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Emerging Support for a Role of Exercise in Attention-Deficit/Hyperactivity Disorder Intervention Planning

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Abstract

Recent years have seen an expansion of interest in non-pharmacological interventions for attention-deficit/hyperactivity disorder (ADHD). Although considerable treatment development has focused on cognitive training programs, compelling evidence indicates that intense aerobic exercise enhances brain structure and function, and as such, might be beneficial to children with ADHD. This paper reviews evidence for a direct impact of exercise on neural functioning and preliminary evidence that exercise may have positive effects on children with ADHD. At present, data are promising and support the need for further study, but are insufficient to recommend widespread use of such interventions for children with ADHD.

Keywords

Attention-deficit/hyperactivity disorder; ADHD; Cortical development; Neurocognitive functioning; Aerobic exercise; Cognitive remediation strategies; Nonpharmacological intervention; Neural growth; Cognitive development; Executive functioning; Treatment; Outcomes

Introduction

Attention Deficit/Hyperactivity Disorder (ADHD) is a prevalent, highly impairing, neurodevelopmental disorder defined by developmentally inappropriate symptoms of inattention, impulsiveness and overactivity. ADHD typically emerges early in childhood and commonly persists through adolescence and into adulthood [1], with outcomes characterized by high rates of unstable relationships, academic/occupational failure, criminality and substance use [2,3].

Currently employed evidence-based treatments for ADHD fall into two categories; pharmacological interventions and behaviorally-based psychosocial treatments. Pharmacologic treatments, including stimulant and non-stimulant medications, are quite effective for reducing the inattention and hyperactivity/impulsivity characteristic of ADHD, as well as associated disruptive behaviors [4-6]. Psychosocial treatments, which mainly comprise parent management training and school-based contingency management, have also been reported to improve behavior [7,8]. Importantly, both pharmacologic and psychosocial treatments appear efficacious during active treatment, but few individuals with ADHD are effectively treated throughout the course of the disorder [9,10], and as such, treatment gains

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tend to be short-lived, with limited, if any, long-term beneficial effects [11]. The transient benefits of current treatments may be due to several factors. However, one possibility is that they target symptoms rather than the underlying neural mechanisms of ADHD. As recent neuroscientific research has begun to shed light on the underlying pathophysiology of ADHD, the time is ripe for this knowledge to be translated into the development of new intervention strategies.

Longitudinal neuroimaging data indicate that children with ADHD follow a trajectory of cortical development that is delayed by 2 – 3 years relative to their typically-developing peers [12]. Further, emerging data suggest that normalization of the trajectory of neural development might be associated with a diminution of symptoms and improved outcomes [13]. Our group has posited that irrespective of etiology, the decline of symptoms with age is accounted for by the degree to which later development of higher cortical circuitry and functions can compensate for underlying deficits through ‘top down’ regulatory control [14]. Consistent with these notions, individuals with remitting ADHD symptoms appear to show relative normalization in executive functioning/cognitive control [15,16], as well as the brain circuitry that underlies these cognitive abilities [17,18], relative to those whose symptoms persist. These findings suggest that novel interventions designed to enhance neural growth and development in children with ADHD, particularly in brain regions that mediate executive functioning, may prove to be more efficacious and/or enduring than current treatments [19-21]. With this in mind, several investigations have begun to explore the use of cognitive training as a more enduring intervention for ADHD [22-26]. Another potential treatment approach that is beginning to attract scientific scrutiny is the employment of physical exercise.

Physical Exercise

A rapidly growing literature suggests that physical exercise has powerful effects on brain function and structure, and is one avenue by which neural and cognitive development can be impacted over both the short- and longer-term. Physical exercise is defined as contrived skeletal muscle movement associated with an increase in energy expenditure with the intention to develop or maintain physical fitness and/or health [27]. This includes, but is not limited to, spontaneous physical activity, organized physical education classes or sport competition. Exercise type, intensity, and duration are the main variables of import manipulated in experimental studies. Activities vary from very simple repetitive motions (e.g., running, walking) to complex activities that engage cognitive skills (e.g., sports games, obstacle courses, video games). Intensity is typically defined by percentage of an individual’s maximum workload measured by assessments of oxygen uptake or heart rate. In terms of duration, interventions are generally classified as either short- (single exercise session) or long-term (several weeks or more of sessions at regular intervals) [28].

