Exercise and the Aging Brain

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In 2008, the first comprehensive guidelines on physical activity were published by the US government. These guidelines, entitled *2008 Physical Activity Guidelines for Americans*,[1] were the result of an extensive review of the scientific data on physical activity and health performed by a group of 13 leading experts from the fields of exercise science and public health (Physical Activity Guidelines Advisory Committee, 2008). The report was unique in that the science base available at the time was used to formulate practical guidelines for physical activity from young childhood through old age and also included individuals with chronic medical conditions and physical disabilities. Recommendations were based both on the level of physical activity and its duration, across the course of a week and throughout most of the lifespan. Additionally, recommendations were formulated both in terms of aerobic and muscle-strengthening activities that were appropriate for different populations. More recently, these physical activity guidelines were extended to even younger children in the *Physical Activity Guidelines for Americans Midcourse Report: Strategies for Increasing Physical Activities Among Youth (2012).*[2]

The recommendations in these two reports were based on the large and growing body of studies that have examined the relationship between physical activity (and other factors) and health and disease. Lack of physical activity and exercise has been associated with increased risks for a number of diseases including type 2 diabetes, hypertension, colon and breast cancer, obesity, and coronary heart disease among others.[3] Indeed, lack of activity even has been associated with the onset of "adult" diseases such as diabetes and hypertension among children.[4,5] Finally, physical activity also has been found to result in increased life expectancy and a substantial decrease in medical expenditures across the lifespan.[6,7]

As described above, substantial data suggest that physical activity is important in reducing the risk of various diseases, including those diseases (eg, heart disease, stroke, and obesity) that have been associated with compromised cognitive and brain health and, in turn, independence and quality of life. The development of these diseases and their effects on cognition and brain occur over years and decades. This summary focuses on shorter-acting but equally important effects of physical activity and exercise. That is, effects that in nonhuman animal models can occur in weeks or months and substantially influence the molecular and cellular underpinnings of learning, memory, and other cognitive processes. In humans, such effects, characterized with sophisticated behavioral paradigms and neuroimaging methodologies, take a bit longer to be realized, on the order of several months to a year or so.[8]

This summary is organized around both animal and human research on physical activity and exercise. The animal research potentially enables a low-level mechanistic understanding of how physical activity influences molecules, cells, and neurochemistry—and how such influences affect performance and cognition. On the other hand, while the ability to understand molecular and cellular changes is quite limited with humans, the ability to understand nuanced changes in general and selective aspects of perception, cognition, and action is quite possible. The development of new neuroimaging technologies also has enabled the field of cognitive neuroscience to begin to bridge the gap between animal and human studies of brain structure and function in physical activity and other types of interventions such as cognitive training, nutrition, and social interaction.[9,10] This review will describe both the animal and human literature on physical activity effects on brain and cognition, the overlap between studies with different species, and suggest how cross-species, multimethod research might further address important issues in the study of neural and cognitive plasticity, with a focus on physical activity and exercise.

A rapidly expanding animal literature suggests that increased exercise leads to the birth of new neurons in the hippocampus (a brain region responsible for important aspects of memory), increased connections among neurons throughout the brain, the development of new vasculature structure, increased production of neurotrophic proteins such as brain-derived neurotrophic factor, reduction of proteins associated with neurodegeneration in mouse models of Alzheimer's disease, and enhanced learning and memory.[11] Interestingly, such results have been found across the lifespan and in a multitude of species including rodents, dogs, and monkeys.

The increasing molecular and cellular knowledge of exercise effects with animals provides the basis for human studies of physical activity and exercise. Indeed, the human studies include both prospective observational or epidemiological studies and randomized controlled trials. The observational studies have established the relationship between physical activity (often self-reported) and cognitive maintenance in normal adults or adults diagnosed with neurodegenerative diseases such as Alzheimer's or Parkinson's disease.[12] For example, consider a relatively short-term study by Weuve et al.[13] The leisure-time physical activity and global cognitive function of 18,766 women from 70 to 81 years of age was assessed by self-report. During reassessment 2 years later, it was found that women who initially reported walking the most during initial assessment had a 20% reduced risk of cognitive impairment compared to women walking the least. This kind of relationship has been reported in dozens of studies, with physical activity benefits ranging from 20% to 40%, in terms of maintained cognition, across 2 to 8 years. Although such results are both interesting and potentially important, they do not establish a causal relationship between physical activity and cognition. Hence, there is a need for randomized cognitive trials.

In a meta-analysis of 18 trials by Colcombe and Kramer,[8] a moderate effect size between exercise and cognition was reported. The effect size was moderated by the type of cognition being assessed, with executive control processes showing the largest benefit (Fig 1), females showing larger benefits than males, and exercise programs lasting 6 months or longer showing larger benefits for cognition than shorter exercise programs. Subsequent research has found similar benefits of exercise on cognition.

Across intervention studies (with normal elderly) that find positive effect of fitness training on cognition the cognitive benefits are quite broad—with larger benefits for some cognitive processes...

