Exercise, Brain, and Cognition Across the Lifespan

Michelle W. Voss¹,², Lindsay S. Nagamatsu³,⁴,⁵, Teresa Liu-Ambrose³,⁴,⁵, & Arthur F. Kramer¹,²

¹ The Beckman Institute and Department of Psychology, 405 North Mathews Avenue, University of Illinois at Urbana-Champaign, Urbana, IL, 61801, USA
² Department of Psychology, 603 East Daniel St., University of Illinois at Urbana-Champaign, Champaign, IL 61820
³ The Brain Research Centre, 2211 Wesbrook Mall, University of British Columbia, Vancouver, BC, V6T 2B5 Canada
⁴ Department of Physical Therapy, 2177 Wesbrook Mall, University of British Columbia, Vancouver, BC, V6T 1Z3, Canada
⁵ The Centre for Hip Health and Mobility, 311-2647 Willow Street, Vancouver Coastal Health Research Institute, Vancouver, BC, V5Z 3P1, Canada
⁶ Department of Psychology, 2136 West Mall, University of British Columbia, Vancouver, BC, V6T 1Z4, Canada

Highlighted Topics series "Physiology and Pathophysiology of Physical Inactivity"

*Corresponding Author

Arthur F. Kramer
Beckman Institute for Advanced Science and Technology
Department of Psychology
University of Illinois at Urbana-Champaign
405 N. Mathews Ave
Urbana, IL 61801
mvoss@illinois.edu
akramer@cyrus.psych.illinois.edu
Abstract
This is a brief review of current evidence for the relationships between physical activity and exercise and
the brain and cognition throughout the lifespan, in non-pathological populations. We focus on the effects
of both aerobic and resistance training, and provide a brief overview of potential neurobiological
mechanisms derived from non-human animal models. Whereas research has focused primarily on the
benefits of aerobic exercise in youth and young adult populations, there is growing evidence that both
aerobic and resistance training are important for maintaining cognitive and brain health in old age.
Finally, in these contexts, we point out gaps in the literature and future directions that will help advance
the field of exercise neuroscience, including more studies that explicitly examine the effect of exercise
type and intensity on cognition, the brain, and clinically significant outcomes. There is also a need for
human neuroimaging studies to adopt a more unified multi-modal framework, and for greater interaction
between human and animal models of exercise effects on brain and cognition across the lifespan.

Keywords: physical activity, aerobic training, strength training, brain function, brain structure, mental
health
Introduction

It is increasingly prevalent in the print media, television and the Internet to be bombarded with advertisements for products and programs to enhance mental and physical health in a relatively painless fashion through miracle elixirs, computer-based training or gaming programs, or brief exercise programs. Although there is little convincing scientific evidence for many such claims (46), there have been some promising developments in the scientific literature with regard to physical activity and exercise effects on cognitive and brain health. In fact a number of our forefathers appear to have anticipated some of the potential benefits of an active lifestyle. For example, Thomas Jefferson argued, “a strong body makes the mind strong.” Hugh Blair, a Scottish Theologian from the 18th century suggested that, “Exercise is the chief source of improvement in our faculties.” One of the first noted scientist/physicians, Hippocrates, opined, “If we could give every individual the right amount of nourishment and exercise, we would have found the safest way to health.”

Indeed, there is an increasing amount of research, much of it epidemiological, which argues for numerous long-term health benefits of regular physical activity and exercise. For example, studies have reported an inverse relationship between physical activity and the risk of type II diabetes (58), cardiovascular related disease and death (89), osteoporosis (52), colon and breast cancer (62), and mental disorders (29). Despite this increasing wealth of knowledge concerning the relationship between physical activity and health we have become an increasingly sedentary society. For example, it has been estimated that less than 50% of children (6-11 years) and only 8% of adolescents (12-19 years) are active the recommended 60 minutes most days of the week, whereas only less than 5% of adults (20-59 years) and elderly (60+ years) are active the recommended 30 minutes a day for this age group (99). Furthermore, it has been suggested that our current sedentary nature represents a maladaptation of our evolutionary history in which high levels of physical activity were required for survival (6).
In the present brief review we focus on the relationship between physical activity and cognitive and brain health. We briefly review molecular and cellular exercise-related changes in our discussion of the animal literature. However, the majority of our review will focus on aerobic and strength training effects on human cognition and brain health across the lifespan in healthy populations. Finally, we conclude with prescriptions for additional research on this important topic.

