

By Andrea M. Weinstein and Kirk I. Erickson

Healthy Body Equals Healthy Mind

Adopting a physically active lifestyle early on may be the best way to prevent brain decay.

The number of adults older than sixty-five is expected to increase dramatically as baby boomers age. Unfortunately, this trend is also expected to increase the prevalence of age-related cognitive impairment and dementia. The costs associated with health and long-term-care services for dementia reached approximately \$172 billion in 2010 (Alzheimer's Association, 2010). Such staggering costs demonstrate the need for research to identify effective preventions and treatments for cognitive decline.

Physical activity, such as aerobic exercise, might be both an effective prevention and treatment for late-life brain atrophy and cognitive decline. In contrast to most medications, aerobic exercise interventions are consistently associated with increased cognitive performance and greater brain volume in older adults. Physiologically, aerobic exercise is thought to improve brain health by creating new brain cells, blood vessels, and by enhancing communication between neurons (van Praag et al., 2005; Ding et al., 2006). Newly created vasculature increases blood flow and the transport of nutrients to newly formed cells, resulting in better brain function and increased brain mass.

The studies reviewed in this article used both structural and functional magnetic resonance imaging (fMRI) to examine the effects of exercise

on the brain. This method takes advantage of the magnetic properties in brain tissue to create high-resolution images. Different tissue types, such as axons that make up white matter, and cell bodies that make up gray matter, resonate at different magnetic frequencies. By sensing these frequencies, the magnetic resonance scanner can create a detailed image of gray and white matter and form snapshots of how the brain functions during cognitively demanding tasks. We can then identify how physical activity influences the integrity of brain circuits in late life.

Aerobic exercise interventions increase cognitive performance and brain volume in older adults.

Three study designs will be reviewed: epidemiological, cross-sectional, and experimental. Epidemiological research examines factors that predict disease risk or mortality at a population level, often sampling hundreds or thousands of individuals. These studies usually follow participants over time (prospectively) or assess relevant data from their past (retrospectively). In contrast, cross-sectional studies sample participant data from a single time-point to assess correlations between variables. Finally, experimental studies manipulate some variable of interest (e.g., an exercise intervention to change fitness levels). After the manipulation, data are

sampled to determine whether there are causal relationships between independent and dependent variables.

What Are Normal Brain Changes?

To understand cognitive and physical brain changes that lead to cognitive aging and dementia, first we must understand normal age-related brain changes. The parietal, frontal, and temporal cortices all experience significant tissue loss throughout life. Healthy adults lose approximately 15 percent of their neocortical tissue between ages thirty and ninety, with disproportionately higher losses in areas crucial for executive control (Raz, 2000).

And, healthy adults older than fifty-five experience approximately 1 to 2 percent decline annually in hippocampal volume—an area crucial for forming and recalling memories (Raz et al., 2004). Hippocampal atrophy accelerates in patients experiencing dementia. Decreases in cortical and hippocampal volume often precede and lead to the executive function and memory declines seen in normal aging.

If age-related brain atrophy occurs because of cell shrinkage, death, and loss of vasculature, then exercise is well-suited to rebuild the decaying brain. While it was once thought that the adult brain was incapable of adapting, it is now known that the brain remains relatively plastic throughout life. Neural efficiency, capacity, and flexibility differences result in variations in the ability to withstand damage to the brain's processing system. A more resilient neural system likely leads to better long-term brain health by withstanding neural injuries. Aerobic exercise is poised to capitalize on this plasticity and beneficially impact both the structure and function of the human brain.

Can Physical Activity Induce Structural Changes in the Brain?

Epidemiological studies point toward a link between physical activity and brain volume in older adults (Rovio et al., 2010; Erickson et al.,

2010). For example, one prospective longitudinal study found that midlife physical activity levels were associated with more gray matter volume twenty-one years later, even in individuals diagnosed with pathological cognitive problems (Rovio et al., 2010). This study suggests that physical activity in midlife may prevent late-life brain atrophy, even in patients experiencing cognitive decline.

Erickson and colleagues (2010) also examined the association between physical activity and brain volume. At baseline, 299 healthy older adults reported the average number of blocks walked per week. Participants who reported walking more at baseline had larger volumes of cortical and sub-cortical brain structures nine years later. Greater gray matter volume in both frontal and temporal regions was associated with a reduced risk of cognitive impairment thirteen years post-baseline. And, gray matter volume was largest in participants who reported walking at least seventy-two blocks per week. This implies there may be a threshold that needs to be reached before the brain can reap the benefits of physical activity. This study indicates that walking about one mile per day may be enough to stave off cognitive deterioration and reduce brain atrophy for nine to thirteen years.

Findings from cross-sectional studies have strengthened these claims, indicating that higher levels of cardiovascular fitness are associated with greater gray and white matter volume in the brains of older adults (Gordon et al., 2008; Honea et al., 2009; Erickson et al., 2009; Bugg and Head, in press). In one study, self-reported physical activity was associated with greater tissue retention in the medial temporal lobe ten years later (Bugg and Head, in press). In this study, participants who engaged in fewer physical activities experienced more age-related atrophy of the medial temporal lobe.

