The Dissertation Committee for Jungyun Hwang Certifies that this is the approved version of the following dissertation:

PHYSICAL ACTIVITY, VASCULAR RISK AND COGNITIVE PERFORMANCE IN YOUNG ADULTS

Committee:

Darla M. Castelli, Supervisor

John Bartholomew

Robert Matthew Brothers

Louis Harrison

Xiaofen Keating

PHYSICAL ACTIVITY, VASCULAR RISK AND COGNITIVE PERFORMANCE IN YOUNG ADULTS

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Jungyun Hwang, B.A.; M.A.; M.A.

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Dedication

For My Father and Mother

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Physical Activity, Vascular Risk and Cognitive Performance In Young Adults

Jungyun Hwang, PhD

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Supervisor: Darla M. Castelli

A growing body of literature suggests that higher levels of physical activity and cardiorespiratory fitness, as well as an alternative treatment such as low level laser therapy (LLLT), have beneficial effects on cognition, while sedentary lifestyle-induced obesity and vascular risk negatively influence cognition. However, the relationship between cardiorespiratory fitness and vascular risk on cognitive function and the effect of an acute bout of very vigorous aerobic exercise (acute exercise) on cognitive performance has not yet been investigated. Additionally, the effects of combined acute exercise and LLLT treatments on cognitive performance have not yet been characterized. Therefore, the goal of this dissertation was to conduct a series of three research studies ranging from a cross-sectional exploratory study about the association of cardiorespiratory fitness, obesity, and vascular risk on cognitive function, to an experimentally designed study that compared the effects of acute exercise, LLLT, and the combination of these two treatments on cognitive performance in young adults. Study1 examined the relationship among cardiorespiratory fitness (maximal oxygen consumption, VO_2max), obesity indices (body mass index, BMI; waist circumstance), and vascular risk (C-reactive protein; CRP). Cognitive function included crystalized intelligence (Kaufman Brief Intelligence Test; KBIT), executive functions of inhibition (Stroop test), switching (Trail

making test; TMT), attention (Psychomotor Vigilance Task; PVT), and working memory (Delayed-Match-to-Sample, DMS). Study 2 determined the effect of acute exercise on cognitive performance including executive response inhibition (Stroop test) and response switching (TMT) and brain-derived neurotrophic factor (BNDF). Study 3 compared the effectiveness of LLLT and acute exercise on cognitive performance, which included attention (PVT) and working memory (DMS).

Results demonstrated there was a beneficial effect of physical exercise-induced improvements in cardiorespiratory fitness on vascular risk and cognitive functions particularly in working memory and inhibitory control (Study1). Acute exercise improved performance in inhibitory control and increased the BNDF level compared to the control condition, suggesting the acute exercise-induced the increase in BDNF level may be at least in part of mediating the cognitive performance improvement (Study 2). All three conditions (acute exercise, LLLT, or the combination) improved performance in attention and working memory, as measured by reaction time and response accuracy, when compared to a control group. Specially, the combined group showed a trend of greater improvement in attention and worming memory performance (Study 3). Taken together, the results of this research series suggest that acute exercise and LLLT can improve cognitive performance, which is also mediated by health indices including cardiorespiratory fitness, obesity, and vascular risk. It is anticipated that these findings will make substantive contributions to the empirical literature concerning the beneficial effect of exercise and LLLT on cognitive health in young adults, given the current paucity of research.

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Chapter I: Introduction

Physical activity participation when actualized at a moderate to vigorous intensity improves cardiorespiratory fitness and provides beneficial, possibly therapeutic, effects on biological and cognitive health. Like eating, we need physical activity everyday. As such, national associations recommend at least 60- and 30- minutes (mins) of moderate to vigorous physical activity (MVPA) each day for children and adults, respectively [(US Department of Health and Human Services; (USDHHS, 2008a)]. Although the importance of physical activity across the lifespan is increasingly highlighted, inadequate physical activity, or not meeting the children and adult's physical activity recommendations (USDHHS, 2008b), is common among young adults. Expectedly, the prevalence of obesity in young people has been dramatically increased over the past three decades in America because young people are embedded in obesogenic environments that manifest sedentary lifestyles (Ogden et al., 2006; Ogden, Carroll, Kit, & Flegal, 2014). When sedentary behavior is coupled with the abundance of readily available, nutrient poor foods, pandemic levels of obesity result. Accordingly, physical activity declines strikingly with advancing age, with the most rapid declines in physical activity occurring in the period between adolescence and young adulthood (Allison, Adlaf, Dwyer, Lysy, & Irving, 2007; Cairney, Veldhuizen, Kwan, Hay, & Faught, 2014; Kwan, Cairney, Faulkner, & Pullenayegum, 2012). Correspondingly, the greatest increase in obesity was among young adults aged 18 to 29 years (Mokdad et al., 1999). Further, the prevalence of obesity has continued to increase among young people (Ogden et al., 2014). Scientific evidence suggests that physical activity engagement leading to increased cardiorespiratory fitness influences biological and cognitive health and therefore is considered to be a key contributor to the reversal of current trends.

Although most studies focus on the beneficial effects of physical activity in relation to biological health, mounting evidence demonstrates that cognitive health also benefits from physical exercise and fitness across all populations (Castelli et al., 2014; Hillman, Erickson, & Kramer, 2008). Sustaining and improving cognitive health is crucial across the lifespan as information processing and decision-making are an embedded part of our daily lives. Higher order thinking may be the most important function in our life, particularly when considering things like learning, academic achievement, and other task performances through childhood and adolescence. Academic success and the establishment of professional goals are an important factor in achieving autonomy during young adulthood. This optimization of an individual's potential to gain independence by the end of young adulthood supports quality of life and longevity into late adulthood.

Furthermore, cognition is able to assist in the higher order thinking through cognitive control processing (Anderson & Krathwohl, 2001). Developed through young adulthood, cognition is stabilized and eventually declines during adulthood (Craik & Bialystok, 2006). The growth, stability, and decline of cognition are modulated by various factors including genetics, environment, health, and fitness (Craik & Bialystok, 2006). Physical activity is a behavior that has especially contributed to the beneficial effects of health and fitness, and is associated with therapeutic effects of cognition throughout the lifespan (Hillman, Erickson, & Kramer, 2008). The relationship between physical activity and cognition may be mediated at least in part by our biological health like vascular health. Although previous studies demonstrate the association between physical activity and cognition in young adults, few studies reports the link between physical activity and cognition with vascular risk factor and cognitive biomarker. Vascular risk, like small vessel disease producing a clinical syndrome of subcortical

frontal executive dysfunction, is related to young-onset dementia as diagnosed by vascular cognitive impairment and vascular dementia (Sampson, Warren, & Rossor, 2004). The prevalence of dementia occurs not only in the elderly population, but also in the young adult population (Rossor, Fox, Mummery, Schott, & Warren, 2010). Therefore, increasing rates of physical activity participation and fitness level, along with decreasing vascular risk, are cornerstones of the improvement of cognitive health. Moreover, the importance of research focusing on young adults who are at peak in cognitive health is of clear importance in order to prove the effectiveness of physical activity on cognition.

Another non-invasive therapeutic treatment that enhances cognitive health is low level laser therapy (LLLT) which is a safe and convenient tool for mitochondrial enhancement and may be part of a comprehensive approach for treatment of neurological conditions featuring neurodegeneration and cognitive impairment (Gonzalez-Lima & Barrett, 2014). The beneficial effects of transcranial LLLT on prefrontal cortex functions such as those related to neurological and cognitive functions have been discovered in animal (Rojas, Bruchey, & Gonzalez-Lima, 2012) and human studies (Barrett & Gonzalez-Lima., 2013). Both transcranial LLLT and acute aerobic exercise might have a similar biological consequence (e.g., aerobic capacity, cerebral blood flow) for brain function (Rojas & Gonzalez-Lima, 2013); therefore, it is warranted to explore whether the additive effects of both LLLT and acute exercise are beneficial for cognitive performance.

STATEMENT OF STUDY SIGNIFICANCE

The series of three studies was designed to answer the following research questions: 1) How are cardiorespiratory fitness, physical activity level, obesity, and vascular risk related to cognitive function when cognitive function is measured through

the use of various cognitive tasks such as crystalized intelligence, executive function, attention, and working memory?; 2) How does an acute bout of very vigorous exercise impact executive function?; and 3) How do LLLT and an acute bout of very vigorous exercise impact attention and working memory?.

With regard to the first study, although previous research has demonstrated the association between vascular risk and cognitive function, and between physical activity/fitness and cognitive function, no previous studies have explored the link among vascular risk, cardiorespiratory fitness, physical activity level, and obesity with cognitive function in a young adult population. Accordingly, a relationship between the health indices and cognitive function is mediated, at least in part, by vascular mechanisms, including cerebrovascular reserve and cardiovascular risk (Davenport, Hogan, Eskes, Longman, & Poulin, 2012). Further, the target population of young adults is largely understudied. Health risks often manifest during youth and early adulthood; therefore, the findings from this study have the potential to inform prevention initiatives aimed at young adults.

With regard to the second study, the effects of an acute bout of aerobic exercise are quantified in relation to cognitive performance as mediated by cognitive markers. Although previous research has shown exercise-induced change in cognitive performance and cognitive markers [i.e., brain-derived neurotrophic factor (BDNF)] with moderate- and vigorous- exercise intensity protocols (Ferris, Williams, & Shen, 2007), no previous research has examined a single, short bout of very vigorous exercise (i.e., > 85% HRmax) (Thompson, Gordon, & Pescatello, 2010) on the cognitive and molecular changes dependent on the exercise intensity.

With regard to the third study, to the best of our knowledge, this is first study to use combined low-level light therapy (LLLT) and an acute bout of exercise (EX) to

enhance neural metabolism in the prefrontal cortex of humans, and measure the effectiveness of LLLT and EX on reaction time and correct responses using computer programs to implement prefrontal-based tasks for attention and working memory.

Through the series of three studies, this project would identify the relationships between fitness and vascular risk with cognitive function, and would point out mediators and moderators of these relationships, which can help explain the complexities of this cognitive process among young adults. Once these relationships are identified, the knowledge generated can be used to inform the evolution of the conceptual model of how health risk involves cognitive processes among young adult groups. Additionally, determining the exercise intensity-induced cognitive benefits can help develop physical activity programming based on parameters such as intensity and amount. Furthermore, LLLT that contributes to improvements in cognitive health is proposed to be part of a holistic neurotherapeutic construct in combination with aerobic exercise.

The archival data for the proposed series of studies involves populations who were young, healthy men and women between the ages of 18 and 30 years old, and who were able to speak and understand the English language. Individuals were excluded from participation if they were pregnant, diagnosed with a psychotic disorder, had a history of violent behavior, diagnosed with cardiovascular disease or cerebrovascular disease, and had been currently taking medications known to influence the autonomic nervous system. The researcher focused on the following specific aims for the series of three studies throughout the recruitment process.

OBJECTIVES

Study 1: Examine the relationship among vascular risk, physical activity/fitness, and cognitive function. The objectives are to determine (a) the relationship between cardiovascular risk, physical activity, fitness, body mass index, and cognitive function variables such as crystalized intelligence [Kaufman Brief Intelligence Test (KBIT)], executive function [Trail making test (TMT), Stroop test], attention [psychomotor vigilance task (PVT)], working memory ([Delayed-Match-to-Sample memory task (DMS)]; (b) independent associations between vascular risk, physical activity, cardiorespiratory fitness, body mass index and cognitive function variables; and (c) whether cardiorespiratory fitness, physical activity level, obesity indices and cognitive functioning is mediated, at least in part, by vascular mechanisms, including vascular risk.

Study 2: Determine very vigorous exercise intensity-induced effects on cognitive performance and molecular factors. The objectives are to examine: (a) whether an acute bout of very high-intensity exercise improves the frontal lobe functions by measuring ability of inhibitory control and response switching using executive functioning tests (TMT, and Stroop); (b) whether an acute bout of very high-intensity exercise changes the magnitude of the cognitive marker (BNDF) associated with executive function in young adults.

Study 3: Compare effectiveness of LLLT and a short bout of very vigorous exercise (EX) on cognitive function. The objectives are to (a) determine whether combined LLLT and EX enhances neural metabolism in the prefrontal cortex of humans, and to measure the effectiveness of LLLT and EX on reaction time and correct responses using computer programs to implement prefrontal-based tasks such as PVT for attention and DMS for working memory; (b) determine the relationships between fitness level and attention and working memory.

HYPOTHESES

Study 1: Physical activity and cardiorespiratory fitness (VO_2max) levels are expected to be positively associated with cognitive function. Vascular risk factor [i.e., C-reactive protein (CRP)] is expected to be negatively associated with cognitive function. The researchers expected that findings could lead to the development of a theoretical path model showing direct effects of physical activity/fitness level and body mass index on cognitive function variables and vascular risk factors (i.e., CRP), as well as the indirect effects of body mass index on cognitive function variables while considering the vascular risk factor as a potential mediator.

Study 2: Inhibitory control for executive function, or magnitude change among the cognitive biomarker, is expected to significantly improve or increase following an acute bout of very vigorous exercise when compared with a control. Increased magnitude of the cognitive biomarker is expected to be positively related to the improvement of the inhibitor control for executive function. In addition, cardiorespiratory fitness level is expected to be significantly associated with the improvement of inhibitory control for executive function

Study 3: In comparison with the control, LLLT, EX, or the combined treatment is expected to enhance the prefrontal cortex functions such as those related to cognitive functions by measuring reaction time and correct response trial in attention and memory retrieval latency and correct match-to-sample trials in working memory. In comparison with the control, LLLT or EX, the combined treatment is expected to additively enhance the prefrontal cortex functions.

LIMITATIONS AND DELIMITATIONS

Study 1: This study has several strengths and potential limitations. The strengths of our study include the most accurate measure of cardiorespiratory fitness use of a metabolic cart on a cycle ergometer to measure VO_2max. This study benefitted from accurate information on VO_2max, which we were, therefore, able to examine a valid and reliable association of cardiorespiratory fitness with CRP and cognitive function. Although the variable of cognitive tasks was restricted to the variation in demographic variable (i.e., age, gender, race), our study was used for the variable measures after controlling for the demographic characteristics to reduce potential confounding effects. Lastly, as the study used a neuropsychological test battery including crystallized intelligence, executive function, attention, and working memory measures, we were, also, able to identify the relationship of major cognitive domain with health indices and vascular risk in young adults. The limitations of our study include physical activity data based on a self-reported data, which undermines the accurate classification of physical activity. The self-reported measure of physical activity was derived from a seven-day physical activity recall.

Study 2: This study was controlled for cofounding factors such as age, IQ, VO_2max, and gender, which influence the cognitive performance at pre- and post-exercise and benefitted from the controlled factors between the exercise and control conditions. This permitted a valid and reliable examination of cognitive performance and BDNF response to the acute vigorous exercise. A final strength was the sample size, which was considerably larger than several other studies. Therefore, we were able to observe a stronger statistical power on the data of cognitive performance and BDNF response to the exercise. The limitations of this study include the absence of a lower-intensity exercise group comparable with high intensity-exercise. However, the aim of

this study was to identify whether the acute very vigorous exercise still generate a beneficial effect on cognitive performance in healthy, young adults relative to the control group.

Study 3: The strengths of our study included a randomized, blind, placebo-controlled study of LLLT and EX on cognitive performance in healthy young adults. In addition, confounding factors influencing pre- and post- cognitive performance were well-controlled among four groups as indicated by non-significant difference in the confounding variables, which included age, IQ, VO_2max, education year, obesity indices (i.e., waist circumstance, body mass index), blood pressure, and physical activity level with appropriate gender distribution among the groups. We were, therefore, able to examine the valid and reliable data of cognitive performance respond to the LLLT or EX treatment. With regard to the limitation of this study, although every attempt was made to blind participants in active exercise placebo control similar to the 1/12th of the total light energy to be transmitted in the active LLLT placebo control treatment, it is possible that participants perceived the active placebo treatment.

Chapter II: Literature Review

Cognition is defined as the mental process by which external or internal input is transformed, reduced, elaborated, stored, recovered, and used (Neisser, 1967). It involves a variety of functions such as perception, attention, memory, retention and recall, decision-making, reasoning, problem solving, imaging, planning and executive functioning (Brandimonte et al., 2006). It is important to note that cognition changes across the lifespan. Development and refinement of cognitive capacities transform from infancy to young adulthood, at which point and then these capacities begin to decline with aging, perhaps as early as during the third decade of life (Salthouse, Atkinson, & Berish, 2003). The cycle of cognitive development is complex and multifactorial, encompassing biologic, environmental, and social elements or a combination of such factors (Schwartz et al., 2004). Although there are patterns of cognitive abilities across the lifespan, how health risk and behaviors influences cognitive health is understudied among those individuals in their twenties (Craik & Bialystok, 2006) because it is commonly believed that these individuals are at their optimal cognitive and physical health.

Processes of cognitive change are essential to the construction of cognition. The term cognitive ability is defined as the capacity to learn and is a predictor of learning and cognitive performance (Schmidt, 2002). Throughout the lifespan the process of cognitive components such as representation, control, and their interaction are what determine cognitive ability (Cattell, 1987). For example, crystallized and fluid intelligence both contribute to logical thinking, because they draw on declarative knowledge and personal experience to solve problems (Cattell, 1987). Specifically, crystallized intelligence is representative of learned behaviors drawn from memory and knowledge while fluid

intelligences is cognitive control that enables intentional processing and adaptive cognitive performance (Bugg, Shah, Villareal, & Head, 2012). In addition, the representations influence the selection of information from environmental support while control processes determine the construction of representations (Kihlstrom & Park, 2002). Throughout the lifespan, representations including general knowledge and acquisition of language increase markedly during childhood and continue to accumulate at a slower pace throughout adulthood, but remain relatively stable well into old age (Craik & Bialystok, 2006). Although the representations are largely stable, the following occur: a) the maintenance of accumulated knowledge is dependent upon continuing use and b) there must be the functional capacity to performance adequate levels of control (Craik & Bialystok, 2006).

Cognitive control increases in power, speed and complexity from infancy to young adulthood, and decrease thereafter (Cattell, 1987). The frontal lobes of the brain play a major role in cognitive control including planning, decision-making, conflict resolution, and executive functions (Shallice, 1988). During childhood and in early young adults, cognitive control mediates the frontal lobes (Craik & Bialystok, 2006). Although both representation and control have different aspects of processing, they collectively respond to stimuli (Bugg et al., 2012). Different parts of the brain, as well as the interaction between representation and control, are central in explaining significant aspects of cognitive performance (Juan & Muggleton, 2012). Thus, the mechanism of cognitive control can be explained through growth and stability of representational systems and the decline of processes (i.e. biological and cognitive) acting on these systems in later life.

Importantly, the growth, stability and decline of cognition are modulated by various factors including genetics, environment, health, and fitness (Craik & Bialystok,

2006). For instance, cognitive function is linked with active behavior on health (i.e. physical activity) whereas cognitive dysfunction is associated with sedentary behavior on health [i.e. obesity and physical inactivity; (Liang, Matheson, Kaye, & Boutelle, 2014)]. Further, our health behavior is related to cognition change, indicating that further investigation will be needed to address the potential mechanism specific to physical activity-induced change in cognition.

MEASURMENT OF COGNITIVE FUNCTIONING TASKS

There are approximately 128 cognitive functioning tasks used in a variety of academic disciplines to measure cognitive functioning (Chang, Labban, Gapin, & Etnier, 2012) because cognitive functioning variables are strongly related to cognitive abilities (Salthouse, 2005). In this literature review, cognitive functioning following literature (Liang et al., 2014; Salthouse, 2005) is organized into four different areas and their tasks (Table 2.1). The four different areas cognitive functioning include general intellectual functioning, executive functioning, working memory, and attention. General intellectual functioning encompass a variety of different content areas, such as verbal, quantitative, spatial ability, processing speed and memory (Liang et al., 2014); all of which comprise both crystallized and fluid intelligence (Kaufman, 1990).

Executive Function

Executive functioning is cognitive control process that recruits neural activation in the prefrontal cortex and is known as having a set of processes and skills that involve mental control and self-regulation. It encompasses functions such as planning, decision-making, problem-solving, inhibition, abstraction, mental flexibility, set-shifting and delayed gratification (Marie T. Banich, 2009; Fabes, Eisenberg, Karbon, Troyer, & Switzer, 1994; Perry & Hodges, 1999; Royall et al., 2002). For example, the Stroop test

has been characterized as a standard measure of executive functioning and has been in use for over 70 years (Stroop, 1935). It is often used to examine the neural mechanisms involved in attentional and inhibitory control and shifting, given that the assessment contains both congruent and incongruent trials. Magnetic resonance imaging (MRI) studies of the Stroop effect have shown that prefrontal cortical regions play a role in this task, possibly by regulating attentional and inhibitory processes (Banich et al., 2000; Milham, Banich, & Barad, 2003). In addition, the Trail Making Test (TMT) that has been widely used in neuropsychological assessments and that is an indicator of speed in cognitive processing and executive functioning (Strauss, Sherman, & Spreen, 2006).

Working Memory

The control processes of acquisition, encoding, rehearsal, storage and retrieval of information, which are important for remembering (Unsworth, 2010) and thus facilitate working memory and the movement of information from short to long term repositories. Individuals who are better able to control the process can demonstrate enhanced performance on a number of working memory tasks. Specifically, the Delayed-Match-to-Sample (DMS) task (Nieder & Miller, 2004) which is mediated by a front-parietal network in brain, measures short-term memory component or the ability to hold information and recall call it later. It is known that prefrontal cortical neurons are specifically active during the delay portion of DMS task (Mueller & Piper, 2014).

Attention

The construct of attention encompasses identification, selection and retention of specified aspects of the environment containing competing stimuli. This cognitive process includes the ability to sustain focus and inhibit the detraction from other stimuli (Liang et al., 2014). Across adulthood, attention can be measured using the Psychomotor Vigilance Task (PVT; Dinges & Powell, 1985), which requires an individual to sustain

focus and amidst multiple stimuli. These attentional processes are mediated by the frontal cortical regions (Marklund et al., 2007) and PVT has been shown to be a reliable indicator of frontal function (Drummond et al., 2005).

PHYSICAL ACTIVITY AND COGNITION

Physical activity, the act of using skeletal muscles for gross motor movements that expends energy, has many health benefits for young adults (Hillman, Erickson, & Kramer, 2008). According to the 2008 Physical Activity Guidelines for Americans (U.S. Dept. of Health and Human Services. 2008a), there are many benefits to regular engagement in physical activity, such as: a) improved a quality of life, b) prevention of heart disease and stroke, c) reduced high blood pressure and undesirable blood lipid patterns, d) protection from certain cancers, including colon and breast cancer, and possibly lung and endometrial (uterine lining) cancer, e) prevention of type 2 diabetes and metabolic syndrome, f) reduced bone loss, g) reduced risk of falling, h) improved cognitive function, i) reduced risk of depression and anxiety improve heart-lung and muscle fitness, and j) improved sleep.

Physical activity is a non-pharmacologic therapy that can improve cognitive performance or reverse cognitive decline. A growing body of literature has demonstrated that physical activity improves cognitive performance (Castelli et al., 2014; Hillman, Erickson, & Kramer, 2008). Cognitive indices such as inhibitory control task (Buck, Hillman, & Castelli, 2008) and executive functioning (Castelli, Hillman, Hirsch, Hirsch, & Drollette, 2011), cognitive control of attention (Hillman et al., 2009), working memory (Kamijo et al., 2011), inhibition (Pontifex, Hillman, Fernhall, Thompson, & Valentini, 2009), planning (Chang & Etnier, 2009), switching (Pesce, 2012), and executive

attentional control (Pesce, Cereatti, Forte, Crova, & Casella, 2011) have been widely measured to determine change in cognition through physical activity intervention studies.

In general, the effects of physical activity interventions are difficult to quantify because many studies fail to adequately report the exercise type, exercise intensity, exercise duration, participant fitness level, type of cognitive task including a timing of cognitive function administration, and/or type of the cognitive function (Chang & Etnier, 2009). A recent meta-analysis review examined 79 studies in an attempt to identify potential moderators that influence the relationship between acute exercise and executive function (Lambourne & Tomporowski, 2010). Included in the list of moderators were: a) timing of the cognitive test administration (i.e. largest positive effects observed following 11 - 20 min of delay compared to following 0-10 min of delay and following 20 min of delay), and b) cognitive task types (e.g., effects for tasks including measures of crystallized intelligence and executive function such as verbal fluency, incompatible reaction time, decision making, and Stroop interference tasks). Other indicated mediators were: a) exercise intensity (i.e., following a delay of exercise, more intense exercise resulted in the biggest effects while very light intensity exercise no longer had positive effects), b) exercise duration (i.e., exercise sessions longer than 20 min resulted in positive significant effects while exercise for only 11–20 min resulted in a negative effect on executive function), and c) fitness level (i.e., higher fitness level is relevant to positive effects on executive function while low fitness level is related to negative effect during exercise or following). Given these considerations, it is recommended that these variables be measured and accounted for within future research designs.

Furthermore, these findings suggest that future studies should employ experimental designs, including cognitive tests administered 11–20 min after exercise, and an acute exercise protocol consisted of at least 20 min of intense exercise. It should

be recognized that exercise lasting longer than 20 min might be detrimental to executive function due to physical fatigue and dehydration or cognitive fatigue (Yerkes & Dodson, 1908; Tomporowski & Ellis, 1985) . Prospective research is needed to better understand mechanisms underlying cognitive benefits impacted by the intensity and dose of physical activity because physiological and biological indices may be potential mediators.