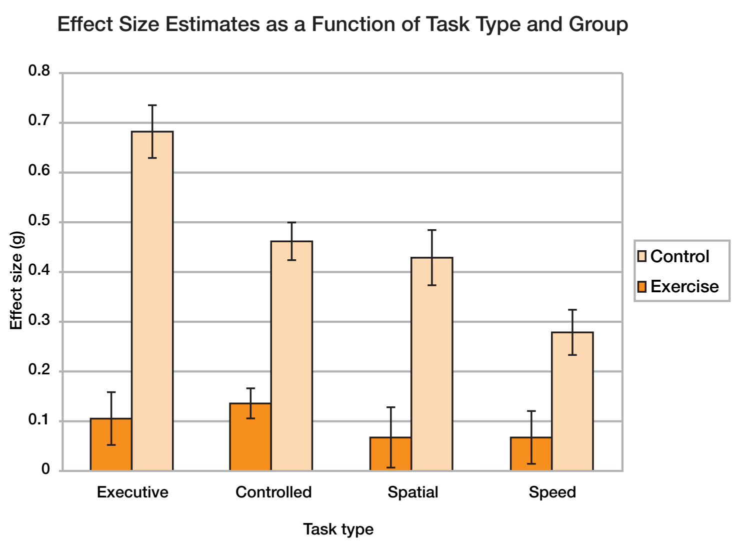

Fig 1. Effect size between exercise and cognition in a meta-analysis of 18 trials.[8] The effect size was moderated by the type of cognition being assessed, with executive control processes showing the largest benefit.

Source: Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychol Sci.* 2003 Mar;14(2):125-130. Published by Sage Publications, Inc.

More recently, human studies also have begun to include measures of brain function and structure along with behavioral measures of cognition. Thus, these studies might be viewed as a way to narrow the gap between the focus on brain function and structure with animals and the focus on sophisticated measurement of cognitive effects with humans. These human studies have reported that relatively brief fitness programs result in increased brain volume in a variety of brain regions such as the hippocampus that have shown declines during the normal course of aging[14,15] and increases in the integrity of white matter tracts[16] and patterns of brain activation, including measures of functional connectivity of different brain regions, which suggest more efficient memory, attention, and decision making (Fig 2).[17,18]

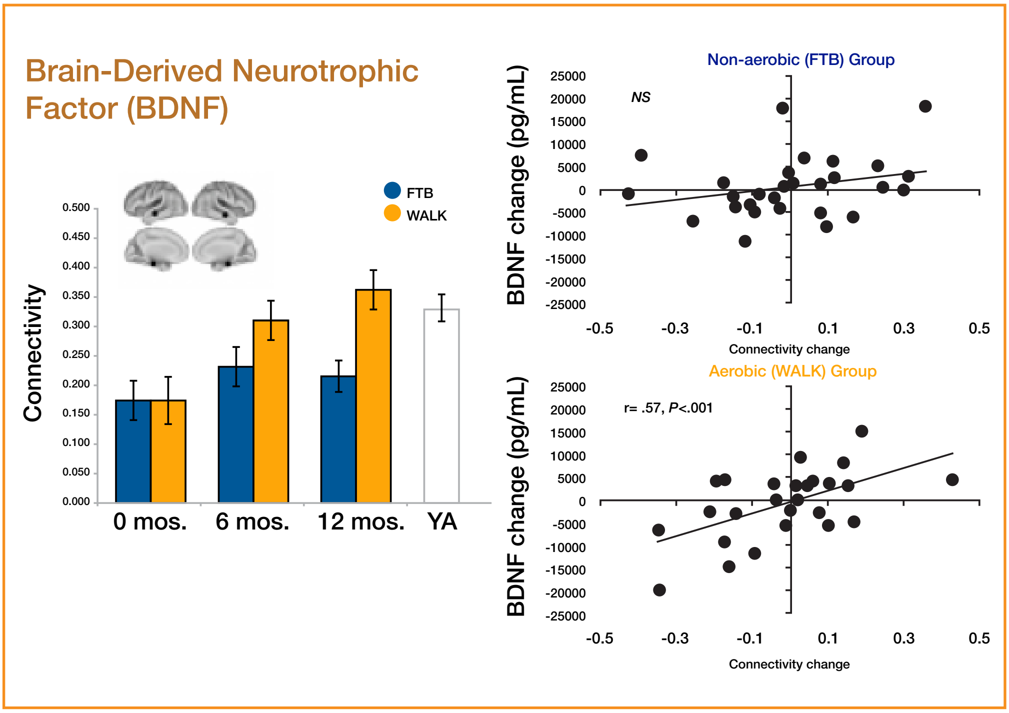

Fig 2. Neurobiological mechanisms for exercise-induced brain plasticity.[16]

FTB=flexibility, toning, balance (group), YA=young adult (comparison group)

Source: Voss MW et al. Neurobiological markers of exercise-related brain plasticity in older adults. *Brain Behav Immun*. 2013 Feb;28:90-99. Reprinted by permission of Elsevier.

Indeed, while the great majority of studies conducted in the past decade or so focused on adults, more recent studies have reported similar cognitive and brain benefits, as a function of exercise and physical activity, for children.[19-21] Such findings are important to understanding the effects of lifestyle choices on cognitive and brain development as well as the impact of the increasing sedentary nature and levels of obesity among children in today's society.

In summary, the last decade has led to a substantial increase in our knowledge concerning the influence of at least one lifestyle choice on healthy minds and brains—ie, physical activity and exercise. However, many important questions remain unanswered. What forms of exercise lead to the largest cognitive and brain benefits? What are the optimal doses of exercise (in terms of length and intensity of exercise programs) and to what extent does the definition of optimality differ with age, health, and other factors? Do other lifestyle choices show cognitive benefits similar to those of exercise that are based on similar mechanisms? How do lifestyle choices interact with our genome with regard to cognitive benefits? Finally, can a combination of nutrition and exercise bestow greater benefits to healthy minds and brains than either of these factors alone?

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