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A Hierarchical Approach to Assessing the Effects of Exercise on Cognition

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Abstract

Using a hierarchical approach across three studies, the aim of my thesis was to assess the relationship between exercise and cognition. In experiment one, based on a large, diverse sample, I found that regular exercise was positively associated with reasoning and verbal performance. In experiment two, I examined whether measures of strength and cardiovascular health were related to cognition. I found that the plank (a measure capturing aspects of both strength and aerobic capacity) was associated with performance on tasks relying on verbal and memory function in young adults. However, when aerobic or resistance exercise was introduced to a group of sedentary participants (experiment three), I found neither intervention had an effect on cognitive performance. Taken together, these results suggest that exercise benefits cognition when it is a regular part of an individual's lifestyle, however, introducing exercise for a transient period, even to those who are sedentary, provides no benefit.

Keywords

Exercise; Physical Activity; Training; Cognitive Function; Young Adults

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Chapter 1

1 Introduction

The importance of exercise to our overall well-being is well documented. Exercising regularly is important for sustaining a normal bodyweight, and can help in the maintenance of normal blood lipid levels and blood pressure (Fletcher et al., 1996) The benefits of exercise extend beyond physiological changes; exercise also benefits mental health, having been shown to improve self-esteem and self-confidence and to reduce symptoms of depression (Fletcher et al., 1996). The benefits of exercise are so systematic and profound that it is recommended in the prevention and management of various medical conditions including cardiovascular disease, metabolic syndrome, osteoporosis, a number of neoplastic diseases and various mental illnesses, such as anxiety (Fletcher et al., 1996). However, an often-overlooked aspect of exercise is the effect it has on cognition and the brain.

1.1 Exercise and the Brain

In fact, there is accumulating evidence that exercise can have drastic effects on almost all aspects of brain health, including improved learning and memory, reduced symptoms of depression, better outcomes associated with brain injury and delayed onset and magnitude of cognitive decline associated with various neurodegenerative diseases (Cotman, Berchtold, & Christie, 2007a). One of the most prominently researched avenues explaining these exercise dependent benefits to cognition is altered gene expression. Various growth factors have been shown to have exercise-induced expression, such as Vascular Endothelial Growth Factor (VEGF), Insulin Growth Factor-1 (IGF-1) and Brain Derived Neurotropic Factor (BDNF), and these growth factors play a central role in regulating exercise dependent neuroplasticity (Fabel et al., 2003; Homolak, Janes, & Filipovic, 2015; Murray & Holmes, 2011). These growth factors promote neurogenesis, the creation of new neurons from neural progenitor cells, neuron survival, synaptic plasticity, and angiogenesis, the formation of new blood vessels from pre-existing ones (Homolak et al., 2015; Lopez-Lopez, LeRoith, & Torres-Aleman, 2004; Murray &

Holmes, 2011). The effects of exercise on learning and memory tend to be mediated by BDNF and IGF-1, whereas VEGF and IGF-1 are responsible for exercise stimulated angiogenesis and neurogenesis (Cotman, Berchtold, & Christie, 2007a).

After exercise, levels of BDNF are found to increase in several areas of the brain; however the most significant increases are seen in the hippocampus (Cotman, Berchtold, & Christie, 2007a). It therefore follows that many of the benefits associated with increased BDNF expression relate to learning and memory formation, processes commonly involving the hippocampus. For example, Vaynman and colleagues (2004) showed evidence that BDNF is involved in learning and memory formation in rodents by using antibodies to the BDNF receptor, TrkB, to block its signalling pathway. When the TrkB receptor in the hippocampus was blocked, exercised rats showed significantly reduced rates of acquisition and retention on a spatial leaning task compared to the rats that were not treated with the TrkB antibody. These rates of acquisition and retention were similar to those of their sedentary counterparts, demonstrating evidence that exercise mediates increased expression of BDNF, which in turn improves hippocampal-dependent learning acquisition and memory retention (Vaynman, Ying, & Gomez-Pinilla, 2004). Interestingly, Ding and colleagues (2006) saw similar effects when an alphaIR3 antibody was used to block the IGF-1 receptor in the hippocampus during a 5-day exercise protocol in rats. Although this treatment did not have any effect on learning acquisition on the Morris water maze task, they did find that it significantly reduced the benefits of exercise on memory recall (Ding et al., 2006). They further found that when the IGF-1 receptor was blocked, the exercise-induced increases in BDNF mRNA and protein levels were lost, suggesting that the IGF-1 and BDNF signalling pathways in the hippocampus converge (Ding et al., 2006). McCusker and colleagues (2006) were able to supplement this finding; they demonstrated that when cortical neurons were treated with IGF-1, the expression of the BDNF receptor increased, and this was accompanied by amplified BDNF activity, as measured by ERK phosphorylation. Overall, BDNF is a growth factor whose expression has been found to mediate several exercise-dependent cognitive benefits. However, further research has shown that this growth factor does not act in isolation, as there are many other signalling pathways that are involved in its expression, and in turn, its downstream effects on learning and memory.

More recently, research has been conducted to determine the molecular mechanisms underlying the exercise-dependent increased expression of BDNF, and one pathway of interest involves the newly discovered hormone Irisin. PGC-1α is a protein whose expression can be amplified via exercise in skeletal muscle (Wrann et al., 2013). It is involved in many aspects of energy metabolism, including mitochondrial biogenesis and respiration, however, lack of PGC-1α expression is associated with neurodegeneration (Boström et al., 2012, Wrann et al., 2013). Recently, Boström and colleagues (2012) discovered FNDC5, a PGC-1α dependent protein, which is secreted and cleaved into Irisin. Irisin has peripheral effects; for example, its ability to induce browning of white adipose tissue, although evidence shows its effects extend to the brain (Boström et al., 2012). Rodents in one study voluntarily ran for 30 days, which resulted in increased expression of PGC-1α in skeletal muscle, and increased FNDC5 expression in skeletal muscle and the hippocampus (Wrann et al., 2013). They also found that both central and peripheral Irisin likely contributed to the positive regulation of BDNF expression in the hippocampus. This demonstrates that the activation of the PGC-1α pathway via endurance exercise is one mechanism contributing to the augmented expression of BDNF (Wrann et al., 2013). However, it is important to note this is not the only exercise related pathway inducing BDNF expression. Additionally, Garcia and colleagues (2003) found that the effects on BDNF due to 1 week of voluntary wheel running were lost when rats had lesions affecting norepinephrine release in the brain, which suggests functional norepinephrine release is essential for BDNF expression in the hippocampus. In addition, there is evidence showing that elevated levels of peripheral IGF-1 crossing the blood brain barrier can induce increased expression of BDNF (Ding et al., 2006). Overall, it is likely that there are multiple pathways necessary for exercise-dependent neurotrophin expression in the hippocampus and further investigation on how they may interact with one another is necessary for understanding how exercise is able to induce neurogenesis and neural plasticity.

Although we have evidence showing that many exercise-dependent cognitive benefits are related to increased expression of various growth factors, there is less known about the signalling pathways underlying these cognitive changes. Two molecules in particular are thought to be involved in hippocampal synaptic plasticity. The first is cAMP-responseelement binding (CREB), a transcription factor that regulates neuronal survival and is involved in long-term memory (Finkbeiner, 2000). Synapsin I is the other protein of interest, as it plays a role in synaptic transmission by maintaining a reserve pool of synaptic vesicles and by regulating the kinematics of neurotransmission (Hilfiker et al., 1999). Vaynman and colleagues (2003) proposed that the signalling pathways underlying the increased expression of these proteins involve BDNF. They suggest that as BDNF binds to the TrkB receptor, the mitogen-activated protein kinase (MAP-K) cascade is activated (Vaynman, Ying, & Gomez-Pinilla, 2003). MAP-K signalling is associated with learning and memory formation, which can be attributed to its ability to regulate and promote the activity of CREB (Blum et al., 1999; Finkbeiner et al., 1997; Hardingham, Arnold, & Bading, 2001). They additionally show that the actions of BDNF are dependent on an interaction with the *N*-methyl-D-aspartate receptor (NMDA-R), which itself is involved in the modulation of long-term potentiation, a neural correlate of learning and long-term memory (Bliss & Collingridge, 1993; Stuchlik, 2014). Interaction with this receptor likely activates calcium/calmodulin protein kinase II, a molecule also commonly shown to be involved in learning and short term memory (Yin & Tully, 1996). Not only does the CAMKII pathway regulate synapsin I mRNA levels, but it also converges on the MAP-K cascade, allowing it to have a role in the regulation of CREB mRNA levels (Vaynman, Ying, & Gomez-Pinilla, 2003). Interestingly, their results show CAMKII signalling cascade also regulates the mRNA levels of TrkB-R and BDNF itself, suggesting BDNF can maintain its effects via a continuous loop (Vaynman, Ying, & Gomez-Pinilla, 2003). Thus, although BDNF plays a critical role in exercise-dependent neuronal plasticity, there are numerous other molecules, beyond those presented, helping to modulate its effects.

Moreover, there are numerous ways these signalling pathways can be interrupted; however, one more recently investigated avenue is chronic systemic inflammation. Inflammation is prevalent in those with metabolic syndrome, a condition associated with hypertension, hyperlipidemia, abnormal cholesterol and abdominal obesity (Yaffe et al., 2007). Interestingly, Yaffe and colleagues (2007) showed that those with metabolic syndrome are at greater risk for cognitive decline. This effect is augmented when serum levels of inflammatory markers are elevated, which demonstrates that these peripheral health conditions have an indirect effect on cognitive health (Yaffe et al., 2007). One explanation for the presence of these cognitive health outcomes is that systemic inflammation exacerbates inflammation in the central nervous system (CNS; Perry, 2004). Inflammatory conditions in the CNS, such as those induced via the pro-inflammatory cytokines TNFα and IL-1β, can impair the signaling of various growth factors. For example, IL-1β has been shown to interfere with BDNF signaling, causing depressed CREB activity, likely due to neurotrophin resistance (Tong et al., 2008). In addition, TNFα has been found to inhibit IGF-1 receptor signaling (Venters et al., 1999). These growth factors prevent apoptosis, and when their signaling pathway is interrupted, neurons become more susceptible to degeneration. However, exercise has the ability to reduce many risk factors associated with metabolic syndrome, and can help minimize the inflammation found in patients with obesity, atherosclerosis and insulin resistance (Petersen & Pedersen, 2005). Exercise first stimulates the release of IL-6, an anti-inflammatory myokine, from skeletal muscle into circulation (Petersen & Pedersen, 2005). IL-6 subsequently stimulates the production of additional anti-inflammatory cytokines, IL-1ra and IL-10, and inhibits the production of TNFα (Mizuhara et al., 1994; Steensberg et al., 2003). IL-10 further impedes the production of both TNFα and IL-1β (Pretolani, 1999). Thus, the protective effects of exercise are not only limited to conditions related to cardiovascular disease, but also extend to inflammation throughout the body, including the CNS. This evidence shows that exercise can indirectly help restore BDNF and IGF signaling that may be lost due to inflammatory conditions, and thus prevent cognitive decline by promoting neuron survival and synaptic plasticity.

Neurotrophins are a class of proteins that are essential for the modifications in neural circuitry brought on by exercise. However exercise also supports these alterations by modulating metabolic cascades and the vascular structure of the brain. Exercise has been shown to alter the levels of various proteins involved in glucose metabolism in the hippocampus, including enzymes involved in glycolysis and proteins necessary for glutamate turnover (Ding et al., 2006). This may further the neuroprotective role of exercise, as excess glutamate at the synaptic cleft can result in excitotoxicity, which can cause damage to neurons. Additionally, in that study there were elevated levels of proteins required for both ATP synthesis and the transport of ATP from the mitochondria to sites of utilization; this is suggested as a mechanism of improved energy transduction when energy demands are heightened (Ding et al., 2006). Exercise has also been shown to impact vascular structure and blood flow in certain regions of the brain. When neurogenesis takes place, metabolic demands increase, resulting in the induction of angiogenesis (Palmer, Willhoite, & Gage, 2000). Angiogenesis prompts an increase in microvascular density in the brain, which in turn increases cerebral blood volume (Cha et al., 2003). Following this, Pereira and colleagues (2007) were able to correlate cerebral blood volume and exercise-stimulated neurogenesis in the dentate gyrus using imaging in mice. Although this same analysis cannot be performed in humans, they found that after 12 weeks of a cardiovascular exercise regime there was increased blood flow to the dentate gyrus, which correlated with improved declarative memory performance (Pereira et al., 2007). Their data supports the necessity of increased blood flow to areas undergoing neural restructuring, likely because of the associated increased energy demands. In support of this, Guiney and colleagues (2015) showed that the relationship between physical activity frequency and performance on an inhibitory control task could be mediated by cerebrovascular responsiveness, and they concluded that enhanced cerebral blood flow regulation may be a possible route by which regular physical exercise brings about improvements in cognition. Thus, it is apparent that exercise modulates numerous other physiological systems in order to support and maintain the exercise-dependent alterations in neuronal circuitry that are stimulated by BDNF, IGF-1 and other growth factors.

Although the exact mechanism by which exercise exerts its beneficial effects on neuron survival and function is unclear, much research has been done to determine whether these neurophysiological changes translate to cognitive enhancements in both animals and humans. It has been shown that adults who have higher cardiovascular fitness levels have greater white matter integrity and higher gray matter volume in the hippocampus and pre-frontal cortex, (Erickson et al., 2009; Johnson et al., 2012; Weinstein et al., 2012). As well, increases in functional connectivity have been shown in healthy elders in the default mode network and hippocampal networks after participation in a long-term aerobic training regime (Burdette et al., 2010; Voss et al., 2010), suggesting prolonged participation in an exercise regime has beneficial effects on brain structure and function.

1.2 Exercise and Cognitive Function

Many of the neurophysiological changes associated with exercise have been shown to have significant effects on cognitive function in both rodents and humans. Various studies have shown benefits of voluntary exercise on spatial learning in rodents, most notably on the Morris water maze task (van Praag et al., 2005; Vaynman, Ying, & Gomez-Pinilla, 2004). Vaynman and colleagues (2004) showed that rodents with unrestricted access to a running wheel for one week had better spatial memory acquisition and retention on the water maze task than their sedentary counterparts. As well, various studies in humans demonstrate positive effects on many cognitive abilities after physical activity. There are generally two types of intervention studies used to investigate these effects. One focuses on the acute effects of exercise, where measures of cognitive performance are completed immediately before and after a single bout of exercise, which may last from a few minutes to several hours. The other avenue focuses on the effects of chronic exercise. These studies often have sedentary adults participate in a novel exercise regime over the course of weeks or months, with cognitive and fitness testing occurring before and after the intervention. The literature suggests that both types of exercise programs result in small, positive effects on cognition (Chang et al., 2012; Colcombe & Kramer, 2003). For instance, in a meta-analysis performed by Chang and colleagues (2012), it was concluded that a single bout of exercise has a small, positive effect on cognitive performance on a wide range of tasks assessing executive functions, attention, reaction time and memory. Similarly, a meta-analysis reviewing long-term intervention studies in healthy older adults found improvements in participant’s visuospatial processing, but the most notable benefits were found in tasks tapping into executive control processes (Colcombe & Kramer, 2003). Despite these parallels, the effects of both types of exercise interventions are not uniform and depend on many factors, including the demographics of the participant pool.

There are several different types of exercise that may have contrasting effects on cognition, but they are generally classified as either aerobic or resistance exercise. Exercise is categorized as aerobic when it raises the heart rate and breathing rate of the individual (e.g. brisk walking, jogging, cycling; American College of Cardiology, 2015).

Resistance training encapsulates any exercise that focuses on building the strength of major muscle groups (e.g. bodybuilding or bodyweight movements; Liu-Ambrose et al., 2012a; van de Rest et al., 2013) While the link between cognition and these different types of exercise has been investigated in different age groups across the lifespan, most of this work focuses on the effects of aerobic exercise on cognition in older adults. In this cohort, there is evidence to suggest that older adults with greater cardiovascular fitness levels tend to experience less severe age related decline in cognitive function (Suominen-Troyer et al., 2016). Other studies have shown that better cardiovascular fitness is also associated with reduced age-related neural degeneration of the prefrontal, parietal and temporal cortices, and increased hippocampal volume (Colcombe et al., 2003; Erickson et al., 2009). These neural changes are accompanied by superior performance on tasks measuring memory (Erickson et al., 2009), executive function, attention (Barnes et al., 2003), and global intelligence (Aberg et al., 2009). When exercise is introduced as an intervention, most studies rely on aerobic exercise, such as walking or jogging. Aerobic exercise has been shown to benefit performance on tasks relying on attention, executive function and speed of processing in this age group (Burdette et al., 2010; Cha et al., 2003; Colcombe & Kramer, 2003; Erickson et al., 2009; Fletcher et al., 1996). Most notably, involvement in an aerobic training regimen is associated with improvement in spatial memory (Erickson et al., 2011; Moreau, Kirk, & Waldie, 2017; Stroth et al., 2009). For instance, Erickson and colleagues (2011) implemented a 1-year walking intervention in healthy older adults. The participants in the aerobic intervention experienced a 2% increase in hippocampal volume, and they found this volume increase significantly correlated with improvements on a spatial memory task. Fewer studies have investigated the effects of resistance training on cognition in this group. However, the few studies in this area have shown improvements on various memory tasks (Best et al., 2015; Cassilhas et al., 2007), but more consistently on tasks assessing executive control (Best et al., 2015; Ikudome et al., 2016; Liu-Ambrose et al., 2012a; Liu-Ambrose et al., 2012b). For instance, Best and colleagues (2015) found that after involvement in a 1-year resistance training program once or twice a week, older adults showed improvements on four measures of executive function. These benefits were also present in both groups at the 2-year follow-up, along with improved memory performance in the group performing resistance training twice per week (Best et al., 2015). In addition, there have been numerous studies directly comparing the effects of a long-term aerobic versus resistance exercise regime. These studies consistently show that each regime has differential effects on various cognitive abilities (Dunsky et al., 2017; Moul, Goldman, & Warren, 1995; Smiley-Oyen et al., 2008). Despite these findings, it should also be noted that there are studies that have not been able to show any cognitive benefits from participating in an aerobic or resistance exercise program. For example, in a study by Blumenthal and Madden (1988), two groups of men were subject to either jogging or strength training for twelve weeks. Although reaction time on a memory search task was related to the participant's initial level of fitness, there was no performance changes on the task after the exercise protocol in either group (Blumenthal & Madden, 1988).

One aspect of this literature to consider is the fact that older adults often display a unique, and specific, overall health and cognitive profile, which may constrain the role different exercise programs have on their cognition. Younger adults on the other hand have more stable cognitive functioning. However, since they are generally thought to be at their peak cognitive health (Hillman, Erickson, & Kramer, 2008), fewer studies have been conducted to investigate the link between exercise and cognitive performance in this population. Whether the relationship between different exercise regimes and cognition in younger adults parallels the relationship found in older adults is unclear because few studies directly compare these two cohorts. However, in studies that do compare these age groups, it has been shown that the benefits to cognition tend to be more robust in older adults (Hawkins et al., 1992). Of the few studies that perform interventions in young adults, it has been shown that high intensity aerobic exercise over a period of 8 weeks has a positive effect on measures of executive function, such as the Trail Making Test and the Stroop Task (Costigan et al., 2016; Hwang et al., 2016). However, very few studies have examined the cognitive effects of a chronic resistance exercise regime in young adults. Moving forward, studying young adults will be fundamental to understanding the relationship between cognitive function and exercise. Because young adults are at their peak cognitive health, they can provide important information about how exercise affects cognition, without the confounds of age related cognitive decline or neurodegenerative disease.

In summary, it is difficult to draw conclusions about the relationship between exercise and cognition based on the existing literature. This is due in part to the limited overlap between studies that combine comparable exercise interventions, the different cognitive tests used and populations studied; most of the research in this area is confined to a particular population (e.g., older adults), using a single type of exercise (e.g., aerobic training), and a limited set of cognitive tasks (e.g., memory tasks). Therefore, the exact relationship between the nature of exercise and the accompanying cognitive benefits

The current study aims to ameliorate these issues by using Cambridge Brain Sciences (CBS) to assess cognitive performance. CBS is a set of 12 online tests used to measure different aspects of cognitive function. The collection of tests assess aspects of inhibition, selective attention, reasoning, verbal short-term memory, spatial working memory, planning and cognitive flexibility. Together, the tasks collectively and comprehensively assess three cognitive domains: short term memory (STM), reasoning and verbal abilities, based on behavioral data (from over 44,000 individuals) and neuroimaging studies that have demonstrated that each domain is supported by a separate brain network (Hampshire et al., 2012). They have been validated in patients (Owen et al., 1990; Owen et al., 1991; Owen et al., 1993) and healthy populations (Owen et al., 1996a; Owen et al., 1996b), and have been shown to be sensitive to subtle cognitive changes due to neurodegeneration (Owen et al., 1992; Owen et al., 1993) or pharmacological intervention (Lange et al., 1992; Mehta et al., 2000). In addition, the tests are designed to be engaging to maximize participant compliance. Completion of the battery requires between 35 to 45 minutes, which is faster and more convenient than many other pen and paper neuropsychological batteries. Taken together, the CBS battery is ideal to use in the current study because it is easy and fast to complete, can be used to assess even the most subtle changes to cognition and the categorization of tasks into latent cognitive domains will help to provide an objective definition of exactly which cognitive processes are influenced by physical activity.

1.3 Objectives and Hypotheses

The overall aim of this thesis is to provide a general landscape of the relationship between exercise and cognition. This will be done across three studies that address this relationship in a hierarchical manner. First, in experiment one, I evaluate whether regular exercise influences cognitive performance. Participants in this study were asked "How often have you exercised, such that you work up a sweat, in the past month". They could select an answer from: everyday, 3 or more times a week, 1-2 times a week, less than once a week, and not in the past month. I then determine whether their response has any relationship with their performance on the CBS task battery. In experiment two, I explore whether measures of cardiovascular fitness and muscle strength are associated with cognitive performance in young adults. To test this, I had participants perform all 12 tasks comprising the CBS battery, in addition to a predictive VO_2 Max test, which estimates maximal oxygen consumption, and four other measures of strength. Together, these physical measures provide an estimation of each participant's overall fitness level. I then evaluate whether any of these measures of fitness are related to cognitive performance. Next, to delineate the aspects of cognition that are most influenced by different exercise regimes, experiment three was designed to determine which cognitive domains are most affected by a long-term aerobic and resistance exercise intervention in young adults. Overall, by adopting a comprehensive task battery and by examining diverse measures of exercise, I hope to be able to more clearly elucidate the relationship between exercise and cognition in humans.

Although the findings of previous studies tend to show inconsistencies in the cognitive effects of exercise, patterns throughout the literature have informed my hypotheses for each experiment. Based on the existing literature (e.g. Hillman et al., 2014 & Liu-Ambrose et al., 2012a), I hypothesize that in experiment one, more frequent involvement in exercise will be associated with improved cognitive performance across various tasks, but, in particular, those tasks that tap into executive function. In experiment two, I hypothesize that there will be a positive association between cognitive performance and measures of cardiovascular fitness. More specifically, previous studies have revealed an association between aerobic capacity and memory function (Chaddock et al., 2010; Erickson et al., 2009; Schwarb et al., 2017); thus I hypothesize that my measure of aerobic capacity will correlate with performance on tasks falling into the memory domain. Conversely, in young adults, muscle strength has been shown to be associated with lower global intelligence scores (Aberg et al., 2009), and thus I do not predict that cognition will be positively correlated with any measures of strength. Lastly, in experiment three, past literature has led me to hypothesize that participants in the aerobic exercise group will show more improvement on tasks relying on executive functions (Costigan et al., 2016; Hillman et al., 2014; Smiley-Oyen et al., 2008; Stroth et al., 2009). However, the limited number of studies regarding the effects of resistance interventions makes it difficult to predict which cognitive functions will be most improved upon. Nonetheless, based on previous work (Liu-Ambrose et al., 2012a; van de Rest et al., 2014), I hypothesize that tasks relying on verbal and memory abilities will show the most improvement.

