EFFECTS OF AN EIGHT-MONTH RANDOMIZED CONTROLLED EXERCISE INTERVENTION ON CHILDREN'S BRAIN STRUCTURE AND FUNCTION

by

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Under the Direction of Jennifer McDowell

ABSTRACT

Children with lower aerobic fitness have demonstrated worse performance on various cognitive tasks and differences in brain function compared to those with higher fitness. There is evidence that exercise improves cognitive function. This dissertation includes a series of three studies examining the effect of a randomized controlled exercise intervention on brain function and structure in overweight children. Participants in each study were subsets of individuals participating in the overall intervention study, who were unfit, overweight (body mass index ≥ 85th percentile) children 8-11 years old. Participants were randomly divided into either an aerobic exercise or attention control group. Each group was offered a separate instructor-led after-school program every school day for 8 months. Before and after the program, subsets of children participated in cognitive control tasks (antisaccade and flanker) during functional magnetic resonance imaging (fMRI), resting state fMRI, and/or diffusion tensor imaging (DTI). Changes over time in these measures were then compared between the exercise and control groups. Exercise altered brain activation during the cognitive control tasks. Specifically, the exercise group decreased activation in several brain regions related to antisaccade performance and increased activation in several regions related to flanker performance. During the resting state, exercise caused greater refinement of the default mode, cognitive control, and motor resting state networks compared to the control group. The motor network also showed an opposite pattern of increased synchrony with a frontal region. Finally, DTI data demonstrated a group by attendance interaction for white matter integrity such that attendance at the exercise intervention but not at the control group was associated with improved white matter integrity in the superior longitudinal fasciculus. In sum, exercise causes alterations in brain function during both cognitive control and a resting state in overweight children and is associated with alterations in white matter integrity in a tract supporting cognitive control. These results indicate that exercise improves the development of brain function and structure supporting cognitive control in overweight children.

INDEX WORDS: Aerobic exercise, Overweight, Obesity, Development, Cognitive control, Default mode, Functional magnetic resonance imaging, Resting state, Diffusion tensor imaging, Superior longitudinal fasciculus

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DEDICATION

This dissertation is dedicated to my parents, Gary and Susanne Krafft, for their support throughout my education.

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TABLE OF CONTENTS

Page

ACKNOWLEDGEMENTS……………..…………………………………………………………v

CHAPTER

1 INTRODUCTION AND LITERATURE REVIEW……………………………...1

2 AN EIGHT MONTH RANDOMIZED CONTROLLED EXERCISE TRIAL ALTERS BRAIN ACTIVATION DURING COGNITIVE TASKS IN OVERWEIGHT CHILDREN …..…………………………………………..27

3 AN EIGHT MONTH RANDOMIZED CONTROLLED EXERCISE INTERVENTION ALTERS RESTING STATE SYNCHRONY IN OVERWEIGHT CHILDREN…...…………………………………………..61

4 IMPROVED FRONTO-PARIETAL WHITE MATTER INTEGRITY IS ASSOCIATED WITH ATTENDANCE IN AN AFTER-SCHOOL EXERCISE PROGRAM…………………………………………………………………85

5 CONCLUSIONS……………………………………………………………103

REFERENCES……………………………………………………………………………110

CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

In the United States, 32% of children and adolescents aged 2 – 19 years old are overweight or obese (Ogden, Carroll, Kit, & Flegal, 2012). Over the past 30 years, childhood obesity has nearly tripled in the U.S., along with a decrease in pediatric aerobic fitness. Specifically, there is evidence that pediatric aerobic fitness in North America decreased by 0.74% per year between 1970 – 2000 (Tomkinson & Olds, 2007). The rapid rise in childhood obesity may have slowed recently (Ogden et al., 2012) but even so, the current high rates have significant implications for physical and cognitive health. There are many physical health risks associated with obesity and low fitness which include: sleep apnea, asthma, type 2 diabetes, and hypertension (Herouvi, Karanasios, Karayianni, & Karavanaki, 2013). These problems may present long term consequences, especially because those who are obese as children are at higher risk of adult obesity (Whitaker, Wright, Pepe, Seidel, & Dietz, 1997).

In addition to the myriad physical health concerns, obesity and low fitness also have been associated with worse cognition. The majority of studies investigating these relationships have been conducted in adults and so although studies of children are the most relevant for this dissertation, studies with all age groups will be reviewed here. There are many similarities across age groups, as both adults and children with higher adiposity or less fitness have demonstrated lower cognitive performance than their leaner or more fit peers. These deficits manifest in many domains of cognition, including but not limited to cognitive control and memory.

Cross-sectional Studies of Brain Function During Task Performance

Overweight and Obesity in Adults

Cognitive control may be the most frequently investigated type of cognition in research on obesity and fitness, with a wealth of evidence indicating that it differs at various adiposity and fitness levels. Cognitive control includes functions such as attentional control, working memory, planning, and inhibition (Diamond, 2011). Overweight adults across a wide age range (20 – 82 years old) have shown lower cognitive control performance than healthy-weight adults even when controlling for IQ, education, sex, and self-reported depression, anxiety, and stress. For instance, overweight adults have shown comparatively lower visual working memory as well as higher Stroop interference (Gunstad et al., 2007). In the Stroop task, participants are required to name the colors that words are printed in when they are either the same colors as the words themselves (e.g., “blue” printed in blue ink; congruent trials) or different colors than the words (e.g., “blue” printed in red ink; incongruent trials). Stroop interference is a measure of how much longer an individual takes to complete incongruent trials compared to congruent trials and is considered a measure of selective attention and cognitive flexibility. Altered cognitive control has been related to lower regional cerebral blood flow found in overweight compared to healthy-weight adults in brain regions supporting these processes, specifically prefrontal cortex and anterior cingulate (Willeumier, Taylor, & Amen, 2011). Parietal regions also have shown differences. In a functional magnetic resonance imaging (fMRI) study, obese 40 – 60 year olds showed lower activation during a 2-back task (which requires participants to indicate when the current stimulus matches the one from two steps earlier in a sequence) than those who were overweight or normal weight, suggesting worse working memory processing (Gonzales et al., 2010).

The relationship between obesity and cognitive control may differ by gender. Obese female undergraduate students have shown greater delay discounting of monetary rewards than those of healthy weight, which is a measure of how much more an individual is driven by immediate gratification compared to larger, but delayed, rewards. Obese and healthy male students in the same study did not differ from one another (Weller, Cook, Avsar, & Cox, 2008). A follow-up study conducted fMRI scans with obese women aged 19 – 50 years old during delay discounting at two timepoints separated by 1.3 – 2.0 years. Activation in frontal and parietal regions, as well as posterior cingulate and cerebellum on hard compared to easy trials was negatively correlated with percent of weight gain per year, indicating that executive control inefficiency was related to weight gain (Kishinevsky et al., 2012).

Cognitive control in obesity may differ especially in relation to food cues, which has been a topic of at least two electroencephalography (EEG) studies. In one study, obese adults (21 – 50 years old) were compared to those of healthy weight during an oddball paradigm, in which participants are asked to respond to target stimuli that occur rarely within a series of more common stimuli. Face, food, and landscape targets were enlarged by 25% along the horizontal axis during target trials. During food trials, the amplitude of medial prefrontal P300 sources was lower in obese than normal-weight subjects, indicating that prefrontal attentional processes to food size were abnormal in obese subjects (Babiloni et al., 2009). The P300 event-related brain potential occurs in tasks that require participants to discriminate between various stimuli and has been associated with attention and memory updating (Polich & Kok, 1995). Even earlier information processing has been shown to differ in obesity, as obese adults (average age of 23) have shown higher P200 amplitude in frontal and central electrode clusters to food-related words in a Stroop task compared to normal-weight individuals. These results demonstrated that although obese adults showed lower P300s related to food size, they showed greater early, automatic processing of food-related compared to neutral stimuli overall (Nijs, Franken, & Muris, 2010).

Obesity has not only been associated with differences in cognitive control, but also with significant differences in reward processing. In obese adults compared to those of healthy weight (average age of 47), the caudate nucleus has shown higher glucose metabolism during positron emission tomography (PET) scanning and higher connectivity with the amygdala and posterior insula while viewing appetizing versus bland foods during fMRI (Nummenmaa et al., 2012). Obese subjects also showed higher activity compared to healthy-weight subjects for appetizing versus bland foods in the right caudate but lower activity in frontal and parietal regions, left insula, and superior temporal gyrus. Generally speaking, this study indicated that obesity was associated with more active reward circuitry (e.g., caudate nucleus) and less active cognitive control systems. In this study, differences were especially notable in the caudate nucleus, which has been related to stimulus-response learning, motivation, and reward signaling. Further support for a central role of the caudate nucleus was seen in a study which followed women (average age of 21) over a 6 month period. Those who gained weight over this time showed a reduction in right caudate activation to palatable food consumption over the 6 month study relative to weight-stable women, suggesting that low sensitivity of reward circuitry could increase risk for overeating (Stice, Yokum, Blum, & Bohon, 2010). In sum, the greatest cognitive differences associated with obesity in adults may be seen in cognitive control and reward systems. A limitation of these studies, as well as in studies of obesity in youth, is that they did not attempt to control for fitness. Because low fitness is often associated with obesity, low fitness rather than obesity may have contributed to some of these findings.

Overweight and Obesity in Youth

Fewer studies of cognitive differences associated with obesity have been conducted in children than in adults. There is evidence that children show similarly differing cognitive control and reward processing. Greater adiposity in children 7 – 11 years old has been associated with worse parent and teacher ratings of behavior, math achievement, and cognitive control task performance (the Planning scale of the Cognitive Assessment System) (Davis & Cooper, 2011). Lower cognitive control performance has also been observed in obese adolescents compared to lean peers (14 – 21 years old), who have shown worse performance on Stroop accuracy, trail making, verbal fluency, and other tasks involving cognitive control (Maayan, Hoogendoorn, Sweat, & Convit, 2011). In the trail making task, participants are instructed to connect a set of dots as quickly and accurately as possible. The portion of the test that measures cognitive control involves connecting dots that alternate between numbers and letters (1, A, 2, B, etc.) and thus is considered a measure of selective attention and mental flexibility. Gunstad et al., however, showed no relationship between BMI and cognitive performance in youth (Gunstad et al., 2008).

At least one fMRI study in youth has shown similar differences in cognitive control and reward circuitry compared to adults using a go/no-go task. In this task, participants are presented with a series of stimuli that either require them to make a motor response (go trials) or require them to withhold the motor response (no-go trials, which are typically less frequent than go trials). When required to inhibit responses to appetizing food during a food-specific go/no-go task, body mass index (BMI) in female high school students has been associated with worse response inhibition at both behavioral and neural levels. Higher BMI was associated with greater impulsivity, lower activation of frontal inhibitory regions, and higher activation of food reward regions (the right temporal operculum, frontal operculum, and insula) (Batterink, Yokum, &

Stice, 2010). These effects may differ with task, gender, age, or some other factor however, as another study showed different patterns associated with obesity. Obese youth (10 – 18 years old) showed higher activation than healthy-weight peers in the left dorsolateral prefrontal cortex in response to food pictures. They also showed lower activation in the anterior cingulate, thalamus, caudate, hippocampus, and visual cortex in response to food cues (suggested to reflect differing vigilance), and lower activation in the anterior cingulate and thalamus (areas involved in attention and arousal) regardless of stimulus type (Davids et al., 2009).

Fitness and Physical Activity in Adults

While obesity has been associated with cognitive differences, the focus of this dissertation will be on exercise and fitness. Physical activity, exercise, and fitness are different but related concepts; while they will be discussed as a group, the differences between them should be acknowledged. Physical activity was defined by Caspersen, Powell, and Christenson as any bodily movement produced by skeletal muscles that results in energy expenditure. Exercise is a subset of physical activity that is planned, structured, and repetitive and has as an objective the improvement or maintenance of physical fitness. Fitness is a set of attributes that are health- or skill-related (Caspersen, Powell, & Christenson, 1985).

Evidence has been accumulating for several decades indicating that higher fitness levels are associated with better cognition. Powell and Pohndorf conducted one of the earliest studies demonstrating that fitness is associated with better cognitive performance, finding that in men between the ages of 34 and 75 years old, fitness was related to fluid intelligence scores (Powell & Pohndorf, 1971). Soon thereafter, Spirduso reported that physically active older men (50 – 70 years old) had the same simple and choice reaction times as younger men (20 – 30 years old), while sedentary older men were slower than either active older men or younger men of either fitness level (Spirduso, 1975). In adults aged 58 – 81 years old, higher fitness also has been associated with less interference on the Stroop task and higher accuracy on a spatial working memory task (Weinstein et al., 2012). Even in adults who are obese, higher aerobic fitness has been associated with better processing speed (Symbol Search and Letter Comparison tasks, requiring participants to report whether various stimuli match each other as quickly as possible) and cognitive control (Stroop and Operation Span performance), indicating that while obesity is associated with worse cognitive performance, it does not preclude the benefits of fitness for cognition (Bugg, Shah, Villareal, & Head, 2012).

Much research into the relationship between fitness and cognition has focused on older adults, in part because of interest in whether fitness prevents cognitive decline later in life. Older adults (62 – 70 years old) who were either still working or physically active and retired from work were compared to inactive retirees. After four years, those who were still working or who were active retirees showed relatively constant cerebral blood circulation compared to baseline measurements (while inactive retirees showed decreased cerebral blood circulation), as well as higher cognitive performance (Rogers, Meyer, & Mortel, 1990). Another study observed women over the age of 65 without cognitive impairment over 6 to 8 years. Physical activity was measured by self-reported blocks walked per week and energy expended in recreation, walking, and stair climbing. Women who reported being highly physically active showed less cognitive decline as measured by the Mini-Mental State Examination than those with a low physical activity level (Yaffe, Barnes, Nevitt, Lui, & Covinsky, 2001). Self-reported frequent and vigorous physical activity also has been associated with lower risks of cognitive impairment, Alzheimer’s disease, and dementia (Laurin, Verreault, Lindsay, MacPherson, & Rockwood, 2001).

In addition to behavioral work, several EEG studies of fitness have been conducted, mostly focusing on differences in the latency and amplitude of the P300. Dustman et al. conducted one of the first EEG studies of fitness, comparing older (50 – 62 year old) and younger (20 – 31 year old) men of low and high fitness. Older men with lower fitness had longer P300 latency (possibly indicating slower cognitive processing speed) on an oddball task than any of the other three groups, which did not differ from each other (Dustman et al., 1990). Longer P300 latency with lower fitness was observed in another study on both incongruent and neutral conditions of a flanker task. In the flanker task, participants are asked to make a motor response to a central stimulus while ignoring flanking stimuli. Trials can be neutral (in which there is only a central stimulus), congruent (in which all stimuli indicate the same response), or incongruent (in which flanking stimuli indicate the opposite response of the central stimulus). Low active older adults (average age of 66) demonstrated the slowest latencies, followed by moderately active older adults, highly active older adults, and younger adults (average age of 20) (Hillman, Belopolsky, Snook, Kramer, & McAuley, 2004). Longer P300 latency with lower fitness also has been observed during task switching. Less physically active younger and older adults (average ages of 19 and 65, respectively) showed slower reaction times and longer P300 latency than those who were more active, but only during heterogeneous task blocks (those containing two tasks) and not during the homogeneous task blocks (containing only one task), indicating that conditions requiring maintenance of multiple task sets in working memory may be particularly susceptible to fitness (Hillman, Kramer, Belopolsky, & Smith, 2006).

Not only latency but also amplitude of the P300 has been associated with fitness. In a previously mentioned task-switching paradigm, both younger and older adults who were more physically active had larger P300 amplitude along midline sites than those who were less active, suggesting differences in attentional processing (Hillman et al., 2006). Compared to younger adults (average age of 20), low-active older adults but not those who were high-active (average age of 66) showed lower P300 amplitude on the neutral condition of a flanker task at the central parietal site (Hillman et al., 2004). Even younger adults (average age of 32 years old) have shown similar differences, as those who are high-active had higher P300 amplitude for both visual and auditory oddball tasks than those who were low-active (Polich & Lardon, 1997).

EEG studies also have been used to investigate responses after errors. Error positivity is a positive component that is generated in the rostral anterior cingulate and which peaks about 300 ms after an incorrect response. Higher-fit undergraduate students have shown higher error positivity amplitude during a flanker task compared to lower-fit peers, which may reflect increased top-down attentional control from frontal regions to downstream effector regions in high-fitness individuals following an error. The idea of better top-down control following errors in high-fitness individuals was supported by behavioral data showing that higher-fit individuals had greater post-error slowing compared to lower-fit adults (Themanson & Hillman, 2006). Error-related negativity, a component of an event-related potential that peaks shortly after errors are committed and the source of which is at or very near the anterior cingulate, also has become a topic of study in EEG investigations of fitness. In a previously mentioned study, higher-fit undergraduate students showed smaller error-related negativity amplitude during a flanker task compared to lower-fit peers (Themanson & Hillman, 2006). This was thought to reflect a difference in conflict monitoring, meaning the ability of the ACC to detect response conflict and transmit this information to other brain regions. The relationship between fitness and error-related negativity differs depending on task instructions, however. While participants in the prior study were instructed to respond as quickly as possible, a later study compared conditions in which participants were instructed to respond either as accurately as possible or as quickly as possible. That study found an opposite effect of fitness in the accuracy condition, in which participants with higher fitness showing higher error-related negativity amplitude than those with lower fitness. In addition, those with higher fitness compared to those with lower fitness showed higher post-error accuracy and a greater difference in error-related negativity between the speed and accuracy conditions, possibly reflecting more flexible modulation of cognitive control (Themanson, Pontifex, & Hillman, 2008).

Task instructions also may affect the relationship between fitness and other EEG measures. In a study comparing undergraduate students with higher and lower fitness, frontal contingent negative variation was larger for lower-fit participants compared to higher-fit participants on a working memory task under speed instructions, an effect not found for accuracy instructions. Contingent negative variation is a component of an ERP elicited during the interval between warning and imperative stimuli reflecting preparatory motor activity when a motor response is required to the imperative stimulus. The authors suggested that lower-fit individuals rely to a greater extent on cognitive control processes to respond under speeded conditions, whereas higher-fit individuals maintain a more constant level of control irrespective of task instructions, resulting in more efficient cognitive preparation during the speed condition (Kamijo, O'Leary, Pontifex, Themanson, & Hillman, 2010).

Relatively little work has been conducted thus far using fMRI to investigate the cognitive associations of fitness. Colcombe et al. conducted one of the first studies of this type, demonstrating that older adults (average age of 67) with higher fitness compared to those with lower fitness had higher activation on incongruent versus congruent trials of a flanker task in frontal and parietal regions (supporting attentional control), as well as visual cortex, but lower activation in anterior cingulate, suggesting less conflict (Colcombe et al., 2004). In sum, higher fitness in older adults is associated with better cognitive performance, different event-related brain potential amplitudes and higher P300 latency, and different brain activation as measured by fMRI.

Fitness and Physical Activity in Youth

Similarly to adults, higher-fit youth have shown better performance in a variety of higher-order cognitive tasks compared to their lower-fit peers. For instance, higher-fit 9- and 10-year-old children have shown less flanker interference (a measure of how much slower participants are to respond to incongruent compared to congruent trials) and better relational memory performance than those with low fitness even when accounting for socioeconomic status (Chaddock, Erickson, Prakash, Kim, et al., 2010; Chaddock, Erickson, Prakash, VanPatter, et al., 2010). As in adults, higher fitness in 7 – 12 year old children has been associated with higher accuracy on the Stroop task (Buck, Hillman, & Castelli, 2008). A more recent addition to human studies of cognition in fitness is spatial learning, with higher fitness in males aged 15 – 18 years old being correlated with better learning on a virtual Morris Water Task (Herting & Nagel, 2012). Higher fitness has been associated with better cognitive performance at least as early as preschool (Niederer et al., 2011).

EEG studies in children demonstrate cognitive associations with fitness that are similar to those found in adults. Higher-fit children (averaging 9 or 10 years old) compared to lower-fit children have shown more accurate flanker performance (perhaps with a greater disparity between fitness levels for incongruent than congruent trials), larger P300 and error positivity amplitudes, faster P300 latency, and lower ERN amplitude (Hillman, Buck, Themanson, Pontifex, & Castelli, 2009; Pontifex et al., 2011). EEG studies also have demonstrated that higher-fit children show more flexible modulation of cognitive control, as measured by modulation of P300 and error-related negativity amplitudes. Specifically, a previously mentioned study found that higher-fit children showed greater P300 amplitude modulation (i.e., a greater difference) between congruent and incongruent conditions of a flanker task than lower-fit children. Higher-fit children also showed comparatively smaller error-related negativity amplitude in the congruent condition, with greater modulation between the congruent and incongruent conditions than their lower-fit peers, who demonstrated large error-related negativity amplitudes across both conditions. The authors suggested that lower-fit children had more difficulty in flexibly modulating cognitive control to meet task demands (Pontifex et al., 2011).

fMRI studies of fitness have recently been increasing in frequency in order to more accurately characterize the spatial location of fitness-related alterations in brain function. One of the first such studies in children (9 – 10 years old) compared high- and low-fit participants. Those with low fitness had a higher error rate on incongruent trials of a flanker task and more interference than their higher-fit peers. Even when lower- and higher-fit children were matched for performance, they still showed differences in brain activation, with the lower-fit children having higher activation compared to higher-fit children on incongruent compared to congruent trials in several regions, including left post-central gyrus, left insula, and left middle frontal gyrus. The authors suggested that lower-fit children may be less able to efficiently utilize cognitive control circuitry (Voss et al., 2011). It is important to note, however, that another study using a flanker task reported some activation differences that appear contradictory to the earlier study. Chaddock et al. investigated 9 – 10 year old children with high and low fitness on a flanker task which was divided into an early and late task block for analysis. This study focused on changes in performance over the two blocks of the task and reported that higher-fit children maintained accuracy across the task blocks but the lower-fit children decreased accuracy over the time between the early and late task blocks. This study found that higher-fit children showed decreased activation over time on incongruent trials in the left middle frontal gyrus, supplementary motor area, and left superior parietal lobule. Lower-fit children showed increased activation over time on both congruent and incongruent trials in the right middle frontal gyrus. Interestingly, this study showed some opposite patterns compared to the prior study, as children who were lower in fitness showed lower activation than children higher in fitness on incongruent trials compared to fixation (rather than the previously reported higher activation) in regions supporting flanker performance, including the bilateral middle frontal gyrus, supplementary motor area, anterior cingulate, and left superior parietal lobule (Chaddock, Erickson, et al., 2012). In sum, fitness in children has many cognitive parallels to fitness in adults. Children with higher fitness have shown higher cognitive performance than their lower-fit peers, as well as altered EEG amplitudes, faster P300 latency, and more flexible modulation of event-related brain potentials. fMRI studies, however, have shown conflicting patterns that have not yet been clarified.

