

Physical activity and brain plasticity in late adulthood: a conceptual review

Kirk I. Erickson,^{1,2} Destiny L. Miller,¹
Andrea M. Weinstein,^{1,2}
Stephanie L. Akl,¹ Sarah E. Banducci¹

¹Department of Psychology, University of Pittsburgh; ²Center for the Neural Basis of Cognition, Pittsburgh, USA

Abstract

A growing body of evidence from neuroscience, epidemiology, and kinesiology suggests that physical activity is effective as both a prevention and treatment for cognitive problems throughout the lifespan. Given the expected increase in the proportion of older adults in most countries over the next 40 years, physical activity could be a low-cost and relatively accessible method for maintaining cognitive function throughout later life. Despite the emerging recognition of physical activity as a powerful method to enhance brain health, there is continued confusion from both the public and scientific communities about what the extant research has discovered about the potential for physical activity to improve neurocognitive health and which questions remain unanswered. In this review, we outline four overarching themes that provide a conceptual structure for understanding the questions that have been asked and have been addressed, as well as those that have yet to be answered. These themes are descriptive, mechanistic, applied, and moderating questions. We conclude from our review that descriptive questions have been the first and most thoroughly studied, but we have much yet to learn about the underlying mechanisms, application, and moderating factors that explain how and to what extent physical activity improves brain health.

Introduction

One of the greatest misconceptions of the adult brain is that it is incapable of plasticity. In other words, the layman view of the brain is that it is capable of rapidly adapting during childhood or young adulthood, but by middle or late adulthood it becomes brittle and unchangeable. In contrast, considerable evidence now suggests that although older adult brains are less plastic than younger brains, they still retain some capacity for plasticity.¹ Physical activity, at least at a moderate intensity, has

emerged as a powerful method to take advantage of the brain's natural capacity for plasticity.

Finding methods, such as physical activity, to improve cognitive function is paramount to an international health care initiative given the increasing aging population in most developed countries and the expected rise in the prevalence of Alzheimer's disease over the next 40 years.^{2,3} Even in older adults that do not develop dementia, some degree of cognitive decline is common. If increased physical activity improves cognitive function, it may be a relatively low-cost and low-tech solution to slow down, prevent, or reverse cognitive impairment in old age.⁴

The scientific literature on physical activity has established three important findings. First, starting a moderate intensity physical activity regimen in late adulthood is not futile. As will be discussed in this review, even very sedentary individuals can improve cognitive and brain function by increasing physical activity. Second, only moderate intensity exercise is needed to observe significant changes in brain and cognition. Third, a broad set of cognitive functions are influenced by physical activity, including memory, attention, and the domain of executive control, which includes our ability to manage multiple tasks, plan for future events, and switch between tasks.

In this manuscript, we extend prior reviews⁴⁻⁶ of this literature by describing several conceptual themes that provide structure to this rapidly growing field. The types of questions that can be asked can be broadly categorized as descriptive, mechanistic, applied, and moderating. The next sections briefly discuss each of these categories of questions, their relative importance, and the scientific evidence that attempts to answer them.

Descriptive questions

Descriptive questions describe the effect of physical activity on brain and cognition without inquiring about the mechanisms or applicability of the effect. For example, questions related to the types of exercise that might be most effective at augmenting brain and cognition might describe the effect of physical activity but would not address the mechanisms or applicability of the effect. Other questions that could be categorized as descriptive might include: How much physical activity is necessary to detect an effect on the brain? How quickly do the benefits dissipate when physical activity patterns are interrupted or discontinued?

Although descriptive questions are often dismissed as scientifically rudimentary, they are not easy to address empirically. Nonetheless, the answers to these questions have practical significance. For example, if

Correspondence: Kirk I. Erickson, University of Pittsburgh, 3107 Sennott Square
210 S. Bouquet St., Pittsburgh, PA 15260, USA.
Tel. +1.412.624.4533 - Fax: +1.12.624.4428.
E-mail: kiericks@pitt.edu

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physical activity is going to be prescribed as either prevention or as treatment for cognitive and brain diseases, then patients need to know how much physical activity is necessary and what types might be most beneficial. Without this explicit information, patients will be unlikely to adopt physical activity as a non-pharmaceutical method to enhance or protect brain function.

In this section, we discuss the studies that attempt to address two descriptive questions: i) which cognitive and brain functions are enhanced by physical activity; and ii) how much physical activity is necessary to detect an effect on cognitive and brain function?

Which cognitive and brain functions are enhanced by exercise?

The most comprehensive investigations of physical activity on cognitive and brain function have been conducted in older adults aged over 65 who are free of dementia but still experiencing decline in cognitive function. Unfortunately, cognitive decline is a relatively ubiquitous characteristic of late adulthood, yet decline does not occur uniformly across all cognitive domains. Working memory, episodic memory, control of directed attention, maintenance of goals, and switching between multi-

ple ongoing tasks tend to show disproportionate age-related losses.⁷⁻⁸ These functions are often categorized under the umbrella term of *executive function*, which largely refers to controlled processes that are supported by frontal and parietal brain regions.

Studies on physical activity have demonstrated that the cognitive functions and brain regions showing the most rapid decay in late adulthood are the same processes and regions amenable to improvements. For instance, in one study, 124 sedentary older adults aged 60 to 75 were randomly assigned to either a walking group or to a stretching control group.⁹ The walking group reported to a track three times per week and walked at a moderate intensity for 45 min each day. The stretching control group also attended sessions, but instead of walking, they participated in low intensity stretching exercises. The results from a neuropsychological evaluation found that the walking group showed enhanced executive function compared to the stretching control group after six months of exercising, but little improvement on tasks that were not executive in nature. These results suggested that: i) six months of moderate intensity aerobic exercise could improve cognitive function; ii) the benefits of aerobic exercise are greatest on tasks of executive function; and iii) those cognitive domains that show the greatest rate of decline in late adulthood remain tractable.

Consistent with this conclusion, a meta-analysis of 18 randomized aerobic exercise trials found that the effect of aerobic exercise on cognition is both general and specific.¹⁰ The effect is general in that most cognitive functions improve with physical activity but specifically executive functions improve more than speed, spatial, or controlled tasks. A more recent meta-analysis of 29 randomized controlled trials confirmed that aerobic exercise elicits modest improvements in attention, executive function, and memory performance across the lifespan, but with limited benefits to working memory.¹¹

Despite these highly consistent patterns across studies, several reviews and meta-analyses have questioned the direct link between improvements in cardiovascular fitness and improvements in cognition.¹² These theories suggest that physiological changes, other than improvements in cardiorespiratory fitness that accompany increased physical activity, might be influencing cognitive function. For example, physical activity decreases insulin resistance,¹³ reduces inflammation¹⁴ and improves sleep quality,¹⁵ all of which could be independently influencing cognitive and brain function. However, an alternative explanation is that the results of exercise are dose-dependent¹⁶ and that changes in aerobic fitness levels are associated with improvements in cognition only when baseline fitness levels

are low, an explanation that will be addressed in more detail below.

The specificity of the effect of aerobic exercise on executive function and memory led to the hypothesis that it would also have a regionally specific effect on the brain. That is, if aerobic exercise selectively improves executive function, then it might be most effective at enhancing the size and function of brain regions that support executive function. In one cross-sectional study, magnetic resonance imaging (MRI) was used to investigate brain volume in 55 adults between 55 and 79 years of age. Cardiorespiratory fitness levels were obtained for each participant by using an estimated VO_2 max, the gold-standard measure of aerobic fitness, and brain volume was calculated by a semi-automated segmentation routine that provides an estimate of tissue volume on a point-by-point basis throughout the brain.¹⁷ It was found that higher cardiorespiratory fitness levels moderated age-related deterioration of prefrontal, parietal, and temporal brain regions (Tables 1 and 2). This effect remained significant even after controlling for several potentially confounding factors, such as socioeconomic status, years of education, and sex. Importantly, this result is in line with results suggesting that executive function, and the brain regions supporting executive function, are the most affected by aerobic fitness.^{4-6,9-11} Unfortunately, the small sample size in this study precluded the ability to reliably examine correlations with other physical activity measures or cognitive variables, so the implications of greater brain volume on cognitive function remained unknown.