Chapter 2

2 Experiment One

2.1 Introduction

Many experimental approaches have been used to probe the effects of exercise on cognition. A common approach is to run population-based studies, which have many strengths; chief among them include aggregating data from very large and diverse groups of people across the lifespan. As a consequence, findings emerging from these studies have high ecological validity. For instance, the objective of the National Health and Nutrition Examination Survey was to garner a better understanding the effects of exercise by first characterizing the role of exercise in the daily lives of a large population. Between 1999 and 2006, 22,545 participants were asked about their exercise habits, including the types and duration of different exercise programs (Dai et al., 2015). The results of their study suggested that exercise regimes varied based on demographic variables, including age, gender, race and educational attainment. For example, men were found to more frequently participate in sports and bicycling, and women more often participated in walking/hiking, dancing/aerobics and conditioning exercises; however, the amount of exercise for both sexes decreased with age (Dai et al., 2015). In addition, they found that for most activities, participation was significantly higher for non-Hispanic Caucasians and those with higher education. They also found exercise patterns that were true across the population, for example walking was the most common form of physical activity (Dai et al., 2015). It is these types of studies that provide valuable insight into exercise habits at a population level, which can then be used to guide and promote physical activity programs for target populations.

Observational studies, at the population level, have also been valuable for examining the complicated relationship between exercise and cognition. For instance, they do not arbitrarily assign an exercise program that may not be ideally suited to a particular group of people. As well, the challenging task of having a large number of people engage in the same exercise is circumvented. Instead, the idea is to get a general snapshot of reality;

these studies evaluate what people regularly do, which presumably reflects real world habits. These benefits featured prominently in an investigation by Jedrziewski and colleagues (2010), which adopted a large-scale longitudinal approach to determine if continuous exercise involvement affects age-related changes in cognition. They used the National Long Term Care Survey over a 10-year period to determine if exercise habits were associated with the onset of cognitive impairment, as measured by the Mini-Mental State Exam (MMSE) and the Short Portable Mental Status Questionnaire (SPMSQ; Jedrziewski et al., 2010). Participants were asked about their participation in physical activity over the previous two-week period; more specifically, they were asked what types of activity they participated in, the number of sessions per week they engaged in the activity, and the length of each session. At 5-year (2,488 participants) and 10-year (1,260 participants) follow-ups they found that participants who engaged in a greater number of activities in the first 5-years performed better on the MMSE and had fewer errors on the SPMSQ at the 10-year assessment. In addition, they showed that the number of exercise sessions lasting at least 20 minutes in the previous two weeks was related to a higher MMSE score. These results demonstrate that greater exercise frequency and involvement in a greater number of types of exercise is positively related to later onset cognitive decline in older adult populations (Jedrziewski et al., 2010).

However, exercise can influence cognition in various ways across the lifespan. For instance, exercise has been shown to improve or maintain the cognitive function of children and young adults, whereas in older adults, it is thought to delay age related cognitive decline (Hillman et al., 2008). For instance, Hillman and associates (2014) had 8 and 9 year-old children engage in a 70-minute aerobic physical activity intervention everyday after school. Their results followed a dose-response relationship; students with a higher attendance rate performed better on tasks assessing cognitive flexibility and attentional inhibition (both executive control tasks) than those who attended fewer classes (Hillman et al., 2014). In studies focusing on older adults, it is not uncommon for the control group to show declines in cognitive performance. Thus, these studies tend to focus on the extent to which different exercise regimes can attenuate cognitive decline. For example, in a study comparing different amounts of resistance training in senior women, Liu-Ambrose and associates (2012a) found that both resistance interventions resulted in improved performance on a test of attentional control; however those in the balance and toning control group experienced a small deterioration in performance.

Age is not the only factor that influences the effects of exercise on cognition; the relationship between exercise and sleep, and its subsequent effects on cognition, is also important. A meta-analytic review of 66 studies demonstrated a consistent relationship between chronic exercise participation and sleep habits. That is, regular exercise had a small, but positive effect on total sleep time and sleep efficiency (time spent sleeping/time spent in bed x 100%), a small-moderate beneficial effect on sleep onset latency and a moderate positive effect on sleep quality (Kredlow et al., 2015). Further investigation has revealed that the cognitive benefits of exercise are dependent on sleep. Lambiase and colleagues (2014) recorded sleep and physical activity habits of 121 women over the course of 7 days, as well as performance on various cognitive tasks. They showed that exercise involvement mitigates the cognitive deficits associated with less sleep; poorer sleep efficiency was associated with worse performance on tasks assessing executive function (the Digit Symbol task and the Trail Making Test) in women with lower levels of physical activity, but not in those with higher levels (Lambiase et al., 2014). The relationship between exercise and sleep clearly affects cognitive performance, and thus sleep quantity and quality should be considered in experiments investigating the connection between exercise and cognition.

While a lot of research has been done to examine the effects of different exercise regimes on cognition, a lot of this work has been done in a piecemeal manner. That is, a common issue found across many studies is the use of a narrow cognitive task battery. This results in a limited number of cognitive functions being investigated, and makes it more likely that some exercise-dependent benefits will go unobserved. Moreover, very few studies use a sample that includes a wide age range, which makes it difficult to compare the effects of exercise on different age groups. This is important because as we age, our ability to perform a certain intensity or type of exercise diminishes. As a consequence individual studies must tailor their interventions to the age group under investigation, which ultimately limits the generalizability of those findings. These concerns have contributed to the difficulty in clearly defining the relationship between exercise involvement and cognition. What is lacking in the literature is a large-scale examination, providing a landscape perspective on the effects of exercise on cognition. In this study, I sought to resolve this by focusing on exertion rather than specific forms of exercise, by assessing various cognitive functions, and by examining how factors such as age and sleep may interact with exercise to influence cognition.

The primary aim of experiment 1 was to use a large and diverse sample to evaluate the aspects of cognition that most benefit from various levels of exercise. The secondary aim was to determine whether there are any other variables, such as age or sleeping patterns, which influence the relationship between exercise and cognition. To do this, I conducted a large-scale internet-based study by recruiting just shy of 11,000 participants, each of whom completed the 12 tasks that comprise the Cambridge Brain Sciences cognitive task battery. Based on the existing literature (e.g. Hillman et al., 2014 & Liu-Ambrose et al., 2012a), I hypothesized that more frequent involvement in exercise would be associated with improved cognitive performance across various tasks, but, in particular, those tasks that tap into executive function.

2.2 Methods

2.2.1 Participant Demographics and Procedure

Participants were recruited using Cambridge Brain Sciences, an online cognitive testing platform (www.cambridgebrainsciences.com). Before completing the study, participants gave informed consent. The Health Sciences Research Ethics Board of the University of Western Ontario approved this study.

This study consisted of two phases. First, participants were asked to complete a questionnaire, which included questions about demographic variables (e.g., age, handedness, gender, and education) and one question about their exercise habits: "How often have you exercised, such that you worked up a sweat, in the past month?" (response: "not in the past month", "less than once a week", "1-2 times a week", "more than 3 times a week" and "everyday"). After completing the questionnaire, participants were able to begin the second phase of the study, which involved completing the 12 cognitive tasks included in the CBS platform. Collectively, these tasks measure many aspects of cognition, including short-term memory, verbal ability, reasoning, and inhibitory control, all of which have been associated with specific patterns of neural activity (Hampshire et al., 2012), and have been used to detect subtle changes in cognition due to neurodegeneration (Owen et al., 1992; Owen et al., 1993) or pharmacological intervention (Lange et al., 1992; Mehta et al., 2000). A description of each of the 12 tasks can be found in the "Cognitive Measurements" section of this chapter. Only participants who completed the questionnaire and all 12 cognitive tasks were included in the analysis. In total, 10,985 participants (7011 female, 3885 male, 89 did not identify as male or female) between the ages of 10 and 87 (M=40.45, SD=14.01) were included in this study. Of the 10,985 participants who completed the study, a total of 613 reported exercising every day, 2,760 participants reported exercising 3 or more times a week, 3,193 participants exercised 1-2 times a week, 2,422 participants reported exercising less than once a month and 1,997 participants reported that they had not exercised in the past month. Table 1 provides more information on population demographics.

Table 1: Participant Demographics

Measure	**Percentage or Mean (SD)**						
	Everyday	**3 or more times a week**	**1-2 times a week**	**Less than once a week**	**Not in the past month**	χ^2(df) or *F*(df)	*p*
N	613	2760	3193	2422	1997		
Age	41.0 (15.4)	40.7 (14.2)	39.6 (13.7)	39.7 (13.72)	42.2 (14.0)	12.30 (4, 10980)	<0.001
Gender						63.48 (4)	<0.001
Female	52.7%	61.4%	63.9%	65.7%	68.1%		
Male	46.7%	38.0%	35.2%	33.2%	30.8%		
SES						25.52 (4)	<0.001

At or above poverty line	92.5%	94.6%	92.8%	92.6%	91.1%		
Education						109.14 (16)	<0.001
None	3.9 %	2.5%	2.4%	2.9%	3.7%		
High School	20.0%	18.9%	21.9%	25.1%	27.7%		
Post-secondary	43.3%	42.5%	41.2%	44.2%	39.6%		
Master's degree	21.9%	23.9%	23.5%	18.5%	20.5%		
Doctorate/Professional	10.8%	12.2%	10.9%	9.2%	8.5%		

Note. *F*-test was used to compare age; χ^2 was used to compare gender, SES and education.
Only individuals identifying as male or female were included in the gender analysis.

An analysis of the descriptive statistics revealed there was a greater proportion of males in the group that exercised 3 or more times a week compared with those who exercised at the lowest frequencies ($X^2(1) > 11.72$, $p < 0.001$). This was also true for the group that exercised everyday ($X^2(1) > 27.95$, $p < 0.001$). The mean age in the sample was similar across the groups; however those exercising <1 a week and 1-2 times a week were significantly younger than those who reported the other three levels of exercise ($t_{(873)} > 1.97$, $p < 0.049$; $t_{(807)} > 2.09$, $p < 0.037$). The groups who had not exercised in the past month or less than once a week also had a larger proportion of people who grew up in low socioeconomic households than those who exercised 3 or more times a week ($X^2(1) = 21.25$, $p < 0.001$; $X^2(1) = 8.30$, $p = 0.004$ respectively). Finally, the highest proportion of participants held a Bachelor degree, followed by those with higher degrees (either a Master's or Doctoral degree), followed by high school graduates and those with no education. The groups with the greatest proportion of people holding a Bachelor degree were those exercising less than once a week, everyday and 3 or more times a week, with a significantly lower proportion in the groups exercising 1-2 times a week ($X^2(1) = 5.07$, $p = 0.024$), or not in the past month ($X^2(1) = 9.15$, $p = 0.002$). Further information about the demographics of the sample can be found in the appendix.

2.2.2 Cognitive Measurements

Spatial Span The spatial span is a task used to measure spatial short-term memory, and is based on the Corsi block tapping task (Corsi, 1972). In this task, there is a 4 by 4 grid with 16 squares (Figure 1). A random sequence of squares will flash at a rate of 1 square every 900ms. The participant must use their cursor to repeat this sequence. If the participant correctly recalls the sequence, the following sequence length will increase by 1, and if not, it will shorten by 1. After 3 errors, the task ends.

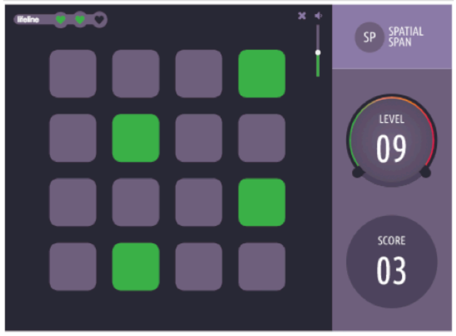


Figure 1: Spatial Span Task.

Token Search This task is based on a non-human primate test used to measure strategy during search behavior (Collins et al., 1998). There is an invisible 5 by 5 grid in which sets of boxes are displayed in random locations (Figure 2). To begin, the participant is instructed to find a token beneath one of the boxes by clicking on each box to reveal their contents. Once the token is found, it then becomes hidden beneath a different box and the participant must search each of the boxes until the token has been found under each one. However, the token will not appear in the same box more than once in each trial. They are instructed to not click on a box again after the token has been found underneath it. If they search in a box the token has been previously found under, the trial ends and in the next trial there will be one less box to search through. If the participant finishes the trial with no errors, the next trial will include one more box. After 3 errors, the task ends.

Figure 2: Token Search Task.

Monkey Ladder This task has been historically used to measure numerical working memory in the primate literature (Inoue & Matsuzawa, 2007). In this task, there is an invisible 5 by 5 grid and at the beginning of each trial, there is a set of numbered squares that appear in random locations (Figure 3). After a period of time (number of square multiplied by 900ms), the numbers on the squares disappear. The participant must remember the ascending sequence of numbers and click on the squares in the sequence. If the trial is completed without error, the number of squares will increase in the next trial. If the participant makes an error, the next sequence has one less square. After 3 errors, the task ends.

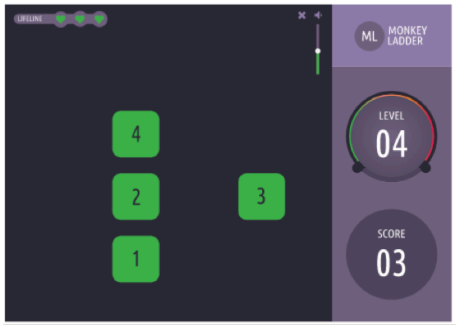


Figure 3: Monkey Ladder Task.

Paired Associates This task is based on tests that are widely used to assess memory impairments in aging clinical populations (Gould et al., 2005). This task consists of an invisible 5 by 5 grid. Boxes are displayed at random locations on the grid, and one after another, they open to reveal an image (Figure 4). Following this, the same images are presented to the participant in a random order and they must click on the box that was shown to contain that image. If the participant successfully pairs all the object-location sets, they move on to the next trial, which contains an added pair. If they don't, the next trial contains one less pair. After 3 errors, the task ends.

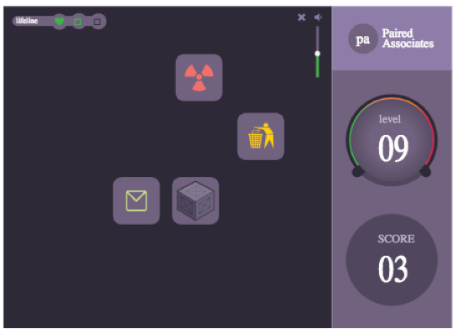


Figure 4: Paired Associates Task.

Spatial Planning This task was formulated based on the Tower of London task and is used to measure planning abilities (Shallice, 1982). There is a tree shaped frame, which has numbered beads positioned along the branches (Figure 5). The goal is for the participant to reposition the beads in ascending numerical order, from left to right, from the top to the bottom of the tree. Participants have 3 minutes to solve as many problems as they can and the goal is complete the problem in as few moves as possible. The problems progressively become more difficult as the required total number of moves and planning complexity increases. The trial ends if the participant uses more than twice the number of moves required to solve the problem. The scoring system rewards efficient planning.

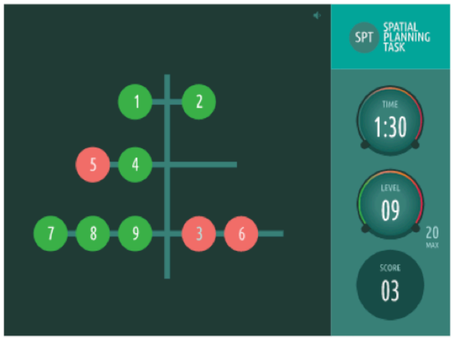


Figure 5: Spatial Planning Task.

Spatial Rotations This task measures the ability of the participant to manipulate the spatial orientation of objects ‘in their mind’ (Silverman et al., 2000). In this task, there are two grids side by side, but one grid is rotated by a multiple of 90 degrees (Figure 6). The two grids are either identical, or differ by the position of one square. The participant must determine whether or not the grids are identical or not, and solve as many problems as they can in 90 seconds. If correct, the score increases by the number of squares in the grid and the next trial has more squares. If incorrect, the total score decreases by the number of squares in the grid and the next trial has less squares.

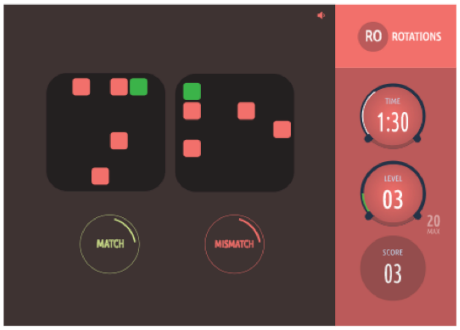


Figure 6: Spatial Rotations Task.

Feature Match Feature search tasks are commonly used to measure attentional processing (Treisman & Gelade, 1980). In this task, there are two grids that each contains a set of abstract shapes. In half the trials, the grids differ by 1 shape (Figure 7). The participant must determine whether or not the grid’s contents are identical or not and they have 90 seconds to complete as many trials as possible. If correct, their total score increases by the number of shapes in the grid, and the subsequent grid increases by 1 shape. If incorrect, their total score decreases by the number of shapes in the grid, and the subsequent grid decreases by 1 shape.

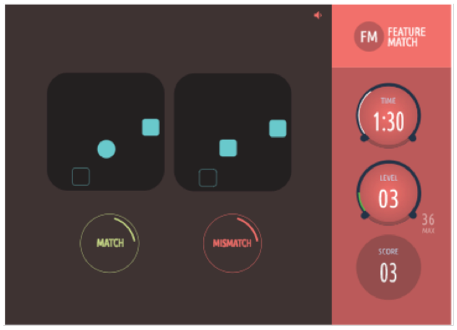


Figure 7: Feature Match Task.

Interlocking polygons This task is based on interlocking pentagons, which is part of a battery used to clinically measure the cognitive state of older adults (Folstein, Folstein, & McHugh, 1975). Participants are given a pair of interlocking polygons on one side of the screen. They are also given a third shape on the other side of the screen, and participants are required to indicate whether the shape they are given matches one of the interlocking polygons (Figure 8). They are instructed to solve as many problems as they can in 90 seconds. If their response is correct, the total score increases by the difficulty level and the differences between the polygons becomes increasingly subtle. If the response is incorrect, the total score decreases by the difficulty level and the difference between the polygons become more pronounced.

Figure 8: Interlocking Polygons Task.

Odd One Out This task is based on a set of problems from the Cattell Culture Fair Intelligence (Cattell & Cattell, 1949). There is a 3 by 3 grid on the screen and each cell contains a variable number of copies of a colored shape (Figure 9). The features making up the objects in each cell (color, shape, number of copies) are connected throughout the grid via a set of rules, and participants must deduce the rules that relate the object features and select the one cell whose contents do not correspond to those rules. The participant has 90 seconds to complete as many problems as possible. If they respond correctly, the total score increases by one point and the next problem is more complex. If incorrect, the total score decreases by 1 point.

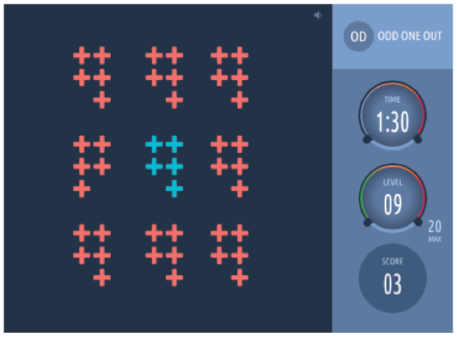


Figure 9: Odd One Out Task.

Digit Span This task is a computerized version of a verbal working memory component of the Welscher Adult Intelligence Scale – Revised (Welscher et al., 1989). Participants will view a sequence of digits on the screen one after another that they need to remember and reproduce using their keyboard (Figure 10). If the participant completes the trial correctly, the next sequence is one digit longer, and if not, it is one digit shorter. The task is complete after 3 errors.

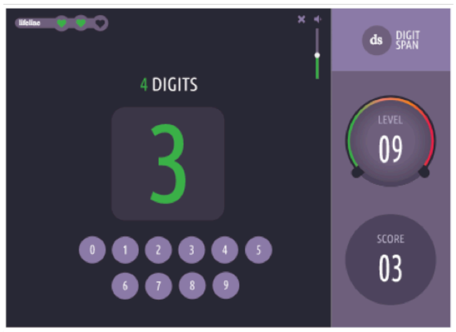
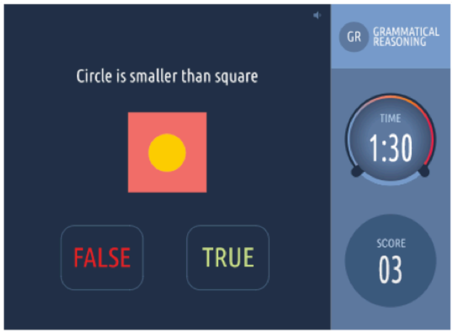


Figure 10: Digit Span Task.

Grammatical Reasoning This task is based upon Alan Baddeley's 3 minute grammatical reasoning task (Baddeley, 1968). Statements appear on the screen with the structure "The circle is not encapsulated by the square". The participant must then indicate whether the statement is true or not for a pair of shapes displayed in the center of the screen (Figure 11). The participant has 90 seconds to complete as many problems as possible. If they respond correctly or incorrectly, their score correspondingly increases or decreases by one.



Circle is smaller than square

Figure 11: Grammatical Reasoning Task.

Double Trouble This task is a more challenging variant of the Stroop task (Stroop, 1935). On the screen, a colored word will appear, for instance BLUE written in red ink. The colors BLUE and RED will be displayed at the bottom of the screen, and the participant must indicate which color the word they are given is written in (Figure 12). The color word mappings may be congruent, incongruent, or doubly incongruent, depending on whether or not the colors that a given words describes matches the color that it is drawn in. The participant has 90 seconds to complete as many problems as possible. If they respond correctly or incorrectly, their score correspondingly increases or decreases by one.

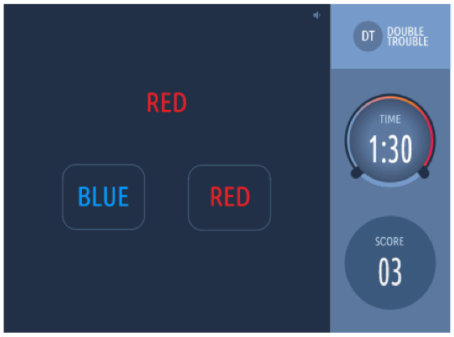


Figure 12: Double Trouble Task.

2.2.3 Statistical Analysis

The data were first cleaned in order to remove improbable responses (for example, reporting an age greater than 120 years) and outliers on the 12 CBS tasks, in two passes: first six, then four standard deviations from the mean. In addition to the 12 CBS tasks, three latent cognitive domain scores were included, which reflect short term memory, verbal and reasoning abilities (Hampshire et al., 2012). These domain scores were calculated by multiplying each participant's score on the 12 tasks with the Moore-Penrose pseudoinverse of a set of component weights (factor loadings) that are computed from a principle component analysis (PCA) on an independent set of 75,000 participants who had completed the same set of CBS tests. Scores on all cognitive tasks and the three cognitive domains were all converted to z-scores.

I first determined whether the frequency of exercise participation had any impact on cognitive abilities. More specifically, I investigated whether regular participation in exercise offers a cognitive advantage over not exercising at all. To do this, I ran multiple linear regressions where I constructed models to predict performance on each of the 12 CBS tasks, in addition to the three latent domains scores from the frequency of exercise. Gender, socioeconomic status (SES), age and level of education were included as categorical covariates of no interest with N-1 regressors (where N = the number of categories for each variable). Following this, I also examined whether exercise frequency interacts with sleep quantity, quality or age to predict cognitive performance by adding the interaction term between exercise and age, and exercise and sleep to the model. All results were corrected using a False Discovery Rate (FDR). In addition, to ensure the results were not due to differences in sample size, I carried out a 5 (group: exercise frequency) x 3 (latent domains) mixed design ANOVA, as well as a 5 (group: exercise frequency) x 12 (tasks) mixed design ANOVA, using demographically matched samples.

2.3 Results

As both exercise and cognitive performance may be influenced by variables such as age, it was important to estimate the contribution of exercise on cognition while controlling for these variables. To do this, I constructed two general linear models to predict cognitive scores for each of the 12 tasks and the 3 latent cognitive domains. The null model included SES, sex, age, and education level as regressors of no interest. The second of the two models, termed the full model, included the same set of regressors, plus exercise frequency as the explanatory variable. I then compared these two models using an F-test to determine if exercise frequency significantly predicted cognitive performance beyond what can be explained by the variables of no interest. I found that exercise was associated with better performance on token search ($F_{(4,\ 10969)} = 4.03$, $p_{FDR} = 0.012$), polygons ($F_{(4,\ 10969)} = 3.18$, $p_{FDR} = 0.038$) and grammatical reasoning tasks ($F_{(4,\ 10969)}= 7.88$, $p_{FDR} = 0.003$). Of the three cognitive domain scores, I found that exercising significantly predicted performance on the reasoning ($F_{(4,\ 10969)} = 3.99$, $p_{FDR} = 0.012$) and verbal domains $F_{(4,\ 10969)} = 5.47$, $p_{FDR} = 0.002$), as seen in figure 13.

