MONOGRAPHS OF THE SOCIETY FOR RESEARCH IN CHILD DEVELOPMENT

COMMENTARY

MECHANISMS AND CORRELATES OF A HEALTHY BRAIN: A COMMENTARY

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ABSTRACT In this monograph, the message is that early inactivity and obesity lead to later chronic disease, and, as such, physical inactivity should be recognized as a public health crisis. Sedentary behavior, to some extent, serves a purpose in our current culture (e.g., keeping children indoors keeps them safe), and, as such, may not be amenable to change. Thus, it is important that we understand the underpinnings of later-developing chronic disease as this complex public health issue may have roots that go deeper than sedentary behavior. In this commentary, I speculate on the mechanisms for physical activity exacting positive changes on cognitive abilities. Three potential mechanisms are discussed: glucose transport, postnatal neurogenesis, and vitamin synthesis, all of which are inextricably linked to nutrition. This discussion of mechanisms is followed by a discussion of tractable correlates of the progression to non-communicable disease in the adult.

In this monograph, the authors review the literature on the relation between physical activity during childhood and brain health as measured by subsequent cognition. They also offer original data (Chapter 5) in support of their ultimate goal, that of providing evidential support for the improvement of physical health during development to maximize brain function and health later in life—put simply, in support of the adage that a healthy body equals a healthy mind. The authors make a convincing case and provide comprehensive support for their hypothesis that physical activity improves cognitive performance. The impetus of this work is a desire to stimulate public action to increase physical activity in children given the connection between inactivity

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and non-communicable diseases (e.g., type 2 diabetes, cardiovascular disease, and cancer) in adulthood. At its most basic, the message is that early inactivity and obesity lead to later chronic disease, and as such, physical inactivity should be recognized as a public health crisis.

The message as stated is important, and if the intended audience is able to respond, it could start humankind on a healthier path. Yet, sedentary behavior may be only a symptom of a much larger problem and may not be amenable to change given its utility in the current social milieu (e.g., keeping children indoors for their safety). If we are to truly exact change, we must understand the issue on an even deeper level. At a minimum, the quality of diet must be considered. It is a fact that a body not properly fueled will not run well and, thus, will be inactive. Importantly, just as nutrition is the fuel that runs the body, nutrients are responsible for brain function. In this commentary, I provide food for thought with regard to two questions: what are the mechanisms behind the improvement of cognition through physical activity and what are the more tractable correlates of sedentary behavior and disease progression? I will first explore the mechanisms underlying the improvement of brain function with increases in physical activity. Then, I will discuss other correlates that may be involved in the progression to a state of disease.

Cognitive abilities, even brain development itself, depend on the quality of diet. Three aspects of a child's environment may manifest in obesity and sedentary behavior in the United States: (1) maternal factors, (2) overfeeding of low nutrient foods, and (3) environmental toxicity. Physical inactivity alone is not responsible for the so-called "obesity epidemic" or for the decrease in cognitive abilities that accompanies it. Case in point, after controlling for factors such as socio-economic status (SES), gender, and ethnicity, total hours spent in sedentary behavior on a daily basis does not differ between healthy-weight children and overweight/obese children in any age group (Whitt-Glover et al., 2009). Moreover, 67% of children are sedentary, but only 20% are overweight or obese (National Association for Sport and Physical Education, 1999). Clearly, other factors besides physical activity and obesity are at play. If we are to comprehensively address the issue, we must clarify the mechanisms and their correlates that work in support of brain health.

