Exercise, cognitive function, and aging

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BY THE YEAR 2030, it is estimated that >20% of United States residents will be over 65 yr of age (55). While increasing life expectancy is certainly an encouraging trend, substantial social and economic implications will ensue if this increase in lifespan is accompanied by poor health. The challenge for the medical community is working to maintain a high quality of life and lowering morbidity in older adults. Advancing age is associated with an increasing disease risk for dementia. Between 2000 and 2010, mortality from cardiovascular disease, stroke, and human immunodeficiency virus has declined, whereas the number of deaths attributed to AD have increased by 68% (2). By 2030, an estimated 9 million adults in the United States will have AD, not including other dementias (24).

AD and Dementia

For the purposes of this physiology review, data on AD will be combined with data on dementia. However, AD is a specific neuropathology that eventually leads to dementia, whereas multiple pathologies, independent of AD, may cause dementia. Specifically, AD is characterized by abnormal clusters (amyloid plaques) and bundles of fibers (tau neurofibrillary tangles) in the brain. Amyloid precursor protein is cleaved to form the amyloid-β peptide. The formation of amyloid-β is normal, and, typically, amyloid-β production in the brain is matched by clearance, preventing accumulation. In early AD, however, these amyloid-β fragments accumulate and aggregate to form plaque within the cellular membrane. Amyloid-β plaques can lead to neurodegeneration and are associated with cognition (11). However, not all individuals with significant amyloid deposition develop AD (42, 48). Furthermore, interventions targeting amyloid-β through immunization to improve amyloid clearance and reduce the amyloid burden have not been successful in changing disease progression (27) or providing successful clinical results (34). This is not to say that amyloid-β is not involved in AD pathophysiology, but it suggests that preventing AD is a multifaceted problem. There is a complex interplay between AD pathology and changes within the aging brain.

Neurofibrillary tangles are also characteristic of AD pathology. These tangles are aggregates of hyperphosphorylated tau protein and affect neurodegeneration (18). Tau was once thought to play a limited role in AD progression, although now it is recognized as an important mediator in AD pathology. Tau phosphorylation may prevent stabilization of microtubules (35), alter regulation of synapse function, or impact neuronal signaling (40), which can lead to changes in cognition. The increased deposition of amyloid-β and tau are considered neuropathological and are characteristic to AD.

Clinically, the first signs indicating AD or dementia manifest as subjective memory complaints. Patients may be identified as having mild cognitive impairment (MCI), which describes individuals with some cognitive impairments but do not have AD or dementia. These patients have deficits in one or more areas of cognitive function, but they are able to maintain most daily activities. MCI patients may remain classified as such or demonstrate further cognitive decline and eventually be diagnosed with AD or dementia.

Resistance to Cognitive Decline

The accumulation of amyloid-β and tau in the brain, alongside the hypothesized changes in neuronal function, do not completely explain AD pathophysiology. The failure of large-scale immunization trials combined with autopsy evidence indicating that cognitively normal individuals may have had significant AD pathology suggest that there are additional
mechanisms to consider. One recent study examined why some individuals had higher resistance to dementia despite high AD pathological burden as determined by neuroimaging. In individuals with significant AD pathology, larger total brain and hippocampal volumes explained the difference between cognitively normal adults and dementia patients (20). Larger brain volumes may result in greater reserve or higher baseline. Therefore, a higher amount of AD pathology may be present before there are noticeable changes in cognition. Additionally, cognitively normal individuals with high AD pathology may have compensatory mechanisms to protect from neurodegeneration, such as differences in number of synapses (45) or differences in apoptotic pathways (13).

Both brain volume and gray matter volume decrease with advancing age (12, 41). Importantly, higher cardiorespiratory fitness is associated with lower rates of age-related decline in gray matter, particularly in the prefrontal, superior parietal, and temporal cortices, in cognitively normal older adults (12). In a longitudinal study (30) that followed cognitively normal older adults, those who exercised three or more times per week were more likely to remain dementia free during the 6-yr followup period, independent of other risk factors for dementia. Along similar lines, the amount of walking, expressed in blocks per week, was predictive of higher gray matter volume measured over a 9-yr period (19). Walking >72 blocks/wk was the threshold determined for protection against age-related changes in the hippocampus, prefrontal, and temporal brain regions. The amount of physical activity was associated with lower risk of developing MCI or dementia during the 9-yr followup. Taken together, these studies highlight the significance of regular exercise in attenuating the age-related decline in brain volume as a preventative measure against AD and dementia.