BIOLOGICAL FACTORS WITH PHYSICAL ACTIVITY AND COGNITION

An acute bout of exercise optimizes the level of arousal and increases neurotransmitters such as epinephrine and dopamine by increasing cerebral blood flow and cerebrovascular function (Cahill & Alkire, 2003). Brain derived neurotropic factor (BDNF) acutely modulating presynaptic neurotransmitter release (Jovanovic, Czernik, Fienberg, Greengard, & Sihra, 2000) is proposed to play an important role in facilitating cognitive processing. Further, long-term, sustained exercise stimulates neuroplasticity by facilitating structural changes in the brain (Erickson et al., 2011) and brain function (Voss et al., 2010) associated with the improvement of cognitive function. Exercise can improve vascular health by increasing cerebral blood flow, improving vascular functionality, and decreasing proinflammatory factors (Ito, Kanno, Ibaraki, Hatazawa, & Miura, 2003). Given this, the relationship between the exercise-induced increases in BDNF and cognitive function may be mediated at least in part by vascular health, yet this phenomenon has yet to be invested in young adults.

BDNF and Cognition

BNDF a member of the neurotrophic factors family, is an important molecular mediator of structural and functional plasticity in the brain (Rosenfeld et al., 1995). BDNF is broadly expressed in the developing and adult mammalian brain (Yu & Chen, 2011). By activating its major tropomyosin receptor kinase B, BDNF plays an important

role in various aspects of brain plasticity, including proliferation, differentiation, and survival of neurons, neurogenesis, and synaptic plasticity, as found in the animal literature (Cotman & Engesser-Cesar, 2002). BDNF is a crucial mediator of the benefits of exercise for brain health. Animal and human studies have identified BDNF as an important mediator of the beneficial effect of exercise on brain health (Ferris et al., 2007; S. Vaynman, Ying, & Gomez-Pinilla, 2003).

BDNF and Physical Activity

In animal studies, levels of BDNF mRNA and protein were increased in the hippocampus and other brain regions after voluntary chronic exercise (Cotman & Engesser-Cesar, 2002) whereas the beneficial effect of exercise on cognitive function was disappeared when BDNF signaling was blocked in the hippocampus (Ito et al., 2003). Similar effects were observed in human studies showing that the magnitude of increase in BDNF was varied due to different exercise intensity or duration. Specifically, Rojas Rojas Vega et al. (2006) reported that there was no significant change of serum BDNF levels during 10 min of moderate exercise in the warm-up period in healthy male athletes, but there was significant change of serum BDNF concentrations following an exercise test to exhaustion. To further support the finding, Ferris et al. (2007) reported that 30 min of cycling at the intensity of 10% above the ventilatory threshold resulted in a significant increase in serum BDNF concentrations from baseline, whereas 30 min of cycling at 20% below ventilatory threshold had no significant change in serum BDNF concentrations following the exercise. The increased plasma BDNF is mostly released from the brain, which is a major source (i.e., 70-80% output from brain) in response to exercise (Rasmussen et al., 2009). This evidence suggests that sufficient exercise intensity and/or duration contribute to the increased serum BDNF concentration, which is a crucial factor for cognitive processing.

Studies have shown the impact of acute exercise on cognitive function and BDNF (Ferris et al., 2007). Following 30 min of intense cycling exercise, scores on the Stroop Color and Word scores significantly increased relative to baseline. However, Ferris et al. (2007)'s study showed there was no significant relationship between BDNF change and the Stroop change, which was possibly due to a small sample size (n=15). These results imply that the association between BDNF and cognitive function in response to acute exercise may involve other factors such as fitness level and vascular risk factors, particularly when considering that previous studies showed that fitness level has an (Billinger, Coughenour, Mackay-Lyons, & Ivey, 2012). Additionally, BDNF is regulated by nitric oxide (NO) and plays a role in mediating endothelial dilation and influence cognition because both factors are involved in oxygen uptake (Davenport et al., 2012).

Vascular Risk Factors and Cognition

Advanced age is associated with cognitive dysfunction and vascular disease. Cardiovascular risk factors become more prominent with age and exacerbate age-related cognitive declines (Meyer, Rauch, Rauch, & Haque, 2000). In addition, increased vascular risk at middle age predicts brain deterioration and exacerbates cognitive declines in late adulthood (Beason-Held, Moghekar, Zonderman, Kraut, & Resnick, 2007). Given that cardiovascular risk factors often manifest themselves earlier in life, young adults who choose a less healthy lifestyle may be vulnerable to development of hyperglycemia and hypertension and cognitive dysfunction in later life. Vascular risk factors related to cognitive function are assessed through multiple indices including arterial stiffness, cerebrovascular reserve (i.e., cerebral vasomotor reactivity), and proinflammatory markers (i.e., C-reactive protein).

Arterial Stiffness Arterial stiffness describes the decreased capability of an artery to expand and contract in response to pressure changes. Vessel stiffness includes

compliance, that is a measure of volume change in response to a change in blood pressures (Davenport et al., 2012). As vessel stiffen the volume change and thus compliance is decreased for any given pressure change (Cecelja & Chowienczyk, 2012). As indirectly indicated by pulse wave velocity (PWV), when the speed of a pulse wave traveling between two selected sites of measurement decreases, arterial stiffness increases. The measurement of PWV between the carotid and femoral sites reflects arterial stiffness along the aorta, which is the primary site of age-associated arterial stiffening. This approach is considered to be the gold standard in the non-invasive assessment of large artery stiffness (Boutouyrie, Revera, & Parati, 2009). While arterial stiffness is an established determinant of cardiovascular health, arterial stiffness is an emergent predictor of executive function, cognitive decline, and even dementia (Waldstein et al., 2008). Arterial stiffness causes cognitive deficits possibly because augmented pressure pulses, caused by aortic stiffness, penetrate and damage small cerebral vessels which are not protected against pulsatile blood flow (Duron & Hanon, 2008). Physical activity engagement, particularly aerobic exercise, is associated with a positive change in arterial stiffness. For example, endurance-trained young adults have lower levels of arterial stiffness than less active individuals (Edwards & Lang, 2005). In addition, long-term exercise reduces arterial stiffness in young adults. As reported by Cameron and Dart (1994), as little as four weeks of aerobic training (1.5hr/session, 3 sessions/week) had significant improvements in systemic arterial compliance in 13 sedentary adults. Consistent with these findings, Kakiyama, Matsuda, and Koseki (1998) showed a significant reduction of arterial stiffness after 8 weeks of aerobic training (60 min/ session, 3-4 session per week at 70% VO_2 man) in 10 sedentary young males (19-24 years). Even a short aerobic training (2 hours/day at 65 % VO_2 max for 6 days) was associated with significant reductions in central and peripheral PWVs (Currie, Thomas,

& Goodman, 2009). Overall, aerobic exercise training is associated with the deceleration of PWV and acute elevation in arterial compliance related to reduction of arterial stiffness. One possible explanation of this relationship is that aerobic exercise results in increased blood flow that produces NO in response to endothelial sheer stress and, thus, induces vasodilatation in smooth, vascular muscle (Davenport et al., 2012).

Acute exercise has also been shown to reduce arterial stiffness. A bout of 30-min cycling at 65% of maximal oxygen consumption (VO_2max) has been shown to cause decreases in both central and peripheral arterial stiffness at 30 minutes post-exercise in healthy young adults (Kingwell, Berry, Cameron, Jennings, & Dart, 1997). Additionally, Naka et al. (2003) reported a 23% decrease in upper and lower limb arterial stiffness (measured by PWV) in normal, sedentary adults (<45 years old) that lasted an hour before returning to pre-exercise levels.

Following acute exercise, arterial stiffness is reduced due to a decrease in vascular muscle tone through changes in neural (sympathetic activity) and vascular (peripheral vasodilator substances) factors (Sugawara et al., 2004). However, these changes are only transient, and alterations in arterial wall properties and improved endothelial function are most likely the result of long-term chronic exercise rather than an acute bout of exercise. Additionally, Zhu et al. (2013a) reported that 3 months of aerobic exercise training improved brain perfusion in sedentary elderly women, which may be related to reduction of arterial stiffness due to a link between endothelial function and cerebrovascular function (Hoth et al., 2007).

Thus, aerobic exercise-induced improvement of endothelial and cerebrovascular function may contribute to the improvement of cognitive function. Although many of the key findings have been discovered in older adults populations, the study of young adults

is important because it is believe that this portion of the lifespan is important for developing a cognitive reserve.

Cerebrovascular Reserve Cerebral blood flow (CBF) declines with age, as does humans' ability to repair cells. Cerebrovascular reserve is the ability of cerebral blood vessels to respond to increased metabolic demand and chemical, mechanical, or neural stimuli (Davenport et al., 2012). Cerebral blood flow is sensitive to changes in partial pressure of arterial carbon dioxide (PaCO2) such that hypercapnia induces cerebral vasodilation and increases CBF and hypocapnia induces cerebral vasoconstriction and decreases CBF (Ito et al., 2003). The responses of CBF to changes in PaCO2, termed cerebral vasomotor reactivity (CVMR), have been measured extensively in both clinical and research settings to assess cerebrovascular function (Willie et al., 2011).

CVMR is determined by both the local effects of PaCO2 on the cerebral vasculature as well as the systemic effects on arterial blood pressure (Ringelstein, Sievers, Ecker, Schneider, & Otis, 1988). Impaired CVMR has been linked with advancing age (Rogers, Meyer, Mortel, Mahurin, & Thornby, 1985), depression (Tiemeier, Bakker, Hofman, Koudstaal, & Breteler, 2002), cognitive decline (Vicenzini et al., 2007a), pathogenesis of white matter lesions (i.e., Sierra), and stroke risk (Dahle, Jacobs, & Raz, 2009). A longitudinal study reported that lower cerebral vasomotor reactivity is associated with an increased risk of death regardless of incident stroke (Portegies, de Bruijn, Hofman, Koudstaal, & Ikram, 2014). This finding suggests that a lower cerebral vasomotor reactivity reflects a generally impaired vascular system. Reduced cerebrovascular reserve can lead to hypoxia in vulnerable areas of the brain, negatively influencing brain health. For example, those presenting with Alzheimer disease (Lee & Silva, 2009) and vascular dementia (Vicenzini et al., 2007a) show lower cerebral flow velocities and CVMR compared with healthy aged-matched individuals.

Moreover, decreased CVMR is associated with cognitive impairment (Dahle et al., 2009) and dysfunction of cerebral vascular auto-regulation contributes to the pathogenesis of white matter lesions in advancing age (De Groot et al., 2002). Cerebral white matter lesions are an early marker of cerebrovascular disease and are considered a risk factor for the development of cognitive impairment (De Groot et al., 2002). Lastly, depressive symptoms are linked with reduced CBF velocities and lower CVMR (Tiemeier et al., 2002).

Cerebrovascular reserve and physical activity It has been demonstrated that long-term aerobic exercise enhances cerebrovascular system. Ivey, Ryan, Hafer-Macko, and Macko (2011) reported that CVMR was improved among stroke survivors after 6-months of aerobic training (40 min of three session/week at 60% to 70% heart rate). A 6-month aerobic exercise training enhanced CVMR, at least in part, due to the aerobic capacity change (V02), which was positively correlated with CVMR change. Further, Vicente-Campos et al. (2012) reported that CVMR was increased among participants engaged in a 7-month aerobic training (50 min/session, 3-4 sessions/week, at 70% maximum heart rate) compared to non-exercising participants, which demonstrated a higher blood flow velocity in the middle cerebral artery.

From a different perspective, a single acute of exercise can positively contribute to the health of the cerebrovascular system. As evidence of this effect, one study with emphasis on the effects of post-exercise performance reported that a single bout of aerobic exercise (i.e., 25-min cycling exercise at 70% maximal heart rate) resulted in increased resting cerebral perfusion in the left somatosensory region at 40-min after exercise compared to pre-exercise among young healthy adults (MacIntosh et al., 2014). This finding implicates that acute exercise appear to have a robust cerebrovascular effect that varied in time and brain region.

C-Reactive protein. C-reactive protein (CRP) as an acute phase reaction is a marker of chronic systemic inflammation and a risk predictor of the cardiovascular events due to coronary heart disease, which may even be present in healthy individuals (Pepys & Hirschfield, 2003). It was reported that CRP and pro-inflammatory cytokines levels (i.e., interleukin-6) correlate with metabolic risks including diabetes, insulin resistance, obesity, dyslipidemia, level of triglycerides, high-density lipoproteins and marker of endothelial dysfunction (Bucova, Bernadic, & Buckingham, 2008). In addition, it has been suggested that CRP is a biomarker for cognitive impairment (Noble et al., 2010).

A one year follow-up study showed that higher CRP levels were associated with visuospatial impairment and memory impairment, but not with executive function and language among elderly individuals (Hoth et al., 2008). In middle aged adults, CRP level was not related to cognitive functioning, memory, language, attention-executive-psychomotor functioning or visual-spatial ability (Eagan et al., 2012), which was possibly due to mean CRP levels (2.72 mg/L) falling below the high-risk category (average = 1.0 to 3.0 mg/L) for cardiovascular disease events according to the American Heart Association. Interestingly, CRP levels were significantly associated with cognitive dysfunction among school-aged children with obstructive sleep apnea (Gozal, Crabtree, Sans Capdevila, Witcher, & Kheirandish-Gozal, 2007). These findings illustrate that even young adults who have higher CRP levels may be associated with lower executive function. Potential mechanisms through which higher CRP level could affect cognition are that systemic inflammation may lead to impaired endothelial function and cerebral blood flow (Lavi, Gaitini, Milloul, & Jacob, 2006).

CRP and physical activity. The acute response of CRP to physical activity has been reported extensively. Studies regarding the impact of acute exercise on CRP level showed inconsistent results that may be mediated by the intensity and type of exercise as

well as the type of cognitive task. For instance, CRP was significantly increased in untrained subjects, 24 hours after performing 60 minutes of cycling at only 60% of maximal oxygen uptake (J. A. Smith, Telford, Baker, Hapel, & Weidemann, 1985). Similarly, Meyer et al. (2000) reported a significant elevation in CRP at post-24 hours after 12 trained males performed an anaerobic cycle ergometer test. In contrast to these findings, there was no significant elevations observed for CRP following eccentric exercise such as 70 eccentric quadriceps contractions (Sorichter et al., 1995) and 45 minutes of downhill running respectively (Malm et al., 2004). Therefore, it was proposed that intense acute bouts of exercise are more commonly associated with muscle damage and, thus, CRP level was increased in response to the acute exercise.

In contrast, a long-term exercise study showed CRP level significantly decreased over time. Pitsavos et al. (2003) reported that CRP levels were 33% lower in the subjects who partook in high-physical activity levels compared with the sedentary group. Compared with sedentary individuals, the baseline level of CRP was markedly lower in the marathon athletes (Tomaszewski et al., 2003). Further, Fallon, Sivyer, Sivyer, and Dare (1999) reported significantly decreased levels of CRP following 9 months of soccer training in elite women. Because CRP is considered a risk factor for inflammation, any known reduction has corresponding benefits. However, there is a paucity of research on CRP and acute bouts of exercise among young adults.

Evidence Linking Physical Activity, Cognition, and Vascular Health

Although primarily examined among older adults, there appears to be a link between pathology and cognitive behavioral responses. The link between aerobic exercise and cognitive performance is at least in part by processes that involve the cerebral circulation (Davenport et al., 2012). Aerobic exercise causes increased blood flow (Hiura et al., 2014) that mechanically stimulates sheer stress leading to the increase

in NO-dependent vasodilation and an increase in basal CBF (Davenport et al., 2012). Additionally, aerobic exercise decrease oxidative stress mediated inhibition of NO production by increasing antioxidants (Pialoux et al., 2009) and inflammation and proinflammatory cytokines (Gleeson et al., 2011) and, thus, improved endothelial function. The improved endothelial function is associated with the increase in CBF (Zhu et al., 2013c), which in turn improves the function of cerebrovascular reserve, contributing to neurogenesis. BDNF increases neurogenesis, which is associated with improved cognitive function. Therefore, exercise-induced vascular health is likely to be associated with the improvement of cognitive function.

Interventions Beyond Physical Activity: The Emergence of Low Level Laser Therapy

Low Level Laser Therapy (LLLT) involves using a red to near-infrared light energy to facilitate mitochondrial response in the prefrontal cortex. Recently, the LLLT has gained attention, as a new scientific approach with therapeutic applications and has been developed to address a variety of medical conditions. Specifically, LLLT has been used in the domain of pain and wound healing. In recent years studies support the notion that LLLT has potential benefits in retinal disease, stroke, neurodegeneration, neuromuscular disorders, and memory and mood disorders (Rojas, Bruchey, & Gonzalez-Lima, 2012). The LLLT can be defined as the use of directional low-power and high-fluency monochromatic or quasimonochromatic light from lasers or light-emitting diodes in the red to near-infrared wavelengths (λ = 600–1100 nm) to modulate a biological function or induce a therapeutic effect in a nondestructive and nonthermal manner (Gonzalez-Lima, Barksdale, & Rojas, 2014). While laser therapy with high energy levels has a role in heating and tissue destruction through dissection, ablation, coagulation, and

vaporization, laser therapy with low energy levels such as LLLT has negligible effects on heating and tissue destruction, but is still high enough to modulate cell functions (Rojas & Gonzalez-Lima, 2011).

LLLT can increase mitochondrial cytochrome oxidase activity and thus, results in increasing oxygen consumption and mitochondrial membrane potential, activating the mitochondrial permeability transition pore in the rat brain (Rojas, Lee, John, & Gonzalez-Lima, 2008). Correspondingly, LLLT can improve the aerobic capacity of other tissue such as skeletal muscle (Hayworth et al., 2010). Evidence suggests that the oxidative metabolism of tissue exposed to LLLT can be enhanced. The LLLT also has a beneficial effect in the brain because its light is able to penetrate the cranium and reach the brain (Rojas et al., 2012). As the light travels into the brain, the LLLT also appear to have in vivo transcranial neurochemical effects that involve whole-brain metabolic-and antioxidant beneficial effects, as measured by increases in cytochrome oxidase and superoxide dismutase activities (Rojas et al., 2012). The beneficial effects induce increases in cerebral blood flow in humans (Rojas & Gonzalez-Lima, 2011). Consequently, LLLT are expected to enhance normal brain function and the treatment of cognitive impairment such as memory loss and mood disorders. The cognitive impairment and neurodegeneration associated with dementia have been shown to have regional brain metabolic deficits in early stages of the neurodegenerative process. For example, early decreases in brain metabolic activity can be detected in patients at risk for developing Alzheimer's disease, especially reductions in cytochrome oxidase activity (Mosconi et al., 2011). LLLT enhance the metabolic capacity in those regions showing functional deficits and thus, results in increasing the functional connectivity of the networks in the brain (Rojas & Gonzalez-Lima, 2011).

LLLT and Cognition. Previous studies have shown the benefits of LLLT on cognitive function in both humans and non-human animals. In animal studies, Khuman et al. (2012) found that LLLT reduced cognitive deficits by improving spatial learning and memory as assessed by a Morris water maze paradigm. In addition, LLLT can improve working memory in middle-aged mice tested in a spatial navigation task (Michalikova, Ennaceur, van Rensburg, & Chazot, 2008). This report demonstrates that LLLT facilitates cytochrome oxidase activity, cortical oxygenation and cerebral blood flow and thereby improves memory retention in animal model (Rojas et al., 2012). In human studies, a single LLLT treatment to the forehead resulted in a significant beneficial effect in patients with major depression and anxiety (Schiffer et al., 2009). The daily use of LLLT to the head also improved attention, executive function, and memory in two patients with chronic traumatic brain injury (Naeser, Saltmarche, Krengel, Hamblin, & Knight, 2011). Further, LLLT improved cognitive function by reducing reaction time on the PVT and DMS (Barrett & Gonzalez-Lima, 2013).

Ultimately, the LLLT treatment as a non-invasive, non-pharmacologic, therapeutic intervention is crucial for both healthy humans and for those in need of rehabilitation efforts under conditions including neuromuscular function and neurobiological disorders. Furthermore, aerobic exercise has similar biological beneficial effects as those of LLLT treatment(s). It has been demonstrated that a sufficient amount and intensity of aerobic exercise increases whole-body metabolic activity, improves antioxidant systems, enhances mitochondria function, as well as increases cerebral blood flow and cerebrovascular function (Davenport et al., 2012). Future studies should examine whether both treatments of aerobic exercise and LLLT has additive benefits of cognitive function in human subjects.

Table 2.1. ***Categories of Cognitive Functioning***

Domain of cognitive functioning	Cognitive functioning Task
General intellectual functioning	• Wechsler Adult Intelligence Scale • Mini–mental state examination • Kaufman Brief Intelligence Test
Executive functioning	• Logical reasoning (Raven's progressive matrix) • Decision-making (Iowa Gambling Task) • Cognitive Flexibility (Trail Making Test Part B) • Response inhibition (Stroop Task) • Impulsivity and inhibition (Stop signal task) • Inhibitory control (Go-NoGo) • Digit Symbol or Symbol Digit • Wisconsin Card Sorting Test • Letter Fluency, Category Fluency, and Alternating Fluency tasks
Working memory	• Free- recall memory task • Memory of Digit span (Wechsler Intelligence Scale for Children) • Working Memory Index (Wide Range Assessment of Memory and Learning) • Visual short-term memory (Delayed-Match-to-Sample) • Figural learning test • Sequential memory
Attention	• Woodchuck–Johnson test of concentration • Psychomotor vigilance task • Attention and visual scanning (d2 attention test) • Concentration (Frankfurter Test) • Attention and working memory (digit span) • Attention (Trail Making Test Part A) • Attention/Concentration Index (Wide Range Assessment of Memory and Learning) • Attention processing (Imbedded word task)

Chapter III: Study 1

ASSOCIATION OF CARDIORESPIRATORY FITNESS AND VASCULAR RISK ON COGNITIVE FUNCTION IN YOUNG ADULTS

ABSTRACT

PURPOSE: To examine the independent association between health indices [i.e., cardiorespiratory fitness, physical activity, body mass index (BMI)], C-reactive protein (CRP) and cognitive function in young adults. We proposed that a theoretical regression model showing direct effects of the health indices on cognitive function and CRP as well as the indirect effects of the health indices on cognitive function while considering CRP as a potential mediator.

METHODS: Young adults (N=93; 57.0% female, aged 23.01± 3.67 years) volunteered in this study. Cardiorespiratory fitness (VO_2 max) was measured through metabolic cart on cycle ergometer and physical activity was assessed using a 7-day physical activity recall based on self-reported measures. Objective measures of height (cm) and weight (kg) were obtained for BMI calculation. Cognitive function was assessed using neuropsychological test battery [i.e., Kaufman Brief Intelligence Test, KBIT; Trail Making Test, (TMT); Stroop test; Psychomotor Vigilance Task, (PVT); and Delayed-Match-to-Sample memory task, (DMS)]. Serum high sensitivity CRP (mg/L) was determined using a quantitative enzyme immunoassay assay.

RESULTS: A one-way ANOVA analysis revealed the effect of CRP risk was significant on Stroop interference in Stroop test ($F_{2, 77} = 2.94$, $P = .049$) and memory retrieval latency in DMS ($F_{2, 77} = 3.32$, $P = .045$). Post hoc analyses using the LSD post hoc criterion for significance indicated that the average scores in the Stroop interference was significantly lower in the high CRP risk (M = 3.61, SD = 6.95) than in the low CRP

risk (M = 9.41, SD = 8.21). In addition, average time in memory retrieval latency (msec) in DMS was significantly slower in the high CRP risk (M = 2265.96, SD = 610.89) than in the low CRP risk (M = 1727.31, SD = 601.42). These results suggest that CRP level in the high-risk condition causes deleterious effect on cognitive function especially such as inhibitory control and working memory. In addition, CRP was positively associated with BMI (β = 0.46, P = 0.001), but negatively related to cardiorespiratory fitness (β = -0.57, P = 0.003) after adjustment for age, gender, and race. CRP had the greatest significant effects on reaction time in DMS (β = 0.36, P = 0.012) and scores in Stroop interference (β = -0.27, P = 0.020). After the adjustment for age, gender, and race, the greatest positive relationship on DMS and Stroop interference was found in cardiorespiratory fitness (β = -0.37, P = 0.04) and physical activity (β = 0.26, P = 0.05), respectively. Although no significant negative direct effect was found for BMI on working memory (β = 0.06, P = 0.66), when CRP was considered as a potential mediator of the relationship between BMI and working memory, the indirect effect of BMI on working memory may be dependent on CRP as indicated by increased β weights (β = 0.327, P = 0.128).

CONCLUSION: Our findings confirmed that CRP level in the high-risk condition causes deleterious effect on cognitive function especially for inhibitory control and working memory. However, we observed the beneficial effect of physical exercise-induced improvements in cardiorespiratory fitness on vascular risk and cognitive functions particularly in working memory and inhibitory control. Improved cardiorespiratory fitness may reduce or suppress vascular risk with potential positive effects on cognitive health.

Keywords: cardiorespiratory fitness; C-reactive protein; cognitive function

INTRODUCTION

A growing body of literature shows evidence indicating that higher levels of physical activity and cardiorespiratory fitness are associated with positive effects on cognitive and brain health (Castelli et al., 2014). Although the importance of physical activity across the lifespan is increasingly highlighted, inadequate physical activity, or not meeting the adult recommendations of 150 minutes of moderate to vigorous physical activity (MVPA) per week (USDHHS, 2008a), is common among young adults. Meeting this recommendation will help to maintain cardiovascular health (Pate et al., 1995), yet a recent report showed that almost two-third (74%) of U.S. adults don't meet this guideline (USDHHS, 2008c) Insufficient physical activity is also a contributor to overweight and obesity that is related to the development of metabolic disease. Consequently, obesity has risen dramatically in U.S. adults; more than two-thirds of individuals over the age of 20 are classified as overweight or obese in the U.S. (Ogden et al., 2014)

Physical inactivity, pooper cardiorespiratory fitness, and obesity are strong independent risk factors associated with cardiovascular disease. CRP, known as a biomarker of systemic inflammation and an independent predictor of future cardiovascular events is emerging as a biomarker for cognitive dysfunction among older adults (Ge et al., 2013; Zhu et al., 2013c). Higher levels of CRP are correlated with poorer performance on tasks involving executive function (Wersching et al., 2010). Cognitive assessments of executive function are focused on two primary measures of reaction time and accuracy (Komulainen et al., 2007; Noble et al., 2010). Cross-sectional studies (Jae et al., 2009; LaMonte et al., 2002) and a longitudinal study (Church et al., 2002) found an inverse relationship between higher cardiorespiratory fitness and the serum concentration of CRP, which may involve processes of cognitive function. Not

only has CRP been implicated in cognitive dysfunction, but it has even been related to structural brain damage (Wersching et al., 2010).

