MIND, BRAIN, AND EDUCATION

# Childhood Markers of Health Behavior Relate to Hippocampal Health, Memory, and Academic Performance

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**ABSTRACT—** There has been an increasing body of evidence that a variety of factors, including physical activity, nutrition, and body composition, have a relationship with brain structure and function in school-aged children. Within the brain, the hippocampus is particularly sensitive to modulation by these lifestyle factors. This brain structure is known to be critical in learning and memory, and, we suggest, for progress in the classroom. Accordingly, the aims of this article include (1) examining the role of hippocampus and hippocampal-dependent memory in supporting academic performance; (2) reviewing the literature related to the associations between hippocampal-dependent memory and a number of lifestyle factors, including physical activity, nutrition, and body composition; and (3) discussing the implications of these findings in an educational setting. The findings discussed suggest that, through interventions that target these lifestyle factors, it may be possible to improve hippocampal function and academic performance in school-aged children.

Understanding lifestyle factors that contribute to cognitive health is of growing concern globally and considerable research is focused on both identifying factors that affect cognition and developing interventions to improve cognitive function. Understanding contributing health factors during childhood, when the brain and body are developing rapidly, is of particular interest to families, physicians, educators, and lawmakers. Indeed, there is a growing body of literature touting the contributions of physical activity, nutrition, and obesity to cognition across the lifespan (for reviews see Gomez-Pinilla, 2011; Hillman, Erickson, & Kramer, 2008). In the case of school-aged children, cognitive performance is often quantified using measures of academic achievement, and an emerging body of literature suggests that these factors play a role in academic performance as well (Hillman, Khan, & Kao, 2015). Specifically, aerobic fitness and physical activity are positively associated with academic achievement in cross-sectional studies (Carlson et al., 2008; Castelli, Hillman, Buck, & Erwin, 2007; Desai, Kurpad, Chomitz, & Thomas, 2015; for a review see Howie & Pate, 2012), and a number of physical activity interventions have produced improvements in this area (Caterino & Polak, 1999; Gabbard & Barton, 1979; McNaughten & Gabbard, 1993; Tomporowski, Lambourne, & Okumura, 2011). Similarly, overall dietary quality may also play a role in academic achievement. Children and adolescents who adhere to recommended dietary guidelines or patterns have been shown to exhibit superior academic achievement, relative to counterparts who regularly consume poorer quality diets (Esteban-Cornejo et al., 2015; Florence, Asbridge, & Veugelers, 2008; Glewwe, Jacoby, & King, 2001). Conversely, overweight and obesity are negatively related to measures of academic performance, including grade point average and standardized reading and math scores (Datar, Sturm, & Magnabosco, 2004; Li, Dai, Jackson, & Zhang, 2008; Shore et al., 2008), though these associations are not universally

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observed (Gunstad, Spitznagel et al., 2008; LeBlanc et al., 2012).

Complemented by the animal literature, studies of the relationship between physical activity, nutrition, obesity, and cognitive function in humans have allowed researchers to identify promising targets within the brain for physical activity and nutritional interventions. One such target, and the neural focus of this review, is the hippocampus, a highly metabolically active brain structure located within the medial temporal lobe that has long been known to support declarative memory and more specifically relational memory—the ability to bind together and store relations among the constituent elements of an experience (Eichenbaum & Cohen, 2001; Konkel & Cohen, 2009).

In this review, we examine the ways in which the hippocampus and hippocampal-dependent memory contribute to academic achievement. We review the research to date exploring the relationship between specific health factors—physical activity/fitness, nutritional intake, and obesity—and hippocampal structure and function and focus primarily on studies involving school-aged children. We conclude by discussing the implications of these findings in an educational setting.

