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The Relation of Childhood Physical Activity and Aerobic Fitness to Brain Function and Cognition: A Review

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Physical inactivity has been shown to increase the risk for several chronic diseases across the lifespan. However, the impact of physical activity and aerobic fitness on childhood cognitive and brain health has only recently gained attention. The purposes of this article are to: 1) highlight the recent emphasis for increasing physical activity and aerobic fitness in children's lives for cognitive and brain health; 2) present aspects of brain development and cognitive function that are susceptible to physical activity intervention; 3) review neuroimaging studies examining the cross-sectional and experimental relationships between aerobic fitness and executive control function; and 4) make recommendations for future research. Given that the human brain is not fully developed until the third decade of life, preadolescence is characterized by changes in brain structure and function underlying aspects of cognition including executive control and relational memory. Achieving adequate physical activity and maintaining aerobic fitness in childhood may be a critical guideline to follow for physical as well as cognitive and brain health.

Keywords: executive function, relational memory, pediatrics

Regular physical activity has been shown to be protective against the development of several diseases including obesity, cardiovascular disease, certain cancers, and Type II diabetes (73). Given that these diseases have also been associated with reduced cognitive and brain health among older adults (21,35), physical activity is suggested to indirectly improve cognition and brain health by attenuating the risk for disease. However, research from rodent models demonstrates that physical activity is a potent stimulator of processes underlying neurogenesis, synaptogenesis, as well as brain vasculature (53,72). In addition, physical activity training has been shown to counter age-related hippocampal tissue loss and improve spatial memory function among older adults (31). Taken together, the findings from both rodent and older human studies suggest that physical activity may indirectly or directly modulate cognitive function and brain health.

Converging lines of research indicate that regular physical activity and enhanced aerobic fitness may improve cognitive function and brain health in childhood as well. Higher-fit preadolescent children exhibit greater attention (42), faster information processing speed (43), and achieve higher scores on standardized achievement tests (11,27), relative to their lower-fit counterparts.

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These benefits were highlighted by a recent Institute of Medicine (48) committee charged with examining the status of physical activity and physical education in schools, how physical activity and fitness affect health outcomes, and ways to help schools get students to become more active. While acknowledging the fiscal and policy challenges involved, the final committee report recognized that attaining over 60 min of moderate to vigorous physical activity (MVPA) during the school day is necessary for optimal learning in the classroom. To represent the full scope of the positive contribution of regular physical activity to overall health and function, a team of kinesiologists validated the Human Capital Model (HCM) of physical activity (3). The HCM is supported by a growing community of public, private, and civil sector organizations. It considers physical activity an investment and consolidates the evidence for physical activity benefits into six domains including physical, emotional, individual, social, intellectual, and financial. Taken together, the Institute of Medicine report and the HCM place an emphasis on childhood health and provide a platform for implementing physical education and other physical activity opportunities in schools along with a holistic conceptual model that incorporates physical activity benefits for cognitive function and brain health.

However, much remains to be learned regarding the influence of physical activity on specific cognitive processes and their neural substrates. Knowledge from the developmental literature is largely based on observational/cross-sectional studies. Thus, information on the efficacy of improving physical activity and/or aerobic fitness for cognitive function and brain health in childhood remains limited. It is of particular importance to examine how the protracted development of specific brain structures provides opportunities for environmental modulation by health behaviors including physical activity. Keeping this in mind, our laboratory and colleagues have focused efforts on examining physical activity effects on the cognitive processes of executive control and relational/associative memory because the key neural structures subserving these processes—the prefrontal cortex and hippocampus—continue to develop throughout childhood. Furthermore, these cognitive processes and their neural substrates provide the foundation for successful learning and scholastic achievement, thereby influencing overall health and well-being throughout life.

In this article, we review the brain developmental trajectory and evaluate observational and intervention studies examining relationships between physical activity and fitness with cognitive performance and brain health in childhood.

Brain Development

The human brain undergoes a fourfold increase in volume from birth to adolescence resulting in an adult brain that is highly structured and functionally specialized (49). Gestation represents a period of rapid brain development involving several synchronized processes including neurogenesis, migration, programmed cell death, myelination, and synaptogenesis (56). In addition, sulci and gyri formation is nearly complete by birth (57) and by 2 years the brain achieves 80% of its adult weight (25).

Despite the fact that the brain achieves 95% of its maximum size by 6 years, the processes underlying functional connectivity—including competitive elimination of synapses, myelination, and dendritic and axonal arborization—continues throughout life (56). The early rapid increase in synaptic density is followed by a period during which synaptic connections that are not used are eliminated or pruned (58). This elimination increases both computational capacity and speed of information processing and serves as a functional mechanism for plasticity, which supports the hypothesis that the immature brain is sculpted to fit the individual's environment (2). Further, synaptic pruning occurs at varying velocities in different parts of the brain with sensory regions—such as the visual cortex—achieving maturity by 7 years while the middle frontal gyrus—a region involved in executive function not maturing until 20 years (47). One of the implications of this hierarchical growth model is that development of executive control—which consists of inhibition (resisting distractions or habits to maintain focus), working memory (mentally holding and manipulating information), and cognitive flexibility (multitasking)—is guided by the late maturation of the prefrontal cortex (10). Furthermore, protracted myelination throughout the cortices supports the position that childhood and adolescence are periods of modification in connectivity between distant brain circuitries as well as prefrontal specialization (38).