Although the relationship between cardiorespiratory fitness and cognitive function have been observed in childhood (Hillman, Castelli, & Buck, 2005), middle adulthood (Zhu et al., 2014), and late adulthood (Hayes, Forman, & Verfaellie, 2014), the association of cardiorespiratory fitness and CRP with cognitive function in young adults is less clear. Young adult CRP-cognitive function data is limited to small samples, as risk is not as prevalent in this age group (Castelli et al., 2013). CRP–cognition relationship was not observed through measure of cardiorespiratory fitness, physical activity and BMI in young adults. As both CRP and the cardiorespiratory fitness have been reciprocally associated with cognitive function the complex interactions and pathways among these variables have not yet been explored but may be crucial for understanding cognition.

Given this paucity of research and equivocal relationships, this current investigation sought to examine the independent associations between health indices of cardiorespiratory fitness, physical activity, BMI, CRP and cognitive function in young adults. We proposed that a theoretical path regression model including direct effects of the health indices on cognitive function and CRP as well as the indirect effects of the health indices on cognitive function while considering CRP as a potential mediator.

INSTRUMENTS AND METHODS

Selection of Participants

The study procedure was approved by The University of Texas at Austin Institutional Review Board. Healthy, English-speaking adults of either sex, of ages ranging from 18 to 30 years, and of any ethnic background were considered for the study.

Potential subjects who were recruited by word-of-mouth or email in a university environment contacted the lab and underwent a short screen over the phone to determine if they wanted to participate and if they met inclusion/exclusion criteria. The exclusion criteria for subject participation were as follows: (a) presence of cardiovascular disease or cerebrovascular disease, (b) diagnosis of psychotic disorder, (c) history of violent behavior, (d) history of neurological condition, (e) current pregnancy, and/or (f) prior institutionalization or imprisonment; however, no participant was excluded on these bases. A total of 93 participants were recruited over two years.

Assay of High-Sensitivity CRP

Serum high sensitivity CRP was determined using a quantitative enzyme immunoassay assay (BioCheck, Inc., USA) that includes a mouse monoclonal-CRP antibody coated onto 96-well polystyrene microplates. According to the manufacturer's assay procedure (Schultz & Arnold, 1990), all standards, control, and samples were assayed in duplicate. Optical density of each wall was determined using a microplate reader (BioTek Inc., VT, USA) set to 450nm. CRP concentrations were calculated using standard curves.

Anthropometric Measurements

Height and weight were measured using established standards (Lohman, Roche, & Martorell, 1988). Participants' height and weight were recorded to the nearest 0.1 cm and 0.1 kg, respectively. BMI was calculated in accordance with standard anthropometric techniques.

Measurement of Cardiorespiratory Fitness

For the first step, participants were appropriately positioned on the cycle ergometer (Velotron Dynafit Pro, Seattle WA). Participants then completed four incremental, two-minute stages of submaximal cycling for determination of the VO_2

consumption and work rate relationship. This was followed by a bicycle ergometer test to determine maximal oxygen consumption (VO_2 max). VO_2 max is the greatest rate the body uses oxygen for sustained energy production, which correlates highly to endurance performance [American College of Sports Medicine (ACSM, 2013)]. This test required subjects to breathe into a mouthpiece for the monitoring of oxygen consumption while cycling continuously at increasing exercise intensities. The test was ended upon volitional fatigue of the subject or when cadence falls below 60 rpm. The test lasted approximately 8 to 12 minutes.

Assessment of Physical Activity Level

The International Physical Activity Questionnaire (IPAQ) was used to assess a 7-day physical activity recall and is based on self-reported measures of physical activity. The IPAQ instruments have acceptable measurement characteristics (Craig et al., 2003). The frequency and duration in the previous week of time spent walking briskly and in moderate and vigorous intensity leisure-time physical activities were reported. A physical activity score was calculated as the sum of the products of total time in each of the three categories and a metabolic equivalent (MET) value assigned to each category as reported previously (Rosenberg, Bull, Marshall, Sallis, & Bauman, 2008). This included duration × frequency per week × MET intensity: (walking min × 3.0 metabolic equivalent values) + (moderate leisure-time physical activity × 4.0 metabolic equivalent values) + (vigorous leisure-time physical activity × 7.5 metabolic equivalent values). A weighted estimate of total physical activity was presented as MET·min·wk-1.

Measurement of Cognitive Tasks

Five cognitive measurements for this study included the Kaufman Brief Intelligence Test (KBIT), Stroop test, Trail Making test (TMT), Psychomotor vigilance task (PVT) and Delayed match sample test (DMS), which include various domains of

cognitive function such as crystallized intelligence, executive function, attention, and working memory Except for the KBIT, each of the cognitive function tests consisted of very short (1-minute) practice trials (i.e., this data will not be recorded) in order to familiarize the participants with the task. Following this, individuals then participated in one actual trial.

KBIT. This assessment is a brief, individually administered measure of verbal and nonverbal intelligence for individuals from 4 to 90 years of age (Kaufman, 1990). The KBIT contains verbal and nonverbal subscales to estimate intelligence quotient (IQ) composite. The verbal scale is composed of two combined subtests that assess receptive vocabulary and general information as well as comprehension, reasoning, and vocabulary knowledge. The nonverbal scale uses a Matrices subtest to tap the ability to complete visual analogies and to understand relationships. Participants were asked in a quiet setting to identify the object in a picture or puzzle, which served as a representation of their vocabulary. All responses required a one- word oral or signed (point with his/her finger) response within 45 sec and took approximately 15 to 30 minutes to administer.

Stroop Test. This classic test was used to examine three conditions (word, color, and color-word) by requiring the participants to respond orally to as many items as possible in 45 seconds (Stroop, 1935). The Stroop Test consisted of a short (1-minute) practice trial prior to each condition (i.e., this data will not be recorded) and one actual trial per congruent and non-congruent condition. Participants are also screened for color-blindness. For the congruent Word condition (Task A), participants were provided with a list of color words written in black ink and instructed to read orally as many words as possible. The Color condition (Task B) contained a list of "XXXX" printed in different ink colors and required the participant to say the ink color aloud. In the incongruent Color-Word condition (Task C), participants read a list of color words written in

incongruent color ink relative to the printed word. The latter condition necessitates the greatest amount of interference control, as participants were required to state aloud the color of the ink and inhibit the automatic task of reading the printed word and the Stroop interference score was calculated using the following formula (Golden, 1978). Stroop Interference score = Task C – [(Task A × Task B) ÷ (Task A + Task C)]. The positive interference score indicates an ability to inhibit word reading, while the negative interference score represents when the word reading actively interferes with the color naming process.

TMT. This cognitive assessment was used to examine executive function through congruent and non-congruent conditions of TMT-A (i.e., low executive demand) and TMT-B (i.e., high executive demand; (Smith, Servesco, & Edwards, 2008). TMT consisted of short (1-minute) practice trial (i.e., these data will not be recorded) and one actual trial. TMT-A and TMT-B involved drawing a line connecting consecutive numbers from 1 to 25 and drawing a similar line, connecting alternating numerical and alphabetical order, respectively. For example, on TMT-A students draw a line from 1 to 2 to 3, until reaching the number 25. On TMT-B participants were asked to draw a line from 1 to A to 2 to B, until reaching the final number of 25 as fast as possible. The direct score of each part was represented by the time of completion of the tasks. If an error was made during the process, it was corrected during the time sequence. The direct score of the tasks provided a difference score which was calculated by subtracting the time (in seconds) of TMT-B from the time (in seconds) of TMT-A (Sanchez-Cubillo et al., 2009). For the data analysis, cognitive tasks were organized according to congruency in the Stroop test and executive demand in the TMT. These cognitive tasks and task conditions were organized according to congruent trials and incongruent trials in the Stroop tests, and by low executive demand and high executive demand in TMT for analysis purposes.

PVT. This cognitive task is a reaction time test for attention in which participants attend to a small fixation point at the center of a computer screen (Dinges & Powell, 1985). At random intervals, a bright millisecond timer appears in the center of the rectangle. Participants were given short (1-minute) practice trials of the PVT to familiarize them with the task. Participants were instructed to respond via button press as rapidly as possible upon detection of the counter stimulus (i.e. participant response stops the counter from updating). The final counter value corresponded to the participant's reaction time. The success or failure trial is displayed on-screen for 1 second, thus providing feedback for that particular trial. Participants were given 30 seconds to make a response before the computer aborts a trial. Information about each trial's reaction time, and success or failure, was stored by the computer for later analysis. The block of PVT trials was approximately five minutes long. Because intertrial intervals are pseudorandomly chosen without replacement from between two and 10 seconds or an average of six seconds. The test was organized into blocks of five minutes and consisted of approximately 45 trials. After five minutes, the block of trials terminated, regardless of how many trials had elapsed (the post-treatment block of PVT trials was identical to the first).

DMS. The task is measured in both memory retrieval latency and correct match-to-sample trials (response accuracy) (Chudasama & Yogita, 2010). Participants were also given short (1-minute) practice trials of the DMS to familiarize them with the task. Participants viewed a 5x5 grid of brightly colored yellow and red squares with a unique pattern. Then, with the press of a key, the stimulus disappeared and the screen was blank throughout a delay period (6 seconds). Two stimuli then were presented on the screen (a "match" and "nonmatch"). Participants were asked to indicate which stimulus was the correct "match" with a key press and to respond as quickly and as accurately as possible.

Correct match-to-sample trials and memory retrieval latency were measured by the computer and stored for later analysis. The average inter-trial interval in the DMS was 7.5 seconds, so depending on how long the subject examines each post-delay stimulus to choose the "match", which took approximately 5-6 minutes. There were 30 trials per block. The PVT and DMS were implemented with a program called the Psychology Experiment Building Language (PEBL), an open-source programming language that can be run on any Windows computer (Mueller & Piper, 2014). One desktop computer in a closed office was designated as the testing apparatus. The data gathered by the PEBL program is output as a .txt file, which includes each trial's intertrial interval in seconds, reaction time and study time in milliseconds, and a code number indicating whether the trial was a success (response in less than 30 seconds), a lapse (no response in 30 seconds), or a false alarm (responded with a button press prior to the onset of the cue). Participants were identified by a code number (their randomly-assigned subject number), which was typed into the program prior to the start of each block of trials.

Study Procedure

The study consisted of two testing days of approximately 90-mins, with a maximum of seven days between sessions. On a day 1 of testing, the participants reported to the laboratory after having refrained from strenuous exercise and alcoholic beverages for 24 hours and from caffeine and food for 12 hours. All participants signed the informed consent for participation in this study and immediately completed a health research screening survey. After blood pressure was measured, an approximate 10 ml blood sample was obtained from venipuncture of the non-dominant arm. Once a whole blood sample collected, blood sample was immediately transferred into the red-topped tubes and were centrifuged for 10 minutes at 3000 rpm at 4°C in a Sorvall RC-6 centrifuge (Thermo Fisher Scientific Inc, Waltham, Mass, USA). After centrifugation, 0.6

mL of serum were transferred to new three 12 × 75-mm test tubes and immediately stored at −80°C for analysis of CRP. Once the blood samples were being analyzed the blood were discarded following appropriate bio-safety procedures. Following the blood sample draws, participants' height and weight were assessed and then participants performed baseline cognitive testing on KBIT, Stroop, and TMT, in this order. Following the completion of cognitive testing, participants performed a maximal graded exercise test to volitional fatigue on a cycle ergometer (Velotron Dynafit Pro, Seattle WA) to measure participants' VO_2 max, which is considered to be the criterion measure for cardiorespiratory fitness (American College of Sports Medicine, 2000). On day 2 of the testing, participants also reported to the laboratory after having refrained from strenuous exercise and alcoholic beverages for 24 hours and from caffeine and food for 12 hours. Participants completed baseline cognitive testing including the psychomotor vigilance task and delayed-match-to-sample task, in this order (See Figure 3.1).

Data Analysis

Statistical analyses were performed using SPSS Statistical Packages (SPSS Inc, Chicago, USA). First, it was determined whether each dependent variable was normally distributed, by assessing its skewness and kurtosis. Descriptive statistics were used to represent characteristics of the participants and to confirm data entry. Mean differences in dichotomous variables (i.e., gender) and other sample characteristics (i.e., ethnicity, BMI category) for CRP (mg/L) were compared using independent t-tests. Correlations were conducted and significantly associated variables were used as covariates. A one-way analysis of variance was employed to compare mean differences of cognitive variables on three CRP risk levels such as low risk (<1.0 mg/L; n=39), intermediate risk (1.0 to 3.0 mg/L; n=20), and high risk (>3.0 mg/L; n=21). Post hoc analyses using the LSD were performed to evaluate the mean difference. A multiple linear regression analysis was

used to examine the associations of health indices upon CRP and cognitive variables and develop a model for predicting (1) CRP level from health indices, (2) each cognitive variable from CRP level, and (3) each cognitive variable from health indices without (model1) and with (model2) adjustment for age, gender, and race. Based on the findings of the regression analyses, we then performed a path analysis to assess the possibility of CRP as a mediator of the relationship between health indices and each cognitive variable on CRP. The path analysis was used to examine concurrently the direct and indirect effects of BMI on the cognitive variable after considering CRP as a mediating factor. The path analysis was conducted using the SPSS regression analysis.

RESULTS

Of the 98 volunteers who participated in the study, 5 were excluded because of incomplete data, leaving a total of 93 (95%) available for subsequent analyses. Sample characteristics are presented in Table 3.1. In gender comparison, male participants (n=40) had significantly higher BMI ($P = 0.002$), waist circumstance ($P = 0.001$), systemic blood pressure ($P < 0.001$) and VO_2 max ($P < 0.001$), compared to female participants (n = 53). There was no significant difference of CRP level in gender and ethnicity. However, underweight/normal weight participants (BMI < 25) had significantly higher CRP (Mean ± SD: 1.49 ± 1.52 mg/L) compared with overweight/obese (BMI > 25) participants (2.54 ± 1.90 mg/L) as indicated by (t = -1.68, P = 0.024).

Correlation Between Health Indices and Cognitive Variables

Table 3.2 and Appendix A displays the correlations of all variables. CRP was significantly correlated with BMI ($r = 0.31$, $P = 0.009$), waist circumstance ($r = 0.42$, $P = 0.003$) and VO_2max ($r = -0.27$, $P = 0.022$), suggesting a positive relationship of CRP

with BMI and waist circumstance and a negative relationship between CRP and VO_2max. In cognitive variables, CRP is significantly related to scores in Stroop color word (r = -0.27, P = 0.019) and Stroop interference (r = -0.29, P = 0.012) for executive function and memory retrieval latency in DMS test (r = 0.38, P = 0.007) for working memory, indicating higher CRP is negatively related to inhibitory control and working memory. There is no significant relationship between CRP and other cognitive variables such as KBIT for crystallized intelligence (r = 0.19, P = 0.089), PVT for sustained attention (r = 0.17, P = 0.237), and TMT B-A for switching control (r = -0.12, P = 0.237). In contrast, there was significant correlation between VO_2max and memory retrieval latency (r = -0.32, P = 0.012) and correct match-to-sample trials (r = 0.29, P = 0.023) in DMS test for working memory and reaction time (r = -0.257, P = 0.047) in PVT for sustained attention suggesting a greater working memory control relative to high cardiorespiratory fitness. In addition, physical activity level was significantly related to memory retrieval latency (r = -0.29, P = 0.021) in DMS test and reaction time (r = -2.88, P = 0.026) in PVT. Further, physical activity level is also significantly related to inhibitory control as indicated by a positive correlation with Stroop Color Word (r = 0.31, P = 0.015) and interference (r = 0.28, P = 0.028). Significant correlation between VO_2max and physical activity level was observed (r = 2.99, P = 0.016), suggesting a more intense physical activity participation might improve or maintain cardiorespiratory fitness level.

C-Reactive Protein Risk Level and Cognitive Function

Figure 3.2 shows mean difference of Stroop interference (score) in Stroop test and memory retrieval latency (msec) in DMS on three CRP risk levels such as low risk (<1.0 mg/L; n=39), intermediate risk (1.0 to 3.0 mg/L; n=20), and high risk (>3.0 mg/L; n=21). One-way ANOVA analysis revealed the effect of CRP risk was significant on Stroop interference in Stroop test ($F_{2, 77}$ = 2.94, P = .049) and memory retrieval latency in DMS

($F_{2, 77} = 3.32$, $P = .045$). Post hoc analyses using the LSD post hoc criterion for significance indicated that the average scores in Stroop interference was significantly lower in the high CRP risk (M = 3.61, SD = 6.95) than in the low CRP risk (M = 9.41, SD = 8.21). In addition, average time in memory retrieval latency (msec) in DMS was significantly slower in the high CRP risk (M = 2265.96, SD = 610.89) than in the low CRP risk (M = 1727.31, SD = 601.42). These results suggest that CRP level in the high-risk condition causes deleterious effect on cognitive function especially such as inhibitory control and working memory.

Predictor Variables on Cognitive Function

Multiple linear regression analysis was used to develop a model for predicting (1) CRP level from health indices (i.e., BMI, VO2max, physical activity level), (2) each cognitive variable (i.e., Crystalized intelligence, inhibition, switching, attention, working memory) from CRP level, and (3) each cognitive variable from health indices without (model1) and with (model2) adjustment for age, gender, and race.

As shown in Table 3.3.A, the multiple regression analysis was used to test if health indices significantly predicted CRP. Two predictors such as BMI and VO2max explained 39.1% of the variance ($R^2 = .38$, $F_{3, 76} = 9.622$, $P = 0.001$: Model1) and 43.0% of the variance ($R^2 = .43$, 6.73 = 5.286, $P = 0.001$: Model2) after adjustment for age, gender, and race (model 2). CRP was significantly predicted from increased BMI ($\beta = 0.46$, $P = 0.001$), while significantly related to decreased cardiorespiratory fitness ($\beta = -0.57$, P = 0.003). Although physical activity level was not significantly related to CRP, increased physical activity level was significantly associated with increased cardiovascular fitness ($\beta = 0.19$, $P = 0.048$) in the model ($R^2 = .489$, $F_{4,82} = 15.15$, $P < 0.001$: Model2).

As displayed in Table 3.3.B, the multiple regression analysis was used to test if CRP significantly predicted each cognitive variable. After adjustment for age, gender, and race, CRP as a predictor explained 17.8% of the variance (R^2 = .178, $F_{4.74}$ = 5.286 P=0.05: Model2) and significantly predicted memory retrieval latency in DMS (β = 0.378, P = 0.007). In addition, CRP significantly predicted score in Stroop interference (β = -0.27, P=0.02) although it did not have significant effect in the model (R^2 = .1, $F_{4.74}$ = 2.294 P=0.06: Model2), but it showed a significant trend. However, CRP didn't predict crystalized intelligence in KBIT (β = 0.18, P = 0.107) in the model 2 (R^2 = .144, $F_{4.74}$ = 5.286 P=0.028) and completion time in TMT B-A (β = -0.12, P = 0.286) in the model 2 (R^2 = .02, $F_{4.74}$ = 0.353 P=0.841: Model2), and reaction time in PVT (β = 0.166, P = 0.269) in the model 2 (R^2 = .031, $F_{4.74}$ = 0.356 P=0.839: Model2). These results indicated the increased CRP had the significant negative direct effects on memory retrieval latency (msec) in in DMS for working memory and scores in Stroop interference for inhibitory control while there was no significant effect on reaction time in PVT for attention, completion time in TMT for executive function, and scores in KBIT for crystalized intelligence.

Table 3.3.C shows the multiple regression analysis was used to test if health indices significantly predicted each cognitive variable. Two predictors such as VO2max and physical activity level except for BMI explained 12.7% of the variance (R^2 = .127, $F_{3, 83}$ = 2.757, P = 0.051: Model1) and 18.6% of the variance (R^2= .186, $F_{6.80}$ = 2.062, P = 0.06: Model2) after adjustment for age, gender, and race (model 2). Memory retrieval latency in DMS was significantly predicted from increased VO2max (β = -0.37, P = 0.04) and weakly predicted from increased physical activity level (β = -0.24, P = 0.07), but it was not significantly predicted from increased BMI (β = 0.06, P = 0.66). In addition, score in Stroop interference was significantly predicted from increased physical activity

level (β = 0.26, P = 0.05) although it didn't have significant effect in the model (R^2= .168, $F_{6.80}$ = 1.848, P = 0.107: Model2). Any health variable did not predict crystalized intelligence in KBI [R^2 = .222, F(6.80) = 0.494 P=0.810], score in Stroop interference (R^2 = .168, $F_{6.80}$ = 1.848 P=0.107) completion time in TMT B-A (R^2 = .201, $F_{6.80}$ = 2.26 P=0.06: Model2), and reaction time in PVT (R^2 = .067, $F_{6.80}$ = 0.647 P=0.692: Model2). These results indicated the increased VO2max and physical activity level had the significant negative direct effects on memory retrieval latency (msec) in in DMS for working memory, suggesting a faster control process of working memory process. Additionally, the increased physical activity level was also related to a greater inhibitory control.

Path Model From the Regression Analysis

Using the predictors that emerged from the regression analysis, a theoretical model was developed (Figure 3.3). Cardiorespiratory fitness level (VO_2max) had significant negative direct effects on CRP (β = -0.57, P = 0.003) associated with BMI (β = 0.46, P = 0.001). Although there was no direct relationship between physical activity level and CRP, a positive relationship between cardiorespiratory fitness level and physical activity level (β = 0.19, P = 0.048). Positive and significant direct effects were found for those who maintained cardiorespiratory fitness level (β = -0.37, P = 0.04) on working memory. A significant negative direct effect was observed for CRP on working memory (β = 0.378, P = 0.007). However, no significant negative direct effect was found for BMI on working memory (β = 0.06, P = 0.66) in the model (R^2= .186, $F_{6.80}$ = 2.062, P = 0.06: Model2) in Table 3.C. When CRP was considered as a potential mediator of the relationship between BMI and working memory, the indirect effect of BMI on working memory may be dependent on CRP as indicated by increased β weights (β = 0.327, P = 0.128) in the model (R^2= .334, $F_{6.73}$ = 2.506, P = 0.036: Model2).

DISCUSSION

The purpose of this study was to examine the relations of various health indices, physical activity, physical fitness, and cognitive performance among, seemingly healthy young adults in the second decade of life. This study is timely and warranted because the relationship between such variables have been largely unexamined because this age group is considered to be at their cognitive peak and have few differences in reaction time and accuracy (Whiteman et al., 2014). Given the paucity of research the findings from this study help to establish a distinct and needed area of study given the results of this study.

CRP and Health Indices

This study found that the potential beneficial effects of regular physical activity participation and body weight control on the vascular and cognitive health of young adults have been previously highlighted (Zhu et al., 2014; Zhu et al., 2013c). Evidence suggests that physical inactivity, pooper cardiorespiratory fitness, or obesity increases CRP level and impairs cognitive dysfunction, but cardiorespiratory fitness have not been examined collectively in healthy young adults. Furthermore, our study contributes to the existing literature by assessing CRP as a potential mediator or moderator of the relationships between cardiorespiratory fitness and cognitive function. The results of this present study confirmed the relationship of cardiorespiratory fitness, physical activity, and BMI and CRP with cognitive function in young adults (Ford, 2002; Kasapis & Thompson, 2005).

Specifically, the findings from adjusted regression analysis showed that cardiorespiratory fitness and BMI were the strongest predictors of altered CRP level. Although our participants are healthy young and mostly within a normal range of BMI, BMI was significantly a predictor of the increased CRP level. This finding is consistent

with a previous a study demonstrating that CRP predicts future risk for cardiovascular disease in apparently healthy individuals (Jialal, Devaraj, & Venugopal, 2004). BMI commonly is a strong predictor of CRP levels relative to other lipid profiles such as triglyceride and cholesterol, suggesting that obesity is the major factor associated with elevated CRP in individuals by increasing adipose tissue that produces proinflammatory cytokines such as tumor necrosis factor-alpha and interleukin-6 (Hotamisligil, Arner, Caro, Atkinson, & Spiegelman, 1995). Particularly, Interleukin-6 is the major stimulator of the production of CRP in the liver (Heinrich, Castell, & Andus, 1990). In contrast, a previous study demonstrated an inverse relationship of physical activity and cardiorespiratory fitness and the serum concentration of inflammatory markers with CRP (Kasapis & Thompson, 2005). The inverse association between physical activity and CRP levels was dependent on greater amount of leisure-time physical activity (Ford, 2002) and higher levels of physical activity (Albert, Glynn, & Ridker, 2004). Yet, in the present study, physical activity level based on a self-reported data was not significantly related to a deceased CRP level possibly due to the self-reported data and reporting biases, which undermine the accurate classification of physical activity. In the present, however, the physical activity level was positively associated with cardiorespiratory fitness level as the most accurate measure of eliminating self-reporting bias. The theoretical regression model demonstrated that cardiorespiratory fitness level has the strongest negative effect on CRP level. This finding consistently matches with previous studies reporting an inverse association between cardiorespiratory fitness level and CRP level (Ford, 2002; Kasapis & Thompson, 2005). The beneficial effects of chronic physical activity and cardiorespiratory fitness on reducing or suppressing systemic CRP levels by potential mechanisms, including a decrease in proinflammatory cytokine production by adipose tissue, skeletal muscles, endothelial and blood mononuclear cells,

a improved endothelial function and an antioxidant effect (Kasapis & Thompson, 2005). Although the theoretical path regression model highlights the potential pathways of health indices on CRP and cognitive function, our findings do not establish a causal relationship. It is therefore possible that those having higher cardiorespiratory fitness level and lower BMI may have lower CRP level, perhaps mediating cognitive function (Ge et al., 2013; Zhu et al., 2013c).