Regular physical activity and exercise are protective against cardiovascular disease, and this likely extends to the risk of AD and dementia. Barnes and Yaffe (6) recently calculated population attributable risks that include the prevalence of the risk factor and strength of association of that risk factor with AD diagnosis. Of all of the modifiable risk factors for AD (including diabetes, hypertension, obesity, smoking, depression, physical inactivity, and cognitive inactivity), increasing the proportion of the population who are physically active by 25% was statistically the most effective measure in countering AD. This action may prevent as many as 230,000 AD cases in the United States alone (see Fig. 1) (6). This may underestimate the true effectiveness because physical activity may also indirectly modify prevalence of other risk factors such as hypertension, obesity, or depression.

**Why Might Physical Activity Be Part of the Solution?**

When we study human physiology, we often start by studying young, healthy humans. Yet, the majority of the population is sedentary with subclinical risk factors. This reality provides a challenge when examining the relationship among aging, exercise, and cognition. Should we consider sedentary humans as the “norm”? As many excellent reviews have emphasized, studying sedentary or inactive humans may be a departure from our innate physiology in which humans were meant to move and work to survive (see Refs. 9 and 23). Evaluating the age-related changes in neurodegeneration is likely confounded by the fact that the majority of the population in the United States does not exercise regularly (6). Perhaps we should study physically active humans to study the true effect of aging on cognition.

During exercise, brain blood flow increases, although it is dependent on the mode and intensity of exercise. During steady-state cycling, for example, global brain blood flow increases in parallel with cardiac output and O2 consumption, despite the fact that mean arterial pressure remains constant (26). The increases in regional brain blood flow correspond to the neural networks associated with central command and skeletal muscle afferents (37). Central command in the brain initiates parallel activation of skeletal muscle contraction and autonomic nervous system changes at the onset of exercise. Therefore, the elevation in brain blood flow at the beginning of exercise is not simply due to the increase in cardiac output but also due to changes in brain metabolism to supply increased neural activation.

Brain blood flow during exercise is also dependent on intensity of exercise. From low- to moderate-intensity exercise (cycling), blood flow through the carotid artery, vertebral artery, and middle cerebral artery (MCA) increases in healthy humans. At higher exercise intensities, blood flow velocities plateau or decrease (depending on the vessel), whereas carotid artery blood flow continues to rise (for a review, see Ref. 39). This effect is thought to be due to elevated blood flow through...
the external carotid artery to maintain thermoregulation during higher-intensity exercise (44). Therefore, moderate-intensity exercise results in acute augmentation of blood flow to the brain. However, it is unclear whether regular exercise chronically elevates resting brain blood flow.

**Age-Related Cognitive Decline and Vascular Risk**

Information that links AD pathology and neurodegeneration with blood flow regulation is lacking. However, many studies have shown how vascular risk is associated with an increased incidence of AD or dementia. Roberts et al. (43) reported a difference in the cumulative incidence of MCI between adults with and without cardiac disease. In this study, cardiac disease included atrial fibrillation, coronary heart disease, and/or congestive heart failure. The hazard ratio for MCI in individuals with cardiac disease was 1.77 compared with the referent group (1.0) without cardiac disease (43). In addition to cardiac disease, other cardiovascular disease risk factors, such as hypertension, obesity, and diabetes, are all associated with an increased risk of AD or dementia (31). Currently, it is difficult to determine cause and effect of how vascular risk influences the development of AD or dementia.