In addition to modifications in connectivity, different regions of the cortices display varying growth trajectories. Gray matter volume, which consists of neuronal cell bodies, dendrites, and unmyelinated axons, peaks between 10 and 12 years in the frontal and parietal lobes while temporal lobe gray matter volume does not peak until 16–17 years of age (37). Indeed, the dorsolateral prefrontal cortex—a cortical area subserving control of impulses, judgment, and decision-making—reaches adult levels of cortical thickness last (56).

The relatively delayed rate of maturation of the human brain, compared with other mammals, may provide opportunity for postnatal environmental modulation. The discovery that the dentate gyrus of the hippocampus in the adult brain continues to undergo neurogenesis—previously assumed to be complete at birth—may provide additional support to this theory (1). Thus, the protracted development of the prefrontal cortex and neurogenic capacity of the dentate gyrus offer the possibility of exciting mechanisms by which physical activity may affect cognitive function and brain health. Rodent models have been particularly useful in examining the role of physical activity in neurogenesis, and older human studies have provided further empirical support for this relationship (19,20,31).

Mechanisms Underlying Physical Activity-Brain Relationships

Although brain development is complete by the third decade of life, it is now well accepted that that the adult human brain has the capacity to form new neurons throughout life. The two brain regions that exhibit adult neurogenesis are the subventricular zone of the lateral ventricle and the dentate gyrus in the hippocampus (59). Evidence from rodent studies has revealed that several factors affect neurogenesis including stress, aging, environmental enrichment, and physical activity (40,50,54,68). However, physical activity has been identified as a critical neurogenic component of environmental enrichment (29,67). Indeed, wheel running in rodents enhances performance on hippocampal-dependent tasks including spatial memory and novel object recognition (61,69). Subsequent studies established that the neurogenic effects of exercise are localized to the dentate gyrus of the hippocampus and not the subventricular zone/olfactory bulb; thus, providing a model to explain the enhanced hippocampal function observed following exercise (6). This is further supported by the observation that long-term potentiation (LTP)—a persistent increase in synaptic strength that may underpin certain forms of learning or memory—is enhanced in the dentate gyrus of running mice compared with controls (72). However, the granule cells in the dentate gyrus can be influenced by a variety of factors including neurotransmitters, neural peptides, and growth factors.

Although several neurotrophins are involved in the maintenance of neural function and plasticity, brainderived neurotrophic factor (BDNF) is proposed to be one of the key mediators of exercise effects on the brain (22). BDNF is expressed in several tissues including the brain, muscle, and adipose tissue and plays an important role in various aspects of developmental and adult brain plasticity, including proliferation, differentiation, and survival of neurons (46). Studies in animals have shown that exercise-induced increases in BDNF mRNA are specific to the dentate gyrus (34), an area vital for learning and memory. Among humans, circulating BDNF has been related to hippocampal volume, with aerobic fitness related to the upregulation of BDNF serum levels and greater hippocampal volume among older adults (31,55). Although differences in hippocampal volume as a function of fitness have been recently observed in children as well (discussed below), additional studies are needed to determine exercise effects on neurochemical factors that mediate the effects of physical activity on cognition in childhood. A complete review of possible mechanisms for the effects of physical activity on brain and cognition is beyond the scope of this article, but several informative reviews on the topic exist in the literature (39,70).

Aerobic Fitness and Hippocampal-Dependent Memory

The hippocampus is essential for relational/associative memory, which refers to the ability to form and use representations among the constituent elements of an event or scene (18,23). This form of memory is particularly important because it is critical for binding arbitrary associations between pieces of information and their flexible expression (30), thus representing a continuous cognitive process that is integral to learning in school and everyday life. Therefore, elucidating whether factors such as physical activity or fitness can enhance relational memory could be crucial for achieving optimal learning and cognitive development, potentially influencing life outcomes beyond childhood.

Given that wheel running increases neurogenesis in the hippocampus and enhances hippocampal-dependent memory in rodents (51), the impact of physical activity and aerobic fitness on hippocampal structure and function has received much attention in recent years. Among older adults, Erikson et al. (32) found that higher aerobic fitness was associated with increased hippocampal volumes, which translated to superior performance on a spatial memory task. Recent evidence has emerged indicating that differences in hippocampal structure and function may extend to children as well.

Specifically, Chaddock et al. (12) examined differences in hippocampal volumes and performance on a relational memory task between higher- (\geq 70th VO_{2max} percentile) and lower- (\leq 30th VO_{2max} percentile) fit 9- to 10-year-olds. Higher-fit children exhibited larger bilateral hippocampal volumes and greater accuracy on the

relational memory task. Furthermore, the hippocampal volume mediated the positive association observed between fitness and relational memory performance. No differences were observed—across fitness levels for item memory performance and nucleus accumbens volume (assessed as a control region), demonstrating the selectivity of fitness to specific aspects of memory and their neural substrates. In a subsequent study, the behavioral findings were extended to a different relational memory task among a unique sample, as selective associations with fitness were only observed for the relational task (15). To test whether the provision of physical activity would enhance relational memory, Monti et al. (60) used eye-movements—an implicit measure of hippocampal activity—to demonstrate that 8- to 9-yearolds who participated in a 9-month physical activity intervention showed eye movement patterns indicative of superior relational memory without any difference in the item condition (an aspect of memory subserved by regions outside the hippocampus). Although pretest eyemovement data were not collected, the observation that there was a significant group difference on eye-movement measures specific to the relational memory condition at posttest provided additional support for the selective link between the hippocampus, relational memory, and fitness.