## THE ROLE OF THE HIPPOCAMPUS IN LEARNING, MEMORY, AND ACADEMIC ACHIEVEMENT

Scoville and Milner's work involving the patient known as "H.M." was the first to establish that the hippocampus is necessary for episodic memory (Scoville & Milner, 1957). Since then, research has sought to better characterize the ways in which the hippocampus supports memory function. There is substantial evidence that the hippocampus specifically plays a role in relational memory, which is defined as the ability to create and flexibly use bindings between arbitrary elements that make up an experience to guide behavior (Cohen & Eichenbaum, 1993; Eichenbaum & Cohen, 2001; Konkel, Warren, Duff, Tranel, & Cohen, 2008). Examples of the situations in which the relational memory system is engaged include learning new information in science class, remembering a friend's name when you see their face, or integrating the places, people, and dates you learned about when it comes time to write that history paper. These examples highlight the fact that the relational memory system is critically important in an educational setting, in which individuals are expected to acquire vast amounts of knowledge in a variety of subject areas.

The rich and flexible representations built by the hippocampus also play a role outside of what is traditionally considered "memory." Beyond its role in supporting memory for all manner of relations, the hippocampus interacts with other structures to play a vital role in the learning strategies (Voss, Gonsalves, & Federmeier, 2010; Voss et al., 2011). According to proponents of "active learning," the effectiveness of this educational practice stems from the control students have over their individual learning processes, and it is this control over the learning process in which the hippocampus, along with the prefrontal cortex, plays a part. Voss et al. (2011) demonstrated that the hippocampus serves as the hub of a network involving prefrontal and parietal regions that supports effective learning strategies, which are in turn associated with superior memory for learned information. In addition to its role in the implementation of learning strategies, the hippocampus also operates as part of a network of brain regions that support flexible cognition, which includes critical thinking and problem solving, creative thinking, and social behavior (Buckner, 2010; Duff, Kurczek, Rubin, Cohen, & Tranel, 2013; Rubin, Watson, Duff, & Cohen, 2014). The development of effective learning strategies and flexible cognition is particularly important amongst school-aged children as these processes lay the groundwork for future academic success.

The hippocampus is particularly sensitive to the effects of a number of health factors. Specifically, a number of activity- and nutrition-related maladies like type II diabetes (Korf, White, Scheltens, & Launer, 2006), hypertension (Korf, White, Scheltens, & Launer, 2004), and obesity (Dore, Elias, Robbins, Budge, & Elias, 2008; Jagust, Harvey, Mungas, & Haan, 2005), all appear to detrimentally influence hippocampal volume. The effects of health factors on hippocampal volume may be especially pronounced during childhood when the hippocampus is still developing and hippocampal volume is rapidly changing (Casey, Giedd, & Thomas, 2000; Gogtay & Thompson, 2010). Furthermore, given the relationship between hippocampal volume and memory ability (Chaddock et al., 2010; Erickson et al., 2011; Maguire et al., 2000), it is likely that those health factors that affect hippocampal volume may, in turn, impact memory performance. Thus, for children, whose academic success relies upon hippocampal-dependent memory, these kinds of health issues could have a substantial impact.

At the cellular and molecular level, the maladies mentioned previously lead to decreased hippocampal neurogenesis and synaptic plasticity, and increased neuroinflammation (Stranahan et al., 2008; Tucsek et al., 2014), all of which decrease the functional capabilities of the hippocampus. However, while it is highly prone to stress induced by metabolic dysregulation, the hippocampus is also a highly plastic structure and the detrimental effects of metabolic dysregulation can be ameliorated through physical activity and nutritional interventions. Physical activity and nutritional interventions, either individually or in combination, result in increased rates of hippocampal neurogenesis and upregulation of key neurotrophic factors within the hippocampus (Casadesus et al., 2013; Gómez-Pinilla, Ying, Roy, Molteni, & Edgerton, 2002; Molteni et al., 2004; van Praag, Christie, Sejnowski, & Gage, 1999; van Praag, Shubert, Zhao, & Gage, 2005; Vaynman, Ying, & Gómez-Pinilla, 2004a,b). Furthermore, intervention in one area can offset the detrimental outcomes in another. For example, Molteni et al. (2004) demonstrated that exercise was capable of offsetting the harmful effects of an unhealthy diet by positively influencing the same systems that are disrupted by poor diet. The sensitivity of the hippocampus to the damaging effects of obesity and beneficial effects of physical activity and proper nutrition make it a prime target when examining the cognitive outcome of interventions that aim to reduce obesity and/or promote physical activity or improve diet quality.