The effect of aerobic exercise on regional volume measures has also been examined in randomized controlled trials. In one study, high-resolution MRI of the brain was obtained both before and after a six-month intervention in which 59 sedentary older adults were randomized to either moderate intensity walking or to a stretching and toning control group three days per week. Voxel-based morphometry was used to estimate gray and white matter volume throughout the brain both before and after the intervention. Although the stretching-toning control group showed a slight decline in volume over the six-month interval, the walking group showed a significant increase in volume over the same period.¹⁸ Increased volume was localized to the gray matter in the dorsolateral and medial prefrontal regions and lateral temporal cortices, as well as the genu of the corpus callosum (Table 1).¹⁷⁻²⁸ The genu of the corpus callosum contains axonal fibers that connect prefrontal brain areas across the hemispheres while the dorsolateral and medial frontal cortices are involved in executive function. Again, this result confirms that an aerobic exercise regimen for previously sedentary older adults is

not futile and that relatively modest amounts of activity are effective at increasing brain volume in later life.

Although the prefrontal, parietal, and temporal cortices are larger in more aerobically fit individuals, other brain regions also seem to be influenced by exercise. Most rodent research has focused on the effect of exercise on the hippocampus, a medial temporal lobe structure involved in memory formation (see below). In humans, the association between aerobic fitness and hippocampal morphology and function has only recently been examined. These studies have found that the size of the hippocampus and medial temporal lobes are larger in older adults that are more aerobically fit or physically active. For example, after controlling for age, sex, years of education, and intracranial volume, more aerobically fit older adults had larger hippocampal structures than their less fit peers.²² Furthermore, more aerobically fit individuals had better memory performance compared to less fit individuals, and memory performance was better in individuals with larger hippocampal volumes (Figure 1). Therefore, although the hippocampus deteriorates in late adulthood, remaining aerobically fit helped to preserve volume.²⁴

Intervention results have demonstrated that an aerobic exercise regimen is effective at increasing prefrontal cortex and lateral temporal lobe volume,¹⁸ and cross-sectional research described above has shown associations between aerobic fitness and hippocampal volume. To assess whether a randomized intervention could increase hippocampal volume, 120 older adults were randomized to either a walking exercise group or to a stretching and toning control group three days per week for a period of one-year.²⁸ Brain MRI sessions were conducted at baseline before randomization, after six months, and then again after completion of the intervention. Hippocampal volume was calculated using an automated segmentation algorithm on the MR images. Although both the stretching control group and the walking exercise group began the study with comparable hippocampal volumes, the control group showed a 1.5% decline in hippocampal volume over the 1-year period while the walking exercise group showed an increase in hippocampal volume of nearly 2%. There were no differences in either the size of the caudate nucleus or the thalamus. These results suggest that hippocampal volume could be increased in late life by one year of regular walking (Table 1).

Functional MRI (fMRI) has provided converging evidence for the benefits of exercise on prefrontal and parietal circuits (Table 2).²⁹⁻⁴⁵ For instance, several studies have reported that exercise is associated with increased brain activity in prefrontal and parietal regions.^{33,39,43} In a recent cross-sectional fMRI study using the digit symbol substitution test, a test of process-

ing speed, divided attention, and executive function, individuals who were more physically active over a 2-year period outperformed and had greater prefrontal brain activity than their more sedentary counterparts.³⁹ In addition, the amount of physical activity obtained has been positively associated with the amount of activity in the prefrontal cortex.^{33,39}

In short, in a period of life in which cognitive function declines and the brain undergoes significant decay, moderate intensity exercise enhances cognitive function by influencing the integrity of brain regions supporting higher-level cognitive function including the prefrontal and hippocampal areas. These results are in line with meta-analyses and suggest

that the effects of aerobic exercise on the brain are both general and specific: general in the sense that several areas of the brain are affected by exercise, and specific in the sense that prefrontal and hippocampal regions are affected the most consistently and robustly.

How much exercise is necessary?

One of the more pressing questions in this field is: how much exercise is necessary to observe detectable effects on cognitive or brain function? This question asks whether there is a threshold that needs to be reached before physical activity can exert any beneficial effects on cognition. From a practical perspec-

tive, this question is critical. If physical activity is to be prescribed to prevent or to treat brain diseases, patients need to know how much physical activity is necessary.

The most scientifically laudable methods for testing this question are dose-response studies in which the intensity and frequency of physical activity is systematically manipulated over a period of some controlled interval. Unfortunately, dose-response studies of physical activity on brain and cognition have not yet been conducted. Therefore, any conclusions drawn in this section need to be interpreted with caution. Future research that manipulates the dose of exercise will be capable of more accurately addressing this important question.

Table 1. A description of studies examining the association between physical activity, exercise, fitness, and brain volume in older adults.

Study (Year)	Sample size (Mean _{age})	Method	Summary of finding
Colcombe <i>et al.</i> (2003b) ¹⁷	55 (66.5)	<i>Design:</i> Cross-sectional <i>Measures:</i> VBM, Rockport & VO _{2peak}	Age-related loss of white and gray matter in prefrontal, temporal, parietal regions was moderated by higher aerobic fitness levels.
Colcombe <i>et al.</i> (2006) ¹⁸	59 <i>Exercisers:</i> (65.5) <i>Stretchers:</i> (66.9) <i>Younger:</i> 20 (Not reported)	<i>Design:</i> 6-mo randomized exercise intervention <i>Measures:</i> VBM, VO _{2peak}	Increases in white and gray matter volume in frontal and temporal regions after aerobic exercise intervention.
Erickson <i>et al.</i> (2007) ¹⁹	54 (69.6)	<i>Design:</i> Cross-sectional <i>Measures:</i> VBM, VO _{2peak} & hormone replacement therapy (HRT)	Higher fitness augmented increased cortical volume related to short-term HRT and offset volume-losses related to long-term HRT.
Gordon <i>et al.</i> (2008) ²⁰	<i>Older:</i> 40 (71.5) <i>Younger:</i> 20 (22.5)	<i>Design:</i> Cross-sectional <i>Measures:</i> VBM, VO _{2peak} , & neuropsychological battery	Higher fitness related to greater gray matter volumes in temporal, parietal, and inferior frontal area.
Burns <i>et al.</i> (2008) ²¹	<i>Normal:</i> 64 (72.7) <i>Early AD:</i> 57 (74.3)	<i>Design:</i> Cross-sectional <i>Measures:</i> Total volume, VO _{2peak}	Higher fitness was related to larger whole brain and white matter volumes. Not significant in older adults without dementia.
Erickson <i>et al.</i> (2009) ²²	165 (66.6)	<i>Design:</i> Cross-sectional <i>Measures:</i> Automated segmentation, VO _{2peak}	Higher aerobic fitness was related to greater hippocampal volume. Volume partially mediated a fitness-memory association.
Honea <i>et al.</i> (2009) ²³	<i>Normal:</i> 56 (73.3) <i>Early AD:</i> 60 (74.3)	<i>Design:</i> Cross-sectional <i>Measures:</i> VBM, VO _{2peak} , Physical activity scale for the elderly (PASE)	Higher fitness was related to larger gray and white matter volumes in inferior frontal and medial temporal in early AD. APOE genotype did not moderate the effects.
Bugg & Head (2009) ²⁴	52 (69.0)	<i>Design:</i> Cross-sectional <i>Measures:</i> 10-year retrospective physical activity survey	Higher levels of self-reported exercise were associated with larger superior frontal volume. Exercise moderated age-related atrophy of the medial temporal lobe.
Flöel <i>et al.</i> (2010) ²⁵	75 (60.5)	<i>Design:</i> Cross-sectional <i>Measures:</i> VBM, physical activity, aerobic fitness	Increased physical activity was associated with increased cerebral gray matter volume in prefrontal and cingulate cortex.
Rovio <i>et al.</i> (2010) ²⁶	<i>Active:</i> 32 (52.1) <i>Sedentary:</i> 43 (48.8)	<i>Design:</i> Cross-sectional <i>Measures:</i> VBM, physical activity questionnaire	Higher reported physical activity was associated with greater gray matter volumes, however, the association between mid-life physical activity level and white matter value fell to non-significance after controlling for relevant covariates.
Erickson <i>et al.</i> (2010) ²⁷	299 (78.0)	<i>Design:</i> Longitudinal <i>Measures:</i> VBM, physical activity self-report,	Self-report walking at least 72 blocks per week was associated with greater volume of frontal, occipital, entorhinal, and hippocampal regions 9-years later.
Erickson <i>et al.</i> , (2011a) ²⁸	Total N=120 Exercise group=60 (67.6) Stretching Control group =60 (65.5)	<i>Design:</i> Randomized Clinical Trial <i>Measures:</i> automated segmentation of hippocampus, caudate nucleus, thalamus, serum BDNF, VO _{2peak} , memory measures.	Walking for one-year was associated with an increase in hippocampal volume while the stretching control group exhibited a decline in volume over the same interval. Changes in hippocampal volume were correlated with changes in BDNF and memory for the exercising group.