Aerobic Fitness and Executive Control: Evidence From Structural and Functional MRI

Unlike the study of physical activity and aerobic fitness effects on hippocampal plasticity—which has predominantly been studied using animal models—the relationship between physical activity and aerobic fitness and the prefrontal cortex has been illuminated by several studies among humans. Of particular interest has been the influence of fitness on executive control; goal-directed cognitive processes underlying perception, memory, and action. Indeed, much of the currently available evidence suggests disproportionately larger effects of fitness on executive control processes—relative to controlled, visuospatial, and speed tasks—among adult populations (21,45).

Subcortical structures subserving the fronto-striatal connection are also suggested to modulate efficient recruitment of executive control and these structures may be influenced by fitness. Chaddock et al. (13) investigated the relationships between aerobic fitness, performance on a modified flanker task, and volume of the basal ganglia, a group of structures located at the base of the forebrain and implicated in action selection and execution (41). The flanker task is an executive control task that specifically requires variable amounts of inhibitory control. It consists of arrays of congruent and incongruent stimuli, with the instruction to respond to the directionality of the central (i.e., target) stimulus and ignore flanking stimuli. Higher-fit children exhibited larger volumes of dorsal striatum (eg, left caudate nucleus, bilateral putamen, globus pallidus), which was negatively associated with behavioral interference attributed to the incongruent flanking stimuli, providing a behavioral sequelae for the observed structural differences between groups. Indeed, lower-fit children exhibited over a twofold higher interference effect indicating less efficient management of conflicting cues compared with higher-fit children.

Beyond MRI measures of brain structure, the availability of functional MRI (fMRI) allows for a proxy measure (eg, blood flow) of underlying brain activation during task performance, thereby detecting regional locations and networks that are associated with higher aerobic fitness. Although research is limited, a handful of studies have used fMRI to assess how physical activity or aerobic fitness changes patterns of brain activation (14,17,24,52,71). Specifically, Chaddock et al. (14) compared performance on early and later blocks of a flanker task between higher and lower fit 9- and 10-year-olds using fMRI. During congruent trials requiring lower amounts of executive control, both groups showed greater activation in the prefrontal and parietal cortex (eg., left middle frontal gyrus, supplementary motor area, anterior cingulate cortex [ACC], left superior parietal lobe) during the early blocks when the paradigm was more novel, followed by a decrease in activity during the later blocks. However, during incongruent trials requiring the upregulation of executive control, higher-fit children maintained accuracy across blocks and exhibited increased activation in the left middle frontal gyrus, right middle frontal gyrus, supplementary motor area, ACC, and the left superior parietal lobe during the early task block and reduced activity in the later block. In contrast, the lowerfit children declined in accuracy across blocks without displaying any changes in brain activity. These findings are consistent with studies that have used event-related brain potentials (ERPs, discussed later) to indicate that higher-fit children may have greater ability to upregulate neural processes involved in executive control to meet task demands and maintain performance.

Differences in underlying brain activity have also been found as a function of physical activity interventions. Davis et al. (24) tested the effect of 3 months of physical activity training on executive function in overweight children using cognitive assessments, achievement measures, and fMRI. Participants were randomized into high (40 min) and low-dose (20-min) exercise and control groups. Exercise selectively enhanced executive control tasks and math achievement in a dose-dependent manner. The improvement in math achievement was particularly important because no educational instruction was given. Relative to the fMRI data, the exercise group (high and low-dose exercise groups were collapsed for fMRI analyses) exhibited increased bilateral prefrontal cortex activity and decreased activity in the posterior parietal cortex. Similarly, Chaddock et al. (17) observed differences in brain activity between children participating in a 9-month physical activity intervention, relative to children assigned to a wait-list control. In addition to improved performance on an attentional task of inhibitory control, intervention participants exhibited decreased

activation in the right prefrontal cortex while the control group showed no changes in brain function from baseline to posttest. Furthermore, posttest brain activity among the intervention group showed similar anterior frontal brain patterns and incongruent accuracy performance to a group of college-aged adults while the control group children failed to show such a pattern.

A third physical activity intervention study examined changes in accuracy and brain function among 8- to 11-year-old overweight children using flanker and antisaccade tasks (52). Relative to the control group, intervention participants exhibited decreased activity in several areas subserving the antisaccade performance, including the precentral gyrus and posterior parietal cortex. However, increased activity was observed in regions involved in flanker accuracy including the ACC and superior frontal gyrus. This observation for ACC activation was in contrast with Chaddock et al. (17) who did not observe any changes in ACC activation using the flanker task. Nevertheless, evidence from fMRI studies suggests that that physical activity may influence the modulation of neural circuitry supporting executive control in prepubertal children, but also suggests that further work is needed to better determine the differential patterns of activation across various cognitive tasks.

Aerobic Fitness and Executive Control: Evidence From Neuroelectric Studies

In addition to fMRI, other neuroimaging tools have been used to study the relation of physical activity to brain function. Findings from our laboratory have indicated that fitness has a positive relationship with performance on cognitive tasks requiring variable levels of executive control in children (7). Several subsequent studies have assessed ERPs during stimulus engagement and response production to determine which aspects of cognition are influenced by fitness. ERPs refer to patterns of neuroelectric activation that occur in response to, or in preparation for, a stimulus or response. Although ERPs have low spatial resolution, they have high temporal resolution; therefore, reflecting specific neural operations that occur between stimulus encoding and response execution. The P3 (P300 or P3b) is a positive-going component observed in the stimulus-locked ERP waveform that has captured considerable attention in the literature and is believed to represent the updating of memory once sensory information has been analyzed (26). P3 amplitude and latency are thought to be directly proportional to the amount of attentional resources allocated during stimulus engagement and information processing speed during stimulus evaluation, respectively (28,63). Thus, this endogenous component provides rich information regarding brain function underlying behavior within the stimulus environment.