Exercise Interventions and Brain Function During Task Performance

Exercise Interventions in Adults

While cross-sectional studies are informative, they clearly cannot determine whether fitness plays a causal role in altering brain function. Thus, exercise interventions are being conducted with increasing frequency to determine whether individuals who exercise show improved brain function and whether exercise-induced alterations parallel cross-sectional studies of high-fit versus low-fit participants. Young provided some of the first evidence demonstrating that an aerobic exercise intervention benefits cognition, finding that after a 10 week exercise program, adults ranging from 23 – 62 years old showed improved performance on several different cognitive tests including trail making, a measure of cognitive control (Young, 1979). In Young's study, there was no control group, however. Others have used study designs in which participants signed up autonomously for either aerobic exercise or control groups, showing that those who signed up for the exercise group showed improved performance after training in tasks involving inhibition and working memory (Stroth et al., 2010).

The strongest evidence that aerobic exercise leads to cognitive benefits can be found in randomized controlled trials in which participants are randomly assigned to either an aerobic exercise group or a control group. One of the first randomized exercise trials was conducted by Dustman et al., who reported that adults aged 55 – 70 years old assigned to an aerobic exercise group (1 hour/day, 3 days/week for four months) demonstrated more improvement on several cognitive measures (such as interference on the Stroop task) than those assigned to either a strength exercise group or a sedentary control group (Dustman et al., 1984). Later exercise interventions also have compared aerobic exercise training to other types of non-aerobic exercise (most commonly stretching and/or toning) as the control group. One study of older adults (65 – 78 years old) compared an aerobic exercise program to a stretching program (three times per week for 12 weeks). The adults in the aerobic training group showed a significantly decreased error rate on the Wisconsin Card Sorting Task compared to the stretching group, which showed increased errors, indicating that aerobic exercise enhances older adults' ability to flexibly shift between successive rules held in working memory (Albinet, Boucard, Bouquet, & Audiffren, 2010). Other trials comparing adults assigned to aerobic exercise training versus non-aerobic or non-exercise control groups have found that aerobic exercise improves relational memory (Griffin et al., 2011), task switching reaction times and accuracy (Hawkins, Kramer, & Capaldi, 1992), and Stroop performance (Smiley-Oyen, Lowry, Francois, Kohut, & Ekkekakis, 2008).

Many studies of exercise indicate that exercise benefits cognitive control, possibly to a greater extent than other types of cognition. Kramer et al. conducted one of the earlier studies that emphasized this possibility, in which previously sedentary older adults (60 – 75 years old) were randomly assigned to either aerobic (walking) or non-aerobic (stretching and toning) exercise. Those with aerobic training showed improved performance on the aspects of task-switching requiring cognitive control (they became faster at switching between tasks) but there was no difference between the groups in non-switch trials. In a flanker task, the aerobic training group decreased interference but there was no difference between groups on congruent trials. In a countermanding saccade task, the reaction time for stopping a planned eye movement was reduced for the aerobic compared to control subjects, but simple reaction time was the same for the two groups. The authors thus suggested that the beneficial effect of aerobic exercise was selective, in that it benefitted cognitive control more than other types of task performance (Kramer et al., 1999). This theory was supported by a later meta-analysis which demonstrated that the effects of fitness training were greatest for tasks involving cognitive control as compared to other types of tasks, such as visuospatial performance (Colcombe & Kramer, 2003).

While most studies focus on the cognitive benefits of aerobic exercise, sometimes using strength training as a control group, it should be mentioned that strength training alone may improve cognitive performance. Liu-Ambrose et al. compared women aged 65 to 75 years old who were assigned to a once-weekly or twice-weekly resistance training group or a twice-weekly balance and tone training group over one year. Both resistance training groups showed improved

Stroop interference compared to the balance and tone group, which deteriorated slightly (Liu-Ambrose et al., 2010). A later study by the same group reported alterations in flanker task performance and brain activation in the same participants. Only the twice-weekly resistance training group showed reduced flanker interference compared to the balance and tone group. The twice-weekly resistance training group showed increased percent signal change for incongruent compared to congruent trials in the left anterior insula, lateral orbitofrontal cortex, and middle temporal gyrus compared to the balance and tone group. The once-weekly resistance training group showed no task performance or brain activation differences compared to the balance and tone group. The authors suggested that the twice-weekly resistance training group might show more flexible use of resources to successfully inhibit incorrect responses in the flanker task (Liu-Ambrose, Nagamatsu, Voss, Khan, & Handy, 2012).

Few studies have used fMRI to investigate effects of aerobic exercise interventions. One previously mentioned study investigated fitness and exercise effects in older adults (averaging 67 years old) assigned to either an aerobic group or a stretching and toning control group for 40 – 45 minutes per day three times per week over 6 months. The results were very similar to those seen when high- and low-fit adults were compared cross-sectionally, with those in the aerobic group improving interference on the flanker task more and showing increased activation in middle and superior frontal gyri and superior parietal lobule (suggesting enhanced attentional control), but decreased activation in the anterior cingulate, perhaps indicating reduced conflict (Colcombe et al., 2004). Another study investigated how exercise alters neural correlates of spatial learning, based on evidence that exercise induces hippocampal neurogenesis in rodents that co-occurs with improved spatial learning. Adults (40 – 55 years old) were randomly assigned to aerobic training (cycling) or non-endurance training (stretching and coordination) 1 hour/day, 2 days/week for 6 months. They also were assigned to either spatial training or cognitive control training 40 minutes per session 1-2 sessions per week for the last month of the physical activity interventions. For participants in the spatial training group only, brain activation in the medial frontal gyrus and cuneus during a virtual maze task (in which participants were moved through a virtual town and instructed to infer the spatial layout of the environment) was correlated with increased fitness, indicating that exercise may benefit brain function during spatial learning (Holzschneider, Wolbers, Röder, & Hötting, 2012). In sum, exercise interventions in adults benefit cognitive performance (perhaps especially cognitive control) and alter brain activation during cognitive control and spatial learning.

Exercise Interventions in Youth

Recent research, motivated in part by increasing awareness and concern about the high rates of obesity and low fitness in children, has begun to focus on how exercise benefits cognition in children. One study assigned children aged 7 – 9 years old to either a nine-month exercise intervention for two hours per day or a sedentary control group. In the exercise group, more time spent above the target heart rate zone during the exercise intervention was associated with more improvement in the Stroop and Trails B tasks (Castelli, Hillman, Hirsch, Hirsch, & Drollette, 2011). A limitation of that report was that it only reported associations in the exercise condition without reference to the control group. A later report from the same exercise intervention did directly compare between groups. Those assigned to exercise showed improved working memory performance and increased initial contingent negative variation amplitude as measured by EEG (with the greatest change at the frontal site) compared to the control group, interpreted as more effective cognitive control (Kamijo et al., 2011). Our group previously conducted an intervention which randomized 171 sedentary, overweight children aged 7 – 11 years old to approximately 13 weeks of an exercise program (20 or 40 minutes per day) or a no-intervention control condition. At baseline, lower fitness and higher fatness were related to lower cognitive scores (the Planning and Attention scales of the Cognitive Assessment System), lower math and reading achievement, and worse teacher and parent ratings of behavior (Davis & Cooper, 2011). There was a dose-dependent effect of the exercise intervention, with more exercise benefitting math achievement and cognitive control (the Planning scale of the Cognitive Assessment System). In addition, 20 children participated in fMRI scans during an antisaccade task, which indicated that children who exercised increased prefrontal cortex activation and decreased posterior parietal cortex activation compared to children in the control group (Davis et al., 2011). In conclusion, two randomized controlled exercise interventions in children show that exercise benefits cognitive control task performance and alters brain activity.

Brain Function During Resting State

Converging evidence from many behavioral studies, as well as those using EEG and fMRI, indicates that obesity is associated with lower cognitive performance, while fitness and physical activity are associated with higher cognitive performance. One issue that has not been explored as thoroughly is whether obesity and fitness are associated with differences in a resting state, in which participants do not perform an explicit task. Even when there is no task, individuals exhibit similar resting state networks which can be evaluated. Several networks have been consistently identified in the literature, each of which consists of specific brain regions that spontaneously fluctuate together and are known to share cognitive functions in common. The correlation of these spontaneously fluctuating signals between brain regions is known as synchrony or functional connectivity. Synchrony within and between resting state networks can be compared between groups. Resting state synchrony is a useful measure especially in studies of children because participants are not required to comprehend and participate in a task. In addition, if differences are observed between groups, they cannot be attributed to differences in task performance. It does have relevance for task performance, however. Responses at both the voxel and individual participant level have been related to responses during a task (Kannurpatti, Rypma, & Biswal, 2012) and have been associated with reading competence and memory (Koyama et al., 2011; Tambini, Ketz, & Davachi, 2010).

Kullmann et al. compared the default mode network in overweight and obese subjects to lean subjects using fMRI (21 – 29 years old). The default mode network is the most-studied resting state network and is hypothesized to support self-referential processing (Kim, 2010), such as autobiographical memory retrieval (Buckner, Andrews-Hanna, & Schacter, 2008). This network generally consists of several distinct nodes: anterior cingulate cortex and medial prefrontal cortex, posterior cingulate cortex and precuneus, and bilateral inferior parietal regions. The obese group showed lower synchrony between the default mode network as a whole and the right anterior cingulate but higher synchrony between the default mode network and the precuneus. The authors suggested that obese individuals might show an imbalance between cognitive and emotional processing, as these regions may be involved in integration of cognitive and emotional stimuli (Greicius, Krasnow, Reiss, & Menon, 2003; Kullmann et al., 2012). Dubbelink et al. used magnetoencephalography (MEG) to conduct what may be the only such study with children or adolescents thus far, including female participants aged 12 – 19 years old. Obese participants had higher synchronization (averaged over all pairs of sensors) in delta and beta frequency bands compared to lean controls, which is a similar measure to resting state synchrony as used in fMRI studies and indicated that temporal interactions between brain regions were more interdependent. The authors suggested that this could reflect differences in motivational pathways, white matter, or metabolism (Dubbelink et al., 2008).

Resting state studies of fitness have only been reported in adults thus far. Dustman et al. used EEG to conduct one of the first studies of resting state and fitness, comparing older (50 – 62 year old) and younger (20 – 31 year old) men of low and high fitness. Older men with lower fitness had larger coupling values during resting EEG between electrodes along the midline (i.e., more homogeneity) compared to the other three groups (Dustman et al., 1990). Another study compared resting state EEG in adults averaging 32 years old who engage in regular intensive physical exercise (12+ hours/week) compared to control subjects (2+ hours/week). Power was less for the exercise group than the control group in the delta band, but greater in all other bands, possibly attributable to higher cerebral blood flow (Lardon & Polich, 1996).

Voss et al. conducted one of the first studies investigating the relationship between fitness and the resting state using fMRI. They investigated the default mode network in adults aged 55 – 80 years old, as aging has been associated with disruptions between nodes comprising the DMN. They selected regions which were sensitive to age-related disruption and reported that higher fitness was associated with higher synchrony between these regions (Voss, Erickson, et al., 2010). Another study by the same group assigned 55 – 80 year olds to an aerobic walking group or a stretching and toning control group three days per week for one year. Analyses were conducted for several resting state networks within ROIs that showed age-related disruption. The walking group showed increased within-network synchrony for both the default mode and frontal executive networks between aspects of frontal, posterior, and temporal cortices. They also reported an increased negative correlation between the right anterior prefrontal cortex in the frontal executive network and a region in the left hippocampus in the default mode network, suggesting that aerobic exercise training increased task-independent differentiation between executive and default mode networks, potentially allowing for greater regulation of interactions between the default mode and task networks (Voss, Prakash, et al., 2010). In sum, there is evidence that obesity and fitness are associated with differences in resting state networks, some of which may reflect differences in motivation, cognitive/emotional integration, or simply blood flow. Exercise may lead to greater intra-network but less inter-network synchrony in older adults.

White Matter Structure

Differences in white matter structure have been shown to underlie some (though certainly not all) differences in brain function (Gordon et al., 2011). Therefore, it can be useful to integrate functional and structural information to provide a more complete representation of whether altered brain function is related to brain structure. Diffusion tensor imaging (DTI) is an MRI technique that provides information about white matter integrity. One of the DTI measures most commonly used to describe white matter integrity is fractional anisotropy, which is a value between zero and one describing the anisotropy (i.e., the directional dependence) of water diffusion. A value of zero indicates that water can move equally in all three dimensions and a value of one means that water can move only along one dimension. As white matter becomes more coherent and myelinated, the movement of water is restricted in the direction perpendicular to the axons, meaning that it becomes more anisotropic. Thus, higher fractional anisotropy is thought to reflect greater coherence and myelination of white matter.

In adults (average age of 30 years old), BMI has been associated with worse white matter integrity (as indicated by lower fractional anisotropy) throughout the brain (Verstynen et al., 2012). Others have shown that obese adults (21 – 86 years old) had lower fractional anisotropy than those who were overweight or healthy weight in the fornix, genu, splenium, and body of the corpus callosum, while no fractional anisotropy differences were observed in the corpus callosum between those who were healthy weight and overweight (Stanek et al., 2011).

Fitness has been positively related to fractional anisotropy in the corpus callosum in adults aged 60 – 69 years old, primarily due to less radial diffusivity. Radial diffusivity is a DTI measure that is thought to reflect primarily myelination, with lower values indicating that myelination is higher. The portions of the corpus callosum associated with fitness primarily involved those interconnecting frontal regions associated with high-level motor planning (Johnson, Kim, Clasey, Bailey, & Gold, 2012). Higher fitness in adults also has been associated with fractional anisotropy in the cingulum and uncinate fasciculus, while higher waist size and BMI have been related to lower FA in the right posterior cingulum (Marks, Katz, Styner, & Smith, 2011; Marks et al., 2007).

In one of the first studies of how an exercise intervention affects white matter integrity, Voss et al. randomly assigned adults 55 – 80 years old to either an aerobic walking group or a flexibility, toning, and balance control group. Both were one year in duration and consisted of three 40-minute exercise sessions per week. Increased aerobic fitness was associated with increased prefrontal, parietal, and temporal FA in the aerobic group but changes in FA did not account for training-induced changes in cognitive performance (increased aerobic fitness was associated with increased backward digit span in the walking group) (Voss et al., In press). In sum, while no studies to date have investigated how obesity or fitness relates to white matter structure in children, studies in adults indicate that lower adiposity and higher fitness are related to higher white matter integrity as measured by fractional anisotropy in many different brain regions.

Remaining Issues to be Addressed

The vast majority of studies investigating the cognitive differences associated with fitness in children have been cross-sectional. There are many confounding factors associated with high body fat or low fitness, such as genetic predisposition or socioeconomic status. Thus, studies examining the causal role of exercise are necessary to more precisely delineate its cognitive benefits. The causal role of exercise can be investigated using a randomized, controlled trial, which is the methodology that the studies reported here utilize.

Exercise interventions comparing exercise to control groups in children thus far have only used sedentary, no-intervention control groups (Castelli et al., 2011; Davis et al., 2011). Therefore, the control groups have not controlled for non-exercise related components of these after-school programs that could influence children’s performance, such as social interaction with peers and adult supervision. The studies reported here are the first to use what we have termed an “attention control group.” The control intervention in these studies was as similar as possible to the aerobic exercise group on non-exercise related factors and was only different in that they participated in sedentary instructor-led activities (e.g., games or arts and crafts) rather than aerobic exercise. For instance, the groups were similar in that both were bused daily after school to the Georgia Prevention Center (where the exercise and control programs took place), both groups had the same instructors (who were rotated between groups on a regular basis), both had the same supervised daily homework time and snacks, and both groups were given rewards for desired behaviors.

This dissertation contains a series of three neuroimaging studies which were designed based on prior work by our group (Davis et al., 2012; Davis et al., 2011) and conducted with subsamples of participants in a larger exercise study. Participants in the intervention were sedentary, overweight (BMI $\geq 85^{th}$ percentile), and predominantly Black children 8 – 11 years old, randomly divided into either an aerobic exercise or attention control group, both of which were offered as after-school programs for approximately eight months. Chapter 2 is the largest study to date using fMRI during cognitive tasks to investigate how a randomized controlled exercise intervention alters brain activation in children. Participants (N = 43; 24 in the exercise group and 19 in the attention control group) performed two cognitive control tasks during fMRI before and after the intervention. The antisaccade task was performed as in the preceding study (Davis et al., 2011) to replicate and extend the earlier findings with a larger sample (43 versus 20 children), longer intervention (8 versus 3 months), and a more robust control group. We hypothesized that children assigned to exercise would show increased prefrontal cortex and decreased posterior parietal cortex activation compared to children in the control group. Participants also performed the flanker task, which is used frequently in neuroimaging studies of fitness and exercise. Cross-sectional fMRI studies of fitness in children have revealed inconsistent results; higher fitness has been associated with both higher and lower activation on this task (Chaddock, Erickson, et al., 2012; Voss et al., 2011). We hypothesized that children would show similarly altered circuitry on the flanker task compared to the antisaccade task.

Chapter 3 investigated whether an exercise intervention altered resting state synchrony in children. Children (N = 22; 13 in the exercise group and 9 in the attention control group) participated in a resting state fMRI scan before and after the intervention. Independent components analysis was then used to identify resting state networks in this group, four of which were selected for between group analyses. Specifically, we investigated the salience network (due to evidence implicating reward circuitry in obesity), the default mode network (which has been altered by exercise in older adults), the cognitive control network (as a great deal of evidence indicates that exercise affects cognitive control), and the motor network (because skilled motor training can affect resting state synchrony with motor regions). Based on the literature relating obesity and fitness to resting state synchrony, we hypothesized that children assigned to exercise would show altered resting state synchrony with all of these networks compared to children in the control group. Specifically, we hypothesized that children in the exercise group would show a greater distinction between and more refinement of these resting state networks.

Finally, Chapter 4 reports findings based on diffusion tensor imaging analysis. Eighteen children (10 in the exercise group and 8 in the attention control group) participated in diffusion tensor imaging scans before and after the intervention. Analyses were conducted to investigate whether white matter integrity in the superior longitudinal fasciculus (a tract involved in higher-order cognition) was affected by exercise. This tract was selected for analysis because it connects frontal and parietal regions (which demonstrated altered activation in the prior exercise study) and because it is involved in cognitive control, which showed an exercise-induced benefit in the prior study (Davis et al., 2011). Because lower adiposity and higher fitness have been related to higher fractional anisotropy in adults, we hypothesized that children assigned to exercise would show increased white matter integrity values compared to controls.

In sum, the following text reports three studies conducted with subsets of participants from a larger exercise study. To our knowledge, these studies were the first to control for many factors that have not been previously considered in exercise interventions with children (e.g., social interaction, attention from adults, and supervised homework time). The participants in these studies were also predominantly Black, which is a strength given that participants in the current exercise literature tend to be primarily or entirely Caucasian. Chapter 2 reports exercise-induced alterations in brain function on two cognitive control tasks during fMRI, with the goal of replicating and extending prior experimental findings and clarifying conflicting results from cross-sectional studies in the literature. Alterations in resting state synchrony and white matter structure as measured by diffusion tensor imaging are discussed in Chapters 3 and 4. While the sample sizes for Chapters 3 and 4 are relatively small in terms of neuroimaging investigations, these studies are valuable as the first resting state fMRI and diffusion tensor imaging investigations of exercise in children.

CHAPTER 2

AN EIGHT MONTH RANDOMIZED CONTROLLED EXERCISE TRIAL ALTERS BRAIN ACTIVATION DURING COGNITIVE TASKS IN OVERWEIGHT CHILDREN[1]

[1] Krafft, C.E., Schwarz, N.F., Chi, L., Weinberger, A.L., Schaeffer, D.J., Pierce, J.E., Rodrigue, A.L., Yanasak, N.E., Miller, P.H., Tomporowski, P.D., Davis, C.L. and McDowell, J.E. Accepted by *Obesity*.

Abstract

Objective: Children who are less fit reportedly have lower performance on tests of cognitive control and differences in brain function. This study examined the effect of an exercise intervention on brain function during two cognitive control tasks in overweight children.

Design and Methods: Participants included 43 unfit, overweight (BMI ≥ 85th percentile) children 8-11 years old, who were randomly divided into either an aerobic exercise (n=24) or attention control group (n=19). Each group was offered a separate instructor-led after-school program every school day for 8 months. Before and after the program, all children performed two cognitive control tasks during functional magnetic resonance imaging (fMRI): antisaccade and flanker.