CRP and Cognitive Function

Previous studies have shown that cardiorespiratory fitness was independently associated with CRP and cognitive function (Komulainen et al., 2007; Noble et al., 2010). Parallel with this association is evidence linking CRP levels with cognitive function. Our adjusted regression analysis demonstrated significant negative relationships between CRP level and cognitive function particularly such as inhibitory control and working memory. These relationships were reinforced by a significant causal relationship of CRP-cognition, observed in the relationship between CRP risk level and cognitive function. In the present study, CRP level in the high-risk condition compared to that in low risk was related to lower score in Stroop interference and slower memory retrieval latency in DMS suggesting that high CRP risk might causes deleterious effect on cognitive function especially such as inhibitory control and working memory. Evidence suggests that the Stroop interference is widely used as frontal lobe functioning (Stuss, Floden, Alexander, Levine, & Katz, 2001), however, higher CRP level is associated with cerebral microstructural disintegration that predominantly affects frontal pathways and corresponding worse executive function (Wersching et al., 2010). In addition, impaired memory assessed with Selective Reminding Test including delayed recall and delayed recognition was related to higher CRP level. The higher CRP level as a systemic inflammatory marker leads to impaired endothelial function, which was associated with

vascular dementia (Vicenzini et al., 2007c). Systemic inflammatory markers are also independently associated with impaired cerebral blood flow (Novak et al., 2006) and cerebrovascular reserve (Davenport et al., 2012), particularly in the hippocampus which is important to memory (Semmler, Okulla, Sastre, Dumitrescu-Ozimek, & Heneka, 2005). Combined, these studies, and our regression analysis, demonstrated that CRP might be associated with impairing cognitive function and could be use as a biomarker of cognitive dysfunction in individuals without dementia.

Health Indices and Cognitive Function

Physical activity and cardiorespiratory fitness examined were significantly related to executive function and working memory. Although BMI was not directly related to any variable of cognitive function tests, the strong negative association that BMI has with CRP appears to contribute to cognitive dysfunction. In the present study, the path analysis form regression model showed the indirect effect of BMI on working memory might be dependent on CRP as indicated by increased standardized coefficient (0.33) from a standardized coefficient (0.06) in direct effect between BMI and working memory. Although the regression model didn't have a significant effect to explain the relationship possibly due to our small sample size relatively, we could observe a trend showing CRP might be a potential mediator of the relationship between BMI and working memory. Otherwise, other studies confirmed that obesity was associated with lower cognitive functioning measured as tests of learning and memory and more cognitive deficit if there are more cardiovascular risk factors involved (Elias, 2003) and obesity itself has a compounding negative impact on the brain by increasing low-grade systemic inflammation (Smith, Hay, Campbell, & Trollor, 2011)The impact of obesity and vascular risk on cognition needs to be further investigated, given obesity has risen dramatically in adults (Ogden et al., 2014). Physical activity level had a significant and

positive direct effect on cognitive function, particularly including Stroop interference and working memory, independent of CRP. This finding is aligned with other findings demonstrating the beneficial effects of physical activity on brain function during adulthood, particularly frontal lobe-mediated cognitive processes including planning, inhibition, and working memory (Drummond et al., 2005; Nieder & Miller, 2004) as well as the protecting effect of physical activity on cognitive decline in nondemented participants followed for 1-12 years (Sofi et al., 2011). Further, our theoretical path model suggests that the most powerful effects of health indices on working memory through CRP occur from the level of cardiorespiratory fitness. The cardiorespiratory fitness level had both direct effect and indirect effect through CRP on working memory. This result suggests that those having higher cardiorespiratory fitness level could have a greater working memory directly and indirectly by reducing CRP level. A recent study also confirmed that cardiorespiratory fitness was positively related to neuropsychological performance, particularly, including memory (Wendell et al., 2014).

In the current study, our regression analysis after adjustment for age, gender, and race revealed the significant relationship of any health indices and CRP with sustained attention was not observed, however, cardiorespiratory fitness and physical activity was significantly correlated with sustained attention (Hillman et al., 2005). Possible explanation is that rather than comparing the baseline reaction time in PVT, this test was appropriate for the pre-test and post-test (Dinges et al., 1997; Dinges & Powell, 1985) as mostly used in acute exercise-induced the sustained attention improvement (Mahon et al., 2013; Pontifex, Saliba, Raine, Picchietti, & Hillman, 2012)

The beneficial effects of physical exercise-induced improvements in cardiorespiratory fitness on cognitive functions have been supported by several potential mechanisms including enhancement of endothelial function and decline of arterial

stiffness, oxidative stress, and vascular inflammation, which increase resting cerebral blood flow and improve function of cerebrovascular reserve (Davenport et al., 2012) and incline of brain volume and size, particularly in hippocampus (Erickson et al., 2011), and release of neurotrophins, particularly, brain-derived neurotrophic factor (BDNF), which promote neuronal growth and survival and mediate learning and memory (Shoshanna Vaynman, Ying, & Gomez-Pinilla., 2004). Our findings suggest that the theoretical path model among health indices, CRP, and cognitive function are crucial to our understanding for implementing future strategies to tackle inadequate physical activity/cardiorespiratory fitness levels and poorer body weight control in young adults.

Delimitations and Limitations

This study has several strengths and potential limitations. The strengths of our study include the most accurate measure of cardiorespiratory fitness through metabolic cart on cycle ergometer to measure VO_2max. This study benefitted from accurate information on VO_2max, which we were, therefore, able to examine the valid and reliable association of cardiorespiratory fitness with CRP and cognitive function. Although the variable of cognitive tasks was restricted to the variation in demographic variable (i.e., age, gender, race), our study was used for the variable measures controlling for the demographic characteristics to reduce potential confounding effects. Lastly, as the study used neuropsychological test battery including crystallized intelligence, executive function, attention, and working memory, we were, therefore, able to identify the relationship of major cognitive domain with health indices and vascular risk in young adults.

The limitations of our study include data collected on physical activity based on a self-reported data, which undermines the accurate classification of physical activity. The self-reported measure of physical activity was derived from a 7-day physical activity

recall, but the physical activity instruments have been acceptable measurement characteristics. Future studies should utilize more objective measures of physical activity such as accelerometer and activity monitor although this would be difficult from financial perspective for population studies.

Implications

The present findings represent a novel investigation of how health indices influence physical fitness and mediate cognitive performance. Continued study is valuable as it has substantial public health implications. Sedentary lifestyles increase vascular risk and deplete cognitive function. These findings confirm the beneficial effects of physical exercise-induced improvements in cardiorespiratory fitness on vascular risk and cognitive functions particularly in working memory. The second decade of life represents the cognitive peak; unlike previous studies there was a differentiated cognitive performance among the participants, based on health the presence of health risk such as elevated CRP. This physical activity has both physical and cognitive benefits among young adults. As such, increasing physical activity participation in moderate to vigorous physical activity to improve cardiorespiratory fitness and to promote healthy BMI may reduce or suppress vascular risk with potential positive effects on cognitive health.

Table 3.1.

Participants Characteristics

Variable	Total (n=93)		Male (n=40)		Female (n=53)	
	Mean	SD	Mean	SD	Mean	SD
Age, yrs.	23.01	3.68	23.73	3.64	22.47	3.64
Height, cm	169.54	9.23	177.26**	6.20	163.86	6.58
Weight, kg	65.17	13.61	74.62**	12.89	58.04	9.08
BMI	22.51	3.33	23.71**	3.20	21.62	3.17
25<BMI, n (%)	75		72.5		88.6	
25>BMI, n (%)	18		27.5		11.3	
Waist circumstance, cm	77.90	9.14	82.30**	9.20	74.92	7.91
SBP, mmHg	109.11	12.18	117.22**	11.71	102.87	8.28
DBP, mmHg	73.05	8.35	74.38	8.81	72.04	7.91
MET	697.41	415.26	772.23	431.76	646.22	401.28
VO_2max ml.kg/min	37.78	9.63	43.93**	9.36	33.23	6.98
HRmax, beats/min	181.06	13.54	181.81	13.99	180.50	13.31
RER, CO_2/O_2	1.11	0.09	1.11	0.09	1.11	0.10
CRP, mg/L	1.84	1.91	1.87	2.21	1.80	1.63
Ethnicity, n (%)						
Caucasian	37	39.8	19	47.5	18	34.0
Asian	35	37.6	4	10.0	6	11.3
African	10	10.8	13	32.5	22	41.5
Hispanic	8	8.6	2	5.0	6	11.3
Other	3	3.2	2	5.0	1	1.9

Abbreviations: BMI, body mass index, SBP, systolic blood pressure, DBP, diastolic blood pressure, VO2max, maximal oxygen consumption; HR, heart rate; MET, metabolic equivalent; RER, respiratory exchange ratio; CRP, C-reactive protein.

Asterisks in the Male column indicate sex differences.

* $P < 0.05$.

** $P < 0.01$

Table 3.2.
Correlations of Variables

Variables	Mean (SD)	Age	BMI	WC	VO2 max	MET	CRP	Skewness,	Kurtosis
Age, year	23.68 (3.68)	–						0.65	-0.62
BMI	22.51 (3.33)	0.07	–					0.95	2.02
WC	77.9 (9.14)	-0.07	.761**	–				0.67	0.13
VO2 max	37.78 (9.63)	-0.04	0.03	0.06	–			0.75	-0.13
MET	697.41 (415.25)	-0.13	0.06	0.07	.299*	–		0.29	-0.52
CRP	1.83 (1.91)	0.03	.252*	.426**	-0.12	-0.23	–	1.91	4.34
KBIT									
KBIT Vocabulary	102.06 (12.24)	-0.18	0.02	-0.02	0.14	0.05	.253*	-0.99	2.26
KBIT Mat	106.39 (6.99)	.283**	0.02	-0.07	0.18	0.04	0.01	0.65	0.13
KBIT Composition	104.59 (8.17)	-0.03	0.03	-0.05	0.20	0.06	0.22	-0.45	1.65
Stroop test									
Stroop Word (score)	107.32 (14.90)	-0.16	0.17	0.07	0.12	-0.04	-0.08	-0.41	2.15
Stroop Color (score)	78.65 (12.74)	-.352**	0.13	-0.01	0.18	0.22	-0.08	-0.38	0.93
Stroop Color Word (score)	53.01 (10.83	-0.15	0.03	0.00	0.19	.303*	-.273*	0.42	0.51
Stroop Interference (score)	7.81 (8.73)	0.06	-0.08	-0.02	0.10	.279*	-.290*	0.24	0.08
TMT									
TMT A (sec)	15.79 (5.03)	-0.03	0.12	0.23	-0.13	-0.11	0.20	1.22	2.55
TMT B (sec)	38.26 (11.46)	0.05	-0.13	-0.13	-0.09	-0.09	-0.03	0.92	2.02
TMT B-A (sec)	22.10 (10.07)	0.10	-0.18	-.310*	-0.02	-0.01	-0.13	0.92	2.62
PVT									
Reaction time (msec)	358.38 (27.23)	-0.1	-0.004	-0.121	-.257*	-.287*	0.177	0.33	-0.65
DMS									
Correct trial (score)	27.06 (1.96)	0.193	-0.119	0.055	.294*	0.106	-.323*	-0.80	1.00
Reaction time (msec)	1931.70 (590.2)	-0.129	0.005	0.147	-.323*	-.297*	.373**	0.40	-0.43

Abbreviations: KBIT, Kaufman Brief Intelligence Test; BMI, body mass index; WC, waist circumstance; VO2max, maximal oxygen consumption; MET, metabolic equivalent; CRP, C-reactive protein; TMT, Trail Making Test; PVT, Psychomotor vigilance task; DMS, Delayed match sample test.

*P<0.05

**P<0.01

Table 3.3.

Mean difference of Confounding and Cognitive variables on Levels of C-Reactive Protein Risk

Variables	Low Risk <1.0 mg/L N=39		Intermediate Risk 1.0 to 3.0 mg/L N=20		High Risk >3.0 mg/L N=21		*F*	*P*
	Mean	SD	Mean	SD	Mean	SD		
C-reactive protein, mg/L	0.57	0.19	1.77	0.58	4.65	1.78	120.02	0.00
Body Mass Index, kg/m2	22.06	2.23	23.97*	3.30	24.31**	4.43	4.12	0.02
Waist Circumstance, cm	75.58	6.09	85.74**	7.01	84.30**	13.21	7.71	0.00
VO2 max, ml/kg/min	40.00	9.83	37.61	10.73	34.76	11.16	1.50	0.23
PA level, MET	754.30	434.87	567.25	416.80	554.00	315.55	1.29	0.29
Cognitive variable								
Crystallized intelligence								
KBIT Vocabulary	99.36	15.35	102.00	10.17	106.94	8.17	2.15	0.13
KBIT Mat	106.56	7.98	107.59	6.97	105.67	4.90	0.32	0.73
KBIT Composition	103.13	10.15	105.24	6.49	106.94	5.84	1.31	0.28
Stroop test					0.82			
Stroop Word (score)	106.79	17.29	110.88	15.28	105.78	15.58	0.49	0.61
Stroop Color (score)	78.00	15.99	78.88	9.76	77.39	9.51	0.06	0.95
Stroop Color Word (score)	54.13	11.59	54.65	12.17	48.22	8.12	2.08	0.13
Stroop Interference (score)	9.41	8.21	8.76	10.78	3.61*	6.95	2.93	0.05
Trail taking test								
Trail Making A (sec)	14.76	4.73	16.54	4.75	16.30	5.68	1.03	0.36
Trail Making B (sec)	36.27	10.94	42.09	13.58	34.26*	7.06	2.53	0.09
Trail Making B-A (sec)	21.51	9.15	25.55	13.36	17.96*	8.14	2.50	0.09
Psychomotor vigilance task								
Reaction time (msec)	343.97	67.23	352.75	26.29	364.61	38.06	0.50	0.61
Delayed match sample test								
Correct trial (score)	26.44	5.24	27.38	1.60	26.30*	2.31	0.17	0.85
Reaction time (msec)	1727.31	601.42	2060.42	660.61	2265.96	610.89	3.32	0.04

Abbreviations: BMI, body mass index; VO2max, maximal oxygen consumption; MET, metabolic equivalent; CRP, C-reactive protein.

Data are presented as mean ± SD; asterisks indicate differences in levels of C-reactive protein risk

* $P < 0.05$.

** $P < 0.01$

Table 3.4.
Linear Relationships of Health Indices and C-Reactive Protein with Cognitive Function

		Model 1				Model 2			
		Unst	SE	St	P value	Unst	SE	St	P value
A. Predicting CRP level from health indices									
Health indices	BMI	0.23	0.05	0.50	0.001	0.21	0.06	0.46	0.001
	VO2 max	− 0.06	0.02	− 0.36	0.004	− 0.09	0.03	− 0.57	0.003
	MET	− 0.01	0.01	− 0.17	0.166	− 0.01	0.01	− 0.17	0.182
B. Predicting each cognitive variable from CRP level									
Cognitive variable	Intelligence	0.99 (0.52)		0.22	0.060	0.82	0.5	0.18	0.107
	Inhibition	− 1.34	0.52	− 0.29	0.012	− 1.26	53	− 0.27	0.02
	Switching	− 0.67	0.63	− 0.13	0.287	− 0.69	0.64	− 0.13	0.286
	Attention	6.14	0.13	0.17	0.237	5.98	0.34	0.17	0.269
	Working memory	152.23	53.81	0.38	0.007	143.16	54.92	0.36	0.012
C. Predicting each cognitive variable from health indices									
Intelligence	BMI	0.17	0.32	0.07	0.60	0.23	0.34	0.09	0.50
	VO2 max	0.13	0.13	0.13	0.32	0.12	0.18	0.12	0.52
	MET	0.01	0.00	0.02	0.89	0.01	0.00	0.03	0.85
Inhibition	BMI	0.01	0.31	0.00	1.00	− 0.01	0.31	0.00	0.98
	VO2 max	0.10	0.12	0.10	0.44	0.15	0.16	0.15	0.38
	MET	0.01	0.00	0.25	0.06	0.01	0.00	0.26	0.05
Switching	BMI	− 1.03	0.30	− 0.41	0.00	− 1.10	0.32	− 0.44	0.00
	VO2 max	− 0.10	0.12	− 0.10	0.40	− 0.18	0.17	− 0.18	0.28
	MET	0.01	0.00	0.08	0.53	0.01	0.00	0.09	0.48
Attention	BMI	2.11	1.97	0.14	0.29	2.31	2.09	0.15	0.27
	VO2 max	− 0.10	0.77	− 0.01	0.89	0.10	1.06	0.02	0.93
	MET	− 0.02	0.02	− 0.19	0.15	− 0.02	0.02	− 0.20	0.14
Working Memory	BMI	17.22	22.42	0.10	0.45	10.18	23.16	0.06	0.66
	VO2 max	− 13.65	8.94	− 0.20	0.13	− 25.46	11.89	− 0.37	0.04
	MET	− 0.37	0.21	− 0.23	0.08	− 0.38	0.21	− 0.24	0.07

Abbreviations: BMI, VO2max, Cardiorespiratory Fitness; MET, metabolic equivalent (Physical activity level); ST, standardized coefficient; SE, standard error; Unst, unstandardized coefficient. Model 1: unadjusted. Model 2: adjusted for age, sex, and race.

Day 1						Day 2
• Consent form • Health Screening	→	• Blood pressure • Height & weight • Blood sample	→	• KBIT • Stroop • TMT	• VO_2 max	• PVT • DMS

Figure 3.1. ***Experimental Protocol Sequence***

Abbreviation: Kaufman Brief Intelligence Test, KBIT; Trail making test, TMT; PVT, Psychomotor vigilance task; DMS, Delayed-match-to- sample task.

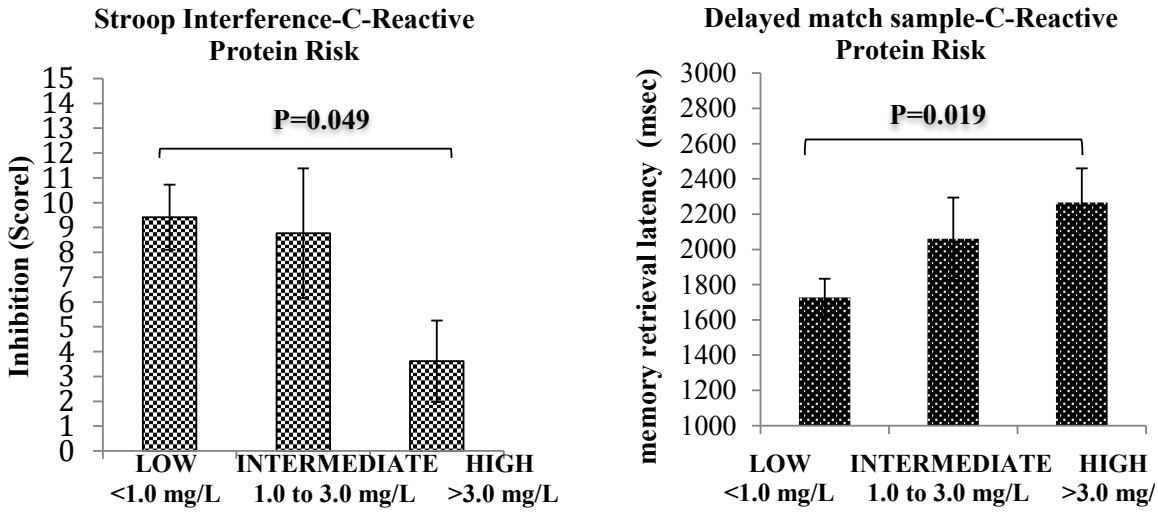

Figure 3.2. ***C-Reactive Protein Risk- Stroop Interference and Memory Retrieval Latency***

The mean difference of Stroop interference (score) in Stroop test indicating the inhibitory control for three CRP risks are shown in (left). The mean difference of Memory Retrieval Latency (msec) in Delayed match sample test indicating the working memory for three CRP risks are shown in (right). Data are presented as Mean (standard errors).

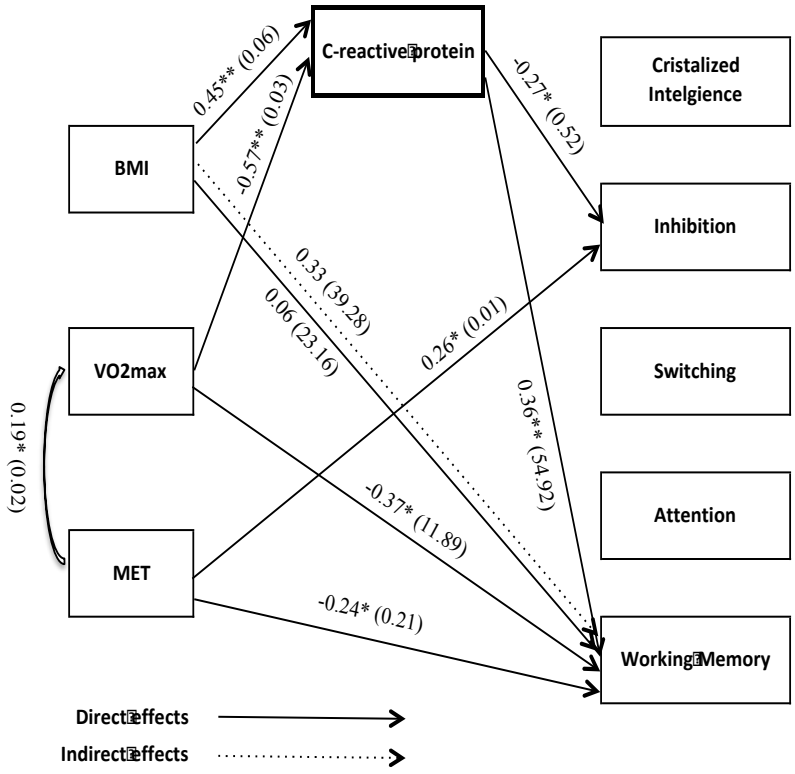

Figure 3.3. ***Path Theoretical Model From Regression analysis***

Abbreviations: BMI, BMI; VO2max, Cardiorespiratory Fitness; MET, metabolic equivalent (Physical activity level); Data are presented as standardized coefficients (standard errors) adjusted for age, sex, and ethnicity.

*P<0.05

**P<0.01.

Chapter IV: Study 2

IMPACT OF A SINGLE SHORT BOUT OF VERY VRGOROUS EXERCISE ON COGNITIVE PERFORMANCE AND BRAIN-DERIVED NEUROTROPHIC FACTOR IN YOUNG ADULTS

ABSTRACT

OBJECTIVE: To examine whether the short bout of very vigorous exercise on performance in executive functioning tasks and serum level of brain-derived neurotrophic factor (BDNF) in healthy, young adults. It was proposed that acute exercise-induced enhancements in cognitive performance might be associated with the release of BDNF.

METHODS: Young adults (n=58; 55.0% female, aged 23.68 ± 3.64 years; range of 18 to 31) were randomly assigned to one of two experimental conditions: (a) exercise condition [a short bout of very vigorous aerobic exercise (a 10 min of 85 ~ 90% VO_2max); VEX) or (b) control condition (CTL). Cardiorespiratory fitness (VO_2max) was measured through a metabolic cart on a cycle ergometer to determine an individual's exercise intensity (85 ~ 90% VO_2max). Kaufman Brief Intelligence Test (KBIT) was administered to assess crystallized intelligence. To evaluate cognitive performance before and after the exercise condition or control condition, response inhibition was measured by interference score from Stroop task while response switching was assessed by the Part B – Part A difference time from the Trail-Making Test (TMT). To determine serum BDNF level, blood samples were withdrawn at the baseline, immediately following exercise (Post- 0min) and after 30-minute (Post- 30min). Serum high sensitivity BDNF (pg/ml) was determined using a quantitative enzyme immunoassay assay.

RESULTS: Two-way repeated ANOVA revealed that VEX improved scores in all three Stroop conditions and interference, as indicated by a significant interaction

between the group and the session in score of Stroop Word ($\underline{F}_{1,56} = 10.48$, $P = 0.002$, $\eta^2 = 0.16$), Stroop Color ($\underline{F}_{1,56} = 5.04$, $P = 0.029$, $\eta^2 = 0.08$), Stroop Color-Word ($\underline{F}_{1,56} = 13.87$, $P = 0.001$, $\eta^2 = 0.19$), as well as Stroop Interference ($\underline{F}_{1,56} = 7.92$, $P = 0.007$, $\eta^2 = 0.12$). In addition, two-way repeated-measures ANOVA revealed a significant interaction between the group and the session in time of TMT-B ($F_{1, 56} = 9.45$, $P = 0.003$, $\eta^2 = 0.14$) and TMT Part B – Part A difference time; ($F_{1, 56} = 2.88$, $P = 0.049$, $\eta^2 = 0.09$). One-way repeated ANOVA within-subject factors in VEX exhibited a significant main effect of the sessions (baseline, P0, P30) on serum BNDF level as indicated by ($F_{1,28} = 19.69$, $P = 0.001$, $\eta^2 = 0.47$), suggesting that the level of BDNF was significantly increased immediately (P0), but decreased at 30 min (P30) following the exercise condition. In addition, there was a significant relationship between the change of pre- and post- TMT-A and the change of pre- and post-BNDF level ($r = -0.38$, $P = 0.035$) following the acute exercise.

CONCLUSION: The present findings suggest the beneficial effect of short bout of very vigorous exercise on cognitive performance in healthy, young adults. The acute exercise-induced the increase in BDNF level may be at least in part of mediating the cognitive performance improvement.

