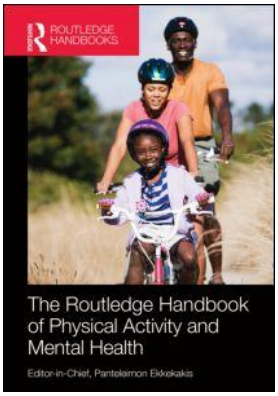

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EXERCISE EFFECTS ON BRAIN AND COGNITION IN OLDER ADULTS

Michelle W. Voss and Kirk I. Erickson

The United States Census Bureau predicts 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 by 2050 (US Census Bureau). Along with this increase comes an expected inflation in the prevalence of age-related diseases. For example, the number of persons with Alzheimer's disease (AD) is expected to increase from approximately 5.1 million in 2010 to nearly 13.5 million by 2050 (Alzheimer's Association, 2010). An increase in the prevalence of AD will be accompanied by elevated costs to treat and care for people with the disease. These costs are estimated to reach US$172 billion in 2010 and to increase to nearly US$1.078 trillion by 2050 (Alzheimer's Association, 2010).

Although not everyone develops AD, cognitive decline in late adulthood is quite common. For example, longitudinal studies in adults without dementia have found that there is often relative stability in cognitive function until about 55 years of age followed by a steady decline in several cognitive domains including inductive reasoning, perceptual speed, verbal ability, spatial orientation, numeric ability, and verbal memory (Hertzog, Kramer, Wilson, & Lindenberger, 2009). Preceding the decline in cognitive function is a decline in brain integrity as measured by both volumetric and functional measures. Several brain areas, such as the dorsolateral prefrontal cortex, begin to deteriorate at about the age of 30 and continue on a declining course throughout late life (Raz et al., 2005). On the other hand, regions like the hippocampus, a smaller structure located in the medial temporal lobe, remain relatively preserved until about the age of 50, and then decline in volume at about 1% per year in individuals without dementia; in adults with dementia there is an escalated rate of decline in volume of the hippocampus to over 3% annually (Jack et al., 1998). Coupled with age-related structural atrophy is alteration in the functional properties of many brain regions. Depending on the cognitive demands of the task, older adults have shown sometimes greater and sometimes less neural recruitment than younger adults. Therefore, unlike brain morphology, there is not always a straightforward translation between whether more or less neural recruitment reflects better or worse brain integrity. Thus, it is often necessary to interpret age-related differences in brain activation in the context of behavioral performance (Grady, 2008) and preferably following a targeted behavioral intervention or longitudinal assessment (Lustig, Shah, Seidler, & Reuter-Lorenz, 2009).

A measure of brain function that is a more consistent index of brain integrity than the magnitude of neural recruitment assesses the tendency for brain regions within distinct networks

to co-activate during rest or task states. Co-activation is often termed functional connectivity, and studies have consistently found that older adults have decreased functional connectivity during the rest state in several brain networks. Three of these networks include the default network and two networks involved in cognitive control – a fronto-executive and fronto-parietal network (Andrews-Hanna et al., 2007; Voss, Prakash et al., 2010). While researchers have linked the functional connectivity of these cognitively relevant networks to the structural integrity of white matter tracts, there is also evidence that functional connectivity reflects unique variance associated with the functional interactions between brain regions (Van Dijk et al., 2010).

Despite the general age-related decline in brain integrity evidenced by volumetric and functional measures, there is significant individual variability in the rate and prevalence of decline, with some people showing more rapid decay and others aging quite successfully with minimal impairment. This suggests that cognitive and brain decay might not be ubiquitous and begs the following question: what factors explain variation in cognitive and brain function in late life? If factors can be identified that explain individual variability in the rate and prevalence of brain atrophy and dysfunction, could we develop interventions that prevent decline from occurring? In this chapter, we discuss the possibility that physical activity (PA), especially in the form of aerobic exercise, could act to not only prevent brain decay and dysfunction in late adulthood, but could also reverse atrophy and impairment already present.

Why aerobic exercise?