Table 2. A description of studies examining the association between physical activity, exercise, and fitness, and brain function or perfusion in older adults.

Study (Year)	Sample size (Mean _{age})	Method	Summary of finding
Rogers <i>et al.</i> (1990) ²⁹	Old working: 30 (64.4) Old retired, high activity: 30 (64.9) Old retired, low activity: 30 (64.4)	Design: Prospective longitudinal Measures: Cerebral blood flow (CBF)	Physically inactive retirees showed less CBF after 4-year follow-up. Older working and active retirees retained greater CBF and better cognition than less active peers.
Dustman <i>et al.</i> (1990) ³⁰	Old: 30 Fit: (53.8) Low-Fit: (55.9) Young: 30 Fit: (24.1) Low-Fit: (26.3)	Measures: EEG, VO ₂ max, cognitive testing	Physically active men showed shorter ERP latencies, stronger central inhibition, better cognitive performance, and better visual sensitivity.
Hillman <i>et al.</i> (2002) ³¹	Old Fit: 12 (63.5) Old Low-Fit: 12 (65.0) Young Fit: 12 (22.1) Young Low-Fit: 12 (23.3)	Design: Cross-sectional Measures: EEG, VO ₂ max, physical activity self-report	Higher fitness was associated with reduced P3 latency and decreased amplitude of contingent negative variation.
McDowell <i>et al.</i> (2003) ³²	Old Active: 18 (66.1) Old Inactive: 18 (69.3) Young Active: 21 (22.3) Young Inactive: 16 (23.1)	Design: Cross-sectional Measures: EEG, VO ₂ max	Active elderly and young exhibited reduced P3 than inactive suggesting reduced allocation of neural resources.
Colcombe <i>et al.</i> (2004) ³³	Cross-sectional=41 High Fit: (66.2) Low-Fit: (67.9) Intervention=29 Exercisers: (67.9) Stretchers: (66.7)	Design: Cross-sectional and randomized controlled trial Measures: fMRI, VO ₂ peak and Rockport	High fit (Study 1) or aerobically trained (Study 2) older adults show greater task-related activity in prefrontal and parietal cortices during selective attention task.
Hatta <i>et al.</i> (2005) ³⁴	Active: 20 (69.2) Sedentary: 20 (66.9)	Design: Cross-sectional Measures: EEG, VO ₂ max	Active adults showed faster reaction times on oddball task and larger P3 amplitudes.
Hillman <i>et al.</i> (2006) ³⁵	Old Active: 17 (63.7) Old Inactive: 15 (65.9) Young Active: 18 (19.4) Young Inactive: 16 (19.4)	Design: Cross-sectional Measures: EEG, self-report of physical activity	In a task-switching paradigm, response times were faster and P3 amplitudes were larger for active adults.
Themanson <i>et al.</i> (2006) ³⁶	Old: 32 (Range 60-71) Young: 42 (Range 18-21)	Design: Cross-sectional Measures: EEG, self-report of physical activity	Greater physical activity was associated with reduced global switch cost in task-switch paradigm and decreased amplitude of error related negativity.
Pontifex <i>et al.</i> (2009) ³⁷	Old Fit: 10 (66.2) Old Low-Fit: 13 (67.4) Young Fit: 12 (20.3) Young Low-Fit: 13 (20.1)	Design: Cross-sectional Measures: EEG, VO ₂ max	Higher fitness was associated with better cognitive performance and greater P300 for older adults.
Kamijo <i>et al.</i> (2009) ³⁸	Old: 12 (65.5) Young: 12 (21.8)	Design: Acute exercise Measures: EEG, VO ₂ max	Exercise reduced reaction time and P3 latencies during a flanker task.
Rosano <i>et al.</i> (2010) ³⁹	Exercisers: 20 (80.8) Educational Control: 10 (81.5)	Design: Cross-sectional follow-up to physical activity intervention Measures: fMRI, self-report of physical activity	Two years after intervention, exercisers demonstrated better cognitive performance and greater brain activity during digit symbol task
Burdette <i>et al.</i> (2010) ⁴⁰	Control: 5 (74.0) Physically Active: 6 (77.6)	Design: Intervention Measures: fMRI CBF and connectivity	Physical activity enhanced hippocampal CBF and increased connectivity between hippocampus and anterior cingulate cortex.
Voss <i>et al.</i> (2010 ^a) ⁴¹	Old Exercises: 30 (67.3) Old Stretchers: 35 (65.4) Young Control: 32 (23.9)	Design: Randomized controlled trial for 1 year Measures: fMRI resting state and default mode networks.	Aerobic training improved efficiency and connectivity between frontal, posterior, and temporal cortices within the Default Mode Network and Frontal Executive Network.
Voss <i>et al.</i> (2010 ^b) ⁴²	Old: 120 (66.5) Young: 32 (24.1)	Design: Cross-sectional Measures: fMRI, VO ₂ max, cognitive testing	Enhanced default mode network connectivity mediates the relationship between fitness and cognition in old adults.
Prakash <i>et al.</i> (2011) ⁴³	70 (65.0)	Design: Cross-sectional Measures: fMRI, VO ₂ peak and Rockport, cognitive testing	Higher fitness levels were associated with better Stroop performance and increased activity in prefrontal and parietal cortices, but not posterior regions.
Smith <i>et al.</i> (2011) ⁴⁴	Low-Risk AD/Sedentary: 17 (73.3) Low-Risk AD/Active: 17 (74.3) Hi-Risk AD/Sedentary: 17 (72.9) Hi-Risk AD/Active: 17 (70.7)	Design: Cross-sectional Measures: fMRI, self-report physical activity, cognitive testing, APOE genotype	High physical activity and high risk for AD was associated with greater activity during a semantic memory task. Physical activity moderated risk status on brain activity.