Several studies in our laboratory have demonstrated differences in the P3 component between higher- and

lower-fit children. Hillman et al. (42) assessed neuroelectric differences between higher and lower-fit 9- to 10-yearolds on a modified flanker task. Higher-fit children not only out-performed lower-fit children, they also exhibited larger P3 amplitude, indicating greater attentional resource allocation during stimulus evaluation. Interestingly though, the findings were observed across both flanker conditions requiring variable (ie, lower and higher) amounts of inhibition. In a subsequent study among another group of children (mean = 10.1 years) the flanker task was manipulated by adding an incompatible stimulus-response condition during which participants were instructed to press a button that opposed the direction of the central stimulus (64), necessitating greater inhibitory control and cognitive flexibility. Higher-fit children maintained their response accuracy (which was higher than lower-fit children) regardless of the stimulus-response compatibility condition. However, lower-fit children exhibited reduced accuracy with increases in task difficulty. Inspection of the underlying ERPs showed that higher-fit children exhibited larger P3 amplitude relative to lower-fit children, but also for incompatible compared with compatible conditions; modulation that was not evidenced in the lower-fit group. Furthermore, higher-fit children had shorter P3 latencies than their lower-fit counterparts. These results indicated that higher-fit children have greater attentional resource allocation and enhanced cognitive flexibility during tasks that modulate cognitive control demands. Given that cognitive processing speed was also faster, the data suggest that higher amounts of fitness are related to better acquisition of information within the stimulus environment. In summary, our initial findings suggested that fitness had a general relationship with cognition across tasks requiring variable amounts of executive control. Subsequent studies in our laboratory modified the flanker paradigm to extend the literature further by demonstrating selective effects of fitness on inhibitory control, suggesting a need for sensitive assays to bore out the selective or disproportionate nature of the fitness-cognition relationship.

In addition to improved cognitive function during stimulus acquisition, higher-fit children also exhibit enhanced action monitoring during response execution; another important aspect of executive control. To carry out goal-directed behavior, individuals must continuously monitor interactions between intended and executed actions. The error-related negatively (ERN)—localized to the dorsal portion of the ACC—is a negative-going component observed during a response and is suggested to index the action monitoring system (33,36). Findings from both Hillman et al. (42) and Pontifex et al. (64) indicated that when instructed to respond as quickly as possible, higher-fit children exhibited smaller ERN amplitudes and higher response accuracy following commission errors, relative to their lower-fit counterparts. Interpreting these findings in the context of the conflict monitoring theory—which posits that the ACC detects response conflicts and transmits signals to several regions of the brain, including the dorsolateral prefrontal cortex, which in turn regulate executive control in support of ongoing environmental interaction (5,9)—suggests that higher-fit children exhibit lower response conflict during task execution. Furthermore, similar to findings for the P3, Pontifex et al. (64) observed that the ERN was significantly larger for the incompatible condition compared with the compatible condition of a modified flanker task among the higher-fit children; an effect that was not observed among lower-fit children. Although the ERN in the incompatible condition did not differ across fitness groups, the lower-fit group did not exhibit significant changes in ERN. Therefore, higher-fit children not only exhibit less conflict, but they also appear to flexibly modulate action monitoring processes depending on executive control demands to optimize behavioral interactions within the task environment (44).

Therefore, cross-sectional studies indicate that higher-fit children allocate greater attentional resources during stimulus engagement (P3 amplitude) and have greater capability to flexibly regulate executive control, relative to their lower-fit counterparts. This difference in strategy may account for some of the variability observed in task performance across fitness levels. Furthermore, a recently concluded randomized controlled trial in our laboratory demonstrated that 8- and 9-year-olds receiving 9 months of physical activity (5 days/week) exhibited greater improvements in attentional inhibition and cognitive flexibility coupled with increased attentional resources (eg, increased P3 amplitude) during tasks requiring the upregulation of attentional inhibition and cognitive flexibility; an effect not observed for the waitlist control (Hillman et al., submitted for publication).

Considering both the hippocampal and prefrontal cortex literature, fitness has selectively positive effects on volumes of particular structures that subserve relational memory and executive control. In addition, the positive associations between fitness and brain structure were only found for performance on hippocampal-dependent/ relational memory tasks and not item memory tasks, further reinforcing the fitness-brain relationship to the hippocampus. These findings are consistent with those from animal studies indicating that the hippocampus is positively influenced by physical activity. Emerging evidence from neuroimaging studies suggests that higher-fit children demonstrate differential patterns in brain activity while performing executive control tasks, relative to their lower-fit counterparts. Furthermore, the provision of physical activity appears to alter efficiency and flexible modulation of neural circuitry that supports executive control in children.

Translational Applications of Physical Activity to Academics, Learning and Real-World Tasks

The relationship between physical activity, fitness, and academic achievement has received attention in recent years due to the increased prevalence of children who are lower-fit and overweight. Several publications on the topic indicate that regular physical activity and higher levels of aerobic fitness have weak but positive effects

on academic achievement (4,11). Given that much of this evidence is based on cross-sectional studies (however, see Donnelly et al. (27) for an exception), the magnitude of the effect of physical activity on academic achievement remains an issue of debate. However, there is no empirical data in the literature that suggests that increasing time spent in physical activity in schools has a detrimental effect on academic achievement.