It may at first be surprising to hear that PA influences brain function. Indeed, usually when people think of methods that exercise the brain, they think of intellectual activities such as crossword puzzles, Sudoku, or reading. However, exercise appears to be an effective method for enhancing both the body and brain. Animal studies with rats and mice in which the intensity and duration of exercise can be monitored and manipulated allows for a controlled environment to assess the effect of exercise on brain morphology and function. From these studies, it has been found that a moderate amount of exercise increases the number of new neurons produced in the dentate gyrus of the hippocampus, even in aged animals (Kronenberg et al., 2006). With an increased number of new neurons comes an increased need for nutrients. Therefore, in concert with increased cell proliferation is an exercise-induced increase in blood flow and blood volume. 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 (for reviews, see Cotman & Berchtold, 2002; Kramer, Erickson, & Colcombe, 2006). Exercise also increases the number of connections, or synapses, between neurons, and increases levels of neurotrophins in the brain that modulate processes of synaptic plasticity, which together lead to enhanced learning and memory (Christie et al., 2008; van Praag, Shubert, Zhao, & Gage, 2005; Vaynman, Ying, & Gomez-Pinilla, 2004). In sum, rodent studies have revealed some of the underlying molecular and cellular mechanisms by which exercise exerts its effects on the brain. These findings provide a biological foundation for examining the effects of exercise on brain integrity in humans.

Aerobic exercise, cognition, and brain morphology in humans

Early cross-sectional research found that older adult athletes outperformed their more sedentary peers on several cognitive tasks (Spirduso, 1975; for review, see Kramer, Erickson, & Colcombe, 2006). This cross-sectional work was followed by exercise interventions in which older adults were randomly assigned to a moderate-intensity exercise group or a control group (often

consisting of stretching and toning exercises). Several of these interventions showed that aerobic exercise enhanced cognitive function. In a meta-analysis of 18 randomized clinical trials, exercise was found to have both general and specific effects on cognitive function (Colcombe & Kramer, 2003). The effects were general in the sense that most of cognition was enhanced with exercise, but specific in the sense that executive function (EF) was enhanced more than other cognitive domains. EF is an umbrella term that refers to several higher-level cognitive functions such as selective attention, task-coordination, planning, and maintaining items in working memory. EF is often found to be the most negatively affected with increasing age, yet appears to remain tractable, and exercise has the capacity to take advantage of this modifiability.

The results from intervention studies suggest that the brain regions supporting EF, such as the prefrontal and parietal cortex, are the ones most affected by exercise. To test this prediction, Colcombe and colleagues (2006) randomly assigned a group of older sedentary adults to a moderate-intensity aerobic exercise group that walked for 40 minutes 3 days per week or a non-aerobic stretching and toning control group that exercised in a group setting in the lab for the same amount of time as the walking group. A control group that experiences the same social setting as the experimental exercise group is important since social activity has also been linked to cognitive function in older adults (Bassuk, Glass, & Berkman, 1999; Lovden, Ghisletta, & Lindenberger, 2005). Both groups participated for 6 months. High-resolution brain scans from magnetic resonance imaging (MRI) were obtained before and after the intervention. 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 was the first to suggest that age-related loss of brain volume might not be an inevitable consequence of getting older, and that moderate amounts of exercise could increase brain volume.

The hippocampus is of great interest in aging research because of its role in memory formation and because it shows considerable atrophy in late adulthood, which is hypothesized to contribute to AD and memory loss. Research in rodents has demonstrated that exercise unequivocally influences the hippocampus (Cotman & Berchtold, 2002; van Praag et al., 2005; Vaynman et al., 2004). This research led to the hypothesis in humans that higher fitness levels might be associated with less hippocampal atrophy and spared memory function. To test this, Erickson and colleagues (2009) examined cardiorespiratory fitness levels in a sample of 165 older adults without dementia and used MRI techniques to identify and measure the volume of the hippocampus. They found that after controlling for age, sex, and education, older adults who were more aerobically fit had larger hippocampal volumes than their less fit peers (see Figure 17.1). In addition, higher fit older adults performed better on a spatial memory task, and greater hippocampal volume partially mediated the fitness-memory association. These results directly linked for the first time cardiorespiratory fitness, age-related hippocampal atrophy, and memory function. There have now been other studies that have replicated this effect by showing that higher fitness levels are associated with greater hippocampal volumes across different populations (Chaddock et al., 2010; Honea et al., 2009).

