EXERCISE, AGING, AND COGNITION

INVESTIGATING THE EFFECT OF AEROBIC EXERCISE ON COGNITIVE FUNCTION IN OLDER ADULTS

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ABSTRACT

Aging is associated with cognitive decline and an increased risk for neurodegenerative disease. Physical exercise may be an effective intervention to enhance cognitive function in older adults; however, the optimal dose for maximal cognitive benefit is unknown. Additionally, the mechanism through which exercise may promote cognition in older adults is poorly understood. The present study investigated the effect of aerobic exercise intensity on cognitive function in three domains: memory, processing speed, and executive functions. Brain-derived neurotrophic factor (BDNF), a protein that supports the growth and survival of neurons, was examined as a potential mechanism underlying the effect of exercise on cognition. Sixty-four sedentary older adults (39 females; mean age=72 years; age range=60-88 years) were randomly assigned to one of three groups: 1) high-intensity interval training group (HIIT; n=21), 2) moderate continuous training group (MCT; n=20), or 3) active control group (n=23). Cognitive function was assessed pre- and post-intervention using a *Mnemonic Similarity Task* (memory), a *Go-nogo task* (processing speed and executive function), and a *Flanker task* (executive function). Serum BDNF concentrations were assessed using enzyme-linked immunosorbent assays (ELISAs). It was hypothesized that HIIT would result in the greatest cognitive benefit, followed by MCT. The control group was not expected to improve. It was predicted that improvements in cognition would be accompanied by increases in serum BDNF. HIIT resulted in better performance on the *Mnemonic Similarity Task* [$F(2, 55)=6.04$, $p=0.004$] compared to both MCT and control. The MCT

group had faster processing speed on the *Go-nogo task* [$F(2, 59)=4.16$, $p=0.02$] compared to control. HIIT and MCT both had a trend toward better performance on the *Go-nogo task* [$F(2, 59)=2.54$, $p=0.088$] compared to control. Only HIIT resulted in a trend toward better performance on the *Flanker task* [$F(2, 56)=2.41$, $p=0.099$] compared to both MCT and control. No significant differences were found in BDNF concentration between groups. This is one of the first trials to directly compare the effect of different intensities of aerobic exercise on cognitive function. Consistent with prior literature, the results suggest that aerobic exercise can enhance cognitive function in older adults, and critically, HIIT was the most effective. However, BDNF may not mediate the changes in cognition in older adults. This research may help inform exercise prescription for optimal cognitive health in the growing population of older adults.

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LIST OF ABBREVIATIONS

ANCOVA	Analysis of covariance
BDNF	Brain-derived neurotrophic factor
CA3	Coru ammonis 3
ELISA	Enzyme-linked immunosorbent assay
HIIT	High-intensity interval training
IES	Inverse efficiency score
IQR	Interquartile range
LDI	Lure discrimination index
MCT	Moderate continuous training
MST	Mnemonic similarity task
RPE	Rated perceived exertion
SD	Standard deviation
VO_2 peak	Peak oxygen uptake

DECLARATION OF ACADEMIC ACHIEVEMENT

A. Kovacevic's role:

- Contributed to study concept, design, and measurement selection
- Recruited study participants
- Prepared lab settings and materials
- Trained and supervised students and volunteers who assisted with data collection
- Led data collection, analysis, and interpretation
- Responsible for manuscript preparation

J.J. Heisz's role:

- Contributed to study concept, design, and measurement selection
- Obtained study funding
- Contributed to data analysis and interpretation

INTRODUCTION

Good cognitive abilities are crucial for independent functioning in daily life. However, aging is associated with a progressive decline in critical aspects of cognition including memory, processing speed and executive functions, which interferes with the individual's ability to fully engage with life. Physical activity is a promising modifiable lifestyle factor that can mitigate cognitive decline in older adults and reduce their dementia risk. Although many studies have shown that regular aerobic exercise can promote cognition across the lifespan, the optimal intensity remains unknown. High-intensity exercise has been shown to elicit greater increases in brain derived neurotrophic factor (BDNF), which is thought to improve cognition through neurogenesis; however, the dose-response effects have not been examined. The present study examined the impact of different aerobic exercise intensities on memory, processing speed and executive function. Serum BDNF was examined as a potential mechanism. The ultimate goal of this study was to determine the optimal intensity of aerobic exercise for maximal cognitive benefits in older adults to help inform exercise prescription for cognitive health.

Aging and Cognitive Function

Increasing age is associated with a progressive decline in cognitive function. However, not all cognitive abilities decline with age. Pragmatic aspects of cognition, such as semantic knowledge, generally improve or remain preserved, while mechanistic aspects, those that are necessary for processing and manipulating information, tend to decline (Burke & Barnes, 2006; Hedden & Gabrieli, 2004; Heisz & Kovacevic, 2016). Critically, these mechanistic aspects are necessary for navigating one's environment in

daily life and thus declines may lead to functional impairment. Unfortunately, mechanistic aspects of cognition begin to decline in early adulthood, driven by structural and functional changes in the brain (Salthouse, 2009). They continue to decline at a steady rate until approximately 60 years of age, beyond which point the rate of cognitive decline accelerates (Salthouse, 2009). The subsequent sections will review the behavioural and mechanistic changes in cognition with normal aging in more detail. This thesis will focus on three cognitive domains: memory, processing speed, and executive function.

Memory

Memory decline can begin as early as 20 years old and progress throughout the lifespan (Salthouse, 2003), accelerating to four times the rate beyond age 60 (Salthouse, 2009). Memory function is controlled by the medial temporal lobe system and the hippocampus (Buckner, 2004), which are particularly vulnerable to advancing age (Hedden & Gabrieli, 2004). Structurally, the medial temporal lobe undergoes age-related shrinkage (Raz, Rodrigue, Head, Kennedy, & Acker, 2004) with a six percent decrease in hippocampal volume each decade after the age of 50 (Raz, Gunning-Dixon, et al., 2004). This loss is concerning given that hippocampal volume is associated with memory performance in older adults (Rosen et al., 2003).

The medial temporal lobe and hippocampus are responsible for encoding and retrieving episodic and spatial memories (Burgess, Maguire, & O'Keefe, 2002; Kirwan & Stark, 2007). However, interference of highly similar memories poses a challenge to accurate retrieval (Kirwan & Stark, 2007). The ability to correctly distinguish these

similar memories is called high-interference memory, and is governed by interactions between subregions of the hippocampus, specifically, the dentate gyrus and the Coru ammonis 3 (CA3) (Berron et al., 2016; Marr, 1971; Rolls, 2013). The CA3 receives inputs from dentate granule cells along the mossy fiber network. Numerous similar inputs from the dentate gyrus create sparse and random connections with the CA3, which allows for similar memory traces to remain distinct (Rolls, 2013).

Unfortunately, the dentate gyrus is particularly vulnerable to aging, which manifests in high-interference memory deficits that worsen as inputs become more similar (Yassa et al., 2011; Yassa & Stark, 2011). However, the dentate gyrus is one of the two brain regions in which neurogenesis can persist throughout the lifespan (Zhao, Deng, & Gage, 2008). Neurogenesis in the dentate gyrus creates more random, nonoverlapping memory traces in the CA3, thereby reducing interference of similar memories (Becker, 2005). Therefore, it is hypothesized that interventions that induce hippocampal neurogenesis may mitigate the effects of age on high-interference memory. Physical exercise is a promising intervention strategy, as it has been shown to increase neurogenesis in the dentate gyrus (Erickson et al., 2011). The present study therefore tested the optimal intensity of exercise for performance on a putative neurogenesis-dependent task in older adults.

Processing Speed

Processing speed is necessary for receiving and appropriately responding to information in a timely manner. It is critical in situations where one must react quickly, such as avoiding an accident while driving. Unfortunately, processing speed slows

substantially with advancing age (Colcombe & Kramer, 2003; Hale, Myerson, Smith, & Poon, 1988; Hedden & Gabrieli, 2004; Nettelbeck & Rabbitt, 1992), and is one of the first functions affected by age-related cognitive decline (Finkel, Reynolds, McArdle, & Pedersen, 2007).

Mental processing is a global function that relies on multiple brain regions. It is therefore plausible that widespread age-related damage would underlie slowed processing. Indeed, white matter damage throughout the brain predicts the age-related decline in processing speed (Penke et al., 2010; Turken et al., 2008; Vernooij, Ikram, Vrooman, & et al., 2009). Accordingly, other cognitive functions may also suffer from these structural losses. Studies have shown that slower processing speed is indicative of decline in other cognitive domains (Salthouse, 1996), making it a useful biomarker of overall cognitive aging (Deary, Johnson, & Starr, 2010).

Executive Functions

Executive functions comprise a number of different abilities or control processes that govern cognition including planning, inhibition, attention, and working memory. They also tend to decline significantly with age (Heisz & Kovacevic, 2016; Park & Reuter-Lorenz, 2009). One executive function that shows particular decline is inhibition (Hasher, Stoltzfus, Zacks, & Rypma, 1991; Hasher & Zacks, 1988; Heisz & Kovacevic, 2016). Inhibition is the ability to focus attention and ignore prepotent responses, and is commonly assessed using a *Flanker* task. In this task, a participant must identify a central stimulus that is flanked by either congruent or incongruent stimuli. This is most typically done with arrows in either congruent (i.e., <<<<< or >>>>>) or incongruent (i.e., <<><<

or >><>>) formation. The task is more difficult in the *incongruent* condition, in which the participant must ignore the distraction of the dissimilar flanking arrows. This challenge is known as the *Flanker* effect. The *Flanker* effect is known to increase (worsen) with advancing age due to a decline in inhibitory control (Zhu, Zacks, & Slade, 2010).

Age-associated changes in the frontal-striatal circuit (Buckner, 2004) are responsible for declines in executive functions. The prefrontal cortex, which governs executive function, exhibits the most severe age-related decline (Hedden & Gabrieli, 2004; Raz, Gunning-Dixon, et al., 2004) including preferential volumetric losses with advancing age (Hedden & Gabrieli, 2004). White matter in the frontal lobe is particularly vulnerable to the aging process (Buckner, 2004). There is evidence to show that the extent of white matter lesions, as seen in magnetic resonance imaging, is linked to the severity of cognitive decline (de Groot et al., 2000). Given that the prefrontal cortex is especially vulnerable to age-related decline, interventions targeting this region are critical in order to maintain executive function ability for longer into the lifespan.

Addressing Cognitive Decline

Aging is associated with a decline in cognitive function and is the most important risk factor for developing dementia (Lindsay et al., 2002). Without effective intervention the prevalence of dementia is projected to increase dramatically, with 1 in 85 people expected to be living with Alzheimer's disease by 2050 (Brookmeyer, Johnson, Ziegler-Graham, & Arrighi, 2007). Unfortunately, there is no treatment currently available for dementia (T O'Brien & Burns, 2011).