In addition, the literature thus far has focused predominantly on the ability to perform cognitive tasks. That is, human physical activity studies have focused on differences in task performance as a function of fitness or engagement in a physical activity program, rather than the ability to acquire or learn new information per se. Demonstrating that learning is positively influenced by physical activity or aerobic fitness would provide an important link between physical activity and cognitive and brain health that is directed toward the everyday acquisition of information with implications for lifelong cognitive wellbeing. A recent study in our laboratory examined the influence of fitness on learning and memory among 9- to 10-year-olds (65). Higher- and lower-fit children performed a task requiring them to learn the names of specific regions on a fictitious map, under a condition in which they only studied the maps and names versus a condition in which they were tested during studying process. Testing during studying has been previously shown to enhance accuracy for retrieval and assists learning through the provision of a strategy (8). The retention day occurred one day after initial learning and involved two different recall conditions: free recall and cued recall. No differences in performance at initial learning were observed between higher-fit and lower-fit participants. However, during the retention session higher-fit children outperformed lower-fit children, particularly when the material was learned without an explicit strategy (ie, the study only condition). Therefore, fitness appears to be associated with enhanced learning, particularly during conditions in which learning is more challenging. Given the greater retrieval among higher-fit children and the lack of interaction between fitness and the cued condition, the beneficial influence of fitness may primarily occur via enhancements during initial encoding for novel information, rather than through the enhancement of retrieval processes. These findings extend the literature by showing that differences in learning are evident among prepubertal children as a function of fitness.

A last example of how fitness influences aspects of children's everyday life examined the role of fitness in successful street crossing among 8- to 10-year-olds (16). Higher- and lower-fit children were asked to navigate trafficked roads—while walking on a manually driven treadmill—within a modeled virtual environment. Child pedestrians crossed the street while undistracted, listening to music, or conversing on a hands-free cellular phone. There was an interaction between fitness and street crossing condition such that higher-fit children maintained street crossing rates across all conditions, regardless of the amount of distraction. In contrast, lower-fit children exhibited decreases in street crossing success rates when

on the phone, compared with the undistracted and music condition. Therefore, higher levels of aerobic fitness may attenuate impairment typically observed with multitasking during street crossing. These findings are particularly important considering that pedestrian accidents are the second leading cause of injury and mortality in children between the ages of 5 and 14 in the U.S. (66).

Research Needs

Additional longitudinal studies are needed to better examine the association between changes in fitness, physical activity, brain, and cognition. It should be noted that neuroimaging evidence is limited in its generalizability because of the typically lower sample sizes and variability in subject characteristics. Therefore, additional randomized controlled trials are needed to elucidate how changes in physical activity and fitness predict changes in brain structure and function in children. Further research is needed to determine to what extent genetics, motivation, personality characteristics, nutrition, and intellectual stimulation play roles in mediating the fitness-brain relationship observed in cross-sectional studies. Critically missing from the literature is the examination of the relationship between chronic physical activity, independent of aerobic fitness, and cognitive function in childhood. Thus, future studies should objectively assess physical activity in addition to aerobic fitness. Given that much of the current knowledge is based on studies among normally developing and healthy children, additional studies among children with autism, ADHD, and other disorders are needed to enhance the generalizability of findings.

General Conclusions

Evidence from rodent models strongly indicates that physical activity is a potent stimulator of molecular and cellular components underlying brain structure and function. Furthermore, studies in humans suggest that physical activity may be protective against age-related brain tissue loss and may be positively associated with brain health and cognitive function in children as well. Childhood presents a critical period in brain growth characterized by prolonged maturation of structures involved in executive function and relational memory as well as fine-tuning of the brain circuitry intended to support operations of the adult brain (58). Therefore, this protracted development may provide opportunity for physical activity to optimize cognitive function and brain health during childhood. However, longitudinal studies are needed to examine how changes in physical activity affect the physical and functional developmental trajectory of the brain.

Considering the rise in physical inactivity and obesity in the U.S. and other industrialized nations, the results from the studies reviewed in this article have significant public health and educational implications (62). Although additional experimental studies are warranted, the current evidence points to the benefits of physical activity and aerobic fitness for cognitive and brain health in childhood.