Results: Compared to the control group, the exercise group decreased activation in several regions supporting antisaccade performance, including precentral gyrus and posterior parietal cortex, and increased activation in several regions supporting flanker performance, including anterior cingulate and superior frontal gyrus.

Conclusions: Exercise may differentially impact these two task conditions, or the paradigms in which cognitive control tasks were presented may be sensitive to distinct types of brain activation that show different effects of exercise. In sum, exercise appears to alter efficiency or flexible modulation of neural circuitry supporting cognitive control in overweight children.

Introduction

One third of school-age children in the U.S. are overweight or obese (Ogden et al., 2012). The increase in obesity has been concomitant with decreased fitness (Tomkinson & Olds, 2007), with potential implications for cognition and brain function. In some studies, lower-fit and overweight children show worse cognitive performance, including lower academic achievement and cognitive control (CC), than their fitter or leaner peers in several studies (Davis & Cooper, 2011; Taras & Potts-Datema, 2005), although others have shown no relationship (LeBlanc et al., 2012). In adults, it may be the case that fitness training benefits CC more than other types of cognition (Colcombe & Kramer, 2003).

CC reportedly varies between children of different fitness levels, an issue which may be optimally evaluated by functional magnetic resonance imaging (fMRI) studies. Existing neuroimaging investigations of fitness often use flanker tasks, which require response selection within the context of response-congruent or -incongruent information (Eriksen & Eriksen, 1974). In one cross-sectional study, activation was investigated during an incongruent vs. congruent condition of a flanker task in higher- and lower-fit children who were matched on performance (Voss et al., 2011). Higher-fit children showed lower activation in prefrontal cortex (PFC), anterior cingulate cortex (ACC), and superior parietal lobule (SPL), consistent with greater efficiency. Another study using the flanker task compared higher- and lower-fit children on performance and activation across time (Chaddock, Erickson, et al., 2012). Lower-fit children showed a decline in incongruent accuracy across task blocks. Higher-fit children maintained accuracy across task blocks and had higher PFC, ACC, and parietal activation early on in the incongruent condition with lower activation later (though activation did not decrease to below that of the lower-fit group). This pattern suggests improved adaptation of neural recruitment among the high-fit.

To determine whether exercise plays a causal role in altering brain function, randomized controlled trials are necessary. Randomized controlled trials using fMRI, however, are rare. In one of the few extant studies, older adults randomly assigned to an exercise group showed improved task performance and altered brain function compared to controls (Colcombe et al., 2004). The exercise group increased activation on a flanker incongruent vs. congruent condition in attentional regions (middle frontal gyrus [MFG], superior frontal gyrus [SFG], and SPL), but reduced activation in a region associated with conflict monitoring (ACC). Given the involvement of PFC and other regions that develop later in children, CC is potentially more responsive to intervention at a younger age (Luna, Velanova, & Geier, 2008). A recent study of 8- to 9-year-old children demonstrated that those assigned to physical activity for 9 months showed decreased brain activation in right anterior PFC compared to those in a waitlist control group on an incongruent flanker condition compared to fixation (Chaddock-Heyman et al., 2013). An earlier study by our group randomized 222 overweight children 7-11 years old to a three-month exercise intervention, which showed cognitive and fitness benefits (Davis et al., 2011). Twenty children provided fMRI data, with results showing that children assigned to exercise decreased posterior parietal cortex and increased PFC activation during an antisaccade task (a CC task) compared to controls.

In the current study it was hypothesized that exercise training would improve performance and alter brain activation in overweight children during CC task performance (antisaccade and flanker tasks). This study built upon our previous neuroimaging work by: (1) enhancing the sample size (*N*=20 to *N*=43), (2) extending the exercise intervention (3 months to

8 months), and (3) including a robust attention-control group rather than a no-intervention control condition. If exercise training affects the brain during childhood, when circuitry and performance are rapidly changing, developmental trajectories potentially could be altered with positive long-term consequences.

Material and Methods

Participants

Participants were recruited from public schools around Augusta, GA and were eligible if they were 8-11 years old, overweight (BMI ≥ 85th percentile (Ogden et al., 2002)), and inactive (no regular physical activity program ≥ 1 hr/week). Participants in the current imaging study (powered to detect differences between groups on change in brain activation) are a subsample of participants from a larger exercise intervention study. Exclusions included any medical condition that would limit physical activity or affect study results (including neurological or psychiatric disorders). Children and parents completed written informed assent and consent in accordance with the Human Assurance Committee of Georgia Regents University. Each child's parent or guardian reported the child's age, sex, race, and health status. Parents also reported their own educational attainment, which was used as an index of socioeconomic status (1 = grade 7 or less; 2 = grades 8-9; 3 = grades 10-11; 4 = high school graduate; 5 = partial college; 6 = college graduate; 7 = post-graduate). The schools from which study participants were drawn report 80% of their students were eligible for free or reduced cost school meals (SD = 14%), with a range of 51 – 98%. The study took place at the Georgia Prevention Center at Georgia Regents University.

FMRI data were collected for 54 children at baseline and 43 children at post-test. Of the 11 participants lost after baseline, 4 refused to participate before randomization, 5 dropped out after randomization (1 from the exercise group, 4 from the control group), 1 refused to participate in post-test MRI (from the control group), and 1 was ruled out based on a neurological anomaly observed in the MRI scan (from the control group). Twenty-five children in the exercise group provided fMRI data at baseline and 24 at post-test. Twenty-five children in the control group provided fMRI data at baseline and 19 at post-test. The 6 children who participated in at least a portion of the study but refused to provide post-test MRI data did not significantly differ from the participants who provided post-test data in any of the baseline characteristics (variables listed in Table 2.1), or in baseline activation in any of the clusters that were significant in the group analysis (listed in Table 2.3). Participants were included in analyses only if they had both baseline and post-test MRI data, resulting in a total of 43 participants (exercise group n=24, control group n=19). Characteristics of the sample are provided in Table 2.1.

Cognitive and Health Measures

The Cognitive Assessment System (CAS), a standardized individual assessment of children's cognitive processes, was administered (Naglieri & Das, 1997). The Full Scale score of the CAS takes into account the four scales (Planning, Attention, Simultaneous and Successive processing), each of which include 3 subtests. A number of health measures also were collected at baseline and post-test. Body fat was measured with a dual-energy x-ray absorptiometry (DXA) scan using a Hologic Discovery W (Hologic Inc., Bedford, MA). VO_2 peak was measured with an aerobic fitness treadmill test (Modified Balke Protocol for Poorly Fit Children (American College of Sports Medicine, 2000)). The test used a Cardiac Science TM65 treadmill (Cardiac Science, Waukesha, WI) with a ParvoMedics TrueOne 2400 Metabolic Measurement System (ParvoMedics, Sandy, UT) . The proportion of each group in each Fitness Zone was also obtained according to current Fitnessgram criteria for children 10 and older (Meredith & Welk, 2010).

Intervention

Participants were assigned randomly to one of two conditions: aerobic exercise or a sedentary attention control. Randomization (balanced by race, sex, and school to avoid imbalances on factors linked with differences in achievement) was performed by the study statistician after baseline testing was completed, at which point the study coordinator informed the families. Both groups were offered an after school program every school day for approximately 8 months (average number of days offered = 138, SD = 9). All participants were transported by bus daily after school to the Georgia Prevention Center where they spent half an hour on supervised homework time and were provided with a snack. Lead instructors were rotated between the two groups every two weeks and assistants were rotated between the two groups every week. Both groups could earn points that were redeemed for small prizes weekly for performing desired behaviors. The reward schedule was periodically calibrated to keep the rewards offered to the groups similar. Participants were at the Georgia Prevention Center for a total of approximately 90 minutes per day, which included their assigned program (exercise or control), homework time, and breaks (for water, changing clothes, etc.).

The groups differed in that they participated in either an aerobic exercise or an attention control program, each of which occurred for 40 minutes per day. The aerobic exercise group engaged in instructor-led aerobic activities (e.g., tag and jump rope). They wore heart rate monitors every day (S610i; Polar Electro, Oy, Finland) with which they could monitor their own performance and from which data were collected daily. Points in the exercise group were earned for an average daily heart rate above 140 beats per minute, with more points for higher average heart rates. Participants in the exercise group had an average heart rate of 161 beats per minute (SD = 9) at the intervention. The attention control group engaged in instructor-led sedentary activities (e.g., art and board games). Points in the control group were earned for participation and good behavior.

Data Collection and Analysis

MRI parameters. Images were acquired at Georgia Regents University on a GE Signa Excite HDx 3 Tesla MRI system (General Electric Medical Systems, Milwaukee, WI). For all MRI scans, head positions were stabilized with a vacuum pillow and/or foam padding. High-resolution T1-weighted structural brain images were acquired using a 3D FSPGR protocol (repetition time (TR) = 9.436 ms, echo time (TE) = 3.876 ms, flip angle = 20°, field of view (FOV) = 240 x 240 mm, acquisition matrix = 512 x 512, 120 contiguous axial slices, slice thickness = 1.3 mm, total scan time = 3 min, 33 sec). For functional scans, a single blocked antisaccade run (TR = 3000 ms, TE = 35 ms, flip angle = 90°, FOV = 240 x 240 mm, acquisition matrix = 128 x 128, 30 interleaved axial slices, slice thickness = 4 mm (skip 1 mm), 104 volumes) was always followed by 2 event-related flanker runs (each: TR = 2500 ms, TE = 35 ms, flip angle = 90°, FOV = 240 x 240 mm, acquisition matrix = 128 x 128, 30 interleaved axial slices, slice thickness = 4 mm (skip 1 mm), 168 volumes per run). For each functional run, 4 volumes were acquired and discarded before stimulus presentation began to allow for scanner stabilization. Each functional run was collected obliquely, with the slices aligned to the superior margin of the participant's anterior commissure and the inferior margin of the posterior commissure.

Antisaccade task. Antisaccade tasks require inhibition of a glance to a newly appearing cue and redirection of gaze to its mirror image (Hallett, 1978; Luna et al., 2008). This task was presented in a blocked design alternating between fixation and antisaccade blocks. A blocked design was selected for the antisaccade task in order to replicate our previous study and to achieve greater detection power than might be available with an event-related design (Amaro & Barker, 2006). During each of 7 fixation blocks, participants were asked to look at a cue consisting of a blue filled circle that appeared at central fixation for 24 seconds. During each of 6 antisaccade blocks, 8 trials were presented (3 seconds each for 24 second blocks and a total of 48 total trials across the run). An antisaccade trial began with a blue filled circle (the same cue as for a fixation trial) at central fixation for 1600 ms. Then fixation was extinguished and the cue was presented in the periphery ($\pm 10^{o}$ of visual angle on the horizontal plane; half of trials in each visual field) for 1400 ms (see Figure 2.1). Participants were instructed to look at the cue when it was in the middle of the screen, but when it appeared at a peripheral location, to look to the mirror image (opposite side of the screen, the same distance from the center). Before entering the scanner, flash cards were used to explain the task and to have participants demonstrate their understanding.

Stimuli were constructed using Presentation software (Neurobehavioral Systems, Inc., Albany, CA) and presented using a dual mirror system that both displayed visual stimuli on a rear projection screen and projected an image of the participant’s eye to an infrared camera. The infrared camera was part of an MRI-compatible system (IView X MRI-LR, SensoMotoric Instruments, Inc., Berlin, Germany) that showed eye position in real time and recorded it for further analysis. Prior to the antisaccade task, eye position was calibrated.

Individual antisaccade trials were scored as a correct or an error response based on eye direction relative to target direction, with corrections to errors also quantified. Latencies for the correct, error and error correction responses (with error correction responses being those in which the initial glance was toward the cue but was then corrected to the mirror image location) were generated using Matlab (The Mathworks Inc., Natick, MA) and procedures that have been previously (Dyckman, Camchong, Clementz, & McDowell, 2007). Trials were eliminated from performance analysis if the latency was faster than 90 ms, if the eye movement was less than 10% of the distance to the target, if there was a blink before the saccade, if there was no response, or if the data were too noisy to be scored.

FMRI data were acquired during antisaccade performance from 43 participants who had data available at both baseline and post-test. One participant was excluded for excessive motion (> 2 mm shift in x, y, or z directions), resulting in 42 complete datasets for this task (*n*=24 exercise, *n*=18 control). Of this group, eye movements were recorded for 93% of participants at baseline and 95% at post-test (failure to do so was because of technical difficulties, such as insufficient contrast between the pupil and iris or eyelashes rather than participant non-compliance).

Flanker task. Flanker tasks require response selection within the context of response-congruent and -incongruent information (Colcombe et al., 2004; Eriksen & Eriksen, 1974). This task was presented in an event-related design due in part to context effects that have been reported showing decreased activation in several brain regions (including ACC, PFC, and parietal cortex) as the number of preceding incongruent trials increased (Durston et al., 2003). As such, a blocked design (in which incongruent trials would happen consecutively) might not achieve maximum statistical power. In addition, an event-related design is similar to a previous flanker study in children (Chaddock, Erickson, et al., 2012). The flanker task contained fixation trials (60 trials per run, 120 total trials) and two types of trials: congruent and incongruent (40 trials of each type per run, 80 total trials of each type). During fixation trials, participants were asked to look at a cross that appeared at central fixation for 3 seconds. During flanker trials, a cross was presented at central fixation to start the trial. After 500 ms, the cross was extinguished, and an array of five symbols was presented for 2500 ms, in which each of the symbols pointed either right (>) or left (<). Symbols could be arrayed in either a congruent fashion, in which all of the symbols were oriented in the same direction, or in an incongruent fashion, in which the flanking symbols pointed in the opposite direction of the central symbol (see Figure 2.1). Participants were instructed to identify the orientation of the central symbol while ignoring the orientation of the flanking symbols, and they indicated their response by pressing a button with the corresponding hand. Before entering the scanner, flash cards were used to explain the task and to have participants demonstrate their understanding.

Stimuli were constructed using Presentation software (Neurobehavioral Systems, Inc., Albany, CA) and presented using a dual mirror system that both displayed visual stimuli on a rear projection screen and projected an image of the participant's eye to an infrared camera (see antisaccade task description). In the flanker task, the image of the participant's eye was observed to ensure that the participant was alert and attending to the stimuli. The response to the visual stimuli was a button press of either the right or left index finger, which was recorded using MRI-compatible button pads (Lumina system, Cedrus Corporation, San Pedro, CA).

Individual trials were scored as correct or error based on hand of button press relative to indicated target direction. Latencies for correct and error responses were also quantified. Measures were calculated separately for congruent and incongruent trials using SAS (SAS Institute, Inc., Cary, NC). Each individual's interference effect was also calculated similarly to previous studies of exercise: [(average incongruent correct latency – average congruent correct latency) / average congruent correct latency] * 100 (Voss et al., 2011). Trials were eliminated from performance analysis if the latency was faster than 100 ms, if there was a response during the fixation period, or if there was no response.

FMRI data were acquired during flanker task performance from 42 participants who had data available at both baseline and post-test (one fewer than the antisaccade task due to scanner malfunction on a flanker run). Two participants were excluded for excessive motion (> 2 mm shift in x, y, or z directions), resulting in 40 complete datasets for this task (*n*=23 exercise, *n*=17 control). Of the number analyzed, button responses were recorded for 98% of participants at both baseline and post-test (failure to do so was because of technical difficulties rather than participant non-compliance).

Performance data analysis. Analysis of task performance variables of interest was conducted in SPSS Version 20 (IBM, Armonk, NY). Between-group differences at baseline were investigated using independent samples *t*-tests. Repeated measures ANOVAs with a test of group by time interaction on task performance were used to investigate whether the groups significantly differed in how they changed over time. Performance variables that were analyzed are listed in Table 2.2.

MRI data analysis. FMRI analyses were conducted as in previously published data from our laboratory (Davis et al., 2011) using Analysis of Functional Neuroimages (AFNI version 2011_12_21_1014 (Cox, 1996)). For each functional run, volumes were despiked, slice time corrected, and registered to a representative volume to correct for head movement. The representative volume was identified by the following criteria: the median volume of the longest window of time points with the lowest number of outlier voxels. Each run was then aligned to each individual’s T1-weighted structural MR image, transformed into a standardized space based on a publicly available template created for 7-11 year olds in MNI space (Fonov et al., 2011), and resampled to 4 x 4 x 4 mm voxels. A 4 mm full-width at half-maximum (FWHM) Gaussian filter was applied to each functional dataset and data were normalized to a mean of 100.

Following preprocessing, hemodynamic response function (HRF)-convolved stimulus timing was entered into a general linear model analysis, along with three nuisance motion regressors (rotation in each plane: x, y and z) and nuisance regressors detrending for linear, quadratic, and cubic drift. At this point the two flanker runs were concatenated in time during the regression analysis resulting in one flanker dataset per person. The HRF for each of the flanker and the antisaccade functional datasets was represented by the convolution of the stimulus duration and a gamma variate. For the antisaccade task, the contrast of interest was the antisaccade blocks vs. fixation. For the flanker task, there were 3 contrasts of interest: congruent trials vs. fixation, incongruent trials vs. fixation, and incongruent vs. congruent trials.

A two-way group (exercise, control) by time (baseline, post-test) ANOVA was performed on the datasets to compare activation changes between the two groups and results at $p < .025$ are reported. To protect against false positives, a threshold/cluster method derived from Monte Carlo simulations (accounting for the smoothness of the data and with a connectivity radius of 4 mm) was applied to the F-map (Ward, 1997). Based on these simulations, a family-wise alpha of 0.05 was preserved with three-dimensional clusters having a minimum volume of 35 voxels for the antisaccade task and 37 voxels for the flanker task. The resulting clustered F-maps were used to identify significant group by time interactions. Because between-group differences in brain activation were evident at pre-test, supplementary analyses were conducted for each cluster that showed a significant group by time interaction. Post-test between group t-tests were conducted. In addition, group by time ANOVAs were conducted for each cluster that showed a significant group by time interaction while controlling for pre-test activation. This was done in order to investigate whether group by time differences remained significant regardless of between-group differences at pre-test. Both left- and right-handed children were included in analyses to maximize generalizability. Sensitivity analyses compared results excluding the left-handed children. Correlation analyses were conducted between attendance and change in brain activation for the exercise and control groups separately.

Correlations of brain activation with health, cognition, and task performance. We conducted exploratory correlation analyses of change over time in task performance, CAS Full Scale score, and health variables versus change over time in brain activation. First, change scores were calculated for each performance, cognitive, and health variable and for percent signal change in each reported fMRI cluster for each individual. Next, for every variable, correlations were conducted across groups to investigate whether there was a relationship between the change in the variable of interest and the change in activation in each cluster.

Results

Health and Task Performance Results

The groups did not significantly differ at baseline on any of the characteristics listed in Table 2.1. No group by time interactions were found in adiposity, fitness, or cognition in this subset of participants in the trial (data not shown). In performance measures, the exercise and control groups differed at baseline on antisaccade error latency (the exercise group had slower latency, $t(37) = -2.755$, $p = .009$) and on flanker congruent correct latency (the exercise group had slower latency, $t(37) = -2.109$, $p = .042$). Controlling for either of these variables did not alter any of the results in this study. There were no significant group by time interactions in any of these variables (see Table 2.2).

The groups did significantly differ in the percentage of days attended at the program out of the number of days offered, $t(41) = 2.25$, $p = 0.03$. The control group attended 75% of days offered (standard deviation = 20%). The exercise group attended 58% of days offered (standard deviation = 29%). There were no significant correlations between percentage of days attended and change in activation over time in any of the fMRI clusters reported in either the control or exercise group.

Antisaccade Imaging Results

The antisaccade vs. fixation contrast was examined. Saccadic circuitry includes regions that are important for visual perception, visuo-spatial attention, inhibitory control, and generation of a saccade to a spatial location (Ettinger et al., 2008; McDowell, Dyckman, Austin, & Clementz, 2008). Collapsing across all participants, activation in typical saccadic circuitry was observed at baseline (see Figure 2.2; see also (Davis et al., 2011)). Results from the whole-brain group (exercise, control) by time (baseline, post-test) ANOVA revealed that the following regions showed a significant group by time interaction: bilateral precentral gyrus, medial frontal gyrus, paracentral lobule, postcentral gyrus, superior parietal lobule (SPL), inferior parietal lobule (IPL), and anterior cingulate cortex (ACC); right inferior frontal gyrus (IFG) and insula; and left precuneus. In all of these regions, the exercise group showed a pattern of decreasing activation over time, while the control group showed the opposite pattern, increasing activation over time. All of these regions showed significant between-group differences at post-test, and all group by time interactions remained significant when controlling for pre-test activation. These results remained significant when left-handed children were excluded for a sensitivity analysis. For further details, see Table 2.3 and Figure 2.3.

Flanker Imaging Results

Three contrasts were examined: (1) congruent vs. fixation, (2) incongruent vs. fixation, and (3) incongruent vs. congruent. Flanker circuitry includes regions important for visual perception, visuo-spatial attention, conflict monitoring, and motor responses (Casey et al., 2000; Hazeltine, Poldrack, & Gabrieli, 2000). Collapsing across all participants, activation in typical flanker circuitry was observed at baseline (see Figure 2.4 for an example of incongruent vs. fixation activation). Results for congruent vs. fixation from the whole-brain group (exercise, control) by time (baseline, post-test) ANOVA revealed no significant group by time interactions. The ANOVA for the incongruent vs. fixation contrast revealed a significant group by time interaction for the following regions: left medial frontal gyrus, superior frontal gyrus (SFG), middle frontal gyrus (MFG), superior temporal gyrus (STG), cingulate gyrus, and insula. In all regions in this contrast, the exercise group showed increased activation over time, while the control group showed decreased activation. The cluster including left STG and insula, but not the cluster including medial frontal gyrus, SFG, MFG, and cingulate gyrus, showed significant between-group differences at post-test and its group by time interaction remained significant when controlling for pre-test activation. All results remained significant when left-handed children were excluded for a sensitivity analysis.