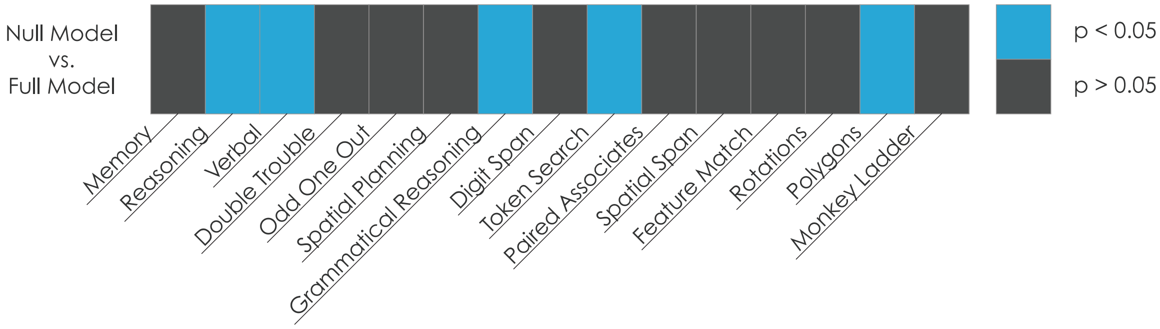


Figure 13: Results of the F-test comparison between the null model, controlling for age, SES, gender, education and task type, and the full model, which controlled for the same set of regressors and included exercise frequency. Blue squares represent cognitive scores where the full model better predicted cognitive performance than the null model ($p<0.05$; n=10,985). All p-values are FDR corrected for multiple comparisons.

These results indicate that relative to exercising less than once per week in the last month, any amount of exercise was associated with better performance on a series of cognitive tests that tap into reasoning and verbal abilities. Next, I examined how well each level of exercise was associated with the same set of cognitive measures. I found that those who exercise less than once a week performed *better* on the grammatical reasoning, token search and rotations tasks, as well as in the reasoning domain, when compared to those who did not exercise in the past month (no exercise was set as the intercept in the regression analysis; Figure 14). Relative to those who did no exercise in the past month, those who exercised 1-2 times a week performed better on the grammatical reasoning, token search, spatial span and polygons tasks, as well as in the reasoning and verbal domains (Figure 14). Those who exercised 3 or more times a week scored higher than those who hadn't exercised in the past month on the digit span, grammatical reasoning and token search tasks, as well as in the verbal domain (Figure 14). Surprisingly, those who exercised everyday did not perform significantly better on any task, or in any domain, when compared to those who hadn't exercise in the previous month (Figure 14).

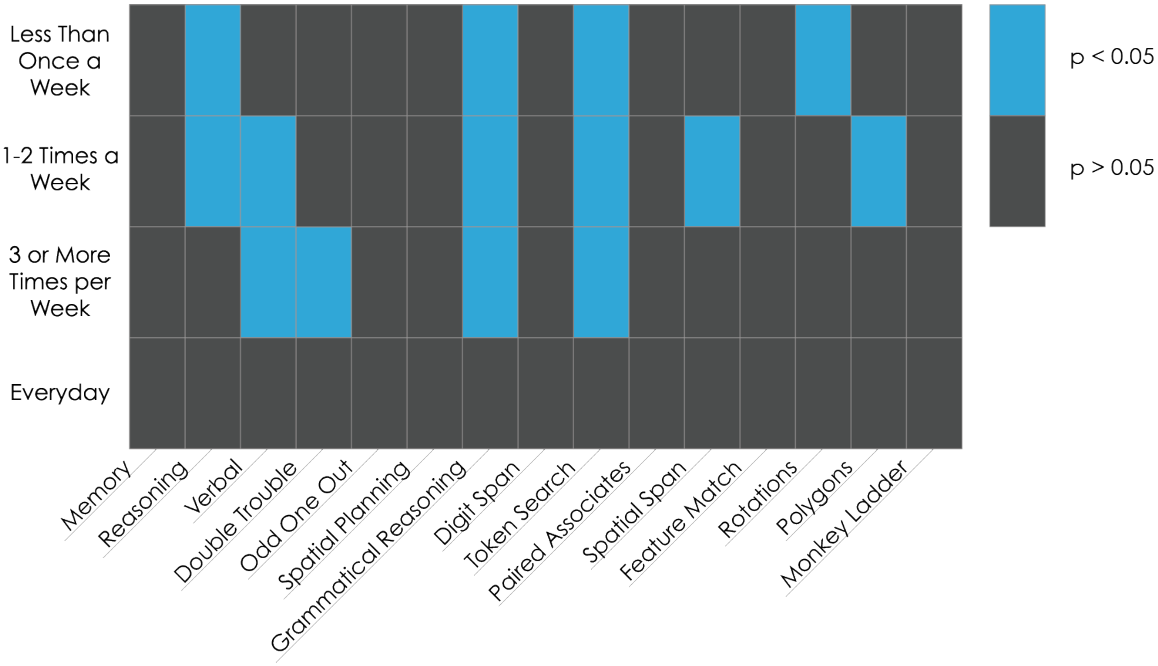


Figure 14: Summary of significant β-values from a multiple linear regression predicting cognitive scores from age, SES, gender, education, task type and exercise frequency. Blue squares represent the cognitive scores that were significantly better when compared to the group that had not exercised in the past month (*p*<0.05; n=10,985). All *p*-values are FDR corrected for multiple comparisons.

Although I found that exercise predicted performance in cognition above and beyond the covariates of no interest, I was interested in whether age and sleep, which are variables shown to have strong links to cognition, interacted with benefits to cognition attributed to exercise I just found. To do this I ran two linear regression analyses by adding the interaction term between exercise and age, and exercise and sleep, to the full model. I found no significant interaction between sleep and exercise ($F_{(4,\ 10965)}$=2.3, p_{FDR}=0.55) or between age and exercise ($F_{(4,\ 10965)}$=3.51, p_{FDR} = 0.084) for any of the cognitive measures.

To be sure the results were not due to large differences in the size of the sample, I performed a matched 5 (group: exercise frequency) x 3 (latent domains) mixed design ANOVA. That is, I matched 609 participants across all levels of exercise based on age, gender and SES. The results of the ANOVA revealed a significant main effect of exercise frequency ($F_{(4, 9120)} = 4.00$, $p = 0.003$), however there was no main effect of latent domain, nor an interaction between the variables ($F_{(2, 9120)} = 2.45$, $p = 0.086$; $F_{(8, 9120)} = 1.12$, $p = 0.3444$). I similarly performed a matched 5 (group: exercise frequency) x 12 (task) mixed design ANOVA, and found a significant main effect of exercise frequency and task ($F_{(4, 45600)} = 6.00$, $p < 0.001$; $F_{(14, 45600)} = 16073.42$, $p < 0.001$), as well as a significant interaction between the two variables ($F_{(56, 45600)} = 1.54$, $p = 0.006$). To isolate which tasks interacted with exercise level, I conducted 15 one-way ANOVAs for each cognitive measure (12 tasks, plus 3 latent cognitive domains). I found performance on the verbal ($F_{(4, 3040)} = 3.26$, $p = 0.011$) and reasoning ($F_{(4, 3040)} = 2.53$, $p = 0.039$) domains improved with exercise; however the memory domain did not show the same effect ($F_{(4, 3040)} = 0.396$, $p = 0.812$). I also found a significant effect of exercise frequency on four of the cognitive tasks: double trouble, spatial tree, rotations and grammatical reasoning ($F_{(4, 3040)} = 2.89$, $p = 0.021$; $F_{(4, 3040)} = 2.57$, $p = 0.036$; $F_{(4, 3040)} = 2.51$, $p = 0.040$; $F_{(4, 3040)} = 6.06$, $p < 0.001$).

Following these analyses, I next determined which exercise frequencies were significantly different from each other on the verbal and reasoning domains, as well as the 4 individual tasks; double trouble, spatial tree, rotations and grammatical reasoning. Independent t-tests revealed significant differences in performance on the verbal domain between those who exercise less than once a month and those who exercise 1-2 times a week ($t_{(1215)} = 2.85$, $p_{(\text{Bonferroni corrected})} < 0.01$; Cohen's d = 0.163), and between those who exercise less than once a month and those exercising 3 or more times a week ($t_{(1215)} = 2.97$, $p_{(\text{Bonferroni corrected})} < 0.01$; Cohen's d = 0.170). After Bonferroni correction, there were no significant differences in performance in the reasoning domain between any of the levels of exercise. Turning to the individual cognitive tasks, I found those who exercise less than once a month performed worse than those who exercise 1-2 and 3 or more times a week on the grammatical reasoning task ($t_{(1215)} = 4.61$, $p_{(\text{Bonferroni corrected})} < 0.001$; Cohen's d = 0.263; $t_{(1212)} = 2.99$ $p_{(\text{Bonferroni corrected})} = 0.028$; Cohen's d = 0.171). In addition, those who exercised 1-2 times a week performed significantly better than those who exercised less than once a week ($t_{(1216)} = 3.16$, $p_{(\text{Bonferroni corrected})} = 0.016$; Cohen's d=0.181) on the grammatical reasoning task. Moreover, those who exercised 1-2 times a week performed significantly better from those who exercised less than once a week

($t_{(1213)} = 2.66$, $p_{(\text{Bonferroni corrected})} = 0.043$; Cohen's d = 0.152) on the double trouble task.

2.4 Discussion

In this study, I aimed to evaluate how voluntary exercise practices influence cognitive function using a large and diverse sample across the lifespan, focusing on physical exertion rather than on specific forms of exercise. This way, the relationship between exercise and cognition can be compared across different age groups. I found that the frequency with which people exercise significantly predicted performance in the reasoning and verbal domains, above and beyond what was explained by other demographic factors. Specifically, I found any amount of exercise beyond less than once monthly was associated with better performance on the polygons, token search and grammatical reasoning tasks, as well as the reasoning and verbal domains. However, I also found that each level of exercise was associated with improved performance on specific tasks compared to those who exercise less than once per month, demonstrating that generally, greater frequencies of exercise were associated with improved cognitive performance. Moderate levels of exercise were most consistently associated with better performance on the grammatical reasoning and token search tasks, in addition to the reasoning and verbal domains. However, this relationship did not extend to those who exercise everyday; daily exercisers were not found to perform differently than those who had not exercised in the past month on any task or latent domain. In addition to these findings, I discovered that neither sleep quality, sleep quantity, nor age significantly interacted with exercise to better cognitive function. This suggests that exercise is a strong predictor of cognitive ability and the effects of exercise on cognition are independent of different sleep metrics and age. In other words, exercise is directly beneficial to certain aspects of cognition.

Generally, my results supported my hypothesis; performance on different cognitive measures was better as people exercised more frequently. However, I found no differences between those who exercise every day and those who exercise less than once a month, which was unanticipated. However, there are a few potential explanations for this result. First, there may be differences in how participants interpreted the question: "How often have you exercised, such that you worked up a sweat, in the past month?"

For instance, individuals prone to sweating regularly may consider short bouts of non-strenuous activity sufficient evidence that they engaged in “exercise”. Contrast this with a person who only begins to sweat after a significant amount of exertion. This distinction may be different for younger and older participants, which becomes a greater issue when these participants are grouped together. Relatedly, I do not have any data to quantify the intensity with which people were exercising. Swagerman and colleagues (2015) suggest that for exercise to be beneficial to cognition, it needs to be carried out at a moderate to vigorous intensity. Thus a possible explanation for my results is that the intensity of exercise that allows you to exercise every day is not sufficiently high so as to produce detectable benefits to cognitive functioning (Colcombe & Kramer, 2003; Swagerman et al., 2015). Conversely, it is also possible that daily exercise is cognitively taxing, as the body needs time to rest after moderate-vigorous activity. In addition, I considered the possibility that those who exercise most frequently (i.e., everyday) have a lower baseline of cognitive abilities. However, after examining the demographics of this group, specifically by focusing on factors such as SES and education level, which have been shown to be strongly linked to performance across various cognitive measures, I did not find patterns that would support this hypothesis. Lastly, this result may reflect a true quadratic relationship between the frequency of exercise and cognitive performance, such that too little or too much exercise is not beneficial for cognition, but any amount in between offers a benefit. Similar results have been found throughout the literature. For example, Chang and associates (2015) found that when looking at various durations of exercise, 20 minutes of moderate intensity on a stationary bike offers the greatest benefit on the Stroop task (Stroop, 1935), whereas there was no improvement on the task after 10 or 45 minutes of exercise. In addition, in an experiment performed by Chang and Etiner (2009), participants completed resistance workouts at 40%, 70% and 100% of their maximal effort and they found a significant quadratic trend between exercise intensity and performance on executive function tasks. Thus, it would not be unreasonable to suggest that a quadratic relationship between exercise frequency and cognitive performance could be used to help interpret my results.

An interesting result emerging from the matched ANOVA analysis is that, across multiple comparisons, those who exercise 1-2 or 3 or more times per week consistently outperformed those in the other groups at the grammatical reasoning task, which is likely associated with better performance in the verbal domain. While exercise has been shown to benefit performance on diverse cognitive tasks, improvements to memory related functions are most consistently seen (Chaddock et al., 2011; Erickson et al., 2011; Hillman et al., 2008; Vaynman, Ying, & Gomez-Pinilla, 2004). Interestingly, various studies have shown the utilization of working memory during sentence verification, which happens to align closely to the properties of the grammatical reasoning task (Hitch & Baddeley, 1976). Paradoxically, none of the measures of working memory exhibited improvements. Nonetheless, exercise-related benefits to grammatical reasoning are a novel finding and worthy of future investigation.

Despite finding an array of tasks associated with exercise involvement, there were also a number of tasks whose performance was not related to any of the exercise frequencies. This finding echoes the heterogeneity of the literature, and further suggests that not all cognitive functions equally benefit from exercise involvement. This trend has been identified in a number of studies, but it was initially discovered by Kramer and colleagues (1999), who subsequently developed the selective improvement hypothesis. Although this hypothesis was suggested with regards to aerobic exercise selectively improving various executive functions (Kramer et al., 1999), I believe it may also be useful in helping to explain the results I obtained in this experiment. For example, despite clusters of tasks falling into the same latent domain, or being classified as relying on the same cognitive skills (e.g. executive functions or pattern separation), there were instances where some tasks exhibited relationships with exercise that were distinct from the rest of the cluster. For example, the digit span was the only task relying on the verbal domain to not be associated with any level of exercise. One reason for this may be a difference in the exact cognitive mechanisms employed by seemingly similar tasks. Following this, it may be the case that the effects of voluntary exercise are localized to specific regions of the brain, and the tasks that were shown to have a relationship with exercise recruit cognitive mechanisms that rely on these distinct regions (Smiley-Oyen et al., 2008). In addition, other researchers have suggested that exercise tends to have the most robust effects on timed tasks, compared to those that are non-timed (Chodzko-Zajko & Moore, 1994; Smiley-Oyen et al., 2008). This could explain the associations I observed between exercise involvement and tasks such as grammatical reasoning, double trouble and polygons. Overall, it is unclear exactly why some tasks are more responsive to exercise than others, however it may be related to the exact cognitive requirements of each task, and in turn, the associated brain regions and their responsiveness to exercise.

The benefits to cognition that I have found to be associated with moderate levels of exercise may arise via various physiological pathways. Exercise has been associated with augmented synthesis of growth factors including BDNF, VEGF and IGF-1, which act to amplify neurogenesis, synaptic plasticity and angiogenesis in the brain (Homolak et al., 2015; Lopez-Lopez et al., 2004; Murray & Holmes, 2011). The effects of these growth factors are hypothesized to support cognitive enhancements (Borror, 2017). Although, numerous molecules and growth factors experience augmented expression following exercise, BDNF and its downstream pathways are generally regarded as one of the top contenders for moderating the cognitive benefits of physical activity. Increased levels of BDNF are commonly found in the hippocampus after exercise, and elevated levels are associated with improvements in memory function and learning (Piepmeier & Etnier, 2015; Vaynman, Ying, & Gomez-Pinilla, 2004; Wrann et al., 2013). However, it is also believed that differences in the BDNF gene may contribute to how the protein is produced and distributed; the methionine allele of the BDNF Val66Met polymorphism is associated with decreased BDNF secretion and poorer memory (Erickson et al., 2013). Erickson and colleagues (2013) used a genotyping approach on a sample of 1,032 participants to further understand the role of this BDNF polymorphism and whether it plays any role in moderating the beneficial effects of exercise. Participants filled out the Paffenbarger Physical Activity Questionnaire, commonly used to estimate energy expenditure, and completed a battery of cognitive tasks. First, they found that greater amounts of physical activity, dictated by kilocalorie expenditure, were associated with enhanced working memory performance. Additionally, in accordance with their hypothesis, they found that on tasks evaluating working memory, specifically different variations of the N-back, those with the Met polymorphism benefit more from exercise than those who are Val homozygous. This result provides further evidence of the significant role BDNF plays in the relationship between exercise and cognition and could help to explain why there is significant variation in the extent to which one benefits cognitively from exercise (Erickson et al., 2013).

In addition to the structural changes induced via growth factors, exercise is associated with increased cerebral blood flow (CBF). Greater CBF increases the metabolic capacity of the brain due to the increased oxygen and glucose being carried, which could be one mechanism contributing to the better performance seen on certain cognitive tasks that I observed for those who engage in moderate levels of exercise (Borror, 2017). For example, Guiney and colleagues (2015) proposed that improved cerebral blood flow, which is associated with greater exercise participation, may also be an avenue by which exercise benefits cognition. As well, over time the physiological effects of exercise result in structural and functional changes to the brain. For example, those with a greater cardiovascular capacity, which is indicative of greater aerobic exercise involvement, have been shown to have a larger gray matter volume in the hippocampus and pre-frontal cortex and greater functional connectivity in the hippocampus and default mode network (Burdette et al., 2010; Küster et al., 2016; Voss et al., 2010; Weinstein et al., 2012). The exact mechanisms by which exercise results in cognitive benefits is unknown, however performing exercise on a regular basis likely instigates many of these pathways, resulting in long-term structural changes to the brain.

Some of the most notable strengths of the current study include the large and diverse sample collected and the battery of outcome measures used, which assesses various aspects of cognition. These two elements allowed for the most effective evaluation of the cognitive effects of real world exercise regimes. Nevertheless, there were limitations to this study that should be addressed in future investigations. The demographic questionnaire in the current study was devised to ask a broad set of questions, while being succinct. Thus, I chose a single question that would allow me to most valuably compare exercise levels across the lifespan. I reasoned that physical abilities adapt with age, and while an individual's ability to exercise at the same level (with respect to type, intensity and duration) may change, the frequency of exercise involvement is likely most resistant to variation. This allowed for me to compare exercise across all ages. However, in an attempt to be brief, I sacrificed certain details that may have added to the understanding of the relationship between voluntary exercise and cognitive function. Thus, in subsequent studies it would be valuable to include questions regarding how many years one has exercised for, the type of exercise, and the duration and intensity of their exercise routine. This would allow me to tease out specific aspects of exercise and their potentially differential effects on cognition. Including these factors will not only help to further the understanding of the effects of voluntary exercise, but may also give insight into the characteristics of exercise regimes that are most beneficial to cognition.

Chapter 3

3 Experiment Two

3.1 Introduction

In chapter one, I have outlined the benefits of using large population-based studies to address the exercise-cognition relationship. For instance, this approach provides a landscape perspective on the effects of diverse exercise habits on different aspects of cognition and how this influence may be moderated by various lifestyle factors. However, probing specific aspects of exercise and their influence on different cognitive processes is difficult using only this approach. As the data are based on self-report and provide no direct measure of exercise, this leaves many questions regarding the cognitive effects of exercise unanswered. One such question is the link between cognitive functioning and specific measures of physical fitness, such as aerobic capacity (measured by VO_2 Max) and strength. Therefore, the central aim of this chapter is to attempt to link those two measures of physical health to different aspects of cognition in order to provide a better understanding of the exercise-induced benefits to cognitive function.

Various physical tests are used to estimate an individual’s overall aerobic endurance, however, the VO_2 Max test is the gold standard, as it measures maximal oxygen consumption (Pereira et al., 2007; Schwarb et al., 2017). While different variations of this test are used, the main principle is the same; push an individual to their maximum effort while measuring oxygen uptake. Various studies have used this test to estimate cardiovascular capacity and have found that it is associated with performance on a collection of cognitive tasks. The relationship between VO_2 Max and cognition seems to be particularly strong in younger participants. For example, in adolescents it was found that aerobic capacity, measured by VO_2 Max, correlated with relational memory performance (Schwarb et al., 2017). Similarly, in pre-adolescents, performance on a relational memory task was related to VO_2 Max; the higher the VO_2 capacity, the better the score on the relational memory task (Chaddock et al., 2010). Thus, these studies reveal the trend that a larger VO_2 Max is associated with improved performance on tasks relying on memory function.

In addition to links between cardiovascular health and specific cognitive abilities, other studies show there are real-world benefits associated with regular physical activity. Castelli and colleagues (2007) investigated the relationship between academic achievement in grade school and physical fitness. They discovered that aerobic capacity in 3rd and 5th grade students was positively associated with achievement in both mathematics and reading. Moreover, students who scored higher on different metrics of physical fitness – aerobic capacity, measured by the Progressive Aerobic Cardiovascular Endurance Run, and various muscular endurance tests – were more likely to score better on standardized tests (Castelli et al., 2007).

As discussed earlier in this thesis, it is not only younger cohorts who appear to show exercise related benefits to cognition. These benefits also extend to other age groups, most notably in older adults who are susceptible to age-related cognitive decline. In the Baltimore Longitudinal Study of Aging, it was found that those with a higher maximal oxygen consumption (i.e., VO_2 Max) experienced less prospective cognitive decline, specifically on visual and verbal memory tasks (Wendell et al., 2014). These trends suggest that regular physical activity, which supports a larger cardiovascular capacity, is beneficial throughout the lifespan, and is associated with practical cognitive implications.

Overall, previous research indicates a relationship between cognitive function and physical fitness, however the reason for this association is not entirely clear. One possible mediator is structural changes in the brain associated with improved aerobic capacity, particularly in brain areas associated with performance on memory related tasks. For instance, the hippocampus is involved in memory function and has thus been a region of interest. In pre-adolescent children, fitter individuals (determined by VO_2 Max measurements) had greater hippocampal volumes (Chaddock et al., 2010), and performed better on relational memory tasks relative to less fit children (Schwarb et al., 2017). Erickson and colleagues (2009) confirmed this result in older adults as well, demonstrating that individuals with higher aerobic fitness had superior spatial memory performance, and this relationship was mediated by greater hippocampal volume. However, volume may not be the only change to the hippocampus that is important to produce cognitive improvements after exercise. Despite finding no correlation between aerobic fitness and hippocampal volume, Schawrb and colleagues (2017) did find that hippocampal viscoelasticity mediated a positive association between cardiovascular capacity and relational memory recall. These results collectively demonstrate that the association between higher cardiovascular fitness and cognitive functioning may be mediated by hippocampal volume, and physical activity may also produce microstructural differences in the brain that eventually drive improvements to memory-related aspects of cognition.

Aerobic capacity is not the only measure of physical fitness that appears to be associated with better cognitive functioning. More recently, the relationship between muscle strength and cognition has been studied, and strength appears to also be positively associated with cognition in older adults. For instance, using handgrip force as a metric of strength, Kobayashi-Cuya and colleagues (2018) discovered a significant correlation between grip strength and performance on the Mini Mental State Exam (MMSE), a battery used to screen for cognitive decline, in older adults. However, this review examined individuals between the ages of 49-100 using the MMSE, and to fully understand the role of strength-based exercise on cognition, this relationship must be studied across the lifespan, using tasks that assess a variety of cognitive abilities.