References

- Altman J, Das GD. Post-natal origin of microneurones in the rat brain. *Nature*. 1965; 207(5000):953–956. PubMed doi:10.1038/207953a0
- Andersen SL. Trajectories of brain development: point of vulnerability or window of opportunity? *Neurosci Biobehav Rev.* 2003; 27(1–2):3–18. PubMed doi:10.1016/ S0149-7634(03)00005-8
- 3. Bailey R, Hillman C, Arent S, Petitpas A. Physical activity: an underestimated investment in human capital? *J Phys Act Health*. 2013; 10(3):289–308. PubMed
- Biddle SJ, Asare M. Physical activity and mental health in children and adolescents: a review of reviews. *Br J Sports Med.* 2011; 45(11):886–895. PubMed doi:10.1136/ bjsports-2011-090185
- Botvinick MM, Braver TS, Barch DM, Carter CS, Cohen JD. Conflict monitoring and cognitive control. *Psychol Rev.* 2001; 108(3):624–652. PubMed doi:10.1037/0033-295X.108.3.624
- Brown J, Cooper-Kuhn CM, Kempermann G, et al. Enriched environment and physical activity stimulate hippocampal but not olfactory bulb neurogenesis. *Eur J Neurosci*. 2003; 17(10):2042–2046. PubMed doi:10.1046/j.1460-9568.2003.02647.x
- Buck SM, Hillman CH, Castelli DM. The relation of aerobic fitness to stroop task performance in preadolescent children. *Med Sci Sports Exerc*. 2008; 40(1):166–172. PubMed doi:10.1249/mss.0b013e318159b035
- Carpenter SK, Pashler H. Testing beyond words: using tests to enhance visuospatial map learning. *Psychon Bull Rev.* 2007; 14(3):474–478. PubMed doi:10.3758/BF03194092
- Carter CS, Van Veen V. Anterior cingulate cortex and conflict detection: an update of theory and data. *Cogn Affect Behav Neurosci*. 2007; 7(4):367–379. PubMed doi:10.3758/CABN.7.4.367
- Casey BJ, Giedd JN, Thomas KM. Structural and functional brain development and its relation to cognitive development. *Biol Psychol.* 2000; 54(1–3):241–257. PubMed doi:10.1016/S0301-0511(00)00058-2
- Castelli DM, Hillman CH, Buck SM, Erwin HE. Physical fitness and academic achievement in third-and fifth-grade students. J Sport Exerc Psychol. 2007; 29(2):239–252. PubMed
- Chaddock L, Erickson KI, Prakash RS, et al. A neuroimaging investigation of the association between aerobic fitness, hippocampal volume, and memory performance in preadolescent children. *Brain Res.* 2010; 1358:172–183. PubMed doi:10.1016/j.brainres.2010.08.049
- Chaddock L, Erickson KI, Prakash RS, et al. Basal ganglia volume is associated with aerobic fitness in preadolescent children. *Dev Neurosci*. 2010; 32(3):249–256. PubMed doi:10.1159/000316648
- Chaddock L, Erickson KI, Prakash RS, et al. A functional MRI investigation of the association between childhood aerobic fitness and neurocognitive control. *Biol Psychol*. 2012; 89(1):260–268. PubMed doi:10.1016/j.biopsycho.2011.10.017

- Chaddock L, Hillman CH, Buck SM, Cohen NJ. Aerobic fitness and executive control of relational memory in preadolescent children. *Med Sci Sports Exerc*. 2011; 43(2):344– 349. PubMed doi:10.1249/MSS.0b013e3181e9af48
- Chaddock L, Neider MB, Lutz A, Hillman CH, Kramer AF. Role of childhood aerobic fitness in successful street crossing. *Med Sci Sports Exerc.* 2012; 44(4):749–753. PubMed doi:10.1249/MSS.0b013e31823a90cb
- Chaddock-Heyman L, Erickson KI, Voss MW, et al. The effects of physical activity on functional MRI activation associated with cognitive control in children: A randomized controlled intervention. *Front. Hum. Neurosci.* 2013; 7:72. PubMed doi:10.3389/fnhum.2013.00072
- Cohen NJ, Eichenbaum H. Memory, Amnesia, and the Hippocampal System. Cambridge, MA: MIT Press, 1995.
- Colcombe SJ, Erickson KI, Scalf PE, et al. Aerobic exercise training increases brain volume in aging humans. *J Gerontol A Biol Sci Med Sci.* 2006; 61(11):1166–1170. PubMed doi:10.1093/gerona/61.11.1166
- Colcombe SJ, Kramer AF, Erickson KI, et al. Cardiovascular fitness, cortical plasticity, and aging. *Proc Natl Acad Sci USA*. 2004; 101(9):3316–3321. PubMed doi:10.1073/ pnas.0400266101
- Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychol Sci.* 2003; 14(2):125–130. PubMed doi:10.1111/1467-9280. t01-1-01430
- Cotman CW, Berchtold NC, Christie L. Exercise builds brain health: key roles of growth factor cascades and inflammation. *Trends Neurosci*. 2007; 30(9):464–472. PubMed doi:10.1016/j.tins.2007.06.011
- Davachi L. Item, context and relational episodic encoding in humans. *Curr Opin Neurobiol*. 2006; 16(6):693–700. PubMed doi:10.1016/j.conb.2006.10.012
- Davis CL, Tomporowski PD, McDowell JE, et al. Exercise improves executive function and achievement and alters brain activation in overweight children: a randomized, controlled trial. *Health Psychol.* 2011; 30(1):91–98. PubMed doi:10.1037/a0021766
- Dekaban AS, Sadowsky D. Changes in brain weights during the span of human life: relation of brain weights to body heights and body weights. *Ann Neurol*. 1978; 4(4):345–356. PubMed doi:10.1002/ana.410040410
- 26. Donchin E. Surprise!... surprise? *Psychophysiology*. 1981; 18(5):493–513. PubMed doi:10.1111/j.1469-8986.1981. tb01815.x
- Donnelly JE, Greene JL, Gibson CA, et al. Physical Activity Across the Curriculum (PAAC): a randomized controlled trial to promote physical activity and diminish overweight and obesity in elementary school children. *Prev Med.* 2009; 49(4):336–341. PubMed doi:10.1016/j. ypmed.2009.07.022
- Duncan-Johnson CC. P300 latency: a new metric of information processing. *Psychophysiology*. 1981; 18(3):207–215. PubMed
- Ehninger D, Kempermann G. Regional effects of wheel running and environmental enrichment on cell genesis and microglia proliferation in the adult murine neocortex.