The ANOVA for the incongruent vs. congruent contrast revealed a significant group by time interaction for the following regions: bilateral SFG, medial frontal gyrus, MFG, cingulate gyrus, and anterior cingulate cortex (ACC); and left IFG and insula. In all regions in this contrast, the exercise group showed increased activation over time, while the control group showed decreased activation. None of these regions, however, showed significant between-group differences at post-test and none of these group by time interactions remained significant when controlling for pre-test activation. All results remained significant when left-handed children were excluded for a sensitivity analysis. For further details, see Table 2.3 and Figure 2.5.

Correlations of Brain Activation with Health, Cognition, and Task Performance

There were no significant correlations between change in health variables (percent body fat or VO_2 peak) and change in brain activation. There also were no significant correlations between change in Cognitive Assessment System Full Scale SS and change in brain activation. The only significant correlation between antisaccade activation and task performance was that a decrease in activation in the right superior parietal lobule was correlated with faster error latencies ($r(37) = .33$, $p = .04$). For the incongruent vs. fixation or the incongruent versus congruent contrasts of the flanker task, there were no correlations between performance and activation.

Discussion

Overweight, unfit children randomly assigned to an 8-month exercise intervention showed significantly different changes in brain activation within the context of two separate CC tasks compared to children in the attention control condition, which apart from being sedentary, was very similar to the exercise intervention. Both groups showed improved task performance on antisaccade and flanker tasks, possibly due to common factors, such as maturation, education, practice, or benefits of the after school programs. No group by time interactions were detected in task performance, perhaps because the exercise and attention control conditions were more similar than in prior studies. Importantly, group differences in brain changes were seen even in the absence of performance differences. From baseline to post-test, the exercise group decreased activation during the antisaccade task and increased activation during the incongruent aspect of the flanker task compared to the control group. While the groups differed in attendance, it is unlikely that the difference in attendance between the groups explained differences in brain function, as attendance did not correlate with change in brain activation. These results indicate that functional neuroimaging may be more sensitive than performance measures to exercise-induced changes, and that the groups might differ in task strategies used, given activation differences despite similar task performance.

Decreased activation during the antisaccade task for the exercise group was found in several regions known to support antisaccade performance, including inferior frontal gyrus (IFG) and anterior cingulate cortex (ACC). Specifically, IFG has been implicated in attention and inhibition (Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010), while ACC is likely important for error monitoring (Ford, Goltz, Brown, & Everling, 2005). Within the parietal lobe, exercise-related decreases were seen in superior and inferior regions, which are involved in visuo-spatial processing, attentional shifting and target selection (Ettinger et al., 2008; Krafft et al., 2012). The right insula also was affected by exercise; its role in saccadic performance is less well-understood but it may be important for task-set maintenance and salience detection (Dosenbach et al., 2006). Alterations also were found in two motor regions which support saccade preparation and generation (Brown, Vilis, & Everling, 2007; Connolly, Goodale, Menon, & Munoz, 2002): (1) bilateral precentral gyrus and (2) medial frontal gyrus and paracentral lobule.

The antisaccade results partly replicate our previous exercise intervention, in which children assigned to the exercise condition decreased activation on an antisaccade task in posterior parietal regions compared to those in a no-intervention control condition (Davis et al., 2011). The results from the earlier study showing increased prefrontal cortex (PFC) activation in an antisaccade task in children assigned to exercise, not seen here. It is possible that effects observed after three months of an exercise intervention may no longer exist after eight months. Perhaps exercise initially increases PFC activation, which then decreases as antisaccade circuitry becomes more efficient.

There is precedent for decreased antisaccade activation in least one study in adults in which intensive daily antisaccade practice decreased activation on a blocked-design antisaccade task, possibly reflecting learning or improved efficiency (Lee et al., In press). Decreased sustained (i.e., blocked-design) activation in a CC task with exercise also is consistent with a cross-sectional study that reported that children who were more fit had lower activation in several brain regions on the incongruent vs. congruent condition of a blocked-design flanker task. Although it was a different task (flanker rather than antisaccade), the previous study nevertheless showed that higher-fit children had lower activation than lower-fit children in several regions that were found in the current study with a blocked-design antisaccade task (including precentral gyrus, ACC, and superior parietal lobule (Voss et al., 2011)). Decreased activation patterns may reflect more efficient CC. Another possible explanation is that the decrease in activation may reflect a shift in from reactive control (more transient, occurring after an event) to proactive control (which involves actively maintaining goal-related information in working memory such that the system can respond to subsequent events) in the exercise group (Braver, Barch, Gray, Molfese, & Snyder, 2001). This was not a distinction that we were able to make with our current data, however.

For the flanker task, activation increased in the exercise group compared to the control group. For both the incongruent vs. fixation and incongruent vs. congruent contrasts, the exercise group showed increases in regions supporting CC, including superior frontal, medial frontal, middle frontal, and cingulate gyri, although these interactions did not survive adjustment for pre-test activation. These regions are associated with working memory and spatial attention (Kirschen, Chen, Schraedley-Desmond, & Desmond, 2005). Increased activation was observed in other regions supporting higher-order functions such as the insula, which has been associated with salience detection, as well as successful interference suppression in children (Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002). The interaction in the insula survived adjustment for pre-test activation in the incongruent vs. fixation contrast. In the incongruent vs. congruent contrast alone, the exercise group showed increased bilateral ACC activation, which is important for processing increased conflict in incongruent vs. congruent trials (Luks, Simpson, Dale, & Hough, 2007). Increased activation in the ACC did not survive adjustment for pre-test activation. For the incongruent vs. fixation contrast alone, the exercise group showed an increase in left superior temporal gyrus, which is involved in target detection (Braver et al., 2001) and which did survive adjustment for pre-test activation. In both contrasts, the differences in activation appear to be more extensive in the left hemisphere than in the right hemisphere. This is consistent with Bunge, et al. (2002), who demonstrated that children who perform better than others recruit left prefrontal cortex more extensively and suggested that this could be related to use of a verbal strategy during performance in this task. That is, the exercise group may be utilizing their verbal abilities to perform this task (re-coding nonverbal stimuli with verbal labels), resulting in greater recruitment in the left hemisphere.

The flanker results are consistent with previous exercise literature but frontal regions, especially, should be interpreted with caution due to the fact that they are influenced by pre-test differences. We did not observe differences in the congruent vs. fixation contrast, as expected, lending support to previous evidence that CC may be more susceptible to exercise-induced benefits than other aspects of cognition, such as more basic perceptual or motor tasks (Colcombe

& Kramer, 2003). Since both groups exhibited relatively low congruent error rate at baseline, the congruent vs. fixation contrast may be too simple to reveal an exercise effect.

Both the incongruent vs. fixation and incongruent vs. congruent contrasts demonstrated increased middle and superior frontal gyrus activation in the exercise group compared to the control group in our study. This is consistent with an exercise intervention in older adults in which participants increased activation on a flanker task in those regions (Colcombe et al., 2004). The incongruent vs. congruent contrast in our study showed increased ACC activation in the exercise group compared to the control group, which is the opposite of decreased ACC activation demonstrated in an exercise intervention in older adults. Divergent results between these two studies may be related to differing effects of exercise with age. Alternately, they may underlie between-study differences in interference measures, as interference decreased in the exercise group in the study of older adults but did not differentially change between groups in our study. Increased ACC activity, as reported in our results, however, also is reported by at least one cross-sectional study showing that higher-fit children have higher middle frontal gyrus and ACC activation on an event-related flanker task (Chaddock, Erickson, et al., 2012).

A recent intervention study in 8- to 9-year-old children found different effects compared to our study, with a region-of-interest analysis showing that those assigned to an exercise program for 9 months compared to a waitlist control condition showed decreased activation in incongruent flanker trials compared to fixation (Chaddock-Heyman et al., 2013). One reason why these studies demonstrate differing effects of exercise may be due to the differing samples of children included in the studies. The children in our study are older, predominantly Black, have lower VO_2 and higher BMI, lower cognitive scores (when CAS Full Scale score is compared to IQ reported by Chaddock, et al.) and have slower flanker reaction times. It also is possible that differences in task design between the two studies may contribute to differences in observed effects of exercise (as the flanker task in our study, unlike the study by Chaddock, et al., did not occur within the context of no-go trials).

Interestingly, the antisaccade and flanker tasks demonstrated activation changes with exercise that occurred in opposing directions. This could be related to differing cognitive demands in the two tasks. The group by time brain activation results from the flanker and antisaccade tasks did not spatially overlap, indicating that although they utilize some common cognitive processes, their circuitries (and/or the effects of exercise upon them) may be distinct. Another possible explanation for this difference is inherent in the paradigm designs. The antisaccade task was blocked and the flanker task was event-related. Because a blocked-design is more sensitive to sustained activation and an event-related design is more sensitive to transient activation, it is possible that sustained and transient neural activation are differentially affected by exercise. Sustained activation is maintained throughout performance of a task, whereas transient activation includes processing specifically involved in each trial of a task (Visscher et al., 2003). There is evidence that these types of activation show different developmental patterns. For example, in a study using a letter-matching task, the right lateral inferior frontal gyrus exhibited greater sustained activity in children than adults, but greater transient activity in adults than in children (Burgund, Lugar, Miezin, Schlaggar, & Petersen, 2006).

Experimental support for differing effects of exercise on sustained and transient brain activation patterns comes from two previous cross-sectional studies of exercise conducted in children. Both were versions of a flanker task, with one a blocked-design and the other an event-related design. The blocked-design task showed that higher-fit children had lower activation than lower-fit children on the incongruent compared to congruent condition of a flanker task (Voss et al., 2011). The event-related task found a different pattern, with higher-fit children having higher activation than lower-fit children on the incongruent compared to congruent condition, at least early in the task (Chaddock, Erickson, et al., 2012). In the current study, there is only one modest correlation between change in activation and change in performance, and there were no group by time differences in task performance on either task. Therefore, it may be that changes in activation primarily reflect differences in task strategy between the groups, rather than differences in task performance abilities. Decreased sustained activation in the exercise group could be related to greater efficiency in task set maintenance or performance (Lee et al., In press), while increased transient activation could be related to more flexible modulation of CC processes (Chaddock, Erickson, et al., 2012).

This study provided novel causal evidence for the effects of regular aerobic exercise on neural circuitry in overweight children and is one of the first to demonstrate that exercise alters brain function on two different cognitive tasks in the same sample. Through the use of a robust attention control group, we controlled for potentially beneficial common factors that derive purely from participating in an after school program, such as attention from adults, social interaction, and supervised homework time. Use of a randomized trial with an attention control condition allowed precise delineation of alterations in neural circuitry activation patterns due specifically to exercise. The sample was overweight, unfit and predominantly Black, an understudied population at risk for adverse health and educational outcomes. An additional strength of this study as compared to previous fMRI investigations of exercise interventions by both our group and others is the much larger sample size, with a total of 23 additional children compared to our prior study (Davis et al., 2011) and 20 additional children compared to a recent 9-month intervention (Chaddock-Heyman et al., 2013). Because the groups in the current study did not differ in the change in aerobic fitness or adiposity over the course of the intervention, and change in fitness or adiposity did not correlate with change in brain activation, it is not clear whether the differences observed in brain function were caused by increased fitness or decreased body fat in the exercise group as compared to the control group. The imaging study was a subsample of a larger exercise study powered for such health outcomes.

Future work is needed to determine whether transient and sustained neural activation patterns consistently show differential effects of exercise. It should also investigate whether exercise promotes the development of different task strategies (e.g., proactive versus reactive, or verbal strategies). Some of the differences in activation during the flanker task, while expected given previous literature, were related to group differences at pre-test and thus would especially benefit from replication. Another topic of study should be whether children who are at different developmental stages or who are not overweight demonstrate changes in brain function similar to those reported here. Many promising hypotheses from cross-sectional studies have not been borne out by randomized trials, the most reliable evidence for causality (Davis & Cooper, 2011). It is not clear whether high adiposity and low fitness are associated with different cognitive profiles, or whether an exercise intervention would provide greater cognitive benefits to fatter or more unfit children than their healthier peers. While the groups did not differentially change task performance over time, there may be vulnerable subgroups (e.g., children with developmental disabilities) that show greater performance improvements from exercise.

The current study provides strong new evidence that exercise causes alterations in neural circuitry supporting CC in overweight children. Specifically, children assigned to an aerobic exercise group demonstrated decreased activation in several brain regions on an antisaccade task compared to the control group, possibly reflecting increased efficiency. They also demonstrated increased activation in both the incongruent versus fixation and incongruent versus congruent contrasts of a flanker task compared to the control group, possibly reflecting greater flexible modulation of CC. The opposite patterns of exercise-induced change in brain activation for the two tasks may relate to the different cognitive demands of the two tasks. Another possibility is that opposite patterns of exercise-induced change are related to the task design, as the antisaccade was presented in a blocked design and the flanker task was presented in an event-related design. These designs are more sensitive to sustained versus transient activation, respectively, suggesting that exercise may differentially affect these two types of brain activation. Because there were no group by time differences in task performance and correlations between brain activation and task performance were minimal, it may be that differences in brain activation induced by exercise reflect differences in task strategy, rather than in task performance abilities. While the current study cannot specify which strategies may be altered, possibilities include a shift to verbal strategies supporting nonverbal task performance, or a shift from reactive to proactive control. Changes in these brain functions may have wide-ranging consequences, as CC is associated with other cognitive domains, such as school performance and social functioning (Best, Miller, & Jones, 2009). If exercise improves brain function supporting CC, children could see benefits in many aspects of daily life.

Table 2.1. Baseline characteristics of participants. Mean (SD), or percent.

	Exercise	**Control**
n	24	19
Age (years)	9.7 (0.8)	9.9 (0.9)
Female	71%	58%
Black	92%	90%
Left-handed	4%	16%
Parental education scale	5.0 (1.1)	4.7 (1.2)
Cognitive Assessment System Full Scale Standard Score	94.0 (6.8)	93.2 (12.0)
BMI z-score	1.91 (0.42)	1.93 (0.57)
Overweight	17%	42%
Obese	83%	58%
Body fat	36.9% (6.6)	35.3% (7.7)
VO_2 peak (ml/kg/min)	27.5 (4.6)	28.7 (4.9)
Needs Improvement %	4%	0%
Needs Improvement – Health Risk %	96%	100%

Table 2.2. Performance results of participants included in the fMRI analyses. Mean and SD. Change scores for variables of interest were calculated by subtracting each individual's baseline value from their post-test value. *Significant baseline difference between groups, $p < .05$. **Significant change over time, $p < .05$.

Task	**Variable**	**Baseline**		**Post-test**		**Change (post-test – baseline)**	
		Exercise	*Control*	*Exercise*	*Control*	*Exercise*	*Control*
Antisaccade	*n*	22	17	23	17	21	16
	Percent correct	56 (26)	53 (20)	67 (21)	63 (24)	10 (24)**	10 (13)**
	Correct latency (ms)	461 (80)	425 (110)	480 (91)	438 (92)	11 (90)	11 (159)
	Error latency (ms)	398 (87)*	326 (73)*	370 (106)	359 (83)	-9 (111)	22 (80)
	Percent of errors corrected	76 (20)	65 (27)	69 (33)	69 (29)	-11 (38)	5 (37)
	Error correction latency (ms)	332 (88)	292 (66)	315 (100)	345 (113)	-12 (114)	43 (102)
Flanker	*n*	22	17	22	17	21	17
	Congruent	86 (26)	92 (23)	97 (4)	98 (2)	10 (24)**	6 (22)**

percent correct						
Congruent correct latency (ms)	1122 (224)*	998 (106)*	1024 (158)	1010 (172)	-71 (171)	12 (166)
Incongruent percent correct	73 (35)	88 (21)	85 (26)	89 (25)	9 (33)	0 (35)
Incongruent correct latency (ms)	1278 (292)	1191 (175)	1171 (220)	1143 (194)	-52 (223)	-48 (197)
Interference effect	14 (18)	20 (15)	14 (13)	14 (11)	1 (17)	-6 (14)

Table 2.3. FMRI results: significant clusters in the whole-brain group by time interaction analyses. R = right hemisphere and L = left hemisphere. MNI = Montreal Neurological Institute. ACC = anterior cingulate cortex. IFG = inferior frontal gyrus. SPL = superior parietal lobule. IPL = inferior parietal lobule. SFG = superior frontal gyrus. MFG = middle frontal gyrus.

Anatomical location	**Center of mass (x,y,z in MNI coordinates)**	**Volume (voxels)**	**Direction**
Antisaccade			
1. Bilateral ACC, extending into R medial frontal gyrus	-10.9, -44.4, -1.9	81	Ex < C
2. R precentral gyrus, extending into R IFG, postcentral gyrus, SPL, IPL, and insula	-57.5, 1.5, 22.5	91	Ex < C
3. L precentral gyrus, extending into L postcentral gyrus	59.8, 5.3, 27.3	51	Ex < C
4. R postcentral gyrus, extending into R precentral gyrus, IFG, IPL, and insula	-47.8, 23.4, 46.3	62	Ex < C
5. R SPL	-32.7, 50.8, 68.0	35	Ex < C
6. L precentral gyrus, extending into bilateral medial frontal gyrus and paracentral lobule and L postcentral gyrus, SPL, precuneus, and IPL	20.4, 27.9, 69.5	418	Ex < C
Incongruent vs. fixation			
7. L superior temporal gyrus, extending into L insula	57.5, 4.2, -3.4	55	Ex > C
8. L medial frontal gyrus, extending into L SFG, MFG, and cingulate gyrus	21.6, -33.9, 30.6	153	Ex > C

Incongruent vs. congruent			
9. R ACC, extending into R SFG, MFG, cingulate gyrus, and medial frontal gyrus	-23.5, -29.5, 26.1	86	Ex > C
10. L MFG, extending into L SFG, medial frontal gyrus, IFG, insula, cingulate gyrus, and ACC	26, -19.7, 27.7	225	Ex > C

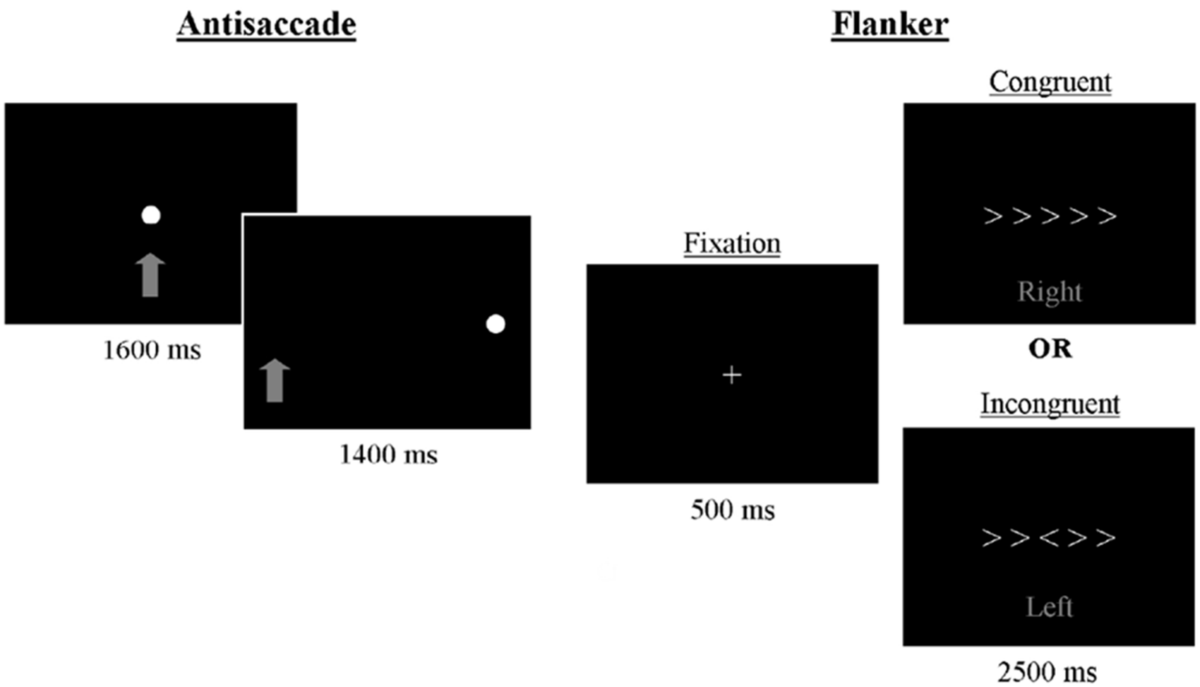

Figure 2.1. Antisaccade and flanker trials. In the antisaccade task, the participant was instructed to fixate on the cue when it was in the middle of the screen. When the cue appeared at a peripheral location, the participant was to look to the mirror image location (opposite side of the screen, the same distance from center). The arrow did not appear on the screen; in this figure it is used to indicate the correct eye position. In the flanker task, the participant was instructed to fixate on the cross. When the symbols appeared, the participant was to identify the direction of

the central symbol and pressed a button with the corresponding hand. The text did not appear on the screen; in this figure, text indicates the correct response hand.