Keywords: short bout of very vigorous exercise, cognitive performance, brain-derived neurotrophic factor

INTRODUCTION

Although most studies focus on beneficial effect to physical health, mounting evidence demonstrates that cognitive health is enhanced by regular engagement in physical activity and the attainment of health enhancing level of physical fitness in all populations (Castelli et al., 2014; Hillman et al., 2008a). The association between physical activity and cognitive function has received attention as measured by neurophysiological studies such as electroencephalograms (Hillman et al., 2009; Hillman, Snook, & Jerome, 2003), functional magnetic resonance imaging (Erickson et al., 2011) and molecular mechanism studies such as brain-derived neurotrophic factor (Ferris et al., 2007; Knaepen, Goekint, Heyman, & Meeusen, 2010; Rasmussen et al., 2009). The measurement of cognitive performance tasks generally, include the completion of executive function tasks that assess perceptual speed, vocabulary and episodic memory (McCabe, Roediger, McDaniel, Balota, & Hambrick, 2010). Particularly, executive functioning plays a central role in neuropsychological behavior (Stuss & Knight, 2002) and therefore, it relation to physical activity has been extensively measured (Chang et al., 2012; C. H. Hillman et al., 2008a). Executive functioning includes a diverse set of cognitive processes intended to elicit goal-directed behavior, especially in non-routine or fluid situations (Banich, 2009). Executive functions include cognitive control related to the inhibition, shifting, monitoring, updating, maintaining, planning, working memory, and cognitive flexibility (Homack, Lee, & Riccio, 2005). A key control process in executive functioning is response inhibition (Barkley, 1997) as measured by interference score from Stroop test (Stroop, 1935), which consists of three conditions (i.e., Word, Color, Color-Word) (Golden, 1978) and response switching as measured by the Part B – Part A difference time from the Trail-Making Test (Reitan & Wolfson, 1885; Sibley, Etnier, & LeMasurier, 2006; Strauss et al., 2006).

Recent studies showed that acute bouts of moderate intensity exercise improved performance in Stroop task (Barella, Etnier, & Chang, 2010; Hyodoa et al., 2012; Lowe, Hall, Vincent, & Luu, 2014; Sibley et al., 2006; Yanagisawa et al., 2010) and in TMT (Gapina, Labbanb, Bohalla, Wootena, & Changc, 2015; Loprinzi & Kane, 2015). A meta-analysis showed an improved cognitive performance was also observed following exercise at a high intensity (Chang et al., 2012). However, the threshold of such of effects is largely undefined and inconclusive (Yerkes & Dodson, 1908; Lambourne & Tomporowski, 2010). For instance, high-intensity exercise may have positive effects on the Stroop performance in one sample (Ferris et al., 2007), while other studies failed to find the additional or significant effect of vigorous intensity exercise on the performance in Stroop task (Lowe et al., 2014). Similarly, using the TMT, there were differential findings (Loprinzi & Kane, 2015). These equivocal results could be due to a moderator effect (e.g., age, gender, physical fitness level, crystallized intelligence) influencing the cognitive performance. Therefore the acute (Chang et al., 2012) and chronic effects of physical activity participation must be further decomposed (Bacon, Carter, Ogle, & Joyner, 2013), if we are to advance our understanding of how physical activity participation can enhance cognitive performance. Therefore, it is the important step to identify specific exercise intensity to the extent of the relationship of physical activity and cognition.

Although a prolonged vigorous-intensity exercise causes fatigue and therefore, may be negatively associated with cognitive performance (Yerkes & Dodson, 1908; Lambourne & Tomporowski, 2010), a short bout of vigorous intensity-exercise may improve additional or significant effect on cognitive performance as evidenced by molecular change of neurotrophins, particularly, brain-derived neurotrophic factor (BDNF), which promote neuronal growth and survival and mediate cognitive control

(Shoshanna Vaynman et al., 2004). As a magnitude change of BNDF is dependent on exercise intensity (Ferris et al., 2007; Knaepen et al., 2010), we still need to confirm the short bout of very vigorous exercise- induced cognitive performance may be related to release of BNDF.

The purpose of this study was to examine the effects of a short bout of very vigorous intensity-exercise (10 min of 85~90%VO2max) on BDNF and executive functioning tasks. A secondary outcome was to identify the relationship between BDNF level and a cognitive variable at baseline and the pre-post change of the cognitive performance following very vigorous physical activity. It was predicted that BDNF would mediate both the baseline and pre-post changes in cognitive performance.

INSTRUMENTS AND METHODLOGY

The study procedure was approved by The University of Texas at Austin Institutional Review Board and involved the use of multiple physiological and cognitive assessments to provide evidence supporting the research questions of this study. Using a randomized experimental design across two days of data collection, the participants experienced a control (rest) or exercise condition.

Instruments

All of the measured used in this study are valid and reliable, standardized measures of cognitive, blood, and physical fitness. Anthropometric measurement of height and weight (Lohman et al., 1988) were used to calculate Body Mass Index (BMI) in accordance with

standard anthropometric techniques. The measures of physical fitness, cognitive performance, and serum BDNF are described below.

Measurement of Cardiorespiratory Fitness

Using a cycle ergometer, the participants were appropriately positioned and proceeded to in four incremental five- minute stages of submaximal cycling for determination of the VO_2 versus work rate relationship (Velotron Dynafit Pro, Seattle WA). This was followed by a bicycle ergometer test to determine maximal oxygen consumption (VO_2 max). VO_2 max is the maximum rate the body uses oxygen for sustained energy production, which correlates highly to endurance performance (Howley, Jr, & Welch, 1995). This test required subjects to breathe into a mouthpiece for the monitoring of oxygen consumption while cycling continuously at increasing exercise intensities. The test was ended upon volitional fatigue of the subject or when cadence falls below 60 rpm. The test lasted approximately 8 to 12 minutes and should be physically stressful and challenging for about 5 minutes. Participants likely felt fatigued for 15 to 20 minutes after the test.

Measurement of Cognitive Tasks

Three cognitive measurements for this study included Kaufman Brief Intelligence Test (KBIT) for crystallized intelligence, Stroop test and Trail Making Test (TMT) for executive function. Except for the KBIT, each of cognitive function tests consisted of very short (1-minute) practice trial (i.e., this data will not be recorded) to familiarize them with the task and then they participated in one actual trial.

KBIT. The KBIT assessment is a brief, individually administered measure of verbal and nonverbal intelligence for individuals from 4 to 90 years of age (Kaufman, 1990). The KBIT contains three subscales to estimate crystallized intelligence composite. Verbal knowledge such as comprehension, reasoning, and vocabulary knowledge was assessed in the first segment. The nonverbal scale uses visual matrices subtest to understand crystallized intelligence. All responses required a one- word oral or signed (point with his/her finger) response within 45-sec and took approximately 15 to 20 minutes to administer.

Stroop test. This classic test was used to examine three conditions (word, color, and color-word) by requiring the participants to respond orally to as many items as possible in 45 seconds (Stroop, 1935). The Stroop Test consisted of a short (1-minute) practice trial prior to each condition (i.e., this data will not be recorded) and one actual trial per congruent and non-congruent condition. Participants are also screened for color-blindness. In the congruent Word condition (Task A), participants were provided with a list of color words written in black ink and instructed to read orally as many words as possible. The Color condition (Task B) is a list of "XXXX" printed in different ink colors and requires the participant to say the ink color aloud. In the incongruent Color-Word condition (Task C), participants read a list of color words written in incongruent color ink relative to the printed word. The latter condition necessitates the greatest amount of interference control, as participants were required to state aloud the color of the ink and inhibit the automatic task of reading the printed word and the Stroop interference score was calculated using the following formula (Golden, 1978). Stroop Interference score = Task C – [(Task A × Task B) ÷ (Task A + Task C)]. The positive interference score indicates an ability to inhibit word reading, while the negative interference score represents when word reading actively interferes with the color naming process.

TMT. This cognitive assessment was used to examine executive function through congruent and non-congruent conditions of TMT-A (i.e., low executive demand) and TMT-B (Smith SR, 2008) TMT consisted of short (1-minute) practice trial (i.e., these data will not be recorded) and one actual trial. TMT-A and TMT-B involved drawing a line connecting consecutive numbers from 1 to 25 and drawing a similar line, connecting alternating numerical and alphabetical order, respectively. For example, on TMT-A students draw a line from 1 to 2 to 3, until reaching the number 25. On TMT-B participants were asked to draw a line from 1 to A to 2 to B, until reaching the final number of 25 as fast as possible. The direct score of each part was represented by the time of completion of the tasks. If an error was made during the process, it was corrected during the time sequence. The direct score of the tasks provided a difference score, which was calculated by subtracting the time (in seconds) of TMT-B from the time (in seconds) of TMT-A (Sanchez-Cubillo et al., 2009). For the data analysis, cognitive tasks were organized according to congruency in the Stroop test and executive demand in the TMT. These cognitive tasks and task conditions will be organized according to congruent trial and incongruent trial in Stroop test and to low executive demand and high executive demand in TMT for analysis purposes.

Biochemical Analysis of Blood Sample

Each blood sample collected and centrifuged for 10 minutes at 3000 rpm at 4°C in a Sorvall RC-6 centrifuge (Thermo Fisher Scientific Inc, Waltham, Mass, USA). After centrifugation, 0.6 mL of serum were transferred to new three 12 × 75-mm test tubes and immediately stored at −80°C for analysis of CRP and BDNF. The remaining serum sample was be placed in a third test tube and saved as a backup. Each participant's blood samples were analyzed in duplicate after completion of the study. Once the blood

samples were being analyzed the blood were discarded following appropriate bio-safety procedures.

BNDF. Serum BDNF will be determined using a quantitative enzyme immunoassay assay method (R&D Systems, Inc. MN, USA) that includes a monoclonal antibody specific for BNDF coated onto 96-well polystyrene microplates. According to the manufacturer's assay procedure, all standards, control, and samples will be assayed in duplicate. Optical density of each wall will determined using a microplate reader (BioTek Inc., VT, USA) set to 450nm. BNDF concentrations will be calculated using standard curves.

Participants

Fifty-eight, healthy, English-speaking adults of either sex, of age ranging from 18 to 30 years, of any ethnic background were considered for the study. Potential subjects who were recruited by word-of-mouth in university environment contacted the lab and undergo a short phone screen to determine if they want to participate and if they meet inclusion/exclusion criteria. The potential subjects were asked if he or she has a history of any of the following, and then all of the exclusionary criteria: presence of cardiovascular disease or cerebrovascular disease, diagnosis of psychotic disorder, history of violent behavior, history of neurological condition, current pregnancy, or prior institutionalization or imprisonment; however, no participant was excluded on these bases.

Study Procedures

The overall study procedure composed of two major steps. First, we determined the VO2max to determine an individual level of physical activity intensity (85~90% VO2max). Second, we examined the effects of a short bout of vigorous physical activity

on executive functioning performance and BDNF level (see Figure 4.1). The study consisted of two days of testing with a maximum of seven days between sessions. Participants were instructed to consume their last meal and caffeine at least 12 hours, during which they were allowed to consume only water, and were asked to refrain from strenuous exercise and alcohol beverage for 24 hours before the visits.

On a first day of testing, all participants signed the informed consent to participate in this study and filled out the participation health research screening form. After blood pressure was measured, participants' height and weight were assessed. Participants then performed a maximal graded exercise test to volitional fatigue on a cycle ergometer (Velotron Dynafit Pro, Seattle WA) to measure participants' VO_2 max, which is considered to be the criterion measure for cardiorespiratory fitness (Thompson et al., 2010). VO_2 max was assessed to determine a participant' exercise intensity (85-90% of VO_2max) for a day 2 testing.

On the second day of testing, participants were randomly assigned to one of two experimental conditions: (a) exercise condition [n = 29, short bout of very vigorous exercise (VEX)] or (b) control condition [n = 29, inactive resting (CTL)]. Before and after the manipulation, participants completed cognitive tests including KBIT, Stroop, and TMT at a baseline. Following the cognitive tests, participants in VEX performed 20 min exercise on the treadmill and then had a 10 min resting. The exercise protocol a 20 min- running on a treadmill included 2 min-warm-up, 5 min-adjusted speed and incline to reach to a target heart rate and 10 min-running at 85-90% of VO_2max (very hard: $\geq$ 85% HRmax; American College of Sports Medicine), and 3 min-cool down (Thompson et al., 2010). Participants also performed post-cognitive tests such as Stroop and TMT. Blood samples were obtained an approximate 10 ml blood sample from venipuncture of the non-dominant arm at a baseline, immediately and 30 min following the exercise in VEX.

Participants in CTL performed the cognitive tests before and after 30 min- inactive resting instead of performing exercise and the participants' blood samples were withdrawn only at a baseline.

Data Analysis

Statistical analyses were performed using SPSS Statistical Packages (SPSS Inc, Chicago, USA). First, it was determined whether each dependent variable was normally distributed, by assessing its skewness and kurtosis. Cronbach's alpha was used an estimate of internal consistency reliability of a cognitive performance variable. Cronbach's alpha coefficient measured the correlation between cognitive variables and the total was 0.69, which is considered reasonable for an instrument (George & Mallery, 2003). Normally distributed variables were analyzed with two-way repeated measures ANOVA (analysis of variance), using session (pre vs. post treatment) measures as the within-subject variable, and group assignment (VEX vs. CTL) as independent variables. A significant effect of acute bout of exercise would be indicated by an interaction between the group conditions and the within-subject variable of pre-post cognitive tasks and biomarkers. In addition, change of BNDF level was analyzed with one-way repeated measures ANOVA, using session (pre, vs. post- treatments) measures as the within-subject variable. One dependent variable, the number of trials (score) on the Stroop test and time completion (sec) on TMT, and BDNF level between pre- and post- treatment was analyzed with post hoc analysis using multiple paired t-tests.

RESULTS

Table 4.1 displays the participants' biological and cognitive characteristics. There were no significant difference in control variables such as age ($P = 0.08$), BMI ($P =$

0.96), VO2max ($P = 0.12$), and KBIT ($P = 0.12$) between VEX and CTL, suggesting that the random group assignment was appropriately distributed for cognitive performance test respond to the acute exercise. Although significant difference of RER was observed between the groups, participants in both groups almost reached to an accepted value for volitional failure (RER > 1.1).

Correlation Between Control Factors and Cognitive Variables

Table 4.2 and Appendix B show the correlations among the bibliographical and cognitive variables. A significant, inverse relationship between age and cognitive variables was observed as indicated by Stroop word (PRE: $r = - 0.32$, $P = 0.012$, POST: $r = - 0.37$, $P = 0.004$), pre-Stroop color (PRE: $r = - 0.47$, P = 0.001, POST: $r = -0.47$, $P = 0.001$), Stroop Color Word (PRE: $r = - 0.29$, $P = 0.026$;, $r = - 0.35$, $P = 0.006$), suggesting there was age effect on the cognitive test. In addition, there was a significant positive association between estimated crystallized intelligence (KBIT composite) and cognitive variables as indicated by pre-TMT B (PRE: $r = - 0.224$ $P = 0.045$, POST: $r = - 0.368$ $P = 0.004$), TMT Part B – Part A (PRE: $r = - 0.28$, $P = 0.029$, POST: $r = - 0.387$, $P = 0.003$). Furthermore, VO2max was significantly correlated with all post cognitive conditions including Stroop color (r = 0.31, P = 0.0399), Stroop Color Word ($r = 0.34$, $P = 0.012$), and TMT A ($r = - 0.26$, $P = 0.050$) while not with a pre- cognitive test condition, suggesting a participant having higher fitness level had a better cognitive performance. These combined results implicated the controllable factors such as the age, crystallized intelligence, and fitness level should be considered for a group assignment particularly in a cognitive experimental condition.

Stroop Test Post Exercise

Significant beneficial effect on the Stroop task was observed in VEX. The results showed that VEX improved scores in all three Stroop conditions and interference, as

indicated by a significant interaction between the group and the session in score of Stroop Word ($F_{1,56}$ = 10.48, P = 0.002, η^2 = 0.16), Stroop Color ($F_{1,56}$ = 5.04, P = 0.029, η^2 = 0.08), Stroop Color-Word ($F_{1,56}$ = 13.87, P = 0.001, η^2 = 0.19), as well as Stroop Interference ($F_{1,56}$ = 7.92, P = 0.007, η^2 = 0.12). There were no main effects of group assignment on score of all three Stroop conditions such as Stroop Word ($F_{1,56}$ = 0.96, P = 0.332, η^2 = .0017), Stroop Color ($F_{1,56}$ = 1.41, P = 0.24, η^2 = 0.02), Stroop Color-Word ($F_{1,56}$ = 0.002, P = 0.96, η^2 = 0.00] and Stroop interference ($F_{1,56}$ = 1.18, P = 0.28, η^2 = 0.02), indicating that the random assignment of participants to one VEX group or the CTL was successful in balancing the groups with respect to their initial (pre-condition) times.

To examine the interaction, we calculated the difference of the score of three Stroop conditions and Stroop interference between post- and pre-sessions and compared the difference between both groups (Table 4.3 & Figure 4.2). Score difference was significantly more positive in the VEX than in the CTL, as indicated by Stroop Word (t_{56} = 3.23, P = 0.002), Stroop Color (t_{56} = 2.245, P = 0.029), Stroop Color-Word t_{56} = 3.716, P = 0.001] and Stroop interference (t_{56} = 2.798, P = 0.007) in Table 4.3 and Figure 4.2 These results suggest that the short bout of very vigorous exercise significantly enhance information process and response inhibition reflecting the Stroop conditions and interference, respectively.

TMT Post Exercise

A repeated-measure ANOVA revealed a significant interaction between the group and the session in time of TMT-B ($F_{1, 56}$ = 9.45, P = 0.003, η^2 = 0.14) and the Part B – Part A difference time ($F_{1, 56}$ = 2.88, P = 0.049, η^2 = 0.09), but there was no significant interaction on TMT-A ($F_{1, 56}$ = 5.65, P = 0.236, η^2 = 0.03). There were no main effects of group assignment on score of all TMT conditions such as TMT-A ($F_{1,56}$ = 0.07, P =

0.793, $\eta^2 = 0.00$], TMT-B ($F_{1,56} = 0.23$, $P = 0.634$, $\eta^2 = 0.004$], and the Part B – Part A ($F_{1,56} = 0.003$, $P = 0.959$, $\eta^2 = 0.00$], indicating that the random assignment of participants to one VEX group or the CTL was successful in balancing the groups with respect to their initial (pre-condition) times. After the significant interaction observed, we conducted the difference of time in TMT-B and in the TMT Part B – Part A between post- and pre-sessions and compared the difference between both groups. The difference was a significantly shorter time in the post VEX than in the CTL, as indicated by TMT-B ($t_{56} = -3.028$, P = 0.004) and the TMT Part B – Part A ($t_{56} = -2.11$, P = 0.039) in Table 4.3 and Figure 4.2. These results revealed that the acute bout of high-intensity aerobic exercise significantly improved executive response switching and working memory as indicated by the TMT-B and the Part B – Part A.

BDNF Post Exercise

The level of BDNF was significantly increased immediately (P0), but decreased at 30 min (P30) following the exercise condition. One-way repeated ANOVA within subject factors in VEX exhibited a significant main effect of the sessions (baseline, P0, P30) as indicated by ($F_{1, 28} = 19.69$, $P = 0.001$, $\eta^2 = 0.47$; Figure. 4.3). These results demonstrated that BDNF could be a possible mediating factor in cognitive process following the exercise condition as supported by significant correlation results between the change of pre- and post- TMT-A and the change of pre- and post-BNDF level ($r = -0.38$, $P = 0.035$) following the acute exercise (Table 4.4).

DISCUSSION

Although a number of studies have demonstrated that an acute bout of moderate exercise (i.e., exercise intensity <76% HRmax) ranging from 5 to 30 min is associated

with improved cognitive performance relative to controls (Barella et al., 2010; Gapina et al., 2015; Hyodoa et al., 2012; Loprinzi & Kane, 2015; Lowe et al., 2014; Sibley et al., 2006; Yanagisawa et al., 2010), the effects of a single, short bout of very vigorous exercise remain unclear (i.e., > 85% HRmax) (Thompson et al., 2010). Of particular interest is the potential to increase performance on an executive functioning task, which may be related to the release of BNDF. The present study therefore tested whether a short bout of vigorous exercise (10 min of 85 ~ 90 %VO_2max) affects performance in executive functioning tasks and serum level of BDNF in young adults. We also examined the relationship of BNDF and VO2max on cognitive variables at baseline and immediately post, and 30 mins post conditions.

In the present study, we observed an effect of an exercise condition (VEX) compared with a control condition (CTL) on cognitive performance. The results demonstrated a significant improvement in all conditions in Stroop and TMT tasks compared with the control condition. Specifically, compared to CTL, VEX had a greater interference score from the Stroop test and a greater the Part B – Part A difference score from the TMT, suggesting a better executive response inhibition and response switching, respectively. Our findings are in general agreement with other studies that reported the performance on Stroop task dependent on exercise intensity, as assessed with a vigorous exercise test (Ferris et al., 2007) group and with a 10 min - high-intensity interval training at 80% of the reserve heart rate (Alves et al., 2014) compared to a low exercise intensity control. Although Ferris et al. (2007) reported post-exercise enhancement in the performance of the Stroop Word and Color conditions, we found significant performance improvements in the all Stroop conditions as well as Stroop interference after the short bout of very vigorous exercise, suggesting that more intense exercise comparably still generates the greater beneficial effects on cognitive performance. However, other studies

including young, healthy adults failed to find the more vigorous exercise-induced enhancement of Stroop task performance (Griffin et al., 2011), possibly due to a different type of cognitive test administration or exercise condition comparable to our study and of TMT (Loprinzi & Kane, 2015). Another plausible explanation may be possibly due to the estimated VO2 max or disparity of VO_2max between group conditions. This may be true because, VO_2max level was significantly correlated with the post-cognitive test, but not with pre-cognitive test, demonstrating that those who have higher level of VO_2max had better Stroop performance following the short bout of exercise. This finding could be explained by a neurophysiology study reporting that a higher fit individual had more efficient brain activity as indicated by a reduction in error-related negativity amplitude in higher fit individuals compared with lower fit individuals (Charles H Hillman et al., 2005). These results suggest that VO_2max as an important facilitator of cognitive performance (Wendell et al., 2014).

In the present study, the improved executive processes including response inhibition and response switching following an acute bout of exercise may be associated with neural activation as measured by difference in the amplitude and latency of the P3 component (Hillman et al., 2008a). The dorsolateral prefrontal cortex and anterior cingulate cortex play an essential role in executive response inhibition and switching, respectively (Gläscher, 2012). Specifically, findings from Yanagisawa et al. (2010) study on healthy adults supported the outcomes of this study as an acute bout of moderate exercise significantly improved performance on the Stroop interference by increasing activation of dorsolateral prefrontal cortex.

The beneficial effects of an acute bout of exercise on cognitive performance might be also associated with the exercise-induced increase in circulating BDNF level dependent on exercise intensity (Ferris et al., 2007; Griffin et al., 2011) and duration

(Rasmussen et al., 2009). In agreement with other studies, this investigation observed acute exercise induced a significant increase in serum BDNF level that returned to baseline at 30 min post-exercise (Griffin et al., 2011; Rasmussen et al., 2009). Specifically, the BDNF level following acute exercise is transient, but this study used a different post exercise time point, whereby BDNF elevation returned to baseline levels. To identify specific parts of the brain responsible for BDNF release, Rasmussen et al. (2009) reported most circulating BDNF levelS respond to acute exercise as measured through arterial-to-internal jugular venous difference was from the specific parts of brain including the hippocampus and cortex, which play an essential role in memory and learning and executive control process, respectively. As the acute exercise induced significant change in cognitive performance and serum BDNF level in the present study, this present study examined the relationship between the change of pre- and post-cognitive performance and the change of pre- and post-BNDF level following the acute exercise. Although the significant association between the change of TMT-A and the change of BDNF was observed, the pure cognitive process including executive response inhibition (Stroop interference) and response switching (TMT B - A) was not related to change of serum BDNF level response to the acute exercise. Possible explanations involve a different time point of blood draws (post- 0min) and cognitive test administrated (post- average of 11 min), a different type of cognitive task, or different parts of brain respond to a specific cognitive task. This possible limitation could be explained by a previous study (Griffin et al., 2011) reporting that there was a parallel association between an increase in serum BDNF concentration response to acute exercise and improved performance of the face–name task including hippocampal-dependent memory. The cognitive tasks in the present study likely activated different neural systems such as the dorsolateral prefrontal cortex and anterior cingulate cortex. If true, it would

explain why this present study did not observe a significant relationship between all cognitive tasks with serum BDNF level response to the acute exercise. The association between the release of BDNF from the brain and enhancement of cognitive performance cannot be ruled out, but future studies on this are warranted.

Delimitations and Limitations

This present study has several strengths and potential limitations. The strengths of our study include the well-controlled factors such as age, estimated crystallized intelligence, VO2max, and gender that influence the cognitive performance at rest or during exercise. This study benefitted from the controlled factors between the exercise and control conditions, which allowed us to produce valid and reliable data of cognitive performance and BNDF response to the acute vigorous exercise. A final strength was the sample size, which was considerably larger than several other studies. Because of this, we were able to work with stronger statistical power in our data on cognitive performance and BDNF response to the exercise.

The limitations of this study included the absence of lower-intensity exercise group comparable with high intensity-exercise. Regardless, the aim of this study was to identify whether the acute, very vigorous exercise still generated a beneficial effect on cognitive performance in healthy, young adults relative to the control group. In addition, it was observed that the baseline BNDF level was significantly greater compared to the returned BNDF level at the post-30 min, possibly demonstrating that some participants already might have exercise effect (e.g., active commuting)-induced change of the resting BDNF level before coming to the laboratory. This similar trend was observed in a previous study (Rasmussen et al., 2009) that suggested the evaluation of the active level was needed before reporting to the laboratory.

In conclusion, the present findings suggest that there are beneficial effects from a short bout of very vigorous exercise (10 min of 85 ~ 90 %VO2max) on cognitive performance among healthy, young adults. The acute exercise bout induced an increase in BDNF level, which may be a result of mediating the cognitive performance improvement. Therefore, if there is no serious physical fatigue and psychological tiredness observed during exercise, a short, very vigorous bout of exercise as a time-efficient activity dependent on exercise intensity contributes to the improvement in cognitive performance in healthy, young adults. Further, contributory acute exercise may have long-term benefits if shorter bouts accumulate and help the individual meet the physical activity guidelines for Americans of 150 minutes of moderate to vigorous physical activity per week.