Evidence for the potential utility of exercise in the development of new interventions for ADHD comes from several distinct lines of research: (1) experimental evidence, primarily in animals, demonstrating the impact of exercise on neural functioning, growth, and development; (2) experimental data indicating that exercise has positive impacts on cognitive/executive control in typically developing children, and most notably on inhibitory control; and (3) preliminary evidence that exercise improves behavior in children with ADHD symptoms. Taken together, this body of evidence suggests that exercise impacts structural brain growth and functional neurocognitive development, which in turn could have lasting effects on the trajectory of ADHD. The aim of this paper is to review each of these lines of evidence and to provide a rationale for new studies investigating the impact of exercise on children with ADHD.

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Neurobiological and Cognitive Effects of Exercise

An extensive literature, primarily in rodents, provides incontrovertible evidence that physical exercise leads to the up-regulation of neurotrophic factors, which regulate neural development, including the survival, growth, and differentiation of neurons [29,30], synaptogenesis and myelination [31], and angiogenesis [32,33] (see [27], [34], [35] for reviews). Specifically, physical exercise in rats increases levels of synaptic proteins [36-38], glutamate receptors [39], brain-derived neurotrophic factor (BDNF) [40] and insulin-like growth factor-1 [41]. Acute physical exercise also promotes monoamine neurotransmission, increasing levels of serotonin, dopamine, and norepinephrine [42,43]. In concert with these biological changes, physical exercise has been shown to enhance spatial learning [44,45] and passive avoidance memory [46] in rats.

Beyond the animal literature, substantial data suggest that physical exercise is protective against general cognitive decline in the aging human population (for reviews see [47,48]). This research supports the notion that aerobic exercise can enhance human brain structure, prevent age-related brain tissue loss, and improve cognitive performance. Physical exercise appears to exert its strongest effects on executive functions in older adults [49].

Physical exercise has also been reported to facilitate catecholaminergic neurotransmission [50,51]; increase BDNF [52-58], improve cognitive performance [52,59,60], and promote brain health [61] in healthy human adults. Notably, BDNF appears to be involved in the differentiation and survival of dopaminergic neurons [62,63]. As such, physical exercise both directly and indirectly affects catecholamine systems which have been purported to play a key role in the pathophysiology of ADHD [64-66].

To our knowledge, only one study has shown differences in BDNF levels in individuals with ADHD [67]. However, animal studies suggest that psychostimulants and the non-stimulant, atomoxetine, both primary treatments for ADHD, increase BDNF expression in the brain [68,69]. Taken together, these findings have led to a hypothetical role for BDNF in the etiology of ADHD [70].

While a direct role of BDNF in the pathophysiology of ADHD remains speculative, it is clear that physical exercise leads to enhanced neural functioning. If, as suggested by recent research [15-18], enhanced neural functioning is linked to a remission of ADHD symptoms, a program of physical exercise has the potential to yield enduring changes in ADHD symptom severity.

Neurocognitive Effects of Exercise in Children

In children, recent neuropsychological (e.g., [71-74], event-related brain potential (ERP) [72,75,76], and functional magnetic resonance (fMRI) [71] studies have reported positive relationships between physical fitness and executive functioning (see also [74,77] for reviews). However, causal inferences cannot be gleaned from correlational research; children who have better executive functioning may be more inclined to participate in routine physical exercise and sports.

Nevertheless, there is an emerging body of experimental research suggesting selective effects of physical exercise on executive functions in children. Several recent reviews have concluded that both chronic and acute aerobic exercise improves executive abilities, most notably inhibitory control, with more limited effects on non-executive cognitive skills such as attention, perception, and visuomotor coordination [74,78-80]. Furthermore, the duration of the exercise intervention (i.e., acute vs. chronic) may differentially affect executive functions. From a review of 23 studies examining the impact of exercise on executive

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functions, Barenberg et al. [79] concluded that longer-term interventions resulted in improvement on tests of singular executive functions (i.e., dual task coordination, shifting), but had less consistent effects on more complex tasks requiring the simultaneous engagement of multiple executive abilities. In contrast, the impact of short-term interventions seemed to differ across executive functions. While there was no evidence for effects on shifting and weak evidence for effects on complex tasks, there was clear evidence that short-term exercise improved inhibitory control.

In addition, we review below six more recent experimental studies that have examined the effect of physical exercise, particularly aerobic exercise, on executive functioning in typically-developing school-aged children [75,81-85]. Although these studies varied greatly in duration of intervention and outcome measures, all found at least nominal improvement in performance on measures of executive functions for both acute and longer-term interventions.