**Effects of aerobic training on brain structure, brain function, and cognition**

As we progress from elementary to high school, our brains rapidly develop structural and functional circuitry that support higher-level cognitive abilities, such as our ability to regulate and inhibit behavior, multi-task, and resist distraction (13). Consequently, behaviors that affect brain function play a vital role in facilitating optimal cognitive development during childhood. Physical activity is no exception. Research indicates that childhood physical inactivity, and subsequently reduced aerobic fitness, is associated with poorer academic achievement (15, 19) and lower performance on standard neuropsychological tests (9, 90). The majority of scientific literature supports a general benefit of aerobic fitness on childhood cognitive performance. For example, a meta-analysis that aggregated results across 44 studies found an overall effect size of 0.32 for the association between childhood physical activity and fitness and cognition, with significant effects across a range of abilities, such as perceptual skills (0.49), creativity and concentration (0.40), academic readiness (0.39) and achievement (0.30), IQ (0.34), and math (0.20) and verbal (0.17) tests (90).

Still some studies have shown selective benefits of exercise on childhood cognition (for review, see 97). For example, one study increased task difficulty and thus pushed the limits of prefrontal function beyond what other studies have done (77). This is consistent with a training study that found 3 months of aerobic exercise training improved prefrontally-mediated executive function abilities in 7-11 year old...
overweight children (27). Other studies demonstrating a selective association have shown, in agreement with a large animal literature, that aerobic fitness is preferentially associated with a type of memory supported by the hippocampus, relational memory, rather than item memory (17, 18). Unlike item memory, relational memory requires forming associations, such as remembering not only the face of a person you met last week, but also remembering their name, what you talked about, and where you met them. Finally, overall there is stronger support for aerobic fitness benefits on accuracy rather than speed of processing (9, 17, 18, 47, 77), which is consistent with the idea that accuracy may be a better measure of cognitive development than speed (26). Yet the majority of literature on physical activity, aerobic fitness, and childhood cognition is cross-sectional in nature, therefore more training studies with temporally extended follow-up testing are needed for stronger support of these summarized findings.

Nevertheless, neuroimaging research provides additional evidence for both general and selective effects of exercise on childhood cognition. Functional brain imaging studies using event-related potentials (ERPs) have shown that more aerobically fit children have larger P300s during information processing (47, 48, 77), an ERP component whose amplitude is associated with our ability to effectively focus attention and which is thought to emerge, in part, from the temporo-parietal cortex (76). ERP brain recordings also indicate that aerobically fit children better regulate and monitor their mistakes, or processing errors, abilities made possible by the anterior cingulate and prefrontal cortices (47, 77). For example, Hillman and colleagues (47) found that higher-fit children who outperformed lower-fit children on the Eriksen flanker task (a test of conflict resolution) showed a smaller error-related negativity (ERN) on error trials, an ERP component thought to index conflict monitoring and error evaluation; higher-fit children also showed a larger positivity error (Pe) component, thought to index awareness of one’s mistake. Overall, higher-fit children were more accurate in trials following errors of commission, while showing a smaller ERN and larger Pe, suggesting higher-fit children’s brains monitor conflict more
efficiently (see also 77). Neuroanatomically, childhood aerobic fitness is associated with more brain volume in structures important for demanding information processing and relational memory, such as the dorsal striatum (16) and the hippocampus (17), respectively.

In sum, cross-sectional and longitudinal training studies support a positive association between aerobic fitness and enhanced performance in both the classroom and laboratory (for reviews, see 90, 97). Furthermore, neuroimaging evidence supports a beneficial association between childhood aerobic fitness and improved brain function and structure.