It is unclear whether dementia is simply the severe end of the cognitive aging continuum, or whether it is a phenomenon distinct from normal brain aging (Buckner, 2004; Hedden & Gabrieli, 2004). One compelling hypothesis is that normal and pathological aging have different underlying mechanisms (Buckner, 2004). In this 'multiple factor framework', the pattern and location of neural pathology in the development of dementia is distinct from that in normal aging (Albert, 1997; Hedden & Gabrieli, 2004). For this reason, it is necessary to examine cognitive decline in healthy and impaired populations in isolation. Alzheimer's pathophysiology can arise many years before clinical manifestation of symptoms (Jack et al., 2013; Rajan, Wilson, Weuve, Barnes, & Evans, 2015) and therefore early intervention before a diagnosis is critical. This observation, in addition to absence of effective treatment and the rapidly growing population of older adults, strongly supports the urgent need to identify effective preventative strategies to mitigate cognitive decline. Critically, just a one-year delay in disease onset would result in nearly 10 million fewer cases worldwide (Brookmeyer et al., 2007).

Although everyone will experience some decline in cognitive ability across the lifespan, there is a large degree of variability in the extent and rate of decline across individuals (Rowe & Kahn, 1987; Schaie & Labouvie-Vief, 1974). Certain individuals may decline more rapidly than others, or to a greater degree (Rowe & Kahn, 1987). While age and genetics largely impact cognitive abilities, a large body of research suggests that external, lifestyle factors play an important role in determining both the rate and severity of decline (Barnes & Yaffe, 2011; Hertzog, Kramer, Wilson, & Lindenberger, 2008;

Hillman, Erickson, & Kramer, 2008). Critically, these factors are modifiable and thus are an important target for intervention. One such factor that has shown promise is physical activity.

Physical Activity and Cognitive Function

Observational Evidence

A substantial body of observational evidence suggests that a physically active lifestyle is conducive to maintaining cognitive function well into old age (Barnes, Whitmer, & Yaffe, 2007; Hertzog et al., 2008; Laurin, Verreault, Lindsay, MacPherson, & Rockwood, 2001; Middleton, Barnes, Lui, & Yaffe, 2010; Middleton & Yaffe, 2009; Rovio et al., 2005; Rowe & Kahn, 1987). Analyses from the Canadian Study of Health and Aging—a large, nation-wide cohort study of Canadians over 65 years old—argue that physical activity considerably reduces the risk of dementia (Fenesi et al., 2016; Laurin et al., 2001; Lindsay et al., 2002). Critically, when compared to other modifiable risk factors, physical activity has consistently been shown to have the largest effect on disease risk, even greater than cognitive inactivity, smoking, or the presence of other chronic diseases including depression and obesity (Barnes & Yaffe, 2011; Lindsay et al., 2002). Importantly, physical activity also improves most other risk factors for developing dementia, such as depression and cardiovascular health, further promoting cognitive health later in life (Barnes et al., 2007; Barnes & Yaffe, 2011; Middleton et al., 2010; Middleton & Yaffe, 2009). Evidently, a physically active lifestyle is strongly associated with maintained neurological health throughout the lifespan.

One factor that may underlie the relationship between physical activity and cognition is cardiorespiratory fitness. Good cardiorespiratory fitness has been associated with better cognitive function across multiple domains including memory and executive functions (Freudenberger et al., 2016; Roever & Bennett, 2016). In a longitudinal study, poor cardiorespiratory fitness at baseline was associated with greater cognitive decline over a 6-year period in healthy older adults, particularly in overall cognitive ability and executive functions (Barnes, Yaffe, Satariano, & Tager, 2003). This finding suggests that a physically active lifestyle may help reduce or protect from age-related cognitive dysfunction by improving cardiorespiratory fitness (Barnes et al., 2003). Increases in fitness have also been associated with changes in brain structure to support better function including volume increases in the prefrontal cortex (Weinstein et al., 2012) and medial temporal lobe (Boots et al., 2014).

However, other studies have contradicted the link between physical fitness and cognition. One review suggests that although exercise improves cognition, there is insufficient data to support that these improvements are mediated by increases in fitness (Angevaren, Aufdemkampe, Verhaar, Aleman, & Vanhees, 2008). Another review found that greater fitness gains were associated with poorer cognitive outcomes (Etnier, Nowell, Landers, & Sibley, 2006). Clearly, more work is needed to determine whether fitness improvements are necessary for cognitive gains.

Intervention Studies

Acutely, exercise improves cognitive function (Chang, Labban, Gapin, & Etnier, 2012); however, chronic exercise is necessary to improve both the size of the beneficial

effects (Etnier et al., 1997) and also for these effects to persist (Cotman & Berchtold, 2002; García-Capdevila, Portell-Cortés, Torras-Garcia, Coll-Andreu, & Costa-Miserachs, 2009; Nokia et al., 2016). For example, one study found that after one year of endurance training, cognitive status was maintained, whereas controls who did not exercise significantly declined (Muscari et al., 2010). This finding suggests that regular exercise can protect healthy older adults from age-related cognitive decline. Furthermore, a 2008 Cochrane review found that exercise has the potential to also improve cognitive function in older adults, particularly processing speed and attention (Angevaren et al., 2008). This is consistent with a review of 18 intervention studies suggesting that executive functions and speed of information processing benefit the most from physical exercise (Colcombe & Kramer, 2003). More recent reviews also yielded similar results (Guiney & Machado, 2013; Northey, Cherbuin, Pumpa, Smee, & Rattray, 2017; Smith et al., 2010).

Despite plenty of evidence supporting an association between exercise and cognition, numerous intervention studies have demonstrated inconsistent results for a causal relationship. A more recent Cochrane review of intervention studies found no evidence for cognitive benefit from exercise in older adults (Young, Angevaren, Rusted, & Tabet, 2015). Another recent review of 30 intervention studies found insufficient evidence to conclude that exercise improves cognitive function in older adults (Snowden et al., 2011). One reason cited by this review is poor study quality, including small sample sizes (many studies below 50 participants), non-randomized studies, and lack of reporting of between-groups effects (Snowden et al., 2011). Etnier et al. (1997) examined the effect of exercise on cognition across the lifespan and found that the size of the effect

was inversely related to study rigor (Etnier et al., 1997), which also suggests that variance in study quality has led to inconsistencies in the literature. Another factor that may contribute to the mixed results is the heterogeneity in intervention characteristics across studies, and lack of reporting of important dosage details such as exercise duration and intensity. Indeed, reviews have reported difficulty concluding an ideal dose of exercise due to considerable variation across included studies (Colcombe & Kramer, 2003). These inconsistencies lead to a poor overall understanding, and limited opportunity for replication in future studies. Rigorous randomized controlled trials are needed to confirm the effects of aerobic exercise on cognition in older adults.

Domain-Specific Effects of Exercise

The effect of exercise on specific domains of cognitive function remains unclear. While all cognitive domains have been shown to improve from exercise, there are variations across studies that warrant further examination.

Memory

Neuroimaging results provide convincing evidence for exercise-induced memory improvement via development of associated brain structures. For example, six months of aerobic exercise training has been shown to increase hippocampal volume in older women with probable mild cognitive impairment (Ten Brinke et al., 2014). Increases in hippocampal volume have also been observed with memory improvements in healthy older adults (Erickson et al., 2011). These studies suggest that exercise can both structurally and functionally change the brain to improve memory.

However, a number of studies fail to support the link between exercise and memory in older adults (Asl, Sheikhzade, Torchi, Roshangar, & Khamnei, 2008; Clark, Vandermorris, & Heisz, 2015; Heisz, Vandermorris, Wu, McIntosh, & Ryan, 2015). Animal literature suggests that exercise may improve memory in young, but not aged rodents (Asl et al., 2008; Creer, Romberg, Saksida, van Praag, & Bussey, 2010). Heisz et al. (2015) observed no relationship between self-reported physical activity and episodic memory. Given these contradicting findings, more work is clearly needed to better understand the effects of aerobic exercise on memory in older adults.

High-interference memory is a particularly interesting memory function and a focus of this thesis because it is governed by the dentate gyrus, which is especially vulnerable to aging (Yassa et al., 2011; Yassa & Stark, 2011). Importantly however, it is one of the few brain regions that can experience neurogenesis throughout the lifespan (Zhao et al., 2008) and is therefore considerably malleable to change. Exercise has been shown to induce neurogenesis in the dentate gyrus in mice (Pereira et al., 2007). Neurogenesis in this region has been linked to improvements in high-interference memory (Becker, 2005). In a study by Creer et al. (2010), running enhanced high-interference memory in adult mice, and this improvement was positively correlated with neurogenesis in the dentate gyrus. In younger human subjects, exercise increased fitness and high-interference memory (Déry et al., 2013). However, the relationship between exercise and high-interference memory has not been established in older humans. It has been shown that exercise increases hippocampal volume, neurogenesis in the dentate gyrus, and enhances other memory functions in older adults (Erickson et al., 2011), thus

high-interference memory would also be expected to improve. To test this prediction, the proposed study will examine the relationship between aerobic exercise intensity and high-interference memory.

Processing Speed

Numerous reviews suggest that processing speed shows particular improvement from exercise (Angevaren et al., 2008; Colcombe & Kramer, 2003; Smith et al., 2010). Physical activity and fitness have been associated with faster reaction times in simple and choice reaction time tasks in adults over 75 years old (Era, Berg, & Schroll, 1995). A randomized controlled trial found that three years of exercise improved processing speed in older women (Rikli & Edwards, 1991). In a more recent trial, only four weeks of exercise training was effective in significantly improving processing speed in older adults, with large effects (Nouchi et al., 2014). Exercise-induced improvements in processing speed have been linked to more widespread neural activation while completing cognitive tasks (Rosano et al., 2010), and potentially neurogenesis, but further studies are needed to confirm this (Nouchi et al., 2014; Rosano et al., 2010). Overall, the literature shows consistent improvements in processing speed from exercise.

Executive Functions

Exercise has been shown to improve executive functions in healthy people across the lifespan. In particular, older adults obtain benefits in the greatest range of executive functions, including inhibitory control on *Go-nogo* and *Flanker* tasks (Guiney & Machado, 2013). Tasks of inhibitory control and attention tend to show particular improvement from exercise (Heisz & Kovacevic, 2016). Two randomized controlled

trials comparing aerobic exercise to resistance exercise or a control group found that only sedentary older adults who engaged in aerobic exercise groups showed improvements in inhibition, measured by the Stroop task (Dustman et al., 1984; Guiney & Machado, 2013; Smiley-Oyen, Lowry, Francois, Kohut, & Ekkekakis, 2008). Aerobic exercise has also been shown to improve inhibitory control in older adults on a *Stop signal* task (Kramer et al., 2001) and on a *Flanker* task (Colcombe et al., 2004). This benefit is important given that attention and inhibition are particularly vulnerable to the effects of aging (Hasher et al., 1991; Hasher & Zacks, 1988; Heisz & Kovacevic, 2016).

Some studies testing the effect of exercise on several cognitive domains have found improvement *only* in executive functions (Masley, Roetzheim, & Gualtieri, 2009), suggesting selective benefits. For example, one study tested processing speed, memory, and executive functions, and only executive functions improved significantly more from exercise than from a no exercise control (Masley et al., 2009). This finding highlights the robustness of the effect of exercise on executive functions.