In contrast, Gordon and colleagues found somewhat different results when examining the effects of both fitness and education on brain volume (Gordon et al., 2008). While higher

fitness levels were associated with greater gray matter volume across several brain regions, higher education, and not fitness, was associated with more anterior white matter volume. Most cross-sectional research supports the idea that engaging in physical activity may slow down, or prevent, age-related atrophy in specific brain regions, and this relationship exists even in the face of pathology.

Epidemiological and cross-sectional research builds a solid foundation for the relationship between physical activity and greater brain volume in late life. However, association studies cannot provide causal conclusions about whether or not exercise directly impacts brain morphology. The direction of the relationship between fitness or physical activity and brain volume is unclear. It is possible that fitness and brain volume co-vary as a function of an unmeasured third variable, such as intelligence. But, introducing an experimental manipulation of exercise can elucidate whether a causal relationship exists between physical activity and brain volume.

Experimental interventions have confirmed that increasing physical activity can enhance brain health. In one six-month intervention, older adults were randomly assigned to either a moderate-intensity aerobic walking group or to a stretching and toning control group (Colcombe et al., 2006). The aerobic exercise group showed an increase in both gray and white matter volume over the six-month period. In contrast, the control group showed a slight decrease in both gray and white matter volume, consistent with age-related atrophy. So a relatively short six-month period of moderate-intensity exercise, in the form of walking, increased cortical gray and white matter volume in a sample of normally aging older adults.

Similar results were found in a one-year exercise intervention study (Erickson et al., 2011). Participants were randomly assigned to either a moderate-intensity aerobic walking group or to a stretching and toning control group, similar to the study described earlier.

Over the year, the control group experienced normal age-related atrophy of the hippocampus. However, the aerobic exercise group experienced a 2 percent increase in hippocampal volume.

Aerobic exercise not only slowed, but reversed, typical age-related hippocampal atrophy. Plus, hippocampal atrophy rates within the control group were inversely related to pre-intervention fitness levels. This experiment provides two valuable conclusions: first, modest amounts of aerobic exercise can reverse age-associated hippocampal atrophy, and second, higher fitness levels can protect against normal brain atrophy.

Can Physical Activity Induce Functional Changes in the Brain?

The studies reviewed thus far provide clear evidence that fitness and exercise can prevent, or even reverse, age-related brain atrophy. However, aging is associated with changes in cognitive function, too. Normal cognitive aging in the absence of clinical impairment is associated with a decline in memory and executive functions (Hertzog et al., 2009). Can exercise improve cognitive and brain function as well as influence brain volume? This question is important if exercise is to be used as a treatment for cognitive aging or cognitive dysfunction.

Several epidemiological studies of aging show that greater physical activity is associated with better cognitive function (Barnes et al., 2003; Dik et al., 2003; Weuve et al., 2004; Andel et al., 2008). For instance, Barnes and colleagues (2003) found that, in a group of adults older than fifty-five, lower baseline levels of cardiovascular fitness were associated with worse global cognitive function, attention, and executive function six years later. In a similar study, Weuve and colleagues (2004) examined physical activity levels eight to fifteen years before cognitive assessment. Participants were then assessed over a two-year period for changes in global cognitive performance (Weuve et al., 2004).

Women in the highest quintile of physical activity had a 20 percent lower risk of develop-

ing cognitive impairment than women in the lowest quintile. Even women who walked at an easy pace (twenty-one to thirty minutes per mile) for at least one and a half hours per week experienced slight improvements in global cognitive performance across the two-year period. These, and other similar studies, indicate that even low intensity physical activity in late life is associated with a reduced risk for cognitive decline years later.

Examining effects of midlife physical activity on cognitive health reveals similar results to the late-life effects described above. For instance, in a case-control analysis of Alzheimer's Disease, light or regular exercise was associated with 37 to 66 percent reduced odds of developing dementia thirty-one years later, when compared to very little exercise (Andel et al., 2008). When examining twin pairs, there was a trend for twins who exercised more to have reduced odds of developing dementia compared with their sedentary twins. This provides more support that midlife physical activity can protect against late-life cognitive dysfunction, even when controlling for genetic and familial factors.

Several studies show that midlife and late-life physical activity reduces the risk for late-life cognitive decline. Do early life physical activity habits predict late-life cognition, too? Dik and colleagues (2003) studied this question in a group of 1,241 adults older than sixty-two. Participants reported levels of early life physical activity (between ages fifteen and twenty-five). Higher levels were associated with better global cognitive performance and better information-processing speed for men, but not for women. This gender difference may be because more men than women reported being physically active in young adulthood, activities tended to take place during work, and, in this cohort, men not only worked more frequently than women, but were also employed at jobs requiring more extensive physical

exertion. Despite this gender difference, early life activity was associated with better cognitive performance more than forty years later.