Why is it important that we identify the correlates of physical activity that may be exacting the effects on cognition? Society did not suddenly cease being active without reason, and those reasons may impede any intervention undertaken to reverse sedentary behavior. For example, sedentary behavior is more prevalent in lower SES children. Nowadays, children are trained to stay indoors for their safety, which may be a more salient rule for children living in low-income neighborhoods or for those who are home alone after school (so-called latchkey kids). Moreover, parents are not available for transportation to and from after-school activities as they are working, and even with two

incomes, many families cannot afford the high cost of participation in sports and other active extra-curriculars. For children of all SES categories, there has been a precipitous drop in active transport, as noted by the authors. The authors of this monograph state that the reasons for this drop are unclear. Anecdotally, parents will say that it is for safety. In fact, many schools no longer allow children to arrive at school by any method other than bus or car as it is considered unsafe for children to walk or ride a bicycle to school. Then, when they arrive at school, they are going to spend a minimum of 6 hr participating in sedentary behavior. These 6 hr are not negotiable: teachers even frown on too much motion while seated in the desk chairs. Therefore, physical inactivity has its utility in the current society, and it becomes important to identify other potential study variables to increase the chances that interventions to improve cognitive health will have positive outcomes. For example, if it were not possible to increase physical activity to the recommended levels due to societal and familial restrictions, perhaps changes in diet could compensate. Possibly, small changes in two or more domains (e.g., diet and physical activity) could compensate for an inability to exact larger changes in one domain (e.g., physical activity). It is also possible that a change to a healthy diet will result in bodies that are ready (and more willing) to be active.

POTENTIAL MECHANISMS

In this section, I will propose three mechanisms through which physical activity may be affecting cognition: glucose transport, postnatal neurogenesis, and vitamin synthesis. Two others worthy of consideration—stress reduction and epigenetic modifications—cannot be done justice in a commentary of this length. Briefly, much has been written about the impact of stress on the memory systems (Gunnar & Cheatham, 2003; McEwen, 1999; Nelson & Carver, 1998; Sapolsky, 1992) as well as the ability of physical activity to reduce stress (Huang, Webb, Zourdos, & Acevedo, 2013). Given that the connection between physical activity, stress reduction, and memory has been established in adults (Erickson, Leckie, & Weinstein, 2014), there is no doubt that a case could be made for the relation in development.

The second, epigenetics, is a burgeoning field that holds promise for the explication of underlying mechanisms (Kaliman et al., 2011). Knowledge of the epigenetic modifications to the individual's genome driven by environmental factors such as diet and physical activity will be invaluable in determining how any one person can improve on her or his disease progression (Zeisel, 2009), but also, the implications for hippocampal neurogenesis are noteworthy (Hsieh & Eisch, 2010). As is discussed later, the hippocampus is one of the brain regions where adult neurogenesis has been

documented (Gage, 2002), and it is a region that, along with the prefrontal lobe, is integral to memory functioning. The study of the response of the hippocampal and prefrontal lobe epigenome to physical activity will be a very lucrative research topic in the coming years. For the purposes of this commentary, epigenetics will be touched on briefly in terms of methyl donors (this section) and fetal programming (next section).

Consideration of the mechanisms involved in the relation between physical activity and cognition requires a consideration of nutrition. At its very basic, nutrition is needed for energy. As mentioned, a body that is not properly nourished will be sedentary. Paradoxically, overfed children can be undernourished given that the Western diet (high fat, high sugar) is calorically dense, but nutrient poor. Case in point, nutrition deficiencies still exist in the United States. For example, iron deficiency is still prevalent in American toddlers (Paoletti, Bogen, & Ritchey, 2014), children (Cole et al., 2010), and adolescent females (Looker, Dallman, Carroll, Gunter, & Johnson, 1997). Importantly, one of the main symptoms of iron deficiency is fatigue (Paoletti et al., 2014), which results in sedentary behavior.

Moreover, the components of diet can differentially influence how quickly one fatigues during exercise (Blomstrand, Moller, Secher, & Nybo, 2005). Indeed, no or low physical activity may be related to diet as studies have shown that fatigue is the result of depleted liver glycogen stores and subsequent decreased blood glucose levels (Coyle et al., 1983; Nybo, Nielsen, Blomstrand, Moller, & Secher, 2003). Glycogen stores are dependent on exogenous carbohydrates, thereby providing further evidence that diet determines the level of energy available to the body. Thus, physical inactivity may be the result of a lack of fuel and nutrients to the body.