Potential Mechanism: BDNF

Physical exercise, particularly aerobic training, has been shown to increase the production of new neurons in the hippocampus (Curlik & Shors, 2013). Over time, the increase in neurogenesis can bolster cognitive abilities governed by the hippocampus, including learning and memory. One peripheral indicator of neurogenesis is BDNF.

BDNF helps to support the growth and survival of neurons (Cotman & Berchtold, 2002). It has been associated with cognitive ability, including memory and executive functions (De Assis & Almondes, 2017; Leckie et al., 2014). Evidence from animal

studies suggests that BDNF is particularly important for high-interference memory, as it facilitates hippocampal neurogenesis (Bekinschtein, Oomen, Saksida, & Bussey, 2011). Aerobic exercise has been shown to increase both BDNF protein and mRNA in the hippocampus of aged rats (Fu, Zhang, & Yuan, 2017). This increase was correlated with an amelioration of induced memory deficits. Thus, BDNF warrants further investigation as a potential mechanism for exercise-induced improvements in cognitive function.

Dose-Response Relationship

There is promising evidence for a positive association between aspects of cognition and physical activity in older adults. However, the optimal *dose* of exercise for maximal cognitive benefits is unknown. Exercise characteristics such as the type of exercise (i.e., aerobic, resistance), frequency, duration, and intensity, may moderate the effect that exercise has on cognitive function (Colcombe & Kramer, 2003). For example, Laurin et al. (2001) found a inverse relationship between the frequency and intensity of physical activity, and the risk of cognitive impairment. Similarly, Larson et al. (2006) found a significant reduction in dementia risk in older adults who exercise three or more times per week compared to those who exercise less than three times per week. These studies suggest that more exercise is better; however, a recent study found that too much exercise can actually have negative consequences (Kennard & Woodruff-Pak, 2012). Specifically, mice that performed fast running exercise (high-impact) for five weeks experienced fitness improvements, but impaired performance on the Morris water maze task, which tests learning and memory. Conversely, the group that did slower running (low-impact) experienced significant improvement on the task (Kennard & Woodruff-

Pak, 2012). This finding suggests that there is an ideal dose of physical exercise for optimal cognitive function.

Exercise duration is one moderator variable that has been well studied in relation to cognitive benefits. Most studies have tested interventions lasting from 6 months to a year, but recent evidence suggests that shorter-term interventions are also effective. Three one-hour aerobic exercise sessions for 12 weeks have been shown to improve cardiorespiratory fitness, and immediate and delayed memory in older adults compared to doing no exercise (Chapman et al., 2013). Importantly, the control group experienced a significant decline in immediate memory over the 12 weeks. The improvement in cognition in the exercise group was associated with an increase in blood flow in the hippocampus, which is responsible for memory function (Chapman et al., 2013). However, this study did not find significant changes in executive functions, a link that has been strongly supported in prior literature. A potential explanation is that the intensity of exercise (moderate: 50-75% heart rate max) was insufficient for gains. In another study examining the dose-response relationship between exercise duration and cognition, longer exercise bouts were found to have beneficial fitness effects in older adults; however this was not the case for cognition (Vidoni et al., 2015). It was found that fitness was more strongly associated with cognition than the duration of the exercise bout (i.e., 75, 150, or 225 minutes per week) and thus interventions should place more emphasis on interventions that increase fitness. Importantly, physical fitness may be more related to exercise intensity rather than duration.

Exercise intensity is an understudied factor for understanding the relationship between exercise and cognition. Most studies have looked at moderate-to-vigorous intensity training (i.e., between 50 and 85% of peak heart rate), but very few have examined high-intensity interval training in comparison to moderate or low intensities. High-intensity exercise has greater benefits for *physical* health; however, the optimal exercise intensity for *cognitive* health is unknown. Given that time is the most commonly cited barrier to engaging in regular exercise (Gibala, 2007), it is important to determine whether shorter bouts of high-intensity exercise are effective.

There is some evidence to suggest that higher intensity physical exercise may lead to greater cognitive benefit. For example, an acute bout of high-intensity aerobic exercise induces significantly greater increases in serum BDNF concentrations than lower-intensity exercise (Ferris, Williams, & Shen, 2007). BDNF supports brain function and therefore this suggests that engaging in high-intensity aerobic exercise training may provide superior cognitive benefits. High-intensity interval exercise has been shown to elicit greater fitness adaptations in older adults with cardiovascular disease compared to moderate-intensity continuous exercise (Rognmo, Hetland, Helgerud, Hoff, & Slørdahl, 2004; Wisløff, 2007). High-intensity training has also been shown to improve cardiovascular health and endothelial function (Wisløff, 2007). Given that fitness is associated with cognition, it is reasonable to predict that high-intensity training would be better for improving cognitive ability. Although the superior benefits of high-intensity training have been observed for physical function, it remains unclear whether the same is true for cognitive function.

While it seems that high-intensity training would be superior for cognitive ability, some studies suggest that moderate-intensity exercise may in some cases be optimal compared to low- and high-intensity exercise (Brisswalter, Collardeau, & René, 2002; Chang & Etnier, 2009). One study showed improvement from exercise over time, but no difference between low- and moderate-intensity training for a host of outcomes including cardiorespiratory fitness and cognitive function (Stevenson & Topp, 1990); however, this study did not include high-intensity training. A recent review of reviews found that while physical activity is beneficial for cognition, there is insufficient evidence to support a dose-response relationship (Olanrewaju, Kelly, Cowan, Brayne, & Lafortune, 2016). Furthermore, this review of reviews found that no existing systematic reviews of exercise and cognition in older adults have reported on the dose-response relationship. Further research is clearly needed to elucidate the optimal intensity of exercise for maximal cognitive benefits in older adults. This dose-response relationship is particularly important to understand for an older adult population that may be more restricted in their abilities and therefore would likely benefit from targeted interventions.

Purpose and Hypothesis

Taken together, the previous sections suggest that physical activity is a promising modifiable lifestyle factor that can be leveraged to improve cognitive function in older adults. However, the domain-specific effects (i.e., memory, processing speed, executive functions), the effect of exercise intensity, and the mechanism (i.e., BDNF) remain poorly understood. Importantly, this knowledge would provide insight to help inform exercise guidelines for cognitive function in older age.

To offer much needed clarity to these issues, this study investigated the effect of exercise intensity on cognitive function across a number of domains in sedentary, but otherwise healthy older adults. Participants were randomly assigned to one of three exercise training groups: a high-intensity group, a moderate-intensity group, or an active control group. Cognitive function was assessed in three domains (memory, processing speed, and executive function) before and after the intervention. Serum blood samples were also collected to measure peripheral BDNF concentrations. The effect of group on cognitive function and BDNF was determined. The hypothesis was that high-intensity exercise training would lead to the greatest improvements in cognitive function, coupled with a respective increase in BDNF.

METHOD

Participants

Based on a meta-analysis of the effects of aerobic exercise on cognition in older adults (Colcombe & Kramer, 2003), a small to moderate-sized effect was expected (Cohen's d=0.41). A total of 61 participants were required to detect a significant difference of this magnitude between groups with 80% power and α=0.05. Participants were over-recruited to account for potential dropout.

The study took place over a period of approximately 2.5 years from August 2014 to March 2017. Participants were recruited on a rolling basis throughout the study period through local news outlets and postings. Participants consisted of sedentary, but otherwise healthy community-dwelling adults over the age of 60 years. Exclusion criteria included engaging in more than one hour of vigorous physical activity per week, or a diagnosis of

cognitive impairment. Eligibility was assessed through verbal or written confirmation via phone or email. Potentially eligible participants completed a stress test with a physician prior to enrolment to screen for any abnormal response to physical exercise. Participants with abnormal responses were deemed ineligible. This study received ethics clearance from the Hamilton Integrated Research Ethics Board. All participants provided written informed consent prior to experimental procedures and were compensated $40 upon study completion.

Procedure

The experimental procedure consisted of a pre and post intervention assessment, separated by a 12-week intervention. Pre and post intervention assessments took approximately 3 hours each and consisted of a fasted blood draw, followed by one hour of cognitive assessments, a half hour of physical and fitness assessments, and a half hour of questionnaire-based assessments. Post-testing was completed within 48 hours of the final intervention exposure.

Participants were assigned to groups by a researcher using blocked randomization and stratified by sex. Randomization took place prior to pre-intervention assessment, but participants did not learn their placement until assessments were completed. Assessors were not blinded to group assignment. Participants trained in one of three groups for the duration of the intervention: 1) High-intensity interval training group (HIIT; n=21), 2) Moderate-intensity continuous training group (MCT; n=20), or 3) Active control group (n=23). The measures used in the pre and post intervention assessments, and the training protocols are described in the subsequent sections.

Pre and Post Intervention Assessment

BDNF

Peripheral blood samples were collected from participants in the morning following 12 hours of fasting. Serum samples were obtained from whole blood collected in BD Vacutainer SST tubes (BD, Franklin Lanes, NJ, USA). The tubes were allowed 30 minutes to clot at room temperature upon collection and were then centrifuged at 4000 rpm for 10 minutes at 4°C. The supernatant was then aliquoted into Eppendorf tubes and stored at -80°C until analysis.

Serum BDNF concentrations were quantified using an enzyme-linked immunosorbent assay (ELISA) according to kit specifications using the human free BDNF Quantikine ELISA kit (R&D Systems; Minneapolis, MN, USA; cat#SBD00). All samples and standards were run in duplicate and the optical density of samples was determined after 10 minutes of adding Stop Solution at 450 nm with wavelength correction set to 540 nm. Samples were measured using BioTek's Synergy Mx Microplate Reader and Gen5 1.11 Microplate Reader and Imager Software (BioTek).

Cognitive Assessment

Memory Task

High-interference memory was assessed using an adapted *Mnemonic Similarity Task* (MST) (Stark, Stevenson, Wu, Rutledge, & Stark, 2015; Stark, Yassa, Lacy, & Stark, 2013). Participants began with an encoding phase in which 60 full colour images of everyday objects on a white background were presented in random order on a computer screen for 2 seconds each. A blank screen preceded each trial for 500 milliseconds.

Participants were instructed to classify each item as indoor or outdoor using the "1" and "2" keys, respectively, on the number pad. Immediately following the encoding phase, participants engaged in a forced-choice visual recognition phase, in which they classified items as "Old" (repetitions), "Similar" (lures), or "New" (foils) using the "1", "2", or "3" key, respectively, on the number pad. The recognition phase consisted of 90 trials presented in random order for an unlimited time until the participant responded: 30 stimuli were repeated from the encoding phase (repetitions), 30 were similar, but not identical (lures), and 30 were not previously viewed (foils). Performance on the task, corrected for response bias, was assessed using the lure discrimination index (LDI): the difference between the proportion of correctly identified lures as "Similar" minus the proportion of incorrectly classified foils as "Similar" [p("Similar"|Lure)-p("Similar"|Foil)] (Stark et al., 2015; Stark et al., 2013).

The data were checked to ensure participants were performing the task correctly. Classifying foils as 'New' is relatively simple, therefore participants who did not classify any foils as 'New' were thought to not have understood the task instructions. One participant's data for the MST were discarded for this reason.

