# Augmenting Brain and Cognition by Aerobic Exercise

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**Abstract.** Cognitive function declines in late adulthood and this is preceded by atrophy of the prefrontal cortex, hippocampal formation, and parietal cortex. Despite significant loss of brain tissue in late adulthood, decline is not ubiquitous across all older adults. In fact, some adults age quite successfully with minimal decline. This suggests that brain deterioration might not be an inevitable consequence of aging. In fact, mounting evidence suggests that participation in regular aerobic exercise is effective at enhancing cognitive and brain health in late adulthood. In this paper we discuss the evidence that cardiorespiratory fitness and aerobic exercise augments cognition by increasing gray matter volume in prefrontal and hippocampal brain regions.

**Keywords:** Aging, brain, atrophy, exercise.

## 1 Introduction

The United States Census Bureau expects that the percentage of people over the age of 65 will increase from approximately 11% of the population in 2000 to nearly 23% of the population in 2050 [1]. With an increase in the percentage of the population over the age of 65 comes an increase in the expected prevalence of age-related diseases. For example, a recent report from the Alzheimer's Association suggests that the number of persons with Alzheimer's Disease will increase from approximately 5.1 million in 2010 to nearly 13.5 million by 2050 [2]. Such an increase in the prevalence of Alzheimer's Disease is paralleled by elevated costs to treat and care for people with the disease. For example, it is estimated that health care costs associated with Alzheimer's Disease will be 172 billion dollars in 2010 and will increase to nearly 1.078 trillion dollars by 2050.

Not everyone will develop Alzheimer's disease. Yet, even in those people who do not develop Alzheimer's Disease, there is still evidence of cognitive decline. For example, longitudinal studies have found that there is relative stability or even growth in cognitive function, across several different cognitive domains until the age of about 55 or 60. After the age of 60 there is gradual decline in most measures of cognitive function including inductive reasoning, perceptual speed, spatial orientation, episodic memory and verbal memory [3]. Therefore, even in adults not experiencing Alzheimer's disease, cognitive decline is still prevalent.

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Preceding, and leading to, cognitive dysfunction in late life is a decline in the volume of cortical and subcortical brain tissue. For example, in one cross-sectional study in two-hundred adults between 18 and 80 years of age, it was found that there is a linear decline in the volume of gray matter in the dorsolateral prefrontal cortex starting as early as about 30 years of age [4]. Similarly, the hippocampus, a small structure located in the medial temporal lobe, also deteriorates in late adulthood, but instead of a liner decline like the dorsolateral prefrontal cortex, the hippocampus shows a non-linear rate of decline. That is, both cross-sectional and longitudinal studies of the hippocampus have found that there is rather little decline in the volume of this structure before the age of 55. After the age of 55 there is a steady decline in volume at about 1-2% per year in individuals without dementia [4] and about 3-5% per year in individuals with dementia [5].

Despite the average decline in volume of the hippocampus and dorsolateral prefrontal cortex in late life, there is a significant amount of individual variability, with some people showing more rapid decay and others showing minimal decay. This variability begs the question: what factors contribute to the individual variability in the rate and extent of brain atrophy? And if we can identify factors that explain this variation could we develop interventions that protect against brain decay or even reverse atrophy that is already manifest. As will be described below, there is now convincing evidence that a modest amount of aerobic exercise not only explains individual variability in the rate of brain deterioration but is also effective at augmenting brain health when an exercise regimen is initiated.

## 2 Why Aerobic Exercise?

When we think of methods to exercise our brains, we generally think of intellectual activities such as crossword puzzles, Sudoku, or reading. However, it turns out that when we work our muscles we also work our brains. In fact, we should no longer think of aerobic exercise as simply affecting our bodies from the neck down. The early seminal research on how exercise influences the brain was discovered by animal studies with rats and mice in which the intensity and duration of exercise could be easily monitored and manipulated. From these studies, it has been found that exercising increases the number of new neurons produced in the dentate gyrus of the hippocampus, even in aged animals. Although the rate of cell proliferation resulting from exercise in aged animals is less than the rate in young animals [6], the finding that older animals are still capable of neurogenesis and that aerobic exercise can take advantage of this plasticity is quite promising. The possibility of neurogenesis in old animals suggests that atrophy may not be inevitable and might even be reversible.

With the growth of new neurons comes an increased need for nutrients. Increased nutrients are supplied to the brain by increasing the vascularization of brain tissue. Exercise has been found to increase blood flow and vascularization in rodents. Angiogenesis, or the proliferation of new vasculature, has been found in several brain regions including the cerebellum, hippocampus, motor cortex, frontal cortex, and basal ganglia [6, 7].