Several reviews have suggested that six months of moderate intensity aerobic exercise is sufficient for observing effects on brain and cognition.⁵⁻⁶ In support of this argument, results from several randomized controlled trials suggest that six months of aerobic exercise improves cognitive function in older adults⁹⁻¹¹ while trials over shorter periods have reported more equivocal findings.⁴⁶ However, several studies of shorter duration have found significant effects of physical activity on the brain.⁴⁷ Unfortunately there is insufficient evidence at this time to conclude that the benefits of aerobic exercise continue to accrue with more than six months of exercise. However, in one randomized trial, one year of aerobic exercise resulted in greater increases in hippocampal volume than six months of aerobic exercise.²⁸

Recent interventions in individuals with memory complaints or early stages of Alzheimer's disease have also reported cognitive improvements over a 6-month training period,⁴⁸⁻⁴⁹ but not over shorter intervals like in a 6-week intervention.⁵⁰ In one study, 138 participants over the age of 50 with self-reported memory problems were randomly assigned to either a home-based exercise regimen or to an educational control group.⁴⁸ Participants in the intervention group demonstrated marked improvements on the Alzheimer's Disease Assessment Scale - Cognitive subscale while the educational control group experienced a slight decline on this measure over the same period. Meta-analyses on interventions with cognitively impaired participants have reported that six months of exercise is sufficient for detecting an effect on cognitive function,⁵¹ but again, dose-response studies have not yet been conducted.⁵²

There have now been several studies that have examined the effect of physical activity earlier in life on the size of certain brain regions later in life. These longitudinal observational studies have shown that physical activity earlier in life is associated with greater brain tissue years later.²⁶⁻²⁷ For example, the association between gray matter volume and physical activity was assessed over a 9-year period in 299 older adults.²⁷ Physical activity was quantified as the number of blocks walked in one week and MRI of the brain was acquired nine years later. It was found that a greater amount of physical activity at baseline was associated with greater gray matter volumes in the frontal, occipital, and medial temporal lobe, including the hippocampus, nine years after the physical activity assessment, even after controlling for baseline measures of brain integrity (Figure 2). This demonstrates that greater amounts of physical activity are protective against age-related decay of brain volume. Furthermore, walking 72 blocks in one week was necessary to detect an effect on gray matter volume, but walking more than 72 blocks

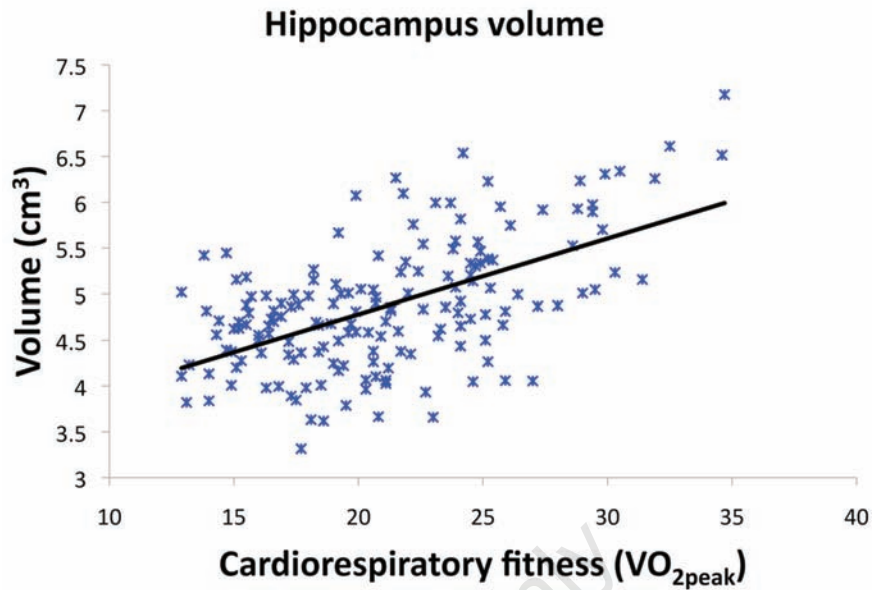


Figure 1. Although the volume of the hippocampus normally declines in late adulthood, Erickson *et al.*²² found that in a group of 165 older adults the volume of the hippocampus was positively associated with cardiorespiratory fitness levels. The results are collapsed across both left and right hemispheres.

per week was not associated with additional sparing of tissue. In relation to understanding how much physical activity is necessary, this study provides some important insights. According to these results, self-reported walking of at least 72 blocks per week was necessary to spare brain volume over a long-term interval (nine years) and to significantly decrease the risk associated with Alzheimer's disease. Seventy-two blocks per week approximates to about six to nine miles per week.

The results from randomized trials and observational studies are compatible with prospective longitudinal studies that have examined the effect of physical activity on the risk for cognitive impairment over a two to ten year period. These studies have demonstrated that greater amounts of physical activity are associated with the maintenance of cognitive function over an 8-year period.⁵³ Several studies have also reported an inverse linear association between energy expenditure and cognitive decline, such that greater amounts of physical activity are associated with a reduced risk of impairment.⁵⁴⁻⁵⁹ However, several other studies have reported an inverse-u function, such that moderate amounts of activity are effective at reducing the risk for cognitive impairment but vigorous activity is not effective.⁶⁰⁻⁶¹

Taken together, data from longitudinal and randomized controlled trials suggest that moderate amounts of activity for a period of six months is sufficient for detecting beneficial effects on brain and cognition, yet several

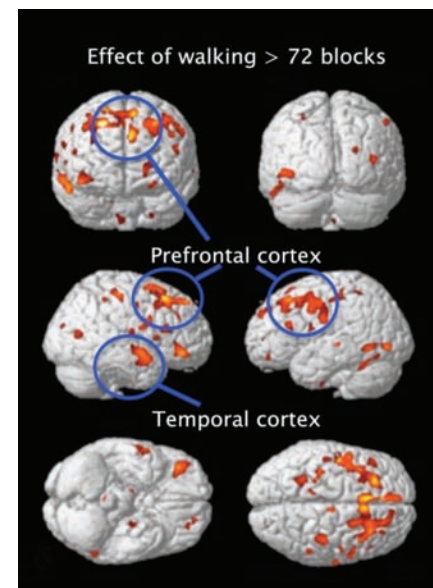


Figure 2. In a sample of 299 older adults, greater amounts of self-reported walking at baseline was associated with greater gray matter volume as assessed by magnetic resonance imaging and voxel-based morphometry nine years later.²⁷ Colored areas in the image are the areas that show greater gray matter volume in those reporting walking 72 blocks per week. Effects were found in frontal, temporal, occipital, and hippocampal brain regions (blue circles). The statistical map was thresholded with a false discovery rate of $P=0.05$ and a minimum cluster threshold of 100 contiguous voxels.

studies have also shown effects at shorter durations.⁴⁷ Further, walking roughly 72 blocks per week is needed for detecting long-term effects of physical activity on brain volume. However, systematic manipulations of exercise in dose-responses have not been conducted to precisely determine thresholds and levels that are necessary to consistently enhance neurocognitive function in later life.

In summary, there is considerable evidence that aerobic exercise influences brain and cognition in a relatively specific fashion. That is, executive functions and memory are enhanced by moderate intensity aerobic exercise and the brain regions that support these functions are consistently influenced by exercise treatments. Although there have been no systematic dose-response studies of physical activity on brain and cognition, inferences from longitudinal and intervention studies suggest that six months of moderate intensity aerobic exercise is sufficient for improving cognition.

There are now preliminary answers for several descriptive questions, but there remain many more that are unanswered. For example, links between increased regional brain volume and enhanced cognition remain poorly understood and largely speculative.²⁸ In addition, whether there are certain types of exercises (e.g. walking) that augment brain health more than other types (e.g. bicycling) remains unknown, and how long the positive effects are retained after a physical activity regimen has been discontinued remains unsettled. In short, although there is much known about the effects of exercise on brain and cognition, there are many gaps in the scientific literature that hinder the active prescription of physical activity as a prevention or treatment for cognitive impairment or age-related cognitive decline.

Mechanistic

A growing body of evidence demonstrates that moderate-intensity physical activity improves brain and cognition. However, what are the mechanisms by which this occurs? From a biological perspective, it is customary to define the term mechanism as the molecular processes that give rise to the system-level changes influencing cognitive function. However, mechanisms can also be defined on several other levels. For example, within a cognitive neuroscience framework, physical activity could enhance cognition by changing or improving the functional connectivity of specific brain circuits involved in executive and memory function. Thus, mechanistic hypotheses can occur on at least two different levels: i) molecular; and ii) systems, or cognitive neuroscience.

What are the molecular mechanisms of exercise on brain and cognition?

