THE EFFECTS OF PHYSICAL ACTIVITY ON THE BRAIN AND COGNITION DURING CHILDHOOD

BY

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DISSERTATION

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ABSTRACT

Introduction. This dissertation investigates the influence of physical activity on the cognitive and brain health of children. It is motivated by experimental studies in rodents and older adults that demonstrate a positive influence of physical activity and aerobic exercise on cognition, brain structure, and brain function. Furthermore, a growing number of cross-sectional studies suggest that physical activity and higher levels of aerobic fitness in children are positively associated with brain structure, brain function, cognition, and school achievement. Higher fit children have larger brain volumes in the basal ganglia and hippocampus, which relate to superior performance on tasks of cognitive control and memory, respectively, when compared to their lower fit peers. Higher fit children also show superior brain function during tasks of cognitive control and better academic achievement compared to lower fit and less active children.

Method. This dissertation extends previous cross-sectional research by examining the influence of a 9-month randomized controlled after-school physical activity program on brain structure, brain function, and cognition in children. Children were randomized into a physical activity intervention group or a wait list control group, and VO\textsubscript{2} max fitness testing, magnetic resonance imaging (MRI) and cognitive testing were conducted before and after the 9-month intervention. Structural brain measures included volumes of the basal ganglia and hippocampus characterized by FMRIB’s Integrated Registration and Segmentation Tool (FIRST) as well as the integrity of white matter tracts using diffusion tensor imaging (DTI). Brain function was assessed using functional magnetic resonance imaging (fMRI) while children performed a task that required attentional, interference and inhibitory control.

Results. Although this dissertation is limited by a small sample size and lack of statistical interactions, it is one of the first studies to use MRI techniques to make preliminary conclusions about the association between participation in an after-school physical activity program and cognitive and brain health in children. Eight- to 9-year-old children who participated in more than the recommended 60 minutes of moderate to vigorous physical activity, 5 days per week, for approximately 9 months, showed within-group increases in the volume of the dorsal striatum of the basal ganglia and the hippocampus. Physically active children also demonstrated within-group increases in fractional anisotropy (an estimation of white matter integrity) and decreased radial diffusivity (an estimation of myelination) in a global network of white matter tracts throughout the brain from pre-test to post-test. Additionally, children in the physical activity program demonstrated within-group improvements in attentional control during a flanker task, which paralleled decreases in fMRI brain activation in the right anterior prefrontal cortex. In fact, their changes in activation and performance led to brain function similar to young adults. Children in the wait list control group did not show changes in anterior prefrontal activation or performance from pre-test to post-test.
Conclusion. Given that children have become increasingly sedentary, unfit and overweight, understanding the benefits of physical activity on cognition is of great significance. This dissertation suggests that physical activity may improve the cognitive and brain health of 8- to 9-year-old children. Although the results are preliminary, they have implications for the biological potential of the brain during periods of maturation and brain development, and suggest that the developing brain is plastic and sensitive to lifestyle factors. In particular, this dissertation demonstrates that physical activity during childhood may influence the volume of the basal ganglia and hippocampus, the integrity of white matter tracts, and brain activation in the prefrontal cortex. Hopefully, the results will raise public awareness of the cognitive benefits of physical activity during childhood.
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CHAPTER 1
INTRODUCTION

An active lifestyle during childhood is beneficial to physical, cognitive and brain health. Physical activity may help prevent chronic diseases such as obesity, cancer, Type II diabetes, and coronary heart disease throughout the lifespan (Centers for Disease Control and Prevention, 2009; United States Department of Health and Human Services, 2008). Physical activity is also associated with enhanced cognitive function as measured in well normed neuropsychological and psychometric tests (Buck, Hillman, & Castelli, 2008; Chaddock, Hillman, Buck, & Cohen, 2011; Sibley & Etnier, 2003). In addition, physical activity and higher levels of aerobic fitness have been found to be associated with superior academic achievement in the primary school classroom (Castelli, Hillman, Buck, & Erwin, 2007; Chomitz et al., 2009; Coe, Pivarnik, Womack, Reeves, & Malina, 2006; Trudeau & Shephard, 2008). The performance differences of higher fit and lower fit children are associated with differences in structural brain volumes (Chaddock et al., 2010a,b) and brain function, measured by event-related brain potentials (ERPs) (Hillman, Buck, Themanson, Pontifex, & Castelli, 2009; Hillman, Castelli, & Buck, 2005; Pontifex et al., 2011) and functional magnetic resonance imaging (fMRI) (Chaddock, Erickson et al., 2012; Davis et al., 2011; Voss et al., 2011).

This research is important because physical activity is decreasing in and out of the school environment (Troiano et al., 2008), and children are becoming increasingly sedentary, unfit, and overweight (Centers for Disease Control and Prevention, 2009). School administrators de-emphasize the importance of physical activity during the school day (Shepherd, Pintado, & Bean, 2011), as educators are under increased pressure to improve academic achievement of their pupils as well as reduce educational spending. These pressures, coupled with the popular belief
that physical education is of less educational value than formal academic topics, have led to the reduction or elimination of physical activity opportunities during the school day (Centers for Disease Control and Prevention, 2010; Sallis, 2010). As a result, children in today’s society have a greater likelihood of poor health (Centers for Disease Control and Prevention, 2009).

This dissertation extends previous research by conducting a randomized controlled experimental intervention over the course of an entire school year (9 months) to examine how physical activity influences brain structure, brain function and cognition. Eight- to 9-year-old children were randomized into a physical activity intervention group or a wait list control group, and aerobic fitness (i.e., VO2 max), magnetic resonance imaging (MRI) and cognitive testing were conducted before and after the 9-month intervention. It is beneficial to understand the role of lifestyle factors, such as physical activity, in the biological potential of the developing brain during a period of maturation.

**The Developing Brain Involved in Cognitive Control and Memory**

To study the relationship between physical activity and neurocognitive health during childhood, it is important to understand changes in cognition during development, the neural mechanisms supporting these changes, and the role of experience. An understanding of typical development and plasticity provides an important context in which to interpret the effects of physical activity and aerobic fitness on the developing brain. The following discussion provides a brief overview of structural and functional brain maturation, specifically highlighting the development of cognitive control and memory.

Cognitive control (also known as ‘executive control’) refers to cognitive processes associated with the control of thought and action and the ability to guide behavior toward specific goals and formulate decisions. These functions include: (1) selective attention to
relevant information and the filtering of distracting information (selective attention and interference suppression); (2) inhibition of inappropriate response tendencies (response inhibition); (3) flexibly switching between tasks and restructuring knowledge and information based on changing situational demands (task-switching); (4) the ability to temporarily store and manage information while learning and performing cognitive challenges (working memory), (5) working with information held in working memory (manipulation); and (6) using context to determine whether an action is appropriate or a thought is relevant (task-set representation) (Bunge & Crone, 2009; Miyake et al., 2000). Over the course of childhood and adolescence, cognitive control improves, and these improvements are said to parallel the structural and functional development of the brain. This dissertation specifically explores the structural and functional roles of the frontal cortex and basal ganglia in cognitive control. The frontal cortex, along with other brain regions, is implicated in attention, interference control, response inhibition, and the selection, maintenance and manipulation of task-relevant information within working memory (Banich et al., 2000; Hazeltine, Poldrack, & Gabrieli, 2000; Liddle, Kiehl, & Smith, 2001; Olesen, Westerberg, & Klingberg, 2003). The frontal cortex projects to the basal ganglia, a group of subcortical structures subdivided into the dorsal striatum, which is implicated in cognitive control, motor control, response selection and resolution, and the execution of learned behaviors, and the ventral striatum, part of an affect and reward pathway involved in reinforcement and motivation (Aron, Poldrack, & Wise, 2009).

The hippocampus, another region examined in this dissertation, is a subcortical brain region located in the medial temporal lobe. This region is critical to learning, remembering relationships among spatial layouts, and creating associative relationships among experiences (Cohen & Eichenbaum, 1993; Hollup, Kjelstrup, Hoff, Moser, & Moser, 2001; Maguire,
Frackowiak, & Frith, 1997; Maguire et al., 1998, 2000; Maguire & Frith, 2003), skills which interact with cognitive control abilities and are important for achievement in and out of the school environment. No developmental studies in middle childhood (ages 7-10 years) have specifically explored age-related changes in the development of hippocampal memory abilities, which include relational / associative memory and declarative / episodic memory. Only the development of working memory, which is said to recruit more prefrontal and parietal areas rather than the hippocampus, has been studied in the context of age-related differences in functional MRI (to be discussed below). In general, memory abilities are said to improve with age and mirror developmental changes in frontal, parietal, striatal, and hippocampal brain regions (Gathercole, 1998).

**Structural Brain Changes During Development**

Several MRI studies have mapped the neuroanatomical course of normal brain development. In general, gray matter volume, which consists of neurons, glia, and capillaries, is said to follow a non-linear curve during development (Giedd et al., 1999), with frontal, parietal and temporal lobes generally showing a pre-pubertal increase, followed by a post-pubertal loss (Giedd et al., 1999; Sowell et al., 2003; Sowell, Thompson, Holmes, Jernigan, & Toga, 1999; Sowell, Thompson, Tessner & Toga, 2001). The process of gray matter loss is said to begin in the dorsal parietal cortices, particularly the primary sensorimotor areas, and then spread rostrally over the frontal cortex and caudally and laterally over the parietal, occipital, and finally the temporal cortex, with the prefrontal and lateral temporal cortices maturing last (Gogtay et al., 2004).

This dissertation had specific hypotheses about the structural brain changes of two subcortical brain regions, the basal ganglia and hippocampus. There is little research on the
developmental trajectory of the basal ganglia, yet some studies suggest a non-linear
developmental curve, with increases in volume during childhood followed by volume loss
around puberty (Toga, Thompson & Sowell, 2006). Temporal lobe gray matter structures, which
include the hippocampus, are said to show non-linear increases and decreases in volume during
childhood and adolescence (Sowell, Delis, Stiles, & Jernigan, 2001; Toga et al., 2006). In a
study in which individuals between the ages of 4 and 25 completed MRI scans every 2 years, for
6-10 years, structural development of specific subregions of the hippocampus were found to be
heterogeneous, with increased volume over time in the posterior hippocampus and decreased
volume over time in the anterior hippocampus (Gogtay et al., 2006).

Structural brain changes likely reflect interplay among changes in cell proliferation and
apoptosis, dendritic branching and pruning, and synaptic formation and elimination, in accord
with the strengthening of relevant neural connections and the pruning of inefficient pathways
(Andersen, 2003). Some investigators hypothesize that intra-cortical myelination might also
play a role in gray matter reductions across development (Paus, 2005). White matter, composed
of myelinated axons, has been found to increase roughly linearly throughout childhood
(Schmithorst & Yuan, 2010). For example, tracts that connect frontal, parietal, motor and striatal
regions have shown increased white matter microstructure across development (e.g., Barnea-
Goraly et al., 2005; Bonekamp et al., 2007; Schmithorst, Wilke, Dardzinski, & Holland, 2002;
see Schmithorst & Yuan, 2010, for review).

This dissertation also examined the structure of developing white matter tracts in the
brain. It focused on the development of the corpus callosum (Barnea-Goraly et al., 2005;
Muetzel et al., 2008) and tracts in the corona radiata (Keller, Rajesh, & Just, 2007), longitudinal
fasciculus (Bonekamp et al., 2007), cingulum (Bonekamp et al., 2007), internal capsule
The corpus callosum connects the left and right cerebral hemispheres. The corona radiata and superior longitudinal fasciculus have ascending and descending tracts from the cerebral cortex that integrate information throughout the brain. The cingulum connects the cingulate gyrus to the medial temporal lobe. The internal capsule projects through the basal ganglia, and the cerebral peduncle is a tract in the brainstem. Some of these tracts have been tied to specific cognitive functions. For example, the corona radiata (Bendlin et al., 2010; Niogi, Mukherjee, Ghajar, & McCandliss, 2010; Olesen, Nagy, Westerberg, & Klingberg, 2003) and superior longitudinal fasciculus (Burzynska et al., 2011) have been found to play a role in attention, memory, and processing speed across the lifespan (see Table 2 in Madden et al., 2012 for review of the associations between white matter structure and cognition across the lifespan). Given the importance of gray matter and white matter in cognitive development, this dissertation explored the capacity for physical activity to influence the structural development of both gray matter and white matter.

**Functional Brain Changes During Development**

Researchers also use fMRI to examine the maturational trajectories underlying developing cognitive skills. Blood oxygen level dependent (BOLD) response is the dependent measure of most fMRI studies, which refers to the microvascular response in blood flow resulting from fluctuations in the metabolic needs of neurons as they become involved in computations which underlie performance of tasks. In general, brain activation is measured while children and adults perform cognitive tasks, and the activation patterns are correlated with age and task performance. The adult model of brain function is often used as the “mature” or “optimal” model to which the patterns of children and adolescents are compared (Luna,
Padmanabhan, & O'Hearn, 2010). Studies of the development of cognitive control in children, the focus of this dissertation, report a variety of results, but generally suggest that children show different activation patterns to support behavioral demands compared to adults.

A number of developmental studies of brain activation during tasks of cognitive control examine attention, response inhibition (e.g., Go/NoGo, flanker, antisaccade tasks) (Diamond, 2006) and working memory (e.g., n-back, visual spatial working memory) (Baddeley, 1986; Bunge & Crone, 2009). These cognitive skills have been found to relate to academic achievement during childhood (Bull & Scerif, 2001; DeStefano & LeFevre, 2004; St. Clair-Thompson & Gathercole, 2006). Across childhood, there are continued improvements in these measures of cognitive control, and the frontal cortex is said to play a primary role in the performance changes. Although there is additional involvement from parietal, temporal and subcortical regions during control tasks, most developmental fMRI studies of cognitive control have mainly focused on frontal areas (Luna et al., 2010). Evidence of late structural changes in the frontal cortex makes this region especially important for understanding cognitive development (Gogtay et al., 2004).

During tasks of attention and response inhibition, the majority of studies of cognitive control across development report increased frontal activity in children relative to adults (e.g., Booth et al., 2003; Casey et al., 1997; Durston et al., 2002; Velanova, Wheeler & Luna, 2008). For example, Booth et al. (2003) showed increased brain activation in children (age 9-12) in fronto-striatal areas relative to adults (age 20-30) during a Go/NoGo task, and the activation differences were coupled with inferior task performance by the children. Durston et al. (2002) also showed increased activity for children in the dorsal and ventral prefrontal cortex and parietal cortex during a Go/NoGo paradigm relative to adults, and task performance positively correlated
with age. Further, Velanova et al. (2008) showed increased activity in the right dorsolateral prefrontal cortex and anterior cingulate cortex in children (age 8-12) compared to adults (age 18-27) during an antisaccade oculomotor task of response inhibition, coupled with lower task performance in the children. These patterns of developmental differences may indicate that children use prolonged and extended computational processes, which may generate increased activation, but still do not allow successful performance at an adult level.

Whereas these studies suggest that the neural mechanisms that support cognitive control are available during childhood, but are immature or less efficient than the adult system (Booth et al., 2003; Durston et al., 2002; Velanova et al., 2008), other studies show different patterns of age-related differences in activation. For example, one study that examined brain function during a flanker Go/NoGo task of interference suppression and response inhibition reported that children failed to activate a region of the right ventrolateral prefrontal cortex that adults recruited to perform tasks of cognitive control at higher levels of performance (Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002). These findings suggest that less mature task performance during childhood may relate to an inability to activate brain regions important for adult-like task performance. Additional studies of inhibitory control suggest both increases and decreases in activation in specific frontal regions with age (Tamm, Menon & Reiss, 2002). For instance, a Go/NoGo study in 8- to 20-year-olds showed age-related decreases in activation in the left inferior frontal gyrus, coupled with age-related increases in activation in the left superior and middle frontal gyrus (Tamm et al., 2002). Participants across all ages did not significantly differ in task performance. Accordingly, the authors concluded that increases in middle frontal gyrus activation with age may reflect improved inhibitory neural processes, while decreases in inferior frontal gyrus activation with age reflect decreased effortful attention required to exert inhibitory
control. To complement the findings of Tamm et al. (2002), a longitudinal study by Durston et al. (2006) suggested a developmental increase in Go/NoGo performance from age 9 to 11 years, coupled with increased focal activation in ventral prefrontal regions (i.e., right inferior frontal gyrus) related to task performance and attenuated activation in the dorsolateral prefrontal cortex (i.e., middle frontal gyrus, precentral gyrus, superior frontal gyrus, posterior cingulate gyrus, superior temporal gyrus) where activation was not correlated with task performance (Durston et al., 2006). The researchers suggested an increase in activation in brain areas associated with enhanced inhibitory control performance and an attenuation of brain areas not critically involved in task performance.

In addition to attention and inhibition, brain function involved in working memory is also said to change with age (Bunge & Wright, 2007). Working memory is defined as an ability to hold and manipulate information. For example, fMRI activation in the superior frontal sulcus and intraparietal sulcus has been found to increase from childhood to adulthood, and these changes in activation are associated with improvements in visual spatial working memory (Klingberg, Forssberg, & Westerberg, 2002; Kwon, Reiss, & Menon, 2002) as well as increased fractional anisotropy (one measure of diffusion tensor imaging [DTI] that characterizes structurally compact fibers with high integrity [Rykhlevskaia, Gratton, & Fabiani, 2008]) in frontal-parietal white matter (Olesen, Nagy et al., 2003). It is noteworthy that these fMRI studies of age-related changes in brain function involved in working memory show different directional changes in activation compared to studies of brain function during tasks of attentional and inhibitory control.

Furthermore, whereas some studies suggest that children and adults recruit similar regions of the brain during tasks of visual spatial working memory (Klingberg et al., 2002; Kwon
et al., 2002; Thomas et al., 1999), another study showed a developmental shift in the location of active voxels during performance (Scherf, Sweeney & Luna, 2006; similar to the findings of Bunge et al., 2002). That is, children showed increased activation in the caudate nucleus, the thalamus and the anterior insula, whereas adolescents showed activation in the right dorsolateral prefrontal cortex, and adults showed concentrated activation in the left prefrontal and posterior parietal regions (Scherf et al., 2006). Behaviorally, children demonstrated poorer task performance compared to adolescents and adults, which may suggest that changes in location of activation may affect age-related performance differences.

Developmental changes in working memory have not only been found while individuals maintain information online, but also while they manipulate information in working memory. In one study, adults engaged the dorsolateral prefrontal cortex and superior parietal cortex when the task required participants to reverse the order of items held in working memory, whereas 8- to 12-year-old children did not engage this circuitry, and their performance on reversal trials suffered (Crone, Wendelken, Donohue, van Leijenhorst & Bunge, 2006). Interestingly, children did recruit these frontal and parietal regions during encoding and response selection, but not during the delay period, when manipulation was required. These findings suggest that a brain region (e.g., prefrontal cortex) can exhibit adult-like patterns of activation in one task condition, but not in another. Additional research is needed to further understand the functional development of memory, and future studies should aim to understand the role of the hippocampus, along with frontal and parietal brain regions, in the developing neural circuits of memory. Other types of memory, such as relational memory and declarative memory, should also be explored in this age range.
Whereas many of these investigations conclude that chronological age or maturation predicts the change in activation patterns, critics raise the possibility that cognitive strategy, learning or experience play a role in the results (Brown, Petersen, & Schlaggar, 2006; Dick, Leech, Moses, & Saccuman, 2006). For example, learning is speculated to parallel a shift toward increasingly sparse patterns of activation, such that the set of central neural resources involved in controlled and novice processing becomes less essential as skilled, automatic and efficient processing emerges (Poldrack, 2010), a pattern that parallels some of the reported results of decreases in activation with age. The roles of plasticity and environmental enrichment (Greenough, Black & Wallace, 1987) are also important factors to consider when making conclusions about developmental changes. Such factors include the role of physical activity, the focus of this dissertation.

**Physical Activity, Aerobic Fitness, and the Brain and Cognition During Childhood**

Does participation in physical activity influence brain structure and function during childhood? This question is motivated by animal and human literature that suggests that physical activity and aerobic exercise can positively influence cognition and the brain in animals and older adults. In young and older rodents, voluntary wheel running has been found to lead to enhanced learning and retention (van Praag, Shubert, Zhao, & Gage, 2005) as well as improved structural integrity of the brain, via the growth of new neurons (van Praag, Christie, Sejnowski, & Gage, 1999; van Praag, Kempermann & Gage, 1999) and vasculature (Clark, Brzezinska, Puchalski, Krone & Rhodes, 2009). Exercise also led to increased production of neurotrophic molecules, such as brain-derived neurotrophic factor (BDNF), involved in cell survival and synaptic plasticity (Cotman, & Berchtold, 2002), and insulin-like growth factor (IGF-1), crucial for exercise-induced angiogenesis (Lopez-Lopez, LeRoith, & Torres-Aleman, 2004) and
neurogenesis in the dentate gyrus of the hippocampus (Trejo, Carro, & Torres-Aleman, 2001).

The majority of physical activity and exercise studies with humans have focused on older adults. This focus appears to be motivated by the question of whether the often observed decline of cognition, brain structure, and brain function that accompanies aging can be slowed or reversed (at least temporarily) with physical activity. This research has, in general, tentatively provided a positive answer to this question. In elderly humans, participation in physical activity and higher levels of aerobic fitness have been shown to be associated with better performance on a variety of cognitive tasks and particularly with regard to executive control and memory processes (Colcombe & Kramer, 2003; Heyn, Abreu, & Ottenbacher, 2004). The cognitive enhancements appear to be driven, in part, by less age-related brain tissue loss in frontal, parietal, and hippocampal brain regions (Colcombe et al., 2006; Erickson et al., 2011; Floel et al., 2010; Gordon et al., 2008; Ruscheweyh et al., 2011) and changes in fMRI activation and functional connectivity with physical activity and exercise (Colcombe et al., 2004; Voss et al., 2010). Together, this evidence provides a mechanistic and, in the case of the non-human animal research, a molecular basis for the effects of exercise on the human brain and cognition. This research also suggests that the beneficial effects of physical activity and aerobic fitness on cognition and the brain may extend to children.

Indeed, a growing literature of cross-sectional studies suggests a positive association among physical activity, aerobic fitness, cognition and the brain in children (e.g., Chaddock et al., 2010a,b, 2012; Hillman et al., 2009; Pontifex et al., 2011; Voss et al., 2011; see Chaddock, Voss, & Kramer, 2012 for a review). This dissertation aims to extend this research by investigating the effects of a 9-month randomized controlled after school physical activity program designed to increase aerobic fitness. Whereas measures of physical activity and aerobic
fitness have been associated with the brain and cognition during childhood, their distinct contributions to cognitive health during development are still under investigation. Physical activity is defined as bodily activity that results in energy expenditure above resting levels, and measurements include daily activity logs, self-report questionnaires and structured interviews, and data collected with pedometers and accelerometers (Buckworth & Dishman, 2002). Aerobic fitness refers to the maximal capacity of the cardiorespiratory system to use oxygen and can be measured by VO$_2$ max testing, sub-maximal exercise testing, or field tests such as the PACER test of the Fitnessgram (Buckworth & Dishman, 2002). Aerobic fitness is one element of the multifaceted concept of physical fitness, a set of health and skill-related attributes associated with one’s ability to perform physical activities, which also includes muscular strength, muscle flexibility, and body composition (Buckworth & Dishman, 2002).

**Aerobic Fitness and Cognition in Children**

A positive association between aerobic fitness and cognition in children has been found in the laboratory, with most research focusing on cognitive control abilities (Buck et al., 2008; Chaddock et al., 2010b; Hillman et al., 2009; Kamijo et al., 2011; Pontifex et al., 2011). Higher fit children have been found to outperform lower fit children on flanker tasks (Chaddock et al., 2010b; Hillman et al., 2009; Pontifex et al., 2011; Voss et al., 2011), Stroop tasks (Buck et al., 2008), which tap aspects of attention and inhibition, as well as memory paradigms (Chaddock et al., 2010a, 2011). For example, during a flanker task, higher fit children are faster to respond to the direction of a central target amid distractors (e.g., >>>>>>, >><<<), as well as more accurate on the task (Chaddock et al., 2010b, Hillman et al., 2009; Pontifex et al., 2011). Performance differences are often more pronounced during incongruent flanker trials (e.g., >><<<), which require increased inhibitory control (e.g., Chaddock et al., 2010b; Chaddock, Erickson et al.,
2012; Pontifex et al., 2011; Voss et al., 2011; but see Hillman et al., 2009 for general effects of aerobic fitness across congruent and incongruent flanker trials). This dissertation extended cross-sectional research by exploring the influence of an after school physical activity program (aimed at improving aerobic fitness) on cognitive control.