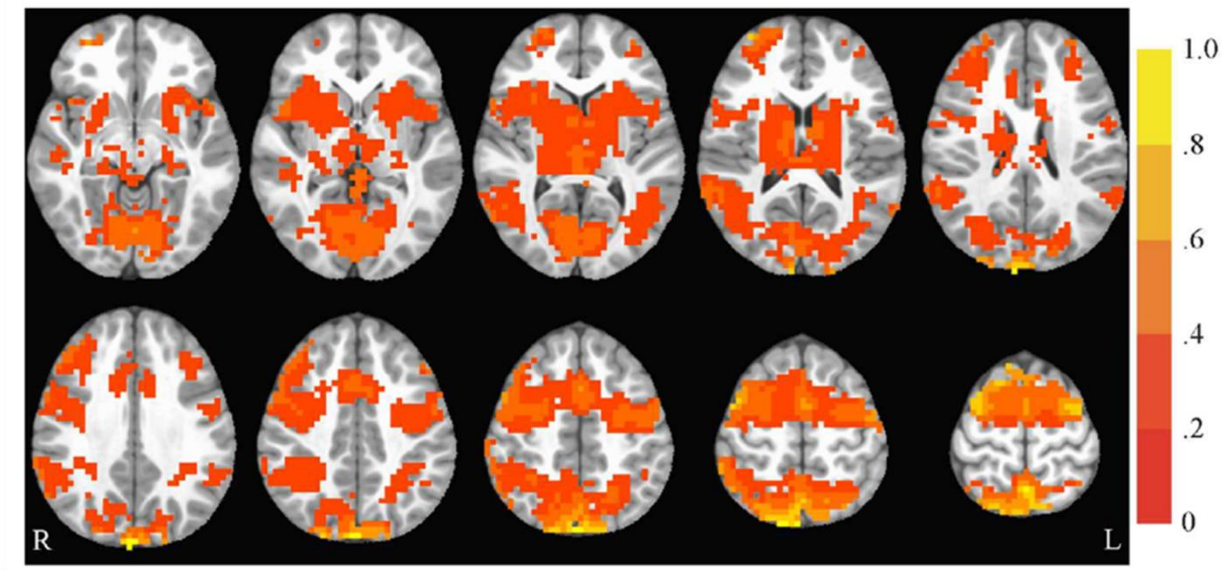

Figure 2.2. Antisaccade activation at baseline. Axial slices (top left z = -8 through bottom right z = 64, spacing = 8 mm) displaying significant antisaccade-correlated activation across all participants at baseline. The background anatomical image is the pediatric template that was used during alignment and is shown using radiological convention. Scale indicates percent signal change.

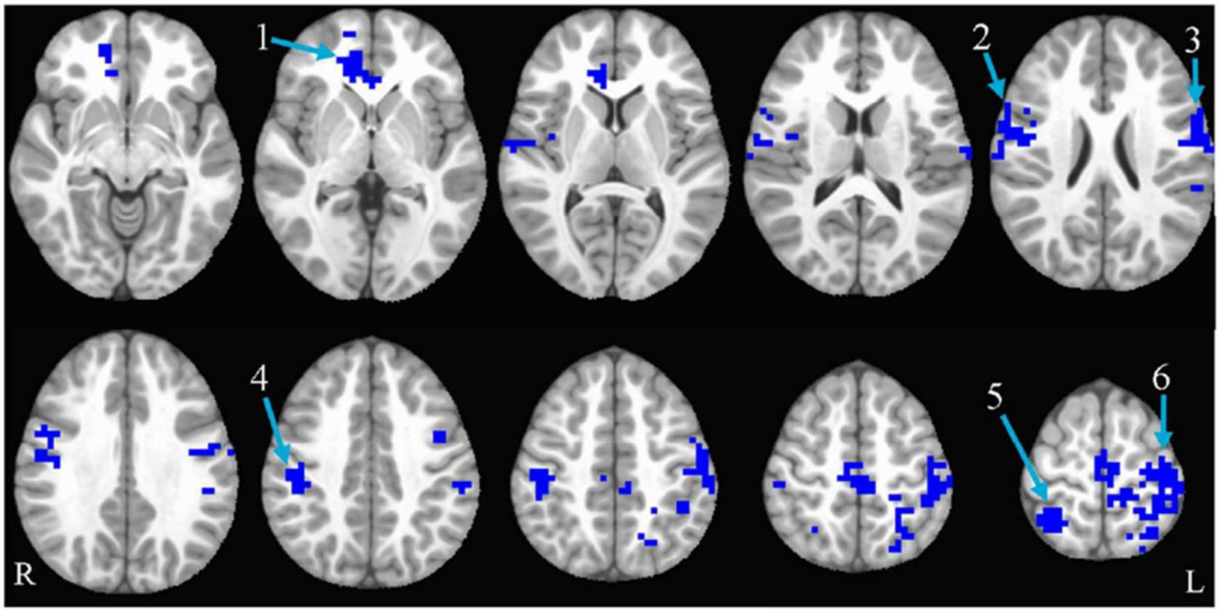

Figure 2.3. Antisaccade group by time interaction. Axial slices (top left z = -8 through bottom right z = 64, spacing = 8 mm) displaying significant group by time interactions in the antisaccade task. All clusters shown are blue, indicating that the exercise group decreased and the control group increased. The background anatomical image is the pediatric template that was used during alignment and is shown using radiological convention. Numbers correspond to labels in the first column of Table 2.3.

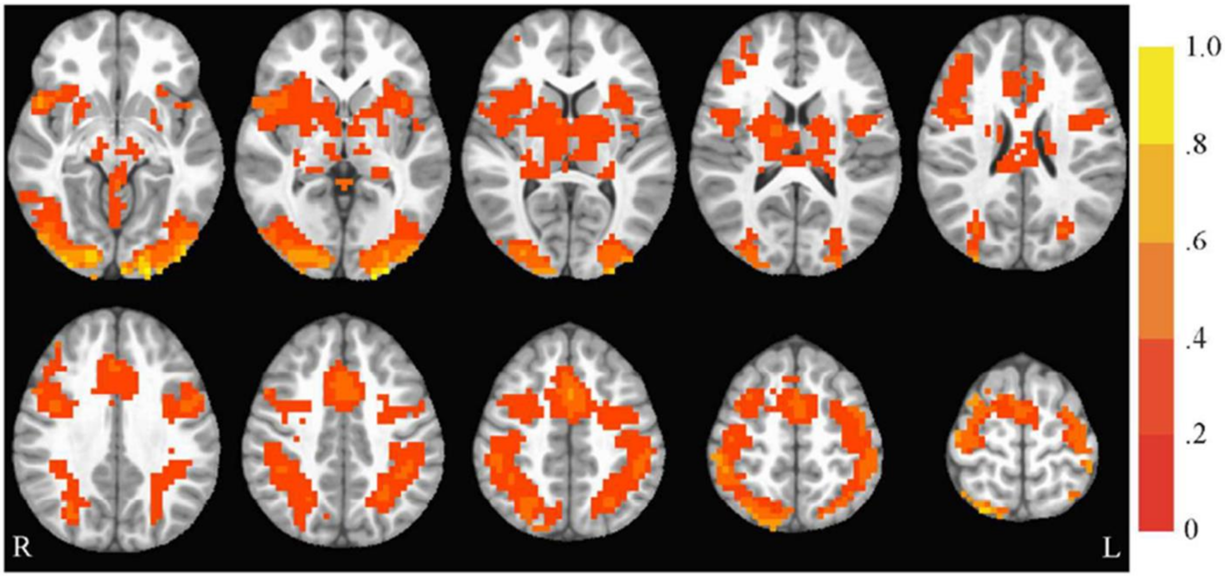

Figure 2.4. Incongruent vs. fixation activation at baseline. Axial slices (top left z = -8 through bottom right z = 64, spacing = 8 mm) displaying significant activation for the incongruent vs. fixation contrast across all participants at baseline. The background anatomical image is the pediatric template that was used during alignment and is shown using radiological convention. Scale indicates percent signal change.

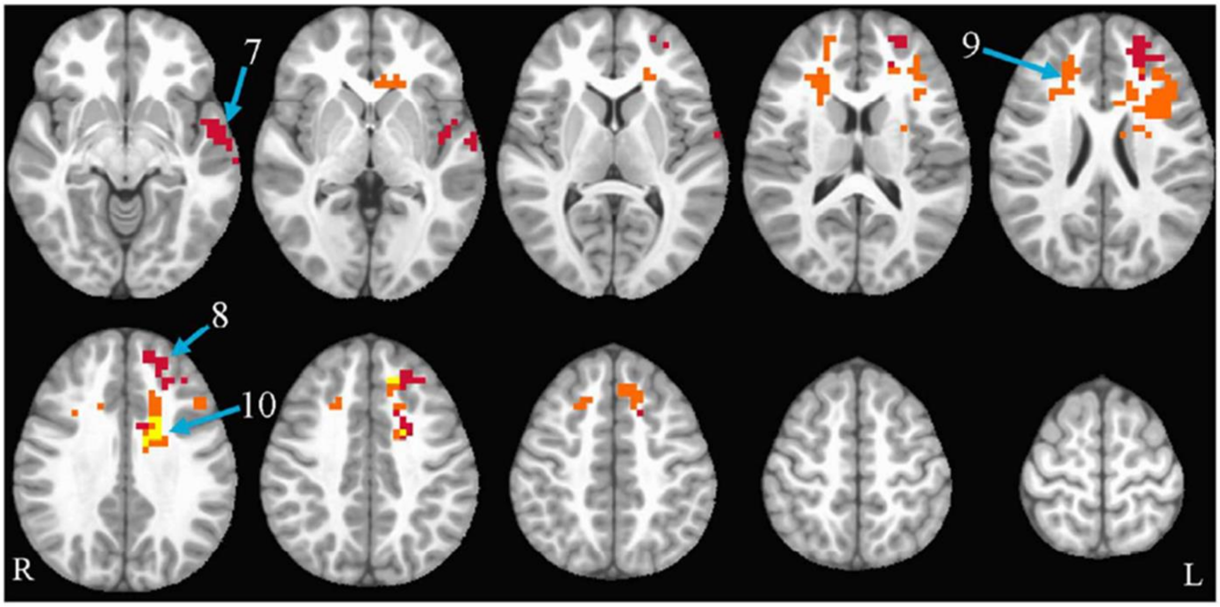

Figure 2.5. Flanker group by time interactions. Axial slices (top left z = -8 through bottom right z = 64, spacing = 8 mm) displaying significant group by time interactions in the incongruent vs. fixation and incongruent vs. congruent contrast. All clusters shown are warm colors, indicating that the exercise group increased and the control group decreased. Red corresponds to incongruent vs. fixation, orange corresponds to incongruent vs. congruent, and yellow shows areas where the two contrasts overlap. The background anatomical image is the pediatric template that was used during alignment and is shown using radiological convention. Numbers correspond to labels in the first column of Table 2.3.

CHAPTER 3

AN EIGHT MONTH RANDOMIZED CONTROLLED EXERCISE INTERVENTION ALTERS RESTING STATE SYNCHRONY IN OVERWEIGHT CHILDREN[2]

[2] Krafft, C.E., Pierce, J.E., Schwarz, N.F., Chi, L., Weinberger, A.L., Schaeffer, D.J., Rodrigue, A.L., Camchong, J., Allison, J.D., Yanasak, N.E., Liu, T., Davis, C.L. and McDowell, J.E. Submitted to *Neuroscience*, 5/3/2013.

Abstract

Children with low aerobic fitness have altered brain function compared to higher-fit children. This study examined the effect of an 8-month exercise intervention on resting state synchrony. Twenty-two sedentary, overweight (body mass index ≥ 85th percentile), and predominantly Black children 8–11 years old were randomly assigned to one of two after-school programs: aerobic exercise (*n*=13) or sedentary attention control (*n*=9). Before and after the 8-month programs, all subjects participating in resting state functional magnetic resonance imaging scans. Independent components analysis identified several networks, with four chosen for between-group analysis: salience, default mode, cognitive control, and motor networks. The default mode, cognitive control, and motor networks showed more refinement over time in the exercise group compared to controls. The motor network showed increased synchrony in the exercise group with the right medial frontal gyrus compared to controls. This study is one of the first to demonstrate that an exercise intervention in children affects resting state synchrony.

Childhood obesity in the U.S. has tripled over the past 30 years (Ogden et al., 2012). This increase has a range of implications from general issues of public health policy to specific issues of individual health and brain function. Altered brain function and lower cognitive performance on a variety of tasks have been found in obese compared to leaner individuals (Carnell, Gibson, Benson, Ochner, & Geliebter, 2012; Davis & Cooper, 2011). The cognitive differences associated with obesity may be offset by fitness and exercise (Bugg et al., 2012). Fitness and exercise have been shown to benefit at least two aspects of higher-order cognition: memory and cognitive control (CC).

Memory and CC systems both have shown consistent improvement with fitness and exercise in meta-analytic studies (Colcombe & Kramer, 2003; P. J. Smith et al., 2010). In children, those who are higher-fit have shown better relational memory performance as well as more accurate and less variable performance on CC tasks compared to those who are lower-fit (Chaddock, Erickson, Prakash, VanPatter, et al., 2010; Chaddock, Hillman, Buck, & Cohen, 2011; C.-T. Wu et al., 2011). Children who are higher-fit also have shown altered brain function on CC tasks compared to lower-fit children (Chaddock, Erickson, et al., 2012; Voss et al., 2011). Furthermore, randomized controlled exercise trials have provided evidence that exercise leads to better memory and CC performance, as well as increased prefrontal cortex activation and decreased posterior parietal cortex activation on a CC task in children (Davis et al., 2007; Davis et al., 2011; Monti, Hillman, & Cohen, 2012).

These relationships between fitness and higher-order cognition have been investigated by several studies to date using task-based functional magnetic resonance imaging (fMRI). This technique requires adapting a relevant task (usually sensory, motor, and/or cognitive) for the scanner environment in order to examine the neural circuitry supporting task engagement. A distinct but complementary technique that can be used to investigate brain function from a different perspective is task-free "resting state" fMRI (rsfMRI), during which data are acquired while participants are asked only to maintain a relaxed, wakeful state. Spontaneous blood oxygenation level-dependent (BOLD) signal changes during resting state reflect coherence in the functional organization of the brain that is free from the constraints of specific task performance (Fox & Raichle, 2007). Patterns of BOLD signal synchrony can reveal networks of regions that show co-activation. Despite the fact that rsfMRI does not involve a task, differences in resting state synchrony may reflect a predisposition to utilize cognitive resources in a different manner during task-based activity (Rubia, In press). Resting state synchrony has been related to multiple measures including tasks of memory (Tambini et al., 2010) and reading competence (Koyama et al., 2011).

A number of co-activated brain regions have been identified and labeled as distinct resting state networks (RSNs). Similar core regions exist in both adults and children (Beckmann, DeLuca, Devlin, & Smith, 2005; Biswal, Yetkin, Haughton, & Hyde, 1995; Gordon et al., 2011), although RSNs in children may be more diffuse and become more specialized and focal as they mature (Jolles, van Buchem, Crone, & Rombouts, 2011; Stevens, Pearlson, & Calhoun, 2009). Differences in resting state synchrony may partly reflect changes in neural architecture, although there is evidence that functional connectivity in children can reach adult-like levels despite weak structural connectivity (Supekar et al., 2010). Several of these networks are implicated in higher-order cognitive processes that have been altered by exercise, and indeed have shown differences in synchrony in participants at various weight and fitness levels (García-García et al., In press; Kullmann et al., 2012). Given the relative paucity of literature investigating the relationship between resting state brain function and either adiposity or fitness, we have chosen to discuss both characteristics. While adiposity and fitness clearly do not represent the same construct, high adiposity and low fitness are often correlated with one another. One network associated with fitness and/or adiposity is the default mode network (DMN), which is likely important for memory (Buckner et al., 2008). In addition, two networks are likely related to CC processes: the CC network and the salience network.

The DMN is the most-studied RSN and is hypothesized to support self-referential processing (Kim, 2010), which includes functions such as autobiographical memory retrieval, considering the perspective of others, and envisioning the future (Buckner et al., 2008). This network generally consists of several distinct nodes: anterior cingulate cortex and medial prefrontal cortex, posterior cingulate cortex and precuneus, and bilateral inferior parietal regions. In one study, obese adults showed higher synchrony between the DMN as a whole and the precuneus but lower synchrony between the DMN and the right anterior cingulate as compared to lean participants (Kullmann et al., 2012), which the authors interpreted as possibly disrupted integration of cognitive and emotional stimuli. A study of older adults found that aerobic exercise training decreased synchrony between the DMN and a frontal executive network. This result indicates that these separate networks show greater differentiation after exercise training, which may be beneficial in older adults, who tend to show decreased specificity of functional brain networks as they age (Voss, Prakash, et al., 2010).

Given the growing evidence showing that CC processes are particularly sensitive to exercise (Colcombe & Kramer, 2003), the CC network is of interest in studies of fitness (Gordon et al., 2011) and primarily includes frontal and parietal regions. While few studies have reported whether resting state synchrony in this network is different at various weight or fitness levels, children and adults with lower fitness have shown lower behavioral performance (C.-T. Wu et al., 2011) and alterations in task-related brain function (Colcombe et al., 2004; Voss et al., 2011) on CC tasks when compared to their higher-fit peers. Another network related to CC processes is the salience network, putatively involved in assessing the relevance of internal and external stimuli in order to redirect attention to salient stimuli. It includes dorsal anterior cingulate and orbital fronto-insular cortices (Seeley et al., 2007), a network that may be altered in obesity. In one report, adults with obesity showed lower synchrony between the salience network and the putamen as compared to lean adults. García-García et al. suggested that this decrease could contribute to overeating through an imbalance between autonomic and reward processing of food stimuli (García-García et al., In press).

All three of the RSNs mentioned above (DMN, CC, and salience) are putatively involved in higher-order cognitive processes that are affected by obesity or fitness. A network involved in more basic processes that also may be affected by fitness or exercise is the motor network. Its main nodes are the bilateral primary motor cortices, along with supplementary motor cortex, thalamus, putamen, and cerebellum (Barber et al., 2012). Like the salience network, the motor network includes the insula, which is hypothesized to mediate interoceptive awareness (e.g., cravings) and thus could be implicated in obesity (Jastreboff et al., 2013; Mehta et al., 2012). Few studies thus far have investigated how exercise *per se* affects the motor network; however, there is evidence that several types of skilled motor training affect synchrony with this network. For instance, training in sequential finger movements in one study caused altered synchrony with right postcentral gyrus and bilateral supramarginal gyri (increasing as behavioral performance improved, and decreasing later once there was no more further improvement in behavioral performance (Ma, Narayana, Robin, Fox, & Xiong, 2011)). In addition, training in a dynamic balance task caused increased synchrony between prefrontal, supplementary motor, and parietal areas (Taubert, Lohmann, Margulies, Villringer, & Ragert, 2011). It is possible that other complex motor training – for example, participation in a supervised aerobic exercise program, including activities such as basketball and jump rope – could alter motor circuitry synchrony.

A growing body of literature indicates that resting state synchrony is altered with excess weight or lower fitness, although few studies have investigated these effects in children. The current study used a randomized controlled trial with assignment of overweight children to 8 months of either exercise training or a sedentary control condition. It was hypothesized that exercise training would cause more refinement of resting state networks in overweight children as compared to the control group.

Experimental Procedures

Participants

Participants were a subset of children in a larger randomized trial (Krafft et al., In press), who were recruited from public schools around Augusta, GA and were eligible if they were 8-11 years old, overweight (BMI ≥ 85^{th} percentile (Ogden et al., 2002)), and inactive (no regular physical activity program ≥ 1 hr/week). Exclusions included any medical condition that would limit physical activity or affect study results (including neurological or psychiatric disorders). Children and parents completed written informed assent and consent in accordance with the Human Assurance Committee of the Medical College of Georgia. Each child's parent or guardian reported the child's age, sex, race, and health status. Parents also reported their own educational attainment, which was used as an index of socioeconomic status (1 = grade 7 or less; 2 = grades 8-9; 3 = grades 10-11; 4 = high school graduate; 5 = partial college; 6 = college graduate; 7 = post-graduate). The study took place at the Georgia Prevention Center at the Medical College of Georgia.

Resting state fMRI data were collected for 37 children at baseline before randomization to one of the two groups and 22 were scanned at post-test. Of the 15 participants lost after baseline, 4 refused to participate before randomization, 2 refused to continue partway through post-test MRI data collection (both from the control group), 8 dropped out during the course of the study (3 from the exercise group, 5 from the control group), and 1 was ruled out based on a neurological anomaly observed in the MRI scan (from the control group). The exercise group contained 16 children at baseline and 13 at post-test. The control group contained 17 children at baseline and 9 at post-test. The 10 children who participated in at least a portion of the study but refused to provide post-test rsfMRI data did not significantly differ from the participants in any of the baseline characteristics (variables listed in Table 3.1). Participants were included in analysis only if they had both baseline and post-test MRI data, resulting in a total of 22 participants (exercise group n=13, control group n=9). Characteristics of the sample are provided in Table 3.1.

Intervention

Participants were assigned randomly to one of two conditions, both of which were offered for 40 min/day: aerobic exercise or sedentary attention control. Randomization (balanced by race, sex, and school) was performed by the study statistician and concealed until after baseline testing was completed, at which point the study coordinator informed the families. Both groups were offered an after school program every school day for approximately 8 months (average number of days offered = 135, SD = 9). All participants were offered bus transportation after school to the Georgia Prevention Center where they spent half an hour on supervised homework time each day. All participants were provided with a snack each day. Lead instructors were rotated between the two groups every two weeks and assistants were rotated between the two groups every week. Both groups could earn points that were redeemed for small prizes weekly for performing desired behaviors. The reward schedule was periodically calibrated to keep the rewards offered to the groups similar.