It is also the case that physical activity improves the availability of fuel to the brain. Exercise increases blood flow to the brain (Hopkins, Suchyta, Farrer, & Needham, 2012). Besides oxygen, blood carries nutrients, not the least of which is glucose, the only molecule of energy for the brain. In fact, it is increased blood flow that is the outcome measure in functional magnetic resonance imaging (fMRI; i.e., blood oxygen level dependent (BOLD) analyses): increased blood flow is assumed to be an indication of brain activity and is a proxy for glucose utilization. Glucose comes from the diet and is either utilized immediately or is converted to glycogen and stored. Between meals, glycogen is converted back to glucose and released into the blood, as glucose levels must be maintained for the body and brain to operate properly. It has long been known that increasing glucose in the brain improves cognitive abilities, specifically memory. Evidence of the positive effects of blood glucose on memory was first shown in an animal model in 1984 (Messier & White, 1984) and in human children soon after (Benton, Brett, & Brain, 1987). Even with advances in methodology, the relation between memory and blood glucose continues to be found (Brown & Riby, 2013). The main connection,

then, between exercise and cognition may well be that it increases the availability of a nutrient, glucose (and most likely others), to the brain.

Importantly, the effects of glucose on memory are specific to declarative memory (studies of implicit memory and glucose have found no relation: Manning, Parsons, Cotter, & Gold, 1997), which, not surprisingly, is the memory system most affected by physical activity (referred to as relational memory in the monograph, see Chapter 3). Declarative or relational memory is subserved by the hippocampus (Eichenbaum, 2000). Not only is the hippocampus extremely susceptible to oxygen and nutrient deficiencies (Gomez-Pinilla & Vaynman, 2005), but also, it is one of the brain areas where neurogenesis can occur across the lifespan (Eriksson et al., 1998). Scientists studying postnatal hippocampal neurogenesis in animal models have linked it to diet. Consumption of a high-fat diet, as is common in children in developed countries, has been shown to decrease neurogenesis in the hippocampus (Boitard et al., 2012). Vitamin A deficiency and a concomitant disruption of the corticosteroid cascade also have been implicated in decreased adult hippocampal neurogenesis (Bonhomme et al., 2014). Neurogenesis may very well be stimulated by a cascade of events set in motion by physical activity (Lafenetre, Leske, Wahle, & Heumann, 2011) and may result in the larger hippocampus in physically fit children mentioned in this monograph. However, nutrition plays a large role in that cascade of events, and in the development and continued optimal functioning of the hippocampus in general.

At its base development, the hippocampus is reliant on a different type of nutrient: the methyl donors. Maternal nutrition, specifically the availability of methyl donors such as choline, may determine the number of stem cells available for postnatal neurogenesis (Zeisel, 2011) as well as the structure of the hippocampus. First, the initial structure and vasculature of the hippocampus is guided by the effects of choline metabolites on DNA expression and subsequent mitosis, differentiation, and apoptosis. Interestingly, the vasculature in the hippocampus is reduced by 25% in rodents whose mothers did not receive sufficient choline in the diet (Mehedint, Craciunescu, & Zeisel, 2010), suggesting that without proper maternal nutrition, blood flow in the hippocampus could be suboptimal (thereby introducing an individual differences component of the benefits of physical activity). Of note, 90–95% of people in the United States consume less than the established adequate intake of choline (Chiuve et al., 2007; Cho et al., 2006; Zeisel & da Costa, 2009), and during gestation, women require more choline (Zeisel & da Costa, 2009).

Second, the choline metabolites are active in setting up the pool of progenitor cells in the hippocampus that will become working neurons through postnatal neurogenesis. Neurogenesis in the postnatal hippocampus mostly originates from the progenitors in the subgranular zone of the hippocampus (Kuhn, Dickinson-Anson, & Gage, 1996). These new cells

develop to be morphologically similar to mature granular cells. With projections to and input from the perforant pathway, they become functionally active in hippocampus, either as replacements for old neurons or as a form of plasticity (van Praag et al., 2002). Either way, now that the new neurons have been shown to form synaptic connectivity in the hippocampus and to fire accordingly, we can assume that they would have a role in hippocampal-based cognition. Importantly, the (currently assumed) finite number of progenitor cells in the dentate gyrus limits neurogenesis in the postnatal hippocampus. This number is thought to be determined by the level of choline provided by the placenta to the fetal brain (Zhu, Mar, Song, & Zeisel, 2004). Once the store of progenitor cells is in place, ensuing factors across the lifespan, such as individual levels of stress or the more positive physical activity, determine the longevity and availability of the progenitors in the birth of new neurons to support memory. Therefore, maternal diet and offspring's lifestyle (including, but not limited to, physical activity), work synergistically to support the neural circuitry underlying declarative memory abilities across the lifespan.