Cross-sectional studies of cardiorespiratory fitness and hippocampal volume are provocative, but fail to demonstrate direct causal links between the variables. To address this, Erickson and colleagues (2011) conducted a 1-year randomized controlled trial (RCT) in which 120 sedentary older adults without dementia were assigned to a moderate-intensity exercise intervention or a stretching and toning control group. Similar to previous intervention studies, both groups received the same amount of social interaction and health instruction. Using MRI, they showed that 1 year of aerobic exercise was sufficient for increasing the size of the hippocampus. These findings support the claim that modest amounts of aerobic exercise can increase the size of some

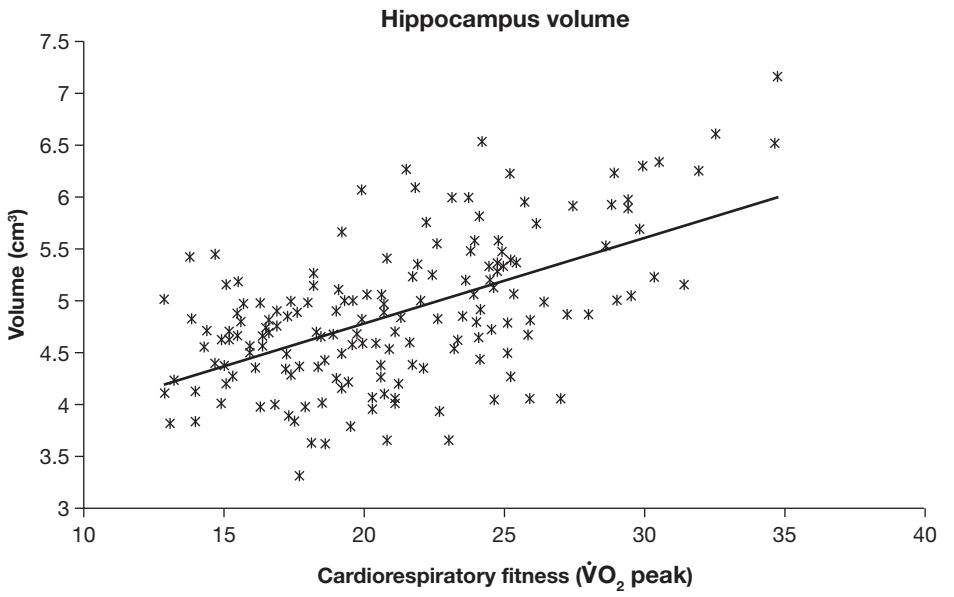

Figure 17.1 Aerobic fitness and hippocampal volume. Cardiorespiratory fitness ($\dot{V}O_2$peak) is positively associated with hippocampal volume (data collapsed across left and right hemispheres) in 165 older adults (data adapted from Erickson et al., 2009).

brain regions that normally undergo deterioration and are involved in memory loss as we age. Furthermore, these results demonstrate that the brain remains modifiable well into late adulthood and that starting an exercise regimen in late adulthood is not futile; even those adults who have been sedentary can still benefit from starting to exercise.

The study by Erickson and colleagues (2011) supports the claim that relatively modest amounts of aerobic exercise are effective in augmenting the brain and cognition in late adulthood. However, how much and what intensity of exercise is necessary to observe effects on brain and cognition? Some epidemiological studies suggest that more strenuous activities are associated with a reduced risk of cognitive impairment (Barnes et al., 2003; Weuve et al., 2004), but dose–response studies in which the frequency, duration, or intensity of exercise is systematically manipulated have not yet been conducted to formally address this question (Chang & Etnier, 2009; Etnier, Nowell, Landers, & Sibley, 2006; Kramer & Erickson, 2007; Middelton et al., 2011).

To help address the question of the dose of PA needed to observe long-term effects on the brain, Erickson and colleagues (2010) conducted a 13-year longitudinal study of 299 adults over the age of 65. In this study, PA was assessed at baseline by asking participants how many blocks they walked on average in 1 week. Nine years later, MRI data were collected to examine whether PA was predictive of brain volume later in life. Erickson and colleagues (2010) found that more PA at baseline was predictive of 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 was only apparent in individuals reporting roughly 1 mile of walking per day. Those walking less than 1 mile daily had less brain volume than their more active peers. This finding suggested that there might be a threshold for the amount of activity needed to observe the benefits of exercise on brain morphology. Furthermore, a 4-year follow-up after the MRI assessment showed 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 (Erickson et al., 2010).