Despite a vast number of studies investigating the relationship between various physical fitness measures and different aspects of cognitive function, surprisingly few have examined this connection in young adults. However, of the studies that have, the relationship between exercise and cognition appears to be mixed in younger participants. For instance, Aberg and colleagues (2009) studied this relationship in 18-year old males, focusing on four cognitive tasks assessing logical, verbal, technical and visuospatial intelligence, in addition to a global intelligence score, which reflects a composite of the four tasks. They found that, overall, cardiovascular fitness was associated with global intelligence, and this result extended to each of the individual cognitive tasks. More recently, this relationship has been extended to relational memory. Healthy young adults who had superior maximal oxygen consumption were shown to also have better performance on a spatial reconstruction task (Schwarb et al., 2017). However, physical strength and cognition did not show the same positive relationship. Measures of strength, including knee and elbow flexion and grip strength, were significantly associated with lower global intelligence scores (Aberg et al., 2009). One limitation shared by these studies is the lack of variety in the cognitive tests used, and therefore, the relationship between physical fitness – in particular strength – and performance on individual tasks tapping into various cognitive processes remains unclear in young adults.

In this experiment, I resolve some of the main issues in the literature by exploring whether different measures of cardiovascular fitness and muscle strength are associated with different aspects of cognitive functioning in healthy young adults. To test this, participants performed a predictive VO_2 Max test (the submaximal treadmill test) along with push-ups, plank, wall sit, and bicep curls, which serve as measures of muscular strength and endurance. Together, performance on these tests was taken as an estimate of each individual's overall fitness level. Alongside the measures of physical fitness, participants also completed the set of 12 tasks comprising the Cambridge Brain Sciences battery, which tap into various aspects of cognitive functioning. This way, I could better examine the true relationship between measures of physical and cognitive health. Based on previous work in this area, I hypothesized that there will be a positive association between cognitive performance and measures of cardiovascular fitness. More specifically, previous studies have revealed an association between aerobic capacity and memory function; thus I hypothesized that my measure of aerobic capacity will correlate with performance on tasks falling into the memory domain. Conversely, in young adults, muscle strength has been shown to be associated with lower global intelligence scores (Aberg et al., 2009), and thus I did not predict that cognition would be positively correlated with any measures of strength.

3.2 Methods

3.2.1 Participant Demographics

Participants were recruited using flyers posted throughout Western University and the

Psychology Research Participant Pool. All participants gave written informed consent, and were compensated monetarily for their involvement. Participants were screened before participating to ensure they did not meet any exclusion criteria, including: any neurological problems or brain injuries, any visual or auditory disorders, poor vision not corrected by contact lenses, pregnant, or trying to become pregnant or any condition that prohibits moderate physical activity. Participants were also screened via the Physical Activity Readiness Questionnaire (PAR-Q+) to ensure they were able to safely perform exercise. Four participants were not able to complete all parts of the study, and were thus excluded from the analysis. In total, there were 37 participants (26 females, 11 males) between the ages of 18 and 34 (M = 22.8, SD = 4.06) who were included in the final analysis for the current study. The Health Sciences Research Ethics Board of the University of Western Ontario approved this study.

3.2.2 Procedure

There were two phases to this study. In the first phase participants completed the set of 12 cognitive tasks that comprise Cambridge Bain Sciences; all tasks were completed twice, in random order to remove practice effects (see the "Cognitive Measurements" section of chapter one for a description of each task). Participants were instructed to complete the CBS tasks before completing any physical activity that day, or on a separate day when they were not exercising (including exercise independent of the study). This was to ensure the acute effects of exercise did not influence any of their test scores (Chang et al., 2012).

In the second phase, participants completed a physical fitness assessment, which was divided into an aerobic and strength component. They performed the assessment unsupervised and in their own time during a routine visit to the gym (see below). In the aerobic component, participants performed the single stage submaximal treadmill test, which is used to predict maximal oxygen uptake (VO_2 Max; Ebbeling et al., 1991). At the start of the assessment, participants were strapped with a Polar H7 Heart Rate sensor around their chest to ensure an accurate recording of their heart rate (HR). This test requires the participant to walk on a treadmill for 4 minutes at 0% incline, at a speed that brings their heart-rate between 50-70% of their age-predicted maximum HR. Following this, they continue walking at the same speed, however the incline on the treadmill is increased to 5%. They continue walking at this speed and incline for 4 minutes. At the end of this period their steady state HR (SSHR), is recorded by taking the average HR from the final 30 seconds. The participant's age, SSHR and walking speed were recorded and entered into the following equation (Ebbeling et al., 1991), which was used to estimate the participant's VO_2 Max:

$$\begin{gathered}15.1+21.8\,(speed\ in\ mph)-0.327\,(SSHR\ in\ bpm)-0.263\,(speed\ x\ age\ in\ years)\\ +0.00504\left(SSHR\ x\ age\right)+5.98\left(gender;\ female=0,\ male=1\right)\end{gathered}$$

For several reasons, the participants were asked to carry out this test on their own and to ensure that they were following instructions, they were asked to take a picture of the treadmill, which showed their speed and incline achieved. Their steady state heart rate was extracted from the polar beat application.

In the resistance component, there were four strength exercises that participants were asked to complete on their own (see below): plank, wall sit, push-ups and bicep curls. For both the plank and wall sit, participants were instructed to hold those positions for as long as they could; duration was recorded with a stopwatch. They were then asked to complete as many push-ups as they were able to without resting and record this number. Lastly, they were asked to perform single arm bicep curls using dumbbells. They were asked to record the weight they were able to curl for 10 repetitions without rest, and the maximum weight they could curl for 1 repetition.

I wanted to ensure that the physical measures were collected on the participant's own time, and completed without experimenter bias. However, to ensure the numbers participants were reporting were reliable and reflected their physical abilities, I randomly selected 12 people from our sample (34%) and asked them to come back and perform the plank and wall sit in my presence. I then compared their independent data to their verified data to ensure there were no differences in performance.

3.2.3 Statistical Analysis

Physical measures

First, I examined whether the verified sample (the physical measures recorded in my presence) were similar to the physical measures recorded by participants on their own. To do this, I ran an independent samples t-test and Pearson's correlation on the subset of participants who had completed both conditions. Once the data had been validated, I next tested whether there was any redundancy in my set of physical measures. Using a correlational analysis, I identified sets of similar and dissimilar measures that measure distinct aspects of physical fitness.

Linking physical and cognitive health

In addition to the test scores on each of the 12 tasks, latent domain scores (reflecting working memory, verbal and reasoning abilities) were generated (see Statistical Analysis section of Chapter 1 for details on how the latent cognitive domains scores were calculated).

I examined the relationship between performance on 15 measures of cognition (12 tasks plus three latent domain scores) and a subset of physical measures of cardiovascular health and strength in two ways: first I investigated whether the degree of cardiovascular fitness and strength was related to cognitive performance. To do this, participants were divided into two groups using a median split: those who scored highest and lowest on the three measures of physical health. I then carried out a 2 (high fitness vs. low fitness) x 15 (cognitive measures) mixed design ANOVA. Second, I correlated performance on the 15 measures of cognitive ability with the three measures of physical health (based on the correlational similarity analysis) to determine whether physical health scaled with cognitive performance across various tasks.

3.3 Results

To investigate whether performance on the wall sit and plank differed between the independent and verified samples, I carried out individual paired t-test's. Performance was not significantly different between the two samples on either the wall sit ($t_{(11)}$=0.567, p=0.582) or the plank ($t_{(11)}$=0.04, p=0.968). In addition, I determined that both the independent and verified measurements significantly correlated for the plank (r=0.973, n=12, p<0.001) and wall sit (r=0.994, n=12, p<0.001). This demonstrated that the independent plank and wall sit measurements taken by the participants were reflective of their true abilities.

Having established that the measures recorded by the participants accurately reflected their cardiovascular and strength capabilities, I next determined whether I could identify a subset of the five measures that encapsulated different aspects of physical health. As can be seen in Figure 15 and 16, I found that all measures were positively correlated with predicted VO_2 Max, aside from the wall sit (r=0.342, n=35, p_{FDR}=0.088). As the predicted VO_2 Max specifically estimates cardiovascular capacity, this result suggests that all measures, but the wall sit, provide a measure of cardiovascular fitness. Conversely, the only measure that correlated with the wall sit was the plank (r=0.450, n=35, p_{FDR} = 0.027), which was also significantly correlated with predicted VO_2 Max (r=0.479, n=35, p_{FDR} = 0.0191), suggesting that the plank is a measure that taps into both strength and cardiovascular fitness. Taken together, these measures are tapping into three distinct aspects of physical health: 1) a cardiovascular measures (predicted VO_2 Max), 2) strength (wall sit), and 3) a hybrid measure of strength and cardiovascular capacity (plank). I used these three measures to determine if there is a relationship between physical health and cognition.

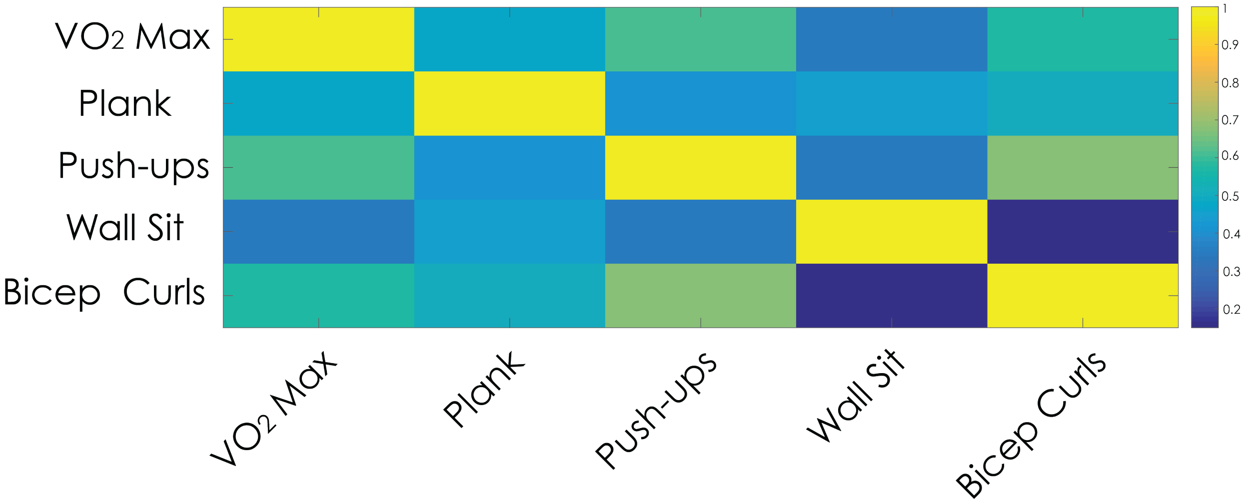


Figure 15: Correlation matrix between VO_2 Max, plank, push-ups, wall sit and bicep curls. The scale ranges from Pearson's r coefficients between 0 and 1. Dark blue represents a correlation of r=0.2 and yellow represents a correlation of r=1 (n=35).

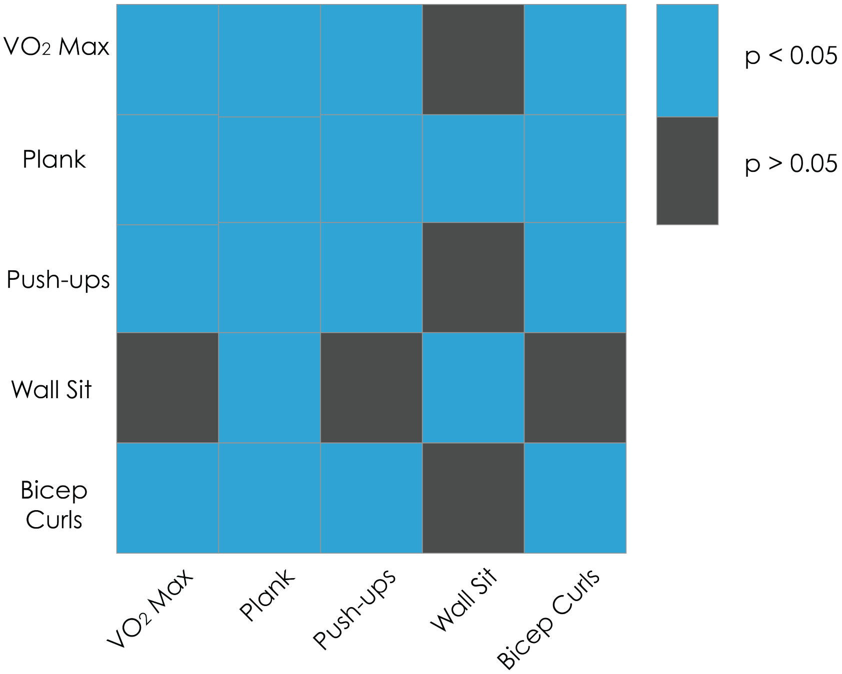


Figure 16: Summary of significant Pearson's r correlations between VO_2 Max, plank, push-ups, wall sit and bicep curls. Blue squares represent the correlations that were significant (p<0.05; n=35).

Using these metrics of physical health, I divided participants into two groups (using a median split), based on their performance on the predicted VO_2 Max, plank, and wall sit, to test whether those with better physical fitness measurements differed in their cognitive abilities. The groups were labeled as “high fitness” or “low fitness” respectively for each exercise. I ran a 2 (high vs. low fitness; the between subjects factor) x 15 (12 CBS tasks plus three domain scores; the within subjects factor) mixed design ANOVA for each measure of physical health (VO_2 Max, plank and wall sit). The results of the ANOVAs evaluating whether there were cognitive differences between participants who held the wall sit longer and had a higher predictive VO_2 Max revealed significant main effects of test ($F_{(14, 476)}= 2.165$, $p = 0.008$ and $F_{(14, 462)} = 2.294$, $p = 0.005$, respectively). However, there was no significant effect of group for either the wall sit or predicted VO_2 Max ($F_{(1,34)} = 0.223$, $p=0.640$ and $F_{(1, 33)} = 0.308$, $p = 0.583$, respectively), nor an interaction between test and group for either ($F_{(14, 476)} = 0.930$, $p = 0.527$ and $F_{(14, 462)} = 1.232$, $p=0.248$, respectively). However, the results of the ANOVA evaluating performance for those with long and short plank durations on the 15 cognitive measures showed a main effect of group ($F_{(1, 33)} = 5.361$, $p = 0.027$) and task ($F_{(14, 462)} = 2.260$, $p = 0.006$), but no interaction ($F_{(14, 462)} = 1.360$, $p = 0.169$). This suggests that the high fitness group generally outperformed the low fitness group on the cognitive measures. I further ran post-hoc independent t-tests and found that the high fitness group scored significantly better on the grammatical reasoning ($F_{(1, 33)} = 2.173$, $p = 0.038$), token search ($F_{(1, 33)} = 2.472$, $p = 0.009$) and paired associates ($F_{(1, 33)} = 3.056$, $p = 0.004$) tasks, as well as on the verbal domain ($F_{(1, 33)}= 2.153$, $p = 0.037$; Figure 17), relative to the low fitness group.

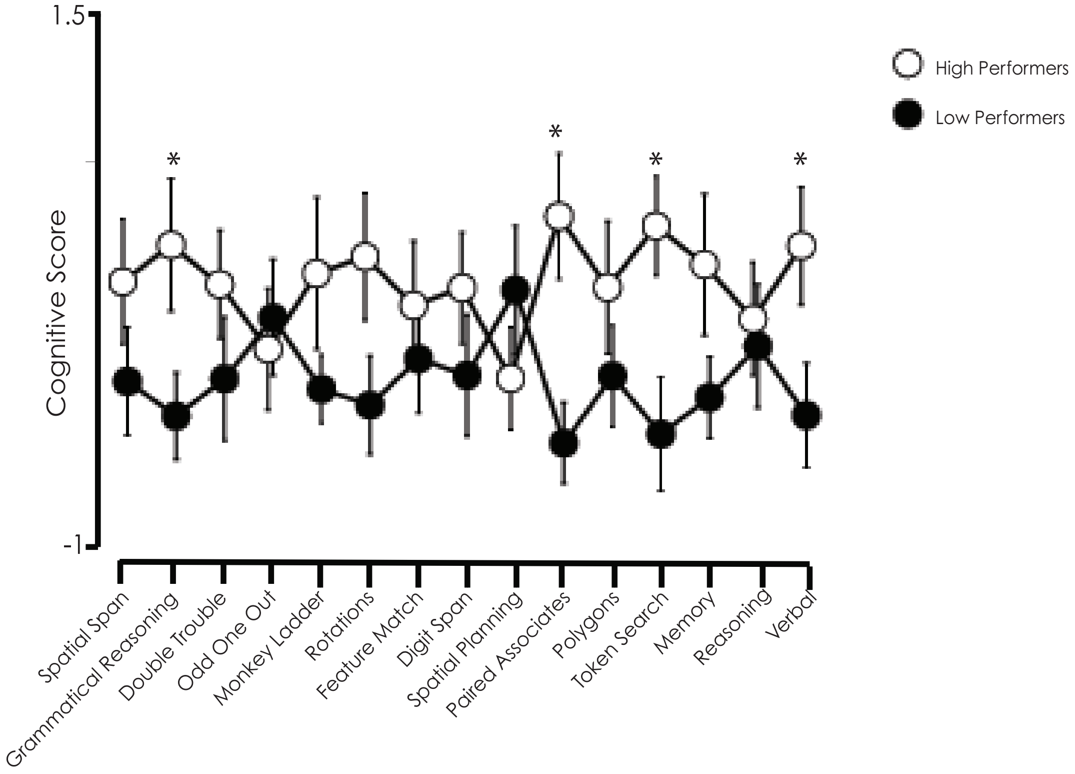


Figure 17: Mean cognitive performance on 12 cognitive tasks and 3 latent domains of high and low exercisers on the plank +/- SEM. Cognitive scores are z-scored. Stars represent significant differences in cognitive abilities between the high and low exercisers on the plank ($p<0.05$; n=37).

I found that those who are in better physical health outperformed those who were not on a number of tasks, however I wanted to determine whether the degree of physical fitness scales with cognitive performance. That is, is there a linear relationship between the two? To test this, I ran a correlation analysis between predicted VO_2 Max, plank and wall sit duration and performance on each of the 12 cognitive tasks, as well as the three latent domains (memory, reasoning and verbal ability). I found muscular strength (the wall sit) and aerobic capacity (predictive VO_2 Max) did not correlate with performance on any of the cognitive tasks or domains. However, the duration one was able to hold a plank significantly correlated with performance on the grammatical reasoning (r=0.340, n=37, p=0.0458) and paired associates tasks (r=0.444, n=37, p=0.0075), as well as the verbal domain (r=0.448, n=37, p=0.007; Figure 18).

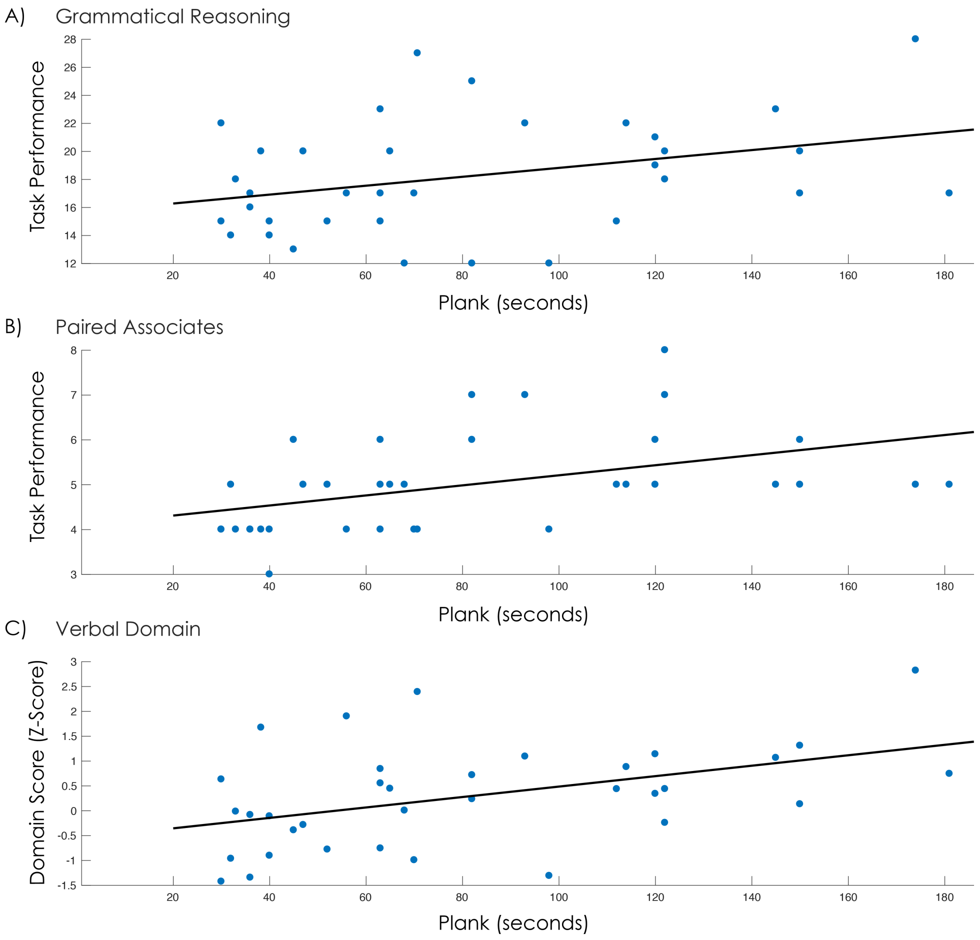


Figure 18: Figures A-C show the relationship between seconds able to hold an isometric plank position and cognitive performance on various tests and domains (n=37). Figure A: performance on the grammatical reasoning task versus seconds holding the plank (*r*=0.340, *p*=0.0458). Figure B: performance on the paired associates task versus seconds holding the plank (*r*=0.444, *p*=0.0075). Figure C: performance on the verbal domain, expressed as a z-score, versus seconds holding the plank (*r*=0.448, *p*=0.007).

3.4 Discussion

The aim of this study was to explore whether different measures of cardiovascular fitness and muscular strength/endurance were associated with different aspects of cognition, specifically in young adults. To achieve this aim, I first identified three metrics of physical health: 1) cardiovascular fitness (predicted VO_2 Max), 2) strength (wall sit) and

3) a hybrid measure encapsulating aspects of both strength and aerobic capacity (plank). Predictive VO_2 Max served as an indirect measure of aerobic capacity. The only measure to be uncorrelated with the predictive VO_2 Max was the wall sit, which was designated as the measure of muscular strength. The final measure, the plank, reflected a hybrid of both muscular strength and cardiovascular capacity. Relying on these three measures, my aim was to identify which, if any, metric of physical health is associated with cognitive functioning.

Overall, I found that performance on the plank measurement was consistently related to cognitive abilities; that is, high-fitness performers on the plank outperformed the low-fitness group on the grammatical reasoning, paired associates and token search tasks, as well as the verbal latent cognitive domain. I also found the duration an individual can hold the plank was significantly correlated with their performance on the grammatical reasoning and paired associates tasks, as well as their score on the verbal domain. Conversely, I found no significant relationship between cognitive performance and the measure of aerobic capacity (predictive VO_2 Max) or strength (wall sit). Thus, only the hybrid measure, which reflects both strength and cardiovascular fitness, was related to specific measures of memory (paired associates and token search tasks) and verbal abilities (grammatical reasoning task) in healthy young adults.

Why is the plank the only measure linked to cognitive performance? The nature of the exercise potentially provides some insight. The plank is an exercise where individuals are required to isometrically hold a prone position supported by their toes and forearms. This exercise improves core stability, which controls the position and motion of the trunk of the body and is essential for both everyday mobility and intense exercise (Imai & Kaneoka, 2016). The dominant muscles involved in holding a plank are those of the lower back, abdomen and hips, but muscles between the sternum and knee are also important (Tong, Wu, & Nie, 2014). Although holding the plank requires strength of the core muscles, it is also requires muscular endurance if it is held for longer than 30-45 seconds (Hibbs et al., 2008). In line with our result that the plank reflects a hybrid measure of physical health comprising aspects of strength and cardiovascular fitness, Imai and colleagues (2016) have shown that the plank is associated with other measures of athletic ability in male high-school soccer players. They find a moderate positive correlation between the length of time the plank can be held and the Cooper test (assessing running endurance), which supports our finding that the plank is positively correlated with predictive VO_2 Max. They also find a strong positive correlation between the plank and the Yo-Yo intermittent recovery test, which involves repeatedly performing high intensity activity while changing directions, confirming greater necessity of core stability in tests requiring greater trunk movement (Imai & Kaneoka, 2016). These results demonstrate that core stability, as assessed by a plank position, is positively associated with aerobic and strength endurance and to a greater extent, aerobic measures involving movement of the trunk.