Interventions that target health behaviors are likely to have particularly beneficial outcomes on hippocampal function in school-aged children. During childhood and adolescence the hippocampus is still developing (Bryan et al., 2004; Johnson, 2001; Lenroot & Giedd, 2006) and is one of only two structures in the human brain capable of undergoing neurogenesis throughout the lifespan (Kaplan & Hinds, 1977; Ming & Song, 2011). Furthermore, improvements in hippocampal function are likely to produce improvements in academic achievement as well, given the vital role of the hippocampus in the implementation of learning strategies and the development of critical thinking and problem solving abilities, which are important for positive educational outcomes.

## AEROBIC FITNESS, PHYSICAL ACTIVITY, AND THE HIPPOCAMPUS

Animal models have allowed researchers to assess the effects of aerobic exercise on hippocampal structure and function at the molecular level and better understand the biological mechanisms by which exercise impacts this region. Research in rodents has determined that engaging in aerobic exercise results in upregulated expression of a variety of key neurotrophic factors, as well as increased angiogenesis and neurogenesis, within the dentate gyrus subfield of the hippocampus (Mustroph et al., 2012; van Praag, Christie et al., 1999; van Praag, Kempermann, & Gage, 1999; Vaynman et al., 2004a,b). It has been well established that both short-term (Berchtold, Chinn, Chou, Kesslak, & Cotman, 2005; Ding, Ying, & Gómez-Pinilla, 2011; Neeper, Gómez-Pinilla, Choi, & Cotman, 1996) and long-term (Berchtold, Castello, & Cotman, 2010; Gómez-Pinilla et al., 2002; Hopkins, Nitecki, & Bucci, 2011) exercise programs increase gene- and protein-level expression of neurotrophic factors like brain-derived neurotrophic factor (BDNF), and these changes in BDNF expression appear to be specific to the hippocampus (Vaynman et al., 2004a,b). Furthermore, long-term potentiation, a physiological process vital to learning and memory, is enhanced following exercise, and this increased synaptic plasticity is associated with superior performance on tasks that depend on the hippocampus (Cotman, Berchtold, & Christie, 2007). Collectively, these findings suggest that the hippocampus and the functions it supports may be uniquely sensitive to the effects of exercise.

It is not currently possible to quantify the biomarkers used in animal models to assess the effects of physical activity on the hippocampus within the human brain, but advances in noninvasive neuroimaging technology that have allowed for the measurement of physical activity–induced changes in hippocampal integrity and a better understanding of the relationship between aerobic fitness and human hippocampal structure and function. In a sophisticated set of experiments, Pereira et al. (2007) utilized cerebral blood volume as an *in vivo* correlate of exercise-induced neurogenesis in humans. The researchers found that change in cerebral blood volume, measured via MRI, was strongly related to exercise-induced neurogenesis in rodents and subsequently applied this technique to young adults before and after they participated in an exercise intervention. The change in cerebral blood volume with exercise was specific to the dentate gyrus, providing strong evidence of exercise-induced neurogenesis in humans.