Animal models are often used to assess the molecular and cellular mechanisms of physical activity. In animal models, exercise is often manipulated by providing a rodent with voluntary access to a running wheel or by forced exercise on a treadmill. Many studies have used a voluntary exercise model with the argument that forced exercise could inadvertently attenuate cognitive function by increasing stress.⁶² In addition, it has been argued that voluntary exercise is more similar to exercise behavior in humans than is forced exercise.⁶³ On the other hand, forced exercise paradigms allow for more control over exercise frequency, intensity, and duration. Nonetheless, using either forced or voluntary models of exercise, animal studies have focused on three main mechanisms by which exercise enhances cognition: neurogenesis, or the proliferation and survival of new neurons; angiogenesis, or the proliferation and survival of new vasculature; and elevated levels of neurotransmitters and neurotrophic factors, the most frequently studied being brain-derived neurotrophic factor (BDNF). There are many other paths and molecules that are influenced by exercise, many of which are only now becoming recognized as important contributors to the enhancing effect of exercise on cognition, but this review should serve only as an overview of some of the molecular pathways involved in the enhancing effects of exercise.

Voluntary access to a running wheel enhances hippocampal-dependent learning and memory. For example, learning on the Morris water maze is accelerated after several weeks of access to a running wheel⁶⁴ for both young and aged animals. Other tasks, such as T-maze,⁴ radial arm maze,⁶⁵ spatial separation,⁶⁶ and avoidance tasks⁶⁷ have also shown enhancements in learning rates for exercising animals. Many of these tasks, such as the Morris water maze, spatial separation, and certain versions of the T-maze and radial arm maze, are considered to be hippocampal-dependent tasks while avoidance tasks are more reliant on limbic circuits including the amygdala, anterior cingulate cortex, and orbitofrontal cortex, in addition to the hippocampus.⁶⁸ Hence, similar to studies of cognitive function in humans, exercising rodents outperform sedentary animals on several learning and memory paradigms that are supported by hippocampal and frontal brain circuits.

Exercise-related improvements in learning and memory have been associated with the number of neurons produced in the dentate gyrus of the hippocampus, even in aged rodents.⁶⁹ In fact, an increase in cell proliferation and cell survival in the dentate gyrus of

the hippocampus is one of the most consistently observed effects of exercise.⁶³ For example, in one study, mice were assigned to either a running condition with voluntary access to a running wheel or to one of a few control conditions.⁶⁹ The total number of new and surviving cells in the dentate gyrus of the hippocampus was increased with exercise and was associated with faster learning rates on the Morris water maze. Running mice also showed an enhancement of long-term potentiation (LTP), a cellular analog of learning and memory formation in the hippocampus. Exercise also enhanced performance on a spatial pattern separation task, and newly generated neurons were linked to better performance.⁶⁶ Importantly, neurogenesis resulting from exercise has been found for both younger and older animals,⁶⁹ but cell proliferation in older animals is attenuated compared to younger animals. This might describe a limit to the amount that exercise can reverse age-related decay in tissue loss.⁷⁰ Consistent with this hypothesis, voluntary exercise prevented an age-related decline in precursor cell activity, but failed to maintain cell activity at the level of younger animals.⁷⁰ It is also important to consider the role of new neurons in enhanced cognitive function associated with exercise. In fact, it likely takes several weeks before new neurons are completely integrated into the system and become functional.⁷¹⁻⁷³ While several studies have demonstrated that exercise-induced neurogenesis is linked to enhanced cognition^{69,74-75} others have focused on the immediate and preceding role of angiogenesis on cognitive function as well as neurovascular adaptations in the hippocampus and their associations with cognitive improvements.⁷⁶⁻⁷⁷

The proliferation of new cells creates an increased need for nutrients. This demand is met by the stimulation of new blood vessels. In one study, rats were exposed to an acrobatic condition with high motor learning demands, a forced exercise condition, a voluntary exercise condition, or an inactive control group.⁷⁸ They found that motor learning in the acrobatic condition caused synaptogenesis, while both forced and voluntary exercise resulted in the proliferation of new vasculature in the cerebellum. Similar results have been found in the motor cortex.⁷⁹⁻⁸⁰ For example, Swain *et al.*,⁸⁰ used functional MRI in rats and found increased blood volume in the primary motor cortex after 30 days of wheel-running. Angiogenic processes probably contribute to learning and memory acquisition⁷⁶ and mediate exercise-induced increases in neurogenesis.⁸¹ Exercise increases the production and secretion of molecules involved with the formation of new blood vessels including insulin-like growth factor (IGF-1)⁸² and vascular endothelial growth factor (VEGF).⁸¹ Several studies have reported that exercise induces the proliferation of new vascu-

lature in the cerebellum,⁷⁸ motor cortex,⁷⁹⁻⁸⁰ hippocampus,⁸² and striatum.⁸³⁻⁸⁴

Neurogenesis and angiogenesis lead to improvements in cognition.^{66,69,74,76} BDNF has been related to long-term potentiation, a cellular analog of memory formation, and to cell proliferation in the hippocampus, olfactory bulb, and striatum.⁸⁵ BDNF levels are increased as a function of exercise in the hippocampus, frontal cortex, striatum, and cerebellum.⁸⁵ In one study, blocking the binding of BDNF to its receptor effectively abolished the exercise-related improvements in Morris water maze performance,⁸⁶ which directly linked BDNF to improved memory performance as a function of exercise. Although the concentration of dopamine, serotonin, and other molecules are also influenced by exercise,⁸⁷ BDNF has received considerable attention for its putative role in learning, memory and neurogenesis, and its upregulation as a function of physical activity.

Exercise also offsets the behavioral symptoms observed in rodent models of Alzheimer's diseases. For example, in a mouse model of Alzheimer's disease, exercising animals show a reduction in beta-Amyloid deposits,⁸⁸ reduced tau formation,⁸⁹ and superior learning rates compared with sedentary animals.⁹⁰⁻⁹² The mechanisms by which exercise offsets pathological markers are unknown, but BDNF might be one pathway. For example, cells with high levels of BDNF are free from tau accumulation while cells with tau do not contain any measurable amount of BDNF.⁹³ In addition, lower levels of serum BDNF are found in more severe stages of Alzheimer's disease.⁹⁴ Further, beta-amyloid disrupts BDNF signaling, but administration of BDNF protects against beta-amyloid toxicity in a dose-dependent manner.⁹⁵ Similarly, administration of BDNF is effective at reversing synaptic loss and enhancing learning and memory in transgenic mouse models of Alzheimer's disease.⁹⁶ Altogether, this research suggests that aerobic exercise might be an effective treatment for slowing or reversing physiological markers of Alzheimer's pathology, and that BDNF might be a critical molecule along this path.

In summary, exercise increases levels of important biomarkers (e.g. BDNF) that may be contributing to exercise-induced neurogenesis and angiogenesis, and offsets the molecular cascades associated with Alzheimer's. The results from these studies overlap with human studies and provide a low-level biological explanation for the effects observed in humans.

What are the cognitive neuroscience and systems-level mechanisms of exercise?

There are several ways in which the network of brain regions involved with complex cognitive function could be altered or enhanced by

physical activity. For example, it is possible that aerobic exercise selectively enhances the functioning of some brain regions (e.g. prefrontal cortex) that allow for a more flexible use of particular strategies. Another possibility is that exercise improves the connectivity between regions, which allows regions to communicate more effectively. This avenue of research is still in its infancy, but a few studies now suggest that there are several system-level changes resulting from aerobic exercise that mediate performance improvements in executive function tasks.

In one study, aerobic fitness levels were quantified using VO₂max, and a network of brain regions active at rest were identified using a resting-state fMRI protocol.⁴¹ The so-called *default-mode* resting-state network includes several brain regions, such as parietal and medial prefrontal regions, and the degree of connectivity between these regions declines with age and with Alzheimer's disease.⁹⁷ Resting state networks are determined based on the coherence of signals across the brain while the subject relaxes in the MR machine. This is clearly different from task-evoked activation in which the subject performs a cognitively challenging task and the periods of cognitive challenge are aligned with the MR signal to determine *brain activity* during the task. In resting state networks, the degree of coherence across brain regions is calculated and regions whose signals fluctuate at the same frequency would be considered *functionally connected*. These areas that are active at rest and that are functionally connected are thought to serve several purposes depending on which networks are examined. The so-called *default-mode network* is thought to be involved in self-focused cognition, body homeostasis, or monitoring the external environment. Importantly, higher fitness levels have been associated with enhanced connectivity of the default resting-state network including prefrontal and hippocampal regions.⁴¹ In addition, increased resting-state connectivity mediated an aerobic fitness-related improvement in executive function. This result suggested that even at rest, the brains of fitter older adults are working more effectively than less fit older adults, and it provides a mechanistic explanation for how physical activity and aerobic fitness are associated with enhanced cognition.