Table 4.1.

Group Means (SD) of Descriptive Data

Variables	VEX	CTL	*P-value*
Age, year	22.84 (3.13)	24.34 (3.00)	0.08
Gender (male, %)	48.3	41.4	
Height, cm	173.86 (8.59)	167.73 (8.74)	0.01
Weigh, kg	68.81 (12.90)	64.08 (14.79)	0.20
Body Mass Index	22.63 (2.82)	22.59 (3.92)	0.96
Systolic Blood pressure, mmHg	109.41 (12.41)	108.50 (11.99)	0.77
Diastolic Blood pressure, mmHg	69.82 (8.45)	74.42 (8.07)	0.04
Cardiorespiratory Fitness			
VO2max	40.11 (9.81)	36.12 (9.21)	0.12
RER	1.10 (0.05)	1.13 (0.06)	0.06
HRmax	180.26 (15.71)	174.14 (11.68)	0.11
Crystallized intelligence			
KBIT Vocabulary	106.79 (8.56)	102.96 (9.58)	0.12
KBIT Mat	106.31 (4.31)	108.65 (8.17)	0.17
KBIT Composition	107.20 (5.32)	105.17 (7.54)	0.24

Abbreviations: VEX, Short bout of very vigorous exercise condition; CTL; Control condition; KBIT, Kaufman Brief Intelligence Test; B, Blood sample withdrawn

Table 4.2.

Correlations Between Variables for Pre- and Post- Cognitive task

	Variables	M ± SD	Age	BMI	VO2max	KBIT	Skewness, Kurtosis
	Age, year	23.68 ± 3.64	−				0.22, −1.00
	Body Mass Index	22.61± 3.38	0.002	−			1.22, 3.00
	VO2max	38.46 ± 10.02	-0.147	0.062	−		−0.01, −0.08
	KBIT composite (IQ)	106.18 ± 6.55	-0.177	-0.015	0.099	−	−0.74, 0.81
	Stroop Word (score)	107.29 ± 13.53	-.326*	0.066	0.151	0.173	0.60, 0.41
	Stroop Color (score)	79.68 ± 11.71	-.472**	0.159	0.215	0.216	0.16, −0.03
	Stroop Color Word (score)	52.86 ± 10.88	-.291*	-0.028	0.185	0.131	0.53, 0.225
PRE	Stroop Interference (score)	7.27 ± 8.80	-0.056	-0.125	0.081	0	0.55, 0.44
	Trail Making A (sec)	15.41 ± 3.87	0.178	0.109	-0.125	-0.05	0.26, −0.01
	Trail Making B (sec)	36.77 ± 10.91	0.097	0.05	-0.054	-0.224	1.42, 4.40
	Trail Making B-A (sec)	22.26 ± 10.16	0.056	-0.038	0.04	-.287*	1.34, 4.19
	Stroop Word (score)	115.03 ± 15.29	-.370**	0.031	0.208	0.074	0.69. 0.77
	Stroop Color (score)	58.84 ± 10.68	-.355**	-0.095	.345*	0.141	0.28,−0.08
	Stroop Color Word (score)	85.56 ± 13.25	-.474**	0.044	.288*	0.205	0.69, 0.18
POST	Stroop Interference (score)	9.67 ± 7.27	-0.091	-0.177	0.24	0.045	0.47, 0.95
	Trail Making Test A (sec)	13.16 ± 3.25	0.25	0.158	-0.264	-0.077	0.15, −0.45
	Trail Making Test B (sec)	31.10 ± 11.80	0.251	-0.029	-0.148	-.368**	1.92, 5.70
	Trail Making Test B-A (sec)	18.04 ± 10.62	0.203	-0.085	-0.092	-.387**	2.34, 8.75

Abbreviations: KBIT, Kaufman Brief Intelligence Test.

*P<0.05

**P<0.01.

Table 4.3.

Cognitive Performance Pre and Post Exercise

	VEX			CTL		
Cognitive Variable	Pre	Post	Δ Post - Pre	Pre	*Post*	Δ Post - Pre
Stroop Word	107.72 (13.93)	119.20 (16.20)	11.48 (5.97)**	106.86 (13.33)	112.86 (13.89)	6.00 (6.89)
Stroop Color	80.72 (9.79)	88.31 (11.52)	7.59 (6.10)*	78.65 (13.46)	82.82 (14.46)	4.17 (5.46)
Stroop Color Word	51.27 (10.25)	60.31 (11.07)	9.03 (5.95)**	54.44 (11.42)	57.37 (10.25)	2.93 (6.55)
Trail Making A	15.44 (4.57)	12.83 (3.51)	− 2.61 (3.25)	15.22 (3.14)	13.49 (2.75)	− 1.90 (2.33)
Trail Making B	39.58 (13.19)	29.39 (9.00)	− 10.19 (12.31)**	33.80 (7.26)	32.74 (13.88)	− 1.16 (10.34)

The mean difference of scores in three Stroop conditions including Stroop Word, Color, Color Word as expressed in score and two TMT parts such as TMT-A and TMT-B as expressed in second are shown in this table.

Abbreviations: VEX, Short bout of very vigorous exercise condition; CTL; Control condition

*P<0.05

**P<0.01.

Table 4.4.

Correlations between Pre- and Post- BDNF and between Pre- and Post-Cognitive Task

		Δ Post - Pre						
Variable		SW	SC	SCW	SI	TMT-A	TMT-B	TMT B-A
BNDF	Δ Post 0 - Pre	-0.061	-0.137	0.277	0.257	-.385*	-0.126	-0.035
	Δ Post 30 - Pre	0.252	-0.013	0.089	0.062	0.046	-0.251	-0.265

Abbreviations: BDNF, brain-derived neurotrophic factor SW, Stroop word; SC, Stroop color, SWC, Stroop Color Word, SI, Stroop Interference; TMT-A, Trail Making A; TMT-B, Trail Making B; TMT B-A, Trail Making B-A.

*P<0.05

	Pre-session	Baseline	Post 0			Post-session	Post 30
VEX	KBIT Stroop Trail making	B	Exercise 20 min	B	Resting 10 min	Stroop Trail Making	B
CTL	KBIT Stroop Trail making	B	Resting 30 min			Stroop Trail Making	

Figure 4.1. ***Experimental Protocol Sequence***

Abbreviations: VEX, short bout of very vigorous exercise; CTL; Control; KBIT, Kaufman Brief Intelligence Test; B, Blood sample withdrawn

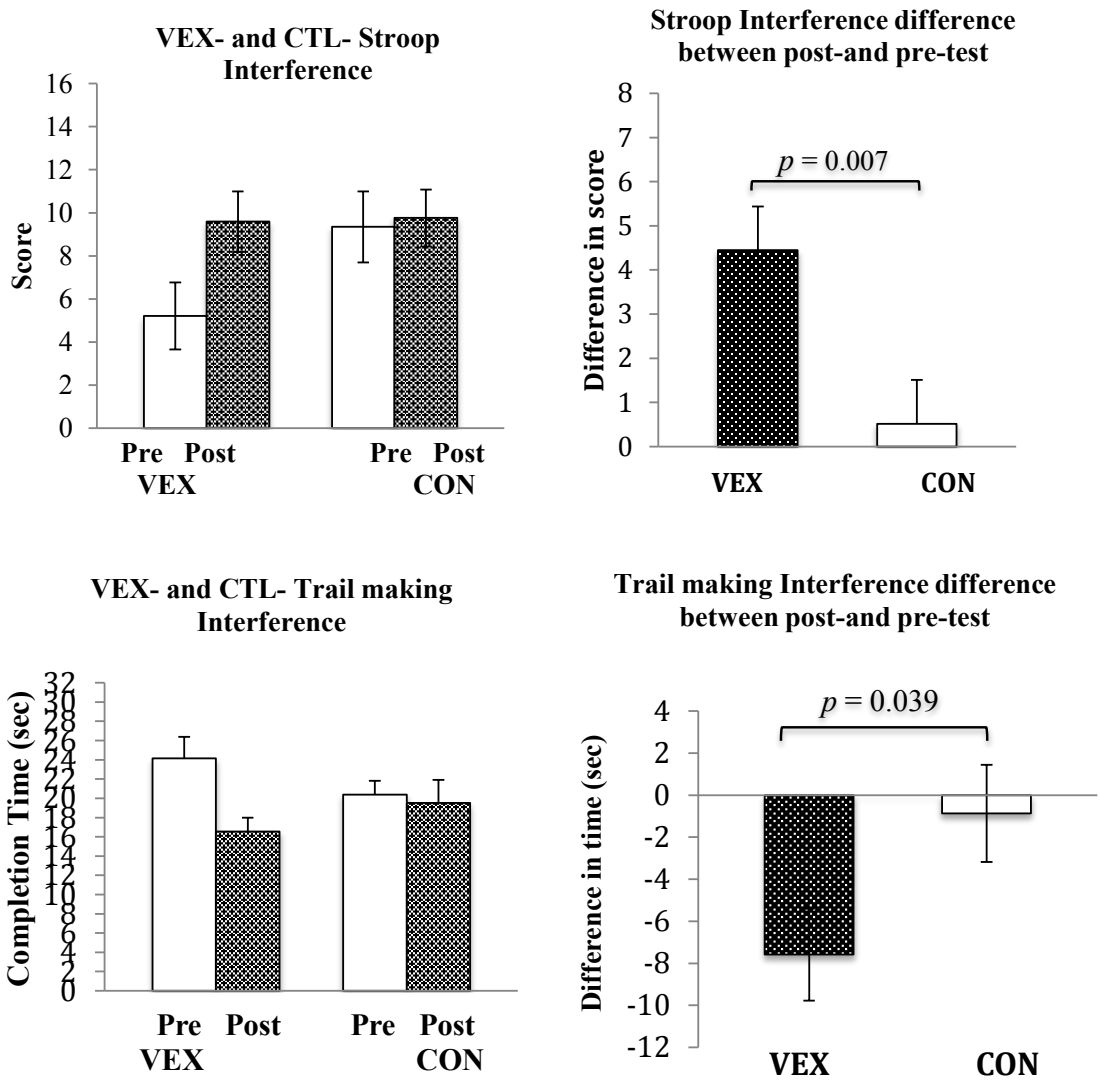

Figure 4.2. ***Stroop and Trail Making Test by Condition***

The mean difference of scores in incongruent and neutral conditions indicating the Stroop interference and TMT B-A for VEX and CTL are shown in left upper and lower). Stroop interference and TMT- B-A difference between post- and pre-sessions in VEX and CTL are shown in (right upper and lower). Abbreviations: VEX, Short bout of very vigorous exercise condition; CTL; Control condition; Data are presented as mean (standard errors).

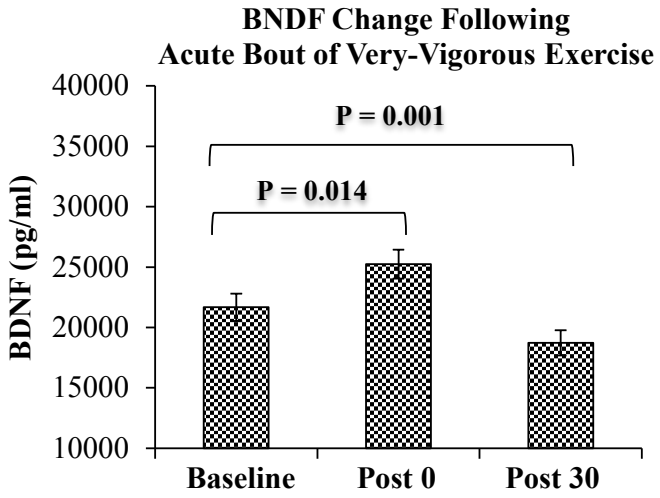

Figure 4.3. ***BDNF Change by Exercise Condition.***

Abbreviations: BDNF, brain-derived neurotrophic factor. VEX, short bout of very vigorous exercise condition. Data are presented as mean (standard errors).

Chapter IV: Study 3

EFFECT OF LOWER LIGHT LASER THERAPY AND ACUTE AEROBIC EXERCISE ON ATTENTION AND WORKING MEMORY IN YOUNG ADULTS

ABSTRACT

PURPOSE: To examine whether transcranial low-level laser therapy (LLLT), acute bout of very vigorous aerobic exercise (EX) or the combined treatments enhance the prefrontal cortex function among healthy, young adults. The researchers proposed that stimulation on the prefrontal cortex function might be dependent on divergent mechanisms from LLLT treatment and acute aerobic exercise converging on the cognitive enhancement.

METHODS: Young adults (N=60; 58.0% female, aged 23.46 ± 3.86 years; range of 18 to 31) were randomly assigned to one of four experimental groups: (a) combined low-level lower therapy and an acute bout of very vigorous aerobic exercise (LLLT+EX; n = 15); (b) low-level laser therapy (LLLT; n = 15); (c) an acute bout of very vigorous aerobic exercise (EX; n = 15); or (d) placebo control (CON; n = 15). To evaluate cognitive performance before and after the LLLT treatment, EX treatment or the combined treatments, we evaluated the performance in prefrontal function tasks of psychomotor vigilance task (PVT) and Delayed-Match-to-Sample (DMS) memory task.

RESULTS: Analysis revealed a significant interaction between group and the pre-post change in reaction time ($F_{1, 56} = 4.13$, $P = 0.01$, $\eta^2 = 0.18$). Post hoc analyses comparing the group difference between post- and pre-sessions revealed significant group difference for the session condition ($F_{1, 56} = 4.13$, $P = 0.01$) as indicated by LLLT+EX ($P = 0.002$), LLLT ($P = 0.011$), and EX ($P = 0.012$). These results demonstrated improved

reaction time in the PVT, as indicated by a significantly shorter reaction time in the treated groups, especially in LLLT+EX, compared to the CON.

However, there was no significant interaction between group and the pre-post change in correct trials in PVT ($F_{1, 56} = 4.13$, $P = 0.451$, $\eta^2 = 0.046$). Analysis demonstrated that there was no significant interaction between group and the pre-post change on memory retrieval latency in DMS ($F_{1, 56} = 0.461$, $P = 0.71$, $\eta^2 = 0.024$). However, the analysis found a significant interaction between group and the pre-post change in correct DMS trials ($F_{1, 56} = 4.69$, $P = 0.005$, $\eta^2 = 0.20$). Post hoc analyses comparing the group difference between post- and pre-sessions demonstrated significant group difference for the session condition ($F_{1, 56} = 4.69$, $P = 0.005$) as indicated by LLLT+EX ($P = 0.008$), LLLT ($P = 0.001$), and EX ($P = 0.024$). These results demonstrated that the treated groups significantly improved DMS trials, as indicated by higher trials in the treated groups compared to the CON. Particularly, LLLT and LLLT+EX showed higher statistical power compared to EX, indicating LLLT treatment might be at least in part of improving working memory when added with EX treatment.

CONCLUSION: Given the results of the present study, it is postulated that stimulation on the prefrontal cortex function might be dependent on divergent mechanisms from LLLT treatment and EX treatment converging on cognitive enhancement. These data imply that LLLT and EX could be used as a non-invasive and efficacious approach to additively increase brain functioning such as those related to executive function. Furthermore, the current exercise protocol (a short bout of very vigorous exercise) extends the optimal threshold for a cognitive task in terms of the inverted U-shape hypothesis.

Keywords: low-level laser therapy, acute aerobic exercise, attention, working memory

INTRODUCTION

Low-level laser therapy (LLLT) and acute aerobic exercise are known as non-invasive therapeutic treatments producing beneficial effects on brain and cognitive health. With mounting evidence on the aerobic exercise-cognition relationship, the beneficial effects of transcranial LLLT on cognitive function have received attention in recent years (Gonzalez-Lima et al., 2014; Gonzalez-Lima & Barrett, 2014). In terms of stimulating biological function, LLLT is known as the transcranial laser stimulation with low-power density (mW/cm^2) and high-energy density (J/cm^2) monochromatic light in the red to near- infrared wavelengths (Gonzalez-Lima & Barrett, 2014) whereas acute aerobic exercise is defined as continuous exercise performed with large muscle groups with substantially increasing cardiac output (CO) and oxygen consumption (VO_2) (Kispert & Nielsen, 1985). Although few studies have shown the beneficial effects of LLLT on cognitive function, the effects of acute aerobic exercise on complex cognitive functions have been increasingly examined using neurocognitive tests subserved by the prefrontal cortex (Hillman et al., 2008a). However, none of studies has reported the effects of LLLT and acute EX on prefrontal cortex functions as measured through cognitive testing.

Previous studies are grounded in the idea that transcranial LLLT and acute exercise may be additively beneficial for brain health and cognition as both treatments have the same target of brain region, such as the prefrontal cortex related to neurological and cognitive functions, but with proposed divergent mechanisms. The transcranial LLLT effects related to cognitive enhancement have been discovered in non-human animals (Rojas et al., 2012) as well as in human studies (Barrett & Gonzalez-Lima., 2013). These studies report that cognitive enhancement might be related to cerebral mitochondria function that increases brain oxygen utilization and metabolic capacity relevant to energy

production, which may enhance normal brain function (Hashmi et al., 2010). Further, the beneficial effect of acute aerobic exercise on cognitive enhancement was primarily observed in the prefrontal cortex relevant to cognitive function, as indicated by cortical activities, neuronal activity, and regional cerebral blood flow which was observed from event-related potential (Hillman et al., 2009; Hillman et al., 2003), functional magnetic resonance imaging (Erickson et al., 2011), functional near-infrared spectroscopy (Yanagisawa et al., 2010), and molecular event studies such as brain-derived neurotrophic factor (Ferris et al., 2007; Knaepen et al., 2010; Rasmussen et al., 2009; Whiteman et al., 2014). Given that both transcranial, LLLT and acute exercise stimulate brain function in the prefrontal cortex, the researchers hypothesized that both LLLT and acute exercise would have an additive effect on cognitive performance. This hypothesis would provide important evidence for the notion that prefrontal cortex related to cognitive function would be dependent on divergent mechanisms converging on the cognitive enhancement if there are additive effects on cognitive performance.

To explore the combined treatment effects on cognitive enhancement, we selected frontal cortex-based cognitive tasks. Namely, a psychomotor vigilance task (PVT) and a delayed match-to-sample memory task (DMS), both of which are associated with the targeted brain regions from transcranial LLLT and acute exercise. The PVT is a test for assessing an individual's sustained attention performance based on reaction time to stimuli that occur at random intervals and therefore, measures vigilant attention (Lim & Dinges, 2008). These sustained attentional processes are mediated by frontal cortical regions (Drummond et al., 2005) and the PVT has been shown to be a reliable indicator of frontal function (Dinges et al., 1997; Dinges & Powell, 1985). Another task that assesses an individual's working memory performance based on memory retrieval latency and correct match-to-sample trial is DMS, which has been shown to be mediated

by a frontoparietal network (Nieder & Miller, 2004). Although most acute exercise-cognition studies focused on executive processes in the prefrontal cortex, few studies involving very vigorous exercise intensity reported sustained attention and working memory performance using PVT and DMS, respectively.

To address the present study's hypothesis, we designed a randomized, blind, placebo-controlled study of transcranial LLLT and acute exercise on cognitive performance in healthy young adults. We sought to examine the hypothesis that transcranial LLLT, acute exercise, or the combined treatments to enhance the prefrontal cortex function as those related to cognitive functions would induce an beneficial effect on performance improvement in the cognitive tasks as measured in reaction time and correct responses using computer programs to implement prefrontal-based tasks for sustained attention and working memory. To test this hypothesis, the researchers evaluated the performance in prefrontal function tasks of the PVT and DMS memory task as responses to transcranial LLLT, acute exercise, and the combined treatments in healthy, young adults.

INSTRUMENTS AND METHODOLOGY

Selection of Participants

Healthy, English-speaking adults of either sex, with ages ranging from 18 to 30 years, of any ethnic background were considered for the study. Potential subjects who were recruited by word-of-mouth in a university environment contacted the lab and underwent a short phone screening to determine if they were interested in participating and if they met inclusion criteria. The potential subjects were asked if they had histories of any of the following conditions. The exclusion criteria for subject participation were

as follows: (a) presence of cardiovascular disease or cerebrovascular disease, (b) diagnosis of psychotic disorder, (c) history of violent behavior, (d) history of neurological condition, (e) current pregnancy, and/or (f) prior institutionalization or imprisonment; however, no participant was excluded on these bases. Sixty participants were recruited over the course of four months. The study procedure was approved by The University of Texas at Austin Institutional Review Board and involved the use of multiple physiological and cognitive assessments to provide evidence supporting the research questions of this study. Using a randomized experimental design across two days of data collection, the participants experienced one of the four conditions, which will be outlined in this section.

Instruments

All of the measurements used in this study are valid and reliable, standardized measures of cognitive, blood, and physical fitness. An anthropometric measurement of height and weight (Lohman et al., 1988) was used to calculate Body Mass Index (BMI) in accordance with standard anthropometric techniques. The measures of cognitive performance and cardiorespiratory fitness are described below.

Measurements of Crystallized Intelligence, Attention, and Working Memory

Three cognitive measurements were used for this study and included the Kaufman Brief Intelligence Test (KBIT) for crystallized intelligence, Psychomotor Vigilance Task (PVT) for attention, and Delayed Match-To-Sample Task (DMS) for working memory. Except for the KBIT, each of the cognitive function tests consisted of very short (1-minute) practice trials to familiarize participants with the tasks. Participants then partook in one actual trial.

KBIT. The KBIT is a brief, individually administered measure of verbal and nonverbal intelligence for individuals from 4 to 90 years of age (Kaufman, 1990). The KBIT contains verbal and nonverbal subscales to estimate the level of crystallized intelligence. The verbal scale is composed of two combined subtests that assess receptive vocabulary and general information as well as comprehension, reasoning, and vocabulary knowledge. The nonverbal scale uses a Matrices subtest to tap one's ability to complete visual analogies and understand relationships. Participants were asked in a quiet setting to identify objects in a picture or puzzle, which served as a representation of their vocabulary. All responses required a one-word oral or signed (point with his/her finger) response within 45 sec and took approximately 15 to 20 minutes to administer.

PVT. This cognitive task is a reaction time test for attention in which participants attend to a small, fixated point at the center of a computer screen (Dinges & Powell, 1985). At random intervals, a bright millisecond timer appears in the center of the rectangle. Participants were given short (1-minute) practice trials of the PVT to familiarize them with the task. Participants were instructed to respond via button press as rapidly as possible upon detection of the counter stimulus (i.e. participant response stops the counter from updating). The final counter value corresponded to the participant's reaction time and success or failure was displayed on-screen for 1 second, thus providing feedback for that particular trial. Participants were given 30 seconds to make a response before the computer eliminated a trial. Information about each trial's reaction time, and success or failure, was stored on the computer for later analysis. The block of PVT trials was approximately five minutes long. Intertrial intervals are randomly chosen from between two and 10 seconds or an average of six seconds. The test was organized into blocks of five minutes and consisted of approximately 45 trials. After five minutes, the

block of trials terminated, regardless of how many trials had elapsed. The post-treatment block of PVT trials was enacted in the same way as the pre-treatment.

DMS. The task is measured in both memory retrieval latency and correct match-to-sample trials (response accuracy) (Chudasama & Yogita, 2010). Participants were also given short (1-minute) practice trials of the DMS to familiarize them with the task. Participants viewed a 5 x 5 grid of brightly colored yellow and red squares with a unique pattern. Then, with a key press, that stimulus disappeared, and the screen was blank through a delay period (6 seconds). Two stimuli then were presented on screen (a "match" and "nonmatch"). Participants were asked to indicate which stimulus was the correct "match" with a key press and to respond as quickly and as accurately as possible. Correct match-to-sample trials, memory retrieval latency, and study time were measured by the computer and stored for later analysis. The average inter-trial interval in the DMS was 7.5 seconds. Scores depended on how long the subject examined each post-delay stimulus and chose the "match," which took approximately 5-6 minutes. There were 30 trials per block.

The PVT and DMS were implemented by a program called the Psychology Experiment Building Language (PEBL), an open-source programming language that can be run on any Windows computer (Mueller & Piper, 2014). One desktop computer in a closed office was designated as the testing apparatus. The data gathered by the PEBL program is outputted as a .txt file, which includes each trial's inter-trial interval in seconds, reaction time and study time in milliseconds, and a code number indicating whether the trial was a success (response in less than 30 seconds), a lapse (no response in 30 seconds), or a false alarm (responded with a button press prior to the onset of the cue). Participants were identified by a code number (their randomly-assigned subject number) which was typed into the program, prior to the start of each block of trials.

Measurement of Cardiorespiratory Fitness

Participants were initially positioned on the cycle ergometer (Velotron Dynafit Pro, Seattle WA) and then engaged in four, incremental five- minute stages of submaximal cycling for determination of the VO_2 versus work rate relationship. This was followed by a bicycle ergometer test to determine maximal oxygen consumption (VO_2 max). VO_2 max is the maximum rate the body uses oxygen for sustained energy production, which correlates highly to endurance performance (Howley et al., 1995). This test required subjects to breathe into a mouthpiece for the monitoring of oxygen consumption while cycling continuously at increasing exercise intensities. The test was ended upon volitional fatigue of the subject or when cadence falls below 60 rpm. The test lasted approximately 8 to 12 minutes and was supposed to be physically stressful and challenging for about 5 minutes. Participants likely felt fatigued for 15 to 20 minutes after the test.

Study Procedures

This placebo-controlled study measured whether both LLLT and acute exercise treatments have an additive effect on measures of attention and working memory. For this purpose, the overall study procedure was composed of two major steps. First, we assessed VO_2max to determine an individual level of exercise intensity (85~90% VO_2max). Second, we examined the effects of EX treatment, LLLT treatment, or the combination of treatments for performance on attention and working memory. Accordingly, the study consisted of two separate days of testing with a maximum of seven days between sessions. Participants were asked to refrain from strenuous exercise, caffeine consumption, and alcoholic beverages for 24 hours before the visits.