Following the rapid cognitive development in childhood, young adulthood (i.e., 18 to 35 years) is characterized by relative stability and peak cognitive performance. This may be one reason that comparatively fewer studies examine cognitive enhancements associated with physical activity and aerobic fitness training during this part of the lifespan. This may also be the reason that studies have generally found mixed support for the association between aerobic fitness and cognition in young adulthood (1, 85, 88). Yet several neuroimaging studies have shown evidence for increased efficiency of brain function without differences in behavioral performance (51, 95, 96). For example, similar to the findings of Hillman and colleagues (47) with children, one study showed that higher-fit young adults also had smaller ERNs coupled with larger Pe amplitude, specific to trials with errors of commission (95). Despite these neuroelectric differences, there were no differences in behavioral performance between lower- and higher-fit adults. Studies like these suggest that aerobic fitness effects on behavior may only emerge in this high-functioning group when the task is extremely difficult or that young adults have a greater range of compensatory strategies compared to children and older adults to achieve enhanced performance. There are very few training studies with young adults, however some studies do support the effectiveness of aerobic training for improving cognition at this age (74, 92), particularly for those with a genetic predisposition for impaired cognition due to lower dopamine levels in the brain (93).
Thus overall, whereas cross-sectional behavioral results are mixed with young adults, neuroimaging and training results seem to support a positive association between greater aerobic fitness and brain function. Future research that examines the effect of task difficulty, uses more diverse imaging techniques, and examines the long-term effects of aerobic fitness during adulthood will help clarify many unanswered questions for this age group.

Older adulthood mirrors childhood in some interesting ways, when brain structure and function again enter a period of high inter-individual variability and lifestyle factors, such as physical activity, increasingly impact mental health. Although epidemiological and prospective studies largely support the role of physical activity and aerobic fitness in healthy cognitive (80, 109) and brain (83) aging and preventing the onset of all types of dementia (60, 64), it is less clear from training studies whether increased aerobic fitness per se is the key ingredient for improved brain and cognition from behavior changes associated with this lifestyle factor (22, 35). Much evidence, however, does support the notion that aerobic exercise benefits cognitive performance (22, 32, 57), brain function (10, 23, 108), and brain structure (21, 34, 68) in elderly adults.

Specifically, aerobic training in late life preferentially benefits executive functions, including brain processes such as multi-tasking, planning, and inhibition, all largely supported by the prefrontal cortex (22, 23, 57). Several fMRI studies have examined the effects of aerobic training on brain function. Colcombe and colleagues (23) examined the effects of a six-month, thrice-weekly aerobic training program for sedentary adults on task-related brain activation during the Eriksen flanker task. Aerobically trained older adults had greater increases in brain activity in the frontal and parietal cortices from pre- to post-intervention, brain areas involved in processes important for task performance, such as conflict resolution and selective attention. Aerobically trained adults also had greater reduction in anterior cingulate cortex activation, a brain area involved in conflict and error monitoring. This pattern
of activation changes suggests that aerobic training led to increased efficiency of conflict and error
monitoring and enhanced regulatory response from the prefrontal cortex following signals of conflict
from the anterior cingulate (8). In line with this theoretical account, functional improvements were
coupled with improvement in conflict regulation performance. This study demonstrated that
participating in an aerobic training program improves the aging brain’s ability to effectively engage task-
relevant resources, particularly under cognitively challenging conditions. Thus, aerobic training had a
selective rather than general effect on task-related brain function.

Another way to assess brain function is to examine not how much the brain activates under
controlled cognitive conditions, but rather how different areas of the brain communicate under little to
no cognitive demand. The benefit of the latter is an absence of group differences in behavioral
performance or strategy that could potentially confound differences in task-related brain activation. Voss
and colleagues (108) examined changes in functional communication, or connectivity, in sedentary older
adults following a one-year, thrice-weekly aerobic training program. The study examined whether
aerobic training would enhance communication in the Default Network (a network whose dysfunction is
proposed to be a biomarker for normal cognitive decline and Alzheimer’s Disease), as well as brain
networks involved in higher-level executive functions, spatial attention, motor control, and audition. Of
all the networks examined, the Default Network was the primary brain network showing enhanced
connectivity following aerobic training, in addition to increased connectivity between the left and right
prefrontal cortices in an Executive Control network. Thus, aerobic fitness training benefits not only task-
related magnitude of brain activation, but also the resting coherence of brain networks important for
cognition and neurological disease status.