Best [81] hypothesized that engagement in executive functioning during acute exercise bouts is an important factor in determining the degree of improvement following exercise. He examined the impact of acute physical exercise and cognitive engagement on Attention Network Task (ANT) performance in a small sample of typically-developing children between 6 and 10 years-old, manipulating both level of physical activity (high vs. low) and cognitive engagement (high vs. low). Children selectively improved on performance measures for the conflict component of the ANT task following acute exercise, but cognitive engagement had no impact. These findings converge with the existing literature indicating improvement in inhibitory control following an acute bout of aerobic activity, but add that executive function engagement may not be necessary during acute physical activity to have an impact on cognitive functioning in children.

The impact of acute intense aerobic activity on cognitive functioning in typically developing 7- and 10-year old boys was assessed by Ellemberg and St. Louis Deschenes [83] using simple and choice reaction time (RT) tasks (n = 36 per age group). Half of the children in each age group completed 30 min of moderately intense aerobic exercise (i.e., cycle ergometer) while watching a TV show; the other half only watched television while sitting on the same cycle ergometer. Cycling did not improve accuracy on either task, but those who engaged in aerobic exercise responded significantly faster on both RT tasks, with a greater enhancement in response speed for the choice compared to the simple RT task. The authors interpreted this difference as greater responsiveness to exercise for cognitive processes relative to sensory and motor processes. However, the choice RT task was twice as long as the simple RT task, which was always administered first. These factors may have accounted for task-related differences. Notably, there was no Age x Exercise interaction – exercise benefitted both age groups equally.

In sum, Best [81] and Ellemberg and St. Louis Deschenes [83] both found that children's performance on RT tasks improved immediately following 30 minutes of moderate aerobic activity. Two notable findings emerged from these studies involving acute exercise. First, contrary to expectations, there was no added benefit from cognitive engagement during the exercise [81]. Second, the tasks used by Ellemberg and St. Louis Deschenes assess primarily non-executive functions (e.g., arousal, response activation, response selection, sustained attention). The fact that their exercise intervention resulted in greater improvement on the choice task, relative to a simpler RT task, may suggest that, acutely, exercise confers greater benefit to more complicated tasks.

Hill et al. [85] used a cross-over design to examine somewhat longer-term benefits of exercise. 552 8 – 12 year-old children were randomized by school into two counterbalanced

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groups to determine whether 15 minutes of daily moderately intense aerobic exercise for one week influenced cognitive functioning several hours later relative to a non-exercise control condition (e.g., storytime, art, music), and whether this influence was moderated by body mass index or symptoms of ADHD. Half of the students underwent the exercise intervention in week 1 and the control condition in week 2, and the other half underwent the two conditions in opposite order. The cognitive test battery consisted of alternate forms of paced serial addition, size ordering, listening span, digit-span backwards, and visual coding, with one subtest administered each day of the week. Scores across tests were averaged to give each child an overall performance score for each week. Participants completed the exercise approximately 30 minutes after lunch and the psychometric testing was conducted in a group setting in the classroom at the end of the school day. Results indicated no main effect of exercise, but a counterbalance group x exercise interaction emerged such that only those who received the exercise intervention during the second week benefited. The authors interpreted this as an “enhancement of practice effect” and suggested that enhanced recall due to improved hippocampal synaptic transmission (i.e., LTP) may be the mechanism. There were no significant interactions with BMI or ADHD symptoms suggesting that the limited benefits were similar for all children, irrespective of weight or ADHD symptom status.

Three additional studies used longer-term interventions that were at least 10 weeks in duration [75,82,84]. Fisher et al. [84] piloted a 10-week physical education (PE) intervention consisting of two hours per week of aerobically intense PE compared to two hours of standard PE. Their main aim was to assess the utility of the intervention and the reliability of the measures for subsequent use in a larger randomized controlled trial (RCT). The study was conducted in two phases: an initial study of practical utility and reliability of the cognitive outcome measures, followed by a 10-week exploratory RCT with 64 healthy 5 and 6 year-old boys from six primary schools. Outcome measures included Spatial Span and Spatial Working Memory from the Cambridge Neuropsychological Test Battery (CANTAB), the ANT, the Cognitive Assessment System (CAS; planning; attention; perceptual processing; memory), and the short form of the Connor’s Parent Rating Scale. Group differences favoring the aerobically-intense PE were observed for CANTAB Spatial Span, CANTAB Spatial Working Memory Errors, and ANT Accuracy, although the authors found that reliability for some of these measures was low in the initial stage of the study. There were no significant differences between intervention and control group changes in CAS scores, but those receiving intense PE showed greater improvements on parent ratings of Cognitive Problems/Inattention.