On day 1 of testing, when participants initially arrived in the laboratory, they were briefed on the details of the study and given the opportunity to sign the informed consent.

Once signed, the participant completed a medical history questionnaire. Following this period, researchers measured the participant's blood pressure, resting heart rate, height, and weight. KBIT was then assessed to serve as a control variable for the cognitive tasks. The participants completed a battery of assessments, to determine an individual's exercise intensity (85-90% of VO_2max) for a day 2 testing. A participant performed a maximal graded exercise test to volitional fatigue on a cycle ergometer (Velotron Dynafit Pro, Seattle WA) and to measure the participant's VO_2 max, which is considered to be the standard measure for cardiorespiratory fitness (Thompson et al., 2010).

On day 2 of testing, (all measurements occurred on a separate day within seven days), participants were randomly assigned to one of four experimental groups: (a) combined transcranial low-level lower therapy and an acute bout of vigorous exercise group (LLLT+EX; n = 15); (b) transcranial low-level lower therapy group (LLLT; n = 15); (c) an acute bout of vigorous exercise only (EX; n = 15); or (d) placebo control group (CON; n = 15). Specifically, 1) LLLT+EX group received 8 min-LLLT treatment (55-sec/min) following 20 min-exercise treatment and 5 min-inactive resting between pre- and post-cognitive testing. 2) LLLT group received 8 min-LLLT treatment following the 2 min-exercise placebo treatment and 23 min-resting between pre- and post-cognitive testing, 3) EX group received 8 min-LLLT placebo treatment (5-sec/min) following 20 min-exercise treatment and 5 min-inactive resting between pre- and post-cognitive testing, 4) CON group received 8 min-LLLT placebo treatment (5-sec/min) following the 2 min-exercise placebo and 23 min-resting between pre- and post-cognitive testing (Figure 5.1). Participants receiving only LLLT or LLLT placebo, or EX placebo as a treatment then sat quietly for the same duration as the exercise protocol. Use of screens or reading was not permitted during this time. Participants were given the chance to rest, have a drink of water, and use the bathroom, if requested. Before and after each

treatment, participants completed two time points of cognitive tasks, including the PVT and DMS. Researchers collected data for dependent variables including response times and successful vs. failed trials in the PVT, response times in the DMS task, and successful vs. failed trials in the DMS task. Having a pre-test (prior to each treatment) and a post-test (after each treatment) for both of the two tasks allowed us to control for individual differences in familiarity/skill with the tasks. Therefore, participants were given one block of the PVT, and one block of the DMS prior to each treatment as a pre-test. After each treatment, participants had another block of the PVT, and another block of DMS. The task order remained the same to determine if cognitive fatigue was a factor in the assessment battery.

LLLT and Active LLLT Placebo Treatments

Administration of LLLT consists of combining light of a specific wavelength (1064 nanometers) that intersects with the absorption spectrum of cytochrome oxidase with a laser diode, the CG-5000 high-density laser (Cell Gen Therapeutics, LLC). The diameter of the circular surface receiving the LLLT is 4 centimeters. The laser power output used is 3.4 Watts. The irradiance (or power density) used, 250 milliwatts/centimeter^2, as well as the cumulative fluency (or energy density) used, 60 Joules / centimeter^2, are the same parameters that showed psychologically beneficial effects in Schiffer et al. (2009) and Barrett and Gonzalez-Lima (2013). Participants receiving either the LLLT treatment or LLLT placebo treatment underwent the same treatment procedure (i.e., receiving the same instructions and having the head positioned in place with the light emitting source, CG-4000), which was activated for the same corresponding number of one-min cycles. However, for active LLLT placebo control treatment, the light exposure was reduced to 5 secs followed by 55 secs of no stimulation for every min cycle, allowing only 1/12th of the total light energy to be transmitted. Thus,

the active placebo control procedure caused all of the same sensations, lights, and sounds associated with the treatment, but using 5 secs per min minimized any possible effect, as demonstrated in a previous LLLT study using this active placebo method (Barrett & Gonzalez-Lima, 2013).

Acute EX Protocol and Exercise Placebo Protocol

The exercise protocol was a 20 min run on a treadmill, which included a 2 min-warm up, 5 min at the adjusted speed and incline in order to reach a target heart rate, and 10 min running at 85-90% of VO_2max. The treadmill session ended with a 3min cool down. The exercise intensity was classified as the very vigorous exercise intensity (very hard: ≥ 85% HRmax), according to the American College of Sports Medicine's (ACSM) classifications (Thompson et al., 2010). However, the active exercise placebo control treatment was composed of 1/12th of the 20 min endurance exercise treatment (corresponding to about 2 min) within 10% of the pre-exercise heart rate level, similar to the 1/12th of the total light energy to be transmitted in the active LLLT placebo control treatment.

Data Analysis

Statistical analyses were performed using SPSS Statistical Packages (SPSS Inc, Chicago, USA). First, it was determined whether each dependent variable was normally distributed, by assessing its skewness and kurtosis. Cronbach's alpha was used as an estimate of internal consistency and reliability for the cognitive performance variables between the pre- and post- tests. Cronbach's alpha coefficient measured the correlation between cognitive variables and the total was 0.69, which is considered reasonable for an instrument (George & Mallery, 2003). Normally distributed variables were analyzed with two-way repeated measures ANOVA (analysis of variance), using session (pre vs. post treatment) measures as the within-subject variable, and group assignment (LLLT+EX,

LLLT, EX, vs. CON) as independent variables. A significant effect of the treatments would be indicated by an interaction between the group conditions and the within-subject variable of pre-post cognitive tasks. One dependent variable, reaction time (msec) and correct trial (response accuracy) on PVT and memory retrieval latency (msec), study time (msec), correct match-to-sample trials (response accuracy)on DMS between pre- and post- treatment was analyzed with post hoc analysis using one-way ANOVA.

RESULTS

Participant characteristics between three treated groups and control group are presented as mean and standard deviation (M ± SD) in Table 5.1. The 60 participants (23.46 ± 3.86) were randomly divided into four experimental groups such as LLLT+EX (N=15), LLLT (N=15), EX (N=15) and CON (N=15) with appropriate gender distribution among the groups. There was no significant difference in confounding variables such as age ($P = 0.84$), education ($P = 0.93$), BMI ($P = 0.34$), KBIT composite (IQ; $P = 0.63$), and VO_2max ($P = 0.96$) among the groups, suggesting that the group assignment was appropriately distributed for cognitive performance test. In addition, Table 5.1 lists the criteria to determine VO_2max from a graded exercise test to exhaustion on a stationary cycle, which indicated that participants in all four groups met the accepted RER > 1.2 value.

Correlation between Confounding Factors and Cognitive Variables

Table 5.2 shows the relationships of the possible confounding factors and cognitive variables as assessed by Pearson's correlation. The positive relationship between VO_2max and cognitive variables was observed as indicated by reaction time in PVT ($r = - 0.27$, $P = 0.039$) and response accuracy ($r = 0.26$, $P = 0.045$) and reaction time

(r = - 0.37, P = 0.003 in DMS, suggesting a participant having higher fitness level had a better cognitive function at baseline. These results confirmed that VO_2max was, as predicted, a confounding factor with cognition.

Performance in Psychomotor Vigilance Task (PVT)

Table 5.3 shows the mean difference of reaction time and the correct trials among groups with an interaction effect between group and test session in PVT. Analysis using a two way repeated measures ANOVA revealed a significant interaction between group and the pre-post change in reaction time ($F_{1,56}$ = 4.13, P = 0.01, η^2 = 0.18). Post hoc analyses comparing the group difference between post- and pre-sessions revealed significant group difference for the session condition ($F_{1, 56}$ = 4.13, P = 0.01) as indicated by LLLT+EX (P = 0.002), LLLT (P = 0.011), and EX (P = 0.012) as shown in Figure 5.2.A. These results demonstrated that the treated groups improved reaction time in a sustain vigilance test, as indicated by a significant shorter reaction time in the treated groups, specially in LLLT+EX, compared to the CON. There was no main effect of group on reaction time, indicating that the random assignment of participants to one treatment group or the other was successful in balancing the groups with respect to their initial (pre-treatment) times ($F_{1,56}$ = 0.15, P = 0.924, η^2 = 0.008). In addition, there was no significant interaction of sex, group, and pre-post reaction times ($F_{1, 56}$ = 0.25, P = 0.864, η^2 = 0.014), indicating that males and females were not differentially influenced in terms of reaction time on the PVT. As such, the effects of treatment collapsed across sex are shown in Figure 5.2.A. However, there was no significant interaction between group and the pre-post change in correct trials in PVT ($F_{1, 56}$ = 4.13, P = 0.451, η^2 = 0.046) as shown in Table. 5.3. Trials on the PVT were considered ‘‘correct’’ if the participant did not have a ‘‘false alarm’’ (respond with a key press prior to the onset of the target) or have a

‘‘lapse’’ (reaction time longer than 500 s) (Dinges & Powell, 1985). The average number of correct trials was 38.13 (pre-test) and 38.46 (post-test) out of 40 for all groups, indicating there was no room for the improvement in the correct trials in PVT, particularly in young, healthy adults as supported by no significant main effect of group ($F_{1,56} = 0.82$, $P = 0.488$, $\eta^2 = 0.042$) and pre-post reaction times ($F_{1,56} = 1.834$, $P = 0.181$, $\eta^2 = 0.032$). However, there was a trend showing that the combined LLLT and EX group maintained the higher correct trial between the pre- and post- test compared to control group (p=0.093) in in Figure. 5.2.B.

Performance in Delayed Match-To-Sample Task (DMS)

Table 5.2 shows the mean difference of memory retrieval latency and correct match-to-sample trials among groups with interaction effect between group and test session in DMS. Analysis demonstrated that there was no significant interaction between group and the pre-post change on memory retrieval latency in DMS ($F_{1, 56} = 0.461$, $P = 0.71$, $\eta^2 = 0.024$). The memory retrieval latency was dependent on how long the participant examines each post-delay stimulus to choose the “match”. Accordingly, tests for normal distribution on the pre-test and post-test memory retrieval latencies on the DMS found that these variables were not normally distributed, with skewness and kurtosis values of 0.332 and 1.999 (pre-test) and -0.394 and 7.724 (post-test), respectively (Table 5.2). This result was also supported by significant main effect of group ($F_{1, 56} = 0.255$, $P = 0.045$, $\eta^2 = 0.15$), indicating there was unsuccessful in balancing the groups with respect to their initial (pre-treatment) times. However, two-way repeated measures ANOVA found a significant interaction between group and the pre-post change in correct match-to-sample trials ($F_{1, 56} = 4.69$, $P = 0.005$, $\eta^2 = 0.20$) as shown in Table 5.2. Post hoc analyses comparing the group difference between post- and

pre-sessions demonstrated significant group difference for the session condition ($F_{1, 56}$ = 4.69, P = 0.005) as indicated by LLLT+EX (P = 0.008), LLLT (P = 0.001), and EX (P = 0.024) as shown in Figure 5.3.B. These results demonstrated that the treated groups improved correct match-to-sample trials, as indicated by a significant higher trials in the treated groups compared to the CON. Particularly, LLLT and LLLT+EX showed higher statistical power compared to EX, indicating LLLT treatment might be at least in part of improving working memory when added with EX treatment. In addition, there was no significant interaction of sex, group, and pre-post reaction times ($F_{1, 56}$ = 1.217, P = 0.313, η^2 = 0.066), indicating that males and females were not differentially influenced in terms of correct match-to-sample trials on the DMS. As such, the effects of treatment collapsed across sex are shown in Figure 5.3.

DISCUSSION

This is the first randomized, placebo-controlled study to demonstrate the additive beneficial effects of combined LLLT and EX treatments on cognitive performance in healthy, young adults. Although the effect on cognitive performance has been shown in LLLT or acute exercise studies, none of these studies have reported the beneficial effects of the combined treatments on cognitive performance. Complementary with these studies, we tested the effects of LLLT treatment, EX treatment, or the combined treatments on performance in PVT and DMS, reflecting sustained attention and working memory, respectively. Our data revealed both LLLT and EX treatments improved sustained attention and working memory performance compared to the CON. The combined treatments also enhanced the cognitive performance with higher statistical power compared to EX treatment or LLLT treatment. These findings provide important

evidence that cognitive function subserved by the prefrontal cortex might be dependent on divergent mechanisms converging on cognitive enhancement.

To examine the effectiveness of EX and LLLT on cognition, the researchers selected cognitive tasks in PVT and DMS as those related to the prefrontal cortex that link with cognitive processing involving: 1) attention that refers to selectively process information in the environment; and 2) working memory that refer to retain task-relevant information in an accessible state over time (Fougnie, 2008). With regard to the cognitive tasks and brain regions, the activation from sustained attention task was related to the right- frontal polar cortical regions (Marklund et al., 2007) and the middle frontal gyrus (Yamasaki, LaBar, & McCarthy, 2002), as supported by a correlation between improved performance on a sustained attention task and increased activation in predominantly right- frontal and parietal regions (Lawrence, Ross, Hoffmann, Garavan, & Stein, 2003). Additionally, short-term memory task was associated with the dorsolateral prefrontal cortex (Funahashi, Bruce, & Goldman-Rakic, 1993) and related to increases in regional cerebral blood flow in right-hemisphere prefrontal and parietal regions with prefrontal cortex mediating convergent processes for increasing the accuracy of visuospatial memory during the delay (Grady et al., 1998).

Regarding the cognitive tasks-brain regions, in the present study, LLLT group and EX group showed beneficial effects on the prefrontal cortex functions for those associated with the cognitive tasks. This study observed a significant interaction effect between the group and the pre-post test suggesting that the beneficial effects on the sustained attention and working memory were improved by the LLLT treatment and EX treatment. The LLLT treatment directly positioned in place at the forehead to emit the monochromatic light produced the beneficial effects on the prefrontal cortex functions such as those related to neurological and psychological functioning (Barrett & Gonzalez-

Lima., 2013; Rojas et al., 2012). The monochromatic light directly excites photoacceptors in the red to near- infrared spectrum to stimulate a brain function or induce a therapeutic effect in a nondestructive and non-thermal manner (Gonzalez-Lima & Barrett, 2014). The main photoacceptor in red-to-near-infrared spectrum is the mitochondrial respiratory enzyme cytochrome oxidase. Rojas et al. (2008) reported that the transcranial LLLT deliver photons to brain neuron cells that are primarily absorbed by the mitochondrial respiratory enzyme cytochrome oxidase and up- regulate its enzymatic activity in *vivo.* The proposed mechanism is that transcranial LLLT stimulates cytochrome oxidase and thereby improves brain oxygen utilization and metabolic capacity relevant to energy production (i.e., ATP, NAD/$NADH^{+}$, Ca^{++}, cAMP, Kinase activity), which may enhance normal brain function (Hashmi et al., 2010) as supported by increases in prefrontal blood flow in human subjects (Schiffer et al., 2009). The mechanism of transcranial LLLT effects related to brain function was observed in animal study that reported the transcranial LLLT increased extinction memory retention as improved by oxygen consumption and functional connectively in the rat prefrontal cortex in vivo (Rojas et al., 2012). A human study (Barrett & Gonzalez-Lima., 2013) also observed cognitive enhancement as measured by reaction time and correct trials, PVT and memory retrieval latency, and correct match-to-sample trials in DMS immediately following the transcranial LLLT treatment. With employing the same transcranial LLLT protocol to the right forehead and targeting the frontal cortex, our data in the present study was also consistent with the previous study's findings as indicated by a shorter reaction time in PVT and a higher correct DMS in the LLLT treated group compared to the control group. Specifically, the right middle frontal gyrus targeted by the LLLT is involved in the most consistent effects for supporting sustained attention (Drummond et al., 2005; Lawrence et al., 2003).

Acute exercise- induced cognitive enhancement was verified from neuroimaging studies that observed increased cortical activation in the network of the prefrontal cortex including dorsolateral prefrontal cortex, the frontal lobe, and the anterior cingulate cortex (Hillman et al., 2008a), all of which are involved in cognitive control including attention and memory (Maguire, Frith, & Morris, 1999). Similar to the results from the LLLT treatment group in the present study, the researchers also observed a significant performance improvement in sustained attention and working memory following our exercise protocol on the cognitive tasks. This revealed a shorter reaction time in PVT and a higher correct match-to-sample trial in DMS in the acute EX group compared to those in the control group. Acute exercise- induced the performance improvement in the cognitive tasks may be due to changes in arousal state that influences cognitive processing (Polich & Kok, 1995), but dependent on physical exertion from acute exercise dose. Although acute exercise beyond an optimal threshold may cause deteriorating cognitive performance (Yerkes & Dodson, 1908; Tomporowski & Ellis, 1985; Tomporowski, Lambourne, & Okumura, 2011), our exercise protocol (10 min of 85~90% VO_2max) consisted of very high intensity, but in short amount, suggesting the optimal point for a cognitive task in terms of the inverted U-shape hypothesis (Yerkes, R. M & Dodson, 1908). Further, acute EX-induced cognitive enhancement may be related to change of physiological levels involving brain neurotransmitter release such as norepinephrine, epinephrine, and serotonin in central nervous system (Gligoroska & Manchevska, 2012). Moreover, the beneficial effects on cognitive performance might be also associated with the exercise-induced increase in circulating BDNF levels dependent on exercise intensity (Ferris et al., 2007; Griffin et al., 2011) and duration (Rasmussen et al., 2009). Rasmussen et al. (2009) reported most circulating BDNF levels respond to acute exercise as measured through arterial-to-internal jugular venous, such that the

differences are from the specific parts of brain including the hippocampus and cortex, which play essential roles in memory, learning and executive control processes (Gomez-Pinilla & Hillman, 2013). A recent study reported the release of BNDF might be regulated by exercise-induced IGF-1 production that plays a role in synaptic plasticity (Ramsey, Adams, Ariwodola, Sonntag, & Weiner, 2005), neurotransmitter release (Anlar, Sullivan, & Feldman, 1999) and that can support cognitive function (Saatman et al., 1997). In addition, a study using positron emission tomography also showed that increased cerebral blood flow during an acute bout of a moderate steady-state cycling exercise was observed in cerebellar vermis, cerebellar hemispheres, and left insula cortex (Hiura et al., 2014). The increased cerebral blood flow is known as one of the fundamental physiological mechanisms during EX (Ogoh & Ainslie, 2009), but it is less clear how increased cerebral blood flow stimulates brain activity related to cognition function. From these observations, more research is necessary to elucidate the biological mechanisms underlying acute exercise-induced cognitive performance enhancement.

Through the proposed mechanisms of LLLT and acute exercise, in the present study, we observed the combined treatments also enhanced sustained attention and working memory following acute exercise treatment and LLLT treatment. The combined group had higher statistical power compared to the EX group or the LLLT group although there was no significant mean difference in the pre-post tests compared to the EX group or LLLT group. However, it was possible that our participants are healthy young adults who are at a cognitive peak, suggesting there was no room to improve cognitive performance in our cognitive tasks. For instance, there was no significant interaction effect between the group and the pre-post test in correct trials as the average number of correct trials in PVT was 38.13 (pre-test) and 38.46 (post-test) out of 40 for all groups. Otherwise, there was a trend showing that the combined group maintained the

higher correct trial in PVT compared to the CON group ($p<0.09$). These results imply that the LLLT treatment and EX treatment would be differentiated in those who have a high vascular risk or need rehabilitation for treating neuropsychological disorders. This complicated brain network, specifically the frontal regions, may be involved in the LLLT and EX-cognition relationship as illustrated by the cognitive benefits present in this study. By augmenting the neural metabolism of the relevant frontal regions, the function of this sustained-attention network improves, leading to better performance on the PVT and DMS.

Delimitations and Limitations

The strengths of our design included a randomized, blind, placebo-controlled study of LLLT and EX on cognitive performance in healthy, young adults. In addition, confounding factors influencing pre- and post- cognitive performance were well-controlled among four groups as indicated by non-significant differences in the confounding variables, which included age, IQ, VO_2max, education year, obesity indices (i.e., waist circumstance, body mass index), blood pressure, and physical activity level with appropriate gender distribution among the groups. We were therefore, able to examine the valid and reliable data of cognitive performance responses to the LLLT treatment or the EX treatment. With regard to the limitations of this study, although every attempt was made to blind participants in active exercise placebo controls similar to the 1/12th of the total light energy transmitted in the active LLLT placebo control treatment, it is possible that participants may have perceived whether they were in the acute exercise treatment or in the exercise placebo treatment. Although a lower exercise intensity group would be needed to solve this issue, the aim of this study was to identify whether the combined treated group would have an additionally beneficial effect on cognitive performance in healthy, young adults relative to the CON group. Lastly, we did not

observe the improvement in memory retrieval latency in DMS compared to the previous study (Barrett & Gonzalez-Lima., 2013), which reported shorter memory retrieval latency in the LLLT treated group. Possible explanations involve 1) a different post-cognitive test time as all participants had an additional 25 minutes for the exercise treatment or the exercise placebo treatment before post cognitive task and 2) a characteristic of DMS task requiring that participants were asked to indicate which stimulus was the correct "match" with the two conditions (as quickly and as accurately as possible). The conditions might have prompted a delay on memory retrieval latency in the DMS task given that they required self-regulation.

Given the results of the present study, it is postulated that stimulation on the prefrontal cortex function might be dependent on divergent mechanisms from LLLT treatment and EX treatment converging on cognitive enhancement. These data imply that LLLT treatment and EX treatment could be used as a non-invasive and efficacious approach additively to increase brain functions such as those related to cognitive dimensions. Furthermore, the current exercise protocol (a short bout of very vigorous aerobic exercise) extends the optimal threshold for a cognitive task in terms of the inverted U-shape hypothesis. This research could ultimately lead to the development of non-invasive, therapeutic, and performance-enhancing interventions for both healthy humans in need of neuroprotection, and for those in need of rehabilitation for the treatment of neuropsychological disorders.

Table 5.1. *Mean (± SD) for Participant' Characteristics*

Control Variable/Gr	TOTAL	CON (n=15)	AE (n=15)	LLLT (n=15)	LLLT+AE (n=15)	*p*
Gender, female n (%)	35 (58.3)	8 (53.3)	9 (60)	9 (60)	9 (60)	
Race n (%)						
Caucasian	17 (28.3)	3 (20)	6 (40)	5 (33.3)	3 (20.0)	
Asian	31 (51.7)	8 (53.3)	6 (40)	6 (40.0)	11 (73.3)	
Mexican	9 (15.0)	2 (13.3)	3 (20)	3 (20.0)	1 (6.7)	
Other	3 (5)	2 (13.3)		1 (6.7)		
Age, years	23.46 ± 3.86	23.60 ± 4.36	23.40 ± 4.03	22.80 ± 2.73	24.07 ± 4.33	0.847
Education, years	16.48 ± 2.92	16.60 ± 2.87	16.53 ± 2.47	16.06 ± 2.57	16.73 ± 3.84	0.935
Anthropometric						
Height	167.69 ± 9.24	166.87 ± 8.70	166.24 ± 9.06	168.64 ± 10.04	169.01 ± 9.76	0.821
Weight	63.99 ± 12.53	60.59 ± 12.53	61.83 ± 13.97	68.23 ± 15.09	65.30 ± 13.81	0.432
BMI	22.59 ± 3.52	21.69 ± 3.48	22.21 ± 3.48	23.87 ± 4.33	22.61 ± 2.53	0.379
Waist	78.20 ± 9.19	77.86 ± 8.83	77.91 ± 9.30	76.72 ± 9.31	80.19 ± 9.91	0.787
Blood pressure						
SBP	109.25 ± 12.22	104.67 ± 12.59	109.07 ± 11.50	112.40 ± 12.28	111.00 ± 12.32	0.341
DBP	74.84 ± 8.02	71 ± 8.09	75.8 ± 7.79	75.73 ± 7.29	77.00 ± 8.83	0.184
Cardiorespiratory Fitness						
Vo_2 max	36.17 ± 9.39	35.95 ± 7.81	36.49 ± 8.85	36.48 ± 11.91	35.76 ± 9.50	0.995
HRmax	180.52 ± 11.82	179.66 ± 5.71	175.53 ± 13.82	182.26 ± 12.64	184.26 ± 12.59	0.192
RER	1.14 ± 0.08	1.15 ± 0.09	1.12 ± 0.08	1.14 ± 0.09	1.14 ± 0.05	0.655
PA level, MET	625.05 ± 419.48	648.23 ± 517.86	708.00 ± 372.93	649.96 ± 423.13	494.03 ± 358.11	0.553
Sedentary level, min	461.19 ± 168.13	488.00 ± 192.24	476.00 ± 198.30	458.57 ± 165.75	422.00 ± 112.51	0.735
KBIT						
Vocabulary	99.95 ± 13.37	102.33 ± 15.29	99.53 ± 14.91	101.13 ± 13.92	96.80 ± 9.21	0.706
Matrices	106.60 ± 8.08	107.47 ± 8.02	107.27 ± 9.07	105.60 ± 6.42	105.67 ± 7.36	0.880
Composite	103.45 ± 9.07	105.47 ± 11.22	103.60 ± 7.90	103.67 ± 9.76	101.07 ± 7.27	0.628

Abbreviations: BMI, body mass index; VO2max, maximal oxygen consumption; PA, physical activity; MET, metabolic equivalent; KBIT, Kaufman Brief Intelligence Test

Table 5.2.