Another way that physical activity may impact cognition is through Vitamin D, the deficiency of which is on the increase in America (Wallace, Reider, & Fulgoni, 2013). This increase is most likely due to children staying indoors as vitamin D is synthesized in the presence of sunshine. Importantly, these deficiencies are more prevalent in low-income households (Wallace et al., 2013), the children of which are also more at risk for low physical activity and high levels of obesity (Whitt-Glover et al., 2009). Vitamin D deficiency is a correlate of obesity and metabolic syndrome (Van Grouw & Volpe, 2013), as well as lower scholastic achievement (Nassar et al., 2012). Vitamin D has been related to neuroprotection in the hippocampus (Brewer et al., 2001) and serotonin (5-HT) regulation (Leonard & Myint, 2006). Serotonin is integral to the regulation of electrical activity in the hippocampus and through this mechanism and others, is thought to influence cognitive abilities (for review see Olvera-Cortes, Gutierrez-Guzman, Lopez-Loeza, Hernandez-Perez, & Lopez-Vazquez, 2013). In addition to the synthesis of vitamin D, sunshine absorption in and of itself may have an effect on cognition (Kent et al., 2014). As many physical activities for children occur outside, scientists conducting studies of the effects of physical activity on cognition should control for any alterations in exposure to the outdoors.

THE IMPORTANCE OF MATERNAL FACTORS

As was detailed in the previous section, the laying down of the progenitor cells in the hippocampus during gestation and the need for maternal intake of methyl donor nutrients to facilitate that process is one example of a

maternal factor that has an effect on cognitive abilities in the offspring. Other maternal factors are important for pre- and postnatal development. Certainly, it has long been known that proper maternal nutrition is required for fetal brain development. The differentiation and migration of newly formed neurons in the fetal brain is disrupted when the mother does not provide proper nourishment (Morgane et al., 1993). Protein, iron, and fatty acids are nutrients that have been studied extensively and have been found to be important to fetal brain development and subsequent cognition. In an animal model, protein malnutrition during gestation has been related to disruption of granule cell production in the offspring that cannot be rescued by restoration of proper nutrition at birth (Debassio, Kemper, Galler, & Tonkiss, 1994; Debassio, Kemper, Tonkiss, & Galler, 1996). Maternal intake of alpha-linolenic acid, an omega-3 fatty acid, has been shown to be integral for fetal hippocampal development (Niculescu, Lupu, & Craciunescu, 2011). Iron deficiency during the perinatal period results in irreversible cognitive dysfunction (Lozoff & Georgieff, 2006; Radlowski & Johnson, 2013; Rao & Georgieff, 2000). These are only three examples of the nutrients that the placenta (and therefore, the mother) must provide to the developing fetus for optimal development.

More recently, scientists have posited that maternal, and even grandmaternal, factors are more far-reaching than ever considered previously, and now consider the developmental origins of disease in discussions of maternal factors (Barker, 1997). The thrifty gene hypothesis is interpreted many ways. It has been suggested in a distal interpretation that due to numerous periods in history where severe food shortage was an issue, natural selection has favored genes that allow survival during times of famine, and that genes promoting, for example, "slothfulness" (promotion of inactivity to conserve energy) and adipogenesis (promotion of fat gain) are famine-thrifty and have possibly been conserved over the past 12,000 years of human history to become contemporarily prominent (Prentice, Rayco-Solon, & Moore, 2005). A more proximal interpretation of the developmental origins of disease posits maternal factors as integral to fetal programming of later outcomes.