Two other recent studies have reported more evidence for this association. These studies have demonstrated that a randomized aerobic exercise intervention for four months⁴⁰ and one year⁴² enhanced the connectivity between regions. In one study, 11 older adults were randomized to a home-based exercise intervention or to an educational control group and scanned in a resting fMRI paradigm both before and after the intervention.⁴⁰ Using a multivariate approach to identify networks of regions influenced by the exercise treatment, the authors found increased connectivity between the hip-

poampus and the anterior cingulate cortex only in those people who were exercising (Table 2). In the second study, a one-year randomized intervention with 65 older adults without dementia found that aerobic exercise selectively increased the connectivity between frontal-parietal-temporal regions.⁴² This effect was only evident after twelve months; six months of exercise was not effective in altering the connectivity patterns. Importantly, improvements in brain connectivity for the aerobic exercise group were associated with exercise-related improvements in executive function.

Similar to animal studies on angiogenesis, human studies have begun to focus on the possible role of increased blood flow and vascularization in mediating cognitive improvements. In fact, several studies have reported that aerobic exercise increases blood flow and volume to the hippocampus,^{40,47} and this was associated with elevated memory function and increased cell proliferation.⁴⁷ Furthermore, in a small study of 14 older adult participants, more active older adults had a greater number of small vessels in the brain compared to less active older adults.⁹⁸ Such increased vascularization could be contributing to both volumetric findings and fMRI findings of exercise.⁴ However, based on the molecular mechanisms described above, it is clear that increased vascularization of brain tissue is unlikely to explain all of the benefits associated with exercise.

Finally, several studies in older adults suggest that physical activity improves the capacity for the brain to prepare to make a response.^{35,99} According to this hypothesis, physical activity improves cognition by enhancing the cortical processors involved with preparation. In one study, 110 older adults were sorted into low and high-fitness groups based on an estimated VO₂ test (Table 2). Using a response time task where the time-to-prepare varied from one to nine seconds, higher-fitness older adults took advantage of the preparatory interval more efficiently than lower-fitness older adults.⁹⁹ Other studies using event-related potentials have also reported differences in preparatory brain signals as a function of fitness.^{31-32,36-38,100}

Although we are far from having a clear understanding of the cognitive neuroscience and system-level mechanisms of how exercise improves brain and cognitive function, physical activity might alter the communication between regions, increase vascularization and perfusion, and improve the functioning of brain regions supporting response preparation. However, it is clear that more research is needed on the cognitive neuroscience mechanisms of physical activity before there can be definitive claims about the specific mediating pathways.

In summary, exercise increases the number of new cells that are born in the hippocampus, increases the amount of capillaries, and

changes the production and secretion of several neurotrophic factors and neurotransmitters, leading to faster learning rates and improved retention of material learned. From a cognitive neuroscience perspective, aerobic exercise might improve cognition by enhancing the connectivity between regions and by improving the efficiency of preparatory states.

Applied

Most of the research on the effect of physical activity on brain and cognition has been conducted in older adults without dementia.⁵⁻⁶ From this research, it is clear that exercise improves cognition, increases brain function, and increases gray and white matter volume in select cortical areas. However, what is not so clear is whether physical activity influences the brain and cognition in other populations such as in individuals with neurological or psychiatric problems. Furthermore, the extent to which physical activity should be considered as a non-pharmaceutical method to prevent neurological or psychiatric diseases is not clear. If physical activity could help to prevent brain disease, could it also be prescribed as a treatment? These types of questions can be classified under the category of *applied* since they do not address the phenomenology of physical activity on cognition or the mechanisms by which physical activity influences the brain. Instead, these questions address fundamental concerns over the ability of exercise to enhance cognitive and brain function across different populations. Fortunately, there has been growing evidence that exercise might be effective at improving cognition in several different populations.

What are the effects of exercise on older adults with cognitive impairment?

The risk for Alzheimer's disease increases with advancing age.^{2,101} The Alzheimer's Association recently reported that, as of 2010, approximately 5.1 million people were living with Alzheimer's disease in the United States, and that the costs associated with caring for and treating people with Alzheimer's disease will reach over 170 billion dollars in 2010 alone.³ Preventions that reduce the risk or delay the onset of the disease could reduce health care costs and ameliorate the emotional unrest of the family members and caregivers of individuals with dementia. What is the evidence that regular amounts of moderate intensity exercise could reduce the risk of Alzheimer's disease or even be an effective treatment for improving memory function in those already suffering from Alzheimer's disease?

As described previously, animal models have

demonstrated that voluntary exercise prevents the accumulation of beta-amyloid and neurofibrillary tangles; two of the putative causes of Alzheimer's disease.⁸⁸ Epidemiological studies have reported that greater amounts of physical activity are often associated with less cognitive decline and a reduced risk of dementia later in life. For example, Podewils and colleagues studied the relationship between physical activity and dementia in 3,375 individuals over the course of 5.4 years.⁵⁷ Physical activity was assessed by a self-report questionnaire in which participants were asked about the frequency and duration of 15 types of physical activities. The authors found that greater amounts of physical activity were associated with a lower incidence of Alzheimer's disease.

Interestingly, intervention studies have recently been examining whether several months of consistent exercise is effective at improving cognitive function in individuals with cognitive impairment. For example, six months of aerobic exercise improved performance on tests of executive function in women with MCI.⁴⁹ MCI is associated with a three to five times greater risk of developing Alzheimer's disease than that found in healthy older adults.¹⁰² In a similar study, six months of exercise improved cognitive function in a sample with self-reported memory problems.⁴⁸ These effects are consistent with several meta-analyses finding that exercise interventions are effective at improving cognitive function in individuals with MCI or dementia.^{52,103}

Alzheimer's disease and MCI are associated with a rapidly deteriorating brain. For this reason, it is imperative to examine the potential for physical activity to offset or slow the rate of brain deterioration. Unfortunately, randomized trials of physical activity and brain function have not yet been conducted to determine whether increasing the amount of aerobic exercise offsets brain deterioration in these populations. However, there have been several cross-sectional studies examining the association between aerobic fitness and brain volume in people with MCI or Alzheimer's disease. These studies have hypothesized that if physical activity improves cognitive function and delays the onset of Alzheimer's disease, then higher aerobic fitness levels might be associated with the sparing of brain volume. In one study, aerobic fitness was assessed in individuals in the early stages of Alzheimer's disease. Using MRI to examine brain volume, individuals with Alzheimer's disease who were more aerobically fit had greater total gray matter volume than less fit peers.²¹ This finding suggested that there might also be regional variation in brain volume as a function of aerobic fitness. In fact, in one study, Honea and colleagues found greater medial temporal lobe volume in aerobically fit individuals with dementia than their less fit counterparts.²³ Therefore, consistent

with meta-analyses of randomized interventions of exercise in cognitively impaired populations and animal models of disease, higher fitness levels were associated with less cortical decay in populations with MCI and Alzheimer's disease.

Elevated beta-amyloid and tau are putative causes of Alzheimer's disease and, as discussed above, animal models of Alzheimer's disease show that exercise reduces amyloid deposits and tau formation.⁸⁸⁻⁹² Consistent with these results, physical activity appears to also reduce the accumulation of amyloid in aged humans.¹⁰⁴ In one study, 69 cognitively normal older adults aged 55 to 88 years reported their activity levels over the past ten years. Cerebrospinal fluid samples of beta-amyloid and tau were acquired in addition to imaging the concentration of amyloid deposits using Pittsburgh Compound B (PiB) with positron emission tomography.¹⁰⁴ The authors found that higher self-reported activity levels were associated with less PiB and tau, and a trend for less beta-amyloid obtained from the cerebrospinal fluid. These results suggest that exercise might reduce the risk of Alzheimer's disease by reducing the build-up of amyloid and tau.