The aerobic exercise group engaged in instructor-led aerobic activities (e.g., tag and jump rope). They wore heart rate monitors every day (S610i; Polar Electro, Oy, Finland) with which they could monitor their own performance and from which data were collected daily. Points in the exercise group were earned for an average daily heart rate above 140 beats per minute (bpm), with more points for higher average heart rates. 140 bpm was used as the goal for several reasons. This is an easily translatable public health approach that could be implemented with children anywhere, with no VO_2 testing required. The variation in 75% of predicted maximum heart rate in children in this age range is only 2 bpm (146 – 148 bpm). We have successfully utilized this approach in previous studies to elicit a substantial dose of vigorous activity which improved aerobic fitness and reduced adiposity and diabetes risk, as well as improving executive function and achievement (Davis et al., 2012; Davis et al., 2011). We have found that this criterion permits every child, however fit, to maintain interest in participating. Finally, heart rate is a physiological index of effort that calibrates to a child’s level of fitness such that as their fitness improves, more effort is required to achieve a given heart rate. Thus, it is fair across children that vary in fitness and keeps children moving at an appropriate, vigorous intensity. Participants in the exercise group had an average heart rate of 164 beats per minute (SD =10) during the intervention. The attention control group engaged in instructor-led sedentary activities (e.g., art and board games). Points in the control group were earned for participation and good behavior.

Data Collection and Analysis

Cognitive data. The Cognitive Assessment System (CAS), a standardized individual assessment of children's cognitive processes, was administered (Naglieri & Das, 1997). The Full Scale score of the CAS takes into account the four scales of the test (Planning, Attention, Simultaneous and Successive processing), each of which include 3 subtests. Analysis of this variable was conducted in SPSS Version 20 (IBM, Armonk, NY). A group by time ANOVA was conducted to investigate whether the groups significantly differed in how they changed over time.

MRI parameters. Images were acquired at the Medical College of Georgia on a GE Signa Excite HDx 3 Tesla MRI system (General Electric Medical Systems, Milwaukee, WI). For all MRI scans, head positions were stabilized with a vacuum pillow and/or foam padding. High-resolution T1-weighted structural brain images were acquired using a 3D FSPGR protocol (repetition time (TR) = 9.436 ms, echo time (TE) = 3.876 ms, flip angle = 20°, field of view (FOV) = 240 x 240 mm, acquisition matrix = 512 x 512, 120 contiguous axial slices, slice thickness = 1.3 mm, total scan time = 3 min, 33 sec). For resting state functional scans, one run was acquired during which participants were instructed to keep their eyes closed without falling asleep (TR = 5000 ms, TE = 25 ms, flip angle = 90°, FOV = 256 x 256 mm, acquisition matrix = 128 x 128, 60 interleaved axial slices, in-plane voxel dimensions = 2 x 2 mm, slice thickness = 2.4 mm [for all scans except 6 participants at baseline, who had a slice thickness of 2 mm], 112 volumes). A TR of 5000 ms was determined to be necessary to collect 60 slices. The first four volumes were discarded to allow for scanner stabilization. Each functional run was collected obliquely, with the slices aligned to the superior margin of the participants' anterior commissure and the inferior margin of the posterior commissure.

MRI data analysis. Resting state fMRI analyses were conducted using FMRIB Software Libraries (FSL (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012)) and Analysis of Functional Neuroimages (AFNI (Cox, 1996)). Standard preprocessing (which has been previously used in other resting state studies (Camchong, Stenger, & Fein, In press)) was applied in FMRIB Software Libraries (FSL version 5.0.1; Oxford, United Kingdom) for each subject. It consisted of motion correction using MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002), non-brain removal using BET (S. M. Smith, 2002), spatial smoothing (full-width at half-maximum [FWHM] = 4 mm), grand-mean intensity normalization, and high-pass temporal filtering (.01 Hz). Due to the 5000 ms TR, slice time correction was not conducted, as the interpolation involved becomes less accurate with a TR over approximately 3000 ms and because there is evidence that this analysis step has a minimal impact on resting state data (C. W. Wu et al., 2011). Registration was carried out using FLIRT (Jenkinson et al., 2002; Jenkinson & Smith, 2001), with which each resting run was aligned to each individual's T1-weighted structural MR image, transformed into a standardized space based on a publicly available template created for 7-11 year olds in MNI space (Fonov et al., 2011), and resampled to 2 x 2 x 2 mm voxels.

Data were inspected for excessive motion but no participants showed an average absolute motion greater than 1 mm of a shift in any of the three planes; therefore, no participants were excluded from analysis due to excessive motion. In order to limit any effect of smaller movements, probabilistic independent component analysis (PICA; (Beckmann & Smith, 2004)) was conducted as implemented in FSL's MELODIC for each participant to denoise individual data. Components that represented noise were selected by spatial and temporal characteristics as detailed by Kelly et al. including head motion (which appeared as “rim-like” artifacts around the brain) or scanner artifacts (such as slice dropouts, high-frequency noise, and field inhomogeneities) and removed (Kelly et al., 2010). A group by time ANOVA conducted to look for difference in the sum of percent of total variance accounted for by components removed showed no group by time interactions in noise, $F(1, 20) = .542$, $p = .470$. In addition, six motion timecourses representing estimated motion in each plane (rotation and shift in x, y, and z planes) for each individual were removed.

A between-subject analysis was carried out using a dual regression approach that allows for voxel-wise comparisons of resting functional synchrony (Filippini et al., 2009; Westlye, Lundervold, Rootwelt, Lundervold, & Westlye, 2011; Zuo et al., 2010). First, preprocessed functional data for each subject (22 participants at both baseline and post-test, yielding 44 functional runs) were temporally concatenated across subjects to create a single 4D (three spatial dimensions x time) dataset. The concatenated dataset was decomposed using ICA to identify large-scale patterns of functional synchrony in the sample. The inclusion of all participants at both timepoints in the ICA analysis is in accordance with previously published rsfMRI studies using similar analyses (Licata et al., 2013; Martínez et al., In press). Thirty spatially-independent components were identified using automatic dimensionality estimation. Components of interest were selected using spatial correlation against a set of maps derived from a previous resting state study in children (Thomason et al., 2011). This method for selecting components of interest has been used in previous resting state studies . The comparison maps were defined as follows: masks for four networks were created by generating regions of interest (ROIs; spheres of 10-mm radius) with centers of mass based on the coordinates reported by the previous study. The four networks were default mode, salience, cognitive control, and motor. These networks were selected due to previous evidence demonstrating that their associated cognitive processes are altered at different weight or fitness levels (Chaddock, Erickson, et al., 2012; García-García et al., In press; Kullmann et al., 2012; Taubert et al., 2011; Voss, Prakash, et al., 2010). These four masks were then spatially correlated with all 30 components and the component that had the highest spatial correlation with each mask was selected for further analysis. A dual regression technique was used to identify, within each subject's fMRI dataset, subject-specific temporal dynamics and associated spatial maps. This technique involves (1) using the full set of group-ICA spatial maps in a linear model fit (spatial regression) against the separate fMRI data sets, resulting in matrices describing temporal dynamics for each component and subject and (2) using these time-course matrices in a linear model fit (temporal regression) against the associated fMRI dataset to estimate subject-specific spatial maps. These subject-specific spatial maps were transformed into z-maps for group comparison (similarly to previous studies (Camchong, MacDonald, Bell, Mueller, & Lim, 2011)).

Further group analysis was conducted using AFNI. In order to illustrate the networks that were selected, a one-sample t-test was performed across the individual z-maps corresponding to each component of interest for all participants at both baseline and post-test. These one-sample t-tests were thresholded at $p < .0001$ for display purposes due to the large number of significant voxels. To investigate group by time changes in functional synchrony, a two-way group (exercise, control) by time (baseline, post-test) ANOVA was performed using the individual z-maps. Results at $p < .025$ are reported. To protect against false positives, a threshold/cluster method derived from Monte Carlo simulations (accounting for the smoothness of the data and with a synchrony radius of 2 mm) was applied to the *F*-map (Ward, 1997). Based on these simulations, a family-wise alpha of 0.05 was preserved with three-dimensional clusters with a minimum volume of 169 voxels. The resulting clustered *F*-maps were used to identify regions with significant differences.

Results

Cognitive Performance

There was not a significant group by time interaction in CAS Full Scale scores. The groups also did not differ significantly at baseline on any of the characteristics listed in Table 3.1. The groups did not differ significantly in the percentage of days they attended the program out of the number of days offered ($t(20) = .849$, $p = .406$), with the groups attending an average of 3.4 days per week ($M = 68\%$ attendance, $SD = 25\%$).

Salience Network

The salience network collapsed across group and time is illustrated in Figure 3.1. The group by time ANOVA showed no significant group by time interactions in functional synchrony with this network.

Default Mode Network

The default mode network collapsed across group and time is illustrated in Figure 3.2. The group by time ANOVA showed a significant interaction in the left middle occipital gyrus, extending into left cuneus, superior temporal gyrus, and posterior cingulate (shown in blue). In this region, the exercise group showed decreased synchrony over time compared to the control group. See Table 3.2 and Figure 3.2 for details.

Cognitive Control Network

The cognitive control network collapsed across group and time is illustrated in Figure 3.3. The group by time ANOVA showed a significant interaction in the bilateral cingulate extending into bilateral precuneus, and in the right culmen. In both of these regions, the exercise group showed decreased synchrony over time compared to the control group. See Table 3.2 and Figure 3.3 for details.

Motor Network

The motor network collapsed across group and time is illustrated in Figure 3.4. The group by time ANOVA showed a significant interaction in the right medial, superior, and middle frontal gyri (where the exercise group showed increased synchrony compared to the control group), and in the left cuneus (where the exercise group showed decreased synchrony compared to the control group). See Table 3.2 and Figure 3.4 for details.

Discussion

Resting state synchrony, which reflects coherence in the functional organization of the brain independent of task performance, showed significant alterations due to exercise training that generally supported a pattern of greater specialization. These alterations were observed in overweight children randomized to an exercise intervention as compared to children assigned to a control condition over the course of 8 months. Results showed a pattern of refined synchrony after exercise training in three resting state networks (with the sole exception of increased synchrony between the motor network and a frontal region). Previous studies suggest that the general pattern of refined synchrony reflects more specialized and efficient RSNs.

The developmental literature suggests an interesting hypothesis of resting state synchrony refinement throughout development. There is evidence that RSNs are more specialized in young adults when compared to adolescents or children. When compared to adolescents or children, young adults have shown higher and more focal within-network synchrony and lower mutual influences between networks (Jolles et al., 2011; Stevens et al., 2009). In this study, it is possible that exercise decreased influences between cognitive control, motor, and other networks, or simply that the networks became more specialized as a result of exercise. Lower mutual influences between networks may reflect greater flexibility in processing (Stevens et al., 2009). Flexible use of strategies is one aspect of CC; CC has been improved by exercise in a previous randomized controlled trial (Davis et al., 2011). Although this interpretation needs to be further examined in longitudinal studies, it provides novel support for cross-sectional task-based work, suggesting that children who are more fit may exhibit greater flexible modulation of CC processes (Pontifex et al., 2011).

Decreased synchrony due to exercise was found in the DMN, which is hypothesized to support processes related to memory and self-referential processing (Kim, 2010), including autobiographical memory retrieval, considering the perspective of others, and envisioning the future (Buckner et al., 2008). The exercise group showed more refined synchrony associated with this network in the posterior cingulate, which is an important hub (Greicius et al., 2003). The decreased synchrony occurred outside the extent of activation of the posterior cingulate in the group map. A decrease in synchrony indicates that synchrony in this region became more focal and refined from baseline to post-test in the exercise group. The DMN also showed decreased synchrony in the exercise group with a visual region. Decreased synchrony was found with the middle occipital gyrus, which has been implicated in spatial localization (Renier et al., 2010), and the cuneus, which is important for comparatively basic visual processing and has been identified as a central hub of the visual RSN (Tomasi & Volkow, 2011). Finally, decreased DMN synchrony was seen in the superior temporal gyrus, which is part of an auditory RSN that has been identified in both children and adults (Cole, Smith, & Beckmann, 2010; Thomason et al., 2011). Together, decreased synchrony in these regions seems to suggest that children in the exercise group show more a refined DMN over time as compared to the control group, including less synchrony with other distinct RSNs.

Refinement of RSNs was supported again by the CC network analysis, which showed decreased synchrony with the bilateral cingulate and precuneus after exercise. The cluster where a significant interaction was seen overlaps spatially with the CC network that was found in this study, possibly indicating that children in the exercise group demonstrated more specialized or focal synchrony of the CC network over time. Since the cingulate and precuneus are involved in both the CC and DMN networks, another possible interpretation is that synchrony between these two networks changed with exercise (Greicius et al., 2003). This difference may be related to an effect that was found in a previous study of older adults, where aerobic exercise training decreased synchrony between an executive network and the DMN (Voss, Prakash, et al., 2010), possibly leading to greater regulation between networks. Similarly, decreased synchrony was found between the CC network and the right cerebellum. This region is part of the CC network identified in at least one study in children (Gordon et al., 2011); however, the region that was found is similar to a region that has been identified as part of the salience network in adults (Habas et al., 2009). Overall, the exact network membership of the areas which show group by time differences in synchrony with the CC network is not yet clarified, as they may be involved in one or more networks, or perhaps shift roles during development. Therefore, the issue of whether exercise decreases inter-network synchrony or whether the CC network becomes more focal due to exercise has yet to be determined. Both processes may be at play and present topical questions for future studies. The pattern of change over the course of the intervention, however, is similar to that of the DMN analysis, with the exercise group showing decreased synchrony over time.

Exercise caused decreased synchrony once more in the motor RSN. The decreased synchrony with this network was seen in the cuneus, which supports basic visual processing and may be a central hub of the visual RSN (Tomasi & Volkow, 2011). While the motor network showed decreased synchrony in the exercise group with the cuneus, it was the only RSN to also show an opposing pattern of increased synchrony within the exercise group. This increase was found in frontal regions, including right medial frontal, middle frontal, and superior frontal gyri. These regions are associated with working memory and spatial attention (Hopfinger, Buonocore, & Mangun, 2000; Kirschen et al., 2005; Lepsien, Griffin, Devlin, & Nobre, 2005; McCarthy et al., 1996; Ptak & Schnider, 2011) and may be involved in regulating execution of complex motor sequences (Rao et al., 2008). For instance, increased synchrony between motor cortex and middle frontal gyrus has been related to improved motor recovery in stroke patients (Park et al., 2011). Additional evidence that this increase in synchrony may be beneficial comes from a study of motor learning, where enhanced motor learning in young adults was related to increased synchrony between dorsolateral prefrontal cortex and supplementary motor area (Lin et al., 2012). The relationship between synchrony of these regions and motor performance is not yet clarified in children but our results indicate that this is an interesting area for further study. Another possible interpretation in the motor network is that because it includes the insula, interoceptive awareness (i.e., cravings) may be altered (Mehta et al., 2012). An increase in synchrony between frontal regions and this network may reflect greater top-down control of these processes in children assigned to the exercise group.

The results of this 8 month randomized controlled trial assessing the impact of an aerobic exercise condition in comparison to a rigorous control condition indicate that exercise *per se* causes decreased resting state synchrony associated with default mode, cognitive control, and motor networks in overweight children. Importantly, in this study, the results of the exercise intervention stand apart from nonspecific influences of an after school program (such as adult attention, interaction with peers, and healthy snacks). Evidence from the developmental literature (Jolles et al., 2011; Stevens et al., 2009) suggests that refinement of resting state networks may be advantageous. The development of more specialized RSNs seen in the exercise group following the 8 month intervention is consistent with the pattern that is found in typical development. More specialization may allow for greater flexibility in neural recruitment (a pattern which has been observed in task-based studies of fitness and effects of exercise). The only increase in synchrony was found in the motor network, which has been involved in acquisition of motor skills (and may allow for better regulation of complex motor skills in the future), or may reflect altered regulation of interoceptive processing (with potential effects for food cravings).

Task-free resting state fMRI may prove to be an important tool for further clarifying potential benefits of exercise for other reasons, as well. It may inform structural imaging findings, as functional synchrony has been associated with structural connectivity in previous studies, although function-structure relationships may become more stable as children mature (Supekar et al., 2010). It also can serve as an efficient proxy for task-based functional imaging studies. Kannurpatti et al. have shown that resting state fMRI predicts both voxel level and individual subject level responses during task-based fMRI (Kannurpatti et al., 2012). As such, resting state fMRI data can be useful in cases in which it is challenging to obtain task-based fMRI data. The ability to evaluate brain activation via functional networks in children by using a relatively simple resting state acquisition is less complicated than requiring stimulus presentation and task performance during data acquisition in the scanner.

Youth obesity is on the rise. As such, identification and evaluation of interventions that counteract any disadvantageous effects of overweight are critically important. The results from the current randomized controlled trial suggest that exercise may be a simple and effective intervention to not only improve physical health, but also to enhance neurocognitive outcomes.

Table 3.1. Baseline characteristics of participants included in analysis. Mean and SD, where applicable. CAS = Cognitive Assessment System. SS = Standard Score.

Characteristic	**Exercise group**	**Control group**
n	13	9
Age (years)	9.5 (0.6)	9.6 (0.9)
Female	77%	56%
Black	100%	89%
Left-handed	8%	22%
Cognitive score (CAS Full Scale SS)	94.2 (7.3)	95.9 (8.9)
Parental education scale	4.8 (1.0)	4.3 (1.4)

Table 3.2. Significant clusters in the whole-brain group by time analysis of synchrony with each resting state network

Anatomical location	**Direction of synchrony change over time (in exercise group with respect to control group)**	**MNI coordinates of center of mass (x,y,z)**	**Voxels**
Salience network			
No significant group by time interactions			
Default mode network			
1. Left middle occipital gyrus, extending into left cuneus, superior temporal gyrus, and posterior cingulate	Exercise decreased	28, 73, 14	291
Cognitive control network			
2. Right culmen, extending into right cerebellar tonsil	Exercise decreased	-17, 47, -32	424
3. Bilateral cingulate, extending into bilateral precuneus	Exercise decreased	8, 44, 37	625
Motor network			
4. Left cuneus	Exercise decreased	10, 72, 12	181
5. Right medial frontal gyrus,	Exercise increased	-4, -66, 18	247

extending into right superior and
middle frontal gyri

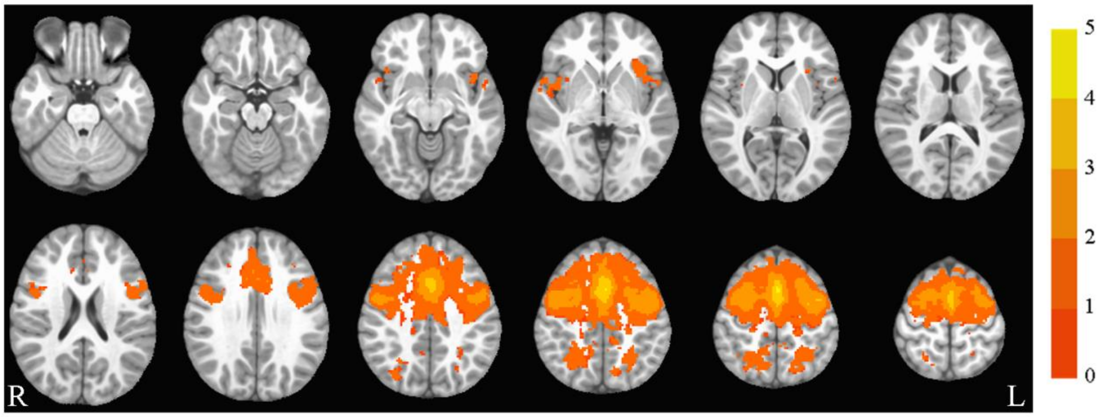

Figure 3.1. Salience network. Axial slices (top left z = -26 through bottom right z = 62, spacing = 8 mm) displaying the salience network across all participants and both time points. Scale indicates z-value. The background anatomical image is the pediatric template that was used during alignment and is shown using radiological convention.

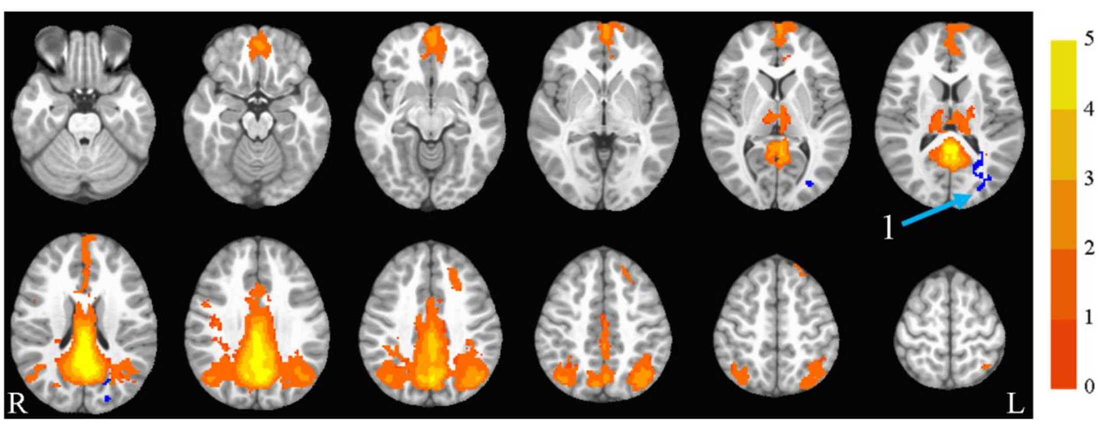

Figure 3.2. Default mode network. Axial slices (top left z = -26 through bottom right z = 62, spacing = 8 mm) displaying the default mode network across all participants and both time

points. Scale indicates z-value. The arrow points to the left middle occipital gyrus, which showed a significant group by time interaction. The region is blue, indicating that the exercise group showed decreased synchrony with the DMN over time compared to the control group. The background anatomical image is the pediatric template that was used during alignment and is shown using radiological convention.