**Aerobic Fitness and Brain Structure in Children**

Recent cross-sectional studies are the first to use MRI to investigate the relationship between aerobic fitness and brain structure in 9- and 10-year-old children. Chaddock et al. (2010b) suggest that enhanced cognitive control associated with higher aerobic fitness may relate to differences in the volume of specific regions of the basal ganglia. Relative to lower fit peers, higher fit children had increased inhibitory control during a flanker task, coupled with a larger dorsal striatum (Chaddock et al., 2010b). No relationship was found among fitness, task performance, and volume of the ventral striatum, a region with functions unrelated to cognitive control (Aron et al., 2009). The study suggests that aerobic fitness differences in flanker task performance may relate to differences in the volume of specific regions of the basal ganglia (Chaddock et al., 2010b). In particular, the dorsal striatum, an important structure for cognitive control, motor integration, and response resolution (Aron et al., 2009), may be particularly sensitive to physical activity behaviors in children.

The findings support studies in non-human animals and older adults as well as extend the findings to a child population. Non-human animal research has observed exercise-induced changes in the basal ganglia, including increases in the production of neurotrophic factors (Aguiar, Speck, Prediger, Kapczinski, & Pinho, 2008; Marais, Stein, & Daniels, 2009) and dopamine (Marques et al., 2008) as well as increases in astrocyte proliferation (Li et al., 2005) and neural activity (Shi, Luo, Woodward, & Chang, 2004). In older adults, the volume of the
caudate nucleus of the dorsal striatum has been found to mediate the relationship between aerobic fitness and cognitive performance on a task requiring mental flexibility (Verstynen et al., 2012). However, in another study, one year of aerobic fitness training was not sufficient to yield a different trajectory of volume changes in the caudate nucleus of physically active older adults, relative to older adults involved in stretching and toning (Erickson et al., 2011).

Volumes of other brain structures have also been found to relate to aerobic fitness in children (Chaddock et al., 2010a). Higher fit children showed larger bilateral hippocampal volumes and superior relational memory task performance compared to lower fit children, and bilateral hippocampal volume served to partially mediate the relationship between fitness and relational memory performance (Chaddock et al., 2010a). Furthermore, hippocampal volume was positively associated with performance on a relational but not a non-relational memory task. The specificity of this hippocampal-memory relationship (Cohen & Eichenbaum, 1993; Eichenbaum & Cohen, 2001) supports a behavioral study indicating that higher fit children had better memory recognition performance when memory items were studied relationally compared to non-relationally (Chaddock et al., 2011). Another study demonstrated that children randomized into a physical activity group designed to improve aerobic fitness showed additional viewing time to faces that had been paired with scenes during relational memory encoding after 9 months compared to children in a wait list control group (Monti, Hillman & Cohen, 2011). No group differences in eye movements were found for non-relational memory trials. The researchers suggested that children involved in a physical activity intervention gained better hippocampal function, but these conclusions are limited due to lack of pre-test eye tracking and task performance data and no group differences in performance on the hippocampal memory task.
The hippocampal results support animal and human models across the lifespan (Chaddock et al., 2010a; Cotman & Berchtold, 2002; Erickson et al., 2009, 2011; Pereira et al., 2007). Findings from rodent models have demonstrated that wheel running positively impacts hippocampal structure and function via increased cell proliferation and cell survival as well as enhanced hippocampal-dependent learning and memory (Cotman & Berchtold, 2002; Vaynman & Gomez-Pinilla, 2006). In older humans, higher levels of aerobic fitness and participation in physical activity have been associated with larger hippocampal volumes and enhanced visual spatial memory performance (Erickson et al., 2009, 2011). In fact, a randomized controlled trial with an elderly population demonstrated that one year of aerobic exercise training was sufficient to increase the volume of the hippocampus, potentially reversing age-related volume loss (Erickson et al., 2011). Alternatively, older adults involved in a stretching and toning program showed significant hippocampal atrophy, typical for the age group in the study, over the year.

Together, the cross-sectional structural MRI investigations in children suggest that cognitive enhancement with higher aerobic fitness may relate to different brain volumes. This dissertation extended the correlational findings by examining whether participation in physical activity that improves aerobic fitness during childhood can influence the volume of the basal ganglia and hippocampus.

### Aerobic Fitness and Brain Function in Children

Other studies use measures of functional neuroimaging (e.g., ERPs, fMRI) to examine the association between aerobic fitness and the brain in children. ERPs are recordings of the brain’s activity, obtained from the scalp, that are linked to the occurrence of an event, such as the presentation of a stimulus or the execution of a response. To compute an ERP, a continuous electroencephalogram (EEG) is recorded by electrodes placed on the scalp during a cognitive
task. Then, epochs of the recorded EEG are time-locked to the onset of a stimulus or the initiation of a response to a stimulus and averaged over a number of trials. As a result of averaging, variation between trials is removed, thereby revealing a characteristic ERP pattern of the brain’s response. The resulting ERP is divided into components; characteristic portions of the response that have been linked to specific psychological processes. For example, a component of the stimulus-locked ERP called the P3 is said to reflect attentional resource allocation in the service of working memory updating (P3 amplitude) and cognitive processing speed (P3 latency) (Donchin & Coles, 1988; Polich, 2007). A component of the response-locked ERP called the error-related negativity (ERN) is reported to reflect response selection related to conflict monitoring and error detection (Yeung, Cohen, & Botvinick, 2004). A component called the contingent negative variation (CNV) is a cortical potential said to be involved in stimulus orientation, stimulus anticipation, and response and cognitive preparation (Hillman, Kamijo & Pontifex, 2012).

In general, ERP studies demonstrate that higher aerobic fitness levels in children are associated with increased performance on tasks of cognitive control, possibly via greater allocation of attentional resources during stimulus encoding (i.e., larger P3 amplitude) and a subsequent reduction in conflict during response selection (i.e., smaller ERN amplitude) (Hillman et al., 2005; 2009; Pontifex et al., 2011). The ERP results provide temporal information regarding discrete cognitive processes that occur between stimulus evaluation and response execution. Spatially, the P3 ERP data raise the possibility that higher fit children are better at adapting recruitment of a cognitive control network of frontal and parietal regions (Gehring & Knight, 2000), and the ERN ERP data suggest that fitness relates to the monitoring of conflict in the anterior cingulate cortex, a brain region that evaluates conflict and errors, and
signals the need to adjust cognitive control (Dosenbach et al., 2007). This spatial framework of ERP findings is consistent with fMRI research, using BOLD (Blood Oxygen Level Dependent) techniques, demonstrating that sedentary older adults who participated in 6 months of aerobic training showed better attentional and interference control, coupled with increased prefrontal and parietal activation and decreased anterior cingulate cortex activation (Colcombe et al., 2004).

Two studies using BOLD fMRI in children (Chaddock, Erickson et al., 2012; Voss et al., 2011) extend the ERP studies by gaining spatial sensitivity in detecting the regional locations and networks that are associated with higher aerobic fitness levels and superior task performance during childhood. That is, specific brain regions are suggested to play a role in the monitoring (anterior cingulate cortex) for alterations in attentional and interference control (middle and inferior frontal gyrus, precentral gyrus) in the presence of distractors and response conflict (superior parietal cortex) as well as the preparation and generation of a motor response (supplementary motor area) (Banich et al., 2000). Voss et al. (2011) showed that higher fit and lower fit children differed in fMRI activity in these regions associated with response execution and inhibition, task set maintenance, and top-down regulation. Behaviorally, higher fit children showed greater overall accuracy and less interference cost than lower fit children. The study examined brain activation in performance-matched higher fit and lower fit children to gain insight into different task strategies as a function of aerobic fitness level during childhood. As the flanker task became more difficult (i.e., during incongruent trials relative to congruent trials), lower fit children showed greater activation in the network of brain regions associated with cognitive control. In fact, higher fit children showed increased activation during congruent trials, whereas lower fit children showed increased activation during incongruent trials.
Chaddock, Erickson et al. (2012) also showed fitness differences in fMRI activity in these frontal and parietal regions during an event-related flanker task design (to extend Voss et al.’s [2011] block design). The study explored task performance and activation as a function of flanker task conditions that varied in cognitive control demands (e.g., congruent, incongruent) (Voss et al., 2011) as well as the time on task (first half of the task, second half of the task) (Chaddock, Erickson et al., 2012). Both higher fit and lower fit children showed increased recruitment of frontal and parietal regions during the early block of the congruent flanker condition when the task was unfamiliar, followed by a decrease in activity in the later block. No within-group changes in congruent accuracy were observed across task blocks, despite a decline in performance across all participants, likely due to fatigue. However, during the incongruent flanker condition, only higher fit children maintained accuracy across blocks, coupled with increased prefrontal and parietal recruitment in the early task block and reduced activity in the later block. Lower fit children showed a decline in incongruent accuracy across blocks, and no changes in activation. These results provide additional support that aerobic fitness in children relates to the modulation of brain circuits involved in cognitive control (Hillman et al., 2009; Pontifex et al., 2011). Together, the ERP and fMRI studies of brain function in children suggest that aerobic fitness is involved in an ability to adapt neural processes to meet and maintain task goals. This dissertation extends these studies by examining whether a physical activity intervention can influence fMRI patterns during childhood, with a particular focus on the frontal cortex.

**Physical Activity Interventions in Children**

The majority of fitness-cognition research designs with children are cross-sectional. Nevertheless, a few researchers have recently begun to conduct randomized, controlled trials in
which children are placed into a physical activity intervention group or a wait list control group. With this design, cognition and/or brain function are examined before and after the intervention to understand how physical activity influences neurocognition. For example, in one longitudinal study (Davis et al., 2011), sedentary, overweight 7- to 11-year-old children were randomized to an exercise program for 13 weeks or to a non-exercise control condition (with no after school program). The treatment group played aerobic games (e.g., running games, jump rope, basketball, soccer) and either met for 20 minutes per day or 40 minutes per day. Only the high-dose aerobics group (40 minutes per day) showed increases in cognitive control (for the most demanding cognitive function measure, “planning,” as measured by the Cognitive Assessment System) and mathematics achievement. Increases in prefrontal cortex fMRI activity and decreases in parietal cortex fMRI activity were also found for the high dose physical activity intervention group during an antisaccade task of cognitive control, but performance on this task was not reported (Davis et al., 2011).

Additionally, Kamijo et al. (2011) demonstrated that children who participated in 9 months of physical activity, 5 days per week, for 1 hour each day, showed improvements in working memory accuracy on a Stenberg task. The memory improvements for the physical activity intervention group, compared to the non-intervention control group, related to greater activation of the contingent negative variation (iCNV), an ERP component likely generated in the frontal cortex and involved in cognitive preparation processes and stimulus orientation processes (Kamijo et al., 2011). The researchers suggest that the changes in iCNV amplitude with participation in physical activity may reflect a strategic change involving more efficient cognitive control, which is associated with a more effective working memory network. Interestingly, a study with young adults showed that the amplitude of another component of the
CNV, the tCNV, was smaller for more fit young adults compared to their less fit adults. This finding suggests that more fit individuals are better at sustaining active maintenance of task goals compared to less fit individuals (Kamijo, O’Leary, Pontifex, Themanson, & Hillman, 2010).

These interventions provide a beginning to understanding the influence of physical activity on the brain during childhood, but additional randomized controlled trials, which include broader measures of cognition and measures of brain structure and fMRI brain function, are needed to gain additional insight into the effects of physical activity on the cognitive and brain health of children.

**Academic Achievement and Real-World Behavior**

It is important to understand whether the benefits of aerobic fitness and physical activity extend outside the laboratory to everyday functions. In a real-world setting, participation in physical activity and higher levels of aerobic fitness are associated with increased academic achievement (Castelli et al., 2007; Chomitz et al., 2009; Coe et al., 2006; Grissom, 2005; Roberts, Freed, & McCarthy, 2010). For example, achievement in mathematics and reading on the Illinois Standardized Achievement Test (ISAT) was positively associated with aerobic capacity in 259 3rd to 5th grade elementary school children (Castelli et al., 2007). In addition, children who completed more physical fitness tests during physical education class showed higher scores on state mathematics and English achievement tests (Chomitz et al., 2009). No studies have found that physical activity adversely affects academic achievement, even if physical activity is not found to improve achievement (Centers for Disease Control and Prevention, 2010; see Shepherd et al., 2011 for review). Academic achievement in the classroom has been found to relate to performance on tasks of cognitive control in the laboratory, including elements of control that involve attention, inhibition and working memory (Bull & Scerif, 2001;
DeStefano & LeFevre, 2004; St. Clair-Thompson & Gathercole, 2006). Given this relationship, the findings of this dissertation may have implications for children’s success in the school environment. Children who can plan, pay attention, and inhibit distractions are likely to stay on task in the classroom and excel academically. Including physical activity aimed to improve aerobic fitness in a child’s school day may be of critical importance to enhance specific elements of cognition important for meeting challenges in school and throughout the lifespan.

Higher levels of fitness during childhood have been found to enhance performance on an everyday real-world task of street crossing. In a study by Chaddock, Neider, Lutz, Hillman, & Kramer (2012), a street intersection was modeled in a virtual environment, and higher fit and lower fit 8- to 10-year-old children navigated trafficked roads by walking on a treadmill that was integrated with an immersive virtual world. Child pedestrians crossed the street while undistracted, listening to music, or conversing on a hands-free cellular phone. Higher fit children maintained street crossing success rates across all three conditions, whereas lower fit children showed decreased success rates when on the phone, relative to the undistracted and music conditions. A lack of fitness group differences in physical measures of crossing speed suggests that multitask performance differences were not driven by differences in walking speed. Together, the results suggest that higher levels of childhood aerobic fitness may attenuate the impairment typically associated with multitasking during street crossing. It is possible that superior cognitive abilities of higher fit children play a role in the performance differences during complex real-world tasks.

**The Dissertation**

This dissertation used state-of-the-art structural and functional neuroimaging MRI measures to examine the influence of a 9-month after school physical activity program on the
cognitive and brain health of 8- to 9-year-old children. Changes in brain and behavioral measures after 9 months were examined in a physical activity intervention group and a non-intervention wait list control group.

**The Dissertation Method**

**Participants**

Eight- to 9-year-old children were recruited from the Urbana, Illinois school district 116. All children completed demographic assessments, a VO$_2$ max test to assess aerobic fitness, and a magnetic resonance imaging (MRI) session at pre-test (i.e., before randomization into a physical activity intervention group or a wait list control group) and post-test (i.e., after the completion of the intervention, approximately 9 months later).

**Demographic Assessments**

To be eligible for the study, children had to have a Kauffman Brief Intelligence Test (KBIT) score greater than 85 (Kaufman & Kaufman, 1990) and qualify as pre-pubescent (Tanner puberty score < 2; Taylor et al., 2001). Children were also screened for the presence of attentional disorders using the Attention Deficit Hyperactivity Disorder (ADHD) Rating Scale IV (DuPaul, Power, Anastopoulos & Reid, 1998), and children were excluded if they scored above the 85$^{th}$ percentile. Body mass index (BMI) was calculated as weight (kg)/height(cm)$^2$, and socioeconomic status (SES) was determined by creating a trichotomous index: participation in a free or reduced-price meal program at school, the highest level of education obtained by the child's mother and father, and the number of parents who worked full-time (Birnbaum et al., 2002; Hillman, Pontifex et al., 2012).

Eligible children were also required to (1) report an absence of school-related learning disabilities (i.e., individual education plan related to learning), adverse health conditions,
physical incapacities, or neurological disorders, (2) report no use of medications that influence central nervous system function, (3) demonstrate right handedness (as measured by the Edinburgh Handedness Questionnaire; Oldfield, 1971), (4) complete a mock MRI session successfully to screen for claustrophobia in an MRI machine, (5) be capable of performing physical activity, and (6) sign an informed assent approved by the University of Illinois at Urbana-Champaign. A legal guardian also provided written informed consent in accordance with the Institutional Review Board of the University of Illinois at Urbana-Champaign. Children were paid for their time ($10/hour for demographic assessments and fitness testing and $15/hour for MRI testing).

**Aerobic Fitness Testing**

Children completed a VO₂ max test at pre-test and post-test to assess aerobic fitness. The aerobic fitness of each child was measured as maximal oxygen consumption (VO₂ max) during a graded exercise test (GXT). The GXT employed a modified Balke Protocol and was administered on a TrackMaster TMX425CLifeFitness 92T motor-driven treadmill (LifeFitness, Schiller Park, IL) with expired gases analyzed using a TrueOne2400 Metabolic Measurement System (ParMedics, Sandy, Utah). Children walked and/or ran on a treadmill at a constant speed with increasing grade increments of 2.5% every 2 minutes until volitional exhaustion occurred.

Oxygen consumption was measured using a computerized indirect calorimetry system (ParvoMedics True Max 2400) with averages for VO₂ and respiratory exchange ratio (RER) assessed every 20 seconds. A polar heart rate (HR) monitor (Polar WearLink+ 31; Polar Electro, Finland) was used to measure HR throughout the test, and ratings of perceived exertion (RPE) were assessed every 2 minutes using the children’s OMNI scale (Utter, Robertson, Nieman & Kang, 2002). Maximal oxygen consumption was expressed in mL/kg/min and VO₂ max was
based upon maximal effort as evidenced by (1) a plateau in oxygen consumption corresponding
to an increase of less than 2 mL/kg/min despite an increase in workload; (2) a peak HR ≥ 185
beats per minute (American College of Sports Medicine, 2006) and an HR plateau (Freedson &
Goodman, 1993); (3) RER ≥ 1.0 (Bar-Or, 1983); and/or (4) a score on the children’s OMNI RPE
scale ≥ 8 (Utter et al., 2002).

**Physical Activity Training Intervention and Wait List Control Group**

The physical activity intervention occurred for 2 hours after each school day, from
September until May, for 150 days out of the 170 day school year. The program, Fitness
Improves Thinking in Kids (FITKids) (http://clinicaltrials.gov/ct2/show/NCT01334359?term=FI
TKids&rank=1) is based on the Child and Adolescent Trial for Cardiovascular Health (CATCH)
curriculum (McKenzie et al., 1994). The program is aimed at improving aerobic fitness through
engagement in a variety of age-appropriate physical activities. The environment was non-
competitive and integrated activities such as fitness activities and organized games (Castelli,

Within a daily lesson, the children participated in an average of 76.8 minutes of moderate
to vigorous physical activity (recorded by E600 Polar heart rate monitors; Polar Electro, Finland,
and Accusplit Eagle 170 pedometers, San Jose CA), thus exceeding the national physical activity
guideline of 60 minutes of moderate to vigorous physical activity per day (Centers for Disease
Control and Prevention, 2011). Children completed stations that focused on a specific health-
related fitness component (i.e., cardiorespiratory endurance, muscular strength). The activities
were aerobically demanding, but simultaneously provided opportunities to refine motor skills.
The program also included consumption of a healthy snack and the introduction of a themed
educational component related to health promotion (i.e., goal setting, self-management). On the
weekends, the children were encouraged to continue their participation in physical activity with their family, and physical activity worksheets were utilized during school holidays to log continued engagement.

The wait list control group was not contacted following randomization. They completed all facets of the pre-test and post-test, similar to those children who were randomized into the after school physical activity intervention. As incentive to stay in the study, children in the wait list control group were afforded the opportunity to participate in the intervention during the following school year.

**MRI Protocol**

Structural and functional MRI techniques are described in detail in each subsequent chapter. In general, structural brain measures included volumes of the basal ganglia and hippocampus characterized by FMRIB’s Integrated Registration and Segmentation Tool (FIRST) and the microstructure of white matter tracts using diffusion tensor imaging (DTI). Brain function involved in attentional control, interference suppression and response inhibition was assessed by the collection of fMRI data in a 3 Tesla MRI magnet during a task of cognitive control.

**The Dissertation Hypotheses**

The hypotheses are motivated by animal and human literature that suggests that physical activity and aerobic exercise can positively influence cognition and the brain in animals and older adults (Cotman & Berchtold, 2002; Kramer & Erickson, 2007) as well as by cross-sectional investigations in children that demonstrate a positive association among physical activity, aerobic fitness, cognition and the brain (Chaddock, Voss et al., 2012).
Structural Hypotheses

Rodent models suggest that aerobic exercise can positively affect the structural integrity of the hippocampus and striatum. Human studies with older adults have also found that physical activity and aerobic fitness can influence the volume of the basal ganglia (Verstynen et al., 2012) and hippocampus (Bugg & Head, 2011; Erickson et al., 2009, 2010, 2011; Honea et al., 2009). In children, cross-sectional studies (Chaddock et al., 2010a,b) have suggested variation in basal ganglia and hippocampal volume as a function of aerobic fitness level. Thus, in this dissertation, it was hypothesized that the basal ganglia and hippocampus might also be modifiable with a physical activity intervention designed to increase aerobic fitness in children. Children in the physical activity intervention group were expected to show a greater increase in basal ganglia and hippocampal volumes compared to the wait list control group from pre-test to post-test. Further, children with greater changes in aerobic fitness levels were predicted to show the greatest volume changes.

Because physical activity and higher aerobic fitness levels in children have been associated with larger structures and improved function of frontal (Chaddock et al., 2011; Davis et al., 2011; Voss et al., 2011), parietal (Chaddock et al., 2011), hippocampal (Chaddock et al., 2010a, 2011), and striatal (Chaddock et al., 2010b) brain regions in children, it was also predicted that physical activity would influence the structural connectivity between these brain regions, as measured by DTI. Children in the physical activity group were expected to show greater increases in the integrity of a global network of white matter tracts from pre-test to post-test compared to children in a wait list control group. Associations among physical activity, fitness, and white matter microstructure have been reported in older adults (Colcombe et al., 2006; Voss et al., 2012).
Functional Hypotheses

Functional neuroimaging measures have also reported an association between physical activity, aerobic fitness and the brain across the lifespan. In general, physically active or higher fit individuals have been found to show different patterns of brain function, relative to less active or lower fit peers (Chaddock, Erickson et al., 2012; Colcombe et al., 2004; Davis et al., 2011; Voss et al., 2011). In this dissertation, it was hypothesized that approximately 9 months of physical activity would lead to changes in the fMRI patterns of recruitment of neural regions involved in attentional control, response inhibition and interference suppression. The changes in activation were expected to correlate with task performance. The directional changes in activation with the intervention could follow a number of different paths, as evidenced by the mixed results of previous developmental investigations with adults and children (Luna et al., 2010). Research about increases and decreases in activation is a complicated literature, and there are many different interpretations of activation changes. This dissertation was not designed to provide an answer to these debates, and changes in activation (increases or decreases) were interpreted with care and in relation to changes in behavioral performance. Further, future research is needed to understand how functional activation and brain structure outcomes are interrelated to impact cognitive performance and academic achievement.

Although directional changes in activation are debatable, it was predicted that children in the physical activity group would show less activation following 9 months of physical activity in the same network of regions activated prior to the intervention. These findings would parallel a number of previous developmental investigations that have shown that children demonstrate increased magnitude of activation compared to adults in equivalent brain regions (Booth et al., 2003; Casey et al., 1997; Durston et al., 2002; Scherf et al., 2006; Tamm et al., 2002; Velanova
et al., 2008). Such results would also parallel the aerobic fitness-fMRI findings in children that show decreased activation in higher fit children relative to lower fit children (Chaddock et al., 2011; Voss et al., 2011). Thus, a decrease in activation with physical activity may imply improved brain function, which was expected to be found to a greater extent in the physically active group. Control children were not predicted to show this decrease in activation.

This dissertation employed an fMRI task with conditions that varied in cognitive control demands and processes (i.e., neutral, incongruent, NoGo) in order to make specific hypotheses about changes in activation and performance as a function of specific condition types. During the neutral task condition which was predicted to require low levels of cognitive control, both physical activity and control children were predicted to show decreases in activation, coupled with a maintenance or increase in task performance. Activation and performance differences were expected to be especially pronounced during incongruent and NoGo conditions, which were hypothesized to require increased interference and inhibitory control. Together, the brain and behavioral measures in a randomized controlled physical activity intervention can help characterize the mechanisms underlying the effects of physical activity and aerobic fitness that promote cognitive health and scholastic achievement during childhood.