The unique combination of cardiovascular capacity and strength that the plank measures may be responsible for the cognitive benefits, specifically to memory abilities, I found in this study. Aerobic capacity has been linked with greater hippocampal volume and viscoelasticity across the lifespan, and these structural changes have been associated with improved cognitive performance on tasks relying on memory function (Chaddock et al., 2010; Erickson et al., 2009; Erickson, Leckie, & Weinstein, 2014; Schwarb et al., 2017). Specifically, greater core stability was associated with better performance on the token search task, which relies on pattern separation, the ability to discriminate between similar instances of the same event (Yassa & Stark, 2011). It has been shown that this ability involves the dentate gyrus of the hippocampus, an area associated with neurogenesis, and increases in BDNF expression following exercise involvement (Bekinschtein et al., 2013; van Praag et al., 2005). In humans, Suwabe and colleagues (2017) have shown improvements on a pattern separation task after acute exercise, and suggested that this relationship was at least partially mediated by the dentate gyrus. Thus, I may have seen improved performance on the token search task in those who demonstrated greater core endurance because of exercise and BDNF-dependent effects on the dentate gyrus. Similarly, episodic memory, measured by the paired associates task, relies on the hippocampus; both the encoding and retrieval phases of the task are dependent on overlapping hippocampal areas (Meltzer & Constable, 2005). Accordingly, structural or volumetric hippocampal modifications related to plank endurance might account for the benefits seen on the paired associates task.

Finally, aerobic capacity has also been associated with greater gray matter volume in the temporal cortex, and more consistently, the pre-frontal cortex, which may mediate some aspects of improved verbal processing (Erickson et al., 2014). The grammatical reasoning task is at least partially reliant on the inferior frontal sulcus and the bilateral temporal lobes (Hampshire et al., 2012). Due to its relationship with aerobic endurance, greater core endurance may be associated with increased volume of the temporal and prefrontal cortices, which may be related to the improved performance on the grammatical reasoning task I observed. Thus, the structural and volumetric benefits associated with greater cardiovascular capacity may have contributed to the superior performance I observed on tasks assessing memory and verbal abilities in those with greater plank endurance. It would be valuable for future studies to more explicitly link these three factors; for instance, by comparing performance on the grammatical reasoning task with gray matter volume in the frontal and temporal cortices, and determining whether these properties fluctuate with the degree of strength and aerobic capacity.

Although the performance on the plank (a mark of cardiovascular capacity and core endurance; Imai A, Kaneoka, 2016), is related to specific aspects of cognition, perhaps paradoxically, I found the predictive VO_2 Max metric was not significantly correlated with performance on any of the 12 tasks or latent domains. This suggests that the cardiovascular endurance aspect of the plank cannot alone explain the differences in performance I found on tasks that measure memory and verbal abilities. However, a similar trend was found in a study evaluating the effects of an intervention combining both aerobic and strength exercises in a group of patients diagnosed with mild to severe dementia. Bossers and associates (2015) divided participants into two groups: in group one, participants completed an exercise regime focused on a combination of strength and aerobic exercises, and group two completed aerobic exercises only. After the 9-week intervention, the combination group improved their global cognitive function score, as well as performance on tasks testing executive function, and visual and verbal memory. However, the aerobic group improved only on executive function tasks, suggesting that a regime combining both aerobic and strength exercises produces benefits to a greater set of cognitive functions than aerobic exercise only (Bossers et al., 2015). Thus, their findings complement my own, and similarly suggest that performing exercise that benefits both strength and cardiovascular capacity improves cognition to a greater extent than aerobic exercise alone.

With this result, there is growing evidence for the importance of resistance exercise and core-strength to cognition. However, the mechanisms that mediate this relationship remain unclear. One possibility that has been suggested is the role of various growth factors. For example, greater muscular strength, as assessed by knee extension, has been associated with increased serum IGF-1 concentrations in older women (Cappola et al., 2001). In addition, a significant increase in serum BDNF concentration was found following a 10-week physical therapy intervention in elderly women, which focused on resistance exercise suitable for this population (Coelho et al., 2012). Together, these two growth factors are associated with neurogenesis, neuron growth and repair, synaptic transmission and plasticity, and neuronal survival (Homolak et al., 2015; Murray & Holmes, 2011). These neuronal consequences of BDNF and IGF-1 are capable of inducing structural changes in the brain, but further research is necessary to determine if greater muscular strength is associated with volumetric or microstructural differences. Thus, the improved cognitive abilities of those with greater core stability may not only be due to structural changes in the hippocampal and frontal areas brought about by aerobic activity, but from core strength and endurance training as well.

Overall, I found a link between general physical fitness and cognitive performance in young adults. My initial analyses showed that the plank represents a hybrid measure of fitness, encompassing both aspects of strength and cardiovascular capacity. I found that those who are able to hold the prone plank position for a greater length of time perform better on tasks relying on memory (paired associates and token search tasks) and verbal abilities (grammatical reasoning task). However, I found no such relationship with measures that tap into only strength or aerobic capacity. Thus, these results suggest that in young adults, better core endurance, representing a combination of strength and aerobic capacity, is associated with better cognitive function on tests of memory and verbal processing.

Chapter 4

4 Experiment Three

4.1 Introduction

In my previous two chapters, I relied on cross-sectional designs to determine whether exercise habits from a large, diverse sample were associated with cognitive functioning (experiment one), and whether different aspects of cognition were related to specific measures of physical health (experiment two). In both chapters, I found evidence that physical activity is positively associated with various cognitive functions. These results align with previous studies that have proposed a number of potential exercise-related physiological mechanisms to account for improved cognitive functioning, such as tissue volume increases (Chaddock et al., 2010; Erickson et al., 2009), microstructural changes (Schwarb et al., 2017), increased oxygenation of the brain (Ide & Secher, 2000; Voss et al., 2010) and increased functional connectivity in the default mode network, the frontal parietal network and the hippocampus (Burdette et al., 2010; Voss et al., 2010). However, based on these studies, I cannot conclude that exercise caused the associated changes to cognition. In order to claim a causal relationship between exercise and cognition, it is essential to conduct an intervention study.

A physical intervention is the ideal design to identify the extent to which exercise *affects* cognition. Although various types of exercise intervention studies have been conducted, the vast majority of them have focused on evaluating changes to cognition after introducing aerobic exercise. The consensus emerging from this literature is that introducing aerobic exercise across the lifespan leads to improved cognitive functioning. For example, Hillman and colleagues (2014) recently investigated the effects of a long-term aerobic exercise intervention in children aged 8-9. Children who routinely engaged in various age-appropriate aerobic activities for approximately two hours per day over the course of 150 days showed improved behavioral indices of executive control, specifically on tasks measuring attentional inhibition and cognitive flexibility (Hillman et al., 2014). In adolescents, a similar effect was seen on executive function. That is, after 24 sessions of high intensity interval training centered around aerobic activity, adolescents saw small improvements on the Trial Making Task, which assesses executive function (Costigan et al., 2016). Interestingly, their intervention lasted only 8-10 minutes per session, much shorter than the intervention study for children aged 8-9, demonstrating that interventions of different intensities and durations can produce significant benefits to executive processing in children and adolescents.

Similar interventions studies have been carried out in older adults, although justifiably less intense exercise interventions have been used. The exercises in these interventions commonly involve walking or cycling. In a study conducted by Jonasson and colleagues (2017), both types of exercise were employed to probe whether older adults showed improved cognition after completing the intervention. After 6 months of a combination of cycling and walking, they found improvement on participants' overall cognitive score, which was a composite measure based on performance on tasks tapping into episodic memory, updating, processing speed and executive function. Interestingly, they did not find improvement on any single task; they concluded that their exercise intervention produced general improvements to cognition, rather than to specific cognitive tasks (Jonasson et al., 2017). Another type of intervention that has been used in older adults is low intensity dancing. Older adults were introduced to Latin dancing for one hour per week for 6 months. This group improved specifically on tasks that measure verbal processing, such as word recognition, delayed word recall (a measure of memory) and verbal fluency (assessing executive function; Kim et al., 2011; Shao et al., 2014). Thus, these studies collectively demonstrate that diverse aerobic interventions have a positive influence on various cognitive processes in young children and older adults.

More recently, there has been a growing interest in the effects of resistance exercise on cognition. In addition to aerobic exercise, there is evidence to suggest that resistance exercise similarly benefits various aspects of cognition. For instance, attention appears to be a cognitive skill that is consistently improved after resistance interventions. Van de Rest and colleagues (2014), demonstrated improvement on the attention and working memory domains of their neuropsychological battery in older adults after completing a bodybuilding exercise regime twice weekly for 24 weeks. Likewise, in a study conducted by Liu-Ambrose and colleagues (2012a), older adults completed a resistance regime, focused on improving full-body strength, twice a week for one year. They first compared performance at the 6 and 12-month mark, and found improvement on the Stroop task (Stroop, 1935), a measure of executive function and more specifically, conflict resolution and selective attention. However, there were no effects found on working memory, unlike in the study by van de Rest et al., (Liu-Ambrose et al., 2012a). Why this discrepancy exists between these two studies is unclear as their interventions were very similar, aside from the length of the intervention. However, one distinction between these studies is the age of the participants; the study by Liu-Ambrose included participants with a mean age of 69.6±2.9, whereas the mean age in van de Rest's study was 79±8. Older adults tend to show greater changes to cognition in response to exercise involvement; this may be the reason for the more robust changes seen after the intervention in van de Rest's study.

Although there are numerous findings indicating that participation in various exercise regimes results in improved cognitive functioning, there are also studies showing that not all forms of exercise are beneficial to cognition. For instance, middle-aged men underwent either a jogging or strength training exercise program over a 12-week period (Blumenthal & Madden, 1988). Relative to their performance before the exercise program started, reaction times on a memory-search task did not change over this period for either training group. Unfortunately, since only reaction time, and not accuracy on the task was assessed, it is unknown whether some memory-related functioning was improved after involvement in either intervention. Similarly, Smiley-Oyen et al. (2008) carried out a randomized control trial assessing the effects of aerobic versus strength/flexibility training over a 10-month period. Benefits of the aerobic intervention were found on the Stroop task (measuring executive function); however their strength/flexibility group demonstrated no improvements on any of the tasks (Smiley-Oyen et al., 2008). These two sets of results suggest that not all interventions are uniformly beneficial to cognition.

Despite the abundance of studies examining the effects of exercise on cognition (Chang et al., 2015; Hwang et al., 2016; Suwabe et al., 2017), there are surprisingly few studies using an interventional approach to explore the potential exercise-related benefits to cognitive functioning in younger adults. Moreover, of the limited number of studies that have targeted this age group, most of them rely on aerobic exercises and probe cognition using a narrow task battery. For example, in a study conducted by Stroth et al. (2009), young adults completed an individually tailored running regime 1.5 hours per week, for six weeks. Cognitive performance was measured on a battery consisting of three tests of memory and concentration, with improvements limited to the visuospatial memory task (Stroth et al., 2009). However, without using various tasks that represent different aspects of cognition, they are not able to approach the exercise-cognition relationship holistically, and thus increase the risk of benefits going undetected.

Studying young adults will be fundamental to understanding the relationship between cognitive function and exercise because they are generally at their peak cognitive health. Eliminating the confounds of developmental and ageing related factors that we know affect cognition while using a comprehensive task battery, I set out to complete a more exhaustive evaluation of the effects on cognition after introducing an exercise regime. Specifically, my aim was to delineate the aspects of cognition that are most influenced by long-term aerobic and resistance exercise regimes in young adults using the extensive Cambridge Brain Sciences cognitive task battery. Based on the existing literature discussed above, I hypothesized that participants in the aerobic exercise group would show more improvement on tasks relying on executive functions, such as working memory (Costigan et al., 2016; Hillman et al., 2014; Smiley-Oyen et al., 2008; Stroth et al., 2009). However, the limited number of studies regarding the effects of resistance interventions makes it difficult to predict which cognitive functions will be most improved upon. Nonetheless, based on the work I describe earlier and the results of experiment two, I hypothesized that tasks relying on verbal and memory abilities would show the most improvement (Liu-Ambrose et al., 2012a; van de Rest et al., 2014).

4.2 Methods

4.2.1 Participant Demographics

Participants were recruited using flyers posted throughout Western University. Before beginning the study, participants first gave informed written consent, and were screened via the Physical Activity Readiness Questionnaire (PAR-Q+) to ensure they were able to safely perform the exercises required to complete this study. Participants were also screened to ensure they did not meet any exclusion criteria, which included any neurological problems or brain injuries, any visual or auditory disorders, pregnant, trying to become pregnant or any condition that prohibits moderate physical activity. Because I was interested in the effects of exercise on cognition, it was important my participants were not actively engaging in any exercise; therefore anyone performing moderate physical activity more than 3 times a week, for greater than 30 minutes per day consistently for the past 3 months did not meet the inclusion criteria.

Of the original sample of 35 participants, twelve participants were excluded from the final analysis; eleven participants chose to withdraw from the study, and one participant withdrew due to a medical condition. Consequently, there were 23 participants (22 females, 1 male) between the ages of 20 and 28 (M = 23.1, SD = 2.93) included in the final analysis for this study. The Health Sciences Research Ethics Board of the University of Western Ontario approved this study. Participants were compensated monetarily for their involvement.

4.2.2 Procedure

There were three phases to this study: the pre-exercise phase, the exercise-training phase and the post-exercise phase. During the pre-exercise phase, participants completed all 12 cognitive tests from the Cambridge Brain Sciences battery in order to establish baseline performance scores for each participant (descriptions of all 12 tasks can be found in the "Cognitive Measurements" section of chapter one). Participants were instructed to not complete the tasks after engaging in any physical activity to ensure the acute effects of exercise did not influence their scores (Chang et al., 2012). Each participant also completed a physical pre-assessment in order to determine baseline measures of strength and aerobic fitness. I used four strength exercises: plank, wall sit, push-ups and bicep curls. For both the plank and wall sit, participants were instructed to hold the position for as long as they could and record that time. They were then asked to complete as many push-ups as they were able to without resting and record this number. Lastly, they were asked to perform single arm bicep curls using dumbbells and record the weight they were able to curl for 10 repetitions without rest, and the weight they could curl for 1 repetition. In the aerobic component, participants performed the single stage submaximal treadmill test, which is used to predict their VO_2 Max (Ebbeling et al., 1991). This test begins with the participant walking on a treadmill for 4 minutes at 0% incline, at a speed that brings their HR between 50-70% of their age-predicted maximum heart-rate (HR; participants wore a Polar H7 Heart Rate sensor throughout this test). After the initial 4-minute period, they continue walking at the same speed, but increase the incline on the treadmill to 5%. They continue walking at this speed and incline for another 4 minutes, and when complete they record their steady state HR (SS-HR), which is the average HR from the final 30 seconds of the time walking at 5% incline. The participant's age, SSHR and walking speed were recorded and entered into the following equation (Ebbeling et al., 1991), which was used to estimate the participant's VO_2 Max:

$$15.1 + 21.8\,(\mathit{speed\ in\ mph}) - 0.327\,(\mathit{SSHR\ in\ bpm}) - 0.263\,(\mathit{speed\ x\ age\ in\ years}) \\ +0.00504\left(\mathit{SSHR\ x\ age}\right) + 5.98\left(\mathit{gender};\ \mathit{female} = 0,\ \mathit{male} = 1\right)$$

In designing this study, I did consider the difficulties associated with altering VO_2 Max when selecting how I was going to measure changes in cardiovascular capacity. Nevertheless, I went ahead with using predictive VO_2 Max for various reasons. First, VO_2 Max is a common measurement used in the literature, and is considered the gold standard for measuring aerobic endurance and cardiovascular fitness (Fletcher et al., 2013; Vanhees et al., 2005). The predictive VO_2 Max measurement was cost-effective and non-invasive, which were also important considerations. Lastly, various studies examining changes in VO_2 Max suggest that although oxygen consumption is difficult to alter, the most drastic changes are seen in those beginning with lower VO_2 Max measurements (Davies & Knibbs, 1971; Wilmore et al., 1970), which I reasoned would reflect my sample of sedentary young adults. Taken together, this knowledge led me to reason that a sedentary population had the capacity to change their maximal oxygen consumption

In the exercise-training phase, participants were randomized to one of two exercise-training interventions, one focused on cardiovascular fitness and the other on resistance training. The cardiovascular fitness regime involved cycling on a stationary spin bike. Participants attended 50-minute group spin-classes that were guided by an instructor who directed the intensity of the class. The strength regime was comprised of a class focused on both upper and lower body strength conditioning using weights tailored to the participant's fitness level. Similarly, the intensity of the class varied during the 50-minutes based on the instructor's guidelines. In both regimes, participants wore the Polar H7 Heart Rate sensor during each exercise class. The sensor recorded the user's HR every second and participants were instructed to save the HR data from each class to a mobile app. Participants were required to complete 15 classes over 40 days. During this period, participants also completed the set of 12 cognitive tasks (the same ones they completed in the pre-exercise phase) at regular intervals – approximately after every 3 exercise classes, including after the last exercise class – in order to track the trajectory of their cognitive performance.

During the post-exercise phase, participants again completed the physical assessment, exactly as they did in the pre-exercise phase. This was to test whether the exercise regimes had the intended effects on the different measures of physical health. Thus, throughout the longitudinal study, participants completed the CBS battery a total of six times and the aerobic and strength components of the physical fitness assessment twice.

4.2.3 Control Participants and Procedure

Participants in the control group were recruited using Mechanical Turk (M-turk), Amazon's online crowdsourcing platform. All participants were over the age of 18, and had to be in good health to be included in this study. Informed consent was obtained from all participants. Once participants logged onto M-turk and agreed to participate, they were provided with information regarding the study and the links required to access the CBS website. By following the link provided, participants were directed to the CBS webpage where they were required to register using the mock email address given to them. Participants were asked to fill out a demographic questionnaire and then were instructed to complete all 12 CBS tasks. Participants completed the CBS battery a total of five times according to this testing schedule: once per day on days 1, 2, 5, 10 and 20 once they started the experiment. I chose this particular sequence to maximize the potential gains from repeatedly completing the tasks. In total, 31 participants (16 females, 15 males) between the ages of 20 and 57 (M = 34.5, SD=8.82) completed all five trials.

4.2.4 Statistical Analysis

Considering the high attrition rate I had due to the long-term nature of this study, I first examined the number of cognitive testing sessions each participant completed. Overall, four participants (2 aerobic and 2 resistance) completed up to testing day 4, six participants (2 aerobic and 4 resistance) completed up to testing day 5, and thirteen participants (8 aerobic and 5 resistance) completed all 6 days of cognitive testing. Because 30% of the aerobic group and 54.5% of the resistance group did not complete the final cognitive testing session, I excluded all scores on the CBS tasks from that day from further analysis.

Following this, I compared how much exercise each participant completed throughout the intervention, to ensure the amount of exertion was matched in both groups. Subsequently, I evaluated whether my exercise regimes were effective in raising the heart rate of those in the aerobic condition and the strength of those in the resistance condition. Using the data collected from the heart rate sensor, I was able to determine the proportion of time each participant spent at or above 70% of their maximum heart rate, the rate at which exercise enters an aerobic zone (American College of Cardiology, 2015). I then compared the amount of time spent at or above 70% of their maximum HR between the aerobic and resistance group. Correspondingly, I compared performance on the measures of physical fitness before and after the exercise-training phase was completed, separately for both aerobic and resistance conditions.

I then determined whether engaging in either exercise regime produced changes in cognitive functioning. Scores were first converted to z-scores on all tasks. Following this, I calculated the slope of performance for each participant on each task and calculated the difference in performance between the first and last day of testing, a metric I will refer to as delta. I then carried out a 12 (task) x 2 (metric; as the within subject factor) x 2 (intervention group; as the between subject factor) mixed design ANOVA to determine whether the different exercise groups (aerobic versus resistance regimes) affected performance, as measured by my two metrics of improvement. These were followed up with two additional 12 (task) x 2 (metric) x 2 (control versus either the aerobic or resistance intervention) ANOVAs to determine if performance of participants in each intervention differed from the controls. Lastly, a 12 (task) x 5 (testing day; as the within subjects factor) x 2 (aerobic versus resistance exercise; as the between subjects factor) mixed design ANOVA was performed in order to determine if there were any patterns in performance that were not reflected in the slope or delta measures.

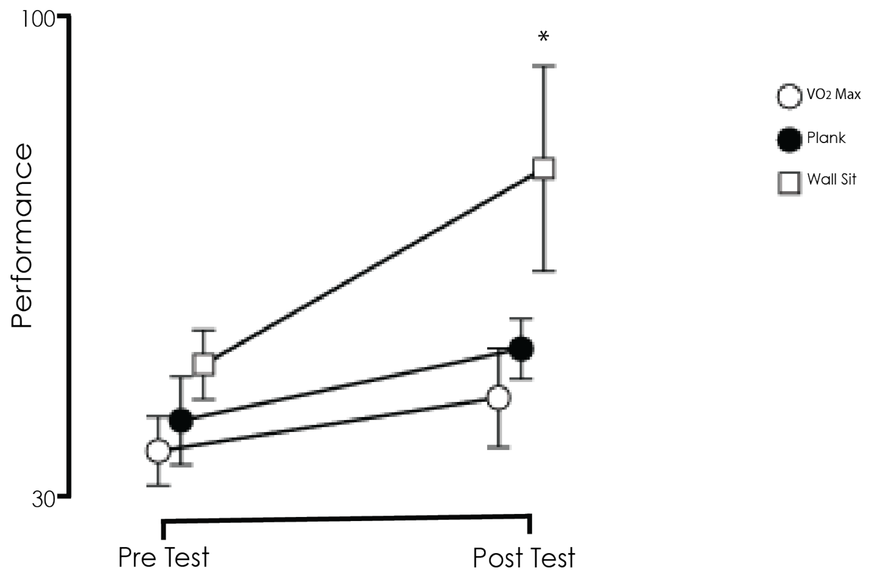
4.3 Results

First, I tested whether both groups were exposed to similar amounts of exercise, and found that participants in the aerobic group completed an average of 14.2 spin classes (n=12, SD=1.58), whereas there was an average of 13.1 classes completed in the resistance group (n=11, SD=3.21). The number of classes performed by each group was not significantly different ($t_{(21)}$= 1.034, p=0.313). However, I did find that the number of days taken to complete the intervention was significantly less in the resistance group (M= 24.3 days, SD= 10.8) compared to the aerobic group (M = 37.2 days, SD=5.0; $t_{(21)}$= 3.725, p<0.001).

Next, I set out to examine whether the exercise interventions employed were effective in raising the heart rate of the participants. I expected that participants in the aerobic exercise regime would spend a greater proportion of time in an aerobic zone. On the other hand, the resistance group would spend a smaller portion of time in an aerobic zone, as this regime focused on strength-based exercises. I found that the aerobic group spent 83.5% (SD = 1.01) of their sessions at or above 70% of their maximum HR, whereas the resistance group spent only 15.7% (SD = 0.84) at or above it. A between-subjects t-test revealed that participants in the aerobic group spent a significantly larger proportion of their time at or above 70% of their maximum HR, compared to the resistance group ($t_{(20)}$ = 16.825, p<0.001).

To determine whether each exercise intervention had an effect on fitness levels, I proceeded to perform paired t-tests between pre and post-test for each of the three physical measures for each intervention group. I found that the only intervention that had an effect on fitness levels was the resistance regime, which produced improvements on the wall sit ($t_{(9)}$= 2.734, *p*= 0.023). This was also the same measure I found in Chapter 2 to reflect a pure measure of strength. There were no improvements seen on the plank ($t_{(9)}$= 2.088, *p*= 0.066) or predictive VO_2 Max ($t_{(9)}$= 1.678, *p*= 0.128). The spin intervention produced no benefits on the wall sit ($t_{(10)}$= 1.192, *p*= 0.261), the plank ($t_{(10)}$= 0.594, *p*= 0.566) or predictive VO_2 Max ($t_{(9)}$= 1.192, *p*= 0.264). Figures 19 A and B display performance changes on all three physical measures from pre to post-test.