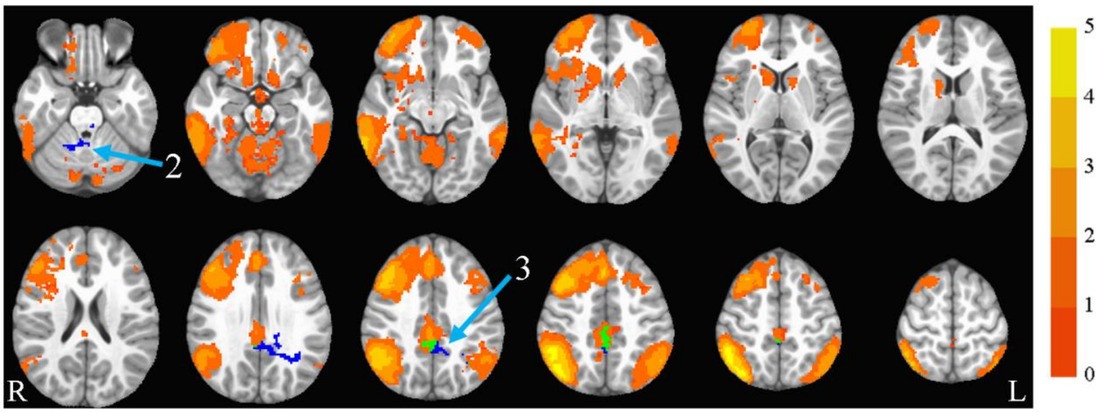

Figure 3.3. Cognitive control network. Axial slices (top left z = -26 through bottom right z = 62, spacing = 8 mm) displaying the cognitive control network across all participants and both time points. Scale indicates z-value. Arrow 2 points to the right culmen and arrow 3 points to the cingulate, both of which showed significant group by time interactions. Both regions are blue, indicating that the exercise group showed decreased synchrony with the cognitive control network over time compared to the control group. Where the clusters overlap with the cognitive control network, the overlap is in green. The background anatomical image is the pediatric template that was used during alignment and is shown using radiological convention.

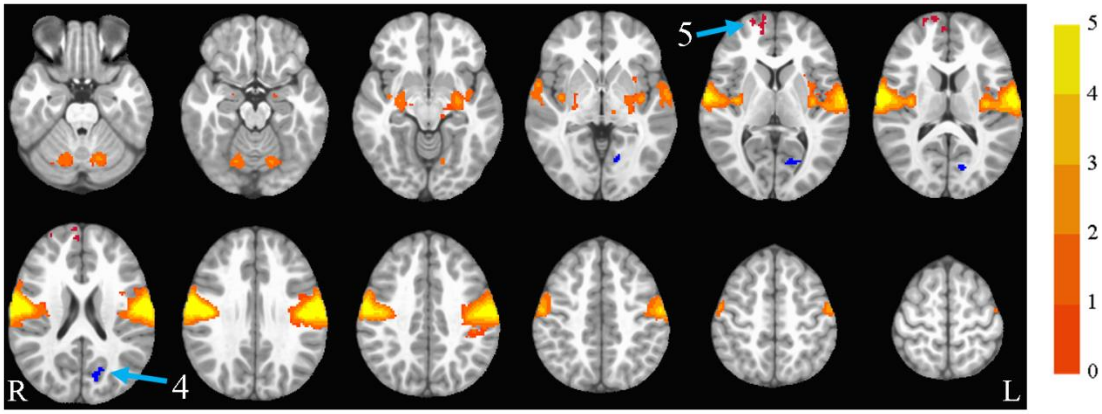

Figure 3.4. Motor network. Axial slices (top left z = -26 through bottom right z = 62, spacing = 8 mm) displaying the motor network across all participants and both time points. Scale indicates z-value. Arrow 4 points to the left cuneus and arrow 5 points to the right medial frontal gyrus, both of which showed significant group by time interactions. The left cuneus is blue, indicating that the exercise group showed decreased synchrony with the motor network over time compared to the control group. The right medial frontal gyrus is red, indicating that the interaction was in the opposite direction, with the exercise group showing increased synchrony with the motor network over time compared to the control group. The background anatomical image is the pediatric template that was used during alignment and is shown using radiological convention.

CHAPTER 4

IMPROVED FRONTO-PARIETAL WHITE MATTER INTEGRITY IS ASSOCIATED WITH ATTENDANCE IN AN AFTER-SCHOOL EXERCISE PROGRAM [3]

[3] Krafft, C.E., Schaeffer, D.J., Schwarz, N.F., Chi, L., Weinberger, A.L., Pierce, J.E., Rodrigue, A.L., Allison, J.D., Yanasak, N.E., Liu, T., Davis, C.L. and McDowell, J.E. Submitted to *Developmental Neuroscience*, 5/21/13.

Abstract

Objective: Aerobic fitness has been associated with white matter integrity (WMI) in adults as measured by diffusion tensor imaging (DTI). This study examined the effect of an 8-month exercise intervention on WMI in children. Design and Methods: Participants were 18 sedentary, overweight (body mass index ≥ 85th percentile) 8- to 11-year-old children, randomly assigned to either an aerobic exercise (n=10) or sedentary attention control group (n=8). Each group was offered an instructor-led after-school program every school day for approximately 8 months. Before and after the program, all subjects participated in DTI scans. Tractography was conducted to isolate the superior longitudinal fasciculus and investigate whether the exercise intervention affected WMI in this region. Results: WMI in the superior longitudinal fasciculus did not change differentially between groups over time. There was a group by attendance interaction such that only the exercise group showed that higher attendance at the intervention was associated with increased WMI. Increased WMI was associated with improved scores on a measure of attention and improved teacher ratings of executive function. Conclusions: This study indicates that attendance at an exercise intervention improves WMI in children with implications for cognitive performance.

Introduction

Aerobic fitness is associated with cognitive performance across the lifespan. In cross-sectional studies, higher-fit individuals showed better performance than lower-fit peers on measures of cognitive control, and higher-fit children demonstrated comparatively better academic achievement and parent and teacher ratings of behavior (Davis & Cooper, 2011; Voss et al., 2011; Weinstein et al., 2012; C.-T. Wu et al., 2011). There is evidence that aerobic exercise plays a causal role in improving cognition, as commencing regular aerobic exercise improves performance on a variety of cognitive tasks. Randomized controlled trials showed that both adults and children who were assigned to chronic exercise improved cognitive performance compared to their peers assigned to control groups (Colcombe et al., 2004; Davis et al., 2011; Kamijo et al., 2011) with more improvement associated with greater attendance (Evers, Klusmann, Schwarzer, & Heuser, 2011). While exercise benefits many types of cognition, there is evidence that exercise-related improvement is greater for cognitive control (higher-order processes including inhibition, working memory, and attentional control) compared to lower-level tasks (Colcombe & Kramer, 2003).

Cognitive control is supported by fronto-parietal circuitry (Luna et al., 2001; Schaeffer et al., 2013). Exercise interventions have improved cognitive control and altered frontal and parietal activation as assessed by functional magnetic resonance imaging (fMRI). Specifically, a 6-month exercise intervention in older adults improved performance and increased prefrontal and posterior parietal activation during a flanker task in an exercise group as compared to controls (Colcombe et al., 2004). Regional alterations also have been found in a study of children. Our group found that a three-month exercise intervention in 7- to 11-year-old children improved cognitive control performance (as measured by the Planning scale of the Cognitive Assessment

System) compared to controls (Davis et al., 2011). The exercise group also increased prefrontal and decreased posterior parietal activation during an antisaccade task compared to controls.

With evidence that fronto-parietal brain activation can be affected by exercise, one issue that warrants investigation is whether fronto-parietal brain structure is affected by exercise. Altered white matter structure may be an underlying cause of functional change, given that inter-individual differences in brain activation have been shown to reflect white matter integrity (WMI) (Gordon et al., 2011). WMI reflects axonal membrane structure and myelination and can be assessed by several diffusion tensor imaging (DTI) measures. Fractional anisotropy (FA) is a frequent measure of interest, with higher values interpreted as more coherently bundled, myelinated fibers. Another measure based on the same tensor model is radial diffusivity (RD), with lower values often interpreted as primarily reflecting greater myelination (Bennett, Motes, Rao, & Rypma, 2012; Song et al., 2002).

WMI has been associated with fitness in several cross-sectional studies. Higher aerobic fitness in adults has been associated with higher FA in the cingulum and corpus callosum, possibly relating to motor planning and control (Johnson et al., 2012; Marks et al., 2011; Marks et al., 2007). Fitness also has been associated with integrity of the uncinate fasciculus, which is involved in memory (Marks et al., 2007). In what may be the only investigation to date of the impact of a randomized controlled exercise intervention on WMI, Voss et al. randomly assigned adults to one year of either an aerobic exercise group or a flexibility and toning control group. Increased aerobic fitness was associated with increases in prefrontal, parietal, and temporal FA in the aerobic group (Voss et al., In press). While literature indicates that exercise may affect WMI in adults, this topic has yet to be investigated in children.

Given evidence that exercise has improved cognitive control and altered associated fronto-parietal brain activation in prior studies, we investigated whether an exercise intervention in children would improve WMI in a tract that connects frontal and parietal regions: the superior longitudinal fasciculus (SLF). Greater integrity of this white matter tract has been related to better performance on several measures of cognitive control, such as working memory and attention (Bennett et al., 2012; Østby, Tamnes, Fjell, & Walhovd, 2011; Vestergaard et al., 2010). As the SLF does not complete maturation until young adulthood (Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008), ongoing development makes it an interesting target for investigation across the ages included in current study (children 8 – 11 years old). The SLF may be particularly susceptible to intervention effects due to its continuing maturation and in fact has been altered by another type of intervention in children. Five weeks of spelling training decreased RD in the right SLF in children 9 to 16 years of age (Gebauer et al., 2012). In sum, the hypotheses were generated based on the literature indicating that exercise improves cognitive control and that fitness is associated cross-sectionally with higher WMI. Specifically, we hypothesized that a randomized controlled exercise intervention in children would increase WMI in the SLF, particularly in children with good attendance.

Methods and Procedures

Participants

Participants were a subset of children in a larger randomized trial (Krafft et al., In press), recruited from public schools around Augusta, GA and eligible if they were 8-11 years old, overweight (BMI ≥ 85^{th} percentile; (Ogden et al., 2002)), and inactive (no regular physical activity program ≥ 1 hr/week). Exclusions included any medical condition that would limit physical activity or affect study results (including neurological or psychiatric disorders).

Children and parents completed written informed assent and consent in accordance with the Human Assurance Committee of Georgia Regents University. Each child's parent or guardian reported the child's age, sex, race, and health status. Parents also reported their own educational attainment, used as an index of socioeconomic status (1 = grade 7 or less; 2 = grades 8-9; 3 = grades 10-11; 4 = high school graduate; 5 = partial college; 6 = college graduate; 7 = post-graduate). The study took place at the Georgia Prevention Center at Georgia Regents University. Magnetic resonance imaging was completed with DTI data available for 41 children at baseline and 30 at post-test. Of the 27 children who had both baseline and post-test data, 8 were excluded due to scanner artifact or excessive motion and 1 was excluded due to a neurological anomaly. Thus the present study included eighteen children (10 exercise, 8 control; see Table 4.1).

Cognitive Measures

The Cognitive Assessment System (CAS), a standardized individual assessment of children's cognitive processes (Naglieri & Das, 1997), was administered and Standard Scores analyzed for all 18 children at both baseline and post-test. The Full Scale score of the CAS takes into account the four scales of the test (Planning, Attention, Simultaneous and Successive processing), each of which include 3 subtests. For the CAS, higher scores reflect better performance. The Behavioral Rating Inventory of Executive Function (BRIEF) was completed by up to three teachers per child (Gioia, Isquith, Guy, & Kenworthy, 2000). This questionnaire provides a standardized measure of executive function behaviors in the school environment, with higher scores reflecting worse performance. For each child, teachers completing the BRIEF were matched at baseline and post-test to maintain consistency. T-scores were obtained for 17 children at baseline (10 exercise, 7 control) and 16 at post-test (9 exercise, 7 control), with 15 children having both baseline and post-test data and thus being included in BRIEF analyses (9 exercise, 6 control). The BRIEF was completed by an average of 1.6 teachers (SD = 0.8) per child, with no significant difference in the number of teachers between groups ($t(13) = 1.02$, $p > 0.3$).

Intervention

Participants were assigned randomly to one of two conditions, both of which were offered for 40 min/day: aerobic exercise or sedentary attention control. Randomization (balanced by race, sex, and school) was performed by the study statistician and concealed until after baseline testing was completed, at which point the study coordinator informed the families. Both groups were offered an after-school program every school day for approximately 8 months (average number of days offered = 139, SD = 9). All participants were offered daily bus transportation after school to the Georgia Prevention Center where they spent half an hour on supervised homework time and were given a snack. Lead instructors were rotated between the two groups every two weeks and assistants were rotated between the two groups every week.

The aerobic exercise group engaged in instructor-led aerobic activities (e.g., tag and jump rope). They wore heart rate monitors every day (S610i; Polar Electro, Oy, Finland) with which they could monitor their own performance and from which data were collected daily. Participants in the exercise group had an average heart rate of 161 beats per minute (SD = 8) during the intervention. The attention control group engaged in instructor-led sedentary activities (e.g., art and board games).

Diffusion Tensor Imaging Procedure and Analysis

MR image acquisition. Images were acquired at Georgia Regents University on a 3T GE Signa Excite HDx MRI system (General Electric Medical Systems, Milwaukee, WI). During scanning, head position was stabilized with a vacuum pillow and/or foam padding. Diffusion images were acquired using an echo planar imaging (EPI) sequence (acquisition matrix = 128 x

128, 60 interleaved slices, voxel size = 1 x 1 x 2.4 mm, FOV = 256 x 256 mm, TR = 15500 ms, TE = min-full, 3 B0 images, 30 diffusion weighted images, b = 1000 s/mm^2).

Image analysis. Raw diffusion images were converted from GE DICOM format to NIFTI format using the dcm2nii tool (Rorden, 2007). For each subject, volumes were visually inspected for motion artifacts; volumes distorted by motion were removed from the image series and b value/vector tables (volumes removed *M* = 2, *SD* = 2.7). To test for inhomogeneity of gradient application due to volume removal, volume gradient vectors were plotted on a sphere after motion volumes were removed. If the any surface of the sphere had a gap greater than the free surface area of 6 non-co-linear directions, the participant was excluded from analysis. Diffusion tensor image preprocessing was conducted using the FMRIB Software Library (FSL; (S. M. Smith et al., 2004)). Non-brain tissue was removed using the Brain Extraction Tool (BET; (S. M. Smith, 2002)). Diffusion images were corrected for eddy-current-induced distortions. Tractography was then conducted with whole brain tensors in individual space for the bilateral SLF following established anatomical markers (Wakana et al., 2007) using the ExploreDTI software package (Leemans, Jeurissen, Sijbers, & Jones, 2009)). Average values for each SLF (right and left) were extracted for four measures of white matter microstructure, all of which were included in analyses: fractional anisotropy (FA), radial diffusivity (RD), mean diffusivity (MD), and axial diffusivity (AD). High MD values are often explained as disorganized development, immaturity, or other structural anomalies in white matter, whereas high AD values may reflect a lower number of axonal fibers or smaller axonal diameter.

Statistical analyses of white matter variables controlling for age and gender were conducted in SPSS Version 21 (IBM, Armonk, NY). Between-group t-tests on the change in WM integrity evaluated the effect of the exercise intervention compared to the control condition.

Group by attendance interactions tested whether attendance was associated with change in WMI differently between groups. Correlations between change in WMI and attendance were conducted separately for each group to examine significant group by attendance interactions. For the exercise group alone, correlations between change in WMI and average heart rate at the intervention were conducted. In addition, the product of average heart rate and attendance was calculated to investigate the dose of exercise administered, and correlation analyses were conducted between this variable and change in WMI.

To explore the differences in cognition between groups that did or did not improve WMI, for each white matter variable that showed a significant group by attendance interaction, the change from baseline to post-test was calculated for each individual, controlling for age and gender. These difference scores were then entered into two separate *k*-means clustering analyses, one each for left and right SLF ($k = 2$, input: FA and RD for the hemisphere of interest; ≤10 iterations). T-tests evaluated differences in cognitive task performance between the resulting clusters.

Results

Cognitive Measures at Baseline

The groups did not differ significantly at baseline on any of the characteristics listed in Table 4.1. Participants attended an average of 3.3 days per week (M = 65% attendance, SD = 6%) and the groups not differ significantly in the percentage of days they attended the program out of the number of days offered ($t(16) = 0.95$, $p = .36$).

White Matter Structure

The groups did not significantly differ in the change in any WMI measure, indicating that the exercise intervention did not differentially affect WMI compared to the control condition.

Group by attendance interactions were significant in left SLF for both FA ($p = .02$) and RD ($p = .04$), and in right SLF for RD ($p = .04$) and at the trend-level for FA ($p = .06$). For all group by attendance interactions, the exercise group showed a significant ($r = .92$ for right SLF FA and $r = -.88$ for right SLF RD, $p < .05$ for both) or trend-level ($r = .68$ for left SLF FA and $r = -.69$ for left SLF RD, $p < .06$ for both) relationship between attendance and change in WMI, with increased WMI associated with more frequent attendance. The control group did not show significant relationships between attendance and change in WMI. Group by attendance interactions were not significant for MD or AD. For further details, see Figure 4.1.

In addition to attendance, the intensity and dose of exercise were related to improved white matter integrity in the exercise group. Higher average heart rate in the exercise intervention was correlated with decreased MD ($r = -.71$) and RD ($r = -.75$) in the left SLF. A measure of the dose of exercise (the product of average heart rate and attendance) was correlated with increased FA in left and right SLF ($r = .73$ and $r = .93$, respectively), decreased MD in the right SLF ($r = -.75$), and decreased RD in the left and right SLF ($r = -.74$ and $r = -.87$, respectively).

Exploratory *K*-means Analyses

Cluster analyses were conducted to divide all participants into two groups based on those who improved WMI (FA and RD) and those who did not for each SLF (left and right). With two groups identified for each SLF, it was then possible to compare alterations in cognitive measures (CAS and BRIEF scores) between the improved and not-improved SLF groups in order to investigate whether improved WMI was associated with improved cognition.

Cluster analysis 1: Left SLF. Two clusters were identified which significantly differed in the change in WMI from baseline to post-test. The cluster that showed greater improvement in

WMI also showed better cognitive outcome as indicated by decreased BRIEF scores. Specifically, Cluster 1 (n = 11) was composed of participants with improved left SLF WMI as indicated by increased FA (t(16) = -6.1, p < .001) and decreased RD (t(16) = 3.7, p = .002) compared to Cluster 2 (n = 7). Cluster 1 was associated with more cognitive improvement, significantly differing from Cluster 2 in change in BRIEF scores over time. Cluster 2 had significantly worse scores on the BRIEF as compared to Cluster 1, including the Global Executive Composite Score t(13) = 3.2, p = .007), as well as both the Behavioral Regulation and Metacognition Indices (t(13) = 2.5, p = .04 and t(13) = 3.04, p = .01, respectively). No differences were observed between the two clusters in CAS scores. For further details, see Figure 4.2.

Cluster analysis 2: Right SLF. Two clusters were identified which significantly differed in the change in WMI from baseline to post-test. The cluster showing greater improvement in WMI also showed better cognitive outcome as indicated by increased CAS Attention Scale scores. Specifically, Cluster 1 (n = 11) was composed of participants with improved right SLF WMI as indicated by increased FA (t(16) = 10, p < .001) and decreased RD (t(16) = 2.5, p = .02) compared to Cluster 2 (n = 7). Cluster 1 was associated with more cognitive improvement, significantly differing from Cluster 2 in changes in attention scores over time. Cluster 1 significantly improved scores on the Attention Scale of the CAS compared to Cluster 2 (t(16) = 2.6, p = .02). No differences were observed between the two clusters in BRIEF scores. While the two cluster analyses (Cluster Analysis 1 and Cluster Analysis 2) did identify similar groups of participants as indicated by a chi-square test (χ^2 (1, N = 18) = 5.1, p = .02), they did not completely overlap with one another, with a total of four participants having different cluster membership between the two analyses. For further details, see Figure 4.2.

Discussion

The current study hypothesized that SLF WMI would be improved by an exercise intervention in overweight children, particularly with greater attendance. This hypothesis was based on evidence that fronto-parietal regions and the cognitive control processes that they support are altered by exercise. While no effect of group on SLF was detected, improved WMI in the SLF of overweight children was associated with attendance at an after-school exercise program as compared to attendance at an after-school sedentary program. Specifically, higher attendance in the exercise condition was associated with increased WMI in bilateral SLF (increased FA and decreased RD) compared to the control group, where attendance was not associated with change in WMI. Not only attendance in the exercise intervention but also the intensity of exercise (higher average heart rate) and dose of exercise (product of heart rate and attendance) were associated with improved WMI. In addition, these results indicated that increasing WMI in the SLF benefited cognitive control. Improved WMI in the right SLF was associated with improved selective attention, while improved WMI in the left SLF was associated with better teacher ratings of classroom behavior.

Improved WMI was associated with better cognitive control as measured by teacher ratings and selective attention scores. The BRIEF teacher ratings evaluate the executive function behaviors of children in the school environment. WMI of the left SLF was associated with a global assessment of executive function and with two component scales. Behavioral Regulation includes items such as children’s ability to control impulses and move freely from one situation to the next. Metacognition includes items such as children’s ability to initiate activities, hold information in working memory, plan and organize future events, and monitor their own performance. The association between increased WMI and improved teacher ratings indicates that the SLF may be important for cognitive control abilities in this sample, as has been shown in previous studies (Østby et al., 2011; Vestergaard et al., 2010). It also indicates that WMI may be reflected in classroom conduct and that it therefore has implications for academic achievement and social behavior.

