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

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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) 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 participated 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 spatial 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. Exercise behavior may enhance brain development in children.

Key words: resting state fMRI, aerobic exercise, obesity, development, default mode, cognitive control.

INTRODUCTION

Childhood obesity in the U.S. has tripled over the past 30 years (Ogden et al., 2012). Altered brain function and lower cognitive performance on a variety of tasks have been found in obese compared to leaner children (Bruce et al., 2011; Davis and Cooper, 2011; Yau et al., 2012). High adiposity and low fitness are often associated with one another (Ortega et al., 2008). Because cross-sectional studies of obesity often do not control for fitness (and vice versa), it is possible that studies reporting differences related to obesity might be confounded with low fitness. Exercise may improve children's brain function and development (Institute of Medicine, 2013) and in fact, fitness and exercise have been shown to benefit at least two specific aspects of children's higher-order cognition: memory and cognitive control (CC). Better relational memory performance as well as more accurate and less variable performance on CC tasks have been observed in higher-fit compared to lower-fit children (Chaddock et al., 2010, 2011; Wu et al., 2011a). Children who are higher-fit also have shown altered brain function on CC tasks compared to lower-fit children (Voss et al., 2011; Chaddock et al., 2012). Furthermore, randomized controlled exercise trials have provided evidence that exercise leads to better memory and CC performance, as well as altered activation on CC tasks in children (Davis et al., 2007, 2011; Monti et al., 2012; Krafft et al., in press).

These relationships between fitness and higher-order cognition have been investigated by several studies to date using task-based functional magnetic resonance imaging (fMRI). 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

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Abbreviations: AFNI, Analysis of Functional Neuroimages; ANOVA, analysis of variance; BOLD, blood oxygenation level-dependent; CAS, Cognitive Assessment System; CC, cognitive control; DMN, default mode network; fMRI, functional magnetic resonance imaging; FOV, field of view; FSL, FMRIB Software Libraries; ICA, Independent Component Analysis; MNI, Montreal Neurological Institute; rsfMRI, resting state fMRI; RSNs, resting state networks; TE, echo time; TR, repetition time.

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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 (Fox and 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, there is evidence that differences in resting state synchrony reflect a predisposition to utilize cognitive resources in a different manner during task-based activity (Kannurpatti et al., 2012; Rubia, in press).

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 (Biswal et al., 1995; Beckmann et al., 2005; Gordon et al., 2011), although RSNs in children are more diffuse and become more specialized and focal as they mature (Stevens et al., 2009; Jolles et al., 2011). Little is known about the relationship of resting state brain function with exercise, adiposity or fitness. Several of these networks are implicated in higher-order cognitive processes that have been altered by exercise, and indeed have shown differences in synchrony after exercise or between obese and lean participants (Voss et al., 2010; Kullmann et al., 2012; García-García et al., 2013).

One network potentially associated with fitness and/or adiposity is the default mode network (DMN), which is likely important for memory (Buckner et al., 2008). 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 precuneus and lower right anterior cingulate functional synchrony 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 et al., 2010).

Given the growing evidence showing that CC performance and associated brain activation are different at various fitness levels (Colcombe et al., 2004; Voss et al., 2011; Wu et al., 2011a) and that CC processes are particularly sensitive to exercise (Colcombe and Kramer, 2003), the CC network was of interest in this study. The CC network primarily includes frontal and parietal regions (Vincent et al., 2008). 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 has been 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. (2013) suggested that this decrease could contribute to overeating through an imbalance between autonomic and reward processing of food stimuli.

All three of the RSNs mentioned above (DMN, CC, and salience) are putatively involved in higher-order cognitive processes that have been 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 (Mehta et al., 2012; Jastreboff et al., 2013). Few studies thus far have investigated how exercise *per se* affects the motor network; however, there is evidence that skilled motor training affects 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 et al., 2011). In addition, training in a dynamic balance task caused increased synchrony between prefrontal, supplementary motor, and parietal areas (Taubert et al., 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 suggests 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 alter resting state synchrony as compared to the sedentary control group in four networks: DMN, CC, salience, and motor. Specifically, based on evidence that exercise causes more mature, efficient patterns of brain activation (Chaddock-Heyman et al., 2013; Krafft et al., in press), we hypothesized that exercise would cause decreased synchrony between these resting state networks and brain regions outside of those networks, reflecting more specialized and focal patterns of resting state synchrony.