In summary, this research expected to demonstrate a positive influence of physical activity on the cognitive and brain health of children. Such results should serve to raise public awareness of the cognitive benefits of physical activity, as children are becoming increasingly sedentary and unfit, with increased risk for disease (Centers for Disease Control and Prevention, 2009; United States Department of Health and Human Services, 2008). Findings in the predicted directions should also help to change educational practices that are contributing to the declining health in youth as physical activity opportunities are being reduced or eliminated during the
school day (Centers for Disease Control and Prevention, 2010; Sallis, 2010). In addition, findings in the hypothesized directions would suggest that physical activity may be important for daily functioning outside the school environment, given that successful daily living requires paying attention and inhibiting distractions (Strong et al., 2005). Previous research has suggested that physical activity and aerobic fitness are important to the development of the brain during childhood (Chaddock, Voss et al., 2012), and this longitudinal intervention design aimed to strengthen these findings. If physical activity is found to enhance the cognitive health of the developing brain during childhood, the results would have far-reaching implications for the biological potential of the brain during periods of maturation and brain development, and suggest that the developing brain is plastic and sensitive to lifestyle factors.
Chapter 1 References


CHAPTER 2

THE EFFECTS OF PHYSICAL ACTIVITY ON THE VOLUME OF THE DORSAL STRIATUM AND ATTENTIONAL AND INTERFERENCE CONTROL IN CHILDREN

Participation in physical activity and higher levels of aerobic fitness positively influence the brain and cognitive health of children (Chaddock et al., 2010a,b; Davis et al., 2011; Hillman, Buck, Themanson, Pontifex, & Castelli, 2009; Kamijo et al., 2011; Pontifex et al., 2011; Sibley & Etnier, 2003; Voss et al., 2011; see Chaddock, Voss, & Kramer, 2012 for a review). Research has shown that aerobic fitness is associated with the volumes of certain brain structures (i.e., basal ganglia, hippocampus) in children (Chaddock et al., 2010a,b). In addition, compared to their lower fit peers, higher fit children show superior performance on tasks of attentional and interference control that challenge the ability to pay attention and suppress distraction (Chaddock et al., 2010b; Hillman et al., 2009; Pontifex et al., 2011; Voss et al., 2011). Attentional and interference control are elements of cognitive control, a general term that also includes inhibitory control, which is the ability to inhibit a prepotent tendency to respond. The present study extends cross-sectional studies by exploring the capacity for participation in a physical activity intervention to influence brain morphology involved in cognitive control in children.

This chapter specifically focuses on the effects of an after school physical activity program (aimed at improving aerobic fitness) on the volume of the basal ganglia, in an effort to extend and strengthen reported differences in basal ganglia structure and function in higher fit and lower fit children (Chaddock et al., 2010b). The basal ganglia are a group of subcortical structures divided into dorsal and ventral subregions, and each subregion is said to have a specific function. The dorsal striatum of the basal ganglia is implicated in cognitive control, motor control, response selection and resolution, and the execution of learned behaviors (Aron, Poldrack & Wise, 2009; Di Martino et al., 2008; Draganski et al., 2008; Graybiel, 2005, 2008;
The ventral striatum is part of an affect and reward pathway involved in reinforcement, motivation, and habit formation (Aron et al., 2009; Casey, Getz, & Galvan, 2008; Di Martino et al., 2008; Draganski et al., 2008; Graybiel, 2005, 2008). The present study examined the influence of an after school physical activity program on the volume of the dorsal and ventral striatum as well as on performance on a task of cognitive control.

Specific subregions of the basal ganglia relate to exercise/physical activity and aerobic fitness in children, older adults, and rodents, and these studies provide a framework for the present study. Higher fit 9- and 10-year-old children were found to have larger volumes of the dorsal striatum (caudate nucleus and putamen) as well as better attentional and interference control during a flanker task compared to lower fit peers (Chaddock et al., 2010b). Volume of the ventral striatum did not differ as a function of childhood aerobic fitness and did not relate to task performance (Chaddock et al., 2010b). To further support the role of the dorsal striatum in the association between fitness and cognition, a study with older adults (mean age of 66 years) reported that the volume of the caudate nucleus of the dorsal striatum mediated the relationship between aerobic fitness and cognitive performance on a task requiring mental flexibility (Verstynen et al., 2012). Rodent models have also shown exercise-induced changes in the basal ganglia, such that voluntary wheel running increased the production of dopamine and brain-derived neurotrophic factor in the dorsal striatum (Aguiar, Speck, Prediger, Kapczinski, & Pinho, 2008; Marais, Stein & Daniels, 2009; Marques et al., 2008).

Together, previous research suggests a positive association among exercise/physical activity, aerobic fitness, and the structure and function of the dorsal striatum. It was hypothesized that children enrolled in a physical activity program would show increased volume of the dorsal striatum coupled with improvements during a flanker task of attentional and
interference control, relative to a wait list control group of children. The present study also examined whether physical activity and basal ganglia volume would relate to response inhibition, another subset of skills involved in cognitive control, during a Go/NoGo task. No changes in the volume of the ventral striatum with physical activity, or associations between the ventral striatum and cognitive control, were predicted, given the lack of association among aerobic fitness, ventral striatum volume, and attentional and interference control in children (Chaddock et al., 2010b; but see Verstynen et al., 2012 for an association between aerobic fitness and ventral striatal volume in older adults).

Method

Participants

Eight- to 9-year-old children were recruited from the Urbana, Illinois school district 116. All children completed demographic assessments, a VO$_2$ max test to assess aerobic fitness, and a magnetic resonance imaging (MRI) session (which included a structural MRI scan) at pre-test (i.e., before randomization into a physical activity intervention group or a wait list control group) and post-test (i.e., after the completion of the intervention, approximately 9 months later).

Forty-nine children were eligible for the study. Five children (2 physical activity intervention, 3 wait list control) were excluded from the analyses because of failure to complete the post-test MRI. Five children (1 physical activity intervention, 4 wait list control) were excluded because they had excessive head motion that created inaccurate brain segmentations. Six children (4 physical activity intervention, 2 wait list control) were excluded for below chance task performance. Therefore, 33 children were included in the final analyses, with 16 children in the physical activity intervention group (9 girls, 7 boys) and 17 children in the wait list control group (8 girls, 9 boys).
Demographic Assessments and Fitness Testing

To be eligible for the study, children had to have a Kaufman Brief Intelligence Test (KBIT) score greater than 85 (Kaufman & Kaufman, 1990) and qualify as prepubescent (Tanner puberty score ≤ 2; Taylor et al., 2001). Children were also screened for the presence of attentional disorders using the Attention Deficit Hyperactivity Disorder (ADHD) Rating Scale IV (DuPaul, Power, Anastopoulos & Reid, 1998), and were excluded if they scored above the 85th percentile. Body mass index (BMI) was calculated as weight (kg)/height(cm)^2, and socioeconomic status (SES) was determined by creating a trichotomous index: participation in a free or reduced-price meal program at school, the highest level of education obtained by the child's mother and father, and the number of parents who worked full-time (Birnbaum et al., 2002; Hillman et al., 2012).

Eligible children were further required to (1) report an absence of school-related learning disabilities (i.e., individual education plan related to learning), adverse health conditions, physical incapacities, or neurological disorders, (2) report no use of medications that influence central nervous system function, (3) demonstrate right handedness (as measured by the Edinburgh Handedness Questionnaire; Oldfield, 1971), (4) complete a mock MRI session successfully to screen for claustrophobia in an MRI machine, (5) be capable of performing physical activity, and (6) sign an informed assent approved by the University of Illinois at Urbana-Champaign. A legal guardian also provided written informed consent in accordance with the Institutional Review Board of the University of Illinois at Urbana-Champaign. Children were paid for their time ($10/hour for demographic assessments and fitness testing and $15/hour for MRI testing).
Aerobic Fitness Testing

Children completed a VO$_2$ max test at pre-test and post-test to assess aerobic fitness. The aerobic fitness of each child was measured as maximal oxygen consumption (VO$_2$ max) during a graded exercise test (GXT). The GXT employed a modified Balke Protocol and was administered on a LifeFitness 92T motor-driven treadmill (LifeFitness, Schiller Park, IL) with expired gases analyzed using a TrueOne2400 Metabolic Measurement System (ParMedics, Sandy, Utah). Children walked and/or ran on a treadmill at a constant speed with increasing grade increments of 2.5% every 2 minutes until volitional exhaustion occurred.

Oxygen consumption was measured using a computerized indirect calorimetry system (ParvoMedics True Max 2400) with averages for VO$_2$ and respiratory exchange ratio (RER) assessed every 20 seconds. A polar heart rate (HR) monitor (Polar WearLink+ 31; Polar Electro, Finland) was used to measure HR throughout the test, and ratings of perceived exertion (RPE) were assessed every 2 minutes using the children’s OMNI scale (Utter, Robertson, Nieman & Kang, 2002). Maximal oxygen consumption was expressed in mL/kg/min and VO$_2$ max was based upon maximal effort as evidenced by (1) a plateau in oxygen consumption corresponding to an increase of less than 2 mL/kg/min despite an increase in workload; (2) a peak HR $\geq$ 185 beats per minute (American College of Sports Medicine, 2006) and an HR plateau (Freedson & Goodman, 1993); (3) RER $\geq$ 1.0 (Bar-Or, 1983); and/or (4) a score on the children’s OMNI ratings of perceived exertion (RPE) scale $\geq$ 8 (Utter et al., 2002).

Physical Activity Training Intervention and Wait List Control Group

The physical activity intervention occurred for 2 hours after each school day, from September until May, for 150 days out of the 170 day school year. The program, Fitness Improves Thinking in Kids (FITKids)
The program is aimed at improving aerobic fitness through engagement in a variety of age-appropriate physical activities. The environment was non-competitive and integrated activities such as fitness activities and organized games (Castelli, Hillman, Hirsch, Hirsch, & Drollette, 2011).

Within a daily lesson, the children participated in an average of 76.8 minutes of moderate to vigorous physical activity (recorded by E600 Polar heart rate monitors; Polar Electro, Finland, and Accusplit Eagle 170 pedometers, San Jose CA), thus exceeding the national physical activity guideline of 60 minutes of moderate to vigorous physical activity per day (Centers for Disease Control and Prevention, 2011). Children completed stations that focused on a specific health-related fitness component (i.e., cardiorespiratory endurance, muscular strength). The activities were aerobically demanding, but simultaneously provided opportunities to refine motor skills. The program also included consumption of a healthy snack and the introduction of a themed educational component related to health promotion (i.e., goal setting, self-management). On the weekends, the children were encouraged to continue their participation in physical activity with their family, and physical activity worksheets were utilized during school holidays to log continued engagement. Average attendance across the 9-month intervention was 89.0% (SD=7.2%).

The wait list control group was not contacted following randomization. They completed all facets of the pre-test and post-test, similar to those children who were randomized into the after school physical activity intervention. As incentive to stay in the study, children in the wait
list control group were afforded the opportunity to participate in the intervention during the following school year.

**Structural MRI Protocol**

High resolution T1-weighted brain images were acquired using a 3D MPRAGE (Magnetization Prepared Rapid Gradient Echo Imaging) protocol with 192 contiguous axial slices, collected in ascending fashion parallel to the anterior and posterior commissures, echo time (TE)=2.32 ms, repetition time (TR)=1900 ms, field of view (FOV)=230 mm, acquisition matrix 256 mm x 256 mm, slice thickness=0.90 mm, and flip angle=9°. All images were collected on a Siemens Magnetom Trio 3T whole-body MRI scanner.

**FMRIB’s Integrated Registration and Segmentation Tool**

Segmentation and volumetric analysis of the dorsal striatum and ventral striatum were performed using a semi-automated, model-based subcortical tool (FIRST; FMRIB’s Integrated Registration and Segmentation Tool) in FMRIB’s Software Library (FSL) version 4.1.9 (Patenaude, 2007; Patenaude, Smith, Kennedy & Jenkinson, 2007a,b).

A two-stage affine registration to a standard space template (MNI space) with 1 mm resolution using 12-degrees of freedom and a subcortical mask to exclude voxels outside the subcortical regions was first performed on each participant’s MPRAGE. Next, the caudate nucleus, putamen, and nucleus accumbens were segmented with 30, 40 and 50 modes of variation, respectively. To achieve accurate segmentation, the FIRST methodology models 317 manually segmented and labeled T1-brain images from normal children, adults, and pathological populations (obtained from the Center for Morphometric Analysis, Massachusetts General Hospital, Boston) as a point distribution model with the geometry and variation of the shape of each structure submitted as priors. Volumetric labels are parameterized by a 3D deformation of
a surface model based on multivariate Gaussian assumptions. FIRST searches through linear combinations of shape modes of variation for the most probable shape (i.e., brain structure) given the intensity distribution in the T1-weighted image, and specific brain regions are extracted (see Patenaude et al., 2007a,b for further description of the method). Modes of variation are optimized based on leave-one-out cross-validation on the training set, and they increase the robustness and reliability of the results (Patenaude et al., 2007b). The segmentations were visually checked for errors. Finally, boundary correction was run, a process which classifies boundary voxels as belonging to the structure (or not) based on a statistical probability (z-score >3.00; p<0.001).

The volume of each participant’s brain region was measured in mm$^3$ and converted to cm$^3$ for presentation. Bilateral (sum of left and right) volumes for the dorsal striatum (sum of bilateral caudate nucleus and bilateral putamen) and the ventral striatum (bilateral nucleus accumbens) were examined given significant correlations between the volumes of the left and right caudate nucleus, putamen, and nucleus accumbens at pre-test and post-test (all r > 0.71, all p < 0.001) (Verstynen et al., 2012) (Figure 2.1).

**Cognitive Control Paradigm**

The task combined an Eriksen flanker paradigm and Go/NoGo paradigm (see Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002 for a similar task design). Five shapes were presented, and participants were instructed to “look at the middle shape.” Three task conditions were included: neutral (-->, --<--), incongruent (<<<<, >><>), and NoGo (<<<<<<, >>X>>>) trials. When the middle arrow pointed to the left, participants were instructed to press a button with their left index finger. When the middle arrow pointed to the right, participants were instructed to press a button with their right index finger. When the middle shape was an X,
participants were told not to press a button. The neutral condition was designed to require less attentional, interference and inhibitory control. The incongruent condition required attentional and interference control to filter potentially misleading flankers that were mapped to incorrect behavioral responses. The NoGo condition required subjects to inhibit a prepotent tendency to respond, given that the majority of trials (i.e., incongruent, neutral) required an active “go” response.

During the task, 40 trials of each of the three possible conditions (--->, --<--, >><<>, <<<<, >>X>, <<X<<) were presented in a random order. The response window included the presentation of the array of shapes for 500 ms, followed by a blank screen for 1000 ms. Each stimulus array was separated by a fixation cross (+) presented for 1500 ms. Forty additional fixation crosses that jittered between 1500 ms and 6000 ms were also randomly presented after the constant 1500 ms fixation cross throughout the task. The jitter prevented participants from expecting a specific frequency of responding. White shapes and white fixation crosses were presented on a black background. The participant was engaged in the task for about 6 minutes. Stimulus presentation, timing, and task performance measures were controlled by E-Prime software (Psychology Software Tools, Sharpsburg, Pennsylvania).

**Statistical Analysis**

Repeated measures ANOVAs were first conducted to explore changes in aerobic fitness, task performance, and basal ganglia volume in the physical activity intervention group and wait list control group from pre-test to post-test. Next, given *a priori* hypotheses, paired t-tests were conducted to compare within-group changes in fitness, task performance, and basal ganglia volume. To further understand the relationship among physical activity, basal ganglia volume, and cognitive control, correlations between basal ganglia volume changes and task performance
changes within the physical activity intervention group and wait list control group were explored (see Table 2.4). Change variables in terms of task performance and basal ganglia volume were calculated for each participant as (post-test – pre-test).

**Results**

**Participant Demographics and Fitness**

Group demographic and fitness data at pre-test and post-test are provided in Table 2.1. Demographic and fitness variables of age, gender, race, KBIT (IQ), SES, pubertal timing, and VO$_2$ max, did not differ between the physical activity intervention group and wait list control group (all t < 1.6, p > 0.1).

The physical activity intervention group showed a 12% increase in VO$_2$ max percentile (Post-Test – Pre-Test) (t (15) = 2.8, p=0.01, d=0.59), and the wait list control group showed an 8% increase in VO$_2$ max percentile (t (16) = 2.1, p=0.053, d=0.32, see Table 2.1). There was also a main effect of time for VO$_2$ max percentile (F (1, 31) = 12.2, p=0.001), but the group (physical activity intervention, wait list control) x time (pre-test, post-test) interaction did not reach significance (F (1, 31) = 0.6, p=0.4). Together, the data show an increase in VO$_2$ max in all children with age and development (Janz & Mahoney, 1997). However, the physical activity intervention group showed additional within-group gains in VO$_2$ max as a function of their daily exposure to physical activity.

**Performance on a Task of Cognitive Control**

No significant differences in task performance (RT, accuracy) were found between the physical activity intervention group and wait list control group at pre-test (p>0.05).
**Reaction time.** A repeated measures ANOVA examining task conditions with reaction time (RT) (incongruent, neutral) at pre-test and post-test revealed a main effect of time (F (1, 32) = 25.2, p<0.001), with shorter post-test RT across incongruent and neutral trials (M=817.6 ms, SE=22.2 ms) compared to pre-test RT (M=903.1 ms, SE=21.7 ms). A main effect of task condition (F (1, 32) = 63.9, p<0.001) showed shorter RT for neutral trials (M=830.5 ms, SE=19.7 ms) compared to incongruent trials (M=890.2 ms, SE=21.4 ms). These findings suggest improvements in RT across 9 months for both groups, as predicted with practice or development, as well as confirm the efficacy of the task, with incongruent trials requiring increased attentional and interference control relative to neutral trials.

The group x task condition (neutral, incongruent) x time interaction did not reach significance (F (1, 31) = 0.2, p=0.8). Because of the *a priori* hypotheses predicting greater changes in task performance for the physical activity intervention group compared to the wait list control group, paired t-tests were conducted to further explore the data. The physical activity intervention group showed shorter RT for both incongruent trials (t (15) = 5.1, p<0.001, d=0.74) and neutral trials (t (15) = 5.0, p<0.001, d=0.70) at post-test relative to pre-test. The wait list control group also showed shorter RT for incongruent trials (t (16) = 2.5, p=0.02, d=0.64) and neutral trials (t (16) = 2.6, p=0.04, d=0.54) at post-test relative to pre-test (see Table 2.2). These planned comparisons replicate the main effect of time yet confirm that both groups demonstrate shorter RT at post-test compared to pre-test.

**Accuracy.** A repeated measures ANOVA examining all task conditions with accuracy rates (incongruent, neutral, NoGo) at pre-test and post-test revealed a main effect of time (F (1, 32) = 7.8, p=0.009), with higher post-test accuracy across all task conditions (M=93%, SE=1.0%) compared to pre-test accuracy (M=90%, SE=1.2%). A main effect of task condition
(F (2, 64) = 64.0, p<0.001) was decomposed to show that neutral accuracy was significantly higher than incongruent accuracy (t (32) = 5.9, p<0.001). Additionally, NoGo accuracy (M=98%, SE=0.3%) was significantly higher than incongruent accuracy (M=85%, SE=1.6%) (t (32) = 8.6, p<0.001) and neutral accuracy (M=90%, SE=1.2%) (t (32) = 7.5, p<0.001), which was not predicted. A condition x time interaction was also significant (F (2, 64) = 7.2, p=0.002), with participants demonstrating higher incongruent accuracy at post-test (M=89%, SE = 1.7%) relative to pre-test (M=82%, SE = 2.2%) (F (1, 31) = 8.4, p=0.007) and higher neutral accuracy at post-test (M=92%, SE=1.3%) relative to pre-test (M=88%, SE=1.5%) (F (1, 31) = 6.1, p=0.02). There were no significant changes in NoGo accuracy from pre-test (M=98%, SE=0.4%) to post-test (M=98%, SE=0.6%).

The group x task condition (neutral, incongruent, NoGo) x time interaction did not reach significance for accuracy rates (F (2, 30) = 1.0, p=0.37). Because of the a priori hypotheses predicting greater changes in task performance for the physical activity intervention group compared to the wait list control group, paired t-tests were conducted to further explore the data. The physical activity intervention group showed increased accuracy for incongruent trials (t (15) = 2.4, p=0.03, d=0.59) at post-test relative to pre-test, but no changes in accuracy on neutral or NoGo trials (see Table 2.2). The wait list control group did not show significant changes in incongruent (t (16) = 1.8, p=0.09, d=0.55) or NoGo accuracy from pre-test to post-test (p>0.05), but did show increases in neutral accuracy from pre-test to post-test (t (16) = 2.2, p=0.04, d=0.57, see Table 2.2).

**Dorsal Striatum Volume**

The physical activity intervention group and wait list control group did not differ in total dorsal striatum volume (sum of bilateral putamen volume and bilateral caudate volume) at pre-
test (p>0.05). A group x time interaction, when controlling for gender and intracranial volume (the sum of total gray matter, white matter and cerebrospinal fluid), did not reach significance (F (1, 29) = 0.2, p=0.6). All mean basal ganglia volumes for the physical activity intervention group and wait list control group, corrected for gender and intracranial volume, are provided in Table 2.3. Because this study was approached with a priori hypotheses, paired t-tests were conducted to examine within-group changes in dorsal striatum volumes from pre-test to post-test. Only the physical activity intervention group showed significant increases in total dorsal striatum volume from pre-test to post-test (t (15) = 3.1, p=0.008, d=0.29, see Table 2.3 and Figure 2.2). The wait list control group did not show significant changes in dorsal striatum volume from pre-test to post-test (t (16) = 1.8, p=0.1, d=0.22) (see Table 2.3). The physical activity intervention group and wait list control group did not differ in total dorsal striatum volume at post-test (p>0.05).

Ventral Striatum Volume

The physical activity intervention group and wait list control group did not differ in ventral striatum volume (i.e., nucleus accumbens) (p>0.05). No significant group x time interaction was found examining ventral striatum volume at pre-test and post-test (F (1, 29) = 0.1, p=0.7), and paired t-tests confirmed that the physical activity intervention group and wait list control group did not show significant changes in total ventral striatum volume from pre-test to post-test (t<0.5, p>0.6) (see Table 2.3).

Physical Activity, Basal Ganglia Volume, and Task Performance

Within the physical activity intervention group (N=16), the change in dorsal striatum volume showed a significant negative correlation with the change in incongruent RT. The change in dorsal striatum volume also positively correlated with change in neutral accuracy (see
Table 2.4). Within the wait list control group (N=17), no correlations between change in basal ganglia volume and task performance reached significance. No associations between change in ventral striatum volume and task performance were found across either group.

**Discussion**

The present study is the first to demonstrate that children who participated in a physical activity after school program for approximately 9 months (and improved their aerobic fitness) showed within-group increases (+0.92%, +0.1 cm$^3$) in the volume of the dorsal striatum of the basal ganglia. A wait list control group did not show within-group changes in dorsal striatum volume (+0.85%, +0.08 cm$^3$) from pre-test to post-test. Although the conclusions are limited by a lack of statistical interactions, the study extends cross-sectional research (Chaddock et al., 2010b) and raises the possibility that physical activity during childhood that leads to gains in aerobic fitness positively affects the structure of the dorsal striatum.

The findings also suggest that physical activity may affect the function of the dorsal striatum, which is involved in cognitive control. In the task, incongruent trials (e.g., >><<>, <<<<) seemed to require increased attentional and interference control compared to neutral (e.g., --<<--, --<<--) or NoGo (e.g., <<x<<, >>x>>) trials; thus, the study focused on performance differences during the incongruent task condition, which provided the greatest challenge to the participants’ ability to pay attention and suppress distraction. Children enrolled in the physical activity intervention demonstrated shorter RT and increased accuracy from pre-test to post-test during incongruent flanker trials. Children in the wait list control group showed shorter RT on incongruent flanker trials (and higher neutral accuracy) from pre-test to post-test, but no within-group increases in incongruent flanker accuracy. Furthermore, there was only an association between change in dorsal striatum volume and change in incongruent RT within the physical
activity intervention group. It is possible that the volumetric increases in the dorsal striatum with physical activity may play a role in the ability to pay attention and ignore distractions (Aron et al., 2009). Children assigned to the wait list control group also showed better task performance from pre-test to post-test for some elements of cognitive control, as expected with 9 months of maturation, but their performance changes were unrelated to volume changes in the dorsal striatum.

Neither the intervention nor control group showed volume changes in the ventral striatum, a subregion of the basal ganglia more involved in reward processes and habit formation (Graybiel, 2005, 2008). Additionally, change in ventral striatum volume was not related to changes in attentional and interference control. The lack of a significant effect in the ventral striatum supports previous cross-sectional research that failed to show differences in ventral striatum volume as a function of aerobic fitness levels in children (Chaddock et al., 2010b; but see Verstynen et al., 2012 that reported larger nucleus accumbens volumes in higher fit older adults compared to lower fit elderly). Brain regions involved in cognitive control and memory are known to be particularly amenable to changes after engaging in physical activity (Chaddock et al., 2010a,b; Colcombe & Kramer, 2003; Kramer et al., 1999), and these findings with children support this framework.