The other measure which was associated with WMI was the Attention Scale of the CAS, a composite measure based on three selective attention tasks: a variation of the Stroop test and two tests requiring children to find visual targets within fields of distracters. There is previous evidence that the SLF is important in attention. FA in the SLF has been associated with similar measures in children, such as the sensitivity index of a rapid visual information processing paradigm, which describes a subject's ability to detect signals independent of answering strategy or bias (Klarborg et al., In press). SLF FA also has been related to visual search in adults (i.e., finding targets among distracters (Bennett et al., 2012)).

Higher FA is generally interpreted as reflecting coherently bundled, myelinated fibers but it is somewhat non-specific in that it can be affected by various tissue characteristics, including myelination, axon diameter, and fiber organization (Scholz, Tomassini, & Johansen-Berg, 2009). It is possible that decreasing RD in the current study could reflect increasing myelination more so than other alterations in axonal structure, for which AD might be a more sensitive measure (Beaulieu, 2009; Song et al., 2002). Therefore, the changes in WMI described in the current study may be more strongly related to myelination. This interpretation is made with caution, as the association of white matter measures with specific tissue characteristics remains a topic of debate (Wheeler-Kingshott & Cercignani, 2009). Nevertheless, the current study indicates that FA and RD are more affected by exercise than AD, which is supported by a previous cross-sectional study in adults showing that higher FA associated with fitness was primarily related to less RD, rather than altered AD (Johnson et al., 2012). While this study is one of the first to investigate how exercise affects white matter structure in children, it is limited by the sample size, which may be why group by time effects were not detected.

The current study demonstrates that children's attendance at an after-school exercise program, as compared to a sedentary program, improves WMI in a tract supporting cognitive control processes. This sample is unique among neuroimaging investigations of exercise in children due to the stringent nature of the control group. Because both groups attended after-school programs, several potentially beneficial effects were controlled for (e.g., social interaction, attention from adults, and supervised homework time). Additional strengths of this study include the 8-month length of the interventions and the predominantly minority sample of children. Improved WMI was related to two different measures of cognitive control – a measure of selective attention and teacher ratings of classroom behavior. Increased integrity of the SLF after attending an exercise intervention may contribute to improved cognitive control, with benefits not only for performance on a standardized cognitive task but also for on-task behavior and interpersonal interactions in the classroom. This may be important to protect school resources for physical activity in the context of unprecedented levels of childhood obesity along with pressure on schools to improve achievement (McMurrer, 2008; Ogden et al., 2012).

Table 4.1. Baseline characteristics and attendance of participants included in analysis. Mean and SD or %. CAS = Cognitive Assessment System. BRIEF = Behavioral Rating Inventory of Executive Function.

Characteristic	**Exercise group**	**Control group**
N	10	8
Age (years)	9.9 (0.6)	9.4 (0.8)
Female	50%	50%
Non-white	100%	88%
Left-handed	10%	25%
Parental education scale	4.8 (1.0)	4.3 (1.5)
CAS Full Scale score	94.2 (8.9)	95.6 (9.5)
CAS Planning Scale score	88.2 (11.7)	89.5 (13.9)
CAS Attention Scale score	98.4 (8.5)	94.8 (7.5)
BRIEF Global Executive Composite score	56.0 (11.8)	47.9 (9.8)
BRIEF Behavioral Regulation Index score	54.3 (11.4)	45.6 (3.7)
BRIEF Metacognition Index score	55.9 (12.0)	49.1 (12.4)
Attendance	60% (10%)	72% (8%)

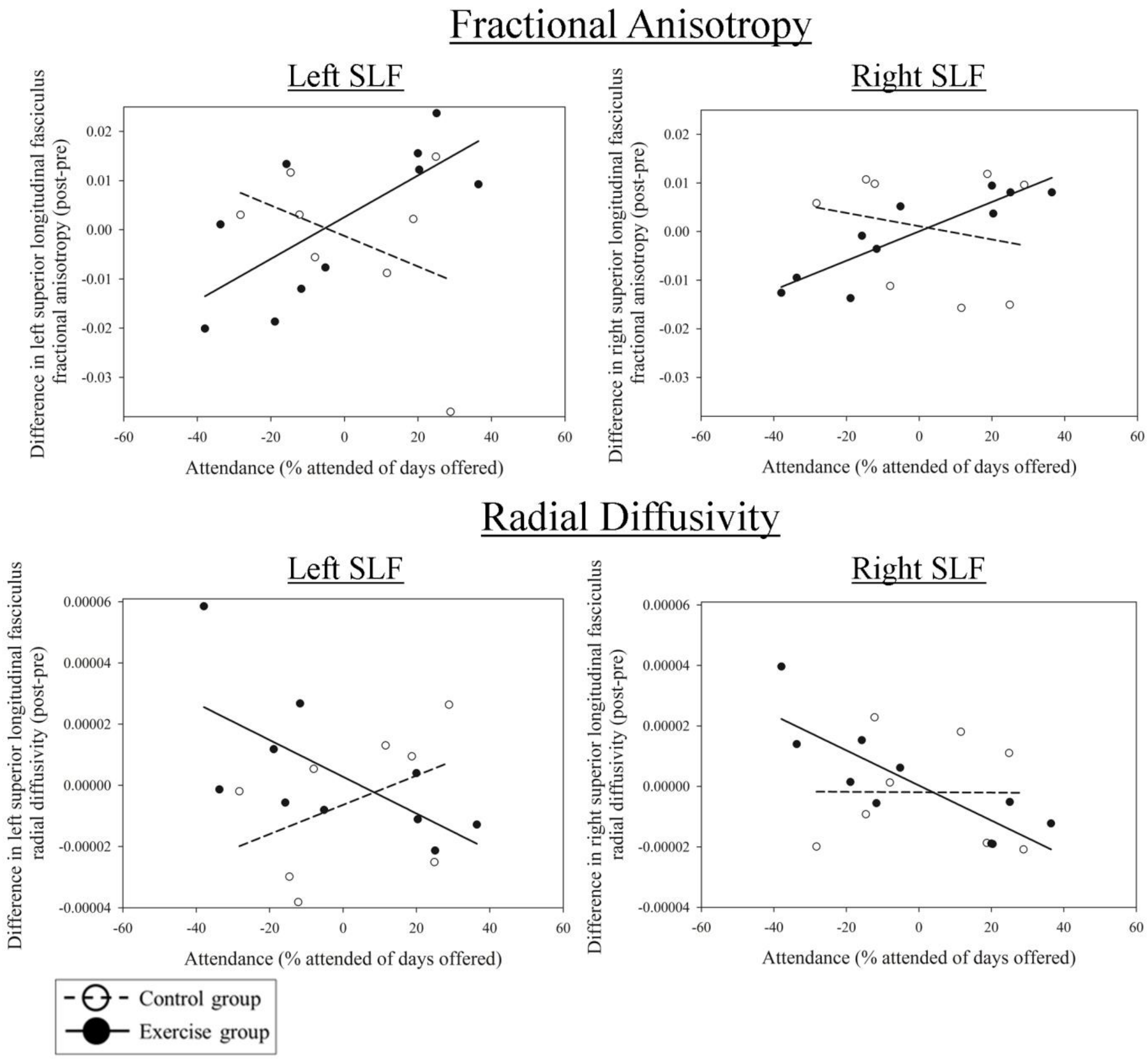

Figure 4.1. Group by attendance interactions. Y-axes show white matter difference scores (changes in integrity from baseline to post-test) and x-axes show attendance. All measures plotted are residuals after controlling for age and gender.

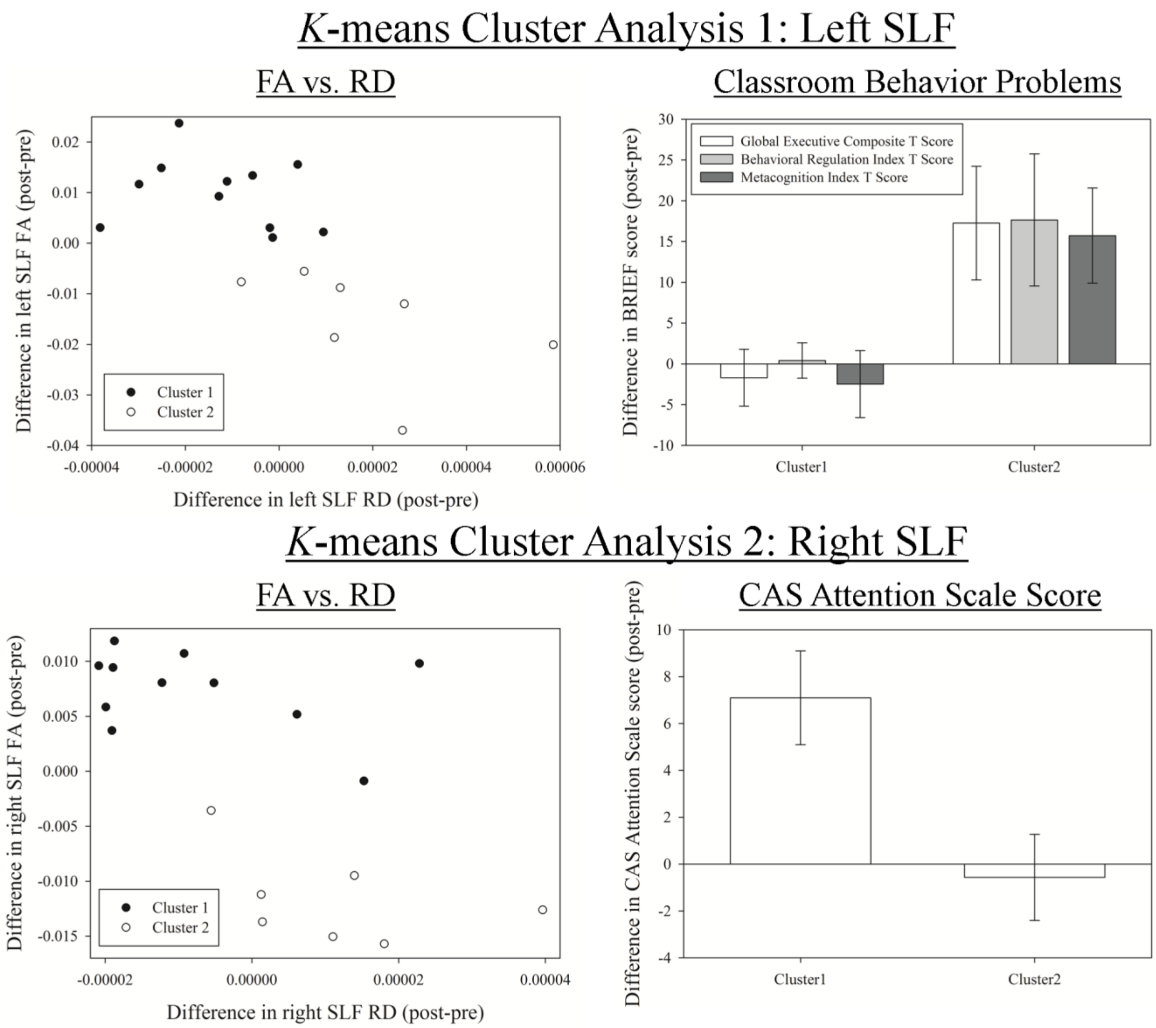

Figure 4.2. Illustrations of *K*-means cluster analyses. The scatterplots illustrate the two clusters identified for each analysis based on the participants' alterations in white matter integrity (FA and RD) over time. These show that for both analyses, Cluster 1 had improved white matter integrity (increased FA and decreased RD) compared to Cluster 2. The bar graphs illustrate the differences in cognition between the two clusters obtained in each analysis. In Cluster Analysis 1, Cluster 2 showed worse teacher ratings of executive function as compared to Cluster 1, indicated by increased BRIEF scores. In Cluster Analysis 2, Cluster 1 showed improved attention scores as compared to Cluster 2, indicated by increased CAS Attention Scale scores.

The two clusters obtained in each *k*-means analysis significantly differed in all measures shown. SLF = superior longitudinal fasciculus. FA = fractional anisotropy. RD = radial diffusivity. BRIEF = Behavioral Rating Inventory of Executive Function. CAS = Cognitive Assessment System. Measures shown are difference scores (change from baseline to post-test).

CHAPTER 5

CONCLUSIONS

Evidence indicates that exercise can improve cognitive performance and alter brain function. Despite a population experiencing considerable increases in obesity and decreases in aerobic fitness in children, the effects of exercise on children's brain function and structure are only beginning to be understood. The studies in this dissertation demonstrate that exercise alters brain function in overweight children during two cognitive tasks and are some of the first to show that exercise is associated with differences in resting state brain activity and white matter integrity in children. Using an 8-month randomized controlled exercise program, we found that exercise played a causal role in altering brain function both during cognitive control and during a resting state, and that attending an exercise intervention improved white matter integrity in the superior longitudinal fasciculus. Specific alterations associated with exercise were related to improved selective attention performance, as well as better teacher ratings of the children's classroom behavior. The addition of an attention control group was novel for neuroimaging studies of exercise in children. The use of this control group served to delineate the alterations related to exercise more specifically than previous neuroimaging studies by controlling for other beneficial factors associated with participating in an after-school exercise program.

In Chapter 2, we investigated the effect of exercise on brain activation during antisaccade and flanker tasks, extending a prior study from our group (Davis et al., 2011). Specifically, it was hypothesized that the exercise group would show increased prefrontal and decreased posterior parietal cortex activation compared to the control group. The exercise-induced decrease in posterior parietal cortex activation that we observed in the previous study was replicated during the antisaccade task. The antisaccade and flanker tasks showed unexpected differential effects of exercise, with the antisaccade task generally showing decreased activation and the flanker task showing increased activation. These effects of exercise may have differed between the tasks for at least two reasons: (1) exercise may have a different impact on the circuitry supporting each task, or (2) exercise may have a different impact on brain activation as measured by the blocked versus event-related task designs that were utilized (Burgund et al., 2006).

With this evidence that exercise alters brain activation during cognitive control, the next study investigated whether exercise could alter brain function even when a task was not being performed. Chapter 3 investigated the effect of exercise on resting state synchrony in four resting state networks, hypothesizing that children assigned to exercise would show decreased synchrony in these networks compared to children assigned to the control group. The default mode, cognitive control, and motor networks did show such a pattern, possibly reflecting more refinement of resting state networks after exercise. Greater refinement of resting state networks after exercise may indicate that exercise causes more developed resting state patterns of resting state synchrony. In addition, the motor network showed increased synchrony in a frontal region, possibly related to improved complex motor control.

Differences in brain function have been related to structural differences in previous studies (Gordon et al., 2011) and exercise has been shown to induce white matter alterations in adults (Voss et al., In press). No study to date had investigated whether exercise induces alterations in white matter integrity in children. Therefore, Chapter 4 hypothesized that the exercise group would show improved white matter integrity over time in the superior longitudinal fasciculus, a white matter tract involved in cognitive control, compared to the control group. The groups did not differ on the change in white matter integrity over time; however, the relationship between attendance and white matter integrity did differ between the groups. Attendance at the after-school program was associated with improved white matter integrity in the exercise group but not in the control group. Improved white matter integrity was associated with increased performance on a test of selective attention and better teacher ratings of executive function in the classroom.

The studies reported here are unique among investigations of exercise in children in that they report the results of several MRI measures from the same intervention. It is noteworthy that some common conclusions can be drawn across these complementary modalities. One interpretation for several of the results is that exercise is related to more effective cognitive control. The antisaccade results are in accordance with a recent study in adults suggesting that decreased activation reflects learning or efficiency (Lee et al., In press). The resting state data suggest that exercise decreases mutual influences between networks. The ability to disengage irrelevant networks has been related to better sustained attention (Weissman, Roberts, Visscher, & Woldorff, 2006). Further support for this effect can be found in a resting state study of exercise in older adults (Voss, Prakash, et al., 2010). Finally, the DTI data also provide more direct evidence that exercise is associated with better cognitive control. Attendance at the exercise intervention (but not at the control group) improved white matter integrity in the SLF, which was associated with improved attention scores on a paper-and-pencil test taken by the children. There is evidence that improvements associated with exercise were observable by others, given that improved white matter integrity was associated with better teacher ratings of cognitive control behaviors in the classroom.

A limitation in making these interpretations based on these three studies is that group differences in task performance were not observed. Therefore, although the results seem to indicate that there may be some benefit to brain function and structure supporting cognitive control, any existing benefits are smaller than reported in previous studies. The lack of group differences in changes in task performance was unexpected in these studies. This is in contrast to previous exercise interventions in children, which have found that exercise groups improved memory and cognitive control task performance (Davis et al., 2011; Monti et al., 2012). A significant contribution of these studies is the use of the attention control group, rather than a waitlist control group used by previous exercise interventions in children. In order to clarify the specific effect of exercise rather than the general effect of an after-school program involving exercise, the attention control group controlled for several mutually beneficial factors (such as attention from adults and supervised homework time) which may have contributed to performance enhancements that were seen in previous studies. It is possible that the control group, as well as nonspecific factors common to both groups such as healthy snacks and homework time, constituted modest interventions which improved performance beyond what children would have attained otherwise. This study isolated the effects of aerobic exercise while controlling for nonspecific factors that may have contributed to cognitive benefits observed in prior exercise studies. Even though the groups did not show differences in task performance changes over time, differences in brain function and structure suggest that exercise causes differences which could more subtly affect cognitive function.

Another common interpretation that can be made across these studies is that exercise may be associated with more developed patterns of brain function and structure. Specifically, resting state networks demonstrated greater refinement over time in the exercise group, which is consistent with resting state alterations that have been observed during typical development (Jolles et al., 2011; Stevens et al., 2009). The DTI data show a pattern of increased white matter integrity associated with attendance at the exercise program (but not at the control program), which again is consistent with the changes that occur during typical development (Lebel et al., 2008). Because the development of circuitry supporting antisaccade and flanker task performance has not been clarified using fMRI, it is unclear whether the patterns of change in the task-based fMRI study also can be interpreted as greater development as a result of exercise. Nevertheless, it is possible that exercise contributed to greater development of specific aspects of brain function and structure for children in this study. More developed brain function and structure might reflect an acceleration of typical development. Alternately, because the children in this study were overweight and sedentary (and therefore at risk of worse brain function compared to healthier peers), exercise may have caused changes in brain function and structure that led the exercise group to more closely resemble their healthy weight, active peers.

The possibility that the trajectory of typical development is altered by exercise raises several topics for future research. The typical developmental changes in many of these variables are unclear and require investigation. In addition, there are relatively few studies of the relationship between obesity and brain function or structure in children 8-11 years old. As such, it is not known whether brain function and structure develop differently in overweight or unfit children compared to their healthy weight or higher-fit peers. Because the children in this study were overweight and unfit, exercise may have affected their brain function and structure in a different manner or to a different extent compared to higher-fit children participating in other studies. It also may be interesting to investigate the effect of exercise in atypically developing populations which may show a greater cognitive benefit from exercise. For example, recent research indicates that 8-10 year old children with attention-deficit/hyperactivity disorder show a greater benefit of exercise for task performance and brain function than typically developing children (Pontifex, Saliba, Raine, Picchietti, & Hillman, 2013). Overall, it will be helpful to further clarify which groups of children show the greatest cognitive benefit from exercise in order to most effectively implement targeted interventions. Finally, many studies have focused on aerobic exercise rather than resistance training due to evidence that it has a greater benefit for cognition (Pontifex, Hillman, Fernhall, Thompson, & Valentini, 2009). It would be interesting to investigate the cognitive effect of resistance training in children, or the effect of both types of exercise in combination. In older adults, resistance training alone has benefitted cognitive control task performance (flanker interference) and brain function (Liu-Ambrose et al., 2012). Recent animal research has indicated that each type of exercise achieves similar results for learning and spatial memory but that they achieve these effects through different mechanisms (Cassilhas et al., 2012).

This collection of studies provides novel evidence that exercise in children is associated with improvements in brain function and structure. It should be noted that another way in which these results can be framed is that rather than exercise benefiting cognition, sedentary activity is detrimental to cognition. Sedentary activity has increased over at least the last 50 years as technological advances have led to fewer physically active occupations, greater automobile dependence with a corresponding decline in walking for transportation, and more labor-saving devices in the home (Brownson, Boehmer, & Luke, 2005). Children 6 – 11 years old are one of the least sedentary age groups in the United States and yet even they spend more than six waking hours per day in sedentary behavior (Matthews et al., 2008). Recent sedentary behavior is at odds with the evolutionary environment for which humans have adapted and likely causes worse physical and cognitive health than what modern humans would otherwise achieve. This dissertation found that even in the absence of group differences in task performance, exercise had widespread effects on brain function (both during a task and during a resting state) and was associated with integrity of an important white matter tract. Structural differences associated with exercise benefited cognitive control as measured by a test of selective attention and teacher ratings of classroom behavior. This research provides additional evidence that exercise benefits children in multiple aspects of their lives, including not only improvements in physical health but also differences in brain function and structure benefitting cognition. These results provide motivation to expand current public policy initiatives toward increasing exercise in children. The duration of cognitive alterations resulting from this exercise program is currently unknown but evidence has shown that children who are more fit at one time point show better cognitive performance than their less fit peers at least one year later (Chaddock, Hillman, et al., 2012). Children from the current study could experience long-term benefits for cognition and for performance in the classroom.

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