In sum, recent research demonstrates that aerobic exercise is effective at augmenting brain and cognitive health in late adulthood and that even a modest amount of exercise is sufficient for increasing brain size in areas involved in memory and EF. At a time of life when memory impairment is prevalent, PA could be a low-cost and low-tech prevention and treatment that is accessible to most people. Although exercise will not cure AD, 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.

Aerobic exercise and brain function

Some of the first studies to link aerobic fitness with better brain function in healthy elderly adults found that aerobic fitness was associated with electrophysiological markers of enhanced attention and processing speed (Bashore, 1989; Dustman et al., 1990). While electrophysiological techniques provide a glimpse of neural activity on a millisecond time-scale, they have poor spatial resolution, which prevents examination of where differences in brain activity originated. Offsetting this disadvantage, functional MRI (fMRI) is a neuroimaging technique that measures blood flow coupled to neural activity with millimeter spatial resolution. Broadly, two fMRI approaches have been used to study the effects of aerobic exercise on brain function. One approach examines how *much* individual brain regions activate during cognitive challenge, whereas a second approach examines how well individual brain regions activate *together* as part of brain networks known to support thoughts and behavior.

Given that previous research on the behavioral outcomes of aerobic training with elderly adults indicated that EF, attention, and processing speed are improved (Colcombe & Kramer, 2003; Smith, Blumenthal, et al., 2010), brain regions that support these processes, such as the frontal and parietal cortices, were hypothesized to be most sensitive to individual variation in aerobic fitness or to change following aerobic fitness training.

This prediction was first supported by a study by Colcombe and colleagues (2004) that examined changes in functional brain activation following a 6-month, thrice-weekly aerobic exercise program compared to a non-aerobic exercise control condition. Participants in both conditions performed a task involving speeded selective attention and EF at baseline and post-intervention. Following the intervention, the aerobic exercise group had increased brain activation during the more cognitively demanding condition of the task in regions that have been theorized to be involved in attentional control, including the right middle frontal gyrus in the prefrontal cortex and bilateral superior parietal lobule. In addition, brain activity in the anterior cingulate cortex decreased for the aerobic compared to the non-aerobic exercise group, which is a brain region theorized to help regulate attentional control enforced by the prefrontal cortices. Importantly, changes in brain activity were independent of local gray matter volume in activated regions, and changes in brain function were coupled with improved performance on the more demanding task condition for the aerobic exercise group only. This pattern of activation changes coupled with performance improvement suggested that aerobic training led to enhanced attentional control and EF via improved prefrontal cortex response to signals for increased attentional control from the anterior cingulate. Similar results have also been found with electrophysiological measures during speeded attention and EF performance (for review, see Hillman, Erickson, & Kramer, 2008). More generally, this study supports the hypothesis that aerobic fitness is not associated with a general increase in brain activity during cognitive challenge, but that specific brain regions such as the prefrontal and parietal cortices show the most benefit (see also Prakash et al., 2011).

The study by Colcombe and colleagues (2004) demonstrated that 6 months of moderate aerobic activity is enough to enhance brain function in regions typically affected by aging. But how might aerobic exercise continued over several years' impact brain function? One study examined this question by measuring brain function with fMRI following 3 years of a physically active lifestyle for 20 elderly adults compared to a group of 10 elderly adults who had been sedentary for the same amount of time (Rosano et al., 2010). All participants were originally part of a 1-year intervention that compared PA with health education treatment, and in this follow-up study, the active group was comprised of those who were in the PA group and stayed physically active for 2 additional years, whereas the control group were those who remained sedentary following their control treatment. Results demonstrated that being active for 3 years was related to greater improvements in a speeded task involving executive control and working memory (digit symbol substitution task), coupled with greater brain activity in the left and right prefrontal cortices during task performance, compared to the control group. Similar to Colcombe et al. (2004), changes in brain activation were independent of group differences in brain volume. This study also included participants who were on average 81 years of age during scanning, which is approximately 13 to 14 years older than participants in Colcombe et al. (2004), who were an average of 67 years of age. Together, these studies provide evidence to support the claim that the human brain remains responsive to benefits from both short- and long-term exercise well into the seventh decade of life.