Strong conclusions cannot be made about the associations among physical activity, basal ganglia structure, and response inhibition. Although incongruent and NoGo task conditions were hypothesized to require increased cognitive control compared to neutral trials, children showed near ceiling accuracy rates on the NoGo task. High NoGo accuracy during childhood has also been reported in studies by Bunge et al. (2002) and Liston et al. (2006), which may suggest that response inhibition abilities mature earlier than other control abilities such as interference.
suppression (Bunge & Crone, 2009; van den Wildenberg & van der Molen, 2004). The task design may also have affected performance outcomes. In most Go/NoGo paradigms, participants press the same button on the go trials and must override this prepotent response when a NoGo trial appears. However, in the task in the present study, participants had to analyze each stimulus array to determine whether they should press a left button, a right button, or withhold their response. Thus, children in the present study were unlikely to have developed a prepotent response tendency because they were unable to plan a motor response until the stimulus appeared. This may have led to the high performance across all children on the NoGo trials (i.e., average 98% NoGo accuracy at pre-test and post-test). Given the limitations of this task, future research is needed to understand how specific elements of cognitive control, such as attentional, interference, and inhibitory control, are influenced by physical activity.

In conclusion, this preliminary study helps to understand how participation in physical activity that leads to gains in aerobic fitness impacts the basal ganglia, an area of the brain important for attentional control. Because cognitive control has been found to relate to achievement in the classroom (Castelli, Hillman, Buck, & Erwin, 2007; Chomitz et al., 2009; Coe, Pivarnik, Womack, Reeves, & Malina, 2006; Trudeau & Shephard, 2008), these results have implications for children’s success in the school environment. In addition, these findings suggest that physical activity is important for daily functioning outside the school environment, given that successful daily living requires paying attention and inhibiting distractions. Overall, despite the limitations of the study, the findings contribute to the growing evidence that physical activity and aerobic fitness may not only help counteract increased rates of obesity and lower fitness in children (Centers for Disease Control and Prevention, 2009; United States Department of Health and Human Services, 2008), but also enhance the brain and cognition.
Chapter 2 References


## Chapter 2 Tables and Figures

Table 2.1. Mean (SD) for physical activity intervention group and wait list control group at pre-test and post-test.

<table>
<thead>
<tr>
<th></th>
<th>Physical Activity</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-test</td>
<td>Post-test</td>
</tr>
<tr>
<td>Age (years)</td>
<td>8.7 (0.6)</td>
<td>9.4 (0.6)</td>
</tr>
<tr>
<td>Gender</td>
<td>9 girls, 7 boys</td>
<td>8 girls, 9 boys</td>
</tr>
<tr>
<td>Race</td>
<td>69% White</td>
<td>76% White</td>
</tr>
<tr>
<td></td>
<td>12% Asian</td>
<td>6% Asian</td>
</tr>
<tr>
<td></td>
<td>13% Black</td>
<td>12% Black</td>
</tr>
<tr>
<td></td>
<td>6% Mixed</td>
<td>6% Mixed</td>
</tr>
<tr>
<td>IQ</td>
<td>120.0 (14.7)</td>
<td>120.0 (12.6)</td>
</tr>
<tr>
<td>Pubertal timing</td>
<td>1.3 (0.4)</td>
<td>1.5 (0.4)</td>
</tr>
<tr>
<td>SES</td>
<td>2.1 (0.9)</td>
<td>2.1 (0.9)</td>
</tr>
<tr>
<td>VO\textsubscript{2} max (mL/kg/min)</td>
<td>38.0 (4.4)\textsuperscript{a}</td>
<td>41.5 (3.4)\textsuperscript{a}</td>
</tr>
<tr>
<td>VO\textsubscript{2} max percentile</td>
<td>15.4 (15.0)\textsuperscript{a}</td>
<td>27.8 (25.9)\textsuperscript{a}</td>
</tr>
<tr>
<td>BMI (kg/cm\textsuperscript{2})</td>
<td>17.8 (2.5)</td>
<td>17.5 (2.0)</td>
</tr>
</tbody>
</table>

*Note:* IQ – composite standardized score of intelligence quotient from the Kaufman Brief Intelligence Test (Kaufman & Kaufman, 1990), SES – Socioeconomic Status. Values that share a common superscript are significantly different at p<0.05.
Table 2.2. Mean (SD) for physical activity intervention group and wait list control group at pre-test and post-test.

<table>
<thead>
<tr>
<th></th>
<th>Physical Activity</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-test</td>
<td>Post-test</td>
</tr>
<tr>
<td>Incongruent RT (ms)</td>
<td>940.8 (149.2)³</td>
<td>830.7 (146.9)³</td>
</tr>
<tr>
<td>Neutral RT (ms)</td>
<td>867.9 (134.8)³</td>
<td>777.3 (125.2)³</td>
</tr>
<tr>
<td>Incongruent accuracy (%)</td>
<td>82.5 (12.1)³</td>
<td>89.2 (10.4)³</td>
</tr>
<tr>
<td>Neutral accuracy (%)</td>
<td>89.8 (6.1)</td>
<td>92.2 (9.3)</td>
</tr>
<tr>
<td>NoGo accuracy (%)</td>
<td>98.3 (2.4)</td>
<td>98.8 (2.0)</td>
</tr>
</tbody>
</table>

*Note:* Values that share a common superscript are significantly different at p<0.05.
Table 2.3. Mean (SE) for physical activity intervention group and wait list control group at pre-test and post-test.

<table>
<thead>
<tr>
<th></th>
<th>Physical Activity</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-test</td>
<td>Post-test</td>
</tr>
<tr>
<td>Dorsal striatum volume (cm³)</td>
<td>11.280 (0.1) a</td>
<td>11.397 (0.1) a</td>
</tr>
<tr>
<td>Ventral striatum volume (cm³)</td>
<td>1.020 (0.04)</td>
<td>1.018 (0.03)</td>
</tr>
<tr>
<td>Intracranial brain volume (cm³)</td>
<td>1365.0 (24.2)</td>
<td></td>
</tr>
</tbody>
</table>

Note: Dorsal striatum and ventral striatum volumes are corrected for gender and intracranial brain volume. Values that share a common superscript are significantly different at p<0.05.
Table 2.4. Correlation matrix (r) (p-value) between change (post-test – pre-test) in basal ganglia volume and change (post-test – pre-test) in task performance for the physical activity intervention group and wait list control group. *p<0.05

<table>
<thead>
<tr>
<th></th>
<th>Change in Incongruent RT</th>
<th>Change in Neutral RT</th>
<th>Change in Incongruent Accuracy</th>
<th>Change in Neutral Accuracy</th>
<th>Change in NoGo Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical Activity Group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change-Dorsal Striatum Vol.</td>
<td>-0.629 (p=0.009)*</td>
<td>-0.335 (p=0.2)</td>
<td>0.239 (p=0.4)</td>
<td>0.58 (p=0.01)*</td>
<td>-0.26 (p=0.3)</td>
</tr>
<tr>
<td>Change-Ventral Striatum Vol.</td>
<td>-0.04 (p=0.9)</td>
<td>-0.46 (p=0.07)</td>
<td>0.24 (p=0.4)</td>
<td>0.22 (p=0.4)</td>
<td>0.09 (p=0.7)</td>
</tr>
<tr>
<td><strong>Control Group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change-Dorsal Striatum Vol.</td>
<td>-0.14 (p=0.6)</td>
<td>-0.20 (p=0.5)</td>
<td>-0.10 (p=0.7)</td>
<td>-0.18 (p=0.5)</td>
<td>-0.04 (p=0.9)</td>
</tr>
<tr>
<td>Change-Ventral Striatum Vol.</td>
<td>0.10 (p=0.7)</td>
<td>0.18 (p=0.5)</td>
<td>-0.11 (p=0.7)</td>
<td>-0.17 (p=0.5)</td>
<td>0.02 (p=0.9)</td>
</tr>
</tbody>
</table>
Figure 2.1. Sample segmentation of the dorsal striatum (red=caudate; blue=putamen; Z=300) and ventral striatum (green=nucleus accumbens; Z=282) on a structural brain reconstruction.
Figure 2.2. Percent change in dorsal striatum volume for the physical activity intervention group and wait list control group. Error bars represent standard error.
CHAPTER 3
THE EFFECTS OF PHYSICAL ACTIVITY ON HIPPOCAMPAL VOLUME IN CHILDREN

Participation in physical activity and higher levels of aerobic fitness positively influence the hippocampus (Bugg & Head, 2011; Chaddock et al., 2010a; Erickson et al., 2009, 2011; Honea et al., 2009; van Praag, Kempermann, & Gage, 1999). The hippocampus, located in the medial temporal lobe, is critical for spatial learning and navigation (Hollup, Kjelstrup, Hoff, Moser, & Moser, 2001; Maguire et al., 1998; Maguire, Frackowiak, & Frith, 1997; Maguire & Frith, 2003) and relational memory formation (Cohen & Eichenbaum, 1993). This brain region is implicated in disease states that involve memory dysfunction and, when damaged, can cause states of amnesia (Cohen & Eichenbaum, 1993). Yet, the hippocampus remains a plastic structure throughout the life course, and physical activity has the capacity to influence the morphology and functional architecture of the hippocampus in both rodents and humans (e.g., Erickson et al., 2011; van Praag et al., 1999).

Young and older rodents that engage in aerobic exercise (i.e., voluntary wheel running) show increased cell proliferation, cell survival, and functional integration of new granule neurons in the hippocampus, coupled with improvements in learning and retention on tests of spatial memory (Gomez-Pinilla, Vaynman, & Ying, 2008; Gould, 2007; van Praag et al., 1999). Exercise in rodents also increases vasculature (Clark, Brzezinska, Puchalski, Krone, & Rhodes, 2009; Van der Borght et al., 2009; van Praag, Shubert, Zhao, & Gage, 2005), growth factors (Neeper, Gomez-Pinilla, Choi, & Cotman, 1996), dendritic structure (Redila & Christie, 2006), and gliogenesis (Uda, Ishido, Kami, & Masuhara, 2006) in the hippocampus, all changes that may directly lead to improvements in memory function.
Similar effects of physical activity and aerobic fitness are found in neuroimaging studies of the hippocampus in humans. Children and older adults with higher aerobic fitness levels have larger total hippocampal volume compared to their lower fit peers (Bugg & Head, 2011; Chaddock et al., 2010a; Erickson et al., 2009) and hippocampal volume partially mediates the relationship between aerobic fitness and spatial and relational memory performance (Chaddock et al., 2010a; Erickson et al., 2009). Additionally, in older adults, greater amounts of physical activity (Erickson et al., 2010) and higher levels of aerobic fitness (Honea et al., 2009) are associated with less atrophy in temporal lobe gray matter and less risk of cognitive impairment (Erickson et al., 2010). To date, a randomized controlled trial has only been conducted with an elderly population (Erickson et al., 2011). The findings indicate that one year of aerobic exercise training was sufficient to increase the volume of the hippocampus, with the potential of reversing age-related volume loss (Erickson et al., 2011). Alternatively, older adults involved in a stretching and toning program showed hippocampal atrophy, typical for the age group in the study, over the year. Furthermore, in the aerobic exercise group, increased hippocampal volume was related to improvements in spatial memory performance. Randomized controlled physical activity interventions are required to formulate stronger conclusions about the role of physical activity in hippocampal morphology in children.

Here, for the first time, this study examined whether the volume of the hippocampus could be increased by physical activity in 8- to 9-year-old children in a randomized controlled intervention designed to increase aerobic fitness. As stated, research has shown that the volume of the hippocampus is influenced by participation in aerobic exercise during late life (Erickson et al., 2011), but, to date, only a single cross-sectional study has been conducted with children that showed a relationship between aerobic fitness and hippocampal structure (Chaddock et al., 2010a; Erickson et al., 2009).
2010a). Because this preliminary study suggested variation in hippocampal volume in preadolescent children as a function of aerobic fitness level (Chaddock et al., 2010a), it was predicted that the hippocampus might also be modifiable with a physical activity intervention designed to increase aerobic fitness in children of this age range. In addition to exploring changes in total hippocampal volume with the physical activity intervention, changes in anterior and posterior hippocampal volume were examined to try to determine the elements of memory influenced by physical activity, as subregions of the hippocampus have been tied to distinct cognitive functions (Kesner, Lee, & Gilbert, 2004; Moser & Moser, 1998; Strange, Fletcher, Henson, Friston & Dolan, 1999). For example, the posterior hippocampus is said to play a role in spatial learning and memory (Bannerman et al., 2004; Colombo, Fernandez, Nakamura, & Gross, 1998; Lee & Kesner, 2003a,b; Maguire et al., 2000; Moser, Moser, & Andersen, 1993), and the anterior hippocampus has been implemented in anxiety-related behaviors and emotional processing (Bannerman et al., 2004) as well as associative memory (Schacter & Wagner, 1999a,b). It was predicted that physical activity would not affect the volume of the nucleus accumbens, another region in the midbrain that was used as a control brain region for the examination of the hippocampus. The nucleus accumbens has not been found, in cross-sectional studies, to relate to aerobic fitness in children (Chaddock et al., 2010a,b). The current research has important implications for the understanding and conceptualization of memory performance and potentially daily functioning in and out of the school environment, as well as far-reaching implications for the biological potential of the brain during periods of maturation and brain development.
Method

Participants

Eight- to 9-year-old children were recruited from the Urbana, Illinois school district 116. All children completed demographic assessments, a VO$_2$ max test to assess aerobic fitness, and a magnetic resonance imaging (MRI) session (which included a structural MRI scan) at pre-test (i.e., before randomization into a physical activity intervention group or a wait list control group) and post-test (i.e., after the completion of the intervention, approximately 9 months later).

Forty-one children were eligible for the study. Five children (2 physical activity intervention, 3 wait list control) were excluded from the analyses because of failure to complete the post-test MRI. Eight children (4 physical activity intervention, 4 wait list control) were excluded because of excessive head motion that created inaccurate brain segmentations. Accordingly, 28 children were included in the final analyses, with 14 children assigned to the physical activity intervention group (9 girls, 5 boys) and 14 children assigned to the wait list control group (8 girls, 6 boys).

Demographic Assessments and Fitness Testing

To be eligible for the study, children had to have a Kaufman Brief Intelligence Test (KBIT) score greater than 85 (Kaufman & Kaufman, 1990) and qualify as prepubescent (Tanner puberty score $\leq 2$; Taylor et al., 2001). Children were also screened for the presence of attentional disorders using the Attention Deficit Hyperactivity Disorder (ADHD) Rating Scale IV (DuPaul, Power, Anastopoulos & Reid, 1998), and were excluded if they scored above the 85$^{th}$ percentile. Body mass index (BMI) was calculated as weight (kg)/height(cm)$^2$, and socioeconomic status (SES) was determined by creating a trichotomous index: participation in a free or reduced-price meal program at school, the highest level of education obtained by the
child's mother and father, and the number of parents who worked full-time (Birnbaum et al., 2002; Hillman et al., 2012).

Eligible children were further required to (1) report an absence of school-related learning disabilities (i.e., individual education plan related to learning), adverse health conditions, physical incapacities, or neurological disorders, (2) report no use of medications that influence central nervous system function, (3) demonstrate right handedness (as measured by the Edinburgh Handedness Questionnaire; Oldfield, 1971), (4) complete a mock MRI session successfully to screen for claustrophobia in an MRI machine, (5) be capable of performing physical activity, and (6) sign an informed assent approved by the University of Illinois at Urbana-Champaign. A legal guardian also provided written informed consent in accordance with the Institutional Review Board of the University of Illinois at Urbana-Champaign. Children were paid for their time ($10/hour for demographic assessments and fitness testing and $15/hour for MRI testing).

**Aerobic Fitness Testing**

Children completed a VO$_2$ max test at pre-test and post-test to assess aerobic fitness. The aerobic fitness of each child was measured as maximal oxygen consumption (VO$_2$ max) during a graded exercise test (GXT). The GXT employed a modified Balke Protocol and was administered on a LifeFitness 92T motor-driven treadmill (LifeFitness, Schiller Park, IL) with expired gases analyzed using a TrueOne2400 Metabolic Measurement System (ParMedics, Sandy, Utah). Children walked and/or ran on a treadmill at a constant speed with increasing grade increments of 2.5% every 2 minutes until volitional exhaustion occurred.

Oxygen consumption was measured using a computerized indirect calorimetry system (ParvoMedics True Max 2400) with averages for VO$_2$ and respiratory exchange ratio (RER)
assessed every 20 seconds. A polar heart rate (HR) monitor (Polar WearLink+ 31; Polar Electro, Finland) was used to measure HR throughout the test, and ratings of perceived exertion (RPE) were assessed every 2 minutes using the children’s OMNI scale (Utter, Robertson, Nieman & Kang, 2002). Maximal oxygen consumption was expressed in mL/kg/min and VO\textsubscript{2} max was based upon maximal effort as evidenced by (1) a plateau in oxygen consumption corresponding to an increase of less than 2 mL/kg/min despite an increase in workload; (2) a peak HR \(\geq 185\) beats per minute (American College of Sports Medicine, 2006) and an HR plateau (Freedson & Goodman, 1993); (3) RER \(\geq 1.0\) (Bar-Or, 1983); and/or (4) a score on the children’s OMNI ratings of perceived exertion (RPE) scale \(\geq 8\) (Utter et al., 2002).

**Physical Activity Training Intervention and Wait List Control Group**

The physical activity intervention occurred for 2 hours after each school day, from September until May, for 150 days out of the 170 day school year. The program, Fitness Improves Thinking in Kids (FITKids) (http://clinicaltrials.gov/ct2/show/NCT01334359?term=FITKids&rank=1) is based on the Child and Adolescent Trial for Cardiovascular Health (CATCH) curriculum (McKenzie et al., 1994). The program is aimed at improving aerobic fitness through engagement in a variety of age-appropriate physical activities. The environment was non-competitive and integrated activities such as fitness activities and organized games (Castelli, Hillman, Hirsch, Hirsch, & Drollette, 2011).

Within a daily lesson, the children participated in an average of 76.8 minutes of moderate to vigorous physical activity (recorded by E600 Polar heart rate monitors; Polar Electro, Finland, and Accusplit Eagle 170 pedometers, San Jose CA), thus exceeding the national physical activity guideline of 60 minutes of moderate to vigorous physical activity per day (Centers for Disease Control and Prevention, 2011). Children completed stations that focused on a specific health-
related fitness component (i.e., cardiorespiratory endurance, muscular strength). The activities were aerobically demanding, but simultaneously provided opportunities to refine motor skills. The program also included consumption of a healthy snack and the introduction of a themed educational component related to health promotion (i.e., goal setting, self-management). On the weekends, the children were encouraged to continue their participation in physical activity with their family, and physical activity worksheets were utilized during school holidays to log continued engagement. Average attendance across the 9-month intervention was 89.0% (SD=7.2%).

The wait list control group was not contacted following randomization. They completed all facets of the pre-test and post-test, similar to those children who were randomized into the after school physical activity intervention. As incentive to stay in the study, children in the wait list control group were afforded the opportunity to participate in the intervention during the following school year.

**Structural MRI Protocol**

High resolution T1-weighted brain images were acquired using a 3D MPRAGE (Magnetization Prepared Rapid Gradient Echo Imaging) protocol with 192 contiguous axial slices, collected in ascending fashion parallel to the anterior and posterior commissures, echo time (TE)=2.32 ms, repetition time (TR)=1900 ms, field of view (FOV)=230 mm, acquisition matrix 256 mm x 256 mm, slice thickness=0.90 mm, and flip angle=9º. All images were collected on a Siemens Magnetom Trio 3T whole-body MRI scanner.

**FMRIB’s Integrated Registration and Segmentation Tool**

Segmentation and volumetric analysis of the hippocampus and nucleus accumbens were performed using a semi-automated, model-based subcortical tool (FIRST; FMRIB’s Integrated
Registration and Segmentation Tool) in FMRIB’s Software Library (FSL) version 4.1.9 (Patenaude, 2007; Patenaude, Smith, Kennedy, & Jenkinson, 2007a,b). The nucleus accumbens was chosen as a control region because, like the hippocampus, it is a subcortical structure in the midbrain, which can be segmented using the same technique, yet this region has not been found to relate to physical activity or aerobic fitness in children (Chaddock et al., 2010a,b).

A two-stage affine registration to a standard space template (MNI space) with 1 mm resolution using 12-degrees of freedom and a subcortical mask to exclude voxels outside the subcortical regions was first performed on each participant’s MPRAGE. Next, the hippocampus and nucleus accumbens were segmented with 30 and 50 modes of variation, respectively. To achieve accurate segmentation, the FIRST methodology models 317 manually segmented and labeled T1-brain images from normal children, adults, and pathological populations (obtained from the Center for Morphometric Analysis, Massachusetts General Hospital, Boston) as a point distribution model with the geometry and variation of the shape of each structure submitted as priors. Volumetric labels are parameterized by a 3D deformation of a surface model based on multivariate Gaussian assumptions. FIRST searches through linear combinations of shape modes of variation for the most probable shape (i.e., brain structure) given the intensity distribution in the T1-weighted image, and specific brain regions are extracted (see Patenaude et al., 2007a,b for further description of the method). Modes of variation are optimized based on leave-one-out cross-validation on the training set, and they increase the robustness and reliability of the results (Patenaude et al., 2007b). The segmentations were visually checked for errors. Finally, boundary correction was run, a process that classifies boundary voxels as belonging to the structure (or not) based on a statistical probability (z-score >3.00; p<0.001). The volume of each participant’s brain region was measured in mm³ and converted to cm³ for presentation. The
hippocampus included the dentate gyrus, the ammonic subfields (CA1–4), the prosubiculum, and the subiculum and did not include the fimbria/fornix behind the posterior commissure.

In an exploratory analysis to try to gain insight into the specific subregions of the hippocampus influenced by physical activity during childhood, anterior and posterior sections of the hippocampus were calculated by determining the center of gravity for both the left and right hippocampus for each participant. The \( y \) coordinate from the center-of-gravity calculation was used to divide the region into anterior and posterior sections, and the left and right volume of each anterior and posterior subsection was determined (Erickson et al., 2011) (see Figure 3.1).

**Statistical Analysis**

Repeated measures ANOVAs were first conducted to explore changes in aerobic fitness (\( \text{VO}_2 \text{ max} \)) and volume of the hippocampus and nucleus accumbens in the physical activity intervention group and wait list control group from pre-test to post-test. Next, given *a priori* hypotheses, paired t-tests were conducted to compare within-group changes in fitness and hippocampal and nucleus accumbens volume. Correlations between change (Post-test – Pre-test) in \( \text{VO}_2 \text{ max} \) and change in total hippocampal volume as well as change in \( \text{VO}_2 \text{ max} \) and change in total nucleus accumbens volume were also conducted.

**Results**

**Participant Demographics and Fitness**

Group demographic and fitness data at pre-test and post-test are provided in Table 3.1. Demographic and fitness variables of age, gender, race, KBIT (IQ), SES, pubertal timing, and \( \text{VO}_2 \text{ max} \), did not differ between the physical activity intervention group and wait list control group (all \( t < 1.6, p > 0.1 \)).
The physical activity intervention group showed a 15% increase in VO\textsubscript{2} max percentile (t (13) = 2.2, p=0.02, d=0.72), and the wait list control group showed a non-significant 8% increase in VO\textsubscript{2} max percentile (t (13) = 2.1, p >0.05, d=0.56). There was also a main effect of time for VO\textsubscript{2} max percentile (F (1, 26) = 8.8, p=0.006), but the group (physical activity intervention, wait list control) x time (pre-test, post-test) interaction did not reach significance (F (1, 26) = 0.6, p=0.4). Together, the data show an increase in VO\textsubscript{2} max in all children with age and development (Janz & Mahoney, 1997). However, the physical activity intervention group showed additional within-group gains in VO\textsubscript{2} max as a function of their daily exposure to physical activity.

**Hippocampal Volume**

Mean hippocampal volume for the physical activity intervention group and wait list control group are provided in Table 3.2. The physical activity intervention group and wait list control group did not differ in total hippocampal volume at pre-test (t (26) = 0.04, p=0.9, d=0.0015). A repeated measures ANOVA which explored a group (physical activity intervention, wait list control) x time (total hippocampal volume at pre-test and post-test) interaction, when controlling for gender and intracranial volume (the sum of total gray matter, white matter and cerebrospinal fluid), showed a non-significant interaction (F (1, 24) = 0.77, p=0.3).

Because the study was approached with *a priori* hypotheses, paired t-tests were conducted to examine within-group changes in total, anterior and posterior hippocampal volumes from pre-test to post-test. Only the physical activity intervention group showed significant increases in total hippocampal volume from pre-test to post-test (t (13) = 2.1, p=0.04, d=0.04; see Table 3.2 and Figure 3.2). Specifically, the mean percent change score ((Post-Test – Pre-
Test) / Pre-Test x 100) for the physical activity intervention group was 2.1%, (SD=2.6%). The wait list control group did not show significant changes in hippocampal volume from pre-test to post-test (all t<1.4, p>0.1, d=0.01; mean percent change score=0.9%, SD=2.2%).