Processing Speed Task

Processing speed was assessed using a *Go-nogo* task (Clark et al., 2015). Participants were presented with 120 letters in white font on a black background in random order on a computer screen for 500 milliseconds each. They were instructed to respond as quickly as possible by pressing the space bar when they saw any letter (go trials) except for "A", "S", or "F" (nogo trials). The nogo trials comprised one third of the

total number of trials. A blank screen preceded the presentation of a stimulus for a jittered duration between 500 millisecond and 1 second. Processing speed was assessed as the mean response time of the correct responses on go trials.

Executive Function Tasks

Executive function was tested using two computer tasks: a *Go-nogo* task (Clark et al., 2015), and a *Flanker* task.

The *Go-nogo* task described above was also used to assess executive functions using an inverse efficiency score (IES) (Bruyer & Brysbaert, 2011). The IES is calculated as the mean response time of the correct responses on go trials divided by the proportion of trials that were responded to correctly. By including accuracy, this calculation accounts for the controlled processing required to complete the task in addition to the speed of response.

In the *Flanker* task, a fixation cross was centered on the computer screen for 1 second, after which a single set of five arrows appeared for 50 milliseconds. The set was either congruent (i.e., "<<<<<" or ">>>>>") or incongruent (i.e., "<<><<" or ">><>>"). There were a total of 90 trials and one third were incongruent. Participants were instructed to indicate whether the center arrow in the set was pointing left or right by pressing the "z" or "/" key, respectively. There were an equal number of left and right target responses. Performance on the task was assessed using an IES whereby the mean response time of the correct responses on incongruent trials was divided by the proportion of incongruent trials that were responded to correctly.

Fitness Assessment

Fitness assessment to predict peak oxygen uptake (VO_2 peak) was performed at pre-test, midpoint, and at post-test according to a modified Bruce protocol on a motor-driven treadmill (Life Fitness 95Ti). Each stage of the protocol was 3 minutes long. Participants walked at a speed of 1.7 mph and 0% grade in the first stage, and 1.7 mph and 5% grade in the second stage, in accordance with the Bruce protocol modifications made by Willemsen et al. (2010). The remainder of the test followed the standardized Bruce protocol (Sheffield & Roitman, 1976). A trained research assistant supervised the test and recorded time at exhaustion, heart rate at each interval and at exhaustion (measured using Polar FT1 heart rate monitors), and Rated Perceived Exertion (RPE) at each interval according to the Borg 6-to-20 scale (Borg, 1982). The test was terminated upon volitional exhaustion or presentation of abnormal symptoms. Predicted VO_2 peak was calculated using the equation below, where the weighting factor was 1 for men and 2 for women (Bruce, Kusumi, & Hosmer, 1973). The duration used in the equation was that achieved on the standardized Bruce protocol, not including the six minutes added as a result of the modification (Willemsen et al., 2010). Since this protocol was a measure of predicted aerobic fitness, participants' results (VO_2 peak and peak heart rate) on the modified Bruce protocol were correlated with performance on the exercise stress test, completed prior to study enrolment, to ensure that the predicted measures are valid.

$$\textit{Predicted } VO_2 \textit{ peak} = 6.70 - 2.82 \textit{ (weighting factor for sex)} + 0.056 \textit{ (duration in seconds)}$$

Participants completed a familiarization at pre-test prior to the full protocol, which took place at a subsequent visit. During the familiarization, participants completed 9.5 minutes (the first 3 stages) of the modified Bruce protocol, unless volitional exhaustion was reached earlier. An additional fitness assessment was completed at midpoint to reassess peak heart rate and progress exercise training if a greater peak heart rate was achieved. Eleven participants who first enrolled in the study completed the Single Stage Treadmill Walking Test, a submaximal aerobic fitness test (Ebbeling, Ward, Puleo, Widrick, & Rippe, 1991) instead of the maximal modified Bruce protocol, which was subsequently used for all participants upon ethics clearance. Participants who completed the submaximal aerobic fitness test were excluded from analysis of aerobic fitness.

Intervention Training

Participants in all groups met three times per week for 12 weeks for intervention training supervised by a trained research assistant. The 18th session was replaced with a midpoint exercise test resulting in a total of 35 training sessions (actual completed M=33.80, SD=3.73). Participants were accommodated for missed exercise sessions and were instructed not to engage in additional physical activity for the duration of the study.

The HIIT and MCT training protocols were adapted from those described in Wisløff (2007). Exercise training was completed on a motor-driven treadmill (Life Fitness 95Ti). The speed and incline of the treadmill were continually adjusted to ensure participants were training at their target heart rate, determined from the peak heart rate achieved in the fitness assessment, and target RPE. In cases where the target heart rate

and target RPE were not both achieved, heart rate took precedence to ensure participant safety, and because it is an objective measure.

HIIT Group

Participants warmed up for 3 minutes at 0% grade and 50% to 70% of peak heart rate, then 10 minutes at 5% grade and 60% to 70% of peak heart rate. Participants then walked four 4-minute intervals at 5% grade and 90% to 95% of peak heart rate (target RPE=16-18+). These intervals were separated by 3-minute active recovery periods where participants walked at 50% to 70% of peak heart rate (target RPE=9-11). After the final high-intensity interval, participants walked a 3-minute cool-down at 50% to 70% of peak heart rate. A final 2-minute cool-down was completed following the protocol pre-programmed in the treadmill. Total exercise time was 43 minutes. Heart rate and RPE were recorded at the end of each interval.

MCT Group

Participants warmed up for 3 minutes at 0% grade and 50% to 70% of peak heart rate before walking continuously at 70% to 75% of peak heart rate for 47 minutes (target RPE=12-14). A final 2-minute cool-down was completed following the protocol pre-programmed in the treadmill, as above. Total exercise time was 52 minutes. Heart rate and RPE were recorded after the warm-up and every 7 minutes for the remainder of the session.

Active Control Group

Participants engaged in a series of non-aerobic seated and standing stretches. The program was specifically designed for older adults and aimed at whole-body stretching.

Stretches were held for approximately 30 to 40 seconds each. Each session was 30 minutes long. RPE was recorded after each 30-minute session. These sessions took place in a large classroom.

Statistical Analysis

Data to be analyzed were checked to ensure that the appropriate assumptions were met for each analysis. All data were checked for outliers and normality. Outliers were defined as values beyond quartiles 1 (Q1) and 3 (Q3) with a step of 1.5 times the interquartile range (IQR; i.e., values <Q1−1.5IQR or >Q3+1.5IQR). Normality was assessed by histograms and significance on the Kolmogorov-Smirnov test (p<0.05 is non-normal). Outliers were removed and non-normal data were transformed prior to analysis. For analyses of covariance (ANCOVAs), homogeneity of variance was assessed using Levene's test (p<0.05 is non-homogenous).

Manipulation Check

The mean number of sessions attended, and heart rate and RPE during exercise were calculated to ensure that the intended prescription was achieved.

To confirm that the interventions induced the expected fitness adaptations from pre- to post-test, a univariate ANCOVA was conducted on post-test predicted VO_2 peak values with a between-subjects factor of group, and with age and pre-test predicted VO_2 peak values entered as covariates. To verify that the modified Bruce protocol used in this study was a valid measure of both aerobic fitness and peak heart rate, two two-tailed partial correlations, controlling for age, were conducted: one between predicted VO_2 peak achieved on the modified Bruce protocol and VO_2 peak achieved on the stress test, and

one between peak heart rate achieved on the modified Bruce protocol and peak heart rate achieved on the stress test.

In accordance with the 2010 Consolidated Standards of Reporting Trials (CONSORT) Statement, baseline differences between groups were not compared statistically (de Boer, Waterlander, Kuijper, Steenhuis, & Twisk, 2015). Since participants were randomized, a statistical test of baseline data would assess the probability of differences occurring by chance, when any variance was indeed by chance due to random assignment (de Boer et al., 2015). Instead, baseline data were considered in the interpretation of results.

Group-Based Analyses

To evaluate the effect of group on cognitive performance and BDNF concentration, univariate ANCOVAs were conducted on the post-test scores of each measure using a between-subjects factor of group. Age and pre-test scores were used as covariates. Post hoc pairwise comparisons were performed to examine group effects. To determine whether changes in predicted fitness were correlated with changes in cognitive function, one-tailed partial correlations, controlling for age, were conducted between VO_2 peak change scores and change scores for each cognitive outcome. All change scores were determined by subtracting pre-test values from post-test values.

RESULTS

Participant flow through the study is presented in Figure 1. A total of 83 interested and eligible participants attended the pre-testing session. Five participants withdrew before beginning training and thus 78 were enrolled in the study. Thirteen participants

(17%) withdrew during training (3 from HIIT, 5 from MCT, and 5 from active control). One participant was excluded from analysis upon becoming ineligible near study completion. This resulted in 64 participants (39 females; mean age=72 years; age range=60-88 years) who completed the study and were included in the analysis. Baseline demographic data are represented in Table 1.

Manipulation Check

All analyzed data met the outlined assumptions including normality and homogeneity of variance. Data from the *Flanker* task were positively skewed and were reciprocally transformed to a normal distribution.

Participants adhered to their respective prescribed exercise interventions (Table 2). Although RPE was low for the desired intensity, target heart rate was achieved and was used as a primary indicator of intensity. An additional consideration was whether participants were taking beta-blockers, which may limit the ability to achieve higher intensities of exercise. The range of peak heart rates amongst participants not on beta-blockers was 88 to 168 beats per minute. Six study completers were taking beta-blockers (3 in MCT, 3 in control). Of the four beta-blocked participants for whom peak heart rate data were available, all were within the range of non-beta blocked participants (97, 120, 122, and 124 beats per minute).

Table 3 presents the mean predicted VO_2 peak values for all groups. The interventions induced fitness adaptations from pre- to post-test, such that exercise training led to the greatest predicted VO_2 peak [$F(2,43)=26.45$; $p<0.001$; $\eta_p^2=0.55$] (Figure 2). Pairwise comparisons revealed that both the HIIT and MCT groups had greater predicted

VO_2 peak at post-test than the active control group (29.84±4.92 vs. 18.69±6.82; p<0.001; d=1.88, and 30.25±3.78 vs. 18.69±6.82; p<0.001; d=2.10, respectively).

Table 1 presents the mean VO_2 peak and mean peak heart rate values at baseline for all groups on both the modified Bruce protocol used in this study and on the stress test conducted prior to study enrolment. Partial correlations between VO_2 peak and peak heart rate measures on the modified Bruce protocol and the stress test were significant. VO_2 peak values achieved on the modified Bruce protocol were significantly correlated with those from the stress test [r(30)=0.74; p<0.001]. Similarly, peak heart rate values achieved on the modified Bruce protocol were significantly correlated with those from the stress test [r(46)=0.71; p<0.001]. Scatterplots of correlations for VO_2 peak and peak heart rate are presented in Figures 3 and 4, respectively.

Group-Based Analyses

Table 3 presents the mean performance on all cognitive tasks and the mean concentration of BDNF for all groups.