Another important question regarding effects of exercise on brain function considers whether exercise is more beneficial for some individuals compared to others. The epidemiological literature has supported an association between PA and decreased incidence of AD (Larson et al., 2006), and there is some evidence that cognitive benefits of aerobic activity are stronger for carriers of the apolipoprotein E (APOE) e4 allele, a genetic risk factor for late-onset AD (Etnier et al., 2007; Schuit, Feskens, Launer, & Kromhout, 2001). Hence, a testable prediction for functional brain imaging studies is that the genetic risk for AD should moderate the association between fitness and brain activity associated with better performance in elderly adults. One study that found partial support for this prediction measured brain activity during a semantic memory task in older adults who varied by PA level (high active/low active) and presence of the APOE e4 allele (carrier/non-carrier) (Smith, Nielson, et al., 2010). The researchers found that only two of the 15 task-related activated regions were different between the high and low active groups for the non-carriers (low risk for AD), whereas a third of the regions differentiated high and low active groups for the carriers (high risk for AD), including the left angular gyrus, left middle frontal gyrus, right angular gyrus, left superior frontal gyrus, and right frontal insula. Further, five regions also differentiated risk among the high active people: left superior frontal gyrus, left medial frontal pole, left ventral medial frontal pole, right inferior parietal lobule, and the right frontal insula. Therefore, PA seemed to have a greater association with brain health for those at genetic risk for AD, and in general, these results provide preliminary support for the prediction that APOE moderates the association between PA and brain function.

In addition to studying how aerobic fitness and PA impact the level of activity in individual brain regions, important insights about exercise effects on brain function can also be gained by studying how well brain regions activate together, or synchronize their neural activity. This is particularly true for brain networks known to be involved in attention, processing speed, and EF. In the first study of this nature, Voss and colleagues examined whether functional connectivity in the default network was associated with aerobic fitness in a cross-sectional sample of 120 healthy older adults between the ages of 60 and 80 years (Voss, Erickson, et al., 2010). Brain regions in the default network encompass the frontal, parietal, occipital, and temporal cortex, including the posterior cingulate cortex, ventral and superior medial frontal cortex, and bilateral

lateral occipital, middle frontal, hippocampal and parahippocampal, and middle temporal cortices (see Figure 17.2; for review, see Buckner et al., 2008). Its function has been assessed either by measuring how much neural recruitment occurs in the network, or how synchronized different regions are with each other. The default network is thought to play a functional role in memory consolidation, self-referential thought, mind-wandering, and autobiographical memory, with an important role in executive control as well (Buckner et al., 2008). For instance, increased synchronization in the default network has been associated with better working memory performance in young adults (Hampson et al., 2006), and better EF performance in older adults (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008). Thus, the default network is important for understanding determinants of healthy cognitive aging. Additionally, its dysfunction has been proposed as a biomarker for AD (Greicius, Srivastava, Reiss, & Menon, 2004).

To test if aerobic fitness was specifically associated with functional connectivity in the default network regions most negatively affected by age, Voss, Erickson, and colleagues (2010) first determined where age differences in functional connectivity were greatest. Almost all brain regions typically in the default network were more disconnected (i.e., out of sync) for the older adults compared to a college-age control group. Then, to test whether aerobic fitness was associated with less age-related network dysfunction, correlations were conducted between functional connectivity in region-to-region pairs disrupted with age and aerobic fitness. Results showed that connectivity between almost half of region-to-region connections disrupted with age was positively correlated with aerobic fitness among the older adults. Consistent with previous research, aerobic fitness was also most strongly associated with the function of the prefrontal cortex. For example, all region-to-region connections associated with fitness included a region in the frontal cortex. Additionally, results supported the hypothesis that default network connectivity is one route by which aerobic fitness benefits cognitive aging: mediation analysis showed that functional connectivity in the default network accounted for a statistically significant amount of variance in EF abilities including task-switching, spatial working memory, and "set shifting" or flexibility to changing rule sets. Therefore this study provided the first evidence that functional connectivity in brain networks may play an important role in how aerobic fitness benefits cognition.