In addition to functional brain changes, studies also support significant changes in regional brain
volume following aerobic training. Following a six-month, thrice-weekly aerobic program, Colcombe and
colleagues (21) found gray matter increases in the lateral prefrontal, anterior cingulate, and lateral temporal cortices, and increased anterior white matter volume. Furthermore, another study found that a one-year, thrice-weekly aerobic training program increased volume of the anterior hippocampus, which houses the dentate gyrus sub-region linked to neurogenesis in animal studies (38, 74, 103); whereas there were no volumetric benefits for the posterior hippocampus, thalamus, or caudate nucleus (33). Also consistent with the animal literature, increased anterior hippocampus volume was associated with increased peripheral brain-derived neurotrophic factor (BDNF) for only the aerobic group. The significance of BDNF will be discussed in more depth below. Finally, while this study found memory improvements for the aerobic and non-aerobic control group, increased anterior hippocampal volume was associated with improved memory for only the aerobic group, trends not shown in the caudate or thalamus. However, change in BDNF was not associated with changes in memory. Thus one caveat of most human studies is the inability to unequivocally determine the nature of the cellular and molecular changes that underlie the observed changes in brain volume and cognitive function. Although one study indicated that cerebral blood volume, potentially an in vivo marker of neurogenesis, is at least one factor that may be involved with increased hippocampal volume and corresponding increases in learning performance (74). Nevertheless, these studies provide continuing support that beginning an aerobic exercise program in late life can still translate into meaningful benefits for the brain and cognition.

Effects of resistance/strength training on brain structure, brain function, and cognition

Although resistance training has a broad range of systemic benefits (7, 61), very few studies to date have specifically focused on the role of resistance training in promoting cognitive health across the lifespan. To our knowledge, no studies have specifically assessed the effect of resistance training on cognitive and brain function in children. A lack of such studies may be partly due to the common
misperception that resistance training is unsafe for children. Likewise, there is a general void in the literature regarding the role of chronic resistance training in promoting cognitive and brain function in young adults.

For older adults, evidence regarding whether or not resistance training has cognitive benefit has been equivocal. However, we note that the trials with negative results were limited by small sample sizes (i.e., 13 to 23 participants per experimental group) or short intervention periods (i.e., 8 to 16 weeks) (32, 55, 75, 100). For example, Tsutsumi and colleagues (100) demonstrated no cognitive benefit of resistance training in their 12-week randomized controlled trial that compared the effect of high-intensity/low volume resistance training and low-intensity/high volume resistance training with no exercise controls on cognitive function in 42 community-dwelling older adults (i.e., 14 participants per group). Recently, Kimura and colleagues (55) also demonstrated no effect of resistance training on the executive process of task switching despite including 119 participants in their 12-week training study. In addition to sufficient duration of resistance training, the intensity or load of training appears to be a key requirement to produce cognitive benefits. For example, Lachman and colleagues (59) conducted a six-month randomized controlled trial of home-based resistance training among 210 sedentary community-dwelling older adults and found no significant between-group differences in memory. The home-based resistance training program was a 35-minute videotaped program of 10 exercises using elastic bands. Participants were instructed to use bands of greater resistance when they could complete greater than 10 repetitions of an exercise without significant fatigue. This is a lower intensity protocol compared with three recent randomized controlled trials with positive findings that used loading protocols ranging from 50% to 80% of a single-repetition maximum lift (i.e., 1 RM) (14). It is important to highlight that while there were no significant between-group differences in cognitive performance, Lachman and colleagues (59) found that the change in resistance used by those in the intervention group was positively
associated with change in memory performance, after controlling for baseline age, education, sex, and disability level. Hence, the investigators suggested that resistance training can benefit memory among older adults, especially when using higher resistance levels.