In an exploratory analysis, posterior hippocampal volume (t (13) = 2.4, p=0.03, d=0.03) showed significant increases in volume in the physical activity intervention group. The wait list control group did not show significant changes in posterior hippocampal volume (t (13) = 1.6, p=0.13, d=0.017). Anterior hippocampal volume did not change within either group from pre-test to post-test. Additionally, changes in relative VO$_2$ max were modestly, but not significantly, correlated with changes in total hippocampal volume (r=0.38, p=0.18).

**Nucleus Accumbens Volume**

Mean total nucleus accumbens volume for the physical activity intervention group and wait list control group are provided in Table 3.2. Nucleus accumbens volume did not significantly differ between the groups. To confirm the specificity of the relationship between physical activity and the hippocampus, no higher-level interaction between group (physical activity intervention, wait list control) x time (total nucleus accumbens volume at pre-test and post-test) was found (F (1, 26) = 0.04, p>0.8). Paired t-tests confirmed no change in total nucleus accumbens volume for either the physical activity intervention group (all t<1.2, p>0.2) or wait list control group (all t<0.8, p>0.3). In addition, changes in VO$_2$ max were not correlated with changes in nucleus accumbens volume (r=-0.22, p=0.26).

**Discussion**

This is the first study to examine longitudinal changes in hippocampal volume in children as a function of chronic participation in a physical activity program that increased aerobic fitness. The results suggest that regular physical activity leading to fitness gains has the capacity to
modify the trajectory of hippocampal maturation in children. Specifically, physically active children showed an average increase in total hippocampal volume of 2.1% (+0.1 cm$^3$) over the course of the intervention, coupled with a 15% increase in VO$_2$ max percentile. In contrast, children in the wait list control group, who were not enrolled in a physical activity program, did not show significant increases in hippocampal volume (0.9%, +0.07 cm$^3$) or VO$_2$ max percentile. Nucleus accumbens volume did not change from pre-test to post-test for either group, which reinforces the specificity of the physical activity effects. However, despite within-group increases in hippocampal volume, the small sample size did not yield a significant interaction of group over time. Thus, while questions remain, the present study provides a first, promising step in the relationship between physical activity and the developing hippocampus.

The effects of increased hippocampal volume on memory function with participation in physical activity during childhood remain unknown, as a hippocampal memory task was absent from the design. Nevertheless, an exploratory analysis of the effects of physical activity on specific subregions of the hippocampus may help determine the elements of memory influenced by physical activity, as individual subregions of the hippocampus have been tied to distinct cognitive functions (Kesner et al., 2004; Moser & Moser, 1998; Strange et al., 1999). The increase in total hippocampal volume with physical activity was driven by increases in the posterior section. The posterior hippocampus has been shown to play a role in spatial learning and memory (Bannerman et al., 2004; Colombo et al., 1998; Lee & Kesner, 2003a,b; Maguire et al., 2000; Moser et al., 1993). Fittingly, one study showed that licensed London taxi drivers, who were skilled in complex spatial navigation, had greater gray matter volume in the posterior hippocampus (Maguire, Woollett, & Spiers, 2006). Thus, it is possible that physically active
children in the intervention would also improve on spatial skills with increases in posterior hippocampal volume. Clearly, future work needs to directly test this assumption.

The findings also partially complement a developmental study by Gogtay et al. (2006) in which individuals between the ages of 4 and 25 completed MRI scans every 2 years, for 6-10 years. The results suggested that the structural development of the hippocampus was heterogeneous, with increased volume over time in the posterior hippocampus and decreased volume over time in the anterior hippocampus (Gogtay et al., 2006). Significant increases in posterior hippocampal volume over time were only shown within the physical activity intervention group, with no significant changes in anterior hippocampal volume for either group (yet trends suggest increases in anterior hippocampal volume). Accordingly, the current data support Gogtay et al.’s (2006) findings of heterogeneous growth in the posterior hippocampus and suggest that physical activity may be one source of variability in this brain region.

The anterior hippocampus has been found to play a role in anxiety-related behaviors and emotional processing (Bannerman et al., 2004), especially given its projections to the prefrontal cortex (Cavada, Company, Tejedor, Cruz-Rizzolo, & Reinoso-Suarez, 2000). These functions have been shown to be less influenced by aerobic fitness in children (e.g., nucleus accumbens in Chaddock et al., 2010b). Nevertheless, the anterior hippocampus has also been found to play a role in associative memory (Schacter & Wagner, 1999a,b), and a randomized controlled physical activity trial in older adults found that elderly individuals who participated in physical activity showed increases in anterior hippocampal volume rather than posterior hippocampal volume (Erickson et al., 2011). Together, these results suggest that children and elderly differ in their response to physical activity. However, in later life, it may be easier to detect changes in brain volume with physical activity, as most aging brains are undergoing brain atrophy (Walhovd et al.,
2011), and physical activity and aerobic fitness may prevent some of this atrophy (Bugg & Head, 2011; Erickson et al., 2011; Honea et al., 2009). During development, on the other hand, “growth” and changes in brain volume in an isolated region that lead to improved cognitive health remain somewhat ambiguous (Amso & Casey, 2006). Future studies with children should continue to explore the specific trajectories of changes in brain structures, such as the hippocampus, with development. Additionally, future randomized controlled interventions with children should include a spatial memory and/or relational memory task to examine how specific volumetric changes in subregions of the hippocampus relate to memory task performance, as well as participation in physical activity.

Additional studies should continue to explore the frequency, intensity, duration, and mode of physical activity that provide the greatest brain and cognitive benefits to children. It is possible that the relatively small effects reported here are not only driven by the small sample size, but also driven by the relatively short amount of time between pre-test and post-test, relative to the full span of development. Nevertheless, whereas the study examined the effects of 60+ minutes of daily moderate to vigorous physical activity for 9 months, that led to improved aerobic fitness levels on brain structure in 8- to 9-year-olds, another investigation found that only 40 minutes per day of aerobic games for 13 weeks was sufficient to improve executive function and math achievement in overweight children between the ages of 7 and 11 years (Davis et al., 2011). The study by Davis et al. (2011) did not measure changes in fitness, and future studies are needed to assess the interactive effects of baseline fitness level, physical activity dosage, length of intervention, and aerobic fitness gains on brain structure and function.

Limitations exist with the use of a wait list control group. For example, it is possible that additional facets of the after school intervention, such as social interaction with exercise
personnel, a healthy snack, or motor skill practice, may have interacted with physical activity participation and influenced the within-group increases in hippocampal volume specifically for the physical activity intervention group. Because both groups were recruited from the same school and did not differ in SES, large effects of additional social interaction or one snack to the daily caloric intake of the children were not expected. Furthermore, whereas the physical activity program was designed to improve aerobic fitness, some of the stations included muscular strength challenges and motor skill practice, and additional research is needed to understand how these elements of the program may have influenced hippocampal structure.

In conclusion, the present study suggests that consistently integrating physical activity into a child’s day can increase the volume of the hippocampus. The hippocampus is a brain region critical to learning, remembering relationships among spatial layouts, and creating associative relationships among experiences, which are skills important for academic achievement and everyday living. These results should serve to raise public awareness of the cognitive benefits of physical activity, as children are becoming increasingly sedentary and unfit, with increased risk for disease (e.g., cardiovascular disease, type-2 diabetes) (Centers for Disease Control and Prevention, 2009; United States Department of Health and Human Services, 2008). These findings should also help to change educational practices that are contributing to the declining health in youth as physical activity opportunities are being reduced or eliminated during the school day (Centers for Disease Control and Prevention, 2010; Sallis, 2010). This research suggests that physical activity is important to the development of the brain during childhood.
Chapter 3 References


Chapter 3 Tables and Figures

Table 3.1. Mean (SD) for physical activity intervention group and wait list control group at pre-test and post-test.

<table>
<thead>
<tr>
<th>Physical Activity</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-test</td>
</tr>
<tr>
<td>Age (years)</td>
<td>8.7 (0.5)</td>
</tr>
<tr>
<td>Gender</td>
<td>9 girls, 5 boys</td>
</tr>
<tr>
<td>Race</td>
<td>57% White</td>
</tr>
<tr>
<td></td>
<td>14% Black</td>
</tr>
<tr>
<td>IQ</td>
<td>113.9 (17.9)</td>
</tr>
<tr>
<td>Pubertal timing</td>
<td>1.3 (0.3)</td>
</tr>
<tr>
<td>SES</td>
<td>1.9 (0.9)</td>
</tr>
<tr>
<td>VO₂ max (mL/kg/min)</td>
<td>37.7 (4.6) a</td>
</tr>
<tr>
<td>VO₂ max percentile</td>
<td>12.9 (9.2) a</td>
</tr>
<tr>
<td>BMI (kg/cm²)</td>
<td>17.7 (1.9)</td>
</tr>
</tbody>
</table>

*Note:* IQ – composite standardized score of intelligence quotient from the Kaufman Brief Intelligence Test (Kaufman & Kaufman, 1990), SES – Socioeconomic Status. Values that share a common superscript are significantly different at p<0.05.
Table 3.2. Mean (SD) for physical activity intervention group and wait list control group at pre-test and post-test

<table>
<thead>
<tr>
<th></th>
<th>Physical Activity</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-test</td>
<td>Post-test</td>
</tr>
<tr>
<td>Total hippocampal volume (cm³)</td>
<td>7.278 (4.23) a</td>
<td>7.428 (4.34) a</td>
</tr>
<tr>
<td>Anterior hippocampal volume (cm³)</td>
<td>4.125 (2.34)</td>
<td>4.211 (2.50)</td>
</tr>
<tr>
<td>Posterior hippocampal volume (cm³)</td>
<td>3.153 (1.99) a</td>
<td>3.217 (2.01) a</td>
</tr>
<tr>
<td>Total nucleus accumbens volume (cm³)</td>
<td>0.938 (0.109)</td>
<td>0.932 (0.103)</td>
</tr>
<tr>
<td>Intracranial brain volume (cm³)</td>
<td>1361.7 (5660.1)</td>
<td>1362.6 (9485.2)</td>
</tr>
</tbody>
</table>

*Note: Values that share a common superscript are significantly different at p<0.05.*
Figure 3.1. Sample segmentation of the hippocampus on a structural brain reconstruction, subdivided into anterior and posterior subsections.
Figure 3.2.  
a. Change in hippocampal volume, from pre-test to post-test, for the physical activity intervention group and wait list control group. There are significant within-group volume increases for only the physical activity intervention group. Error bars represent standard error.  
b. Percent change in hippocampal volume for the physical activity intervention group and wait list control group. Error bars represent standard error.
Participation in physical activity and higher levels of aerobic fitness during childhood are associated with larger brain volumes (Chaddock et al., 2010a,b), superior brain function (Chaddock, Erickson et al., 2012, Davis et al., 2011; Hillman, Buck, Themanson, Pontifex, & Castelli, 2009; Pontifex et al., 2011; Voss et al., 2011), higher performance on tasks of cognitive control (Buck, Hillman & Castelli, 2008; Chaddock et al., 2010b; Sibley & Etnier, 2003) and memory (Chaddock et al., 2010a; Chaddock, Hillman, Buck & Cohen, 2011), as well as better scholastic achievement (Castelli, Hillman, Buck, & Erwin, 2007; Chomitz et al., 2009; Coe, Pivarnik, Womack, Reeves, & Malina, 2006; Trudeau & Shephard, 2008). Despite this quickly emerging cognitive and brain imaging literature, there is a relative paucity of research examining the potential for physical activity to influence white matter integrity between brain areas known to be influenced by activity. Maturation of white matter tracts is an important element of development (Schmithorst & Yuan, 2010), as microstructural integrity of white matter is required for proper transmission of information between brain regions and the integration of brain areas into networks to support cognitive function.

Diffusion Tensor Imaging (DTI) enables an in vivo characterization of properties of white matter fiber tracts given its sensitivity to the motion of water. In areas of the brain with free diffusion (e.g., ventricles with cerebrospinal fluid), the motion of water is isotropic. In white matter, however, water diffuses in a more directionally dependent, or anisotropic, manner. DTI techniques measure both the anisotropy and rate of diffusion in a white matter tract, and the information is represented mathematically in a diffusion ellipsoid. High levels of anisotropy (i.e., water moves more parallel to a tract compared to perpendicularly to the tract) are said to
occur in tightly bundled, structurally compact fibers with high integrity, which yield high fractional anisotropy (FA) values (Basser, 1995; Beaulieu, 2002; Rykhlevskaia, Gratton, & Fabiani, 2008; Sen & Basser, 2005). One component of fractional anisotropy is radial diffusivity, which reflects the rate of diffusivity perpendicular to the major axis/eigenvector of the ellipsoid (Basser, 1995; Pierpaoli & Basser, 1996; Pierpaoli, Jezzard, Basser, Barnett, & Di Chiro, 1996; Song et al., 2002). Low rates of radial diffusion in a white matter tract are said to characterize insulated, myelinated tracts, which yield low radial diffusivity (RD) values (Budde et al., 2007; Nair et al., 2005; Rykhlevskaia et al., 2008; Song et al., 2002; 2003; 2005). For example, Song et al. (2005) used an experimental model of demyelination and remyelination in a mouse brain and demonstrated that RD increased with demyelination and subsequently decreased with the progression of remyelination. Furthermore, radial diffusivity changes were found to be specific to changes in myelin integrity, and distinct from axonal injury (Song et al., 2005). Estimates of white matter integrity (FA) and myelination (RD) in 8- to 9-year-old children were measured before and after the children were randomized into a 9-month physical activity intervention or a wait list control group.

The hypotheses were based on prior research of white matter changes across development (Schmithorst & Yuan, 2010), studies of how physical activity and aerobic fitness are related to the brain during childhood (Chaddock, Voss & Kramer, 2012), and associations among physical activity, aerobic fitness, and white matter volume and microstructure in older adults (Colcombe et al., 2006; Johnson, Kim, Clasey, Bailey, & Gold, 2012; Marks et al., 2007; Voss et al., 2012). Generally, during development, children show increasing FA (i.e., increased estimations of white matter integrity) in a number of tracts that connect frontal, parietal, motor and striatal brain regions. It is thought that these effects are caused by decreasing RD (i.e., increased
estimations of myelination) during this developmental period (e.g., Barnea-Goraly et al., 2005; Bonekamp et al., 2007; Schmithorst, Wilke, Dardzinski, & Holland, 2002; see Schmithorst & Yuan, 2010, for review). Such tracts include specific sections of the corpus callosum (Barnea-Goraly et al., 2005; Muetzel et al., 2008) and tracts in the corona radiata (Keller, Rajesh & Just, 2007), longitudinal fasciculus (Bonekamp et al., 2007), cingulum (Bonekamp et al., 2007), internal capsule (Bonekamp et al., 2007; Schmithorst et al., 2002), and motor regions (Barnea-Goraly et al., 2005).

It is possible that physical activity may be one source of variability in these developmental changes in white matter structure. Greater amounts of physical activity and higher aerobic fitness levels are associated with larger structures and improved function of frontal (Chaddock, Erickson et al., 2012; Davis et al., 2011; Voss et al., 2011), parietal (Chaddock, Erickson et al., 2012), hippocampal (Chaddock et al., 2010a, 2011), and striatal (Chaddock et al., 2010b) brain regions in children. Although studies of the relationship among white matter architecture, physical activity and aerobic fitness have not been conducted in children, a few studies have examined the associations among physical activity, fitness, and white matter microstructure in older adults. For example, in healthy older adults there was a positive relationship between aerobic fitness and FA of white matter tracts in the corpus callosum (Johnson et al., 2012) and cingulum (Marks et al., 2007), coupled with negative correlations between aerobic fitness and RD in the corpus callosum (Johnson et al., 2012). In addition, longitudinal physical activity interventions demonstrated that older adults who participated in a physical activity (i.e., walking) program had increased white matter volume in the anterior corpus callosum (Colcombe et al., 2006), relative to older adults involved in a stretching and toning program. Additionally, older adults who participated in a walking program
and demonstrated improvements in aerobic fitness showed increases in FA and decreases in RD in the frontal and temporal lobes (Voss et al., 2012).

Based on these developmental and aging studies, it was hypothesized that the effects of physical activity on white matter architecture in children would mirror these patterns such that there would be greater FA and reduced RD in white matter tracts across the brain as a function of participation in physical activity. This study has important implications for understanding the biological potential of the brain during periods of development, as axon integrity and myelin sheath thickness likely influence the transfer of information across brain networks (Paus, 2010).

**Method**

**Participants**

Eight- to 9-year-old children were recruited from the Urbana, Illinois school district 116. All children completed demographic assessments, a VO$_2$ max test to assess aerobic fitness, and an MRI session (which included a structural DTI scan) at pre-test (i.e., before randomization into a physical activity group or a wait list control group) and post-test (i.e., after the completion of the intervention, approximately 9 months later). Thirty-six children with pre-test and post-test DTI data were included in the analyses. Twenty children (12 girls, 8 boys) were in the physical activity group, and 16 children (9 girls, 7 boys) were in the non-intervention control group.

**Demographic Assessments and Fitness Testing**

To be eligible for the study, children had to have a Kaufman Brief Intelligence Test (KBIT) score greater than 85 (Kaufman & Kaufman, 1990) and qualify as prepubescent (Tanner puberty score ≤ 2; Taylor et al., 2001). Children were also screened for the presence of attentional disorders using the Attention Deficit Hyperactivity Disorder (ADHD) Rating Scale IV (DuPaul, Power, Anastopoulos & Reid, 1998), and were excluded if they scored above the
Body mass index (BMI) was calculated as weight (kg)/height(cm)$^2$, and socioeconomic status (SES) was determined by creating a trichotomous index: participation in a free or reduced-price meal program at school, the highest level of education obtained by the child's mother and father, and the number of parents who worked full-time (Birnbaum et al., 2002; Hillman et al., 2012).

Eligible children were further required to (1) report an absence of school-related learning disabilities (i.e., individual education plan related to learning), adverse health conditions, physical incapacities, or neurological disorders, (2) report no use of medications that influence central nervous system function, (3) demonstrate right handedness (as measured by the Edinburgh Handedness Questionnaire; Oldfield, 1971), (4) complete a mock MRI session successfully to screen for claustrophobia in an MRI machine, (5) be capable of performing physical activity, and (6) sign an informed assent approved by the University of Illinois at Urbana-Champaign. A legal guardian also provided written informed consent in accordance with the Institutional Review Board of the University of Illinois at Urbana-Champaign. Children were paid for their time ($10/hour for demographic assessments and fitness testing and $15/hour for MRI testing).

**Aerobic Fitness Testing**

Children completed a VO$_2$ max test at pre-test and post-test to assess aerobic fitness. The aerobic fitness of each child was measured as maximal oxygen consumption (VO$_2$ max) during a graded exercise test (GXT). The GXT employed a modified Balke Protocol and was administered on a LifeFitness 92T motor-driven treadmill (LifeFitness, Schiller Park, IL) with expired gases analyzed using a TrueOne2400 Metabolic Measurement System (ParMedics,
Children walked and/or ran on a treadmill at a constant speed with increasing grade increments of 2.5% every 2 minutes until volitional exhaustion occurred.

Oxygen consumption was measured using a computerized indirect calorimetry system (ParvoMedics True Max 2400) with averages for VO$_2$ and respiratory exchange ratio (RER) assessed every 20 seconds. A polar heart rate (HR) monitor (Polar WearLink+ 31; Polar Electro, Finland) was used to measure HR throughout the test, and ratings of perceived exertion (RPE) were assessed every 2 minutes using the children’s OMNI scale (Utter, Robertson, Nieman & Kang, 2002). Maximal oxygen consumption was expressed in mL/kg/min and VO$_2$ max was based upon maximal effort as evidenced by (1) a plateau in oxygen consumption corresponding to an increase of less than 2 mL/kg/min despite an increase in workload; (2) a peak HR ≥ 185 beats per minute (American College of Sports Medicine, 2006) and an HR plateau (Freedson & Goodman, 1993); (3) RER ≥ 1.0 (Bar-Or, 1983); and/or (4) a score on the children’s OMNI ratings of perceived exertion (RPE) scale ≥ 8 (Utter et al., 2002).

**Physical Activity Training Intervention and Wait List Control Group**

The physical activity intervention occurred for 2 hours after each school day, from September until May, for 150 days out of the 170 day school year. The program, Fitness Improves Thinking in Kids (FITKids) (http://clinicaltrials.gov/ct2/show/NCT01334359?term=FITKids&rank=1) is based on the Child and Adolescent Trial for Cardiovascular Health (CATCH) curriculum (McKenzie et al., 1994). The program is aimed at improving aerobic fitness through engagement in a variety of age-appropriate physical activities. The environment was non-competitive and integrated activities such as fitness activities and organized games (Castelli, Hillman, Hirsch, Hirsch, & Drollette, 2011).
Within a daily lesson, the children participated in an average of 76.8 minutes of moderate to vigorous physical activity (recorded by E600 Polar heart rate monitors; Polar Electro, Finland, and Accusplit Eagle 170 pedometers, San Jose CA), thus exceeding the national physical activity guideline of 60 minutes of moderate to vigorous physical activity per day (Centers for Disease Control and Prevention, 2011). Children completed stations that focused on a specific health-related fitness component (i.e., cardiorespiratory endurance, muscular strength). The activities were aerobically demanding, but simultaneously provided opportunities to refine motor skills. The program also included consumption of a healthy snack and the introduction of a themed educational component related to health promotion (i.e., goal setting, self-management). On the weekends, the children were encouraged to continue their participation in physical activity with their family, and physical activity worksheets were utilized during school holidays to log continued engagement. Average attendance across the 9-month intervention was 82% (SD=14.6%).

The wait list control group was not contacted following randomization. They completed all facets of the pre-test and post-test, similar to those children who were randomized into the after school physical activity intervention. As incentive to stay in the study, children in the wait list control group were afforded the opportunity to participate in the intervention during the following school year.

**MRI Acquisition**

Diffusion-weighted images were acquired on a Siemens Magnetom Trio 3T whole-body scanner with TR=4400 ms, TE=98 ms and 1.72 mm² in-plane resolution with 3 mm slice thickness. To obtain whole-head coverage, 32 slices were collected parallel to the anterior-posterior commissure plane with no interslice gap. Four T2-weighted images (b-value = 0
s/mm$^2$) and two repetitions of 30-direction diffusion-weighted echo planar imaging scans (b-value = 1000 s/mm$^2$) were collected.

Diffusion information can be represented mathematically as a diffusion tensor / diffusion ellipsoid. FA is calculated from the three eigenvalues ($\lambda_1, \lambda_2, \lambda_3$) of the diffusion tensor and represents anisotropic (directionally dependent) diffusion (Basser, 1995; Beaulieu, 2002; Sen & Basser, 2005), independently of the rate of diffusion. FA ranges from 0 to 1, with higher values reflecting increased directionality of diffusion (i.e., water traveling more parallel to a tract compared to perpendicularly). In a region with free diffusion, the FA value is 0 and the diffusion is isotropic. If the diffusion is more in one direction, i.e. anisotropic diffusion, the FA value approaches 1.

RD is the average of the second and third eigenvectors ($\lambda_2, \lambda_3$), reflective of diffusivity perpendicular to the major axis of the tensor. RD reflects the rate of radial diffusion, with lower values reflecting less diffusion, and thus, increased estimates of myelination (Basser, 1995; Pierpaoli & Basser, 1996; Pierpaoli et al., 1996; Song et al., 2002).

**Diffusion Data Analysis**

Image analyses and tensor calculations were performed using FSL 4.1.9 (FMRIB Software Library). First, each participant’s data were passed through an automated pipeline consisting of (1) motion and eddy current correction, (2) removal of non-brain tissue using the Brain Extraction Tool (Smith, 2002), and (3) local fitting of the diffusion tensor model at each voxel using FMRIB’s Diffusion Toolbox v2.0 (FDT: http://www.fmrib.ox.ac.uk/fsl/fdt). The products of the multi-step pipeline included FA images. RD maps were calculated as the mean of the second and third eigenvectors (Song et al., 2002).
Next, diffusion data were processed using TBSS v1.2 (Tract-Based Spatial Statistics, Smith et al., 2006). Each participant’s FA data were aligned into the 1 x 1 x 1 mm³ standard Montreal Neurological Institute (MNI152) space via the FMRIB58_FA template using the FMRIB’s Nonlinear Registration Tool (Andersson, Jenkinson, & Smith, 2007a,b), and a mean diffusion image was created. The mean FA image was then thinned to create an average skeleton representing the centers of the tracts shared by all participants, and the skeleton was thresholded at FA>0.20. Each participant's aligned FA data were projected onto the skeleton, taking on the FA value from the local center of the nearest relevant tract. RD skeletons for each participant were formed in a similar manner by projecting the analogous data onto the mean skeleton.