Other studies have focused on hippocampal volume when measuring the effects of physical activity and fitness on the hippocampus. Using structural MRI, Chaddock et al. (2010) found that children with higher aerobic fitness exhibited larger bilateral hippocampal volumes as well as superior performance on a relational memory task compared to lower fit children, and further, bilateral hippocampal volume mediated the relationship between aerobic fitness and relational memory. Additionally, the researchers found that the positive association between hippocampal volume and memory performance was specific to relational memory, because hippocampal volume was not significantly associated with performance on an item memory task. A study of adolescents reveals a similar positive relationship between aerobic fitness and hippocampal volume (Herting & Nagel, 2012) and through the use of functional MRI (fMRI), Herting and Nagel (2013) found that higher fit adolescents displayed a pattern of brain activation indicative of superior memory encoding during a subsequent memory task. The relationship between hippocampal volume and physical activity and fitness has also been observed in cross-sectional and interventional studies in older adults. In a sample of community-dwelling older adults, aerobic fitness was positively related to left and right hippocampal volume and to spatial memory performance (Erickson et al., 2009). A mediation analysis revealed that hippocampal volume partially mediated the relationship between aerobic fitness and spatial memory performance. Additionally, after participating in a 12-month exercise intervention, previously sedentary older adults who walked for 45 minutes 3 times/week increased their hippocampal volume by 1%–2%, whereas individuals who were assigned to a stretching and toning group for the duration of the intervention exhibited a 1%–2% decrease in hippocampal volume (Erickson et al., 2011). These exercise-induced changes in brain structure were specific to the hippocampus; other subcortical regions did not experience increased volume with aerobic exercise.

In addition to neuroimaging approaches, eye-tracking has been successfully employed in studies involving school-aged children to assess the relationship between aerobic fitness and relational memory performance. In one study, Monti, Hillman, and Cohen (2012) utilized an adaptation of a paradigm described by Hannula and Ranganath (2009) using faces and scenes to assess the cognitive effects of a 9-month exercise intervention in preadolescent children. While there were no significant differences in memory performance between the exercise and control groups, children who had participated in the exercise intervention exhibited a pattern of viewing indicative of superior relational memory during the test portion of the task relative to control participants. Specifically, participants in the exercise group demonstrated a greater degree of disproportionate viewing to faces that they had studied with a tested scene compared to control participants. Furthermore, the association between participation in an exercise intervention and memory-driven eye movements was specific to the relational memory condition of the task and was not seen in an item memory condition in which participants were required to identify previously studied faces that were all associated with the same scene. It is important to note that the memory data in this study were collected solely upon completion of the intervention; no pre-intervention memory assessment was conducted. This pattern of results was also observed in a sample of higher fit and lower fit young adults (Baym, Khan, Pence et al., 2014).

Furthermore, there is an increasing body of evidence that higher fit children perform better on tests of hippocampal-dependent memory compared to their lower fit peers. In a 2011 study, Chaddock, Hillman, Buck, and Cohen examined the relationship between aerobic fitness and executive control of relational memory encoding and retrieval in preadolescent children. In this cross-sectional study, higher fit and lower fit children viewed a series of face–house pairings under each of two conditions. In one condition, participants were instructed to encode the faces and houses individually (nonrelational condition) and in the other participants were instructed to encode the relations between the faces and houses (relational condition). Each encoding condition was followed by a recognition memory test that featured both previously studied pairs and novel item pairs. As expected, researchers found that higher fit participants performed better than their lower fit peers specifically for the relational encoding condition. In a separate study, it was shown that higher fit ($VO_2$ max above the 70th percentile according to age-specific norms) children had significantly higher accuracy on a relational memory task relative to lower fit ($VO_2$ max below the 30th percentile) children (Chaddock et al., 2010). Furthermore, the positive effects of superior fitness appear to extend to learning as well. Using a more naturalistic relational map-learning task, Raine et al. (2013) found that higher fit children outperformed lower fit children when no study strategy was supplied. However, when given a specific study strategy, lower fit children's performance improved to a point at which there were no longer significant differences between groups. These findings suggest that fitness may play the largest role in challenging learning situations in which the individual must generate his or her own study strategy. Differences in learning ability have also been observed in higher and lower fit adolescents. Using a virtual analogue of a Morris Water Task, Herting and Nagel (2012) found that aerobic fitness predicted the amount of learning that occurred during the task, with higher fit adolescents demonstrating more learning over the course of the task.

