease up to 16 years before symptoms are present (Preische et al. 2019). Higher levels of Nfl in the blood indicates that an individual is at a higher risk of developing AD (Preische et al. 2019). By analyzing this protein along with BDNF levels in the blood, this could be a promising avenue of research to better understand this link between aerobic exercise and brain health in individuals at risk for developing AD.

In summation of this previous research, there are several benefits of exercise on cognition and memory formation. These studies have shown that exercise enhances cognition, restores neurogenesis, increases hippocampal volume, promotes memory formation and consolidation, and increases neuotrophin levels immediately after exercise (Phillips et al. 2015; Tyndall et al. 2018; Karssemeijer et al. 2019; Etnier et al. 2016; Baird et al. 2018; Intlekofer and Cotman 2013; Colzato et al. 2018; Beckett et al. 2015; Song et al. 2014; Etnier et al. 2016; Song et al. 2014; Wang and Holsinger 2018; Intlekofer and Cotman 2013; Mora 2013; Song et al. 2014; Baird et al. 2018). Recent evidence from earlier this year has found that a specific protein in the blood, called neurofilament light chain (Nfl), can determine whether a patient will develop Alzheimer’s disease up to 16 years before symptoms are present (Preische et al. 2019). Higher levels of Nfl in the blood indicates that an individual is at a higher risk of developing AD (Preische et al. 2019). By analyzing this protein along with BDNF levels in the blood, this could be a promising avenue of research to better understand this link between aerobic exercise and brain health in individuals at risk for developing AD.

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Therefore, aerobic exercise could potentially be used as a therapeutic option to combat the devastating effects of AD on the brain.

**Specific Aim**

There is extensive research and evidence showcasing how aerobic exercise enhances cognition, neurogenesis, increases hippocampal volume, and other cognitive benefits immediately after exercise. Despite this extensive research, there are a few gaps in this link between aerobic exercise, brain health, and whether these beneficial effects endure long enough to possibly help delay or prevent the onset of Alzheimer’s disease. Several studies in this field are short-term studies, which are conducted anywhere from a few weeks to one year (Phillips et al. 2015; Tyndall et al. 2018; Karssemeijer et al. 2019; Etnier et al. 2016; Baird et al. 2018; Intlekofer and Cotman 2013; Colzato et al. 2018; Beckett et al. 2015; Wang and Holsinger 2018; Ma et al. 2017; Brasure et al. 2018; Dougherty et al. 2017; Szuhany et al. 2015; Morris et al. 2017; Peven et al. 2018). There is a need to conduct long-term studies to determine how beneficial exercise can be to delay or prevent against AD (Beckett et al. 2015; Wang and Holsinger 2018; Brasure et al. 2018). There is plenty of evidence to demonstrate how effective short-term exercise programs are on brain health, but there is a need for more research in long-term aspects of this link and how exercise can be used as a therapeutic strategy for AD.

Alzheimer’s disease is plaguing our nation, and something needs to be done to delay or stop this disease from being so prevalent in our society. The Alzheimer’s Association
(2019) claims that one in three seniors dies with AD or another type of dementia each year and that this crippling disease kills more people than breast cancer and prostate cancer combined. It is vital to find a therapeutic strategy to combat this severe disease. As of yet, there is no effective pharmacological treatment for patients suffering with AD (Phillips et al. 2015; Beckett et al. 2015). Pharmacological therapies have not been effective, so research efforts need to focus on other alternatives to delay or prevent the onset of AD. Exercise has emerged as a possible effective, low-cost, low-tech alternative to addressing this disease and we need to turn our focus towards preventive care for individuals at risk for developing AD (Ma et al. 2017; Beckett et al. 2015).

With this knowledge, this study aims to determine whether a long-term aerobic exercise program has lasting effects on enhancing cognition and functional ability in delaying or preventing the onset of Alzheimer’s disease. Can a long-term (15 year-long) aerobic exercise program be used as a preventative therapeutic strategy to delay or prevent the onset of Alzheimer’s disease? I hypothesize that a long-term aerobic exercise program will enhance cognition, functional ability, and prevent hippocampal loss for a longer time period than what has been seen in short-term aerobic exercise programs from previous studies. As a result, long-term aerobic exercise programs can be used for individuals at risk for developing Alzheimer’s disease and be used as a preventative therapeutic strategy to combat AD.

**Methodology**

This study will be measuring executive brain function (cognitive functioning), BDNF levels in the blood, and Nfl levels in the blood of human subjects. In order for the results to
be conclusive, subjects in the aerobic training group should have higher scores on cognition tests, higher levels of BDNF in their blood, and lower levels of Nfl in their blood when compared to the control group. Analysis methods will include magnetic resonance imaging (MRI) analysis for indications of neuropathological changes in the brain, blood tests to measure BDNF levels and Nfl levels, and various neuropsychological tasks/tests to measure cognitive functioning (episodic memory, working memory, and psychomotor speed). These measurements will be taken at baseline (before treatment starts), following every 6-months of treatment, and at the end of the study.