Randomized controlled trials of resistance training that are 6-months or greater in duration and delivered high-loading protocols collectively provide emerging evidence that resistance training has cognitive benefits. Cassilhas and colleagues (14) demonstrated six months of either thrice-weekly moderate or high intensity resistance training improved memory performance and verbal concept formation among 62 community-dwelling senior men ages 65 to 75 years. Moderate intensity was defined as 50% of 1 RM and high intensity was defined as 80% of 1RM. Using a protocol similar to Cassilhas (14), recent work by Busse and colleagues suggests that resistance training may also be beneficial for sedentary older adults at greater risk for Alzheimer's disease – those with objective mild memory impairment (11).

The work of Cassilhas and colleagues (14) also provide valuable insight into the possible mechanisms underlying the benefit of resistance training on cognitive performance. They found serum insulin-like growth factor-1 (IGF-1) levels were higher in the resistance training groups than in the control group. IGF-1 promotes neuronal growth, survival, and differentiation and improves cognitive performance (24), which will be discussed further below. In older adults, resistance training also reduces serum homocysteine (107). Increased homocysteine levels are associated with impaired cognitive performance (84), Alzheimer's Disease (87), and cerebral white matter lesions (106), although the cognitive relevance of reductions in homocysteine in longitudinal study remain unclear (e.g., 3).

Finally, Liu-Ambrose and colleagues (65) demonstrated that 12 months of either once-weekly or twice-weekly progressive resistance training improved selective attention and conflict resolution performance among 155 community-dwelling senior women ages 65 to 75 years. Enhanced selective
attention and conflict resolution was also associated with increased gait speed. Clinically, improved gait speed predicts a substantial reduction in both morbidity (82) and mortality (31, 45). These results illustrate the clinical significance of cognitive gains induced by resistance training. Davis and colleagues (28) also provided novel evidence that cognitive benefits associated with resistance training are sustained for one year after the intervention has ended.

Thus while there is less literature across the lifespan on the effects of resistance training on brain and cognition, compared with aerobic training, preliminary evidence highlights its importance for future study.

**Potential mechanisms from animal models**

Animal models of exercise effects on brain physiology and structure have indicated several key pathways through which aerobic and resistance training may enhance brain function. These pathways include improvement in both the structural integrity of the brain (i.e., growth of new neurons and blood vessels) and increased production of neurochemicals that promote growth, differentiation, survival, and repair of brain cells. In addition, animal models have begun to shed light on how aging interacts with these molecular and cellular models of exercise effects on brain and cognition.

Many studies now suggest that aerobic training results in neurogenesis, or the generation of new neurons, in the hippocampus (102, 103), which has been subsequently linked to improved hippocampal function (25, 74). To our knowledge hippocampal neurogenesis has not been studied in animal models in the context of other forms of exercise programs (e.g., aerobic vs. exercise analogous to resistance training in rodents), therefore future research is needed to understand the specificity of neurogenesis following different forms of exercise. Furthermore, although the rate of hippocampal neurogenesis declines with normal aging, animal studies generally support some protection from such decline with aerobic exercise training (54, 104). Though age does appear to attenuate the effect of aerobic exercise on neurogenesis
compared to young adult animals, for 15- and 19-month old animals respectively (54, 104). One study showed no training-induced neurogenesis in old (22-months) animals despite some improvement on a spatial pattern separation task and positive evidence for young animals (25). Other studies have also found that neurogenesis is not necessary for improved performance (e.g., 53) or that neurogenesis is associated with improvement in some tasks (e.g., spatial memory) and not others (e.g., motor performance, conditioning) (20). Therefore, while hippocampal neurogenesis is a highly replicable effect following aerobic exercise, there are still some questions about how it supports behavioral improvements following aerobic exercise compared to other exercise-related factors.