The fetal programming hypothesis is the idea that the uterus and placenta are preparing the fetus for the world to come (Chmurzynska, 2010). This preparation is accomplished through the epigenome, which is sensitive to the intrauterine environment. Through epigenetic changes, the metabolic and homeostatic systems in the fetus are set for the expected extrauterine environment, thereby programming the organism for life in the external world, while at the same time, it seems, predisposing it for dysfunction if the world to come does not match expectations (for review see Gluckman & Hanson, 2008). Fetal programming has been most often considered in terms of maternal undernutrition (Barker, 1997) and intrauterine growth restriction (Jaquet, Gaboriau, Czernichow, & Levy-Marchal, 2000; Stocker,

Arch, & Cawthorne, 2005), but has more recently been related to maternal overnutrition (Blackmore & Ozanne, 2013; Sun et al., 2012) as well.

The evidence is mounting that later-developing non-communicable diseases are related to fetal programming. The most cited work has been done on children of women who were pregnant during the Dutch Hunger Winter, a famine that occurred after World War II. For example, those whose mothers were exposed to the famine during pregnancy have disrupted glucose tolerance as adults relative to those whose mothers were properly nourished (Ravelli et al., 1998). Fetal programming has been linked to the propensity toward disrupted stress responses (de Bruijn, van Bakel, Wijnen, Pop, & van Baar, 2009) and increased weight gain (Fall, 2012). The development of cardiovascular disease as an adult is related to both gestational undernutrition and overnutrition (for review see Blackmore & Ozanne, 2013). Importantly, maternal smoking during pregnancy is related to obesity (Toschke, Koletzko, Slikker, Hermann, & von Kries, 2002; von Kries, Toschke, Koletzko, & Slikker, 2002) and type 2 diabetes (Montgomery & Ekbom, 2002) in the offspring. Low SES mothers are more likely to smoke during pregnancy and to have dysregulated eating patterns, whether that be under- or overeating. Therefore, we would expect, and indeed do see, higher rates of non-communicable disease progression in adults who were born into low SES families.

Given the evidence that maternal factors predispose the individual to adult disease progression, it is difficult to say whether a person progresses to a disease state because of an epigenetic predisposition or because of lifestyle choices such as sedentary behavior. Most likely, the answer lies in an interaction between the individual's lifestyle and maternal factors. As mentioned, the mismatch between the intrauterine and extra-uterine environments renders the fetal programming ineffectual (Gluckman & Hanson, 2008) and leads to progression to a diseased state. Intriguingly, the epigenome's partial malleability to postnatal life may provide an alternative pathway. That is to say that consistent behavior and healthy lifestyle choices may help overcome any predispositions exacted by maternal factors. However, the preponderance of the evidence to date would suggest that nutrition during gestation has an intractable relation with the outcomes of the offspring.

SUMMARY

The authors of the monograph did an excellent job of presenting the issue of contemporary sedentary behavior, the progression of our society to an obese state, and the relation of physical activity to brain health. They also made a good case for sedentary behavior as a correlate of the current

non-communicable disease epidemic. As discussed in this commentary, several factors are involved with the progression to a diseased state as an adult. Moreover, many heritable, cultural, and familial pressures converge in a "perfect storm" of sedentary behavior compounded by poor fuel consumption. It is not clear if the adult onset of non-communicable diseases is directly related to sedentary behavior or if sedentary behavior is a symptom of a much larger issue that results in disease outcomes. In this commentary, I have proposed a constellation of factors to which scientists might look for answers. Do the genes conserved during famines past predispose humans to disease in the 21st century? Do maternal factors set the stage for the later development of disease? Can nutrition or physical activity at critical or sensitive periods alter the pathway to later disease? Solid answers most likely will not be forthcoming due to the longitudinal and ethical considerations of any study design. Thus, if we are to improve on the lives of future generations, we will need to exact changes in all possible domains. Positive changes in diet and exercise for men and women of child-bearing age will go a long way toward improving cognition and disease outcomes going forward. As proposed in this monograph, teaching our children the importance of physical activity (and good nutrition) will set the stage for better outcomes for not only them but also for generations to come.

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