**Vascular Dysfunction/Physiological Mechanisms**

The mechanism underlying the reported correlations between cardiovascular disease risk factors and cognitive decline is unknown. Each cardiovascular disease risk factor is also associated with altered blood flow regulation and reduced functioning of the vascular system. The term “vascular dysfunction” is often used to describe when blood vessels lose their ability to respond normally. This may occur when there is damage to the endothelial cell layer (caused by inflammation, oxidative stress, advanced glycation end products, etc.) or when there is an increase in the collagen-to-elastin protein ratio within the intimal and medial layers of the vessel wall. Vascular dysfunction disrupts the ability of the arterial tree to supply adequate blood flow to the target organs and eventually manifests as clinical disease (56). For example, in the kidney, systemic vascular dysfunction may cause proteinuria or end-stage renal failure. In this context, dysfunction in one vascular bed is thought to translate to other vascular beds. Therefore, systemic vascular dysfunction will likely alter blood flow to the brain, and clinically this may present as cognitive impairment. Therefore, vascular dysfunction and altered blood flow regulation may be a key link between cardiovascular disease and cognitive decline.

Routine monitoring of the vasculature and blood flow regulation to detect vascular dysfunction has high clinical relevance for cardiovascular disease. Because changes in the vasculature precede the onset of traditional risk factors, this provides a “window of opportunity” to identify individuals who may develop risk factors and actively intervene in an effort to delay or prevent the onset of disease. Because vascular dysfunction will disrupt neurovascular coupling in the brain, it may be a key link among hypertension, diabetes, obesity, and cognitive decline. Therefore, quantifying vascular dysfunction may also have clinical relevance for other organ systems, including the kidneys and brain (36, 56). As shown in Fig. 2, de la Torre et al. (15) outlined one working hypothesis connecting disrupted hemodynamics with neurodegeneration and cognition. How exactly vascular dysfunction may lead to cognitive decline is currently unclear.

Another important barrier to detecting vascular dysfunction is the method to quantify vascular dysfunction in a clinical setting. Peripheral vascular function is often measured in the forearm. Forearm blood flow responses to intra-arterial infusions of a vasodilating substance to give an estimate of the “responsiveness” of the forearm blood vessels have been used for decades. This method of measuring vascular function is not feasible for a clinical setting. There are other methods of assessing vascular function (such as pulse wave velocity or pulse wave analysis) that may be more adaptable for a clinical setting.

Studies showing forearm blood flow responses have provided insights into age-related changes in blood flow regulation and vascular function. DeSouza et al. (17) demonstrated an age-associated reduction in vascular function as measured by lower forearm blood flow responses to acetylcholine in healthy adults between 50 and 76 yr of age. In contrast, there was no age-related reduction in vascular function in older adults who regularly performed structured endurance exercise training (i.e., exercise-trained adults) (17). Additionally, when sedentary adults were enrolled in a 3-mo aerobic exercise training program, their vascular function improved, highlighting the plasticity of the vascular system (17). These data indicate that regular physical activity and exercise training can ameliorate or delay the negative effects of advancing age on the vasculature. The exact mechanism explaining how exercise prevents age-related reductions in vascular function is unclear, and postulated mechanisms been summarized elsewhere (47).

While many studies have focused on the effect of aging and exercise in the peripheral circulation, less is known regarding the cerebral circulation. In animal studies, exercising animals demonstrated elevated cerebral blood flow at rest compared with sedentary control animals (21, 28, 52). Similarly, in humans, cerebral blood flow velocity of the MCA was higher at rest (∼17%) in exercise-trained men versus sedentary men.
The beneficial effect of habitual exercise was independent of confounding variables such as blood pressure or body mass index. This is significant because MCA blood flow velocity, measured using a transcranial Doppler probe as a surrogate for cerebral blood flow, progressively declines with advancing age (1). While it is unknown whether increases in global blood flow in the brain protect cognition, this indicates that exercise may alter global brain blood flow.

There is more evidence from animal studies regarding how exercise alters the cerebral circulation. In animals, capillary growth occurs within 30 days of initiation of a running training program, and the capillary growth is detected primarily within the motor cortex (52). However, others have shown higher total surface area of the capillaries in the whole cortex in middle-aged animals (28). Furthermore, when neovascularization and angiogenesis were inhibited in animals before exercise training, there was no increase in cerebral blood flow at rest compared with control animals (21). This suggests that one mechanism by which structured exercise training may augment cerebral blood flow is by increasing vessel formation within the brain. Although these data give us some indication about the effects of aging and potential protective effects of regular exercise, they do not provide information on the responsiveness of the cerebral vessels or how this influences neurovascular coupling.