Memory Task

Figure 5 depicts the LDI on the MST across groups. There was a significant main effect of group on LDI [F(2, 55)=6.04; p=0.004; η_p^2=0.18]. Pairwise comparisons revealed that the HIIT group performed significantly better at post-test than both the MCT group and the active control group (0.34±0.14 vs. 0.17±0.14; p=0.003; d=1.21, and 0.34±0.14 vs. 0.17±0.17; p=0.004; d=1.09, respectively). The MCT and active control groups were not significantly different.

Processing Speed Task

Figure 6 depicts reaction time on the go trials in the *Go-nogo* task. There was a significant main effect of group on reaction time [$F(2, 59)=4.16$; $p=0.020$; $\eta_p^2=0.12$]. Pairwise comparisons revealed that the MCT group had faster reaction times at post-test compared to the active control group (461.99±50.99 vs. 518.38±65.17; $p=0.006$; d=0.96). There were no significant differences between the HIIT and MCT groups, nor the HIIT and active control groups.

Executive Function Tasks

Figure 7 depicts the IES for the go trials on the *Go-nogo* task and Figure 8 depicts the IES for the incongruent trials on the *Flanker* task. There was a trend towards a main effect of group on IES on the *Go-nogo* task [$F(2, 59)=2.54$; $p=0.088$; $\eta_p^2=0.08$] and on IES on the *Flanker* task [$F(2, 56)=2.41$; $p=0.099$; $\eta_p^2=0.08$].

On the *Go-nogo* task, both the HIIT and MCT groups had a trend toward better IES at post-test compared to the active control group (488.36±51.37 vs. 529.41±70.70; $p=0.056$; d=0.66, and 484.77±64.33 vs. 529.41±70.70; $p=0.057$; d=0.66, respectively). There were no differences between the HIIT and MCT groups.

The HIIT group had a trend toward better performance on the *Flanker* task at post-test than both the MCT group and the active control group (818.08±174.39 vs. 1274.39±919.70; $p=0.060$; d=0.69, and 818.08±174.39 vs. 1315.11±1054.42; $p=0.058$; d=0.66, respectively). There were no significant differences between the MCT and active control groups.

BDNF

Figure 9 depicts BDNF concentrations. There was no main effect of group on BDNF concentrations at post-test [$F(2, 53)=0.17$; $p=0.847$; $\eta_p^2=0.006$].

Changes in Fitness and Cognition

Partial correlations revealed that the change in predicted VO_2 peak was significantly correlated with the change in high-interference memory performance on the MST [$r(44)=0.26$; $p=0.043$] (Figure 10). Correlations between the change in predicted VO_2 peak and change in reaction time on the *Go-nogo* task as well as change in IES on the *Go-nogo* task were nearing significance [$r(44)=-0.20$; $p=0.089$ and $r(44)=-0.20$; $p=0.091$, respectively] (Figures 11 and 12, respectively). There was no significant correlation between change in predicted VO_2 peak and change in IES on the *Flanker* task.

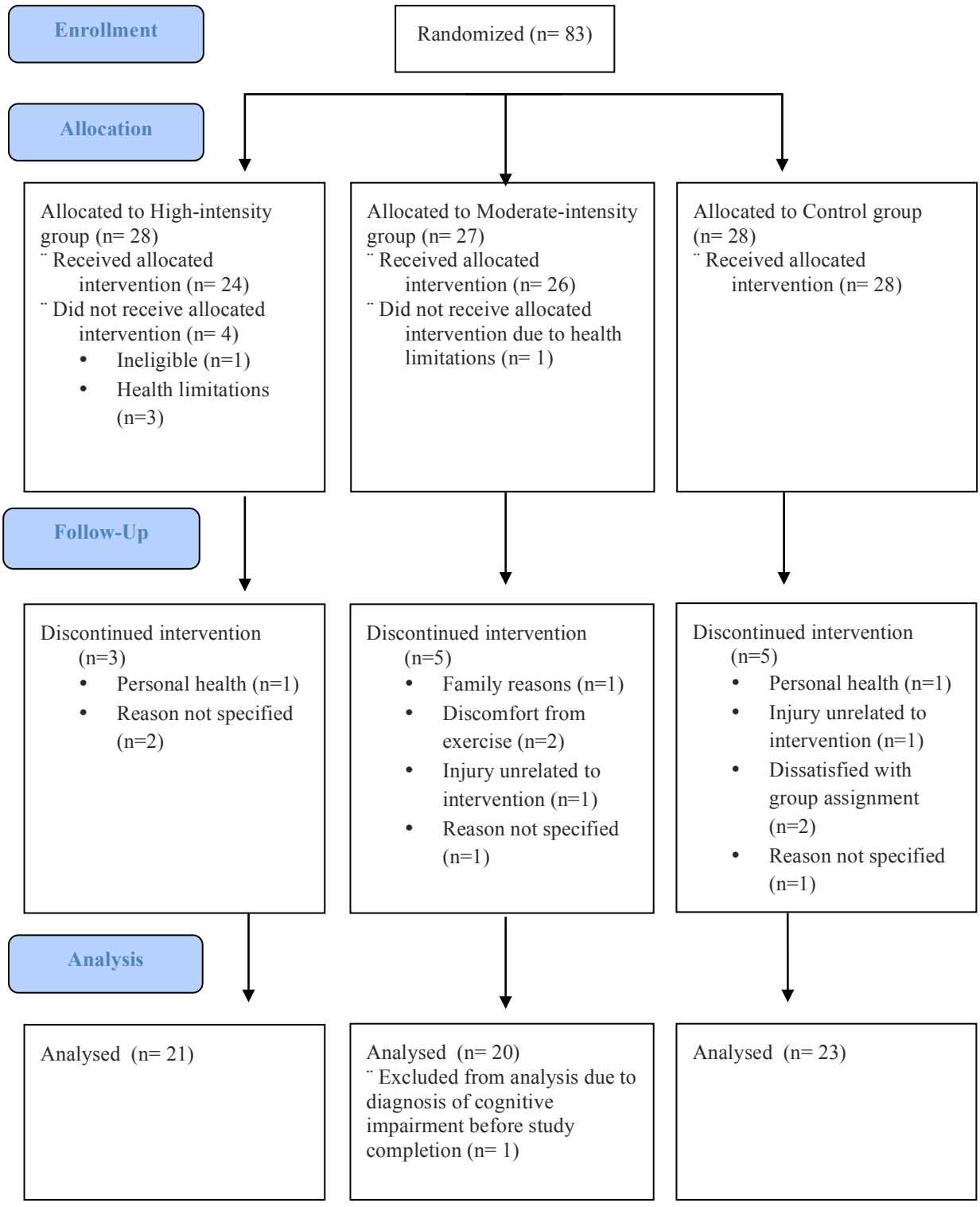

Figure 1. Flow of participants through the study.

Table 1: Demographic characteristics at baseline across groups.

	HIIT (n=21)	MCT (n=20)	Control (n=23)
Age (years)	72.43 (4.40)	72.00 (6.21)	71.48 (6.63)
Sex (female/male)	14/7	10/10	15/8
Education			
Did not complete high school	4	3	3
Completed high school	7	6	9
Completed college/undergrad	10	8	11
Completed postgrad	0	3	0
MoCA (max score = 30)	25.38 (3.06)	26.10 (3.01)	26.30 (2.40)
Body Mass Index (kg/m^2)	27.10 (3.89)	27.99 (3.65)	29.71 (6.00)
Blood pressure (mmHg)			
Systolic	138.69 (17.76)	139.65 (23.77)	140.22 (19.40)
Diastolic	73.12 (9.31)	71.30 (11.05)	69.00 (8.55)
β-blockers			
No	16	15	15
Yes	0	3	3
Unknown	5	2	5
Predicted VO_2 peak (ml/(kg•min))*	25.04 (6.21)	24.90 (5.53)	19.18 (6.69)
Stress test VO_2 peak (ml/(kg•min))*	21.14 (2.96)	20.46 (4.04)	18.13 (3.67)
Peak heart rate (bpm)*	142.65 (12.88)	138.53 (14.47)	134.00 (24.24)
Stress test peak heart rate (bpm)*	142.85 (16.95)	137.65 (19.21)	129.68 (23.72)

Notes: Data are mean (SD) or number of participants. MoCA: Montreal Cognitive Assessment (Nasreddine et al., 2005); bpm: beats per minute.

*:means and SD based on fewer number of participants with available data (Predicted VO_2 peak, HIIT=17, MCT=17, Control=18; Stress test VO_2 peak, HIIT=15, MCT=12, Control=15; Peak heart rate, HIIT=17, MCT=17, Control=18; Stress test peak heart rate, HIIT=20, MCT=20, Control=22).

Table 2: Intervention training characteristics across groups.

Outcome	HIIT (n=21)	MCT (n=20)	Control (n=23)
Training sessions attended	33.81 (3.64)	32.50 (5.05)	34.91 (1.68)
Session heart rate			
Mean heart rate	125.05 (9.17)	104.80 (11.91)	N/A
Mean percentage of peak	87.40 (3.59)	74.56 (5.23)	N/A
Mean session RPE (6-20)	12.91 (1.93)	9.28 (1.59)	8.30 (1.73)

Notes: Data are mean (SD). N/A: not applicable; RPE: Rated perceived exertion.

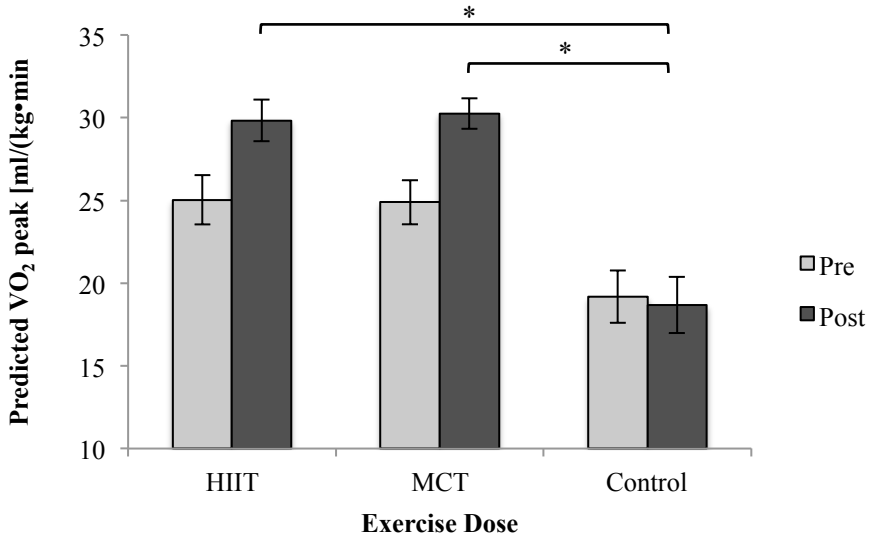

Figure 2. Mean predicted VO_2 peak and standard error at pre- and post-test across groups. *Notes:* * denotes significance (p<0.05).

Table 3: Mean values for predicted VO_2 peak, cognitive outcomes, and BDNF at pre- and post-test across groups.