Correlation between Confounding Variable and Pre-Cognitive Variable

	1	2	3	4	5	6	7	8
1. Age, yrs.	–							
2. BMI	-0.002	–						
3. Vo2 max	-0.017	0.073	–					
Crystallized intelligence								
4. KBIT Composition	-0.033	0.101	0.12	–				
Psychomotor Vigilance Task								
5. Reaction Time (msec)	-0.027	0.047	-.268*	0.178	–			
Delayed match sample test								
6. Response accuracy (score)	0.238	0.073	.260*	-0.072	-0.19	–		
7. memory retrieval latency (msec)	-0.164	-0.004	-.371**	-0.043	0.08	-0.181	–	
8. Study time (msec)	-0.098	0.171	-0.036	-0.051	-0.095	0.126	.485**	–
M	23.46	22.59	36.17	103.45	356.37	27.23	3656.06	1963.94
SD	3.86	3.52	9.39	9.07	28.31	1.77	1710.22	639.44

Abbreviations: BMI, body mass index; VO2max, maximal oxygen consumption; KBIT, Kaufman Brief Intelligence Test; PVT, Psychomotor Vigilance Task; DMS, Delayed Match Sample test

Table 5.3.

Mean (± SD) for Cognitive Task Performance and Interaction Effect Between Session and Group

Cognitive variable		Psychomotor Vigilance Task				Delayed-Match-to-Sample Memory Task					
Group	Session	Reaction Time (msec)		Correct trial (score)		Reaction Time (msec)		Correct trial (score)		Study Time (msec)	
		M	S.D.	M	S.D.	M	S.D.	M	S.D.	M	S.D.
CON	PRE	349.55	(28.67)	38.13	(1.96)	1660.67	(527.24)	27.00	(1.56)	2545.70	(937.12)
	POST	359.52	(23.67)	37.93	(2.46)	1691.92	(544.59)	25.27	(2.34)	2362.21	(1006.58)
EX	PRE	354.96	(25.52)	38.33	(1.45)	1895.02	(644.92)	27.73	(1.53)	3407.30	(1668.24)
	POST	345.0	(16.88)	38.67	(1.23)	1784.21	(660.74)	27.87	(1.46)	2961.52	(1355.33)
LLLT	PRE	360.97	(29.35)	37.87	(1.68)	2122.85	(647.86)	26.60	(1.76)	3667.88	(1797.55)
	POST	350.79	(25.91)	38.13	(1.51)	2237.57	(1130.47)	27.73	(1.83)	3125.29	(2117.45)
LLLT+EX	PRE	360.01	(30.89)	38.20	(1.78)	2177.23	(655.82)	27.60	(2.10)	5003.36	(1449.65)
	POST	345.31	(31.91)	39.13	(1.36)	2275.86	(685.55)	28.07	(1.44)	4530.91	(2308.24)
F		4.134		0.892		0.461		4.69		0.294	
p		0.01		0.451		0.71		0.005		0.829	
η2		0.181		0.046		0.024		0.201		0.016	
Skewness	PRE	0.42		-1.43		0.33		-0.77		0.47	
	POST	0.33		-1.96		2.00		-1.09		1.36	
Kurtosis	PRE	-0.76		2.01		-0.39		1.63		-0.94	
	POST	0.33		5.24		7.27		1.24		1.93	
Cronbach's alpha	PRE POST	0.785		0.554		0.815		0.389		0.898	

Abbreviations: LLLT+EX, combined low-level lower therapy and an acute bout of vigorous exercise group; LLLT, low-level lower therapy group; EX, acute bout of vigorous exercise group; CON, placebo control group.

Group	Pre-test		Treatment						Post-test
LLLT	PVT DMS	→	Exercise Placebo 2 min	→	Rest 23 min	→	LLLT 8 min (60sec/cycle)	→	PVT DMS
EX	PVT DMS	→	Acute Exercise 20 min	→	Rest 5 min	→	LLLT Placebo 8 min (5sec/cycle)	→	PVT DMS
LLLT+EX	PVT DMS	→	Acute Exercise 20 min	→	Rest 5 min	→	LLLT 8 min (60sec/cycle)	→	PVT DMS
CTL	PVT DMS	→	Exercise Placebo 2 min	→	Rest 23 min	→	LLLT Placebo 8 min (5sec/cycle)	→	PVT DMS

Figure 5.1. ***Day 2-Experimetnal Protocol Sequence***

Abbreviations: LLLT+EX, combined low-level lower therapy and an acute bout of vigorous exercise group; LLLT, low-level lower therapy group; EX, acute bout of vigorous exercise group; CON, placebo control group.; PVT, Psychomotor Vigilance Task; DMS, Delayed Match-To-Sample Task.

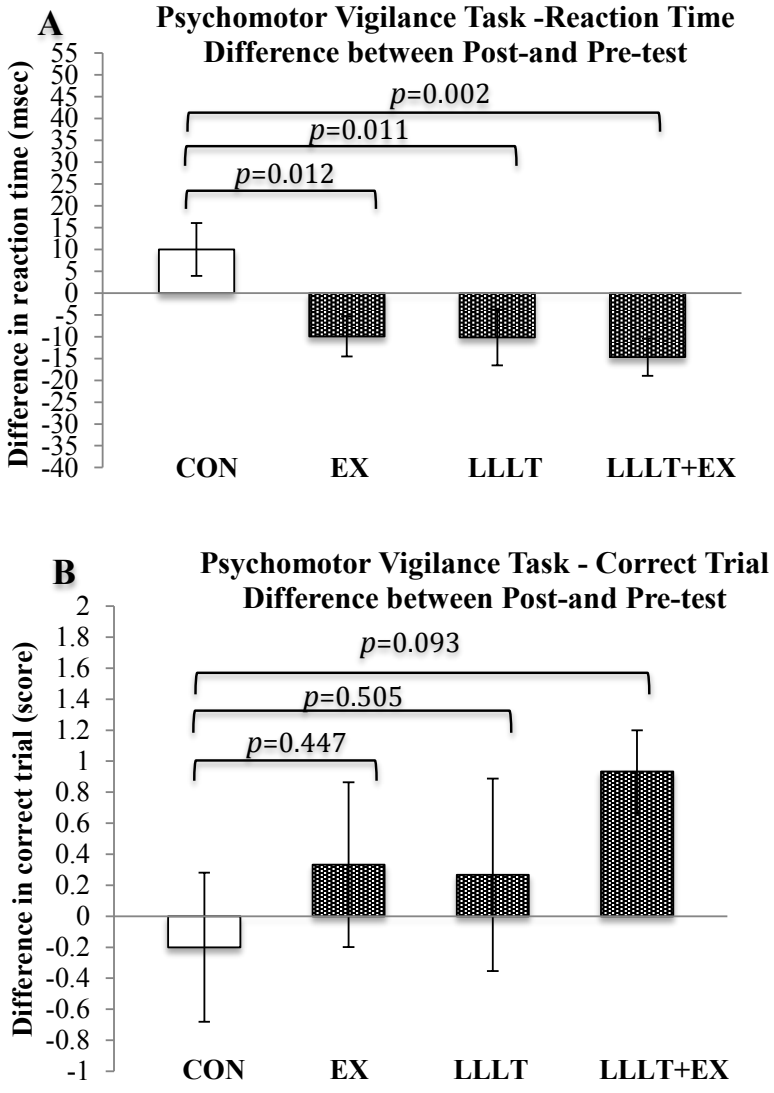

Figure 5.2. ***Psychomotor vigilance task (PVT).***
The mean differences of reaction time (A) and correct trial (B) in PVT indicating the attention performance for three treated groups and CON are shown in this table. Abbreviations: LLLT+EX, combined low-level lower therapy and an acute bout of vigorous exercise group; LLLT, low-level lower therapy group; EX, acute bout of vigorous exercise group; CON, placebo control group. Data are presented as mean (standard errors).

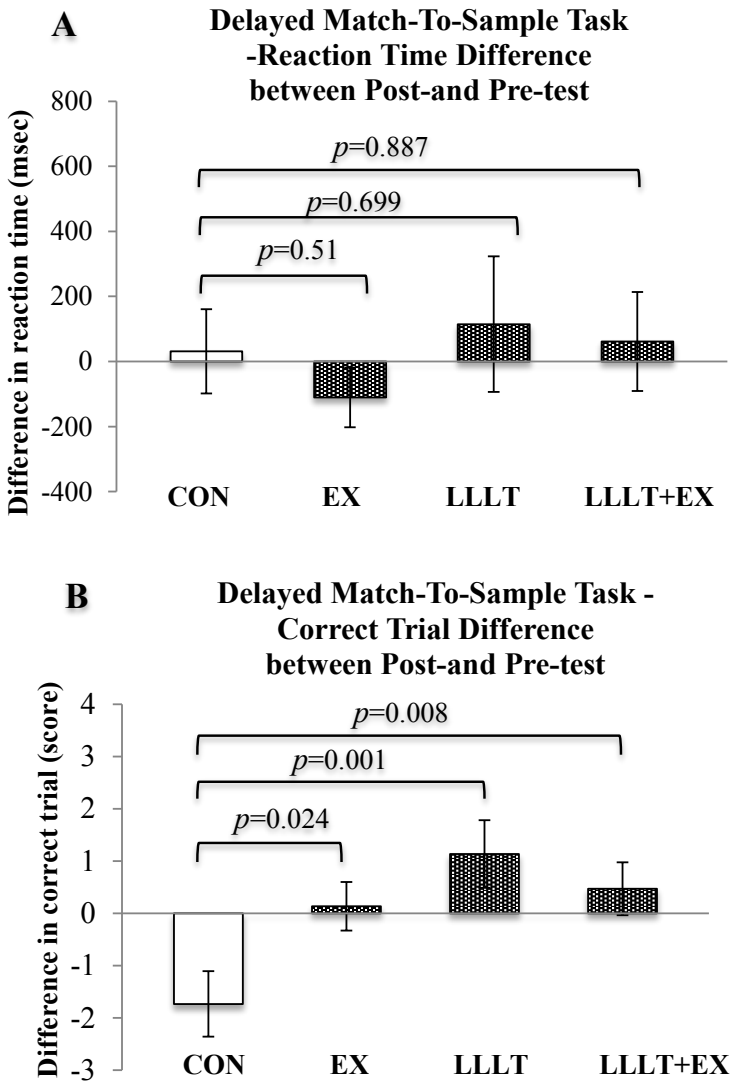

Figure 5.3. Delayed Match-To-Sample Task (DMS).

The mean difference of memory retrieval latency (A) and correct match-to-sample trials (B) indicating the working memory performance for three treated groups and CON are shown in this table. Abbreviations: LLLT+EX, combined low-level lower therapy and an acute bout of vigorous exercise group; LLLT, low-level lower therapy group; EX, acute bout of vigorous exercise group; CON, placebo control group. Data are presented as mean (standard errors).

Chapter VI: Discussion

The goal in this series of dissertation studies was to determine (a) a relationship between cardiovascular risk, physical activity, fitness, body mass index and cognitive function, (b) a very vigorous exercise intensity-induced effects on executive functioning performance and molecular factor, and the potential (c) additive effectiveness of low-level light therapy (LLLT) and an acute aerobic exercise (EX) on attention and working memory. The results of these studies are summarized below.

Although previous research has demonstrated the association between vascular risk and cognitive function (Komulainen et al., 2007; Noble et al., 2010) or between physical activity/fitness and cognitive function (Castelli et al., 2014; Hillman et al., 2008a), no previous studies have explored the link among vascular risk, cardiorespiratory fitness, physical activity level, and obesity with cognitive function in young population. Accordingly, the first study examined the independent association between health indices including cardiorespiratory fitness, physical activity, body mass index (BMI), vascular risk factor such as C-reactive protein (CRP) and cognitive function such as crystalized intelligence and executive control function of inhibitory control, response switching, attention, and working memory in young adults. We found that a higher cardiorespiratory fitness was negatively related to a lower CRP level whereas a lower BMI level was positively associated with the lower CRP level. It was also observed a positive relationship between cardiorespiratory fitness and working memory and between physical activity level and inhibitory control and working memory, suggesting higher physical activity participation-induced improvement of cardiorespiratory fitness would have a greater cognitive function. Although BMI was not directly related to any variable of cognitive function, a strong negative association that BMI has with CRP appears to

contribute to cognitive dysfunction due to an increased indirect effect between BMI and working memory when CRP was considered as a potential mediator. Significantly, it was observed that a high-risk condition (CRP >3mg/L) relative to that in a low-risk condition was associated with worse cognitive function, suggesting that those who have high-CRP risk levels had deleterious effect on cognitive function especially such as inhibitory control and working memory. Thus, it was concluded that the more frequent intense physical exercise participation-induced improvements in cardiorespiratory fitness on vascular risk and cognitive functions particularly in working memory and inhibitory control.

Additionally, although previous research has shown exercise-induced change in cognitive performance and cognitive marker [i.e., brain-derived neurotrophic factor (BDNF)] with moderate- and vigorous- exercise intensity protocol (Ferris et al., 2007), no previous research has examined the single, short bout of very vigorous exercise (i.e., > 85% HRmax) (Thompson et al., 2010) on the cognitive and molecular change dependent on the exercise intensity. Therefore, the findings from the second study perhaps have the greatest potential to impact the filed given that it was determined that very vigorous exercise intensity-induced effects on cognitive performance and molecular factors. The finding that a short bout of very vigorous exercise improved performance in inhibitory control and response switching and increased BNDF level immediately following the exercise protocol also has valuable implications for the identification of underlying mechanisms. The acute exercise-induced increase in BDNF level might be at least in part a representation of the possible mediating effects on cognitive performance improvement, as a significant correlation between a change of pre- and post- response switching and a change of pre- and post-BNDF level was evidenced. Interestingly, it was observed that cardiorespiratory fitness was significantly correlated with all post cognitive conditions

while not with a pre- cognitive test condition, suggesting those having higher fitness levels had a better cognitive performance. Based on these results, it was concluded that a short, very vigorous exercise as a time-efficient exercise dependent on exercise intensity is contributory to the improvement in cognitive performance in healthy, young adults. Furthermore, the exercise protocol (a short bout of very vigorous exercise) extends the optimal threshold for a cognitive task in terms of the inverted U-shape hypothesis.

Lastly, no study has shown that effect of combined low-level light therapy (LLLT) and an acute bout of aerobic exercise (EX) enhances neural metabolism in the prefrontal cortex of humans as those related to neuropsychological tests (Gonzalez-Lima et al., 2014). Accordingly, in the third study, the researchers compared effectiveness of LLLT and EX on reaction time and correct responses using computer programs to implement prefrontal-based tasks for attention and working memory. It was found that LLLT, EX, or LLLT+EX all improved reaction time in a sustained attention test, as indicated by a significant shorter reaction time in the treated groups compared to the CON. Specially, LLLT+EX had a higher statistical power compared to EX and LLLT in the improved reaction time. In addition, the treated groups improved working memory, as indicated by a significant higher correct match-to-sample trial in the treated groups compared to the CON. Especially, LLLT+EX showed higher statistical power compared to EX, indicating LLLT treatment might be at least in part of improving working memory when added with EX treatment. Given the results of this study, it was concluded that LLLT and EX-induced stimulation on the prefrontal cortex function might be dependent on divergent mechanisms converging on the cognitive enhancement. These data imply that LLLT and acute EX could be used as a non-invasive and efficacious approach to increasing brain functions such as those related to various cognitive dimensions (i.e. congruent, incongruent, attention, working memory).

Taken together, the collective findings of these studies suggest that identifying the relationships of fitness and vascular risk with cognitive function, as well as mediators and moderators of these associations, can help to explain the complexities of the cognitive process among young adults. Once these relationships are identified, the knowledge generated can be used to inform the evolution of the conceptual model of how health risk involves cognitive process among young adults groups. Moreover, determining the exercise intensity-induced cognitive benefit can help to develop physical activity programming based on parameters such as intensity and amount. LLLT that contributes to improve cognitive health is proposed as part of a holistic neurotherapeutic construct with aerobic exercise and has the potential as an alternative to pharmacological remedies. These series of studies could ultimately lead to the development of non-invasive, therapeutic, and performance-enhancing interventions in both healthy humans in need of neuroprotection and help those in need of rehabilitation by treating neuropsychological disorders.

IMPLICATIONS AND FUTURE RESEARCH

Our findings suggest that physical exercise-induced the increase in cardiorespiratory fitness can have a positive effect on multiple aspects of cognition through the improvement of vascular health. Although the number of studies on physical activity/fitness and cognition is certainly larger for older adult population than for other age population, our data suggest that physical activity/fitness can have beneficial effects throughout the lifespan. Additionally, our data demonstrate even a short bout of very vigorous exercise improved cognition, which contributing to a development of exercise programme. Importantly, in aspect of physical education, our findings implicate an accumulation of physical activity from the short bout of very vigorous exercise program

contribute to the improvement of cardiorespiratory fitness, which may be a crucial factor to support a relationship between cognitive and physical health and academic performance during childhood. More significantly, our findings not only highlight the importance and necessity of physical activity throughout physical education but also emphasize physical education as an academic subject in a school curriculum. Accordingly, theses findings implicate a undergraduate physical education program needs to address the importance of physical activity on cognition and to instruct the optimized exercise programme for student teachers who deliver the practice and knowledge of cognitive and physical health to their future students.

Several areas deserve attention in future research. Since the associations between the physical exercise-induced cardiorespiratory fitness and cognition for young adults was measured in this study, future studies can focus on how exercise interacts with other health risk factors such as obesity and a high-fat diet in influencing cognition particularly for school-aged children. A recent study reported there is an interaction of exercise and diet at the cognitive behavioral and molecular levels (Gómez-Pinilla, 2008). Therefore, further study is warranted to investigate the interaction of exercise and diet by a long-term intervention. Additional research is needed to shed light on how the interaction between exercise and diet impacts cognitive and physical health and academic performance particularly for school-aged children who are embedded in obesogenic environments that manifest sedentary lifestyles.

CONCLUSIONS

In conclusion, there is converging evidence at the molecular, cognitive and vascular risk levels that physical exercise-induced the improvement of cardiorespiratory fitness is beneficial to cognition. Such evidence highlights the significance of promoting

physical activity across the lifespan to improve cognitive health or prevent cognitive decline, as well as to reverse sedentary behavior causing obesity and metabolic disease. Accordingly, physical activity can serve to promote brain and physical health in individuals.

Appendix A

Correlations between Health Indices and Cognitive Task Variables in Chapter III: Study1

	Variables	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1	Age, year	–																		
2	BMI	0.07	–																	
3	WC	-0.07	.76**	–																
4	VO2 max	-0.04	0.03	0.06	–															
5	MET	-0.13	0.06	0.07	.30*	–														
6	CRP	0.03	.31**	.42**	-0.27*	-0.23														
	KBIT						–													
7	Voca	-0.18	0.02	-0.02	0.14	0.05	.25*	–												
8	Matt	.28**	0.02	-0.07	0.18	0.04	0.01	0.07	–											
9	Comp	-0.03	0.03	-0.05	0.20	0.06	0.19	.87**	.54**											
	Stroop test									–										
10	SW	-0.16	0.17	0.07	0.12	-0.04	-0.08	.39**	-0.01	.33**	–									
11	SC	-.35**	0.13	-0.01	0.18	0.22	-0.08	.41**	0.08	.38**	.56**	–								
12	SCW	-0.15	0.03	0.00	0.19	.303*	-.27*	0.13	.31**	.26*	.40**	.62**	–							
13	SI	0.06	-0.08	-0.02	0.10	.279*	-.29*	-0.18	.35**	0.02	-0.09	0.09	.81**							
	TMT													–						
14	TMT A	-0.03	0.12	0.23	-0.13	-0.11	0.20	-0.12	-0.20	-0.19	-.29**	-.43**	-.37**	-0.15	–					
15	TMT B	0.05	-0.13	-0.13	-0.09	-0.09	-0.03	-0.17	-.32**	-.29**	-.22*	-.237*	-.34**	-.26*	.46**	–				
16	TMT B-A	0.10	-0.18	-.31*	-0.02	-0.01	-0.13	-0.13	-.24*	-.23*	-0.11	-0.06	-.22*	-.21*	0.02	.89**				
	PVT																–			
17	RT	-0.10	0.11	0.05	-0.06	-0.18	0.17	0.02	0.06	0.05	-0.12	-0.13	-0.06	0.03	0.05	-0.15	-0.24			
	DMS																			
18	CT	0.05	0.06	0.14	0.21	0.02	-0.06	-0.21	0.08	-0.13	-0.16	-0.24	-0.10	0.06	0.10	-0.02	-0.09	.67**	–	
19	RT	-0.14	0.06	0.19	-.27*	-.29*	.38**	0.02	-.25*	-0.11	-0.06	-0.24	-0.25	-0.17	.28*	0.23	0.08	.31*	.28*	–
	Mean (SD)	23.68 (3.68)	22.51 (3.33)	77.9 (9.14)	37.78 (9.63)	697.41 (415.25)	1.83 (1.91)	102.06 (12.24)	106.39 (6.99)	104.59 (8.17)	107.32 (14.90)	78.65 (12.74)	53.01 (10.83)	7.81 (8.73)	15.79 (5.03)	38.26 (11.46)	22.10 (10.07)	352.51 (53.23)	26.62 (3.97)	1900.05 (635.41)
	Skewness	0.65	0.95	0.67	0.29	0.75	1.91	-0.99	0.65	-0.45	-0.41	-0.38	0.42	0.24	1.22	0.92	0.92	-4.87	-5.19	-0.01
	Kurtosis	-0.62	2.02	0.13	-0.52	-0.13	4.34	2.26	0.13	1.65	2.15	0.93	0.51	0.08	2.55	2.02	2.62	32.46	34.11	0.40

Abbreviations: KBIT, Kaufman Brief Intelligence Test; Voca, Vocabulary; Comp, Composition; BMI, body mass index; WC, waist circumstance; VO2max, maximal oxygen consumption; SW, Stroop Word; SC, Stroop Color; SCW, Stroop Color Word ; SI, Stroop Interference; MET, metabolic equivalent; CRP, C-reactive protein; TMT, trail making test; PVT, Psychomotor vigilance task; DMS, Delayed match sample test; RT, reaction time; CT, correct trial

*P<0.05

**P<0.01.

Appendix B

Correlations between Variables for Pre- and Post-Cognitive Task in Chapter IV: Study2

	Variables	Age	BMI	VO2max	KBIT	PRE SW	PRE SC	PRE SCW	PRE SI	PRE TMT-A	PRE TMT-B	PRE TMT B-A	POST SW	POST SC	POST SCW	POST SI	POST TMT-A	POST TMT-B	POST TMT B-A
	Age, year	–																	
	BMI	.01	–																
	VO2max	-.14	.06	–															
	KBIT	-.17	-.01	.09	–														
PRE	SW	-.32*	.06	.15	.17	–													
PRE	SC	-.47**	.15	.21	.21	.68**	–												
PRE	SCW	-.29*	-.02	.18	.13	.44**	.61**	–											
PRE	SI	-.05	-.12	.08	.01	-.03	.11	.83**	–										
PRE	TMT-A	.17	.1	-.12	-.05	-.31*	-.43**	-.39**	-.19	–									
PRE	TMT-B	.09	.05	-.05	-.22	-.13	-.26*	-.41**	-.33**	.41**	–								
PRE	TMT B-A	.05	-.03	.04	-.28*	0.01	-.01	-0.2	-.23	.02	.86**	–							
POST	SW	-.37**	.03	.21	.07	.89**	.69**	.42**	-.03	-.29*	-.09	.08	–						
POST	SC	-.35**	-.09	.34*	.14	.46**	.66**	.79**	.55**	-.37**	-.34**	-.14	.57**	–					
POST	SCW	-.47**	.04	.28*	.21	.68**	.89**	.56**	.09	-.39**	-.30*	-.07	.76**	.77**	–				
POST	SI	-.09	-.17	.24	.04	-.07	.15	.66**	.76**	-.18	-.28*	-.21	-.01	.77**	.23	–			
POST	TMT-A	.25	.15	-.26*	-.07	-.29*	-.33*	-.49**	-.36**	.69**	.29*	.01	-.35**	-.52**	-.37**	-.38**	–		
POST	TMT-B	.25	-.02	-.14	-.36**	-.07	-.26*	-.16	-.05	.40**	.43**	.26*	-.15	-.31*	-.28*	-.21	.47**	–	
POST	TMT B-A	0.21	-.08	-.09	-.38**	0.01	-.21	-.03	.05	.24	.38**	.27*	-.06	-.19	-.21	-.13	.22	.96**	–
	M ± SD	23.68 ± 3.64	22.61± 3.38	38.46 ± 10.02	106.18 ± 6.55	107.29 ± 13.53	79.68 ± 11.71	52.86 ± 10.88	7.27 ± 8.80	15.41 ± 3.87	36.77 ± 10.91	22.26 ± 10.16	115.03 ± 15.29	58.84 ± 10.68	85.56 ± 13.25	9.67 ± 7.27	13.16 ± 3.25	31.10 ± 11.80	18.04 ± 10.62
	Skewness	.22	1.22	−.01	−.74	.6	.16	.53	.55	.26	1.42	1.34	.69	.28	.69	.47	.15	1.92	2.34
	Kurtosis	−1.00	3.00	−.08	.81	.41	−.03	.22	.44	−.01	4.4	4.19	.77	−.08	.18	.95	−.45	5.7	8.75
Cronbach's Alpha												0.69							

Abbreviations: BMI, body mass index; KBIT, Kaufman Brief Intelligence Test; SW, Stroop word; SC, Stroop color, SWC, Stroop Color Word, SI, Stroop Inte Abbreviations: BMI, body mass index; KBIT, Kaufman Brief Intelligence Test; SW, Stroop word; SC, Stroop color, SWC, Stroop Color Word, SI, Stroop Interference; TMT-A, Trail Making A; TMT-B, Trail Making B; TMT B-A, Trail Making B-A. *P<0.05; **P<0.01

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Vita

Jungyun Hwang was born in Seoul, South Korea. He received her Bachelor of Exercise Science/Physical Education in 2001 and Master of Health Education in 2003 from Korea National Sport University, Seoul, South Korea. Upon graduation, he worked at the Korean Exercise Instruction Association in South Korea for three years. After completing his work, he entered the University of Texas at Austin and received his Master of Exercise Physiology in 2010. In August of 2011, he started graduate school in the Division of Physical Education Teacher Education at The University of Texas at Austin.

Permanent email: jy_hwang@utexas.edu

This dissertation was typed by the author.