For example, another consistent effect in animal models is exercise-induced increases in angiogenesis, or the growth of new blood vessels (25, 74, 104), which has in turn been linked to improved learning and memory (53, 74). Like neurogenesis, no studies to our knowledge have examined the specificity of angiogenesis following different types of exercise. Unlike neurogenesis, aerobic training produces angiogenesis outside of just the hippocampus, including areas directly activated by locomotion such as the cerebellum (4, 50) and primary motor cortex (56, 94). Furthermore, at least two studies have shown aerobic training-related increases in hippocampal angiogenesis in young but not aged mice (22- and 19-months, respectively) (25, 104). Similar to effects described above, the study by Creer and colleagues (25) showed that despite no significant hippocampal angiogenesis (or neurogenesis), aerobically trained old rodents still showed moderate improvements in performance. Thus while angiogenesis is consistently found in response to aerobic exercise in young animals, the role of training-induced angiogenesis in cognitive improvements across the lifespan is also a topic in need of future study.

Animal models have also indicated several candidates for circulating neurochemicals that may mediate effects of exercise on brain health. Two that have received the most empirical support include BDNF and IGF-1. BDNF is endogenously produced throughout the brain, with particularly high
concentrations in the hippocampus (71), and in animals is known to increase in the brain during single
acute bouts (79) and following chronic aerobic exercise training (72, 73). While BDNF is also produced in
the periphery, some studies have suggested that peripheral BDNF in humans at rest and during an acute
bout of aerobic exercise is predominantly brain-derived (estimated from arterial-to-venous difference of
radial artery and the internal jugular vein), even though it may dip during recovery (79). Also, at least
one training study from the same group has shown that 3 months of aerobic training increases human
resting peripheral brain-derived BDNF but did not affect peripheral estimates of brain-derived BDNF
during aerobic exercise (86). Another study showed that peripheral BDNF in blood serum was
selectively increased following 30 minutes of high-intensity (~85% of heart rate max) compared to lower
intensity (~70% of heart rate max) aerobic exercise (39). Finally, it is interesting to note that there is
evidence that resting peripheral serum BDNF is selectively up-regulated in humans following chronic
aerobic (111) but not resistance training (63). Overall, these studies suggest that BDNF release in the
human cortex and hippocampus during exercise and at rest can be estimated in the periphery from blood
plasma or serum, and demonstrate that examining the effects of acute bouts of exercise on the brain may
help build links to animal models and (although it is unknown whether the mechanisms are the same)
may inform how the brain adapts to cumulative changes in different types of exercise behavior. A noted
limitation of these studies however is small sample sizes of young adults; thus, it will be important for
these results to be replicated with larger samples of a broader age range.

Understanding how exercise affects BDNF production is important because BDNF is considered a
critical factor in exercise-induced benefits on learning and memory. For example, Farmer and colleagues
(38) demonstrated that BDNF is associated with aerobic exercise-induced increases in long-term
potentiation (LTP), which facilitates synaptic plasticity and is considered a cellular model of learning and
memory. Furthermore, blocking BDNF receptors during exercise abolishes downstream effects on
metabolic factors (43) and cognitive performance (43, 44, 105). Although there is overwhelming evidence in support of BDNF as an important factor in exercise-induced improvement in brain and cognition, more research is needed that investigates how age interacts with these results. For example, Garza and colleagues (41) showed that aged rodents (22-months) had increased hippocampal BDNF mRNA following short (i.e., 2 days) and chronic (i.e., 20 days) bouts of running; however, there were substantial differences in the regional pattern of sensitivity for exercise-induced increases in BDNF, which the authors suggested may reflect age-related shifts in hippocampal physiology that in turn impact how exercise affects hippocampal structure and function in old age. Another study found that chronic aerobic exercise was not associated with increases in hippocampal BDNF protein for aged rodents (24-months), despite positive results for young runners (2).