- Cereb Cortex. 2003; 13(8):845–851. PubMed doi:10.1093/cercor/13.8.845
- 30. Eichenbaum H, Cohen NJ. From Conditioning to Conscious Recollection: Memory Systems of the Brain. Oxford: Oxford University Press, 2001.
- Erickson KI, Voss MW, Prakash RS, et al. Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci USA*. 2011; 108(7):3017–3022. PubMed doi:10.1073/pnas.1015950108
- 32. Erickson KI, Prakash RS, Voss MW, et al. Aerobic fitness is associated with hippocampal volume in elderly humans. *Hippocampus*. 2009; 19(10):1030–1039. PubMed doi:10.1002/hipo.20547
- Falkenstein M, Hohnsbein J, Hoormann J, Blanke L. Effects of crossmodal divided attention on late ERP components. II: error processing in choice reaction tasks. *Electroencephalogr Clin Neurophysiol*. 1991; 78(6):447–455. PubMed doi:10.1016/0013-4694(91)90062-9
- 34. Farmer J, Zhao Xv, Van Praag H, Wodtke K, Gage F, Christie B. Effects of voluntary exercise on synaptic plasticity and gene expression in the dentate gyrus of adult male sprague—dawley rats *in vivo. Neuroscience*. 2004; 124(1):71–79. PubMed doi:10.1016/j.neuroscience.2003.09.029
- 35. Fillit HM, Butler RN, O'Connell AW, et al. Achieving and maintaining cognitive vitality with aging. *Mayo Clin Proc.* 2002; 77(7):681–696. PubMed doi:10.4065/77.7.681
- 36. Gehring WJ, Goss B, Coles MGH, Meyer DE, Donchin E. A neural system for error detection and compensation. *Psychol Sci.* 1993; 4(6):385–390. doi:10.1111/j.1467-9280.1993. tb00586.x
- Giedd JN, Blumenthal J, Jeffries NO, et al. Brain development during childhood and adolescence: a longitudinal MRI study. *Nat Neurosci*. 1999; 2(10):861–863. PubMed doi:10.1038/13158
- Goldman-Rakic PS. Topography of cognition: parallel distributed networks in primate association cortex. *Annu Rev Neurosci.* 1988; 11(1):137–156. PubMed doi:10.1146/ annurev.ne.11.030188.001033
- Gomez-Pinilla F, Hillman C. The influence of exercise on cognitive abilities. *Compr Physiol.* 2013; 3(1):403–428. PubMed
- Gould E, Woolley C, McEwen B. Short-term glucocorticoid manipulations affect neuronal morphology and survival in the adult dentate gyrus. *Neuroscience*. 1990; 37(2):367– 375. PubMed doi:10.1016/0306-4522(90)90407-U
- 41. Graybiel AM. The basal ganglia: learning new tricks and loving it. *Curr Opin Neurobiol.* 2005; 15(6):638–644. PubMed doi:10.1016/j.conb.2005.10.006
- 42. Hillman CH, Buck SM, Themanson JR, Pontifex MB, Castelli DM. Aerobic fitness and cognitive development: event-related brain potential and task performance indices of executive control in preadolescent children. *Dev Psychol.* 2009; 45(1):114–129. PubMed doi:10.1037/a0014437
- 43. Hillman CH, Castelli DM, Buck SM. Aerobic fitness and neurocognitive function in healthy preadolescent children. *Med Sci Sports Exerc.* 2005; 37(11):1967–1974. PubMed doi:10.1249/01.mss.0000176680.79702.ce

- 44. Hillman CH, Kamijo K, Scudder M. A review of chronic and acute physical activity participation on neuroelectric measures of brain health and cognition during child-hood. *Prev Med.* 2011; 52(Suppl 1):S21–S28. PubMed doi:10.1016/j.ypmed.2011.01.024
- 45. Hillman CH, Kramer AF, Belopolsky AV, Smith DP. A cross-sectional examination of age and physical activity on performance and event-related brain potentials in a task switching paradigm. *Int J Psychophysiol.* 2006; 59(1):30–39. PubMed doi:10.1016/j.ijpsycho.2005.04.009
- 46. Huang T, Larsen KT, Ried-Larsen M, Møller NC, Andersen L. The effects of physical activity and exercise on brain-derived neurotrophic factor in healthy humans: a review. Scand J Med Sci Sports. 2014; 24(1):1–10. PubMed
- Huttenlocher PR, Dabholkar AS. Regional differences in synaptogenesis in human cerebral cortex. *J Comp Neurol*. 1997; 387(2):167–178. PubMed doi:10.1002/(SICI)1096-9861(19971020)387:2<167::AID-CNE1>3.0.CO;2-Z
- Institute of Medicine (IOM). Educating the Student Body: Taking Physical Activity and Physical Education to School. Washington, DC: The National Academies Press, 2013.
- Johnson MH. Functional brain development in humans. Nat Rev Neurosci. 2001; 2(7):475–483. PubMed doi:10.1038/35081509
- Kempermann G, Kuhn HG, Gage FH. More hippocampal neurons in adult mice living in an enriched environment. *Nature*. 1997; 386(6624):493–495. PubMed doi:10.1038/386493a0
- Kobilo T, Liu Q, Gandhi K, Mughal M, Shaham Y, van Praag H. Running is the neurogenic and neurotrophic stimulus in environmental enrichment. *Learn Mem.* 2011; 18(9):605–609. PubMed doi:10.1101/lm.2283011
- Krafft CE, Schwarz NF, Chi L, et al. An 8-month randomized controlled exercise trial alters brain activation during cognitive tasks in overweight children. *Obesity (Silver Spring)*. 2014; 22(1):232–242. PubMed
- 53. Kramer AF, Erickson KI, Prakash R, Voss M. Risk Reduction Factors for Alzheimer's Disease and Cognitive Decline in Older Adults: Physical Activity. Preventing Alzheimer's Disease and Cognitive Decline Program and Abstracts, 2010, pp. 65–69.
- Kuhn HG, Dickinson-Anson H, Gage FH. Neurogenesis in the dentate gyrus of the adult rat: age-related decrease of neuronal progenitor proliferation. *J Neurosci.* 1996; 16(6):2027–2033. PubMed
- Laske C, Banschbach S, Stransky E, et al. Exercise-induced normalization of decreased BDNF serum concentration in elderly women with remitted major depression. *Int J Neuropsychopharmacol*. 2010; 13(5):595–602. PubMed doi:10.1017/S1461145709991234
- Lenroot RK. Brain development in children and adolescents: insights from anatomical magnetic resonance imaging. *Neurosci Biobehav Rev.* 2006; 30(6):718–729.
 PubMed doi:10.1016/j.neubiorev.2006.06.001
- 57. Levine D, Barnes PD. Cortical maturation in normal and abnormal fetuses as assessed with prenatal MR imaging. *Radiology*. 1999; 210(3):751–758. PubMed doi:10.1148/radiology.210.3.r99mr47751