However, it was still unknown if aerobic fitness would have an association with brain networks other than the default network and if aerobic training would lead to improved functional connectivity. To address these questions Voss and colleagues conducted an RCT with 65 healthy older adults (Voss, Prakash, et al., 2010), comprising a subset of the participants in the studies described above (Erickson et al., 2011; Voss, Erickson, et al., 2010). The study included an experimental walking group (n = 30) and a stretching and toning control group (n = 35). In addition to the default network, researchers also examined networks involved with EF, spatial attention, motor control, and audition. Overall, there were four region-to-region connections enhanced following 1 year of aerobic exercise. One of these connections was between the left and right prefrontal cortices in a network theorized to be involved in executive control and sustained attention. However, three out of four were in the default network. Also of interest, two of the three connections showing improved functional connectivity in the default network for the walking group included a region in the parahippocampus overlapping with the hippocampal dentate gyrus (see Figure 17.2). This is important since the finding makes a link to animal models of exercise effects on the brain, which have found that the dentate gyrus is particularly sensitive to the benefits of exercise, including the birth of new neurons and enhanced synaptic plasticity (Cotman et al., 2007). In addition, this study provides important evidence supporting the hypothesis that aerobic fitness training benefits not only task-related magnitude of brain activation, but also the coherence of brain networks important for cognition and neurological disease status.