A known neurotrophic factor important for both aerobic and resistance training is IGF-1. IGF-1 is produced both in the central nervous system and in the periphery in response to aerobic (12, 30, 98) and resistance (14) exercise. Furthermore, studies have shown that blocking entry of peripheral IGF-1 into the brain during aerobic training also blocks exercise-induced hippocampal neurogenesis (98), angiogenesis (66), and exercise-facilitated brain injury recovery (12). Studies have also supported a dependence between IGF-1 and exercise-induced increases in BDNF (12, 30). For example, one study demonstrated that blocking IGF-1 receptors in the hippocampus during exercise abolished exercise effects on increased hippocampal BDNF mRNA and protein expression, and similar effects were found for hippocampal levels of markers of synaptic plasticity that are presumed to be end-products of BDNF action (exercise-induced increases in synapsin I, p-CAMKII, p-MAPKII) (30). In turn, researchers that have found attenuated exercise-related enhancement of BDNF in aged rodents have speculated that this may be partly due to the reduction in IGF-1 associated with aging (2, 67).
Thus animal models have shown that BDNF and IGF-1 play important roles in mediating the effects of exercise on brain health and performance. Other neurotrophic factors and neuropeptides shown to change with exercise behavior include nerve growth factor (70), fibroblast growth factor type 2 (42), vascular endothelial growth factor (36), and VGF growth factor (49) and galanin (101). Furthermore, aerobic exercise also enhances several neurotransmitter systems in the brain, including increasing circulating dopamine (78), serotonin (5), and acetylcholine (40). Relatively less research has been done on the mechanisms by which exercise affects production of these neurochemicals with links to cognition and learning and memory. Therefore, the extent to which these neurochemicals also contribute to benefits of exercise across the lifespan deserves future study.

In summary, animal models have revealed much about the potential neurobiological mechanisms of exercise effects on brain and cognition across the lifespan. Aerobic exercise has a concentrated benefit on the hippocampus, increasing the growth of new neurons and new blood vessels, and increasing synaptic plasticity which helps facilitate the integration of hippocampal neurons into existing brain networks. Several important neurotrophins are integral to the effects of exercise on brain and cognition. While aerobic exercise seems to selectively up-regulate central BDNF, both aerobic and resistance exercise up-regulate central and peripheral IGF-1. Both are key players in exercise-induced increases in learning and memory, and IGF-1 may be particularly important in mediating the effects of BDNF and promoting exercise-induced neurogenesis and angiogenesis. However, it should be noted that animal models often use cognitive measures of learning and memory that rarely conceptually overlap with the cognitive paradigms used in human research. Thus the extent to which the reviewed potential mechanisms account for benefits of exercise on executive function in humans is a topic that deserves future consideration. In addition, future research is needed to clarify the role of these molecular and cellular pathways in models of aging and exercise. Research has generally supported the idea that
aerobic exercise attenuates age-related declines in neurogenesis and learning and memory, but it is still unclear how much overlap there is between the exercise model for young and aged animals.

**Concluding comments, unresolved issues, and future directions**

The reviewed literature provides an overview of the effects of exercise on brain and cognition throughout the lifespan. Whereas research has focused primarily on the benefits of aerobic exercise in youth and young adult populations, there is growing evidence that both aerobic and resistance training are important for maintaining cognitive and brain health in old age. Our review also points out gaps in the literature and important future directions for the field.

Clearly there is a need for more research that investigates the effect of exercise type on the brain and cognition, and in turn, clinically significant outcomes such as quality of life, memory complaints, mobility, falls risk, and mortality. While standard neuropsychological tests and brain imaging data provide valuable data for characterizing the specific brain systems affected by exercise behavior, the translation of these results into clinically relevant outcomes is also important for building a more interactive relationship between basic research findings and clinical practice. Also important for translating research into practice, will be a greater understanding of how individual differences mediate or moderate the effects of different exercise types on brain and cognition. For instance, it is possible that aerobic training will be more effective for some individuals whereas resistance training would benefit others more, and their combination may be best for yet another group. Some factors important to examine may include (but not limited to) genetics, personality, and personal health history or disease status. Greater understanding of the role of these factors in the effects of exercise training on brain and cognitive health may also help clarify the relative importance of aerobic fitness gains compared to engaging in physical activity without focus on fitness gains *per se*. These issues have important practical
significance for affecting public health recommendations for physical activity behavior to improve brain
and cognition.