- 58. Luna B. Developmental changes in cognitive control through adolescence. *Adv Child Dev Behav.* 2009; 37:233–278. PubMed doi:10.1016/S0065-2407(09)03706-9
- Ming GL, Song H. Adult neurogenesis in the mammalian central nervous system. *Annu Rev Neurosci*. 2005; 28:223–250. PubMed doi:10.1146/annurev.neuro.28.051804.101459
- 60. Monti JM, Hillman CH, Cohen NJ. Aerobic fitness enhances relational memory in preadolescent children: the FITKids randomized control trial. *Hippocampus*. 2012; 22(9):1876–1882. PubMed doi:10.1002/hipo.22023
- 61. O'Callaghan RM, Ohle R, Kelly ÁM. The effects of forced exercise on hippocampal plasticity in the rat: a comparison of LTP, spatial-and non-spatial learning. *Behav Brain Res.* 2007; 176(2):362–366. PubMed doi:10.1016/j. bbr.2006.10.018
- Olshansky SJ, Passaro DJ, Hershow RC, et al. A potential decline in life expectancy in the United States in the 21st century. N Engl J Med. 2005; 352(11):1138–1145. PubMed doi:10.1056/NEJMsr043743
- 63. Polich J. Updating P300: an integrative theory of P3a and P3b. *Clin Neurophysiol.* 2007; 118(10):2128–2148. PubMed doi:10.1016/j.clinph.2007.04.019
- Pontifex MB, Raine LB, Johnson CR, et al. Cardiorespiratory fitness and the flexible modulation of cognitive control in preadolescent children. *J Cogn Neurosci*. 2011; 23(6):1332–1345. PubMed doi:10.1162/jocn.2010.21528
- Raine LB, Lee HK, Saliba BJ, Chaddock-Heyman LC, Hillman CH, Kramer AF. The influence of childhood aerobic fitness on learning and memory. *PLoS ONE*. 2013; 8(9):e72666. PubMed doi:10.1371/journal.pone.0072666
- 66. Safe Kids USA [Internet]. Latest trends in child pedestrian safety: a five year review. 2007 [Accessed 2013 Aug 2].

- Available from: http://www.safekids.org/research-report/latest-trends-child-pedestrian-safety-five-year-review-october-2007.
- 67. van Praag H, Christie BR, Sejnowski TJ, Gage FH. Running enhances neurogenesis, learning, and longterm potentiation in mice. *Proc Natl Acad Sci USA*. 1999; 96(23):13427–13431. PubMed doi:10.1073/ pnas.96.23.13427
- van Praag H, Kempermann G, Gage FH. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nat Neurosci*. 1999; 2(3):266–270. PubMed doi:10.1038/6368
- van Praag H, Shubert T, Zhao C, Gage FH. Exercise enhances learning and hippocampal neurogenesis in aged mice. *J Neurosci.* 2005; 25(38):8680–8685. PubMed doi:10.1523/JNEUROSCI.1731-05.2005
- Vivar C, Potter MC, van Praag H. All about running: synaptic plasticity, growth factors and adult hippocampal neurogenesis. In: *Curr Top Behav Neurosci*. Springer, 2013, pp. 189–210.
- Voss MW, Chaddock L, Kim JS, et al. Aerobic fitness is associated with greater efficiency of the network underlying cognitive control in preadolescent children. *Neuroscience*. 2011; 199:166–176. PubMed doi:10.1016/j. neuroscience.2011.10.009
- 72. Wang Z, Van Praag H. Exercise and the brain: neurogenesis, synaptic plasticity, spine density, and angiogenesis. In: *Functional Neuroimaging in Exercise and Sport Sciences*. Springer, 2012, pp. 3–24.
- Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence. *CMAJ*. 2006; 174(6):801– 809. PubMed doi:10.1503/cmaj.051351