Exercise has also been shown to increase synaptic connections between neurons and to enhance learning and memory [8]. For example, in a hippocampal-dependent

maze task, rodents that had voluntary access to a running wheel demonstrated faster learning rates and enhanced retention compared to their non-exercising counterparts [9]. Both cell proliferation and learning and memory are thought to be dependent on similar cellular cascades. One molecule that is secreted by neurons, is considered to be involved in neurogenesis, and is critical in cellular analogs of learning and memory is brain-derived neurotrophic factor (BDNF). Levels of BDNF generally decline in aging and Alzheimer's disease, but exercise increases the production and secretion of this molecule [9]. Furthermore, blocking the binding of BDNF to its receptor essentially eliminates the exercise-induced enhancement of cognitive function [10]. This is strong evidence to suggest that BDNF plays an important mediating role in determining how aerobic exercise improves brain health.

In sum, studies in rodents have revealed the underlying molecular and cellular mechanisms by which exercise exerts its effects on the brain. These findings provide a low-level biological justification for examining the effects of exercise on brain integrity in humans.

## 3 Aerobic Exercise, Cognition and Brain Morphology in Humans

Research in the 1970's found that older adult athletes outperformed their more sedentary peers on several different cognitive and motor tasks [11]. Indeed, many cross-sectional studies have now found similar associations between higher aerobic fitness levels and better cognitive function in late adulthood [7]. Cross-sectional studies, although informative about associations between exercise and cognition, are inherently limited in determining causal relationships. In order to determine if aerobic exercise is effective at improving cognitive and brain function, randomized clinical trials are needed in which participants are randomly assigned to either receive exercise or a control condition. Importantly, exercise interventions in which older adults are randomly assigned to receive monitored and structured exercise for a period of 3-6 months have found that starting an exercise regimen can enhance cognitive function. In fact, a recent meta-analysis of 18 different randomized exercise interventions found that exercise improves cognition in both a general and specific fashion [12]. That is, the effects of aerobic exercise are general in the sense that nearly all cognitive domains are enhanced with exercise, but specific in the sense that executive functions are enhanced more than other cognitive domains. The term executive function is an umbrella term that broadly refers to several different higher-level cognitive functions such as selective attention, task-coordination, planning, sequencing, and maintaining items in working memory. Executive functions are largely supported by prefrontal and parietal brain circuits and are often found to show the most significant deficits in late adulthood compared to other cognitive domains. The fact that exercise appears to have its greatest effect on executive functions suggests that although executive functions show the greatest decline with advancing age, they remain tractable.

The results from the meta-analysis of exercise interventions [12] suggested that the brain regions supporting executive function, such as the prefrontal and parietal brain regions, would be the ones most affected by exercise. To test this prediction, Colcombe and colleagues [13] randomly assigned a group of older sedentary adults to

either a moderate intensity activity group that walked for about 40 minutes three days per week or to a non-aerobic stretching and toning control group that came into the lab for the same amount of time as the exercising group. Both groups participated for a period of six months. High-resolution brain scans using magnetic resonance imaging (MRI) were obtained both before and after the intervention. Using a voxel-based morphometry technique to examine brain volume on a point-by-point basis throughout gray matter and white matter tissues, Colcombe and colleagues reported that exercise was effective at increasing gray matter volume in the prefrontal, parietal, and lateral temporal regions and at increasing white matter volume in the genu of the corpus callosum. This study was important as it suggested for the first time that brain tissue of older adults remains modifiable and that only six months of exercise is sufficient for taking advantage of the brains natural capacity for plasticity.

As described earlier, the hippocampus has been a region of great focus in aging research because of its role in memory formation, and specifically in the formation of declarative memory. The hippocampus is also important because it shows considerable atrophy in late adulthood and leads to Alzheimer's disease and memory loss. Research in rodents, however, have unequivocally found that exercise can influence the morphology and function of the hippocampus and that BDNF is highly concentrated in the hippocampus and increases with bouts of exercise [8-10]. This evidence leads directly to the speculation that higher fitness levels may be associated with less hippocampal atrophy and spared memory function. To test this hypothesis, Erickson and colleagues examined cardiorespiratory fitness levels in a sample of 165 older adults without dementia and used MRI techniques to identify the volume of the hippocampus [14]. They found that after controlling for potentially confounding factors like age, sex, and education, older adults that were more aerobically fit had larger hippocampal volumes than their less fit peers. In addition, a spatial memory task was used to test memory function in this study. It was found that higher fit older adults performed better on the task, and greater hippocampal volume partially mediated the fitness-cognition association. These results directly linked for the first time, cardiorespiratory fitness, age-related hippocampal atrophy, and memory function. There have now been several other studies in both older adults and children that have replicated this effect showing that higher fitness levels are associated with greater hippocampal volumes [15-16].