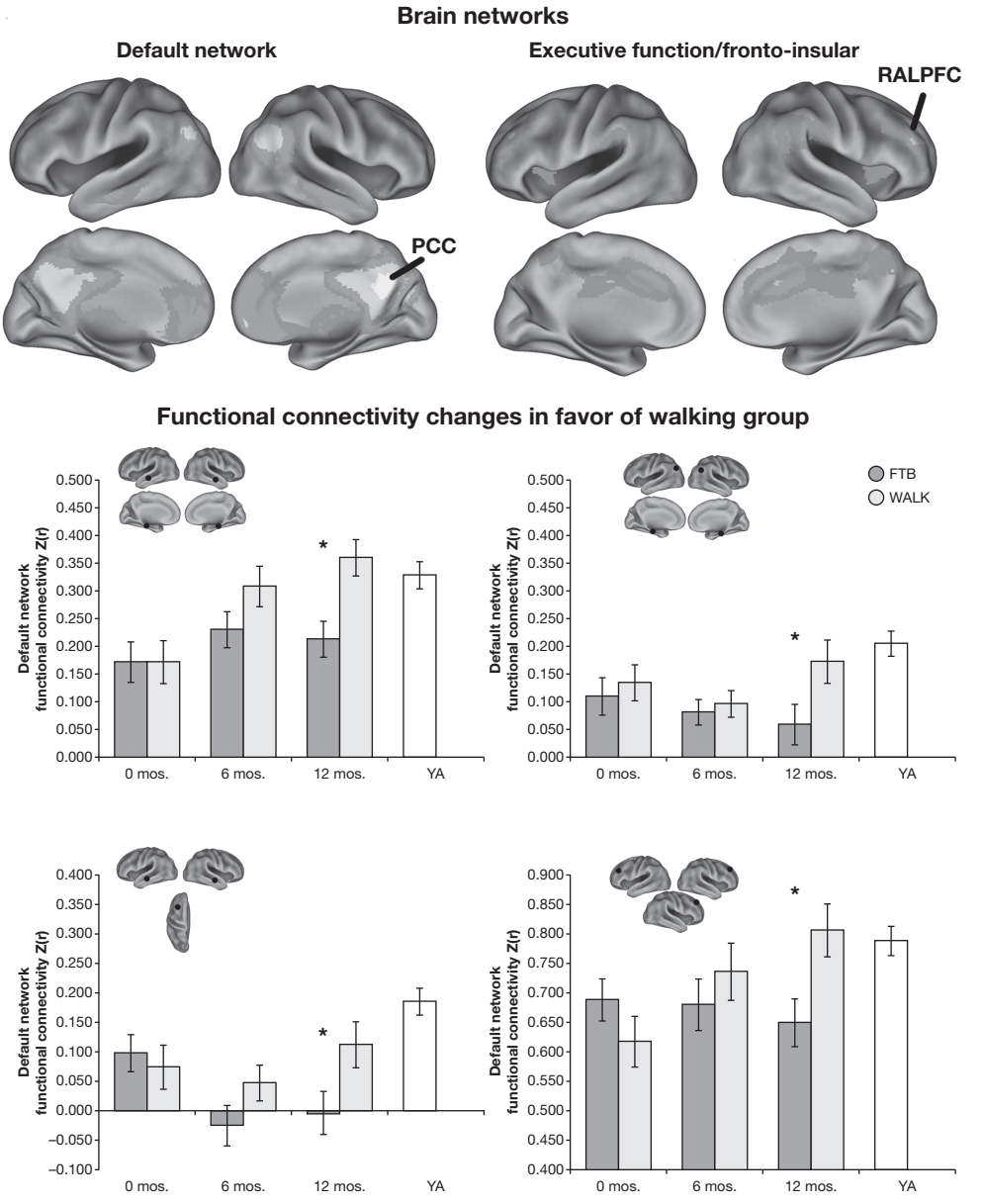

Figure 17.2 Aerobic exercise benefits brain networks. Top panel illustrates two brain networks that benefit from aerobic fitness training (WALK) compared to flexibility, toning, and balance (FTB) non-aerobic exercise training; PCC = posterior cingulate cortex, RALPFC = right anterior lateral prefrontal cortex, indicate regions that are prominent brain areas in the network, brain regions with activation that highly correlates with these regions are considered part of the respective networks. All brains shown in neurological orientation, R = R and L = L. *p<.05 group difference in ANCOVA model, after controlling for group differences at baseline; YA = young adult control group for reference (data adapted from Voss, Prakash, et al., 2010).

Results of the study also showed increases in functional connectivity in favor of the stretching and toning group in the default network following 6 months of exercise. However, functional connectivity in these regions reverted to baseline levels at the end of the 1-year intervention. Since the stretching and toning intervention involved learning novel stretching and balance exercises and light yoga poses for the first 6 months, which were maintained and practiced for the second 6 months, it is possible that increases in functional connectivity for the stretching group reflect learning-related changes in default network connectivity. This would be consistent with the default network's association with cognitive abilities such as inward-focused thought and integrating an external world-view with your own, and suggest the possibility of an intervention based on these activities as a framework for combined exercise and cognitive training.

A third study that has examined the effects of aerobic exercise on brain function from a network perspective assessed whether aerobic exercise was associated with how connected *in parallel* the hippocampus was to all other brain regions (Burdette et al., 2010). Therefore positive results would indicate that not only does aerobic training impact specific inter-regional connections in the brain (Voss, Prakash, et al., 2010), but it also impacts how well connected the hippocampus is to all other brain regions. This could then affect the ease with which large networks simultaneously access the hippocampus during cognitive activity. This study included participants who had just completed a 4-month treatment in an RCT, as part of either an aerobic training group or a non-exercise control group (health education and light stretching). Results showed that aerobic exercisers had increased connectivity between the hippocampus and the rest of the brain compared to the control group, and follow-up analyses found the hippocampus and anterior cingulate were more functionally connected in the aerobic group compared to the control group. The aerobic group also had greater hippocampal blood flow compared to the control group, and increased hippocampal perfusion was positively correlated with increased anterior cingulate connectivity, providing preliminary evidence that increased hippocampal blood perfusion may be one factor associated with greater functional brain connectivity following aerobic exercise. Therefore this study makes an interesting link to the Colcombe et al. (2004) study, which found aerobic training resulted in decreased activity in the anterior cingulate cortex, coupled with improved task performance. Despite the overlap in regional changes, however, the interpretation for how these findings fit together is not straightforward at this time. Future research is needed to better understand how changes in the synchronization of brain regions interact with changes in the magnitude of brain activity, following aerobic exercise.