Davis et al. [82] conducted a RCT to investigate the impact of a 13-week exercise program (20 or 40 min/day), compared to a control condition, on cognitive and academic functioning, and prefrontal functioning in 171 sedentary, overweight 7- to 11-year-old children. The CAS was used to assess cognitive functioning and the Woodcock-Johnson Tests of Achievement III assessed academic achievement. A significant dose-response benefit of exercise on executive functioning (i.e., Planning from the CAS) and math scores emerged. No effects were detected on other scales of the CAS or on reading scores. In addition, 20 children participated in a fMRI pilot study consisting of baseline (control n = 9, exercise n = 11) and post-test (control n = 9, exercise n = 10) brain scans acquired while subjects completed an anti-saccade task. Those participating in the exercise program showed evidence of increased bilateral prefrontal activity and reduced bilateral posterior parietal activity compared with controls.

Finally, Kamijo et al. [75] investigated the effects of a 9-month daily afterschool physical activity program designed to improve cardiorespiratory fitness on ERP measures of working memory in preadolescent children. Increases in cardiorespiratory fitness were found to be

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associated with improvements in the cognitive control of working memory as measured using a modified Sternberg task [86]. Further, the beneficial effects of the physical activity intervention were greater for a task condition requiring greater working memory demands. In addition, the intervention group exhibited a larger initial contingent negative variation component at the frontal electrode site, relative to the waitlist group at post-test; an effect not observed during the pre-test, which the authors suggest is indicative of more effective cognitive control, which in turn may underlie their more accurate task performance. Notably, analysis of a subgroup of children from this study found that increased performance on some executive function measures (i.e., Stroop Color-Word and Trails B) was correlated with the amount of time children spent above the “target heart zone” or in vigorous, as opposed to moderate, physical activity [87].

The Davis and Kamijo studies [75,82], which administered daily aerobic exercise interventions, are particularly notable in that, in addition to finding positive effects of exercise on executive function test performance, their interventions also resulted in changes in neurophysiologic measures of cortical functioning in areas of the brain underlying cognitive control. Taken together, the six studies reviewed above provide tentative, but not overwhelming evidence that intense aerobic exercise enhances cognitive functioning in typically-developing children. Notably, whether the exercise intervention was administered in a single session or over an extended period of time, the post exercise testing was always administered shortly after the termination of the exercise. As such, it is impossible to know from these studies the degree to which exercise might yield short-term versus long-term cognitive benefits.

In addition to studies examining the impact of exercise on cognitive functioning, and equally relevant to the potential utility of exercise as an intervention for ADHD, some studies suggest that exercise improves children’s attention, concentration, and social functioning in the classroom, with greater effects in children with disruptive behaviors (see [88] for review). More recent studies have tested the impact of in-class physical activity breaks or frequent recess breaks on classroom behavior and have found that children spend more time on-task immediately following these physical activities [89-91]. However, the physical activity during these periods tended to be less intense than typical aerobic training and none of these interventions looked at longer-term sustained effects of the interventions on children’s behavior. Finally, Allison et al. [92] conducted a meta-analytic study assessing the impact of physical exercise on disruptive behavior, including aggression, in both children and adults, and concluded that it reduces a variety of disruptive behaviors in a variety of populations. This is particularly relevant given the high rates of comorbidity between ADHD and disruptive behaviors [93].

The impact of exercise on children with ADHD

The acute effects of exercise have been associated with reductions in negative behaviors and improvements in acceptable behaviors and cognitive functions in children with clinical disorders categorized by poor impulse control and attention [94]. Gapin, Labban, and Etnier [95] recently reviewed a handful of preliminary studies (mostly unpublished) suggesting some modest effect of exercise on ADHD behaviors. Five additional studies examining the effect of exercise on ADHD have been recently published [96-100] and are reviewed below.

Gapin and Etnier [99] conducted a cross-sectional correlational study to investigate the relationship between moderate-to-vigorous daily physical activity (MVPA) and executive functioning in 18 school-age boys with ADHD. Participants completed tasks assessing inhibitory control, working memory, planning, and processing speed. Children wore accelerometers during all their waking hours for seven consecutive days to provide the

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number of minutes daily that they were engaged in MVPA. In addition, children were asked to keep a daily log of physical activities, such as riding a bike or swimming, particularly if the accelerometer was left off during that time, and the authors estimated MVPA during these activities to add to the accelerometer measurements. Regression analyses revealed that MVPA was a significant predictor of performance on the Tower of London Total Move Score and Tower of London Total Execution Time such that higher MVPA was associated with lower Total Move Score and faster execution times, indicative of better performance. In addition, although nonsignificant, correlations for five of the other six executive function outcome measures with MVPA were in the hypothesized direction, with higher MVPA predictive of better performance (r's = .20–.45). These results suggest that higher physical activity may be associated with better executive functioning in children with ADHD.