## NUTRITION AND HIPPOCAMPAL FUNCTION

Much of the work relating dietary intake of particular nutrients to hippocampal function has been largely informed by animal studies. However, unlike the physical activity literature, which is often singular in treatment type (i.e., volunteer/forced wheel running), a wider array of nutritional manipulations (e.g., fatty acids, simple sugars, Western diet, and polyphenols) have been attempted in efforts to influence hippocampal function in rodents. The resultant findings suggest that diet composition can both positively and negatively impact hippocampal structure and function. For instance, consumption of nutrients with anti-inflammatory or antioxidant properties, such as polyphenols and omega-3 fatty acids, promotes increased hippocampal neurogenesis (Casadesus et al., 2013; He, Qu, Cui, Wang, & Kang, 2009; Kim et al., 2008), enhances hippocampal BDNF expression and synaptic plasticity (Gómez-Pinilla, 2008; Wu, Ying, & Gomez-Pinilla, 2004), and mitigates the pathology of Alzheimer's disease (Green et al., 2007; Lim et al., 2001; Wang, Beydoun, Liang, Caballero, & Kumanyika, 2008). Conversely, a diet high in saturated fatty acids and added sugars reduces the expression of BDNF and synaptic plasticity in the rodent hippocampus as well as performance on hippocampal-dependent learning tasks

(Molteni, Ying, & Gomez-Pinilla, 2002; Wu, Molteni, Ying, & Gomez-Pinilla, 2003).

Although bridging the gap between rodent models and humans has been challenging, a small number of studies have begun to examine the relationship between diet composition and hippocampal function in school-aged children, and the findings of these studies are consistent with the animal literature. In a study involving children between the ages of 10 and 13 years, plasma concentrations of docosahexaenoic acid (an omega-3 fatty acid) were related to neuroelectric indices of recognition memory (Boucher et al., 2011). A recent cross-sectional study conducted in our laboratory examined the relationship between dietary intake of a number of components, including omega-3 fatty acids, saturated fatty acids, and refined sugar with relational memory in prepubescent children between the ages of 7 and 9 years. These findings demonstrated that accuracy on a relational memory task was positively associated with omega-3 fatty acid intake (Baym, Khan, Monti et al., 2014). Interestingly, this association was selective to relational memory, because there was no significant relationship between omega-3 fatty acid intake and item memory accuracy. On the other hand, higher intake of saturated fatty acids was related to poorer accuracy during both relational and item memory tasks, suggesting a global or less selective negative influence of saturated fat intake on childhood memory systems. Collectively, the aforementioned studies are among the first to demonstrate a relationship between dietary intake and hippocampal function during childhood and indicate that individual dietary components may exert beneficial or detrimental effects on the hippocampus in the developing brain. However, virtually all the research thus far on dietary components and the hippocampal memory system in children has been cross-sectional. Thus, our understanding of the directionality of nutrient–memory interactions remains limited. Given the findings from the animal literature, it is likely that nutrient intake is a determinant of memory function. However, it remains possible that nutrient intake and diet patterns are a consequence of poorer memory or cognitive function. Nevertheless, there is sufficient preliminary evidence from both animal and human studies to warrant long-term or longitudinal studies as well randomized controlled trials to identify nutrients and diet patterns necessary to obtain optimal relational memory during childhood and adolescence.