In sum, a growing number of studies support the claim that, in healthy elderly adults, aerobic fitness and aerobic training have a positive association with brain function. Enhanced brain function has been demonstrated through (a) the extent to which specific brain regions activate to support task-related cognitive processes and (b) how well brain regions coordinate with each other as part of brain networks known to support cognitive abilities affected by aging. In addition, the evidence from functional imaging studies is consistent with brain morphology studies finding that the prefrontal cortex and the hippocampus are two brain regions with high sensitivity to the benefits of aerobic exercise in late adulthood. Given that the prefrontal and hippocampal cortices are also areas that experience accelerated atrophy and dysfunction associated with aging and contribute to cognitive abilities important for everyday living such as EF and memory, evidence from functional neuroimaging studies provides converging evidence to the claim that aerobic exercise has great potential as a lifestyle intervention for improved quality of life.

Considerations for future research

We have outlined the evidence that modest amounts of aerobic exercise are sufficient for enhancing cognition and brain function. By using MRI technology, it has been consistently demonstrated that higher fit older adults have greater amounts of gray matter volume in several brain regions. Furthermore, exercise also increases brain activity and functional coordination in brain networks, which in some cases has been shown 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 even increase the size of some brain areas. Despite these consistent and convincing findings, there remain important methodological issues to consider for future research and many unanswered and unexplored questions.

With regard to methodological issues, one over-arching issue is the generalizability of measures of cognitive function. While meta-analyses provide a means to systematically assess the consistency of exercise training benefits across overlapping cognitive domains (Colcombe & Kramer, 2003; Etnier, Nowell, Landers, & Sibley, 2006; Smith, Blumenthal, et al., 2010), when conceptual overlap among the task-specific cognitive outcomes is weak, the diversity of specialized laboratory paradigms for measuring cognitive benefits can lead to unreliable estimates of cognitive benefits. Therefore, it will be important for future research to strike a balance between innovative measures of specific cognitive mechanisms and standardized tests of cognitive function that permit straightforward comparison across a population of studies. Similarly, few studies of exercise effects on healthy older adults have assessed the transferability of improvements on laboratory tests of cognition to the real world, such as driving behavior or other tasks important for everyday living. However, this will be an important link to consider for understanding how exercise-related improvements in cognition impact everyday function and quality of life.

There are also many questions that are relatively unexplored. For example, one remaining question involves the dose-response relationship of exercise on brain and cognition. That is, as described above, there is relatively little information about 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 exercise is to be used in clinical contexts and be prescribed to patients as prevention or treatment for loss in cognitive function. There is also little known about the underlying mechanisms of aerobic exercise in humans. Is exercise working by influencing the creation of new vasculature or could exercise be directly affecting brain tissue? These are not mutually exclusive possibilities, and it will be important for future studies to consider the interactions between vasculature, neural, and extracellular changes in the brain as a function of exercise training. In addition to direct effects of exercise on the brain and its vasculature, could other mediating factors also be contributing to the effects of exercise on brain and cognition? For example, to what extent do improvements in sleep, reductions in stressor-evoked responses, improved peripheral vascular and metabolic function, or more consistent regulation of hypothalamic-pituitary-adrenal axis factors, contribute to the elevated brain and cognitive responses?

Also, the research described here has been largely limited to older adults free of cognitive impairment. There is little known as to the extent to which aerobic exercise prevents decay of the brain in those already experiencing cognitive impairment and there is a poor understanding of whether exercise could improve brain health in populations with multiple sclerosis, Parkinson's disease, schizophrenia, or other psychiatric or neurologic diseases. In short, more research is needed to understand the degree to which these conclusions can be generalized to other populations.

Finally, not everyone benefits equally from exercise. 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? For example, as briefly discussed in the review, preliminary evidence suggests that a genetic disposition for AD is an important factor in moderating the benefits of aerobic exercise on human brain function. However, larger studies that incorporate multiple perspectives on brain structure and function will be needed for a greater understanding of these factors and others that may impact the link between exercise and cognition.

Conclusion

Overall, we can argue that (a) the brains of older adults remain modifiable and that exercise can take advantage of this plasticity to increase the size of areas that frequently show atrophy in late life; (b) it is never too late to start exercising; even adults who have been sedentary most of their lives can reap the benefits of an exercise regimen; and (c) the effects of exercise are not global throughout the brain, but have some specificity to hippocampal and prefrontal brain areas. Together this research suggests that brain atrophy, dysfunction, and cognitive decline might not be as inevitable a consequence of aging as previously thought.

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