Within the realm of brain imaging, when comparing the effects of different exercise types, it will
be important for future research to incorporate more of a multi-modal framework. Currently our
knowledge of exercise effects in childhood and young adulthood is based primarily from neuroelectric
methods, whereas training studies with older adults have utilized primarily hemodynamic measures of
brain function. Therefore, it will be important for future research to incorporate multiple methods of
measuring brain function across the lifespan. Along these lines, additional methods that will be
important for future research include measures of blood volume and blood flow such as arterial spin
labeling (ASL) and measures of white matter microstructure, including diffusion tensor imaging (DTI).

For example, a recent study demonstrated the feasibility of measuring resting and task-related cerebral
blood flow with ASL following an acute bout of exercise, which will be important for studies examining
effects of acute exercise on fMRI activation (91). In addition, we know of only one study (10) that has
used ASL to examine effects of chronic exercise exposure, which suggested increased hippocampal blood
flow following an aerobic exercise program. Given the increasing reports of effects of chronic exercise on
fMRI activation, this is an important gap to fill. Other cross-sectional research has used DTI to show
preliminary evidence for an association between aerobic fitness and white matter integrity in the
uncinate fasciculus (connecting ventral frontal and temporal lobes) and cingulum bundle (transversing
the midline between anterior and posterior areas) (68, 69). Finally, near-infrared spectroscopy is
another technology that could be applied during exercise, making it another useful tool to compare
effects of acute and chronic exercise on brain and cognition (81, 110). Overall, while these studies
generally have relatively small sample sizes and have examined targeted age groups, they represent a
starting point for future studies to expand on in both sample size and diversity, and in longitudinal
designs.

Finally, it will be important for future research to try to integrate animal and human work. For
example, more animal studies that incorporate a lifespan perspective could help characterize potential
similarities and differences of neurobiological mechanisms for exercise effects on brain and cognition at
different points in the developmental timeline. On the other hand, it will be important for more human
studies to incorporate measures of neurobiological markers such as peripheral measures of BDNF and
IGF-1 during both acute exercise and following chronic exercise exposure. More work of this nature will
help build an understanding of how acute effects are similar to or different from chronic benefits on brain
and cognition across the lifespan, ultimately furthering our understanding of the mechanisms for how
different types of cumulated exercise behaviors affect the brain and cognition. In this spirit, future
studies with humans may also gain valuable insight from animal models about optimal methods for
combining interventions based on different exercise types and/or exercise and cognitive training
programs or diets. For example, a study by Fabel and colleagues (37) supports the idea that the
functional significance of hippocampal neurogenesis resulting from aerobic exercise is further promoted
if followed by environmental enrichment, or cognitive training. This suggests that while aerobic exercise
would be a good starting point for intervention programs, beneficial effects for brain and cognition may
be further enhanced if followed by the addition of other activity types, such as resistance training,
cognitive training, or some combination thereof.

Thus, while all exercise might not be painless or provide the “easy fix” to enhance brain and
cognition across the lifespan, there is ample evidence to support it is one of the most effective means
available to improve mental and physical health, without the side effects of many pharmacological
treatments. In this review we have highlighted some of the best evidence in support of exercise benefits
for non-pathological populations, but also point out important areas for future research to advance the field. It is our hope that this will encourage greater diversity of approaches and methodologies, applied to a larger diversity of populations, in the field of exercise neuroscience. Such advancements promise to improve translation of positive findings in the research laboratory to improved quality of life from childhood to late life.
Acknowledgements

Preparation for this manuscript was supported by funding from the National Institute on Aging at the National Institutes of Health (grant numbers 05 R37 AG025667, RO1 AG25032) for PI Arthur Kramer. Teresa Liu-Ambrose is a Canadian Institute Health Research New Investigator and Michael Smith Foundation for Health Research Scholar.

References


33. Erickson, and etal. Exercise training increases size of hippocampus and improves memory. PNAS 2011.