	HIIT				MCT				Control				ANCOVA	
	Pre		Post		Pre		Post		Pre		Post			
Outcome	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	*F*	*p*
Predicted VO_2 peak (ml/(kg•min))	17	25.04 (6.21)	15	29.84 (4.92)[b]	17	24.90 (5.53)	17	30.25 (3.78)[b]	18	19.18 (6.69)	16	18.69 (6.82)	26.45	<0.001
LDI	21	0.26 (0.15)	21	0.34 (0.14)[a,b]	19	0.24 (0.24)	17	0.17 (0.14)	22	0.12 (0.12)	22	0.17 (0.17)	6.04	0.004
Go reaction time (ms)	21	479.39 (55.79)	21	483.84 (51.29)	19	481.82 (57.08)	20	461.99 (50.99)[b]	23	506.77 (63.12)	23	518.38 (65.17)	4.16	0.020
Go IES (ms)	21	494.42 (66.02)	21	488.36 (51.37)[d]	19	502.07 (65.05)	20	484.77 (64.33)[d]	23	521.67 (71.80)	23	529.41 (70.70)	2.54	0.088
Flanker IES (ms)[e]	21	1862.74 (2140.22)	18	818.08 (174.39)[c,d]	20	1504.74 (1431.41)	20	1274.39 (919.70)	23	1367.66 (1064.42)	23	1315.11 (1054.42)	2.41	0.099

BDNF (pg/mL)	19	29537 (6838)	18	27778 (6879)	19	29102 (7893)	19	25957 (7804)	22	24571 (10415)	21	25036 (10341)	0.17	0.847

Notes: n represents the number of participants used for analysis (differences in n across columns due to missing data and outlier removal).

[a]: significantly different from MCT ($p<0.05$); [b]: significantly different from active control ($p<0.05$); [c] : trending difference from MCT ($p=0.06$); [d]: trending difference from active control ($p=0.06$); [e]: analysis conducted on reciprocally transformed data, means reflect raw values with outliers from analysis removed.

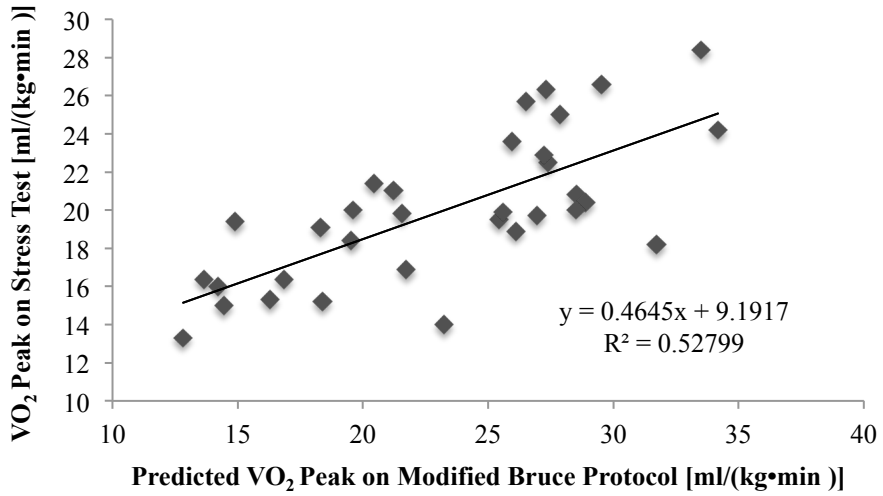

Figure 3: Predicted VO_2 peak at pre-test on modified Bruce protocol and VO_2 peak on stress test.

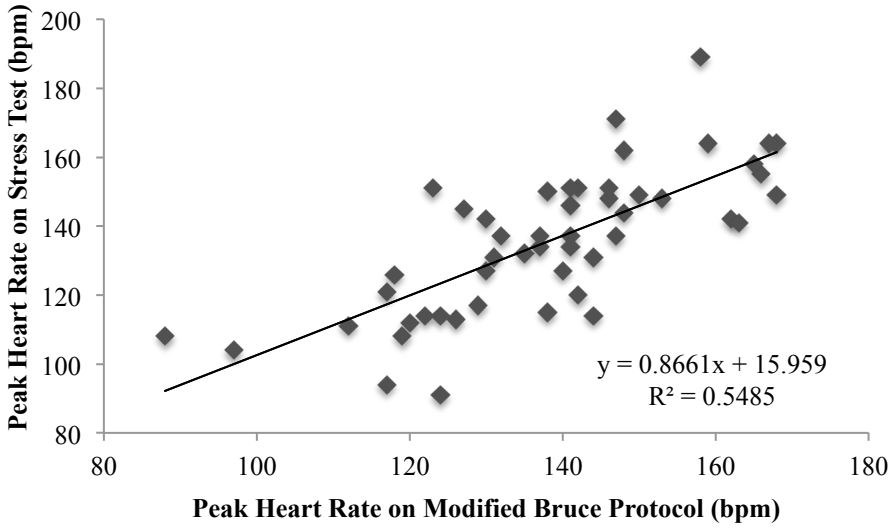

Figure 4: Peak heart rate at pre-test on modified Bruce protocol and on stress test.

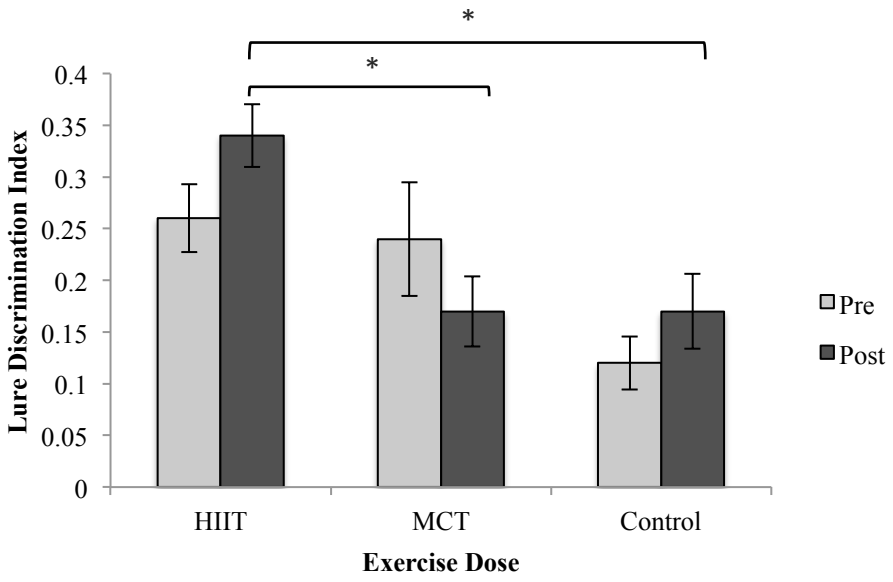

Figure 5. Mean Lure Discrimination Index and standard error for *Mnemonic Similarity Task* at pre- and post-test across groups.
Notes: * denotes significance (p<0.05).

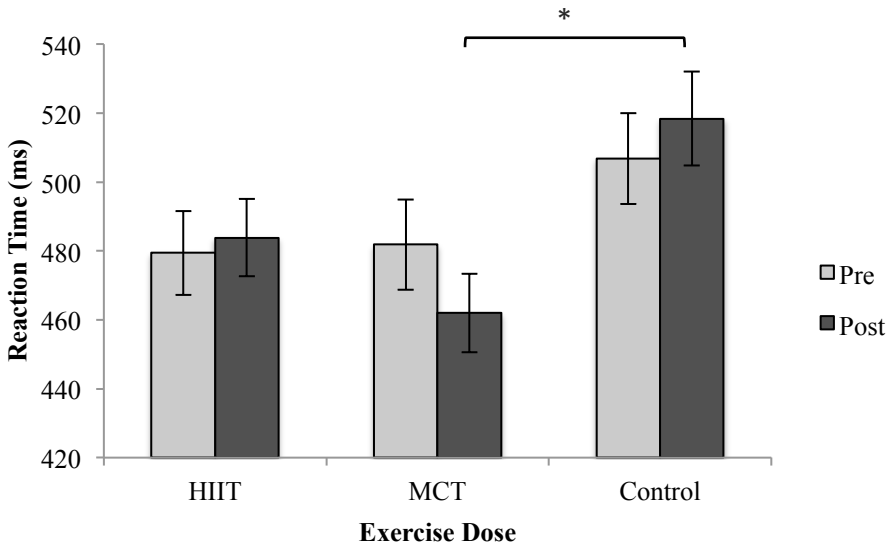

Figure 6. Mean reaction time and standard error for go trials on *Go-nogo* task at pre- and post-test across groups.
Notes: * denotes significance (p<0.05).

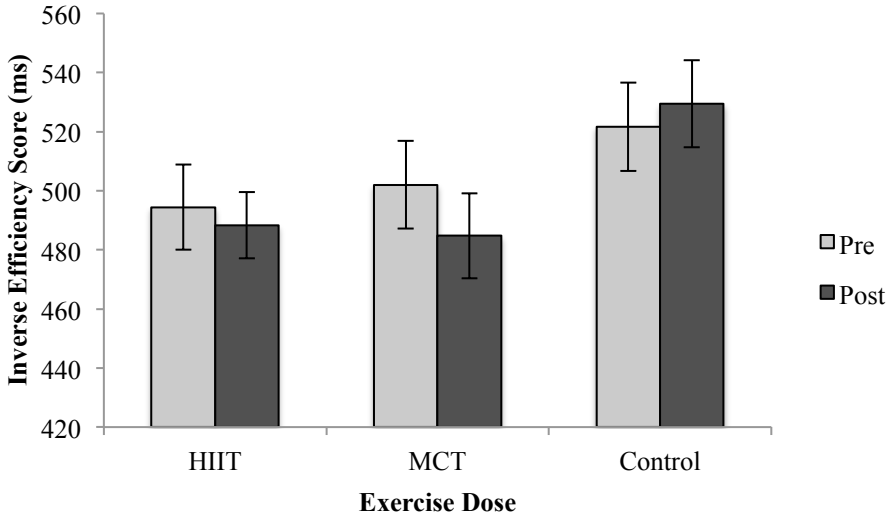

Figure 7. Mean Inverse Efficiency Score and standard error for go trials on *Go-nogo* task at pre- and post-test across groups.