**Participants and Treatment**

Participants will include 60 men and women 50 years of age with relatives (mother, father, grandmother, and grandfather) who were diagnosed with dementia or Alzheimer’s disease. Participants will be randomly assigned to two treatment groups and executive brain functioning along with blood work for BDNF and Nfl levels will be assessed at baseline and then repeated every 6 months after treatment and again following the conclusion of this study (Karssemeijer et al. 2017). The 2 groups include: one experimental group and one control group. The experimental group (30 participants) will be the aerobic training group and the control group (30 participants) will be the active [stretch and toning] control group (Karssemeijer et al. 2017). Heart rate measurements will be taken during the aerobic training group via the Polar T31 heart rate sensor. Each group will have 3 sessions per week for 15 years (~780 weeks).

**Table 1:** Description of treatment groups and what each group will be doing as determined by randomized group placement.
MRI, measurements for executive brain function, and blood tests (for BDNF and Nfl levels)

An MRI will be performed on all participants at the baseline of treatment and at the conclusion of this study. MRI readings will provide any indication of presymptomatic changes in the brain (such as cortical thinning and neuropathological depositions) before and after treatment to determine if there is onset of Alzheimer’s disease (Preische et al. 2019).

Executive function and cognitive measurements will be measured by neuropsychological tasks. These tests will be conducted at baseline, every 6-months during treatment, and at the conclusion of this study. Blood will be draw for BDNF and Nfl levels at baseline of treatment, every 6-months during treatment, and at the conclusion of this study. I will follow the same procedures for BDNF and Nfl sampling and analysis as was done by Baird and colleagues (2018) and Preische and colleagues (2019). The procedures are as follows: 10ml of blood will be collected at baseline, every 6-months...
during treatment, and at the conclusion of this study. Plasma BDNF concentrations and Nfl concentrations will be analyzed in order to determine whether BDNF level increase over time and Nfl levels decrease at the conclusion of this study.

**Data Analysis**

Statistical analysis for measuring executive function and cognitive function will be performed by obtaining the test scores from each test that the participants will perform. These test scores will then be converted into z-scores for each domain based on the mean and standard deviation of the sample at the given time period. An analysis of covariance (ANCOVA) test will be run to assess how the executive and cognitive function measures were affected by the treatment groups (Karssemeijer et al. 2017).

Levels of BDNF response to exercise will be assessed by calculating the percent change from each of the samples taken during this study. A one-way ANOVA test will be run to determine the effectiveness of treatment on BDNF concentration (Baird et al. 2018). For Nfl concentrations, a retrospective pseudo-predictive analysis will be run to determine whether the baseline Nfl levels are able to predict cortical thinning (Preische et al. 2019). A regression analysis between the rates of change in Nfl concentrations and MRI imaging will be performed (Preische et al. 2019).

**Potential Pitfalls**

There are a couple of potential pitfalls that may result from this study. The first being that there is not a mechanism that is employed to assess adherence for participants in the active control group program. Unlike the control group, the experimental group must monitor their heart rate while engaging in their aerobic exercise sessions, which
provides evidence that these participants are engaging in their respective exercise program. This is not the case for the control group. Therefore, to combat this problem, I could provide a way to document when these participants are engaging in their session by utilizing a fitness app or using a “check-in” system.

Another potential pitfall of this study could be that I am only studying how aerobic exercise affects brain health. I am leaving out other forms of exercise, such as resistance training and yoga, that could also be potentially beneficial therapeutic exercise programs aside from aerobic exercise to delay or prevent the onset of AD. A way to counter this pitfall would be to include another treatment group that engages in resistance training, yoga, or another form of exercise that differs from aerobic exercise.

**Potential Conclusions**

This study could have two potential conclusions: (1) individuals in the aerobic training group will have an increase in cognitive functioning, decrease in hippocampal loss, higher levels of BDNF and low levels of Nfl in their blood that persist long after exercise and helps delay or prevent the onset of AD or (2) these individuals in the aerobic training group have these effects listed above but they are only induced immediately following exercise and there is a high rate of individuals with Alzheimer’s disease at the conclusion of the study. In this experiment, the hypothesis would be supported by results that reflect conclusion one. If the hypothesis is supported, then this study would provide major contributions to this field of study and provide substantial support towards using long-term aerobic exercise programs as therapeutic strategies to help delay or prevent the onset of Alzheimer’s disease.
Future directions for this research would be to implement this long-term aerobic exercise program throughout hospitals, nursing homes, and other offices that care for individuals at risk for developing Alzheimer’s disease. This type of preventive care could potentially be more accessible to a wider population of individuals who may not be able to afford pharmacological options of care. In addition to being more cost-effective, long-term aerobic exercise programs are also a very low-tech option that could be implemented in a variety of settings (these programs can even be done in someone’s own backyard) rather than being limited to specific settings and offices like other therapeutic options.

The Alzheimer’s Association emphasizes how debilitating and crippling Alzheimer’s disease is for individuals with this severe disease and for their families or caregivers. Alzheimer’s disease is the 6th leading cause of death in the United States (Alzheimer’s Association 2019). There is a desperate need to change our focus from treating individuals with this disease to preventing its onset. The world’s demographic is beginning to shift and the elderly are becoming a big portion of the population, which is why it is so critical and important to find a way to delay or prevent the onset of Alzheimer’s disease. As a result, research attempting to find alternative therapeutic options to delay or prevent the onset of this disease is extremely valuable and highly important not only to individuals suffering from this disease but to our society as a whole. This study could provide a major contribution to the efforts of finding a way to make Alzheimer’s disease a distant memory.
References