Because aging is associated with memory decline as well as changes in global cognitive function, examining the effect of fitness and physical activity on memory is an essential and salient goal for preventing dementia. As described, the hippocampus is essential for memory function and is susceptible to both age-related and pathological deterioration.

So how does fitness relate to hippocampal function? Erickson and colleagues (2009) found that higher fitness levels were associated with both larger hippocampal volume and better spatial memory performance. Plus, hippocampal volume partially mediated the relationship between fitness and memory. In short, increased fitness levels are associated with increased hippocampal volume, which then leads to improved cognitive function.

In addition to memory, executive functions show substantial age-related deficits. The prefrontal cortex supports executive functioning, and thus is an important brain region to assess in relation to fitness and aging. Prakash and colleagues (2010) found that higher fitness

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levels were associated with enhanced functioning of the prefrontal and parietal cortex during tasks requiring inhibitory control. Rosano and colleagues (2010) reported that individuals who remained physically active for two years after an exercise intervention had greater neural activity in the prefrontal cortex than did control participants. This finding suggests that physical activity has persistent effects on brain activity in regions that support executive functioning. Taken together, these results imply that higher fitness levels in late adulthood relate to enhanced

cognition, which in turn is associated with elevated brain function in areas that support executive function.

But causal claims cannot be conclusively drawn from epidemiological and cross-sectional studies. It is prudent to examine experimental evidence regarding the relationship between exercise and cognitive performance. Several aerobic exercise interventions have been conducted to investigate exercise-induced changes in cognitive and neural health. For instance, one study used fMRI to examine pre- and post-intervention brain function during a task of selective attention and inhibitory control (Colcombe et al., 2004). After six months, the exercise group showed increased task-related brain activity in the prefrontal and parietal cortex, and decreased task-related activity in the anterior cingulate cortex. These changes corresponded to improvements in performing tasks, and demonstrated that six months of

Physical activity has persistent effects on brain activity in regions that support executive functioning.

aerobic exercise was sufficient to improve brain function on a task that typically is affected by the course of normal aging.

Prior research has examined the different regions that change in response to fitness or an exercise treatment, but we know that these regions work in concert with other areas during the performance of cognitively demanding tasks. Using techniques to examine the way in which brain areas communicate with one another, researchers can examine whether fitness or exercise actually alters the communication between brain areas. To address this, Voss and colleagues (2010) examined the default mode network in a group of sixty-five adults older than fifty-five who participated in a one-year aerobic walking intervention. The default mode network is a group of regions that co-activate when an

individual is relaxing in a resting state. After one year, exercising participants showed improved functional efficiency and connectivity in this network; these changes were related to greater improvements in executive function tasks. In this group of individuals, exercise enhanced the neural communication and functional connectivity between brain regions, even at rest.

Summary

Normal aging is associated with both brain atrophy and cognitive decline. We now see that higher fitness levels are associated with less brain atrophy and cognitive decline in late life; early and midlife physical activity can protect against late-life brain decay; and exercise can influence the same cognitive domains and supporting brain regions that are most affected by cognitive aging.

There are several important conclusions to draw from this research. First, it is never too late to start being active. Even sedentary older adults show enhanced brain integrity from increased physical activity. A mere six months of regular walking is sufficient to show enhanced brain volume and function. The human brain remains plastic throughout its lifespan, and exercise can capitalize on this plasticity. In fact, walking at least one mile per day at an easy to moderate pace may be sufficient to use the brain's plasticity and improve brain health.

Higher fitness levels in early and midlife are associated with both a decreased level of brain atrophy and a decreased risk for developing cognitive problems later in life. Thus, adopting a physically active lifestyle early on may be the best way to prevent brain decay. Finally, exercise targets the same cognitive domains of executive function and memory that are typically the first to exhibit age-related changes. The prefrontal cortex and hippocampus, regions that support these cognitive domains, are amenable to exercise interventions. Physical activity provides a robust method to protect against, and treat, age-related changes in the brain.

Despite the wealth of research on physical activity and the brain, there is still much to be discovered. Further research is needed on exercise as a treatment for neurological and psychiatric problems, and specific information regarding the amount and intensity of exercise needed to treat both healthy and impaired individuals is lacking. The field of exercise effects

on the brain is beginning to develop just in time for the aging of the American population. 

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Medications and the Aging Population

Thomas Clark, **Guest Editor**

Medications play critical roles in the lives of most elders: they can help prolong life, manage symptoms of chronic diseases, and improve quality of life and functional status. It is a fact that the number of chronic conditions in older adults increases with age, and this population frequently takes multiple medications, a practice that can have serious—even life-threatening—health effects. This issue of *Generations* reviews the positive (and often controversial) role of medications in the aging cohort, and highlights emerging research about benefits and risks of medications, especially in the fragile elderly. Articles will also address special challenges relating to elders' medication use, including poly-pharmacy, adherence to medication regimens, the potential for medications to contribute to geriatric problems such as falls and delirium, and the vital role of the pharmacist in delivering quality care.

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