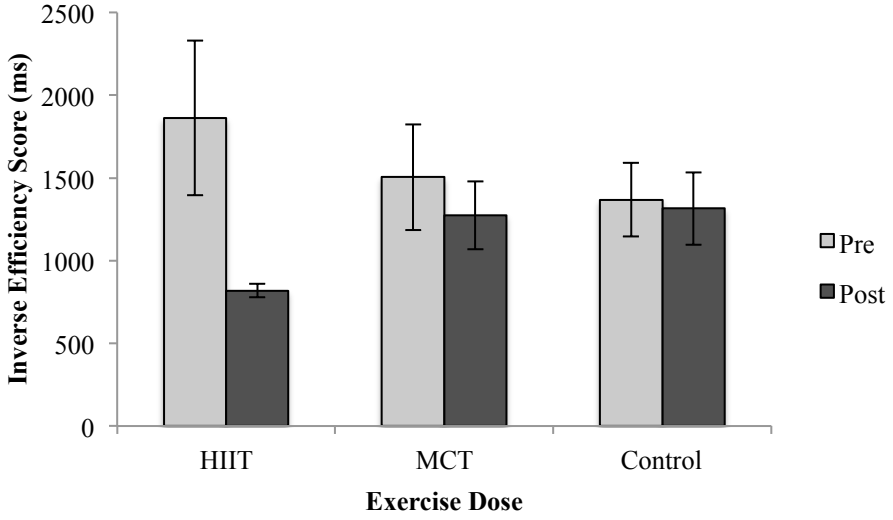

Figure 8. Mean Inverse Efficiency Score and standard error for incongruent trials on *Flanker* task at pre- and post-test across groups
Notes: Reciprocally transformed data were used for analyses.

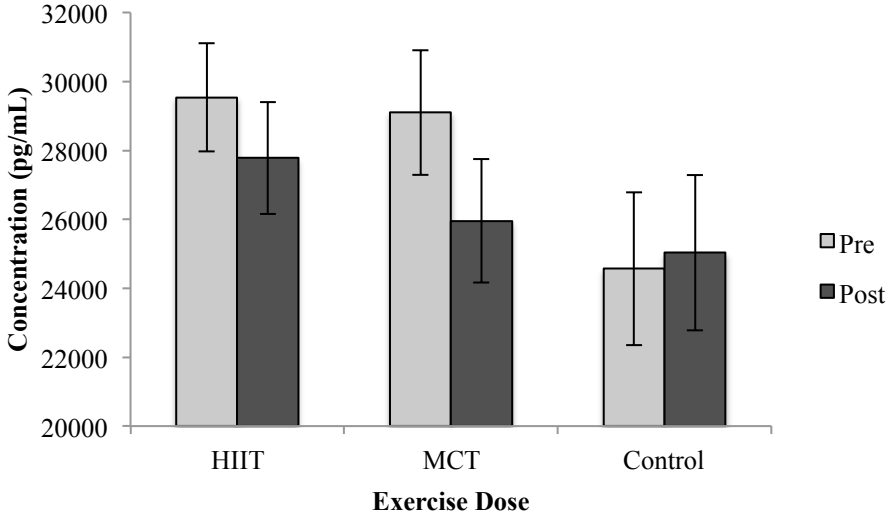

Figure 9. Mean concentration of BDNF and standard error at pre- and post-test across groups.

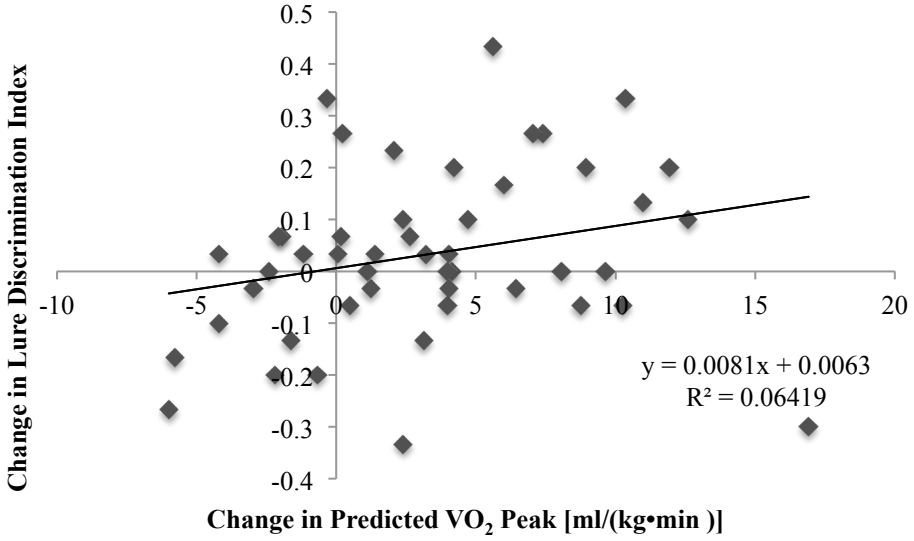

Figure 10. Change in predicted VO_2 peak and change in Lure Discrimination Index on *Mnemonic Similarity Task*.

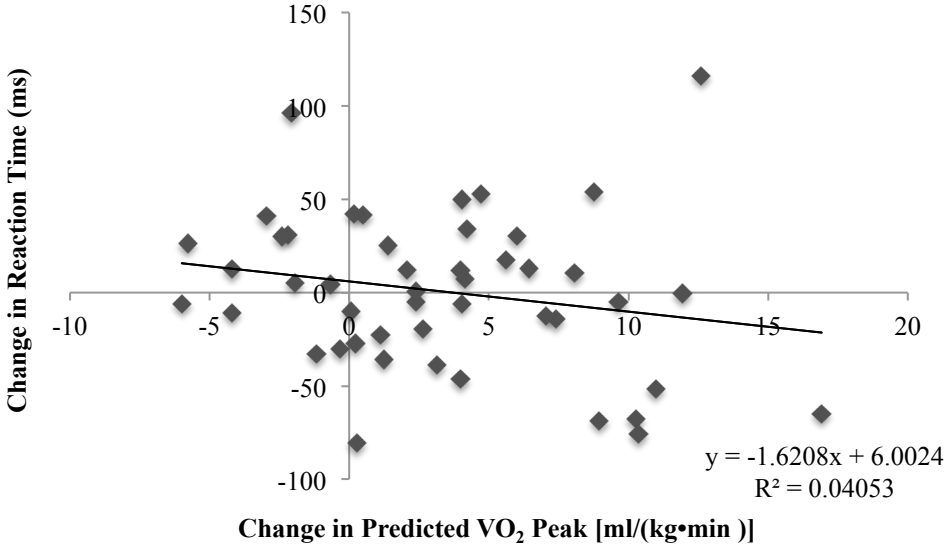

Figure 11. Change in predicted VO_2 peak and change in reaction time for go trials on *Go-nogo* task.

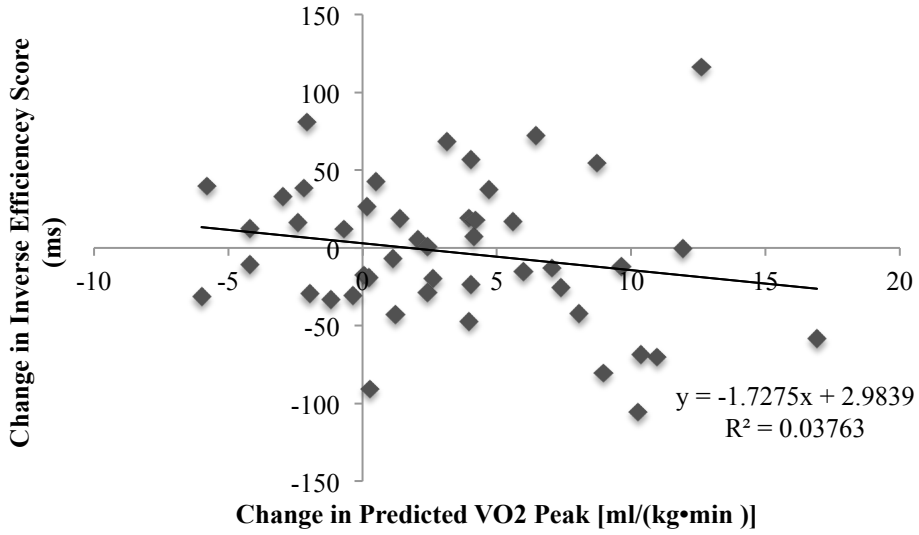

Figure 12. Change in predicted VO_2 peak and change in Inverse Efficiency Score for go trials on *Go-nogo* task.

DISCUSSION

Exercise has been shown to enhance cognitive function (Northey et al., 2017), and this study helps highlight the importance of exercise dose for maximal cognitive benefit in older adults. This study examined the effect of exercise intensity (HIIT, MCT, active control) on cognitive function (memory, processing speed, executive function) in older adults. Changes in BDNF were examined as a potential mechanism. Overall, the exercise groups had better predicted aerobic fitness and cognitive functioning following the intervention, and the HIIT group provided the greatest benefit across domains. There were no significant changes in BDNF concentrations across groups, but the trends indicate decreases in BDNF following exercise intervention. This suggests that BDNF may not mediate the observed changes in cognitive function following exercise. Consistent with previous literature supporting a link between fitness and cognition (Barnes et al., 2003; Boots et al., 2014; Freudenberger et al., 2016; Roever & Bennett, 2016; Weinstein et al., 2012), we found that improvements in fitness were associated with improvements in cognitive function, particularly for high-interference memory. This association suggests that exercise aimed at improving aerobic fitness may be important for cognitive gains. Although a dose-dependent effect was observed in this study, it is important to highlight that RPE reports during exercise sessions were lower than the intended intensity. Therefore, conclusions about prescription cannot yet be made and further research is needed to clarify the optimal exercise intensity for cognitive benefit.

High-interference memory significantly improved following HIIT, but not MCT. This is an important finding given the inconsistencies in the literature with respect to

exercise and memory (Asl et al., 2008; Clark et al., 2015; Creer et al., 2010; Erickson et al., 2011; Heisz et al., 2015). The present study clarifies this relationship by suggesting that exercise intensity may be a critical factor for memory. This finding is consistent with existing literature, where interventions of similar duration (~12 weeks) that used low-to-moderate intensity exercise did not find memory improvements in older adults (Iuliano et al., 2017; Perri & Templer, 1985). In contrast, only six weeks of HIIT has been shown to improve memory, but only in younger adults (Déry et al., 2013). The present study therefore provides new insights by suggesting that higher intensity interval exercise may be necessary for memory improvements in older adults. Moderate-intensity exercise may still be effective, but may require more chronic practice to enhance memory. Indeed, intervention studies that have shown memory improvement from moderate-intensity exercise in older adults have typically lasted from six to twelve months (Erickson et al., 2011; Nagamatsu et al., 2013).

An important consideration is that memory was better in the two exercise groups than in the control group at baseline. Although analyses were adjusted for baseline differences, the HIIT group may have had greater high-interference memory improvement due to better baseline functioning. One potential reason for the baseline difference may be differential withdrawal rates across groups, with fewer participants withdrawing from the HIIT group than the MCT and control groups. This attrition may have been selective, with lower functioning participants withdrawing from the HIIT group and higher functioning participants withdrawing from the control group, which would have resulted in baseline differences when only participants who completed the

study were included. However, despite *both* the HIIT and MCT groups being better at baseline, *only* the HIIT group was better at post-test, and it was significantly better than the MCT group. This observation suggests that the improvement in high-interference memory is likely a result of the HIIT intervention and not baseline differences.