**Region-Of-Interest Analysis**

Diffusion values (FA, RD) were calculated for each participant within bilateral *a priori* regions of interest (ROIs), created from the JHU ICBM-DTI-81 white matter labels atlas (http://www.fmrib.ox.ac.uk/fsl/data/atlas-descriptions.html#wm [Hua et al., 2008; Mori, Wakana, & Van Zijl, 2005; Wakana et al., 2007]). Tract ROIs were created in the corpus callosum, corona radiata, superior longitudinal fasciculus, cingulum, internal capsule, and cerebral peduncle (see Figure 4.1). An FSL command, fslmaths, was used to create each ROI (e.g. fslmaths JHUAtlas –uthr 16 –thr 16 RCerebralPeduncle). An average diffusion value across left and right hemispheres was computed for each ROI for each diffusion measure for each participant.

**Statistical Analysis**

Repeated measures ANOVAs were first conducted to explore changes in fitness and DTI measures in the physical activity and control groups from pre-test to post-test. Next, given *a*
priori hypotheses, paired t-tests were conducted to compare within-group changes in fitness and DTI measures.

Results

Participant Demographics and Fitness

Group demographic and fitness data at pre-test and post-test are provided in Table 4.1. Demographic and fitness variables of age, gender, race, KBIT (IQ), SES, pubertal timing, and VO₂ max, did not differ between the physical activity and control groups (all t < 1.5, p > 0.1).

The physical activity intervention group showed a 13% increase in VO₂ max percentile (t (19) = 3.0, p=0.007), coupled with a within-group increase in relative VO₂ max (t (19) = 3.2, p=0.005). The control group showed a non-significant 5% increase in VO₂ max percentile (t (15) = 1.1, p=0.3), complemented by no significant increase in relative VO₂ max (t (15) = 1.7, p=0.1). There was also a main effect of time for VO₂ max percentile (F (1, 34) = 7.9, p=0.008), but the group (physical activity intervention, wait list control) x time (pre-test, post-test) interaction was only marginally significant (F (1, 34) = 2.1, p=0.1). Together, the data show an increase in VO₂ max in all children with age and development (Janz & Mahoney, 1997). However, the physical activity intervention group showed additional within-group gains in VO₂ max as a function of their daily exposure to the physical activity intervention.

Fractional Anisotropy

FA values for each ROI and for each group can be found in Table 4.2. FA in the corpus callosum, corona radiata, superior longitudinal fasciculus, cingulum, internal capsule, and cerebral peduncle did not differ between the physical activity and control groups (all t < 1.5, p > 0.1). Repeated measures ANOVAs within each tract-based ROI demonstrated a main effect of
time only in the corona radiata, thereby suggesting a significant increase in FA in the corona radiata from pre-test to post-test (F (1, 34) = 7.4, p=0.01) independent of group status. No treatment group x time (ROI FA at pre-test and post-test) interactions reached significance (all p>.05).

Because this was an exploratory pilot study, and part of a larger ongoing intervention, the study was approached with a priori hypotheses. Thus, paired t-tests were conducted to test within-group changes in FA for each ROI from pre-test to post-test. The physical activity group showed significant increases in FA in the corona radiata (t (19) = 3.07, p=0.007), cingulum (t (19) = 3.3, p=0.003), and internal capsule (t (19) = 2.3, p=0.03). The increase for the superior longitudinal fasciculus (t (19) = 1.9, p=0.07) and the corpus callosum (t (19) = 1.5, p=0.1) were marginally significant for the physical activity group. An exploratory analysis of the genu, body and splenium of the corpus callosum showed only an increase in FA for the splenium (t (19) = 2.7, p= 0.01) within the physical activity group. The control group only showed an increase in FA in the cingulum from pre-test to post-test (t (15) = 2.5, p=0.03). No change in FA was shown for the cerebral peduncle for either group. Percent change FA scores ([(post-test – pre-test) / pre-test] x 100%) for each group can be found in Table 4.3.

**Radial Diffusivity**

Radial diffusivity values for each ROI and for each group can be found in Table 4.2. RD in the corpus callosum, corona radiata, superior longitudinal fasciculus, cingulum, internal capsule, and cerebral peduncle did not differ between the physical activity and control groups (all t < 1.5, p > 0.1). Repeated measures ANOVAs showed main effects of time, i.e., a significant decrease in RD in all children from pre-test to post-test, in the corona radiata (F (1, 34) = 8.5, p=0.006), cingulum (F (1, 34) = 11.5, p=0.002) and superior longitudinal fasciculus (F
(1, 34)= 5.0, p=0.03). No treatment group x time (ROI RD at pre-test and post-test) interactions reached significance (all p>0.05).

Again, because this was an exploratory pilot study, and part of a larger ongoing intervention, the study was approached with \textit{a priori} hypotheses. Thus, paired t-tests were conducted to test within-group changes in RD for each ROI from pre-test to post-test. The physical activity group showed significant decreases in RD in the corpus callosum (t (19) = 2.07, p=0.05), corona radiata (t (19) = 3.3, p=0.004), cingulum (t (19) = 3.4, p=0.003), superior longitudinal fasciculus (t (19) = 2.7, p=0.01), and internal capsule (t (19) = 2.9, p=0.009). The control group did not show changes in RD from pre-test to post-test (all p>0.05). No change in RD was shown for the cerebral peduncle for the physical activity group (t (19) = 0.51, p=0.616). Percent change RD scores ([(post-test – pre-test) / pre-test] x 100%) for each group can be found in Table 4.3.

\textbf{Discussion}

The findings demonstrate that 8- to 9-year-old children who participated in a physical activity intervention that improved aerobic fitness showed increased FA, an estimation of fiber integrity, in a global and distributed network of white matter tracts including the splenium of the corpus callosum, corona radiata, cingulum, and internal capsule. The FA effects were driven by reductions in RD, an estimation of myelination (e.g., Song et al., 2005), from pre-test to post-test. Decreases in RD within the physical activity group were found in the corpus callosum, corona radiata, cingulum, superior longitudinal fasciculus, and internal capsule. The changes in FA and RD were specific to the physical activity group, such that the wait list control group, who did not make gains in aerobic fitness across 9 months, did not show these global changes in FA and RD. Although the results are limited by the lack of a group x time interaction, they provide
a first, and preliminary, step to understanding how physical activity may influence white matter integrity of the developing brain. The study raises the possibility that children who participated in more than the recommended 60 minutes of moderate to vigorous physical activity, 5 days per week, for 9 months, show more tightly bundled, structurally compact, and myelinated white matter tracts throughout the brain, relative to a control group not involved in an after school physical activity program.

These preliminary findings support and extend previous research that shows a positive relationship among physical activity, aerobic fitness, brain and cognition. Herein, physical activity during childhood is found to influence FA and RD in the corpus callosum. Because the corpus callosum connects the left and right cerebral hemispheres, these results raise the possibility that physical activity facilitates the integrity of tracts involved in interhemispheric communication and the exchange of cognitive, motor and sensory integration between the hemispheres (Gazzaniga, 1995). This finding also extends research with older adults demonstrating an association between the structure of the corpus callosum, physical activity, and aerobic fitness. Whereas older adults involved in physical activity have shown increases in white matter volume of the anterior corpus callosum (Colcombe et al., 2006), this study demonstrates that the splenium, the posterior portion of the corpus callosum, shows plasticity with physical activity during childhood. Older adults and children may respond differently to a physical activity intervention, although volume changes and microstructural changes of white matter can only be roughly compared.

This study is the first to suggest that a physical activity intervention influences the microstructure of the corona radiata, superior longitudinal fasciculus, cingulum, and internal capsule in children. The corona radiata and superior longitudinal fasciculus have ascending and
descending tracts from the cerebral cortex that integrate information throughout the brain. The cingulum connects the cingulate gyrus to the medial temporal lobe, and the internal capsule projects through the basal ganglia. A number of studies suggest that higher fit and lower fit children have different brain structure and function in these areas, including sections of the frontal and temporal cortex such as the cingulate gyrus (Chaddock, Erickson et al., 2012), medial temporal lobe (Chaddock et al., 2010a), and basal ganglia (Chaddock et al., 2010b). For example, higher fit children have shown different patterns of brain activation in the anterior cingulate cortex (Chaddock, Erickson et al., 2012), as well as larger brain volumes in the hippocampus (Chaddock et al., 2010a) and basal ganglia (Chaddock et al., 2010b), compared to lower fit peers. Furthermore, the differential findings in these brain regions among fitness groups relate to performance on cognitive tasks of attention (Chaddock et al., 2010b; Chaddock, Erickson et al., 2012; Hillman et al., 2009, Pontifex et al., 2011; Voss et al., 2011) and memory (Chaddock et al., 2010a, 2011; Kamijo et al., 2011). It is possible that structural connectivity between these gray matter regions may account for some differences in cognitive performance, and the results of the present study further suggest that physical activity participation and/or gains in aerobic fitness may influence these connections. In fact, both the corona radiata (Bendlin et al., 2010; Niogi, Mukherjee, Ghajar, & McCandliss, 2010; Olesen, Nagy, Westerberg, & Klingberg, 2003) and superior longitudinal fasciculus (Burzynska et al., 2011) have been found to play a role in attention, memory, and processing speed across the lifespan (see Table 2 in Madden et al., 2012 for review of the associations between white matter structure and cognition across the lifespan).

Whereas the overall DTI results suggest that physical activity has a general effect on white matter microstructure across a number of tracts throughout the brain, the results also
demonstrate some specificity. Neither the physical activity intervention group nor wait list control group showed increased microstructure in the cerebral peduncle, a tract in the brainstem known to convey motor information. Some research suggests that cognitive gains with physical activity are specific to tasks that require increased cognitive control (Chaddock et al., 2011; Colcombe et al., 2004; Colcombe & Kramer, 2003; Kramer et al., 1999). For example, in children and older adults, the benefits of higher levels of aerobic fitness are often accentuated for task conditions involving additional cognitive control (e.g., incongruent flanker trials) (Chaddock, Erickson et al., 2012; Colcombe et al., 2004; Hillman et al., 2006; Hillman et al., 2009; Pontifex et al., 2011; Voss et al., 2011), rather than task conditions that require less control (e.g., congruent flanker trials) (but see Hillman et al., 2009 for an exception). In support of these findings, a meta-analysis showed larger effects of aerobic exercise in older adults on tasks involving cognitive control compared to processing speed, visuospatial abilities, or controlled, effortful processing abilities (Colcombe & Kramer, 2003). In terms of the brain, physical activity and aerobic fitness have been found to influence mostly areas of the frontal (Chaddock, Erickson et al., 2012; Davis et al., 2011; Voss et al., 2011), parietal (Chaddock, Erickson et al., 2012), hippocampal (Chaddock et al., 2010a, 2011), and striatal (Chaddock et al., 2010b) cortex, rather than the brainstem. Thus, the present lack of a relationship between physical activity and integrity of a lower-level motor tract observed herein supports these frameworks. Nevertheless, future longitudinal studies, with larger sample sizes that also include cognitive tasks are needed to explore the relationship among physical activity, white matter microstructure, and cognition.

This study provides a first step in identifying the relationship between physical activity and white matter microstructure, but the results should be evaluated in the context of their limitations. Despite within-group increases in DTI measures, there were not significant
interactions of group over time, possibly because of the small sample size. Also, it is important to remember that DTI does not measure tissue parameters (e.g., fiber integrity, myelination) directly, but measures the displacement of water molecules. Thus, indices of underlying microstructural properties can only be deduced from this displacement. Furthermore, since there are many axons within a voxel and Tract-Based Spatial Statistics only selects one axon per voxel, a number of different tissue parameters can result in differences in FA and RD.

These results arrive at an important time, as children become increasingly unfit and sedentary, and educators reduce or eliminate opportunities for physical activity during the school day in favor of academic topics (Centers for Disease Control and Prevention, 2010). In fact, white matter microstructure in the corona radiata has been found to relate to mathematics performance in the classroom (van Eimeren, Niogi, McCandliss, Holloway, & Ansari, 2008), which raises the possibility that the removal of physical activity during the school day may unintentionally have deleterious effects on white matter tracts, potentially reducing scholastic achievement. Because both axonal caliber and thickness of the myelin sheath determine conduction velocity (Paus, 2010), the present study raises the possibility that children who participate in a physical activity intervention that results in aerobic fitness gains may have faster neural conduction between brain regions important for cognition. Hopefully the findings will reinforce the importance of physical activity and aerobic fitness during development and lead to additional physical activity opportunities.
Chapter 4 References


Chapter 4 Tables and Figures

Table 4.1. Mean (SD) for physical activity intervention group and wait list control group at pre-test and post-test.

<table>
<thead>
<tr>
<th>Physical Activity</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-test</td>
</tr>
<tr>
<td>Age (years)</td>
<td>8.6 (0.6)</td>
</tr>
<tr>
<td>Gender</td>
<td>12 girls, 8 boys</td>
</tr>
<tr>
<td>Race</td>
<td>65% White</td>
</tr>
<tr>
<td></td>
<td>10% Asian</td>
</tr>
<tr>
<td></td>
<td>5% Black</td>
</tr>
<tr>
<td></td>
<td>20% Mixed</td>
</tr>
<tr>
<td>IQ</td>
<td>116.6 (14.5)</td>
</tr>
<tr>
<td>Pubertal timing</td>
<td>1.2 (0.3)</td>
</tr>
<tr>
<td>SES</td>
<td>2.2 (0.9)</td>
</tr>
<tr>
<td>VO₂ max (mL/kg/min)</td>
<td>38.1 (5.2) ^a</td>
</tr>
<tr>
<td>VO₂ max percentile</td>
<td>16.3 (17.5) ^a</td>
</tr>
<tr>
<td>BMI (kg/cm²)</td>
<td>17.7 (3.0)</td>
</tr>
</tbody>
</table>

Note: IQ – composite standardized score of intelligence quotient from the Kaufman Brief Intelligence Test (Kaufman & Kaufman, 1990), SES – Socioeconomic Status. Values that share a common superscript are significantly different at p<0.05.
Table 4.2. Mean (SD) for physical activity intervention group and wait list control group at pre-test and post-test.

<table>
<thead>
<tr>
<th>Physical Activity</th>
<th>Physical Activity</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-test</td>
<td>Post-test</td>
</tr>
<tr>
<td>Corpus callosum FA</td>
<td>0.6883 (0.0160)</td>
<td>0.6938 (0.0200)</td>
</tr>
<tr>
<td>Corona radiata FA</td>
<td>0.4734 (0.0211)</td>
<td>0.4807 (0.0247)</td>
</tr>
<tr>
<td>Superior longitudinal</td>
<td>0.4747 (0.0217)</td>
<td>0.4795 (0.0271)</td>
</tr>
<tr>
<td>fasciculus FA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cingulum FA</td>
<td>0.4805 (0.0313)</td>
<td>0.4973 (0.0370)</td>
</tr>
<tr>
<td>Internal capsule FA</td>
<td>0.5978 (0.0168)</td>
<td>0.6045 (0.0246)</td>
</tr>
<tr>
<td>Cerebral peduncle FA</td>
<td>0.6630 (0.0206)</td>
<td>0.6660 (0.0271)</td>
</tr>
<tr>
<td>Corpus callosum RD</td>
<td>0.00041308</td>
<td>0.00040418</td>
</tr>
<tr>
<td>(0.00002)</td>
<td>(0.00002)</td>
<td>(0.00004)</td>
</tr>
<tr>
<td>Corona radiata RD</td>
<td>0.00056153</td>
<td>0.00055212</td>
</tr>
<tr>
<td>(0.000003)</td>
<td>(0.00003)</td>
<td>(0.00003)</td>
</tr>
<tr>
<td>Superior longitudinal</td>
<td>0.0005381</td>
<td>0.0005286</td>
</tr>
<tr>
<td>fasciculus RD</td>
<td>(0.000003)</td>
<td>(0.00003)</td>
</tr>
<tr>
<td>Cingulum RD</td>
<td>0.0005395</td>
<td>0.00052288</td>
</tr>
<tr>
<td>(0.000003)</td>
<td>(0.00004)</td>
<td>(0.00003)</td>
</tr>
<tr>
<td>Internal capsule RD</td>
<td>0.00045801</td>
<td>0.00044857</td>
</tr>
<tr>
<td>(0.000002)</td>
<td>(0.00003)</td>
<td>(0.00002)</td>
</tr>
<tr>
<td>Cerebral peduncle RD</td>
<td>0.00041348</td>
<td>0.0004108</td>
</tr>
<tr>
<td>(0.000002)</td>
<td>(0.00003)</td>
<td>(0.00003)</td>
</tr>
</tbody>
</table>

Note: Values that share a common superscript are significantly different at **p<0.05. *p<0.1.
Table 4.3. Percent change scores: (Post-Pre)/Pre * 100 (SD).

<table>
<thead>
<tr>
<th></th>
<th>Physical Activity</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative VO₂ max</td>
<td>10.7% (15.2%)**</td>
<td>4.6% (8.4%)</td>
</tr>
<tr>
<td>Corpus callosum FA</td>
<td>0.67% (2.5%)*</td>
<td>0.33% (3.05%)</td>
</tr>
<tr>
<td>Corona radiata FA</td>
<td>1.6% (2.4%)**</td>
<td>1.1% (2.6%)</td>
</tr>
<tr>
<td>Superior longitudinal fasciculus FA</td>
<td>0.97% (2.4%)*</td>
<td>0.43% (3.1%)</td>
</tr>
<tr>
<td>Cingulum FA</td>
<td>3.4% (4.6%)**</td>
<td>2.6% (4.1%)Δ</td>
</tr>
<tr>
<td>Internal capsule FA</td>
<td>0.9% (2.2%)**</td>
<td>0.7% (2.6%)</td>
</tr>
<tr>
<td>Cerebral peduncle FA</td>
<td>0.6% (2.9%)</td>
<td>0.6% (4.6%)</td>
</tr>
<tr>
<td>Corpus callosum RD</td>
<td>-2.1% (4.6%)**</td>
<td>-1.2% (5.6%)</td>
</tr>
<tr>
<td>Corona radiata RD</td>
<td>-1.7% (2.3%)**</td>
<td>-1.1% (3.4%)</td>
</tr>
<tr>
<td>Superior longitudinal fasciculus RD</td>
<td>-1.7% (2.9%)**</td>
<td>-0.79% (4.0%)</td>
</tr>
<tr>
<td>Cingulum RD</td>
<td>-3.0% (4.1%)**</td>
<td>-1.6% (4.1%)</td>
</tr>
<tr>
<td>Internal capsule RD</td>
<td>-2.1% (3.2%)**</td>
<td>-0.1% (4.5%)</td>
</tr>
<tr>
<td>Cerebral peduncle RD</td>
<td>-0.6% (5.7%)</td>
<td>0.8% (7%)</td>
</tr>
</tbody>
</table>

*Note*: **p<0.05, *p<0.1 – within-group change in physical activity group. Δp<0.05 – within-group change in control group.
Figure 4.1. Illustrations of the white matter tract ROIs in the corpus callosum (blue=genu; yellow=body; purple=splenium), corona radiata (green), superior longitudinal fasciculus (pink), cingulum (red), internal capsule (orange), and cerebral peduncle (yellow).
Figure 4.1. (Cont.)
Figure 4.1. (Cont.)
CHAPTER 5

THE EFFECTS OF PHYSICAL ACTIVITY ON FUNCTIONAL MRI ACTIVATION ASSOCIATED WITH COGNITIVE CONTROL IN CHILDREN

Physical activity and higher aerobic fitness are associated with improved brain function across the lifespan (Chaddock, Erickson et al., 2012; Davis et al., 2011; Hillman, Buck, Themanson, Pontifex, & Castelli, 2009; Hillman, Castelli, & Buck, 2005; Kamijo et al., 2011; Pontifex et al., 2011; Voss et al., 2011). Prior studies have reported that the largest effects of physical activity occur on tasks that measure cognitive control (Colcombe & Kramer, 2003; Tomporowski, Davis, Miller & Naglieri, 2008), which refers to aspects of cognition that describe the ability to flexibly adapt behavior toward specific goals, to maintain these goals, to monitor errors, and to formulate decisions (Botvinick, Braver, Barch, Carter & Cohen, 2001; Braver & Barch, 2006). To achieve high levels of cognitive control, individuals must be able to selectively attend to relevant information, filter distractions, and inhibit inappropriate response tendencies (Bunge & Crone, 2009). Here, functional magnetic resonance imaging (fMRI) was used to examine the influence of a 9-month physical activity program on brain activation patterns associated with cognitive control during childhood.

Only a few fMRI investigations with children have studied how physical activity and aerobic fitness relate to brain function during cognitive control tasks (Chaddock, Hillman, Buck & Cohen, 2011; Davis et al., 2011; Voss et al., 2011). In one study by Davis et al. (2011), overweight children (age 7-13 years) involved in 13 weeks of aerobic games showed improvements in cognitive control (i.e., a “planning” score said to measure strategy and self-regulation) and increases in frontal fMRI activation during an antisaccade task, which provides a measure of response inhibition. However, the interpretation of the fMRI results was constrained because performance on the antisaccade task at pre-test and post-test was not reported. Whereas
Davis et al. (2011) suggested that increased frontal activation with physical activity may be associated with improvements in cognitive control, two other studies showed that decreased frontal activation in higher fit children is associated with better cognitive control (Chaddock, Erickson et al., 2012; Voss et al., 2011). In a study by Chaddock, Erickson et al. (2012), children with higher aerobic fitness levels showed reduced activation in the frontal cortex from early to late stages of a flanker task, coupled with maintenance of attentional and interference control. It is noteworthy that these fitness differences in activation were only apparent for incongruent flanker trials that required substantial cognitive control. During congruent trials, both higher fit and lower fit children showed decreases in activation and maintenance of task performance. In conjunction with these findings, Voss et al. (2011) showed that higher fit children exhibited less activation than lower fit children in a network of brain regions including anterior frontal areas involved in task maintenance and cognitive control, coupled with higher accuracy rates during incongruent flanker task trials that required increased cognitive control. Together, previous studies suggest that physical activity and aerobic fitness influence brain function in regions such as the frontal cortex as well as the ability to adapt neural processes to meet and maintain task goals (Chaddock, Erickson et al., 2012; Davis et al., 2011; Voss et al., 2011).

The present study examined brain function, in terms of activation and task performance, during a task of cognitive control in children participating in an after school physical activity intervention compared to children in a wait list control group. In addition, brain function of the two groups of children was compared to the activation of college-aged young adults because adult task performance and activation patterns are often characterized as the “mature” or “optimal” model of brain function to which children can be compared (Luna, Padmanabhan, & O’Hearn, 2010). Although fMRI studies of age-related differences in cognitive control report a
variety of results (see Luna et al., 2010 for a review), the majority of studies demonstrate increased frontal activity in children relative to adults (e.g., Booth et al., 2003; Casey et al., 1997; Durston et al., 2002; Scherf, Sweeney & Luna, 2006; Velanova, Wheeler & Luna, 2008), coupled with poorer task performance during cognitive tasks of inhibition (e.g., Go/NoGo, flanker, antisaccade tasks) (Diamond, 2006) and working memory (e.g., n-back, visual spatial working memory) (Baddeley, 1986; Bunge & Crone, 2009). Nevertheless, throughout childhood, there are continued improvements in cognitive control, and the frontal cortex plays a primary role in performance changes (Luna et al., 2010). Thus, this study explored how participation in physical activity during childhood influences brain function in frontal brain regions, as well as how the changes mirror patterns of adult activation and cognitive abilities.

The first goal of this preliminary study was to determine the brain areas, especially prefrontal brain regions, in children that were associated with an fMRI task of attentional and inhibitory control. For example, cognitive control has been associated with frontal regions including (1) the anterior prefrontal cortex, hypothesized to maintain task goals, (2) the lateral prefrontal cortex, hypothesized to initiate flexible adjustments in cognitive control, and play a role in working memory, and (3) the anterior cingulate cortex (ACC), hypothesized to evaluate and monitor conflict and thereby signal the need to adjust control (Botvinick et al., 2001; Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002; Braver & Barch, 2006; Dosenbach et al., 2007; Hazeltine, Poldrack, & Gabrieli, 2000).

The second goal of the study was to examine whether brain function in the regions associated with the task changed from pre-test to post-test in the physical activity intervention group compared to the changes in the wait list control group. It was hypothesized that children involved in 9 months of physical activity would show improvements in performance on the task,
coupled with decreased activation in frontal brain regions from pre-test to post-test, relative to a wait list control group. The third goal was to compare the activation patterns of both groups of children to the activation of young adults. It was predicted that the frontal activation patterns and performance of physically active children at post-test would show greater similarity to the brain function of young adults, relative to the post-test patterns of the wait list control children.

**Method**

**Participants**

Eight- to 9-year-old children were recruited from the Urbana, Illinois school district 116. All children completed demographic assessments, a VO$_2$ max test to assess aerobic fitness, and an MRI session (which included a structural and functional MRI scan) at pre-test (i.e., before randomization into a physical activity intervention group or a wait list control group) and post-test (i.e., after the completion of the intervention, approximately 9 months later).