## CHILDHOOD OBESITY AND THE HIPPOCAMPUS

The rapid rise and elevated prevalence of childhood obesity represents one of the greatest public health challenge facing industrialized nations today. Although obesity has long been known to be a risk factor for a variety of detrimental health conditions, including cardiovascular disease, hypertension, some cancers, and metabolic disorders (Biro & Wien, 2010; Guh et al., 2009), it is increasingly being recognized as a risk factor for cognitive impairment as well. Evidence from rodent models indicates that obesity and its related metabolic disorders reduce synaptic plasticity and BDNF expression in the hippocampus, exacerbate neuroinflammation and oxidative stress, and result in poorer performance on spatial (relational) memory tasks (Stranahan et al., 2008; Tucsek et al., 2014).

In the human literature, the cognitive deficits associated with obesity in later adulthood are well characterized. A growing body of evidence implicates obesity (along with common comorbid conditions including insulin resistance and hypertension) in the development of both Alzheimer's disease and other forms of dementia (Fitzpatrick et al., 2009; Hildreth, Van Pelt, & Schwartz, 2012). Obesity has also been associated with reduced white matter tract integrity (Stanek et al., 2011) and decreased whole brain volume and gray matter volume (Gunstad, Paul et al., 2008). In a sample of young adults, obesity-related differences in brain structure were observed, and those with metabolic syndrome (a cluster of obesity-related factors known to increase subsequent disease risk) exhibited smaller hippocampal volumes and decreased white matter integrity relative to young adults with no metabolic syndrome risk factors (Yau, Castro, Tagani, Tsui, & Convit, 2012). Studies aimed at understanding the relationship between obesity and cognition during childhood have only recently emerged, and the majority of findings have been in the domain of executive control (Kamijo, Khan et al., 2012; Kamijo, Pontifex et al., 2012; Li et al., 2008; Scudder et al., 2014). However, one recent study examined the association between adiposity and hippocampal-dependent memory in school-aged children and found that, among overweight and obese children, total abdominal adipose tissue was negatively associated with relational memory accuracy (Khan et al., 2015). In contrast, the relationship between central adiposity and item memory accuracy was not significant, indicating that the relationship between adiposity and memory performance was specific to relational memory. Taken together, these results are consistent with findings in adults that greater central adiposity and increased waist-to-hip ratio (another indicator of adiposity in central regions) are negatively associated with memory and hippocampal volume (Dore et al., 2008; Jagust et al., 2005). Furthermore, the selective and negative relationship between abdominal adiposity and relational memory points to susceptibility of the hippocampal memory system to underlying metabolic dysregulation. Future research should aim to characterize the molecular and metabolic underpinnings of this relationship.

## EDUCATIONAL IMPLICATIONS

In an effort to boost academic performance, school districts across the country have implemented policies that restrict opportunities for physical activity during the school day in favor of extra time in the classroom (Institute of Medicine, 2013). Unfortunately, these policies have contributed to an increase in rates of obesity and a decrease in aerobic fitness in school-aged children, which may actually have a negative impact on classroom performance, as lower aerobic fitness and overweight status are associated with poorer scholastic achievement (Castelli et al., 2007; Kamijo, Khan et al., 2012). Furthermore, the evidence presented in this review suggests that these health markers affect the structure and function of the hippocampus, a structure known to be critical for successful learning and remembering. Together, these findings suggest that the hippocampus may be a critical factor in the relationships among fitness, body composition, nutrition, and academic performance.

The hippocampus supports learning and memory behaviors critical to day-to-day function across the lifespan, and plays a particularly important role during childhood when children are developing learning strategies and are responsible for memorizing massive amounts of information. Improving hippocampal function and the behaviors this structure supports has the potential to improve academic performance and future educational outcomes for school-aged children. Given the evidence presented here, we propose that the hippocampus and the functions it serves are prime targets for interventions aimed at changing physical activity levels, aerobic fitness, diet, and weight status. Furthermore, these interventions may be particularly advantageous when implemented during childhood when the hippocampus and the structures with which it interacts are still developing. Given that today's children are highly sedentary and increasingly obese, and consistently fail to meet diet recommendations, interventions that affect these health factors hold the promise of improving both physical and cognitive health, laying the groundwork for a lifetime of learning.

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