A surprising finding was that only MCT, but not HIIT, resulted in faster processing speed. Processing speed has been shown to improve substantially with exercise (Angevaren et al., 2008; Colcombe & Kramer, 2003; Smith et al., 2010), even when the intensity is high (Kamijo, Nishihira, Higashiura, & Kuroiwa, 2007). A study of resistance exercise showed that high-intensity exercise was most beneficial for processing speed in younger adults (Chang & Etnier, 2009). Interestingly, the same study found an inverted-U relationship between resistance exercise intensity and executive function (Chang & Etnier, 2009). Whereas Chang and Etnier (2009) used a simple speed of information processing task, we used a choice reaction time task. This task is more complex, as it requires inhibition of prepotent responses in order to respond accurately to only the "go" stimuli. Therefore our task may have challenged executive functions, resulting in selective improvement from MCT only, consistent with the inverted-U relationship found by Chang and Etnier (2009). Indeed, another study that used a choice reaction time task also only found improvements with moderate and not high-intensity exercise in younger adults (Chmura, Nazar, & Kaciuba-Uścilko, 1994).

When we accounted for accuracy on the *Go-nogo* task by calculating an inverse efficiency score (Bruyer & Brysbaert, 2011), a measure of executive functions, both exercise groups performed better than the control group. Although this is inconsistent

with the inverted-U relationship that has previously been proposed between exercise intensity an executive functions in younger adults (Chang & Etnier, 2009; Chmura et al., 1994), older adults may have a different response to high-intensity exercise, such that it does not impair their cognitive performance on executive function tasks. Consistent with the results of this study, other studies in older adults have also shown executive functioning benefits from high-intensity exercise (Baker et al., 2010; Cassilhas et al., 2007).

Interestingly, the HIIT group performed better than *both* the control and MCT groups on the *Flanker* task. Given that the *Go-nogo* and *Flanker* tasks both measure executive functions, it was expected that exercise would have similar effects on both tasks. One potential reason that MCT was effective for the *Go-nogo* task, but not the *Flanker* task, is that the *Flanker* task is more challenging and therefore requires a greater exercise stimulus for improvement. In other words, MCT may not have been sufficient for improvements on the *Flanker* task. Indeed, Kamijo et al. (2007) suggest that exercise may influence performance on these two tasks differently. Specifically, the *Go-nogo* task requires less effort than the *Flanker* (Chodzko-Zajko, 1991; Kamijo et al., 2007). This is evidenced in our study, as IES was greater overall on the *Flanker* task than on the *Go-nogo* task, suggesting that it was more challenging.

It is important to note that executive function improvements were only nearing significance. The relatively small improvements were surprising given that previous studies have shown superior effects of exercise on executive function compared to other cognitive domains (Colcombe & Kramer, 2003; Heisz & Kovacevic, 2016; Masley et al.,

2009). It may be that a longer intervention is necessary to elicit significant gains in executive functions. Interventions that have found improvements on similar inhibition/attention tasks in older adults have typically been at least 6 months in length (Colcombe et al., 2004; Kramer et al., 2001). However, given that attention and inhibition are particularly vulnerable to the effects of aging (Hasher et al., 1991; Hasher & Zacks, 1988; Heisz & Kovacevic, 2016), the promising trends of this study warrant further investigation to better understand the effects of exercise on executive functions in the long-term.

Overall, HIIT had a superior effect on cognition. In considering the mechanism, one possible explanation is that HIIT elicits a greater physiological response. Previous research suggests that physical exercise acutely increases the circulating concentration of BDNF (Ferris et al., 2007; Gold et al., 2003; Schmidt-Kassow et al., 2012; Vega et al., 2006), which is linked with cognitive function (De Assis & Almondes, 2017; Freudenberger et al., 2016; Roever & Bennett, 2016). Critically, HIIT induces a greater increase in BDNF (Ferris et al., 2007; Schmidt-Kassow et al., 2012) than lower intensity exercise. Importantly, in the studies that reported exercise-induced increases in BDNF, blood samples were collected within one hour following an exercise bout (Ferris et al., 2007; Gold et al., 2003; Schmidt-Kassow et al., 2012; Vega et al., 2006). Contrary to our hypothesis, no significant changes in BDNF were found across groups, suggesting that BDNF may not be mediating cognitive improvements. This result may be due to the timing of blood sample collection. Since blood samples were collected 24 to 48 hours after the final exercise exposure, one potential explanation is that the increases in BDNF

from exercise were transient and were thus not reflected in our samples. One previous study observed an increase in BDNF that returned to baseline within only minutes of completing the acute exercise bout (Vega et al., 2006). Another study had a similar conclusion, finding that BDNF increased during exercise, but peaked and declined within hours following termination of exercise (Rasmussen et al., 2009). This suggests that our timing of sample collection may not have captured the transient increase in BDNF.

Surprisingly, the trends in the data suggest that BDNF actually declined in the exercise groups. It remains unclear why there would be a trend towards *lower* resting BDNF levels after the three months of training. Interestingly, a study that examined the influence of both acute and chronic exercise on BDNF found that in chronic exercisers, serum BDNF levels decreased below initial baseline levels after exercise (Nofuji et al., 2012). Other studies have also shown decreased serum BDNF levels with habitual physical activity (Chan, Tong, & Yip, 2008; Nofuji et al., 2008). These findings are consistent with the trend we observed and suggest that the timing of BDNF sampling is critical. Chronic exercise may help facilitate more efficient uptake of circulating BDNF to aid in tissue healing after exercise (Nofuji et al., 2008; Nofuji et al., 2012), resulting in lower circulating levels. Future studies should examine the effect of a chronic exercise intervention on BDNF at multiple time points following exercise exposure. Another important consideration is that, while ideal, it is not possible to directly measure hippocampal BDNF levels in humans. BDNF undergoes bidirectional transport across the blood brain barrier (Pan, Banks, Fasold, Bluth, & Kastin, 1998) and thus serum measures of BDNF have been shown to correlate with concentrations in the brain in rats (Karege,

Schwald, & Cisse, 2002). However, it is possible that this measure is not a completely accurate representation of hippocampal BDNF.

Strengths and Limitations

The present study had numerous strengths. First, there was high adherence to the physical activity intervention (participants attended 97% of prescribed exercise sessions), and broad inclusion criteria for better generalizability of results. Second, there was detailed reporting of exercise characteristics including both those that were prescribed and actually achieved. One problem in the exercise literature is that many studies lack adequate reporting of exercise characteristics (Kelly et al., 2014), in particular, whether the intended prescription was achieved.

However, this study is not without limitations. Firstly, RPE reports during exercise sessions were lower than intended, suggesting that the desired intensity was not achieved. Since fitness was measured using a predictive test and true volitional exhaustion could not be objectively verified, it is possible that the peak heart rate achieved may have been underestimated. Heart rate was used as a primary indicator of exercise intensity and thus an underestimation of peak heart rate would have precluded participants from achieving the desired intensity. Importantly, however, peak heart rates achieved on the modified Bruce protocol used in this study were similar and significantly correlated with those achieved on exercise stress test conducted prior to study enrolment. This suggests that participants did indeed reach maximal exertion on the modified Bruce protocol and that peak heart rates were accurately predicted. Nevertheless, conclusions about dose should be made carefully due to this limitation. While it is evident that

exercise intensity may have a dose-dependent effect, the optimal dose remains unclear. Besides dose, the exercise groups also differed in exercise style, with the HIIT group doing interval training and the MCT group doing continuous training. Interval-style training may be a more enjoyable and preferred form of exercise (Stork, Banfield, Gibala, & Martin Ginis, 2017) and therefore a viable option to maintain in the long-term.

An additional consideration is that some older adults may have been taking beta-blocker medications during the study. This information was retrieved retrospectively from participant stress tests and it was found that six study completers were taking beta-blockers (3 in MCT, 3 in control). These participants' maximum heart rates were found to be within the range of non-beta blocked participants and thus they still likely achieved the desired intensity, as determined by heart rate. Unfortunately, information on medications was not available for thirteen participants who completed the study. While five of these participants were in the control group and would not have been affected since they were not exercising, we cannot be certain that those in the exercise groups were not limited in the intensity they were able to achieve as a result of taking beta blockers. Future studies should take into account medications or other conditions that may interfere with the intensity achieved during exercise.

Another limitation is that the groups were not matched for time. Importantly, the HIIT and MCT conditions were isocaloric (Rognmo et al., 2004; Wisløff, 2007); however, including an additional social component to account for the time difference between groups and extending the duration of the control group would ensure groups are matched for time and thereby confirm if results are due to the intervention itself rather

than time on task. Our results indicate that HIIT was more effective despite being shorter in duration, which is an important finding given that lack of time is the most commonly cited reason for not engaging in regular exercise (Gibala, 2007). However, HIIT may not be appropriate for less functional and frailer older adults so it would be worthwhile to investigate other moderator variables such as duration of exercise. Additionally, the weekly volume of exercise in the HIIT group did not meet the public health recommendation of 150 minutes of moderate-to-vigorous intensity aerobic exercise per week. Despite the shorter duration however, improvements in cognition were still observed, suggesting that exercise guidelines for cognitive health may be different than those for physical health and warrants further research to better tailor exercise prescription for cognitive health. This result is in line with previous research suggesting that exercise intensity is more important for cognition than exercise duration (Angevaren et al., 2007; Kelly et al., 2014; Van Gelder et al., 2004). Although a recent review suggested that exercise intensity does not affect cognitive function (Smith et al., 2010), this is the first study to directly examine the effect of exercise intensity in a randomized trial of aerobic exercise.

Future Directions

Future studies should further investigate a potential mechanism to explain the relationship between exercise and cognitive function in older adults. Specifically, transient changes in BDNF should be examined in addition to changes in resting levels. More direct mechanistic measures such as functional and structural MRI would provide important information about the brain changes elicited by exercise.

This study demonstrated that exercise may be an effective strategy for enhancing cognition in old age, but whether this enhancement may mitigate dementia risk in the long-term requires further exploration. Typically, studies of longer duration (i.e., one year) and follow-up periods (i.e., 18 months post-intervention) have shown positive effects of exercise for cognition more consistently than shorter-term studies (Kelly et al., 2014). Therefore, longitudinal follow-up to exercise intervention studies would provide useful information as to the longer-term benefits of exercise for cognition.

Lastly, this study utilized relatively healthy individuals, which limits generalizability to populations that are cognitively impaired. More research is needed to understand whether exercise may be an effective treatment for those who have already been diagnosed with dementia or other cognitive impairments. This research would provide potential therapies that may be applied into clinical practice to prolong independent functioning for those afflicted with significant cognitive decline.

Conclusion

With the rapidly growing population of older adults and increasing prevalence of neurodegenerative disease, it is critical to identify effective interventions for promoting cognitive function. In this study, HIIT improved high-interference memory and had a trend toward improved executive functions. These results are important given that older adults experience progressive decline in cognitive function that puts them at risk for developing dementia. Overall the findings suggest that a relatively short-term exercise intervention in healthy older adults may be effective at enhancing cognition, and particularly high-interference memory. Importantly, high-intensity interval exercise may

be superior to lower intensities for cognitive benefits; however, further research is needed to clarify the optimal dose. Overall, vigorous exercise may be an effective lifestyle intervention to help older adults maintain their cognitive function for longer into the lifespan.

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