Thirty-two children were eligible for the study. Seven children (3 physical activity intervention, 4 wait list control) were excluded from the analyses for excessive motion during the fMRI task. Two children were excluded from the analyses (2 physical activity intervention) for less than chance task performance. Accordingly, 23 children, with pre-test and post-test fMRI data, were included in the final analyses, with 14 children (7 female, 7 male) assigned to the physical activity intervention group and 9 children (6 female, 3 male) assigned to the wait list. Twenty-four young adults (10 female, 14 male) (average age of 22.5 years) were also recruited from the University of Illinois to compare children’s brain and performance patterns to a young adult group.
Demographic Assessments and Fitness Testing

To be eligible for the study, children had to have a Kaufman Brief Intelligence Test (KBIT) score greater than 85 (Kaufman & Kaufman, 1990) and qualify as prepubescent (Tanner puberty score ≤ 2; Taylor et al., 2001). Children were also screened for the presence of attentional disorders using the Attention Deficit Hyperactivity Disorder (ADHD) Rating Scale IV (DuPaul, Power, Anastopoulos & Reid, 1998), and were excluded if they scored above the 85th percentile. Body mass index (BMI) was calculated as weight (kg)/height(cm)$^2$, and socioeconomic status (SES) was determined by creating a trichotomous index: participation in a free or reduced-price meal program at school, the highest level of education obtained by the child's mother and father, and the number of parents who worked full-time (Birnbaum et al., 2002; Hillman et al., 2012).

Eligible children were further required to (1) report an absence of school-related learning disabilities (i.e., individual education plan related to learning), adverse health conditions, physical incapacities, or neurological disorders, (2) report no use of medications that influence central nervous system function, (3) demonstrate right handedness (as measured by the Edinburgh Handedness Questionnaire; Oldfield, 1971), (4) complete a mock MRI session successfully to screen for claustrophobia in an MRI machine, (5) be capable of performing physical activity, and (6) sign an informed assent approved by the University of Illinois at Urbana-Champaign. A legal guardian also provided written informed consent in accordance with the Institutional Review Board of the University of Illinois at Urbana-Champaign. Children were paid for their time ($10/hour for demographic assessments and fitness testing and $15/hour for MRI testing).
Aerobic Fitness Testing

Children completed a VO$_2$ max test at pre-test and post-test to assess aerobic fitness. The aerobic fitness of each child was measured as maximal oxygen consumption (VO$_2$ max) during a graded exercise test (GXT). The GXT employed a modified Balke Protocol and was administered on a LifeFitness 92T motor-driven treadmill (LifeFitness, Schiller Park, IL) with expired gases analyzed using a TrueOne2400 Metabolic Measurement System (ParMedics, Sandy, Utah). Children walked and/or ran on a treadmill at a constant speed with increasing grade increments of 2.5% every 2 minutes until volitional exhaustion occurred.

Oxygen consumption was measured using a computerized indirect calorimetry system (ParvoMedics True Max 2400) with averages for VO$_2$ and respiratory exchange ratio (RER) assessed every 20 seconds. A polar heart rate (HR) monitor (Polar WearLink+ 31; Polar Electro, Finland) was used to measure HR throughout the test, and ratings of perceived exertion (RPE) were assessed every 2 minutes using the children’s OMNI scale (Utter, Robertson, Nieman & Kang, 2002). Maximal oxygen consumption was expressed in mL/kg/min and VO$_2$ max was based upon maximal effort as evidenced by (1) a plateau in oxygen consumption corresponding to an increase of less than 2 mL/kg/min despite an increase in workload; (2) a peak HR $\geq$ 185 beats per minute (American College of Sports Medicine, 2006) and an HR plateau (Freedson & Goodman, 1993); (3) RER $\geq$ 1.0 (Bar-Or, 1983); and/or (4) a score on the children’s OMNI ratings of perceived exertion (RPE) scale $\geq$ 8 (Utter et al., 2002).

Physical Activity Training Intervention and Wait List Control Group

The physical activity intervention occurred for 2 hours after each school day, from September until May, for 150 days out of the 170 day school year. The program, Fitness Improves Thinking in Kids (FITKids)
is based on the Child and Adolescent Trial for Cardiovascular Health (CATCH) curriculum (McKenzie et al., 1994). The program is aimed at improving aerobic fitness through engagement in a variety of age-appropriate physical activities. The environment was non-competitive and integrated activities such as fitness activities and organized games (Castelli, Hillman, Hirsch, Hirsch, & Drollette, 2011).

Within a daily lesson, the children participated in an average of 76.8 minutes of moderate to vigorous physical activity (recorded by E600 Polar heart rate monitors; Polar Electro, Finland, and Accusplit Eagle 170 pedometers, San Jose CA), thus exceeding the national physical activity guideline of 60 minutes of moderate to vigorous physical activity per day (Centers for Disease Control and Prevention, 2011). Children completed stations that focused on a specific health-related fitness component (i.e., cardiorespiratory endurance, muscular strength). The activities were aerobically demanding, but simultaneously provided opportunities to refine motor skills. The program also included consumption of a healthy snack and the introduction of a themed educational component related to health promotion (i.e., goal setting, self-management). On the weekends, the children were encouraged to continue their participation in physical activity with their family, and physical activity worksheets were utilized during school holidays to log continued engagement. Average attendance across the 9-month intervention was 82% (SD=13.3%).

The wait list control group was not contacted following randomization. They completed all facets of the pre-test and post-test, similar to those children who were randomized into the after school physical activity intervention. As incentive to stay in the study, children in the wait
list control group were afforded the opportunity to participate in the intervention during the following school year.

**Imaging Method**

Children and young adults completed structural and functional MRI scans. Prior to scanning, all participants were tested for visual acuity, and corrective lenses were added to MRI safe plastic frames to ensure a corrected vision of at least 20/40 while in the scanner. The lenses and frames did not obstruct a mirror above participants’ eyes that enabled them to view images on a back projection.

**Structural MRI protocol.** High resolution T1-weighted brain images were acquired using a 3D MPRAGE (Magnetization Prepared Rapid Gradient Echo Imaging) protocol with 192 contiguous axial slices, collected in ascending fashion parallel to the anterior and posterior commissures, echo time (TE)=2.32 ms, repetition time (TR)=1900 ms, field of view (FOV)=230 mm, acquisition matrix 256 mm x 256 mm, slice thickness=0.90 mm, and flip angle=9º. All images were collected on a Siemens Magnetom Trio 3T whole-body MRI scanner.

**Functional MRI protocol.** Functional MRI scans were acquired during an event-related cognitive control task that combined an Eriksen flanker paradigm and Go/NoGo paradigm (see Bunge et al., 2002 for a similar task design; see Figure 5.1). Five shapes were presented, and participants were instructed to look at the middle shape. Three task conditions were included: neutral (-->--, --<--), incongruent (<<><<, >><>), and NoGo (<<X<<, >>X>) trials. When the middle arrow pointed to the left, participants were instructed to press a button with their left index finger. When the middle arrow pointed to the right, participants were instructed to press a button with their right index finger. When the middle shape was an X, participants were told not to press a button. The neutral condition was designed to require less attentional, interference and
inhibitory control. The incongruent condition required attentional and interference control to filter potentially misleading flankers that were mapped to incorrect behavioral responses. The NoGo condition required subjects to inhibit a prepotent tendency to respond, given that the majority of trials (i.e., incongruent, neutral) required an active “go” response.

During the task, 40 trials of each of the three possible conditions (-->-, <---, >><<>, <<<<, >>X>>, <<X<<) were presented in a random order. The response window included the presentation of the array of shapes for 500 ms, followed by a blank screen for 1000 ms. Each stimulus array was separated by a fixation cross (+) presented for 1500 ms. Forty additional fixation crosses that jittered between 1500 ms and 6000 ms were also randomly presented after the constant 1500 ms fixation cross throughout the task. The jitter prevented participants from expecting a specific frequency of responding. White shapes and white fixation crosses were presented on a black background. The participant was engaged in the task for about 6 minutes. Stimulus presentation, timing, and task performance measures were controlled by E-Prime software (Psychology Software Tools, Sharpsburg, Pennsylvania).

For the fMRI protocol during the flanker task, a fast echo-planar imaging (EPI) sequence with Blood Oxygenation Level Dependent (BOLD) contrast was employed. A total of 328 volumes (TR=1500 ms; TE=25 ms; flip angle=80º) were collected for each participant.

**Image analysis.** Neuroimaging data analysis was conducted using FSL 4.1.9 (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). All child data and young adult data followed the same pre-processing, registration, and first level analysis stream. Preprocessing of the functional data included motion correction via a rigid body algorithm in MCFLIRT (Jenkinson, Bannister, Brady & Smith, 2002), removal of non-brain structures using BET (Brain Extraction Technique; Smith et al., 2002), spatial smoothing using a 5.0 mm FWHM (full width at half maximum)
three-dimensional Gaussian kernel, and temporal filtering with a high pass frequency cut-off of 40 seconds. In addition, the high-resolution T1 structural images of each participant were skull stripped using BET (Smith et al., 2002). The functional images of each participant were spatially registered to his/her individual skull-stripped high-resolution anatomical image, and then to an MNI template in stereotaxic space. Registrations were conducted using a 12-parameter affine transformation (FMRIB's Linear Image Registration Tool [FLIRT]; Jenkinson & Smith, 2001, Jenkinson et al., 2002).

Regression-based analysis of each participant’s fMRI data was carried out using FSL’s FEAT Version 5.98 (Beckmann, Jenkinson, & Smith, 2003). The time series at each voxel was modeled against the expected time series model derived by convolving the onset of each event type (incongruent, neutral, NoGo) with a double-gamma function, representing the expected time course of the hemodynamic response function. Only correct task trials were included in the model, and error trials were entered as covariates of no interest. The same high pass temporal filtering applied to the data was applied to the general linear model for the best possible match between the data and model. In addition, the temporal derivative was entered into the model (i.e., shifting the waveform slightly in time) to achieve a better model fit to the data and to reduce unexplained noise. The first level analysis calculated a parameter estimate for the fMRI model at each voxel to estimate how strongly the model waveform fits the data, and this analysis resulted in voxel-wise statistical parametric maps for the entire brain of each participant for incongruent, neutral, and NoGo conditions.

Next, the brains of all children at pre-test and post-test were forwarded to a higher-level mixed-effects group analysis to localize areas of cortex in all child participants at pre-test and post-test that were sensitive to incongruent, neutral, and NoGo trials. Higher-level group
analyses were carried out using FLAME (FMRIB’s Local Analysis of Mixed Effects). To ensure that individual and group differences in gray matter volume did not confound the results, estimated total mean gray matter volume for each child at pre-test and post-test, smoothed with 3mm HWHM kernel, was used as a voxel-wise covariate in the higher level FLAME analyses.

A Z statistic map that showed average activation during all task conditions (incongruent, neutral, NoGo) relative to fixation baseline was created for all children, across pre-test and post-test. This conjunction map was used to locate and extract ROIs so that the regions would be chosen independently of effects associated with group (physical activity intervention, wait list control), task condition (incongruent, neutral, NoGo), and time (pre-test, post-test). This technique helped ensure that the localization of the ROIs was unbiased in relation to the predictor variables.

Because of the widespread activation for the task, a more conservative statistical threshold to identify clusters for the regions-of-interest analysis was employed (Kriegeskorte, Simmons, Bellgowan, & Baker, 2009). Accordingly, the Z statistic maps were thresholded at $Z > 6.00$, with a (corrected) cluster significance threshold of $p < 0.05$ (Worsley, 2001). Of particular interest, two clusters in the frontal cortex were observed: (1) the right anterior prefrontal cortex (right frontal pole) (with $x$, $y$, $z$ voxel coordinates of 27, 94, 40, $Z=6.2$) (see Figure 5.2), and (2) the anterior cingulate cortex (with $x$, $y$, $z$ voxel coordinates of 44, 69, 55, $Z=7.1$) (see Figure 5.2). Eight millimeter (diameter) masks (which contained 125 voxels, 1000 mm$^3$) were created around each peak to use as functionally defined ROIs (see Figure 5.2). Mean percent signal change (versus fixation) was extracted for incongruent, neutral, and NoGo conditions. Note that some activation was also seen in the insula and occipital lobe, but the statistics for these regions are not reported given lack of effects and lack of hypotheses in these
areas.

Statistical Analysis

Multivariate repeated measures ANOVAs were first conducted to explore changes in aerobic fitness ($VO_2$ max) and task performance in the physical activity and wait list control groups from pre-test to post-test. Given *a priori* hypotheses, paired t-tests were also conducted to compare within-group changes in fitness and task performance. In addition, task performance of the physical activity intervention group and wait list control group at pre-test and post-test were compared to the young adult group.

Next, the peaks of activation in the brain during the fMRI task of cognitive control, in all children, across all task conditions, at pre-test and post-test were determined. Within these regions of interest (ROIs), repeated measures 2 (group: physical activity intervention, wait list control) x 3 (task condition: incongruent, neutral, NoGo) x 2 (time: pre-test, post-test) ANOVAs were conducted to explore changes in mean percent signal change in the ROIs. If the omnibus ANOVA reached significance, post-hoc comparisons were performed (with Bonferroni-corrected t tests) to examine how activation patterns within each task condition changed with participation in physical activity or assignment to a wait list control group. Further, independent t-tests were conducted between the physical activity intervention group, wait list control group, and young adults at pre-test and post-test to explore how changes in activation over time in children compared to activation in a young adult sample.

Results

Participant Demographics and Aerobic Fitness

Demographic and fitness data at pre-test and post-test are provided in Table 5.1. Demographic and fitness variables of age, gender, race, KBIT (IQ), SES, pubertal timing,
and VO₂ max, did not differ between the physical activity intervention group and the wait list control group (all p>0.05).

The physical activity intervention group showed a 6% increase in VO₂ max percentile from pre-test to post-test (t (13) = 2.0, p=0.06), and the wait list control group showed a 2% increase in VO₂ max percentile (t (8) = 1.0, p=0.3). There was also a marginal effect of time for VO₂ max percentile (F (1, 21) = 4.1, p=0.057), but no group x time interaction (F (1, 29) = 0.9, p=0.3). Together, the data suggest an increase in VO₂ max in all children with age and development (Janz & Mahoney, 1997). However, the physical activity intervention group showed additional within-group gains in VO₂ max as a function of their daily exposure to physical activity.

**Task Performance**

All task performance data for the physical activity intervention group, the wait list control group, and the young adults can be found in Table 5.2. To confirm the efficacy of the task, performance differences in all children during the three task conditions were explored. In general, the performance data suggested that the incongruent flanker task provided the greatest challenge to the participants’ ability to pay attention, suppress distraction, and maintain a task set. That is, shorter RT for neutral trials (M=805.5 ms, SE=27.2 ms) compared to incongruent trials (M=875.0 ms, SE=31.7 ms) was found at both pre-test and post-test (main effect of task condition, F (1, 21) = 44.1, p<0.001). Higher accuracy for neutral trials (M=94.7%, SD=0.05) compared to incongruent trials (M=90.3%, 0.07%) was also found at both pre-test and post-test (t (22) = 6.1, p<0.001) (main effect of task condition, F (2, 21) = 42.2, p<0.001).

However, inconsistent with predictions, children performed at near ceiling accuracy rates during the NoGo task condition. NoGo accuracy (M=98%, SE=0.3%) was significantly higher
than incongruent accuracy (M=87%, SE=1.6%) (t (22) = 7.3, p<0.001) and neutral accuracy (M=92%, SE=1.3%) (t (22) = 5.0, p<0.001) (main effect of task condition, F (2, 21) = 42.2, p<0.001)). These results suggest that the NoGo task condition was not sufficiently difficult to yield group differences in response inhibition, or that 8- and 9-year-old children may have more “mature” response inhibition abilities than interference control skills (Bunge et al., 2002; Liston et al., 2006; Bunge & Crone, 2009; van den Wildenberg & van der Molen, 2004). The task design may also have affected performance outcomes. In most Go/NoGo paradigms, participants press a button on the go trials and must override this prepotent response when a NoGo trial appears. However, in this modified task presented herein, participants had to analyze each stimulus array to determine whether they should press a left button, a right button, or withhold their response. Thus, children in this study were unlikely to have developed a prepotent response tendency because they were unable to plan a motor response until the stimulus appeared. This may have led to the high performance across all children on the NoGo trials. Given these limitations, the present study focuses on results regarding incongruent and neutral flanker task conditions that required different amounts of cognitive control.

Improvements in task performance after 9 months were found for all children, which were predicted with development and practice. Shorter post-test RT across incongruent and neutral trials (M=797.1 ms, SE=32.5 ms) was found, relative to pre-test RT (M=883.4 ms, SE=28.8 ms) (main effect of time, F (1, 21) = 18.8, p<0.001). A condition x time interaction (F (1, 21) = 8.2, p=0.009) superseded the main effect of time and showed shorter RT for incongruent trials at post-test (M=821.7 ms, 34.0 ms) compared to pre-test (M=928.4 ms, SE=33.1 ms) (t (22) = 5.2, p<0.001) as well as shorter RT for neutral trials at post-test (M=772.6 ms, SE=31.7 ms) compared to pre-test (M=838.3 ms, 25.9 ms) (t (22) = 3.5, p=0.002). The main
effect of time was only marginally significant for accuracy ($F (1, 42) = 2.9, p=0.1$), which suggested only modest increases in task accuracy for all children from pre-test ($M=91.3\%, \text{SE}=1.5\%$) to post-test ($M=93.8\%, \text{SE}=0.8\%)$.

**Physical activity and wait list control groups.** The group x condition x time interaction did not reach significance for RT ($F (1, 21) = 0.17, p=0.68$) or accuracy ($F (1, 42) = 0.29, p=0.59$). Because of *a priori* hypotheses about greater changes in task performance for the physical activity intervention group relative to the wait list control group, paired t-tests were conducted to further explore the data. Consistent with hypotheses, the physical activity intervention group showed shorter RT for both incongruent trials ($t (13) = 6.2, p<0.001$) and neutral trials ($t (13) = 3.3, p=0.006$) at post-test relative to pre-test (see Table 5.2 and Figure 5.3). The physical activity intervention group also showed increased accuracy for incongruent trials (*trend: t (13) = 1.9, p=0.08*) (see Figure 5.4) and neutral trials ($t (13) = 2.5, p=0.03$) at post-test relative to pre-test, but no changes in accuracy for NoGo trials ($t (13) = 0.3, 0.8$) (see Table 5.2). Alternatively, the wait list control group did not show significant changes in RT from pre-test to post-test ($t < 2.1, p>0.07$) or changes in incongruent, neutral or NoGo accuracy from pre-test to post-test (all $t < 0.7, \text{all } p>0.6$) (see Table 5.2). The data raise the possibility that the physical activity intervention group was responsible for some of the general performance improvements across all children from pre-test to post-test.

**Children and young adults.** To gain more insight into changes in task performance within the physical activity intervention group and wait list control group, the pre-test and post-test task performance for the groups of children were compared to a group of young adults (see Table 5.2). It was predicted that children and young adults would differ in task performance at pre-test, due to age effects, but participation in physical activity may reduce the age effects at
As predicted, at pre-test, the physical activity intervention group (PA) and wait list control group (C) showed longer RT than young adults during incongruent (PA: t (36) = 7.3, p<0.001; C: t (31) = 9.1, p<0.001) and neutral (PA: t (36) = 7.7, p<0.001; C: t (31) = 5.6, p<0.001) trials. Both groups of children also showed lower accuracy rates during incongruent (PA: t (36) = 2.8, p=0.03; C: t (31) = 2.6, p=0.01) and neutral (PA: t (36) = 3.6, p=0.01; C: t (31) = 2.8, p=0.008) trials.

However, at post-test, the physical activity intervention group did not differ from young adults in terms of incongruent accuracy (t (36) = 0.7, p=0.5) (see Figure 5.4) or neutral accuracy (t (36) = 0.9, p=0.4). Alternatively, the wait list control group still showed lower accuracy rates than young adults during incongruent (t (31) = 2.2, p=0.04) and neutral (t (31) = 4.1, p<0.001) task trials. In terms of RT, both the physical activity intervention and wait list control groups showed longer RT than young adults during incongruent (PA: t (36) = 4.7, p<0.001; C: t (31) = 9.2, p<0.001) (see Figure 5.3) and neutral (PA: t (36) = 5.2, p<0.001; C: t (31) = 6.2, p<0.001) trials at post-test. No age-related performance differences between the physical activity intervention group, wait list control group and young adults were found for NoGo trials at pre-test (PA: t (36) = 0.2, p=0.9; C: t (31) = 0.3, p=0.7) or post-test (PA: t (36) = 0.1, p=0.9; C: t (31) = 0.3, p=0.7).

In summary, the performance comparisons by age suggest that all children showed significantly longer RT and lower accuracy rates during incongruent and neutral trials than young adults at pre-test. Nine months later at post-test, all children still performed the task more slowly than the young adults, but children who participated in the physical activity intervention did not differ from the adult group in terms of incongruent or neutral accuracy. On the other
hand, the wait list control group still showed lower accuracy rates than the young adults at post-test.

Functional ROIs

Table 5.3 contains mean percent signal change values of each ROI (see Figure 5.2) at pre-test and post-test for incongruent, neutral and NoGo trials in the physical activity intervention and wait list control groups of children. Table 5.3 also contains mean percent signal change values in each ROI for the young adults.

**Right anterior prefrontal cortex.** Consistent with predictions, a significant group x time interaction (F (1, 21) = 5.4, p=0.03) demonstrated that children in the physical activity intervention group and wait list control group showed differential changes in fMRI activation in the right anterior prefrontal cortex, from pre-test to post-test. The physical activity intervention group showed a significant decrease in right anterior prefrontal activation across all task conditions from pre-test (M=0.49, SE=0.09) to post-test (M=0.25, SE=0.11) (see Figure 5.5). No change in activation from pre-test (M=0.47, SE=0.11) to post-test (M=0.58, SE=0.15) was found for the wait list control group in the right anterior prefrontal cortex. In an exploratory planned comparison, this change in activation that was found for the physical activity intervention group was driven by activation decreases during the incongruent condition (t (13) = 3.5, p=0.004) (see Figure 5.5), and no significant within-group changes in neutral or NoGo activation (see Table 5.3).

Similar to the performance comparisons above, pre-test and post-test brain activation in the right anterior prefrontal cortex of the physical activity intervention group and wait list control group of children were compared to the activation of the young adults in this ROI. Consistent with predictions, during incongruent trials, which necessitated increased cognitive control, both
the physical activity intervention group (t (36) = 2.6, p=0.01) and the wait list control group (t (31) = 2.5, p=0.02) differed in activation in the right anterior prefrontal cortex from the young adults at pre-test (see Table 5.3). At post-test, activation of the right anterior prefrontal cortex in the physical activity intervention group became statistically equivalent to the young adults (t (36) = 0.2, p=0.8) (see Figure 5.5), whereas the wait list control group still showed activation differences at post-test (t (31) = 2.9, p=0.008) (see Table 5.3). During neutral trials and NoGo trials, which required less cognitive control than incongruent trials, neither group of children was statistically different in right anterior prefrontal cortex activation at pre-test or post-test (all p>0.05). In sum, children in the physical activity intervention group showed significant decreases in activation in the right anterior prefrontal cortex from pre-test to post-test during incongruent flanker trials, which led to activation patterns that mirrored the patterns of young adults at post-test. Wait list control children did not show changes in right anterior prefrontal cortex activation from pre-test to post-test and showed significant activation differences from young adults at pre-test and post-test.

It is noteworthy that all children showed adult-like activation during task trials that required less cognitive control. Furthermore, the data suggest that the wait list control children were unable to upregulate these processes to support task conditions requiring additional control (e.g., incongruent trials). This framework supports previous fMRI and ERP studies in children (Chaddock, Erickson et al., 2012; Pontifex et al., 2011), which showed that higher fit children and lower fit children had similar brain patterns and performance during trials with low cognitive demands, but only higher fit children were able to maintain performance and adapt neural recruitment to successfully perform trials with increased cognitive demands. Research on fitness training in elderly adults also shows larger effects of physical activity on task conditions.
requiring increased cognitive control (Colcombe & Kramer, 2003; Kramer et al., 1999).

**Anterior cingulate cortex.** In the ACC, the group x time interaction was not significant (F (1, 21) = 0.2, p=0.6) (see Table 5.3 and Figure 5.6). Furthermore, neither the physical activity intervention group nor wait list control group showed significant differences in activation from the young adult group at pre-test or post-test. These findings suggest that brain function in the ACC did not significantly change from pre-test to post-test in children and that children activated the ACC at a similar level to the young adults at both pre-test and post-test.