Along these same lines, a recent longitudinal observational study in 299 older adults over a 13-year span found that greater amounts of walking were associated with sparing of brain volume and that greater brain volume decreased the risk of developing Alzheimer's disease.²⁷ Although very few functional neuroimaging studies have been conducted to examine whether task-related brain activity differs between physically active *versus* physically inactive adults with MCI, one study has recently found increased caudate nucleus activity in more physically active adults with MCI compared to their less active peers.¹⁰⁵ Overall, these results provide a provocative argument that a prescription of regular physical activity might act as prevention for cognitive impairment, but randomized interventions to examine whether aerobic exercise reduces the incidence rate of dementia have not yet been conducted. Furthermore, whether aerobic exercise can be considered a non-pharmaceutical method to treat cognitive impairment remains unknown. Only studies that compare the effectiveness of aerobic exercise to other established methods of treating Alzheimer's disease will be able to establish whether it is a feasible treatment option.

Could aerobic exercise influence other neurological and psychiatric conditions?

Parkinson's disease is a motor disorder that affects approximately 1% of adults over the age of 55 and is characterized by loss of dopamine secreting neurons in the substantia nigra and

function in the basal ganglia. In animal models of Parkinson's disease, exercise increases dopamine release in the basal ganglia and protects against Parkinsonian symptoms.¹⁰⁶ Walking interventions also improve executive function and motor control in Parkinson's disease patients.¹⁰⁷⁻¹⁰⁸ A recent 12-week aerobic exercise intervention found significant improvements in executive function in the walking group as compared to controls.¹⁰⁹ In another study, six months of aerobic exercise enhanced executive function and moderated the decline in cognition associated with Parkinson's disease.¹¹⁰ In short, aerobic exercise has the potential to improve cognition and motor control and to alter the dopaminergic properties of Parkinson's disease; however, there remains a paucity of research on exercise-related brain plasticity in Parkinson's disease patients.¹¹⁰

Aerobic exercise also appears to reduce depressive symptoms in older adults.¹¹¹ Observational epidemiological studies have consistently found that greater amounts of physical activity are associated with a lower prevalence of major depressive disorder.¹¹²⁻¹¹⁴ Randomized trials have also demonstrated beneficial effects of exercise on depressive symptoms.¹¹⁵⁻¹¹⁹ Some studies have compared the effectiveness of exercise to the effectiveness of anti-depressant and cognitive-behavioral therapies on treating major depression. For example, in one study, 156 older adults with major depressive disorder were assigned to 16 weeks of supervised aerobic exercise, anti-depressant medication, or a combination of both medication and aerobic exercise.¹¹⁶ All three groups showed equivalent reductions in depressive symptoms, suggesting that aerobic exercise is equally effective as medication for treating late-life depression. Therefore, while anti-depressant medications often facilitate a quicker therapeutic response than exercise, the sustained effect of aerobic exercise on reducing depressive symptoms is as effective or more effective in the long-term as these same medications.¹¹⁵⁻¹¹⁸

Aerobic exercise has been shown to improve cognitive function and reduce behavioral impairments in a variety of psychiatric disorders including schizophrenia,¹²⁰ bipolar disorder,¹²¹ and post-traumatic stress disorder,¹²² but these studies have not been conducted in older adult populations. Since this review focuses on the effects of physical activity in late adulthood, we recommend the reader to other reviews.¹²³⁻¹²⁵

There is now considerable evidence that aerobic exercise is effective at enhancing neurocognitive function in MCI and Alzheimer's disease. In fact, one recent meta-analysis reported that the effects of aerobic exercise might even be greater in cognitively impaired populations than in older adults without

impairments.¹¹ However, it is also clear that before conclusive statements on the preventive and treatment effects of physical activity can be generated, large, well-controlled randomized trials with neuroimaging outcome measures are needed. Similarly, aerobic exercise appears to improve cognitive function in Parkinson's disease and is effective at reducing depressive symptoms in older adults. Indeed, physical activity appears to have a widespread effect on the brain and more research is suggesting that individuals with psychiatric and neurological diseases could benefit from participating in regular physical activity.

Moderators

It is clear that not everyone benefits at the same rate or to the same degree from physical activity. This suggests that there are factors that moderate the effect of physical activity on brain and cognition. Indeed, physical activity does not occur in isolation of other lifestyle habits such as dietary patterns, intellectual stimulation or education, cigarette smoking, or stress. To what extent do these lifestyles or habits influence the effect of physical activity on brain and cognition? Unfortunately, very few studies have investigated these associations, but the few that have report that dietary patterns, hormone use, and social participation might moderate the rate or extent to which physical activity improves brain and cognition.

There are several different ways that such variables may moderate the effect of physical activity. First, the effects of physical activity may be attenuated by the presence or absence of other lifestyle factors. For example, physical activity may improve cognition, but if it is accompanied by an unhealthy diet, the beneficial effect may be significantly attenuated. Second, other lifestyle factors may potentiate the effect of physical activity on the brain and cognition. Thus, the combination of physical activity with an intellectually stimulating environment may promote a healthier brain than either factor by itself.

Can dietary habits, hormone supplementation, or social activity moderate the effect of physical activity on the brain?

Older adults with a greater vitamin B6 and B12 intake have greater brain volume along the medial portion of the frontal and parietal cortices than older adults receiving less B vitamin.¹²⁶ Such effects of nutrients on cognitive and brain function may be moderated by exercise. In fact, studies in rodents have reported that diet can moderate the effect of physical

activity on BDNF levels and cell signaling. For example, voluntary exercise potentiates the beneficial effects of omega-3 fatty acids on cell membrane proteins involved in synaptic plasticity and cognition.¹²⁷ Furthermore, exercise offsets the negative effects of a high-fat diet on BDNF levels in the hippocampus¹²⁸ and enhances the effect of caloric restriction on hippocampal dendritic spine density and BDNF levels. Thus, combining both a healthy diet and exercise seems to be more beneficial for brain health than either treatment alone. Unfortunately, we can only speculate about the interactive effect of dietary patterns and physical activity on brain and cognition in humans.

Sex hormones may be another factor that could influence the extent to which exercise improves cognitive and brain function. In one meta-analysis, studies including more women tended to show larger effect sizes.¹⁰ It was hypothesized that this might be related to changing patterns of physical activity during the menopausal transition and a moderating effect of hormone therapy on cognition. In support of this claim, the combination of estrogen administration and exercise in ovariectomized rats increased BDNF levels in the hippocampus more than either treatment by itself.¹³⁰ In humans, determining whether hormone therapy has a positive effect on brain function has been a matter of debate. Some studies have found greater hippocampal volumes in women receiving hormone therapy,¹³¹⁻¹³³ while other studies find more equivocal effects on hippocampal volume.¹³⁴⁻¹³⁶ More recent evidence suggests that this variation might be related to a window-of-opportunity near the menopausal transition in which hormone therapy might have transient protective effects against loss of cortical tissue.¹³⁷ However, an alternative explanation is that physical activity levels moderate the influence of hormone therapy on brain and cognition. In support of this claim, one study found that when hormone therapy was administered to postmenopausal women for ten years or longer there was increased brain atrophy in the prefrontal and temporal lobes, but higher levels of cardiorespiratory fitness ameliorated the decline in tissue volume and augmented the effects of short-term hormone therapy use (Figure 3).¹⁹ However, there have also been alternative findings.¹³⁸