The remaining four studies were small experimental pilot studies, with two [98,100] investigating the acute impact of exercise on test performance, and two [96,97] investigating the impact of chronic exercise interventions on various cognitive functions and ADHD behaviors as rated by parents and teachers. Consistent with the literature in typically-developing children, Medina et al [98] found that, compared to a stretching control session, 30 minutes of aerobic treadmill exercise immediately resulted in increased response speed, lower response speed variability, improvements in vigilance and impulsivity (anticipatory responding), and marginal improvements in stimulus discriminability as measured by a go/no-go task in 25 boys with ADHD between 7 and 15 years of age.

Similarly, Chang et al [100] examined the impact of moderate intensity aerobic exercise for 30 minutes relative to a comparison intervention involving viewing exercise videos in 40 school-age children with ADHD. Prior to and immediately following the single bout of the exercise, children were administered the Stroop Color-Word and the Wisconsin Card Sort (WCST) tests as indices of executive functions. Children in the exercise group demonstrated specific significant gains relative to controls on the Color-Word subtest of the Stroop, with no differences on the two control conditions. In addition, those in the exercise group had a significantly greater decrease in non-perseverative errors and a greater increase in categories completed on the WCST, although other indices from the WCST did not differ between the groups and baseline differences between the groups in WCST performance make the findings from that test difficult to interpret.

Smith et al. [97] piloted a before-school physical activity intervention on 17 children (Grades K-3) exhibiting at least four hyperactivity/impulsivity symptoms. These children completed approximately 26 min of continuous moderate-to-vigorous physical activity daily over eight school weeks with good program adherence. Findings indicated significant improvement on post-intervention and weekly measures of response inhibition, as well as parent and teacher ratings of ADHD symptoms and disruptive behaviors. In addition, they found post-intervention improvements in fine and gross motor proficiency.

Using a between-subjects design, Verret et al. [96] assessed the effects of a moderate- to high-intensity physical activity program lasting 10 weeks (45 minutes, 3 times a week in the school gym) on fitness, cognitive functions, and behavior in sample of 21 7-12 year-old children with ADHD. Although the exercise program did not improve fitness of the participants, exercised children experienced significant gains in motor skills, neuropsychological measures of visual search speed and sustained auditory attention, and parent ratings on the CBCL social problems, thought problems, and attention problems indices. There was a trend toward improvement on teacher CBCL ratings in most areas.

Taken together, these five pilot studies – although each limited by small sample size, unblind status of the researchers and raters of behavior, and/or either lack of or poorly designed control conditions – provide preliminary evidence of the potential for exercise interventions to improve both the behavioral symptoms and neuropsychological functioning of school-aged children with ADHD.

Conclusions

ADHD is a neurodevelopmental disorder that is characterized by delayed, if not permanently stunted, cortical development and neurocognitive functioning. Further, data suggest that long-term trajectories and outcomes of individuals with ADHD may be linked to the degree to which neural systems normalize over the lifespan. As such, novel interventions that promote neural growth and cognitive development have the potential to provide lasting improvements in ADHD severity across the lifespan.

Research in animals and human adults provides compelling evidence that aerobic exercise can enhance neural growth and development, and improve cognitive and behavioral functioning. More limited research in children has linked greater fitness to better executive functioning and a limited number of experimental studies have provided tentative evidence for positive effects of physical exercise on executive functioning. As executive function deficits are closely associated with ADHD, it has been posited that programs of sustained physical exercise have the potential to reduce symptoms and yield improved long-term outcomes for youth with ADHD.

To date a very limited number of small, open clinical trials have systematically evaluated the impact of physical exercise on behavioral and cognitive functioning in children with ADHD. Results from these preliminary studies provide some support for the hypothesis that a sustained program of physical exercise is beneficial to children with ADHD. However, far more research is necessary before widespread use of such interventions would be warranted. In addition to larger, better controlled double-blind studies examining the acute effects of such programs on ADHD severity, longer follow-up studies are necessary to determine whether, like psychostimulants and behavior modification, treatment benefits are transient and only persist as long as the exercise continues. On the other hand, it is possible that exercise promotes brain growth and development, and as such can yield enduring behavioral change in children. While unknown at this time, it is possible that exercise, when combined with cognitive remediation strategies or other evidence-based treatments, will be particularly helpful. Finally, future treatment studies should incorporate pre- and post-intervention neuroimaging and biological sampling to elucidate the mechanisms by which physical exercise might ameliorate symptoms of ADHD.

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