**Discussion**

This study had three main goals. First, this study aimed to determine the areas of the brain, especially the prefrontal cortex, associated with a task of attentional, interference, and inhibitory control in children. Research has shown that the frontal cortex is especially involved in cognitive control (Bunge & Crone, 2009; Cabeza & Nyberg, 2000) and development (Gogtay et al., 2004). Second, this study examined whether a 9-month physical activity intervention would influence performance on a task of cognitive control as well as the frontal fMRI activation patterns involved in task demands, relative to a wait list control group. Third, this study explored whether changes in performance and activation in the physical activity intervention group and wait list control group from pre-test to post-test mirrored performance and activation in college-aged young adults. Although this pilot study was limited by a small sample size, the results extend investigations of how physical activity and individual differences in aerobic fitness might be associated with improved brain function (via fMRI, ERP) involved in cognitive control in children (Chaddock, Erickson et al., 2012; Davis et al., 2011; Hillman et al., 2005, 2009; Pontifex et al., 2011; Voss et al., 2011). The preliminary findings provide a foundation for future research to examine, with larger sample sizes, the effect of physical activity on frontal
brain function.

Regarding the first goal, two areas of the frontal cortex were found to be associated with the task of cognitive control (Z-stat > 6), independent of task condition or physical activity group. The task-related frontal regions were found in the right anterior prefrontal cortex and the anterior cingulate cortex (ACC). Both the anterior prefrontal cortex and ACC are known to work together to comprise cognitive control networks (Dosenbach et al., 2007; Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008; Fair et al., 2007). The anterior prefrontal cortex is involved in the maintenance of task context, task goals, and cognitive control over time (i.e., across the trials of a task) (Dosenbach et al., 2006, 2007; Koechlin, Basso, Pietrini, Panzer, & Grafman, 1999; Rushworth, Walton, Kennerley, & Bannerman, 2004). For example, Koechlin et al. (1999) demonstrated that the bilateral anterior frontal lobe (i.e., frontal pole) was activated during a task that required participants to keep in mind a main goal while processing and exploring concurrent subgoals. To add to the specificity of function in the anterior frontal cortex, neither working memory task demands nor dual-tasking (i.e., allocating attentional resources between goals) alone led to activation in anterior frontal regions. Because such goal maintenance skills are useful for planning and reasoning (Koechlin et al., 1999), it is important to understand how factors such as physical activity may influence brain function of this region during development, a critical period in which the brain matures, learns, and forms connections (Amso & Casey, 2006). The ACC is also known to play a role in cognitive control, via the monitoring of response conflict (often engendered through error production) and signaling the frontal cortex to regulate top-down cognitive control (Botvinick et al. 2001; Dosenbach et al., 2007, 2008). Both of these areas have been found to relate to physical activity and aerobic fitness across the lifespan (Chaddock, Erickson et al., 2012; Colcombe et al., 2004; Voss et al.,
The present study used a randomized controlled intervention design in children to explore the effects of physical activity on the fMRI brain function of both of these regions.

In regards to the second goal, a significant group x time interaction demonstrated that children in the physical activity intervention group showed significant decreases in fMRI activation in the right anterior prefrontal cortex from pre-test to post-test, whereas the activation patterns in this frontal region in the wait list control group remained unchanged. It is noteworthy that exploratory planned comparisons revealed that these activation changes in the physical activity intervention group were driven by decreases in activation during incongruent flanker trials that required the greatest challenge to the participants’ ability to pay attention and suppress distraction. In fact, relevant to the third goal, the activation decreases in the physical activity intervention group during the incongruent flanker condition led to post-test fMRI patterns in the right anterior prefrontal cortex that did not differ in magnitude from young adult activation. On the other hand, children in the wait list control group differed from young adults in right anterior prefrontal activation during incongruent flanker trials at both pre-test to post-test.

Together, these group-related and age-related activation patterns raise the possibility that participation in physical activity during childhood can lead to more adult-like recruitment of anterior prefrontal brain areas important for maintenance and goal-oriented cognitive control. Here, improved brain and cognitive function is associated with decreases in anterior prefrontal cortex activation from pre-test to post-test, which is consistent with the framework that less brain activation reflects more mature brain function, as a number of studies show decreased activation and superior performance on cognitive tasks in adults compared to children (Booth et al., 2003; Casey et al., 1997; Durston et al., 2002; Scherf et al., 2006; Velanova et al., 2008). Behaviorally, exploratory planned comparisons demonstrated that the physical activity intervention group
showed within-group performance improvements in terms of both speed and accuracy during incongruent and neutral flanker trials. The incongruent accuracy rates of the physical activity intervention children at post-test also mirrored those of the young adults. In contrast, wait list control children did not show changes in task performance from pre-test to post-test. These performance differences could be driven by changes in maintenance of task context and task goals with the physical activity intervention, which are functions linked to the anterior prefrontal cortex (Dosenbach et al., 2006, 2007; Koechlin et al., 1999; Rushworth et al., 2004).

In fact, previous studies have demonstrated an association between physical activity, aerobic fitness, and anterior prefrontal brain function involved in goal maintenance across the lifespan (Kamijo et al., 2011; Voss et al., 2010, 2011). This longitudinal intervention study in children extends and strengthens these findings. In children, an fMRI study by Voss et al. (2011) demonstrated that higher fit children showed less activation in a network of brain regions including the anterior prefrontal cortex, coupled with better flanker task performance, relative to lower fit children. An ERP study by Kamijo et al. (2011) also demonstrated that children involved in a physical activity intervention showed larger amplitudes in the contingent negative variation (CNV) ERP, known to play a role in cognitive preparation and task maintenance, as well as better working memory performance. In older adults, a physical activity intervention that involved walking three days per week, for one year, led to changes in functional connectivity in a frontal-executive network (Voss et al., 2010), a network that includes the right and left anterior prefrontal cortex (Dosenbach et al., 2006). The results of the present study contribute to this literature and suggest plasticity of the right anterior prefrontal cortex with physical activity and aerobic fitness.

No changes in activation for the physical activity intervention group or wait list control
group were found in the ACC. In addition, no differences were observed in the comparison of child and adult ACC activation at pre-test or post-test. Consistent with these findings, a cross-sectional study of the association between aerobic fitness and cognitive control in children did not demonstrate fitness differences in the ACC during incongruent flanker trials (Voss et al., 2011). Further, Chaddock, Erickson et al. (2012) also reported few fitness-related activation differences in this area. However, higher fit children (Pontifex et al., 2011) and higher fit older adults (Colcombe et al., 2004), as well as older adults involved in a physical activity intervention (Colcombe et al., 2004), have shown smaller ERN amplitudes (an ERP component said to originate in the dorsal portion of the ACC [Carter et al. 1998; Dehaene, Posner, & Tucker, 1994; Miltner et al. 2003; van Veen & Carter, 2002]), and less ACC activation, respectively, which are associated with performance improvements on a flanker task. Such brain patterns in the ACC are usually interpreted as a reduction in conflict or a lower threshold for the detection and signaling of conflict to the prefrontal cortex, which leads to better error detection. To address this divergent evidence, additional research is needed to better understand different responses to physical activity in children and older adults, as well as how ERP components map onto fMRI activity.

The data also raise the possibility that the two groups of children differed in their cognitive strategies at post-test. Cognitive control strategies are theorized to develop from one that is more rapid and reactive (i.e., reactive control) to one that can flexibly sustain goal-oriented control (i.e., proactive control) (Braver, Gray, & Burgess, 2007; Braver, Paxton, Locke, & Barch, 2009; Fair et al., 2007). Participation in physical activity during childhood may influence fMRI brain patterns underlying control strategies, specifically the anterior prefrontal cortex (Fair et al., 2007; Paxton, Barch, Racine & Braver, 2008). That is, physically active
children may learn to maintain a sustained task set during cognitive demands that require selective attention and distraction suppression, which may lead to a more proactive control strategy as well as more accurate and adult-like task performance. This would parallel research that suggests that higher fit children and older adults use a more proactive control neural strategy than lower fit individuals, especially during incongruent flanker task conditions (Colcombe et al., 2004; Pontifex et al., 2011; Voss et al., 2011). Alternatively, children in a wait list control group may be less able to adapt their task strategy and task set at post-test, and may continue to use a more reactive strategy, given that anterior prefrontal activation and performance on incongruent task trials were unchanged.

These results have important implications for public health and the educational environment. Educational practices are reducing and eliminating physical activity opportunities during the school day, and physical activity is decreasing outside the school environment (Troiano et al., 2008). Children are becoming increasingly sedentary and unfit, which leads to an increased risk for disease and obesity (Centers for Disease Control and Prevention, 2009; United States Department of Health and Human Services, 2008), as well as cognitive impairment (Chaddock, Voss, & Kramer, 2012). The present study suggests that physical activity is important to the development of the brain and cognition during childhood. These results should raise public awareness of the cognitive benefits of being active and encourage participation in physical activity.
Chapter 5 References


### Table 5.1. Mean (SD) for physical activity and control groups at pre-test and post-test.

<table>
<thead>
<tr>
<th></th>
<th>Physical Activity</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-test</td>
<td>Post-test</td>
</tr>
<tr>
<td>Age (years)</td>
<td>8.9 (0.7)</td>
<td>9.6 (0.7)</td>
</tr>
<tr>
<td>Gender</td>
<td>7 girls, 7 boys</td>
<td>6 girls, 3 boys</td>
</tr>
<tr>
<td>IQ</td>
<td>122.3 (14.9)</td>
<td>122.6 (11.8)</td>
</tr>
<tr>
<td>Pubertal timing</td>
<td>1.3 (0.4)</td>
<td>1.5 (0.4)</td>
</tr>
<tr>
<td>SES</td>
<td>2.2 (0.9)</td>
<td>2.3 (0.9)</td>
</tr>
<tr>
<td>VO₂ max (mL/kg/min)</td>
<td>38.3 (4.0)</td>
<td>40.6 (4.1)</td>
</tr>
<tr>
<td>VO₂ max percentile</td>
<td>14.0 (14.9)</td>
<td>20.0 (18.6) a</td>
</tr>
<tr>
<td>BMI (kg/cm²)</td>
<td>18.4 (3.6)</td>
<td>18.7 (4.4)</td>
</tr>
</tbody>
</table>

*Note: IQ – composite standardized score of intelligence quotient from the Kaufman Brief Intelligence Test (Kaufman & Kaufman, 1990), SES – Socioeconomic Status. Values that share a common superscript are significantly different at p<0.05.*
Table 5.2. Mean task performance (SD) for physical activity (PA) and control (C) groups at pre-test and post-test.

<table>
<thead>
<tr>
<th></th>
<th>PA Pre-test</th>
<th>PA Post-test</th>
<th>C Pre-test</th>
<th>C Post-test</th>
<th>Young</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incongruent RT (ms)</td>
<td>919.4 (177.3)(^{*\ast\ast})</td>
<td>801.5 (173.7)(^{\ast\ast})</td>
<td>937.3 (108.6)</td>
<td>841.8 (132.6)</td>
<td>606.1 (86.9)</td>
</tr>
<tr>
<td>Neutral RT (ms)</td>
<td>826.6 (139.6)(^{\ast\ast})</td>
<td>755.6 (157.7)(^{\ast\ast})</td>
<td>850.1 (84.1)</td>
<td>789.6 (132.3)</td>
<td>551.8 (83.1)</td>
</tr>
<tr>
<td>Incongruent accuracy (% correct)</td>
<td>85.9 (9.8)(^{\ast})</td>
<td>91.2 (4.9)(^{\ast})</td>
<td>83.9 (14.8)</td>
<td>86.9 (9.9)</td>
<td>92.6 (4.6)</td>
</tr>
<tr>
<td>Neutral accuracy (% correct)</td>
<td>91.6 (6.2)(^{\ast\ast})</td>
<td>95.7 (3.5)(^{\ast\ast})</td>
<td>89.2 (12.6)</td>
<td>91.1 (5.7)</td>
<td>96.5 (1.9)</td>
</tr>
<tr>
<td>NoGo accuracy (% correct)</td>
<td>98.8 (1.6)</td>
<td>98.9 (2.1)</td>
<td>98.6 (1.8)</td>
<td>98.6 (1.8)</td>
<td>98.9 (2.2)</td>
</tr>
</tbody>
</table>

Note: Values that share a common superscript are significantly different at **p<0.05. *p<0.1.
Table 5.3. Mean percent signal change (SD) during incongruent, neutral and NoGo task trials (versus baseline).

<table>
<thead>
<tr>
<th></th>
<th>PA Pre-test</th>
<th>PA Post-test</th>
<th>C Pre-test</th>
<th>C Post-test</th>
<th>Young</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incongruent</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right anterior prefrontal cortex</td>
<td>0.62 (0.5)  a</td>
<td>0.19 (0.6)  a</td>
<td>0.67 (0.5)</td>
<td>0.70 (0.4)</td>
<td>0.22 (0.4)</td>
</tr>
<tr>
<td>Anterior cingulate cortex</td>
<td>0.56 (0.5)</td>
<td>0.37 (0.4)</td>
<td>0.54 (0.4)</td>
<td>0.38 (0.3)</td>
<td>0.38 (0.3)</td>
</tr>
<tr>
<td><strong>Neutral</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right anterior prefrontal cortex</td>
<td>0.53 (0.5)</td>
<td>0.45 (0.7)</td>
<td>0.38 (0.3)</td>
<td>0.51 (0.3)</td>
<td>0.23 (0.5)</td>
</tr>
<tr>
<td>Anterior cingulate cortex</td>
<td>0.75 (0.5)</td>
<td>0.52 (0.3)</td>
<td>0.44 (0.4)</td>
<td>0.44 (0.3)</td>
<td>0.31 (0.3)</td>
</tr>
<tr>
<td><strong>NoGo</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right anterior prefrontal cortex</td>
<td>0.32 (0.6)</td>
<td>0.11 (0.6)</td>
<td>0.38 (0.2)</td>
<td>0.51 (0.1)</td>
<td>0.26 (0.4)</td>
</tr>
<tr>
<td>Anterior cingulate cortex</td>
<td>0.30 (0.5)</td>
<td>0.27 (0.3)</td>
<td>0.18 (0.4)</td>
<td>0.11 (0.3)</td>
<td>0.17 (0.3)</td>
</tr>
</tbody>
</table>

*Note:* Values that share a common superscript are significantly different at p<0.05.
Figure 5.1. Sample stimuli for the cognitive control task.
Figure 5.2. The 8 mm (diameter) box ROIs (1000 mm$^3$) in the frontal cortex, derived from an average activation map during incongruent, neutral and NoGo conditions of the task of cognitive control, across both physical activity and control child groups at pre-test and post-test (thresholded at Z>6). Right anterior prefrontal cortex = yellow; ACC=red.
Figure 5.3. Change in incongruent RT for the physical activity intervention group and wait list control group. Error bars represent standard error. The child groups showed longer RT at pre-test and post-test compared to young adults.
Figure 5.4. a. Change in incongruent accuracy for the physical activity intervention group and wait list control group. The within-group increase in accuracy for the physical activity intervention group led to accuracy rates at post-test similar to young adults. Error bars represent standard error. b. Percent change in incongruent accuracy for the physical activity intervention group and wait list control group. Error bars represent standard error.

a. 

b. 
Figure 5.5. Change in mean percent signal change in the right anterior prefrontal cortex during incongruent flanker trials for the physical activity intervention group and wait list control group. Error bars represent standard error. Significant time x group interaction. The decrease in activation for the physical activity intervention group led to mean percent signal change at post-test similar to young adults.
Figure 5.6. Change in mean percent signal change in the anterior cingulate cortex during incongruent flanker trials for the physical activity intervention group and wait list control group. Error bars represent standard error. No significant time x group interaction, and no differences in mean percent signal change from young adults.
CHAPTER 6
CONCLUSION

This dissertation suggests that participation in an after school physical activity program, 5 days per week, 60+ minutes per day, for approximately 9 months, is associated with brain structure, brain function and cognition in children. Specifically, 8- to 9-year-old children who participated in more than the recommended 60 minutes of moderate to vigorous physical activity every day after school for one school year showed within-group increases in basal ganglia and hippocampal brain volume, increases in estimations of fiber integrity and myelination in a global network of white matter tracts, and changes in fMRI brain activation in the anterior prefrontal cortex that paralleled better attentional control. A wait list control group not involved in an after school program did not show these patterns of brain and cognitive changes from pre-test to post-test. Although the conclusions are limited by a small sample size and lack of statistical interactions, this dissertation is the first to present studies of how brain structure and brain function may change with participation in physical activity during childhood. This conclusion summarizes the results from each chapter as well as suggests some of the cellular processes that may support the structural and functional brain changes and cognitive improvements with physical activity participation during childhood.

Chapter 2 extends previous studies that have shown an association among physical activity, aerobic fitness and dorsal striatum structure and function in children (Chaddock et al., 2010b), older adults (Verstynen et al., 2012), and rodents (Aguiar, Speck, Prediger, Kapczinski, & Pinho, 2008; Marais, Stein & Daniels, 2009; Marques et al., 2008) by exploring the relationship among a physical activity program designed to increase aerobic fitness, basal ganglia volume and performance on a task of cognitive control in children. The physical activity group showed within-group increases in the volume of the dorsal striatum of the basal ganglia, a
region implicated in attentional control and learning. The physical activity group also showed shorter reaction time and higher accuracy from pre-test to post-test during incongruent trials of the flanker task which required greater attentional and interference control. Further, there was an association between increase in dorsal striatum volume and shorter incongruent reaction time within the physical activity group. Children in a wait list control group did not show changes in dorsal striatum volume and showed fewer changes in attentional control processes (i.e., shorter incongruent RT, but no changes in incongruent accuracy) across time. Additionally, change in dorsal striatum volume did not relate to changes in flanker task performance within the control group. Neither group showed changes in the volume of the ventral striatum, a region involved in reward and motivation, which adds specificity to the effects of physical activity on the brain during childhood. The results support the association between participation in physical activity that improves aerobic fitness and the structure and function of the basal ganglia.

Chapter 3 demonstrates that participation in physical activity during childhood also relates to the volume of the hippocampus, a brain region important for learning and memory (Cohen & Eichenbaum, 1993). Children involved in an after school physical activity program showed within-group increases in hippocampal volume from pre-test to post-test. Children in the wait list control group did not show changes in hippocampal volume across time. These results support a number of studies that show a positive effect of physical activity and aerobic fitness on the hippocampus. For example, young and older rodents that engaged in aerobic exercise showed increased cell proliferation and cell survival of new neurons in the hippocampus, coupled with improvements in learning (Gomez-Pinilla, Vaynman, & Ying, 2008; Gould, 2007; van Praag, Kempermann, & Gage, 1999). In humans, children (Chaddock et al., 2010a) and older adults (Bugg & Head, 2011; Erickson et al., 2009; Honea et al., 2009) with higher aerobic
fitness levels had larger hippocampal volumes and better memory performance than their lower fit peers. A longitudinal intervention in older adults also demonstrated that elderly walkers showed increased hippocampal volume with physical activity (Erickson et al., 2011). Alternatively, older adults involved in a stretching and toning program showed significant hippocampal atrophy over the year. This dissertation is the first to use a longitudinal intervention design to show a relationship between participation in physical activity that improved aerobic fitness and hippocampal volume in children.

Chapter 4 demonstrates that physical activity not only relates to structural volume changes of certain gray matter brain regions, but also the structural integrity of a global network of white matter tracts that integrate brain regions into networks. Using diffusion tensor imaging (DTI), the results suggest that children who participated in a physical activity intervention showed increases in fractional anisotropy, an estimation of fiber integrity, in a global and distributed pattern of white matter tracts in the brain. This effect was likely driven by reductions in radial diffusivity, an estimation of myelination, in the corpus callosum, corona radiata, cingulum, superior longitudinal fasciculus, and internal capsule. A wait list control group did not show global changes in white matter microstructure from pre-test to post-test. The results extend previous research to show that physical activity influences white matter pathways involved in cognition and interhemispheric communication during a period of brain development.

Despite statistical limitations, chapters 2-4 provide converging evidence for the positive relationship between physical activity and brain structure during childhood. However, the cellular processes underlying these changes can only be inferred from rodent models. Rodent studies have shown that aerobic exercise improves the structural integrity of rodent brains, via
the growth and formation of new neurons, blood vessels and synapses (Cotman & Berchtold, 2002), as well as increases in the production of neurochemicals (e.g., brain-derived neurotrophic factor, insulin-like growth factor) that promote the growth, survival and repair of brain cells (for review, see Voss, Nagamatsu, Liu-Ambrose, & Kramer, 2011). These changes are coupled with improved learning and memory (Gomez-Pinilla et al., 2008). Given that many of the neurochemical processes involved in neural changes with exercise in rodents are also involved in human brain development and organization, it seems likely that physical activity may influence the brain during childhood, a period of significant cognitive and neural development (Casey, Tottenham, Liston, & Durston, 2005; Caviness, Kennedy, Richelme, Rademacher, & Filipek, 1996). For example, changes in the brain during development are said to reflect the interplay among changes in cell proliferation / apoptosis, dendritic branching / pruning, synaptic formation / elimination, growth factors (e.g., brain-derived neurotrophic factor, insulin-like growth factor), vascularization, glia, and myelination (Anderson, 2003; Giedd et al., 1996, 1999; Gogtay et al., 2004). These cellular underpinnings parallel exercise-induced neural effects including changes in cell number, capillary density, dendritic complexity, synaptic plasticity, and growth factors (e.g., Cotman & Berchtold, 2002). It is important for future research to try to integrate animal and human studies. For example, cerebral blood volume is suggested to provide an imaging correlate of neurogenesis (Pereira et al., 2007). In mice, exercise-induced increases in hippocampal cerebral blood volume were found to correlate with post-mortem measurements of neurogenesis. In humans, exercise was found to have a primary effect on cerebral blood volume in the hippocampus, and the cerebral blood volume changes were associated with cardiopulmonary and cognitive function. Thus, the authors suggest the possibility that hippocampal cerebral blood volume is an imaging correlate of neurogenesis (Pereira et al.,
Chapter 5 uses functional magnetic resonance imaging (fMRI) to examine how the physical activity program influences brain activation patterns involved in attentional and interference control. The blood oxygen level dependent (BOLD) response was the dependent measure of the fMRI study. BOLD refers to the microvascular response in blood flow resulting from fluctuations in the metabolic needs of neurons as they become involved in computations which underlie performance of tasks. Children who participated in the physical activity intervention showed decreases in fMRI brain activation in the right anterior prefrontal cortex coupled with improvements in performance on a task of attentional and interference control. Children assigned to a wait list control group did not show changes in brain function or performance. Furthermore, at post-test, children in the physical activity group showed similar anterior frontal brain patterns and incongruent accuracy rates to a group of college-aged young adults. Children in the wait list control group still differed from the young adults in terms of anterior prefrontal activation and performance at post-test. There were no significant changes in fMRI activation in the anterior cingulate cortex for either group. These results suggest that physical activity during childhood may enhance specific elements of prefrontal cortex function involved in cognitive control. It is possible that physical activity influences the cellular processes involved in the BOLD response, which may include changes in vasculature, neuronal and glia density, growth factors and/or other metabolic processes that require oxygen and glucose (Cotman & Berchtold, 2002). Future research should explore changes in functional networks with participation in physical activity during childhood. In older adults, aerobic training (i.e., one year of walking) has been found to improve the aging brain’s resting functional connectivity in frontal, posterior, and temporal cortices within the Default Mode Network and a
Frontal Executive Network, and increased functional connectivity was associated with greater improvement in cognitive control (Voss et al., 2010). It will be interesting to apply similar techniques to a child population.

In conclusion, this dissertation reinforces the potential for plasticity in the developing brain, and the important role of lifestyle factors such as physical activity during childhood. Although additional research with larger sample sizes is needed to confirm the results, these findings provide a first and preliminary step showing the positive association among participation in physical activity, brain structure, brain function, and cognition in children. The data should help reinforce the importance of physical activity for the cognitive and brain health of children as well as substantiate the need for improved physical activity practices in and out of the school environment. Children are becoming increasingly sedentary and unfit (Centers for Disease Control and Prevention, 2009; United States Department of Health and Human Services, 2008), and educational practices are contributing to declining health in youth by reducing and eliminating physical activity opportunities during the school day, with the philosophy that increased academic time will lead to higher test scores and achievement. However, the results of this dissertation suggest that incorporating physical activity into the school day can in fact enhance the cognitive and brain health of 8- and 9-year-old children. Given that cognitive control has been associated with learning and scholastic achievement in school (Bull & Scerif, 2001; DeStefano & LeFevre, 2004; St. Clair-Thompson & Gathercole, 2006), the findings also have implications for school performance. Maintaining task goals, paying attention, and remembering information are also important skills for success outside the school environment. Hopefully this dissertation will serve to raise public awareness of the cognitive benefits of physical activity in and out of the school environment.
Chapter 6 References


St. Clair-Thompson, H. L., & Gathercole, S. E. (2006). Executive functions and achievements in