A)



B)

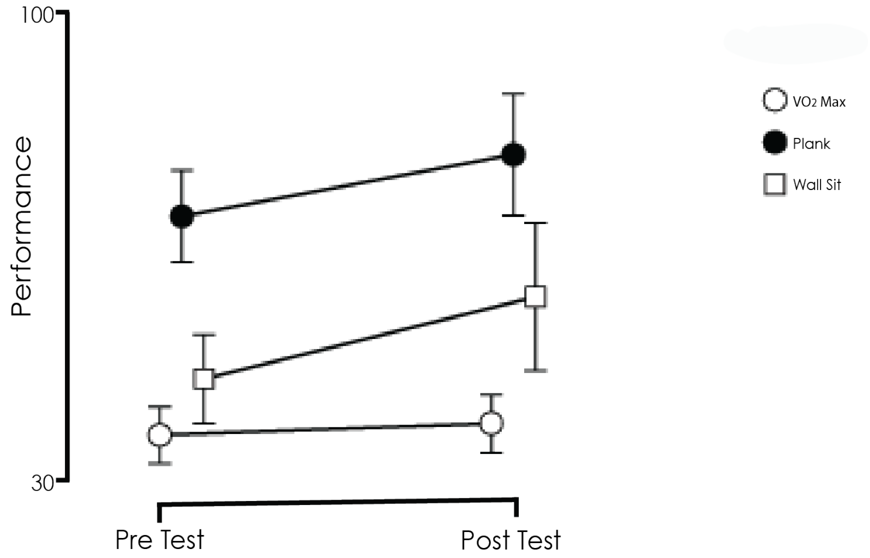


Figure 19: Mean performance (+/- SEM) on the plank (seconds), wall sit (seconds) and VO_2 Max (ml.kg-1.min-1) before and after an exercise intervention. Stars represent significant differences in physical fitness between pre and post-test ($p<0.05$). Figure A represents performance after a resistance exercise regime (n=11). Figure B represents performance after an aerobic exercise regime (n=10).

I then proceeded to determine whether the different exercise regimes (aerobic versus resistance exercise) had differential effects on cognition on two metrics reflecting change in performance over time: slope and delta (computed by taking performance on the last day and subtracting it from the first day). I ran a 12 (cognitive task) x 2 (metric) x 2 (aerobic versus resistance intervention) mixed design ANOVA with cognitive task and metric as the within subject factor, and exercise group as the between subjects factor. Here, I found only a main effect of metric ($F_{(1,7)}=12.679$, $p=0.009$), which reflects the difference in scales of the two measurements. None of the other comparisons reached significance ($F_{(11,77)}<1.817$, $p>0.065$), including no effects involving the group factor. These results suggest that if the exercise intervention affects cognitive function, this effect is the same for both exercise regimes. One interpretation is that both exercise regimes boost performance on at least some of the tasks; however to explicitly test this hypothesis, I compared each exercise group to the controls. To do this I first ran a 12 (cognitive task) x 2 (metric) x 2 (aerobic intervention versus controls) mixed design ANOVA with cognitive task and metric as the within subject factor, and group as the between subjects factor. This similarly revealed a main effect of metric ($F_{(1, 10)}= 17.770$, $p= 0.002$) once again reflecting the fact that slope and delta fall on different scales, and a main effect of task ($F_{(11, 110)}=3.164$, $p<0.001$). The results also revealed an interaction between task and metric ($F_{(11, 110)}=2.916$, $p=0.002$), suggesting that some participants performed better on some tasks more than others. Most notably, there were no significant effects involving the group factor ($F_{(11, 110)}<0.940$, $p>0.505$). This suggests that any changes in cognitive function after completing the aerobic exercise intervention were no different than the control group. I ran the same analysis comparing the resistance group to the controls and found the same pattern of results; there was a main effect of task and metric ($F_{(11, 88)} = 2.709$, $p= 0.005$; $F_{(1, 8)} = 14.162$, $p= 0.006$) and an interaction between metric and task ($F_{(11, 88)} = 2.588$, $p= 0.007$). Again, there were no effects involving the group factor ($F_{(1, 8)} < 0.396$, $p> 0.547$). This likewise suggests that any effect of resistance exercise on cognitive function is no different than the practice effects demonstrated by the control group. Together, these results reveal that not only do both exercise regimes have the same effect on cognition, this effect is no different than that produced by just doing the tasks repeatedly.

This was a surprising result and ran counter to what I expected. To test whether the exercise groups showed some improvement, I ran a one-samples t-test on both the slope and delta measures for both exercise groups. The results of this analysis revealed that only 3 tests had a slope significantly above 0 for the aerobic group ($t_{(11)}>2.759$, $p <0.019$) and 2 tests had a slope significantly above 0 for the resistance group ($t_{(10)}>2.694$, $p <0.023$). The analysis for the delta metric revealed 3 tests with a difference significantly greater than zero for the aerobic group ($t_{(10)}>2.239$, $p <0.049$), and 2 tests with a difference significantly greater than zero for the resistance group ($t_{(8)}>2.535$, $p<0.035$). I compared this to the control group, which showed 3 tests with a slope above 0 ($t_{(30)}>2.762$, $p<0.014$) and 3 tests with a difference above 0 ($t_{(30)}>2.623$, $p<0.010$). Thus, I concluded that much like practice, extensive periods of aerobic and resistance exercise do not result in improvements to cognition in healthy sedentary young adults.

One of the strengths of this study is that participants perform cognitive testing on multiple occasions throughout the intervention. However, slope and delta are insensitive to subtle changes across days, and differences in performance on certain days may have gone undetected (see Figure 20 for performance trajectories for each group over the 5-day testing period). For instance, it could be that the effects of exercise adopt an inverted U-shape, where benefits peak during the middle of the exercise program. For this reason, I also carried out a 12 (task) x 5 (testing day; as the within subjects factor) x 2 (aerobic versus resistance exercise; as the between subjects factor) mixed design ANOVA. I found a main effect of task ($F_{(11, 99)} = 2.859$, $p=0.003$), and day ($F_{(5, 45)} = 5.097$, $p<0.001$) and an interaction between task and day ($F_{(55, 495)} = 1.529$, $p=0.011$). This suggests that performance changes across the testing sessions to a greater extent on some tasks. However, because there was no main effect or interaction with group, these changes appear to be equivalent across the intervention groups.

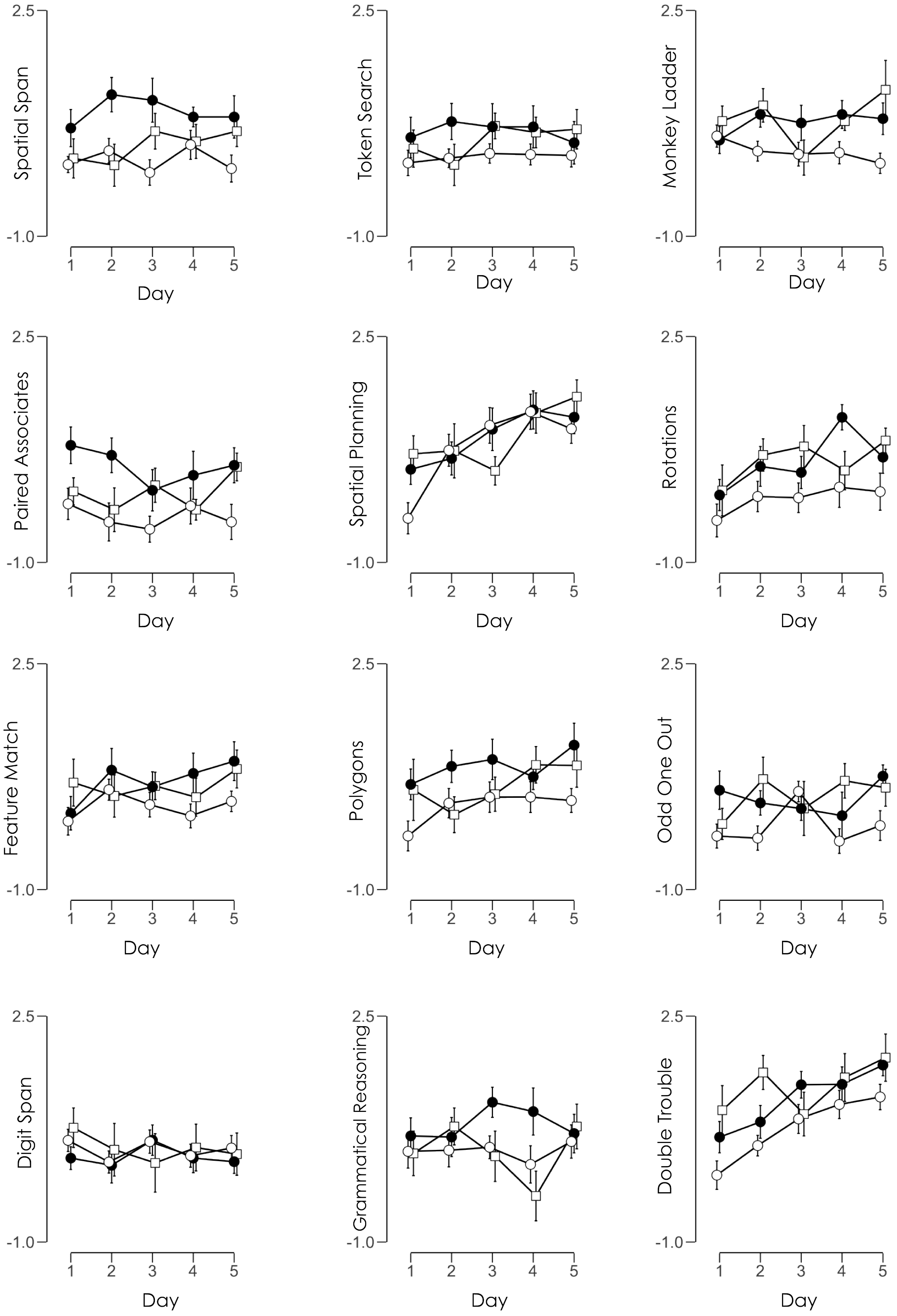


Figure 20: Mean performance on all 12 cognitive tasks (+/- SEM) across 5 cognitive testing sessions for the control (n=31), aerobic (n=12) and resistance (n=11) groups. Performance is expressed as a z-score. Black circles represent the aerobic group's performance, white circles represent the control group's performance and white squares represent the resistance group's performance.

4.4 Discussion

In this experiment, my aim was to determine whether cognitive functioning is affected by long-term aerobic and resistance exercise in young adults. First, I examined whether the exercise regimes were having the desired effect on different metrics of physical fitness by comparing the change in three measures of physical health before and after the interventions for each exercise group (aerobic and resistance training). As expected, participants in the aerobic group spent a significantly greater amount of time in an aerobic zone than those in the resistance intervention, indicating that that the spin class was a sufficiently demanding cardiovascular intervention. Despite the consistent increase in heart rate and time spent in the aerobic zone, I did not find changes to any of the physical fitness measures, including predicted VO_2 max, which I expected to improve.

Although there were no differences in the total amount of exercise performed by each intervention group, the only one to show any benefit to physical fitness was the resistance regime. Following the resistance regime, participants significantly improved on the wall sit measure. As I outlined in Chapter 2, the wall sit represents my only pure measure of strength. Thus, this result indicates that the resistance class, which focused on upper and lower body conditioning, was successful in improving muscle strength and endurance of those in that group.

Despite having established that the resistance class improved wall sit performance and that the spin class raised the HR of participants into an aerobic zone for over 80% of the exercise period, my analysis revealed that neither exercise intervention produced meaningful improvements to cognitive performance. My initial analysis suggested that both exercise interventions boosted performance on at least some tasks. However, after further comparing the interventions to the controls, I concluded that any effect of either intervention on performance is no different than the practice effects demonstrated by the control group. I tested whether there were any effects on performance that were not captured by the two improvements metrics. That is, I examined whether performance changed on certain days for specific tasks, but found no differences between the intervention groups. Thus any trend towards task improvement in either group had nothing to do with exercise and reflects the effects of repeated testing.

As neither of my interventions facilitated the hypothesized effects on cognition, it is necessary to consider the possible reasons for my general lack of findings. First, perhaps the lack of change in the VO_2 Max measurement for those in the aerobic group suggests they did not engage in enough exercise to produce cognitive benefits. While this is a possibility, I do not think it is the only factor. For instance, I did find that those in the aerobic group were in the aerobic zone for over 80% of the exercise period. Another possibility is that VO_2 Max is a stable measure that requires more than 14 spin classes over 37 days to change, and thus may not have been the ideal measure to use. While, changes in VO_2 Max are thought to be dependent on frequency, duration and intensity of exercise (American College of Sports Medicine, 1993), past research has shown that changes in VO_2 Max, when present, are small and require working at a high intensity for prolonged periods of time, with the frequency of exercise being less significant (Davies & Knibbs, 1971). Davies and Knibbs (1971) carried out a study comparing various combinations of exercise intensities, durations and frequencies, and found male individuals participating in exercise sessions lasting greater than 20 minutes over the course of 8 weeks showed the most improvement in VO_2 Max. They also found that participants working at or below 50% of their VO_2 Max showed no improvements in maximal oxygen consumption, whereas those working at or above 80% saw small benefits (Davies & Knibbs, 1971). In my experiment, I had a young sedentary sample who completed nearly 14 sessions lasting approximately one hour, and their HR remained in an aerobic zone for nearly 85% of that time, which met all the requirements to produce an improvement in VO_2 Max (Wilmore et al., 1970). Despite this, I found no changes in my predictive VO_2 Max measurement in my sample. This result suggests that either the participants in the aerobic group did improve their cardiovascular health and the predictive VO_2 Max measure was not sensitive enough to detect these changes, or more likely, transient exercise does not change maximal oxygen consumption because it is a relatively stable marker of cardiovascular health that requires prolonged and regular exercising to alter.

In future studies, other measures could be used alongside VO_2 Max to estimate changes in aerobic capacity. For instance, Stroth and associates (2009) suggest measuring lactate concentration to estimate lactate threshold. This is the intensity of exercise at which lactate in the blood can no longer be cleared as fast as it accumulates, and it further reflects aerobic capacity. As well, because BDNF is hypothesized to mediate the relationship between exercise and cognition, it would be useful to collect peripheral BDNF measurements to determine how each regime affects individuals at the protein level.

Other potential reasons for not seeing a boost in performance on the various cognitive tasks is the possibility that the task battery was not sufficiently sensitive to subtle changes in cognition. However, I believe this is unlikely. The double trouble task, a modification of the Stroop task, is used regularly in this body of literature, and many studies have demonstrated exercise-dependent improvements on this task (Barnes et al., 2003; Liu-Ambrose et al., 2012a; Weinstein et al., 2012). Tasks such as the digit span and grammatical reasoning have also been commonly used to assess cognition and correspondingly show exercise-dependent changes (Cassilhas et al., 2007; Langlois & Vu, 2013; Ngandu et al., 2015; Shay & Roth, 1992). Other tasks in this battery, including the spatial planning, token search and paired associates tasks, have been used to detect subtle changes in cognition due to neurodegeneration or pharmacological intervention (Lange et al., 1992; Mehta et al., 2000; Owen et al., 1992; Owen et al., 1993). Thus, the lack of changes seen in cognitive function is likely not related to the sensitivity of the measures used and is more plausibly related to the exercise regime chosen, or the characteristics of the population being studied.

I may not have observed the anticipated cognitive improvements due to our exercise intervention being too short in duration. The exercise intervention crafted for the current study was informed by past literature. Various studies have found performance benefits of short-term exercise interventions. For example, four weeks of a strength-focused exercise circuit improved executive function, episodic memory and processing speed in older adults (Nouchi et al., 2014). As well, it was noted in Colcombe and Kramer's meta-analysis (2003) that when compared to a null effect, the effect size of interventions lasting 1-3 months was greater than that of those lasting 4-6 months in older adults. Although there are very few intervention studies in young adults to compare the chosen regime to, the intervention adopted by Stroth and colleagues (2009) is similar in duration to my own. Their protocol involved having participants complete 9 hours of aerobic exercise over the course of 6 weeks (30 minutes, 3 times a week). When compared to the regime I designed, participants completed less exercise in a greater amount of time, yet still improved on a measure of visuospatial memory. Thus, although long-term interventions tend to have the greatest effect on cognitive function (Colcombe & Kramer, 2003; Hillman et al., 2014; Ngandu et al., 2015), other investigations of similar duration to my own have found benefits to cognition, suggesting my intervention was likely long enough to promote cognitive improvements. With that being said, this study examined young adults and because this population is already at a high level of cognitive functioning, more exercise may be necessary to support cognitive performance improvements. Future research should focus on chronic exercise interventions to further elucidate the relationship between exercise and cognitive function in a young adult population.

If we assume that participants exercised a sufficient amount, another possible explanation for the results obtained is that exercise does not improve cognitive functioning in healthy, young adults, even if they live a sedentary lifestyle. Cognition has been shown to peak in young adulthood, and thus there may be limited room for cognitive improvement, which could preclude this population from exercise-dependent cognitive benefits (Salthouse & Davis, 2006). It is consistently shown that older adults benefit to a greater extent from exercise involvement than young adults; at the cross sectional level, more fit older adults perform better than their less fit counterparts on tasks assessing immediate and delayed recall, whereas high and low-fit young adults do not perform differently (Shay & Roth, 1992). However this may be due to the selective ability of exercise to remediate cognitive decline, in this case that associated with age. A recent study demonstrated that exercise facilitates improved cognition in young adults with lower level functioning related to psychosis (Hallgren et al., 2018). Young to middle age adults participated an aerobic training circuit for 12 weeks, completing an average of 13.5 hours of exercise. Participants began the intervention with general cognitive deficits in visuospatial processing and working memory, but improvements were noted on tasks measuring visual learning and attention, and processing speed (Hallgren et al., 2018). Thus, even in populations with cognitive deficits unrelated to age, exercise-dependent cognitive improvements are noted. Although interventional research in healthy young adults is scarce, Stroth and colleagues (2009) found performance improvements in visuospatial memory after 6 weeks of aerobic activity, and Costigan and associates (2016) revealed a benefit of high intensity interval training on executive function after 8-weeks. In combination with these results, these studies support the theory that exercise has small effects on cognitive performance in healthy young adults; however these benefits are not as robust as those seen in populations with cognitive deficits. It should be noted that these three regimes were short term (less than 8 weeks). Future work should clarify whether cognitively healthy young adults require longer duration interventions to observe cognitive improvements, or whether robust changes to cognition are unattainable in those at peak cognitive health.

There were numerous strengths to this study, including the use of a large cognitive test battery, which allowed me to examine the effects of exercise on a range of cognitive functions. I also used a sample consisting of young adults, which is rare in this body of literature. Lastly, I compared two distinct exercise regimes, one of which focused on resistance exercise. The effects of long-term resistance exercise regimes have not been studied in young adults, and thus these results are novel.

Despite these strengths, this study had limitations that should be addressed in the future. The first limitation was the disproportionate number of females that participated in this study. Only one male participant was able to complete the entire intervention, which results in the trends found being strictly generalizable to young adult females. In addition, there was a lack of compliance to the study protocol as many participants did not complete all 15 exercise sessions. This could help explain why the expected improvements in general fitness were not seen, and consequently, why no exercise-related cognitive changes were observed. Lastly, I had a large amount of attrition throughout the study due to the length of the protocol, and the time commitment required. For this reason, the sample size was smaller than anticipated and this could have resulted in my study being underpowered for detecting changes in fitness level pre and post-intervention, as well as changes in cognition throughout the regime.

Chapter 5

5 General Discussion

This thesis consisted of three experiments, which facilitated a greater understanding of the relationship between exercise and cognition. Together, they comprised a hierarchical approach to addressing this relationship and each chapter was able to help answer questions the previous chapter left unanswered. In chapter one, I used a large and diverse sample to evaluate the aspects of cognition that most benefit from various levels of exercise. In this study I wanted to examine a wide range of ages, and thus I chose to focus on physical exertion, rather than the type of exercise individuals participated in. In chapter two, instead of examining self-reported measures of physical activity, I focused on the relationship between cognitive function and concrete measures of aerobic capacity and muscular strength in young adults. In my third study, I built on this by assessing the relationship using an interventional approach; in a young adult population, I examined how introducing participants to an aerobic or strength exercise regime affected cognitive function. Overall, through my three studies, I was able to gain a better understanding of the general landscape of the effects of exercise on cognition.

The goal of experiment one was to get a general snapshot of reality; I wanted to determine the exercise habits of a large, diverse sample and further examine how these habits were associated with cognitive performance. Rather than looking at specific aspects of exercise or measures of fitness (which I did in chapters two and three), I first wanted to determine whether there is a relationship between exercise and cognition at the population level after controlling for a set of variables that are often associated with exercise. I found that the frequency with which people exercise predicted performance in the reasoning and verbal domains. More specifically, I found that those who have not exercised in the past month perform worse on the polygons, token search and grammatical reasoning tasks, as well as the reasoning and verbal domains, when compared to all levels of exercise. However, further analysis showed that moderate levels of exercise led to improved performance on specific tasks when compared to participants who exercise less than once per month. This result suggested that with the exception of daily exercise, more frequent exercise involvement was associated with improved cognitive performance. As well, I found the effects of exercise on cognition were independent of different sleep metrics and age. Thus, overall this study revealed that exercise is directly beneficial to certain aspects of cognition at the population level.

After establishing that moderate levels of exercise are positively associated with cognition in specific domains, the next step in my hierarchical framework was to assess whether higher levels of strength and aerobic fitness were associated with better cognition. I first identified three metrics of physical health: 1) cardiovascular fitness (predicted VO_2 Max), strength (wall sit) and a hybrid measure encapsulating aspects of both strength and aerobic capacity (plank). Overall, I found that plank performance was consistently related to cognitive abilities. Firstly, high-fitness performers on the plank outperformed the low-fitness group on the grammatical reasoning, paired associates, and token search tasks, as well as the verbal latent cognitive domain. In addition, the duration an individual could hold the plank correlated with their performance on the grammatical reasoning and paired associates tasks, as well as their score on the verbal domain. However, neither the predicted VO_2 Max, nor wall sit measures were associated with cognitive function. Overall, the results of this study demonstrated that plank performance, my hybrid measure of fitness, was associated with higher levels of cognitive function in certain cognitive domains.

My first two experiments were able to establish strong correlational associations between exercise and various cognitive processes. The final step in my hierarchical approach was to determine whether introducing an exercise intervention to sedentary, but healthy young adults – an often-overlooked population in this literature – led to improvements in cognition. My analysis of both slope and delta revealed that neither the aerobic nor the resistance exercise intervention produced meaningful improvements in cognitive performance, as any effect of either intervention did not differ from the practice effects demonstrated by the ‘no exercise’ control group. This lack of improvement may be due to various reasons, including the duration of the intervention being too short or the limited cognitive plasticity of healthy young adults. Thus, despite the positive relationships found between exercise and cognition in experiments one and two, I did not find any cognitive benefits of either exercise intervention implemented in this study.

Overall, I found that exercise has a positive relationship with cognition. This relationship was shown to extend to various different tasks tapping into diverse cognitive functions, including memory, reasoning and verbal abilities. However, this appears to only be the case if exercise is a consistent part of your life. In both studies one and two, I found that my measures of exercise (frequency of exercise involvement and physical fitness respectively) were associated with improved performance on the reasoning and verbal domains, as well as a small set of memory tasks. My hypothesis is that what we are likely observing here is the cognitive effects of habitual exercise. In experiment one, participants were asked about their exercise involvement in the past month, which presumably reflects real world exercise habits. In line with this, experiment two examined physical fitness levels, and superior plank performance is the outcome of regular exercise over a prolonged period of time. Thus, it may be the case that experiments one and two are similarly tapping into the effects of habitual exercise. However, to substantiate this idea, more information is needed regarding the length of regular exercise involvement prior to cognitive testing.

Transient introduction of exercise into the lives of sedentary young adults, independent of its aerobic or resistance nature, was not shown to have an effect on cognition. This result could have arisen due to various reasons, including the limited cognitive plasticity of young adults. However, as is suggested by the previous experiments, this finding also may be due to the fact that the introduction of a short-term intervention isn’t enough to boost cognitive performance of healthy young adults; exercise needs to be habitual for any cognitive benefits to occur. In future studies, there should be a greater focus on long-term exercise involvement, with interventions lasting as long as 6-months to one year. This would not only allow for a better understanding of the effects of introducing a long-term exercise intervention, but it would also help give insight in to the exercise-dependent plasticity of the young adult brain.