The effects of cross-sectional studies demonstrating associations between cardiorespiratory fitness levels and hippocampal volumes are provocative, but fail to demonstrate direct causal links between increasing exercise and hippocampal volume. In order to determine causality an intervention must be conducted. To address this concern, Erickson and colleagues [17] conducted a randomized one-year intervention in which 120 sedentary older adults without dementia were assigned to either a moderate intensity exercise intervention or to a stretching and toning control group. Similar to previous interventions, both groups received the same amount of social interaction and health instruction from trained health professionals. The main difference between the groups was that the walking group participated in aerobic exercises for one year while the control group participated in non-aerobic activity for one year. Using MRI technology again to examine the volume of the hippocampus and a spatial memory task to measure cognition, Erickson and colleagues [17] reported that one year of exercise was sufficient for increasing the size of the

hippocampus. Furthermore, they reported that increased hippocampal volume was correlated with improvements in spatial memory function suggesting a direct link between hippocampal size and behavioral outcomes. Finally, they also reported that although the exercise intervention did not increase circulating levels of BDNF, the change in BDNF from baseline to post-intervention was associated with increases in hippocampal volume. These findings help to support the claim that modest amounts of exercise can increase the size of brain regions that normally undergo deterioration as we age and may help to prevent memory loss. Furthermore, these results claim that the brain remains modifiable well into late adulthood and that starting an exercise regimen in late adulthood is not futile; even those adults that have been sedentary can still benefit from starting to exercise.

The study by Erickson and colleagues [17] help to support the claim that exercise can augment brain and cognition in late adulthood. However, there are several important questions that remain unanswered from this. For example, how much exercise is necessary to observe its effects on brain and cognition? Epidemiological studies suggest that more strenuous activities are associated with a reduced risk of cognitive impairment [18] and meta-analyses of interventions suggest that about three to six months is sufficient for observing improvements in cognition. However, these studies are not dose-response studies in which the duration and intensity of exercise is manipulated. In fact, dose-response studies for the effects of exercise on cognitive and brain function have not yet been conducted.

To help address the question of the dosage of physical activity and the retention of the benefits of physical activity on brain morphology, Erickson and colleagues [19] conducted a thirteen-year longitudinal study of 299 adults over the age of 65. In this study, physical activity was assessed at baseline by asking participants how many blocks they walked on average over a one-week period. Nine years after this assessment, high-resolution brain images were collected and VBM was used to examine whether physical activity measured nine-years earlier was predictive of brain volume later in life. Consistent with the predictions, Erickson and colleagues [19] found that a greater amount of physical activity was associated with greater gray matter volume in prefrontal, hippocampal, and occipital regions. However, they also found that this occurred in a dose-dependent fashion. That is, sparing of gray matter volume with physical activity was only apparent in those individuals reporting more than 72 blocks of walking per week, or roughly one mile of walking per day. Those walking less than one mile per day showed less brain volume than their more active peers. This finding suggested that not only might there be a lower-bound threshold for the amount of activity needed to observe the benefits of exercise on brain morphology, but also that the effects of physical activity might be long-lasting. Furthermore, a four-year follow-up after the MRI assessment found that those individuals with greater gray matter volume in the inferior frontal gyrus, hippocampus, and supplementary motor area had a two-fold reduced risk of developing cognitive impairment.

In sum, the research described in this section now convincingly demonstrates that aerobic exercise is effective at augmenting brain and cognitive health in late adulthood and that even modest amounts of exercise is sufficient for increasing brain size and improving memory. At a time of life when memory impairment is a salient fear and brain atrophy is progressing at a faster rate, aerobic exercise could be an

important low-cost and low-tech prevention and treatment that is accessible to most people. Although exercise will not be a magic bullet cure for Alzheimer's disease, even if it delays the onset or reduces the risk for developing cognitive impairment, it may save millions of dollars in health care costs and reduce the emotional toll on caregivers and those afflicted with impairment.