Many people exercise together with a friend or family member to help maintain motivation and improve adherence to an exercise regimen. However, does exercising in groups confer greater benefits to cognitive and brain function than exercising alone? Could exercising with a partner or in groups be more beneficial to brain and cognition than exercising in isolation? Unfortunately, answers to these questions remain unknown. However, there have been several studies in rodents that suggest that social isolation may be a key factor in mod-

erating the beneficial effects of exercise on the brain. In one study, socially-housed rats demonstrated more rapid effects of exercise on neurogenesis in the hippocampus than rats that were exercised in isolation.¹³⁹⁻¹⁴⁰ This moderating effect of social participation, however, has not been found in two other studies that have used a similar protocol in which rats received either exercise in social isolation or exercise in combination with social housing.¹⁴¹⁻¹⁴²

Despite the equivocal findings regarding the moderating effect of social interaction and social isolation on exercise effects, some studies have attempted to combine social, intellectual, and physical components into a single program. It is possible that the effect of combining multiple training modalities may be greater than either treatment alone. In the Experience Corps¹⁴³ program, older adults are trained to become teacher aids in the Baltimore school district. This one-year intervention effectively increased physical activity (chasing the children), increased cognitive stimulation (teaching and working on homework), and increased social engagement (with children, staff, researchers, and parents). This program also improved executive function and memory,¹⁴⁴ and improved brain function.¹⁴⁵ Other multi-modal interventions, such as the Senior Odyssey program, combined intellectual stimulation, creative thinking, reasoning, and social engagement in which older adult participants were asked to work in teams to solve problems using creative answers. These studies have found improvements in fluid reasoning abilities in older adults.¹⁴⁶ Although these programs have demonstrated their effectiveness at improving cognition, the mechanism by which these effects occur remains unknown. One explanation is that the benefits of exercise are additive to those of social and intellectual engagement. However, it is possible that only one domain (*e.g.* aerobic exercise) is the driving force behind the observed improvements. Studies that manipulate exercise, social engagement, and intellectual stimulation using different groups are necessary before drawing definitive conclusions.

Are there genetic variants that influence the effect that physical activity has on brain and cognition?

Lifestyle factors are not the only contributors to variation in cognitive and brain function in late adulthood. Clearly, genetics plays an important role, and it is likely that many single nucleotide polymorphisms (SNP) attenuate or enhance the effect of physical activity. For example, BDNF has an SNP that influences the regulated secretion of BDNF. The BDNF polymorphism has been associated with variation in brain volume¹⁴⁷ and cognitive function in older adults over a 10-year interval.¹⁴⁸ Given

that exercise increases the production and secretion of BDNF, it is likely that the polymorphism moderates the effect of exercise on learning, memory, and brain function.¹⁴⁹ In fact, the effect of physical activity on cognitive function and dementia was moderated by the BDNF polymorphism,¹⁵⁰ as was the effect of physical activity on depression,¹⁵¹ indicating that interactions between genes and environment are important for understanding the mechanisms and limitations of exercise on cognitive function and disease.

The APOE e4 allele is an established risk factor for Alzheimer's disease. Based on this, several studies have examined whether exercise could offset the genetic risk of Alzheimer's disease. Unfortunately, the studies examining this question have shown considerable variation with many reporting greater effects of aerobic exercise or physical activity in e4 carriers while other studies have reported either no differences between e4 carriers and non-carriers or stronger effects of physical activity in e4 non-carriers. In one study, the effect of self-reported physical activity levels on beta-amyloid was only evident in non-carriers of the APOE e4 allele.¹⁰⁴ Consistent with this, at least three epidemiological studies have reported that greater physical activity levels only reduce the risk for Alzheimer's disease in APOE e4 non-carriers.^{48,56-57} In contrast, other studies have found that the effect of physical activity on brain volume occurs independently of the presence of the APOE e4 allele^{23,27} and several epidemiological studies have found little evidence for differences in the effects of physical

activity on risk of Alzheimer's disease.⁵⁶ Finally, some studies have reported that the effects of physical activity are more pronounced in e4 carriers. For example, individuals who were both physically active and at high genetic risk of Alzheimer's disease showed greater brain activation compared to less active individuals and individuals at less of a genetic risk of Alzheimer's disease.⁴⁴ Other studies have complemented these effects and have argued that e4 carriers benefit more from physical activity than non-e4 carriers.¹⁵² In fact, some epidemiological studies have reported that greater amounts of physical activity have a larger effect on reducing the risk for dementia in e4 carriers compared to non-carriers.^{59,153-155} Indeed, this range of results makes it challenging to identify a clear pattern of moderation of cognitive function with the APOE e4 risk allele.¹⁵⁶⁻¹⁵⁷

Animal models have taken a significant lead in understanding the factors that moderate the effect of aerobic exercise on brain and cognition, and have found that exercise offsets the negative consequences of a diet high in saturated fats and potentiates the effect of omega fatty acids on cell membranes and transmission. Unfortunately, few studies have been conducted in humans that examine interactions between different lifestyles on brain and cognition. Similarly, gene by environment interactions on brain and cognition are probably contributing a large source of variation to age-related cognitive decline, yet we know very little about the extent of these interactions. It will be critical for future studies to unweave

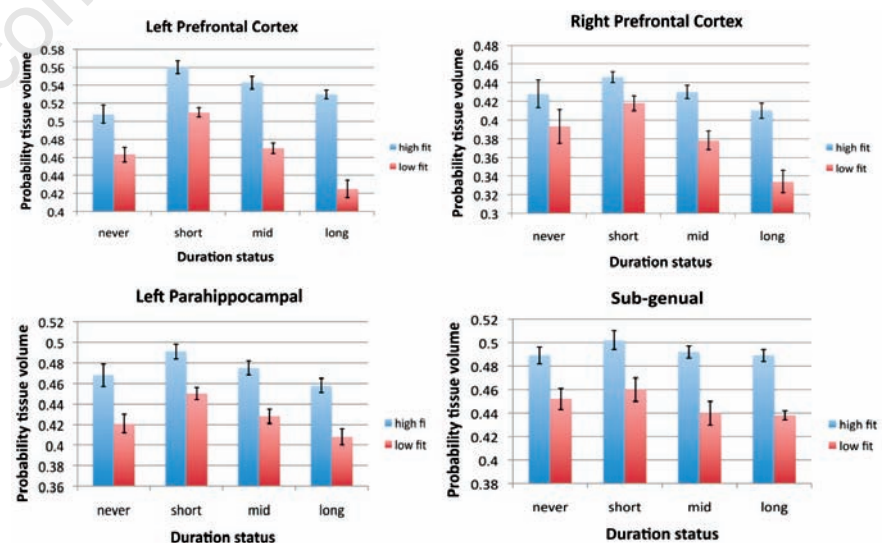


Figure 3. The association between duration of hormone replacement therapy and mean volume in the left prefrontal cortex, right prefrontal cortex, left parahippocampal gyrus, and subgenual cortex. Participants were divided by a median split into high fit (blue bars) and low fit (red bars) groups. There was a significant main effect of treatment duration and fitness on tissue volume for all four brain areas. The left and right prefrontal cortices and the subgenual cortex showed a significant interaction between treatment duration and fitness levels.¹⁹

these moderating effects so that we can gain a better understanding of both the potential and the limitations of physical activity to improve cognitive and brain function.

Conclusions

In this review, we have outlined the evidence that physical activity is effective in enhancing cognitive and brain function in late adulthood. Studies from rodents, epidemiological research, and randomized controlled trials all demonstrate that exercise can improve cognitive and brain function in late adulthood and reduce the risk for developing dementia. It appears that measures of memory and executive function are the most affected by exercise.

Although this pattern of results demonstrates that older adults retain the capacity for brain plasticity, there are many unanswered questions. For example, we know very little about the extent to which exercise can prevent or treat neurological diseases. There has been a growing interest in examining the association between Alzheimer's disease and aerobic fitness levels, and several studies now suggest that exercise interventions may improve cognitive function in populations with manifest impairment, including Parkinson's disease, Alzheimer's disease, and depression. Despite this growing trend of research, very few studies have investigated whether exercise could be considered a treatment for memory problems in populations that are already experiencing decline. In addition, we know very little about the moderating factors that influence the extent and rate of improvement associated with exercise. For example, diet, hormones, and genes may influence the degree to which exercise modifies cognition. Future research is needed to clarify and understand these factors.

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