Although the mechanisms that are responsible for mediating exercise-related cognitive changes are unclear, rodent experiments have provided insight into the numerous changes that occur in the brain following exercise. As previously mentioned, earlier work has shown that BDNF is a key protein mediating the effects of exercise on cognition, exerting its greatest effects on the hippocampus (Cotman, Berchtold, & Christie, 2007b). Increased expression of BDNF is shown to be associated with various factors that are up regulated following exercise, including increased levels of Irisin, norepinephrine and IGF-1 (Ding et al., 2006; Garcia et al., 2003; Wrann et al., 2013). BDNF is a growth factor involved in the growth and differentiation of the nervous system, most notably promoting neurogenesis and neuronal plasticity (Murray & Holmes, 2011). BDNF exerts these effects via various molecular signaling pathways, including the MAP-K and CAMKII pathways, which are both associated with learning and memory (Vaynman et al., 2003; Yin & Tully, 1996). Further evidence in rodents has demonstrated the relationship between BDNF expression and hippocampal function. For example, after blocking the hippocampal BDNF receptor in rodents, rates of acquisition and retention on a spatial learning task were significantly reduced (Vaynman, Ying, & Gomez-pinilla, 2004). This study not only demonstrated that exercise promotes the expression of BDNF, but additionally BDNF expression encourages improved hippocampal function, which in turn could help explain the results of experiments one and two.

Although BDNF is a strong contender for explaining the relationship between exercise and cognitive function, there are other changes that occur in the brain following exercise that may also support improved cognition. For example, exercise adjusts the metabolic demand and vascular structure of the brain. Following exercise, proteins necessary for ATP synthesis and transport are shown to be elevated, which is necessary to support the augmented energy demands associated with BDNF-dependent neurogenesis and synaptic plasticity (Ding et al., 2006). In addition, angiogenesis is necessary to support the increased metabolic demands associated with neurogenesis (Palmer et al., 2000). Angiogenesis in turn increases cerebral blood flow (Cha et al., 2003), which has been associated with improved cognitive function in rodents; after 12 weeks of cardiovascular exercise, Periera and colleagues (2007) noted increased blood flow to the dentate gyrus, which further correlated with performance on a declarative memory task. Although these same experimental designs cannot be carried out in humans, they do provide insight into the changes occurring in the brain after exercise.

Consequentially, these exercise-dependent changes throughout the brain may help to explain the performance improvements noted throughout experiments one and two. In these experiments, there was overlap between the tasks that showed improved performance. In experiment one, I observed an association between exercise frequency and verbal and reasoning performance, as well as performance on the token search, grammatical reasoning and polygons tasks. Similarly in experiment two, I found an association between plank performance and verbal and memory abilities, specifically with the grammatical reasoning, paired associates and token search tasks. Token search performance is reliant on pattern separation. Pattern separation is a hippocampal function, localized to the dentate gyrus (Bekinschtein et al., 2013; Yassa & Stark, 2011). This area of the brain is thought to undergo BDNF-dependent neurogenesis after exercise in rodents (Pereira et al., 2007) and in humans, it has been shown to partially mediate improvement on a pattern separation task after acute exercise (Suwabe et al., 2017). Thus, it is plausible that habitual exercise involvement induces changes in BDNF expression in the hippocampus. The subsequent neurogenesis and augmented plasticity in this region could then in turn support improvement on tasks relying on pattern separation. On that note, superior verbal performance, specifically on the grammatical reasoning task, was found in both experiments. Aerobic endurance is associated with improved verbal capacity, and this is thought to be due to greater gray matter volume in the temporal cortex, and more consistently, the pre-frontal cortex (Erickson et al., 2014). Habitual exercise may be associated with greater aerobic endurance, which in turn may be related to the improved performance on the grammatical reasoning task I observed, as this task relies on similar areas of the brain (Hampshire et al., 2012). Thus, there are numerous explanations for why these specific tasks were consistently associated with exercise in experiments one and two, however their improved performance is likely at least partially related to changes in the brain that are the result of long-term exercise involvement.

In summary, my thesis aimed to use a hierarchical approach to assess the relationship between exercise and cognitive function. Experiment one, which observed the exercise habits of a large, diverse sample, demonstrated that exercise frequency was positively associated with reasoning and verbal performance, as well as performance on specific tasks. Further, experiment two was able to show that core endurance was associated with a variety of tasks relying on verbal and memory function. However, experiment three revealed that the introduction of either an aerobic or resistance exercise intervention had no effect on cognitive performance of sedentary young adults. Thus, the combination of these results suggests that exercise benefits cognition when it is a regular part of an individual's lifestyle, however the transient introduction of a short-term exercise program provides no benefit. These benefits are likely associated with changes in growth factor expression in the brain over a long-term period. The increased expression of these growth factors instigates further changes to the brain in regards to structure and volume, which likely mediates benefits to cognitive function over time.

References

Aberg, M. A. I., Pedersen, N. L., Toren, K., Svartengren, M., Backstrand, B., Johnsson, T., … Kuhn, H. G. (2009). Cardiovascular fitness is associated with cognition in young adulthood. *Proceedings of the National Academy of Sciences*, *106*(49), 20906–20911. http://doi.org/10.1073/pnas.0905307106

American College of Cardiology. (2015). Exercise: Measuring Intensity. Retrieved January 15, 2018, from https://www.cardiosmart.org/~/media/Documents/Fact Sheets/en/abk5262.ashx

Baddeley, A. D. (1968). A 3 min reasoning test based on grammatical transformation. *Psychonomic Science*, *10*(10), 341–342. http://doi.org/10.3758/BF03331551

Barnes, D., Yaffe, K., Satariano, W., & Tager, I. (2003). A longitudinal study of cardiorespiratory fitness and cognitive function in healthy older adults. *J Am Geriatr. Soc.*, *51*(4), 459–465. http://doi.org/10.1046/j.1532-5415.2003.51153.x

Bekinschtein, P., Kent, B. A., Oomen, C. A., Clemenson, G. D., Gage, F. H., Saksida, L. M., & Bussey, T. J. (2013). BDNF in the dentate gyrus is required for consolidation of "pattern-separated" memories. *Cell Reports*, *5*(3), 759–768. http://doi.org/10.1016/j.celrep.2013.09.027

Best, J. R., Chiu, B. K., Liang Hsu, C., Nagamatsu, L. S., & Liu-Ambrose, T. (2015). Long-Term Effects of Resistance Exercise Training on Cognition and Brain Volume in Older Women: Results from a Randomized Controlled Trial. *Journal of the International Neuropsychological Society*, *21*(10), 745–756. http://doi.org/10.1017/S1355617715000673

Bliss, T., & Collingridge, G. (1993). A synaptic model of memory: long-term potentiation in the hippocmapus. *Letters to Nature*, *366*, 461–464.

Blum, S., Moore, A. N., Adams, F., & Dash, P. K. (1999). A mitogen-activated protein kinase cascade in the CA1/CA2 subfield of the dorsal hippocampus is essential for long-term spatial memory. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *19*(9), 3535–44. http://doi.org/10.1002/hipo.10070

Blumenthal, J., & Madden, D. (1988). Effects of aerobic exercise training, age, and physical fitness on memory-search performance. *Psychology and Aging*, *3*(3), 280–285. http://doi.org/10.1037/0882-7974.3.3.280

Borror, A. (2017). Brain-derived neurotrophic factor mediates cognitive improvements following acute exercise. *Medical Hypotheses*, *106*, 1–5. http://doi.org/10.1016/j.mehy.2017.06.024

Bossers, W. J. R., van der Woude, L. H. V., Boersma, F., Hortobágyi, T., Scherder, E. J. A., & van Heuvelen, M. J. G. (2015). A 9-Week Aerobic and Strength Training Program Improves Cognitive and Motor Function in Patients with Dementia: A Randomized, Controlled Trial. *The American Journal of Geriatric Psychiatry*, *23*(11), 1106–1116. http://doi.org/10.1016/j.jagp.2014.12.191

Boström, P., Wu, J., Jedrychowski, M. P., Korde, A., Ye, L., Lo, J. C., … Spiegelman, B. M. (2012). A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature*, *481*(7382), 463–468. http://doi.org/10.1038/nature10777

Burdette, J. H., Laurienti, P. J., Espeland, M. A., Morgan, A., Telesford, Q., Crystal, D., & Madden, D. (2010). Using network science to evaluate exercise-associated brain changes in older adults. *Frontiers in Aging Neuroscience*, *2*, 1–10. http://doi.org/10.3389/fnagi.2010.00023

Cappola, A. R., Bandeen-Roche, K., Wand, G. S., Volpato, S., & Fried, L. P. (2001). Association of IGF-I levels with muscle strength and mobility in older women. *Journal of Clinical Endocrinology and Metabolism*, *86*(9), 4139–4146. http://doi.org/10.1210/jc.86.9.4139

Cassilhas R., Viana, V., Grassmann, V., Santos, R., Santos, R., Tufik, S., & Mello, M. (2007). The Impact of Resistance Exercise on the Cognitive Function of the Elderly.

Medicine and Science in Sports and Exercise, *29*(8), 1401–1407. http://doi.org/10.1249/mss.0b013e318060111f

Castelli, D. M., Hillman, C. H., Buck, S. M., & Erwin, H. E. (2007). Physical Fitness and Academic Achievement in Third- and Fifth-Grade Students. *Journal of Sport and Exercise Psychology*, *29*(2), 239–252. http://doi.org/10.1123/jsep.29.2.239

Cattell, R. B., & Cattell, A. K. S. (1949). *Test of "g": Culture fair*. Champaign, Ill: Institute for Personality and Ability Testing.

Cha, S., Johnson, G., Wadghiri, Y. Z., Jin, O., Babb, J., Zagzag, D., & Turnbull, D. H. (2003). Dynamic, contrast-enhanced perfusion MRI in mouse gliomas: Correlation with histopathology. *Magnetic Resonance in Medicine*, *49*(5), 848–855. http://doi.org/10.1002/mrm.10446

Chaddock, L., Erickson, K. I., Prakash, R. S., Kim, J. S., Voss, M. W., Vanpatter, M., … Kramer, A. F. (2010). A neurogenic investigation of the association between aerobic fitness, hippocampal volume, and memory performance in preadolescent children. *Brain Res.*, *1358*, 172–183. http://doi.org/10.1016/j.brainres.2010.08.049.A

Chaddock, L., Hillman, C. H., Buck, S. M., & Cohen, N. J. (2011). Aerobic fitness and executive control of relational memory in preadolescent children. *Medicine and Science in Sports and Exercise*, *43*(2), 344–349. http://doi.org/10.1249/MSS.0b013e3181e9af48

Chang, Y. K., Chu, C. H., Wang, C. C., Wang, Y. C., Song, T. F., Tsai, C. L., & Etnier, J. L. (2015). Dose-response relation between exercise duration and cognition. *Medicine and Science in Sports and Exercise*, *47*(1), 159–165. http://doi.org/10.1249/MSS.0000000000000383

Chang, Y. K., & Etnier, J. L. (2009). Exploring the dose-response relationship between resistance exercise intensity and cognitive function. *Journal of Sport & Exercise Psychology*, *31*(5), 640–656. http://doi.org/10.1016/j.psychsport.2008.05.004

Chang, Y. K., Labban, J. D., Gapin, J. I., & Etnier, J. L. (2012). The effects of acute exercise on cognitive performance: A meta-analysis. *Brain Research*, *1453*(250), 87–101. http://doi.org/10.1016/j.brainres.2012.02.068

Chodzko-Zajko, W. J., & Moore, K. A. (1994). Physical Fitness and Cognitive Functioning in Aging. *Exercise and Sport Sciences Reviews*, *22*(1), 195–220. Retrieved from https://journals.lww.com/acsm-essr/Fulltext/1994/01000/Physical_Fitness_and_Cognitive_Functioning_in.9.aspx

Coelho, F. M., Pereira, D. S., Lustosa, L. P., Silva, J. P., Dias, J. M. D., Dias, R. C. D., … Pereira, L. S. M. (2012). Physical therapy intervention (PTI) increases plasma brain-derived neurotrophic factor (BDNF) levels in non-frail and pre-frail elderly women. *Archives of Gerontology and Geriatrics*, *54*(3), 415–420. http://doi.org/10.1016/j.archger.2011.05.014

Colcombe, S. J., Erickson, K. I., Raz, N., Webb, A. G., Cohen, N. J., McAuley, E., & Kramer, A. F. (2003). Aerobic Fitness Reduces Brain Tissue Loss in Aging Humans. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *58*(2), M176–M180. http://doi.org/10.1093/gerona/58.2.M176

Colcombe, S., & Kramer, A. F. (2003). Fitness effects on the cognitive function of older adults. *Psychological Science*, *14*, 125–130. http://doi.org/10.1111/1467-9280.t01-1-01430

Collins, P., Roberts, A. C., Dias, R., Everitt, B. J., & Robbins, T. W. (1998). Perseveration and strategy in a novel spatial self-ordered sequencing task for nonhuman primates: effects of excitotoxic lesions and dopamine depletions of the prefrontal cortex. *Journal of Cognitive Neuroscience*, *10*(3), 332–354. http://doi.org/10.1162/089892998562771

Corsi, P. (1972). *Human memory and the medial temporal lobe region of the brain. McGill University, Montreal.*

Costigan, S. A., Eather, N., Plotnikoff, R. C., Hillman, C. H., & Lubans, D. R. (2016).

High-Intensity Interval Training on Cognitive and Mental Health in Adolescents. *Medicine and Science in Sports and Exercise*, *48*(10), 1985–1993. http://doi.org/10.1249/MSS.0000000000000993

Cotman, C. W., Berchtold, N. C., & Christie, L. A. (2007a). Exercise builds brain health: key roles of growth factor cascades and inflammation. *Trends in Neurosciences*, *30*(9), 464–472. http://doi.org/10.1016/j.tins.2007.06.011

Cotman, C. W., Berchtold, N. C., & Christie, L. A. (2007b). Exercise builds brain health: key roles of growth factor cascades and inflammation. *Trends in Neurosciences*, *30*(9), 464–472. http://doi.org/10.1016/j.tins.2007.06.011

Dai, S., Carroll, D., Watson, K., Paul, P., Carlson, S., & Fulton, J. (2015). Particpation in types of physical activitiesamong US adults - National Health and Nutrition Examination Survery 1999-2006. *J Phys Act Health*, *12*(01), S128–S140. http://doi.org/10.1016/j.antiviral.2015.06.014.Chronic

Davies, C. T. M., & Knibbs, A. V. (1971). The Training Stimulus. *Int. Z. Angew. Physiol.*, *29*(4), 299–305. http://doi.org/10.1007/BF00697733

Ding, Q., Vaynman, S., Akhavan, M., Ying, Z., & Gomez-Pinilla, F. (2006). Insulin-like growth factor I interfaces with brain-derived neurotrophic factor-mediated synaptic plasticity to modulate aspects of exercise-induced cognitive function. *Neuroscience*, *140*(3), 823–833. http://doi.org/10.1016/j.neuroscience.2006.02.084

Ding, Q., Vaynman, S., Souda, P., Whitelegge, J. P., & Gomez-Pinilla, F. (2006). Exercise affects energy metabolism and neural plasticity-related proteins in the hippocampus as revealed by proteomic analysis. *European Journal of Neuroscience*, *24*(5), 1265–1276. http://doi.org/10.1111/j.1460-9568.2006.05026.x

Dunsky, A., Abu-rukun, M., Tsuk, S., Dwolatzky, T., Carasso, R., & Netz, Y. (2017). The effects of a resistance versus an aerobic single session on attention and executive functioning in adults. *Plos One*, *12*(4), 1–13. http://doi.org/10.1371/journal.pone.0176092

Ebbeling, C., Ward, A., Puleo, E., Widrick, J., & Rippe, J. (1991). Development of a single-stage submaximal treadmill walking test. *Medicine and Science in Sports and Exercise*, *23*, 966–973.

Erickson, K. I., Banducci, S. E., Weinstein, A. M., MacDonald, A. W., Ferrell, R. E., Halder, I., … Manuck, S. B. (2013). The Brain-Derived Neurotrophic Factor Val66Met Polymorphism Moderates an Effect of Physical Activity on Working Memory Performance. *Psychological Science*, *24*(9), 1770–1779. http://doi.org/10.1177/0956797613480367

Erickson, K. I., Leckie, R. L., & Weinstein, A. M. (2014). Physical activity, fitness, and gray matter volume. *Neurobiol Aging*, *35*, S20–S28. http://doi.org/10.1016/j.neurobiolaging.2014.03.034.Physical

Erickson, K. I., Prakash, R. S., Voss, M. W., Chaddock, L., Hu, L., Morris, K. S., … Kramer, A. F. (2009). Aerobic fitness is associated with hippocampal volume in elderly humans. *Hippocampus*, *19*(10), 1030–1039. http://doi.org/10.1002/hipo.20547

Erickson, K. I., Voss, M. W., Prakash, R. S., Basak, C., Szabo, A., Chaddock, L., … Kramer, A. F. (2011). Exercise training increases size of hippocampus and improves memory. *Proceedings of the National Academy of Sciences*, *108*(7), 3017–3022. http://doi.org/10.1073/pnas.1015950108

Fabel, K., Fabel, K., Tam, B., Kaufer, D., Baiker, A., Simmons, N., … Elisa, S. (2003). VEGF is necessary for exercise-induced adult hippocampal neurogenesis. *European Journal of Neuroscience*, *18*, 2803–2812. http://doi.org/10.1046/j.1460-9568.2003.03041.x

Finck, B. N., & Kelly, D. P. (2006). PGC-1 coactivators: Inducible regulators of energy metabolism in health and disease. *Journal of Clinical Investigation*, *116*(3), 615–622. http://doi.org/10.1172/JCI27794

Finkbeiner, S. (2000). CREB Couples Neurotrophin Signals to Survival Messages.

Neuron, *25*, 11–14.

Finkbeiner, S., Tavazoie, S. F., Maloratsky, A., Jacobs, K. M., Harris, K. M., & Greenberg, M. E. (1997). CREB: A major mediator of neuronal neurotrophin responses. *Neuron*, *19*(5), 1031–1047. http://doi.org/10.1016/S0896-6273(00)80395-5

Fletcher, G., Balady, G., Blair, S., Blumenthal, J., Caspersen, C., Chaitman, B., & Pollock, M. (1996). Statement on exercise: Benefits and recommendations for physical activity programs for all Americans. *Circulation*, *94*(4), 857–862.

Fletcher, G. F., Ades, P. A., Kligfield, P., Arena, R., Balady, G. J., Bittner, V. A., … Williams, M. A. (2013). Exercise standards for testing and training: A scientific statement from the American heart association. *Circulation*, *128*(8), 873–934. http://doi.org/10.1161/CIR.0b013e31829b5b44

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*(3), 189–198. http://doi.org/10.1016/0022-3956(75)90026-6

Garcia, C., Chen, M. J., Garza, A. A., Cotman, C. W., & Russo-Neustadt, A. (2003). The influence of specific noradrenergic and serotonergic lesions on the expression of hippocampal brain-derived neurotrophic factor transcripts following voluntary physical activity. *Neuroscience*, *119*(3), 721–732. http://doi.org/10.1016/S0306-4522(03)00192-1

Gould, R. L., Brown, R. G., Owen, A. M., Bullmore, E. T., Williams, S. C. R., & Howard, R. J. (2005). Functional neuroanatomy of successful paired associate learning in Alzheimer's disease. *American Journal of Psychiatry*, *162*(11), 2049–2060. http://doi.org/10.1176/appi.ajp.162.11.2049

Guiney, H., Lucas, S. J., Cotter, J. D., & Machado, L. (2015). Evidence cerebral blood-flow regulation mediates exercise-cognition links in healthy young adults.

Neuropsychology, *29*(1), 1–9. http://doi.org/10.1037/neu0000124

Hallgren, M., Skott, M., Ekblom, Ö., Firth, J., Schembri, A., & Forsell, Y. (2018). Exercise effects on cognitive functioning in young adults with first-episode psychosis: FitForLife. *Psychological Medicine*, 1–9. http://doi.org/10.1017/S0033291718001022

Hampshire, A., Highfield, R. R., Parkin, B. L., & Owen, A. M. (2012). Fractionating Human Intelligence. *Neuron*, *76*(6), 1225–1237. http://doi.org/10.1016/j.neuron.2012.06.022

Hardingham, G. E., Arnold, F. J. L., & Bading, H. (2001). Nuclear calcium signaling controls CREB-mediated gene expression triggered by synaptic activity. *Nature Neuroscience*, *4*(3), 261–267. http://doi.org/10.1038/85109

Hawkins, H. L., Kramer, A. F., & Capaldi, D. (1992). Aging, Exercise, and Attention. *Psychology and Aging*, *7*(4), 643–653.

Hibbs, A. E., Thompson, K. G., French, D., Wrigley, A., & Spears, I. (2008). Optimizing performance by improving core stability and core strength. *Sports Medicine*, *38*(12), 995–1008. http://doi.org/10.2165/00007256-200838120-00004

Hilfiker, S., Pieribone, V. A., Czernik, A. J., Kao, H.-T., Augustine, G. J., & Greengard, P. (1999). Synapsins as regulators of neurotransmitter release. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *354*(1381), 269–279. http://doi.org/10.1098/rstb.1999.0378

Hillman, C. H., Erickson, K. I., & Kramer, A. F. (2008). Be smart, exercise your heart: exercise effects on brain and cognition. *Nature Reviews*, *9*, 58–65.

Hillman, C. H., Pontifex, M. B., Castelli, D. M., Khan, N. A., Raine, L. B., Scudder, M. R., … Kamijo, K. (2014). Effects of the FITKids Randomized Controlled Trial on Executive Control and Brain Function. *Pediatrics*, *134*(4), e1063–e1071. http://doi.org/10.1542/peds.2013-3219

Hitch, G. J., & Baddeley, A. D. (1976). Verbal reasoning and working memory. *Quarterly Journal of Experimental Psychology*, *28*(4), 603–621. http://doi.org/10.1080/14640747608400587

Homolak, J., Janes, I., & Filipovic, M. (2015). The role of IGF-1 in neurodegenerative diseases. *Gyrus Journal*, *3*, 162–167.

Hwang, J., Brothers, R. M., Castelli, D. M., Glowacki, E. M., Chen, Y. T., Salinas, M. M., … Calvert, H. (2016). Acute high-intensity exercise-induced cognitive enhancement and brain-derived neurotrophic factor in young, healthy adults. *Neuroscience Letters*, *630*, 247–253. http://doi.org/10.1016/j.neulet.2016.07.033

Ide, K., & Secher, N. H. (2000). Cerebral blood flow and metabolism during exercise. *Progress in Neurobiology*, *61*, 397–414.

Ikudome, S., Mori, S., Unenaka, S., Kawanishi, M., Kitamura, T., & Nakamoto, H. (2016). Effect of Long-Term Resistance Exercise on Cognitive Function in Elderly People. *Journal of Applied Gerontology*, 1–15. http://doi.org/10.1177/0733464815625834

Imai, A., & Kaneoka, K. (2016). The relationship between trunk endurance plank tests and athletic performance tests in adolescent soccer players. *The International Journal of Sports Physical Therapy*, *11*(5), 718–724.

Inoue, S., & Matsuzawa, T. (2007). Working memory of numerals in chimpanzees. *Current Biology*, *17*(23), 1004–1005. http://doi.org/10.1016/j.cub.2007.10.027

Jedrziewski, M. K., Ewbank, D. C., Wang, H., & Trojanowski, J. Q. (2010). Exercise and cognition: Results from the National Long Term Care Survey. *Alzheimer's and Dementia*, *6*(6), 448–455. http://doi.org/10.1016/j.jalz.2010.02.004

Johnson, N. F., Kim, C., Clasey, J. L., Bailey, A., & Gold, B. T. (2012). Cardiorespiratory fitness is positively correlated with cerebral white matter integrity in healthy seniors. *NeuroImage*, *59*(2), 1514–1523. http://doi.org/10.1016/j.neuroimage.2011.08.032

Jonasson, L. S., Nyberg, L., Kramer, A. F., Lundquist, A., Riklund, K., & Boraxbekk, C. J. (2017). Aerobic exercise intervention, cognitive performance, and brain structure: Results from the Physical Influences on Brain in Aging (PHIBRA) Study. *Frontiers in Aging Neuroscience*, *8*, 1–15. http://doi.org/10.3389/fnagi.2016.00336

Kim, S.-H., Kim, M., Ahn, Y.-B., Lim, H.-K., Kang, S.-G., Cho, J.-H., … Song, S.-W. (2011). Effect of dance exercise on cognitive function in elderly patients with metabolic syndrome: a pilot study. *Journal of Sports Science & Medicine*, *10*(4), 671–8.