## 4 Aerobic Exercise and Brain Function

The research described above has focused on the role of aerobic exercise and fitness in relation to brain morphology. However, other neuroimaging techniques, such as functional MRI (fMRI) have also provided some important insight regarding how the functioning of the brain is affected by cardiorespiratory fitness and aerobic exercise. In one seminal study by Colcombe and colleagues [20], older adults were randomized either to an exercise walking group or to a stretching and toning control group similar to those interventions described above. In the first part of the study they used fMRI to examine brain function during a selective attention task in a cross-sectional sample of older adults. They found that more highly fit older adults had greater brain activation in prefrontal and parietal brain areas and less activity in the anterior cingulate cortex. These activation differences were accompanied by elevated performance on the selective attention task. This cross-sectional investigation was followed by results from a randomized intervention that demonstrated that these same regions also showed increased brain activity after the intervention. That is, the exercise intervention resulted in elevated performance on the task and increased brain activity in prefrontal and parietal areas. This study was important because it demonstrated that the effect of exercise extends beyond brain morphology by influencing the function of the supporting brain circuitry. These effects have recently been replicated in several other fMRI studies [21-23].

One way in which the brain networks are improved with exercise might be by an augmentation of the connectivity between brain regions. Enhanced brain connectivity resulting from exercise might help to explain how improvements in cognition are elicited. To test this hypothesis, Voss and colleagues [24] first demonstrated in a cross-sectional sample of older adults that individuals who were more aerobically fit had greater resting state connectivity than those adults who were less aerobically fit. Furthermore, enhanced functional connectivity between frontal and hippocampal nodes reliably mediating the fitness-cognition association suggesting that enhanced connectivity plays an important causal role in the augmentation of cognitive function. This cross-sectional study was followed-up by a randomized trial in which older adults were assigned to either a walking exercise group or to a stretching and toning control group and resting state fMRI was collected both before and after the one-year intervention. In this study, Voss and colleagues [25] found that exercise increased the connectivity between fronto-hippocampal regions and that this was paralleled by improvements in memory function. These results are important because they highlight the need to look beyond just the simple descriptive patterns of brain activity towards a more unified conceptualization of how the brain systems and communication network is being influenced by exercise.

In sum, aerobic exercise influences brain and cognitive function and evidence from fMRI demonstrate that enhancements in cognition are associated with enhancements in brain function in specific regions of cortex. Further, improvements in the communication and connectivity between regions probably underlies several of the enhancements commonly observed in studies that find better cognitive function in more fit individuals.

## 5 Conclusion

We have outlined the evidence in favor of the argument that modest amounts of aerobic exercise are sufficient for enhancing cognition and brain function. By using MRI technology, several studies have found that higher fit older adults have greater amounts of gray matter volume in several regions including the prefrontal cortex and hippocampus – areas of the brain that often show the most consistent patterns of deterioration and atrophy in late adulthood. Furthermore, exercise also increases brain activity in these same regions, which appears to parallel improvements in cognition. Overall, this evidence suggests that aerobic exercise can be envisioned as an effective method to prevent brain deterioration, maintain cognitive and brain function, and reverse atrophy that is already present. Despite these consistent and convincing findings, there remain many unanswered and unexplored questions.

One remaining set of questions involves the dose-response of exercise on brain and cognition. That is, as described above, we have relatively little information that tells us how much exercise is necessary, what intensity should be achieved, and what types of exercises are best to enhance cognition. The answers to these questions are critically important if aerobic exercise is to be used in clinical contexts and be prescribed to patients as a prevention or treatment for loss in cognitive function.

We also have very little information about the underlying mechanisms of aerobic exercise in humans. Is exercise working by predominantly influencing the creation of new vasculature? In fact, both morphological and fMRI results could be interpreted in relation to new vasculature resulting from exercise. Some studies have suggested that the effects of exercise extend beyond vascularization of brain tissue and that exercise works directly on the brain. In short, more research is needed to understand how aerobic exercise is exerting its effects on brain and cognition.

The results from research described in this review have been largely limited to older adult populations that are not experiencing signs of dementia. We do not yet know the extent to which aerobic exercise could prevent decay of brain tissue in those already experiencing cognitive impairment nor do we fully understand whether similar exercise interventions could influence cognition in other populations. In short, more research is needed to understand the generalizability of these effects.

Finally, not everyone benefits equally from exercise. Some people show very little benefits from the intervention while others show significant cognitive enhancement. What are the factors that contribute to this individual variability? Could there be genetic factors that moderate the extent to which any single person would benefit from exercise? Are there other factors such as intellectual stimulation or dietary habits that either accentuate or attenuate the effects of exercise.

In conclusion, we can argue that (1) the brains of older adults remain modifiable and that exercise can take advantage of this plasticity to prevent or even reverse brain decay, (2) it is never to late to start exercising, even adults that have been sedentary most of their lives can still reap the benefits of an exercise regimen, (3) the effects of exercise are not global throughout the entire brain, but have some specificity to hippocampal and prefrontal brain areas. Overall, this research suggests that brain atrophy and cognitive decline might not be as inevitable a consequence of aging as previously thought.

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