Kobayashi-Cuya, K. E., Sakurai, R., Suzuki, H., Ogawa, S., Takebayashi, T., & Fujiwara, Y. (2018). Observational Evidence of the Association Between Handgrip Strength, Hand Dexterity, and Cognitive Performance in Community-Dwelling Older Adults: A Systematic Review. *Journal of Epidemiology*, 1–9. http://doi.org/10.2188/jea.JE20170041

Kramer, A. F., Hahn, S., Cohen, N. J., Banich, M. T., McAuley, E., Harrison, C. R., … Colcombe, A. (1999). Ageing, fitness and neurocognitive function. *Nature*, *400*, 418–9. http://doi.org/10.1038/22682

Kredlow, M. A., Capozzoli, M. C., Hearon, B. A., Calkins, A. W., & Otto, M. W. (2015). The effects of physical activity on sleep: a meta-analytic review. *Journal of Behavioral Medicine*, *38*(3), 427–449. http://doi.org/10.1007/s10865-015-9617-6

Küster, O. C., Fissler, P., Laptinskaya, D., Thurm, F., Scharpf, A., Woll, A., … Kolassa, I. T. (2016). Cognitive change is more positively associated with an active lifestyle than with training interventions in older adults at risk of dementia: a controlled interventional clinical trial. *BMC Psychiatry*, *16*(1), 315. http://doi.org/10.1186/s12888-016-1018-z

Lambiase, M. J., Gabriel, K. P., Kuller, L. H., & Matthews, K. A. (2014). Sleep and Executive Function in Older Women: The Moderating Effect of Physical Activity. *The Journals of Gerontology*, *69*(9), 1170–1176. http://doi.org/10.1093/gerona/glu038

Lange, K. W., Robbins, T. W., Marsden, C. D., James, M., Owen, A. M., & Paul, G. M. (1992). L-Dopa Withdrawal in Parkinsons-Disease Selectively Impairs Cognitive Performance in Tests Sensitive to Frontal-Lobe Dysfunction. *Psychopharmacology*, *107*(2–3), 394–404.

Langlois, F., & Vu, T. (2013). Benefits of physical exercise training on cognition and quality of life in frail older adults. *Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *68*(3), 400–404. http://doi.org/10.1093/geronb/gbs069.

Liu-Ambrose, T., Nagamatsu, L. S., Graf, P., Beattie, B. L., Ashe, M. C., & Handy, T. C. (2012a). Resistance Training and Executive Functions: A 12-Month Randomised Controlled Trial. *Arch Intern Med.*, *170*(2), 170–178. http://doi.org/10.1001/archinternmed.2009.494.Resistance

Liu-Ambrose, T., Nagamatsu, L. S., Voss, M. W., Khan, K. M., & Handy, T. C. (2012b). Resistance training and functional plasticity of the aging brain: A 12-month randomized controlled trial. *Neurobiology of Aging*, *33*(8), 1690–1698. http://doi.org/10.1016/j.neurobiolaging.2011.05.010

Lopez-Lopez, C., LeRoith, D., & Torres-Aleman, I. (2004). Insulin-like growth factor I is required for vessel remodeling in the adult brain. *PNAS*, *101*(26), 9833–8. http://doi.org/10.1073/pnas.0400337101

Ma, D., Li, S., Lucas, E. K., Cowell, R. M., & Lin, J. D. (2010). Neuronal inactivation of peroxisome proliferator-activated receptor gamme coactivator 1alpha (PGC-1alpha) protects mice from diet-induced obesity and leads to degenerative lesions. *Journal of Biological Chemistry*, *285*(50), 39087–39095. http://doi.org/10.1074/jbc.M110.151688

McCusker, R. H., McCrea, K., Zunich, S., Dantzer, R., Broussard, S. R., Johnson, R. W., & Kelley, K. W. (2006). Insulin-like growth factor-I enhances the biological activity of brain-derived neurotrophic factor on cerebrocortical neurons. *Journal of Neuroimmunology*, *179*(1–2), 186–190.

http://doi.org/10.1016/j.jneuroim.2006.06.014

Mehta, M. A., Owen, A. M., Sahakian, B. J., Mavaddat, N., Pickard, J. D., & Robbins, T. W. (2000). Methylphenidate enhances working memory by modulating discrete frontal and parietal lobe regions in the human brain. *The Journal of Neuroscience*, *20*(6), RC65.

Meltzer, J. A., & Constable, R. T. (2005). Activation of human hippocampal formation reflects success in both encoding and cued recall of paired associates. *NeuroImage*, *24*(2), 384–397. http://doi.org/10.1016/j.neuroimage.2004.09.001

Mizuhara, B. H., O'Neill, E., Seki, N., Ogawa, T., Kusunoki, C., Otsuka, K., … Fujiwara, H. (1994). T Cell Activation-asociated Hepatic Injury: mediation by tumor necrosis factors and protection by interleukin 6. *J. Exp. Med.*, *179*, 1529–1537.

Moreau, D., Kirk, I. J., & Waldie, K. E. (2017). High-intensity training enhances executive function in children in a randomized, placebo-controlled trial. *ELife*, 1–26. http://doi.org/10.7554/eLife.25062

Moul, J., Goldman, B., & Warren, B. (1995). Physical activity and cognitive performance in the older population. *Journal of Aging and Physical Activity*, *3*(2), 135–145.

Murray, P., & Holmes, P. (2011). An Overview of Brain-Derived Neurotrophic Factor and Implications for Excitotoxic Vulnerability in the Hippocampus. *International Journal of Peptides*, *2011*, 1–12. http://doi.org/10.1155/2011/654085

Ngandu, T., Lehtisalo, J., Solomon, A., Levälahti, E., Ahtiluoto, S., Antikainen, R., … Jula, A. (2015). A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial, 2255–2263. http://doi.org/10.1016/S0140-6736(15)60461-5

Nouchi, R., Taki, Y., Takeuchi, H., Sekiguchi, A., Hashizume, H., Nozawa, T., … Kawashima, R. (2014). Four weeks of combination exercise training improved executive functions, episodic memory, and processing speed in healthy elderly people: Evidence from a randomized controlled trial. *Age*, *36*(2), 787–799. http://doi.org/10.1007/s11357-013-9588-x

Owen, A. M., Beksinska, M., James, M., Leigh, P. N., Summers, B. A., Marsden, C. D., … Robbins, T. W. (1993). Visuospatial Memory Deficits At Different of Parkinson's Disease Stages. *Neuropsychologia*, *31*(7), 627–644.

Owen, A.M., Downes, J. J., Sahakian B. J., Polkey C. E., Robbins T. W. (1990). Planning and spatial working memory following frontal lobe lesions in man. *Neuropsychologia*, *28*(10), 1021–1034.

Owen A. M., Doyon J., Petrides M., Evans A. C. (1996a). Planning and spatial working memory: a positron emission tomography study in humans. *Eur. J. Neurosci* *8*(2), 353–364.

Owen A. M., Evans A. C., Petrides M. (1996b) Evidence for a two-stage model of spatial working memory processing within the lateral frontal cortex: a positron emission tomography study. *Cereb. Cortex* *6*(1), 31–38.

Owen, A. M., James, M., Leigh, P. N., Summers, B. A., Marsden, C. D., Quinn, N. P., … Robbins, T. W. (1992). Fronto-Striatal Cognitive Deficits At Different Stages of Parkinson’s Disease. *Brain*, *115*, 1727–1751.

Owen A. M., Roberts A. C., Polkey C. E., Sahakian B. J., Robbins T. W. (1991). Extra-dimensional versus intra-dimensional set shifting performance following frontal lobe excisions, temporal lobe excisions or amygdalo-hippocampectomy in man. *Neuropsychologia*, *29*(10), 993–1006.

Palmer, T. D., Willhoite, A. R., & Gage, F. H. (2000). Vascular niche for adult hippocampal neurogenesis. *Journal of Comparative Neurology*, *425*(4), 479–494. http://doi.org/10.1002/1096-9861(20001002)425:4<479::AID-CNE2>3.0.CO;2-3

Pereira, A. C., Huddleston, D. E., Brickman, A. M., Sosunov, A. A., Hen, R., McKhann, G. M., … Small, S. A. (2007). An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. *Proceedings of the National Academy of Sciences*, *104*(13), 5638–5643. http://doi.org/10.1073/pnas.0611721104

Perry, V. H. (2004). The influence of systemic inflammation on inflammation in the brain: Implications for chronic neurodegenerative disease. *Brain, Behavior, and Immunity*, *18*(5), 407–413. http://doi.org/10.1016/j.bbi.2004.01.004

Petersen, A. M. W., & Pedersen, B. K. (2005). The anti-inflammatory effect of exercise. *Journal of Applied Physiology*, *98*(4), 1154–1162. http://doi.org/10.1152/japplphysiol.00164.2004.

Piepmeier, A. T., & Etnier, J. L. (2015). Brain-derived neurotrophic factor (BDNF) as a potential mechanism of the effects of acute exercise on cognitive performance. *Journal of Sport and Health Science*, *4*(1), 14–23. http://doi.org/10.1016/j.jshs.2014.11.001

Pretolani, M. (1999). Interleukin-10: an anti-inflammatory cytokine with therapeutic potential. *Clinical and Experimental Allergy*, *29*, 1164–1171.

Salthouse, T. A., & Davis, H. P. (2006). Organization of cognitive abilities and neuropsychological variables across the lifespan. *Developmental Review*, *26*(1), 31–54. http://doi.org/10.1016/j.dr.2005.09.001

Schwarb, H., Johnson, C. L., Daugherty, A. M., Hillman, C. H., Kramer, A. F., Cohen, N. J., & Barbey, A. K. (2017). Aerobic fitness, hippocampal viscoelasticity, and relational memory performance. *NeuroImage*, *153*, 179–188. http://doi.org/10.1016/j.neuroimage.2017.03.061

Shallice, T. (1982). Specific Impairments of Planning. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *298*(1089), 199–209. http://doi.org/10.1098/rstb.1982.0082

Shao, Z., Janse, E., Visser, K., & Meyer, A. S. (2014). What do verbal fluency tasks measure? Predictors of verbal fluency performance in older adults. *Frontiers in Psychology*, *5*, 1–10. http://doi.org/10.3389/fpsyg.2014.00772

Shay, K. A., & Roth, D. L. (1992). Association between aerobic fitness and visuospatial performance in healthy older adults. *Psychology and Aging*, *7*(1), 15–24. http://doi.org/10.1037/0882-7974.7.1.15

Silverman, I., Choi, J., Mackewn, A., Fisher, M., Moro, J., & Olshansky, E. (2000). Evolved mechanisms underlying wayfinding: further studies on the hunter-gatherer theory of spatial sex differences. *Evolution and Human Behavior*, *21*, 201–213. http://doi.org/10.1016/S1090-5138(00)00036-2

Smiley-Oyen, A. L., Lowry, K. A., Francois, S. J., Kohut, M. L., & Ekkekakis, P. (2008). Exercise, fitness, and neurocognitive function in older adults: The “selective improvement” and “cardiovascular fitness” hypotheses. *Annals of Behavioral Medicine*, *36*(3), 280–291. http://doi.org/10.1007/s12160-008-9064-5

Spiegelman, B. M. (2007). Transcriptional control of energy homeostasis through the PGC1 coactivators. *Novartis Foundation Symposium*, *286*, 3–12. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/18269170

Steensberg, A., Fischer, C. P., Keller, C., Møller, K., & Pedersen, B. K. (2003). IL-6 enhances plasma IL-1ra, IL-10, and cortisol in humans. *American Journal of Physiology - Endocrinology And Metabolism*, *285*(2), E433–E437. http://doi.org/10.1152/ajpendo.00074.2003

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology*, *18*(6), 643–662.

Stroth, S., Hille, K., Spitzer, M., & Reinhardt, R. (2009). Aerobic endurance exercise benefits memory and affect in young adults. *Neuropsychological Rehabilitation*, *19*(2), 223–243. http://doi.org/10.1080/09602010802091183

Stuchlik, A. (2014). Dynamic learning and memory, synaptic plasticity and neurogenesis: an update. *Frontiers in Behavioral Neuroscience*, *8*, 1–6. http://doi.org/10.3389/fnbeh.2014.00106

Suominen-Troyer, S., Davis, K., Ismail, A., & Salvendy, G. (2016). Impact of Physical

Fitness on Strategy Development in Decision-Making Tasks. *Perceptual and Motor Skills*, *62*(1), 71–77.

Suwabe, K., Hyodo, K., Byun, K., Ochi, G., Yassa, M. A., & Soya, H. (2017). Acute moderate exercise improves mnemonic discrimination in young adults. *Hippocampus*, *27*(3), 229–234. http://doi.org/10.1002/hipo.22695

Swagerman, S. C., Geus, E. J. C. De, Koenis, M. M. G., Hulshoff, H. E., Boomsma, D. I., & Kan, K. (2015). Brain and Cognition Domain dependent associations between cognitive functioning and regular voluntary exercise behavior. *Brain and Cognition*, *97*, 32–39. http://doi.org/10.1016/j.bandc.2015.04.001

The recommended quantity and quality of exercise for developing and maintaining fitness in healthy adults. (1993). *American College of Sports Medicine*, *47*, 127–137.

Tong, L., Balazs, R., Soiampornkul, R., Thangnipon, W., & Cotman, C. (2008). Interleukin-1β impairs brain derived neurotrophic factor-induced signal transduction. *Neurobiology of Aging*, *29*(9), 1380–1393. http://doi.org/10.1126/science.1249098.Sleep

Tong, T. K., Wu, S., & Nie, J. (2014). Sport-specific endurance plank test for evaluation of global core muscle function. *Physical Therapy in Sport*, *15*(1), 58–63. http://doi.org/10.1016/j.ptsp.2013.03.003

Treisman, A., & Gelade, G. (1980). A feature-integration theory of attention. *Cognitive Psychology*, *12*(1), 97–136. http://doi.org/10.1016/0010-0285(80)90005-5

van de Rest, O., van der Zwaluw, N. L., Tieland, M., Adam, J. J., Hiddink, G. J., van Loon, L. J. C., & de Groot, L. C. P. G. M. (2014). Effect of resistance-type exercise training with or without protein supplementation on cognitive functioning in frail and pre-frail elderly: Secondary analysis of a randomized, double-blind, placebo-controlled trial. *Mechanisms of Ageing and Development*, *136–137*, 85–93. http://doi.org/10.1016/j.mad.2013.12.005

van Praag, H., Shubert, T., Zhao, C., & Gage, F. (2005). Exercise Enhances Learning and

Hippocampal Neurogenesis in Aged Mice. *Journal of Neuroscience*, *25*(38), 8680–8685. http://doi.org/10.1523/JNEUROSCI.1731-05.2005

Vanhees, L., Lefevre, J., Philippaerts, R., Martens, M., Huygens, W., Troosters, T., & Beunen, G. (2005). How to assess physical activity? How to assess physical fitness? *European Journal of Cardiovascular Prevention & Rehabilitation*, *12*(2), 102–114. http://doi.org/10.1097/01.hjr.0000161551.73095.9c

Vaynman, S., Ying, Z., & Gomez-Pinilla, F. (2003). Interplay between brain-derived neurotrophic factor and signal transduction modulators in the regulation of the effects of exercise on synaptic-plasticity. *Neuroscience*, *122*(3), 647–657. http://doi.org/10.1016/j.neuroscience.2003.08.001

Vaynman, S., Ying, Z., & Gomez-Pinilla, F. (2004). Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. *European Journal of Neuroscience*, *20*(10), 2580–2590. http://doi.org/10.1111/j.1460-9568.2004.03720.x

Venters, H. D., Tang, Q., Liu, Q., VanHoy, R. W., Dantzer, R., & Kelley, K. W. (1999). A new mechanism of neurodegeneration: a proinflammatory cytokine inhibits receptor signaling by a survival peptide. *Proceedings of the National Academy of Sciences of the United States of America*, *96*(17), 9879–84. http://doi.org/10.1073/pnas.0907385106

Voss, M. W., Prakash, R. S., Erickson, K. I., Basak, C., Chaddock, L., Kim, J., … Kramer, A. (2010). Plasticity of brain networks in a randomized intervention trial of exercise training in older adults. *Frontiers in Aging Neuroscience*, *2*, 1–17. http://doi.org/10.3389/fnagi.2010.00032

Weinstein, A. M., Voss, M. W., Shaurya, R., Chaddock, L., Szabo, A., White, S. M., … Erickson, K. I. (2012). The association between aerobic fitness and executive function is mediated by prefrontal cortex volume. *Brain, Behavior, and Immunity*, *26*(5), 811–819. http://doi.org/10.1016/j.bbi.2011.11.008

Wechsler, D. (1981). *WAIS-R manual: Wechsler adult intelligence scale-revised.*

Psychological Corporation.

Wendell, C. R., Gunstad, J., Waldstein, S. R., Wright, J. G., Ferrucci, L., & Zonderman, A. B. (2014). Cardiorespiratory fitness and accelerated cognitive decline with aging. *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*, *69*(4), 455–462. http://doi.org/10.1093/gerona/glt144

Wilmore, J., Royce, J., Girandola, R., Katch, F., & Katch, V. (1970). Physiological alterations resulting from a 10-week program of jogging. *Medicine and Science in Sports*, *2*, 7–14.

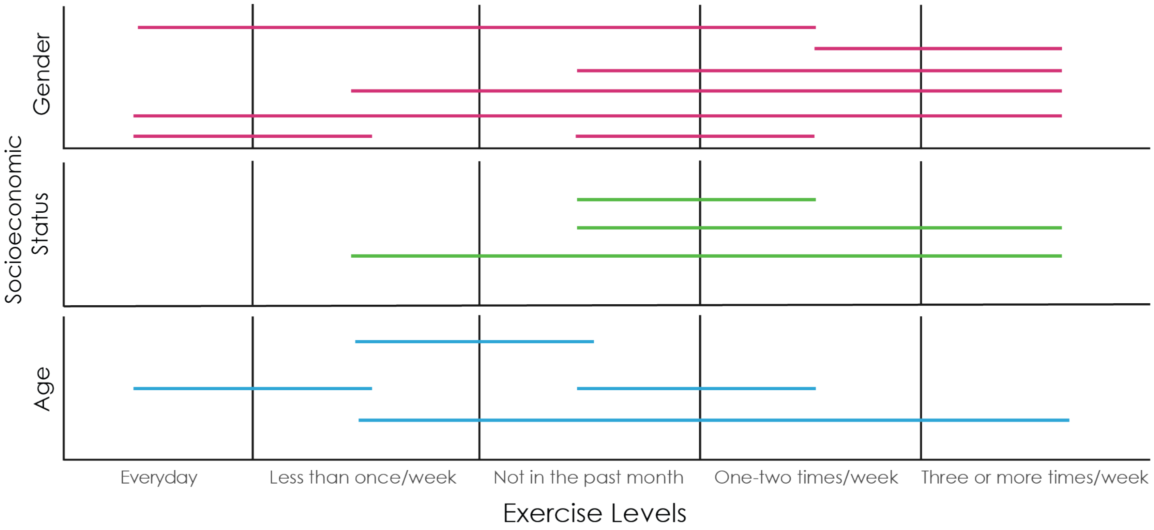
Wrann, C. D., White, J. P., Salogiannnis, J., Laznik-bogoslavski, D., Wu, J., Ma, D., … Spiegelman, B. M. (2013). Exercise induces hippocampal BDNF through a PGC-1α/FNDC5 pathway. *Cell Metabolism*, *18*(5), 649–659. http://doi.org/10.1016/j.cmet.2013.09.008.Exercise

Yaffe, K., Haan, M., Blackwell, T., Cherkasova, E., Whitmer, R. A., & West, N. (2007). Metabolic syndrome and cognitive decline in elderly latinos: Findings from the Sacramento Area Latino Study of Aging Study. *Journal of the American Geriatrics Society*, *55*(5), 758–762. http://doi.org/10.1111/j.1532-5415.2007.01139.x

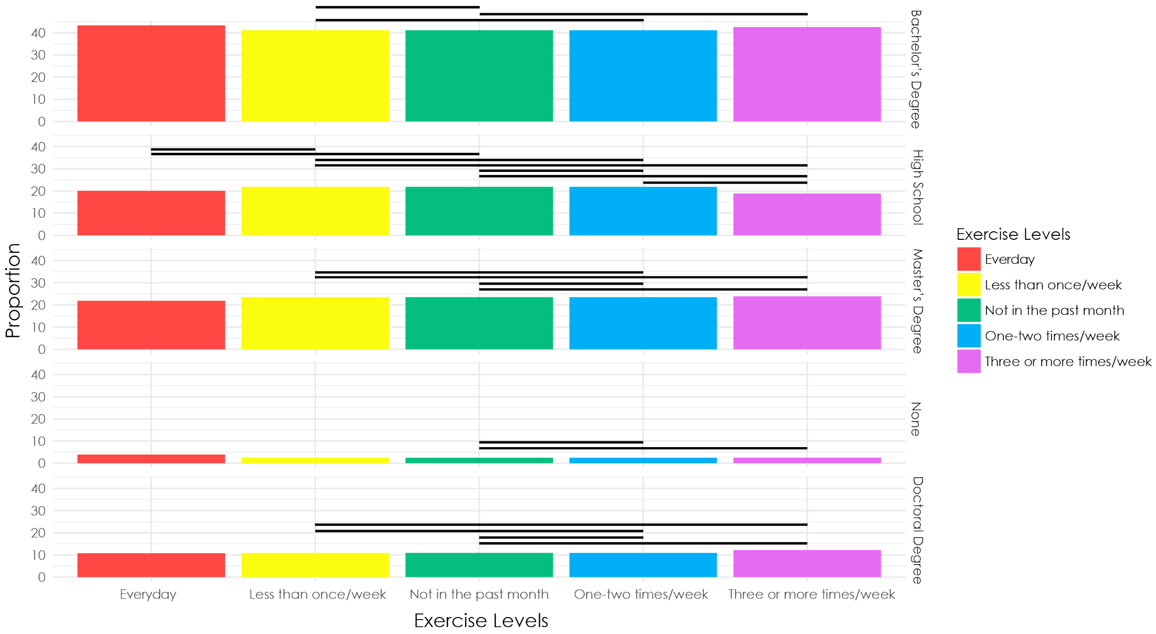
Yassa Michael, S. C. (2012). Pattern Seperation in the Hippocampus. *Trends in Neurosciences*, *34*(10), 515–525. http://doi.org/10.1016/j.tins.2011.06.006.Pattern

Yin, J. C. P., & Tully, T. (1996). CREB and the formation of long-term memory. *Current Opinion in Neurobiology*, *6*(2), 264–268. http://doi.org/10.1016/S0959-4388(96)80082-1

Appendices



Appendix 1: Comparison of age, gender and SES between exercise levels. Red bars represent instances where the proportion of males and females significantly differs between the exercise levels ($p<0.05$; n=10,985). Green bars represent the exercise levels in which the proportion of participants who grew up below poverty line is significantly different from those who grew up at or above the poverty line ($p<0.05$; n=10,985). Blue bars show which exercise levels have significantly different mean ages ($p<0.05$; n=10,985).



Appendix 2: Proportion of participants reporting the various education levels within each exercise frequency is displayed. Black bars represent the exercise levels with significantly different proportions of participants, within an education level ($p<0.05$; n=10,985).

Curriculum Vitae

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Post-secondary Education and Degrees:	The University of Western Ontario London, Ontario, Canada 2012-2016 BMSc
	The University of Western Ontario London, Ontario, Canada 2016-2018 MSc
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Publications:

In review:
Stojanoski B, Lyons K, Pearce A, Owen A. M. Converging evidence against the transferable benefits of online brain training on cognitive function. *Neuropsychologia.*

Poster Presentations

Alexandra Pearce and Adrian Owen. Game Over: Assessing the effects of brain training on cognitive function. James A.F. Stevenson Distinguished Lecture and Research Day, Western University. 2016.

Alexandra Pearce, Kathleen Lyons, Adrian M. Owen and Bobby Stojanoski. Don't Sweat It: Investigating the effects of exercise frequency on cognition. Charles W. Gowdey Distinguished Lecture and Research Day, Western University. 2017.

Kathleen Lyons, Alexandra Pearce, Tram Nguyen, Adrian M. Owen and Bobby Stojanoski Targeted Training: Assessing the effects of online brain training on cognitive function. Lake Ontario Visionary Establishment Conference. Niagara Falls, Ontario. 2017.

Kathleen Lyons, Alexandra Pearce, Tram Nguyen, Adrian M. Owen and Bobby Stojanoski. Targeted Training: Assessing the effects of online brain training on cognitive function. London Health Research Day. London, Ontario. 2017.