We can measure vascular dysfunction in the human brain by administering stepped increases in CO₂, which induces vasodilation of the cerebral microvasculature (7, 58). The change in cerebral blood flow velocity as determined by transcranial Doppler is used as an indicator of changes in cerebral blood flow. For a given increase in CO₂, we would expect individuals with better vascular function to respond with a greater increase in blood flow velocity than those with vascular dysfunction. We and others (7, 58) have used this method to calculate cerebrovascular reactivity as a measure of vascular dysfunction in the brain. This method of estimating vascular dysfunction does have a few methodological issues associated with it, including 1) the assumption that the diameter of the cerebral vessels is unchanged during hypercapnia and 2) we must take into account mean arterial pressure, which helps perfuse the brain and increases with hypercapnia.

Using this technique, our recent work has shown that advancing age is associated with reduced cerebrovascular reactivity in healthy adults (see Fig. 3) (7). Older adults demonstrated both lower MCA velocity and a blunted response to stepped increases in CO₂ at rest. Moreover, we found that the cerebrovascular reactivity was positively associated with aerobic fitness in older adults, although none of our participants were considered “exercise trained” (8). A subsequent study (4) determined that cerebrovascular reactivity in sedentary and exercise-trained adults was associated with maximal aerobic capacity in both young and older adults. Collectively, such studies suggest that, similar to the peripheral circulation, cerebrovascular function is reduced with age and associated with levels of aerobic fitness. Because exercise-trained older adults have greater levels of cerebral blood flow and better cerebrovascular function, their baseline is higher, potentially prolonging the decline in brain/cognitive function (14).

Importantly, similar techniques have been used in AD patients to evaluate cerebrovascular function. Indeed, AD patients have lower cerebrovascular reactivity compared with age-matched controls (16), suggesting that there is an association between impaired ability to regulate blood flow in the brain and cognitive deficits. Teleologically, greater cerebral blood flow and vascular function may lessen the accumulation of AD pathology and, thus, impaired cognition. In support of this, Li et al. (32) demonstrated that, in an AD knockin mouse model, cerebral hypoperfusion coincided with amyloid-β accumulation. However, when cerebral hemodynamics were altered in wild-type mice, there was no net amyloid-β accumulation, suggesting that increasing or decreasing cerebral blood flow does not explain the magnitude of change in AD pathology (32). Therefore, it remains unknown whether AD pathology causes reductions in vascular function or if vascular dysfunction is a mediator of AD pathology through impaired clearance of amyloid-β protein.

**Cognitive Reserve**

In addition to cerebrovascular reserve, cognitive reserve may explain why some cognitively normal individuals have high levels of AD pathology. This paradox in AD research demonstrates a discrepancy between neuropathology in the brain (amyloid-β burden and tau) and cognitive outcomes. It appears some older adults can tolerate greater levels of AD pathology in the form of higher amyloid-β burden and more neurofibrillary tangles without the clinical manifestation of cognitive impairment. Stern et al. (49) has outlined this idea of “reserve,” noting that there is not a direct relationship between AD pathology and cognition and that some individuals simply have higher reserve (see Fig. 4). This higher reserve may either be due to greater brain volumes, as originally hypothesized by...
Stern and colleagues (46), or due to higher levels of education or occupational attainment (50). In addition, adults with larger brain volumes and/or greater cognitive reserve likely have more compensatory mechanisms to deal with increasing AD pathology without a noticeable effect on cognition.

Physiologically, the ability of the brain to function better in adults with high cognitive reserve may be due to neurogenesis as a function of a cognitively stimulating or enriched environment (29, 48). In animal studies, a “stimulating” environment is one that includes social interaction with other animals, a voluntary running wheel, and access to toys (54). Because physical activity increases in a stimulating environment, it is possible that physical activity may have been the key to the improvements in cognition while housed in an enriched environment. Indeed, Kobilo et al. (29) determined that if animals were placed in a stimulating environment with limited locomotor activity, they did not demonstrate hippocampal neurogenesis. Furthermore, animals that were given access to the running wheel performed better on learning and memory tests compared with those that did not (53). These authors concluded that the “most successful remediation so far has been aerobic exercise” in improving cognition.

Taken together, this suggests that cerebrovascular function and cognitive reserve may act synergistically. Davenport and colleagues (14) proposed in a recent review that exercise likely increases resting cerebral blood flow and “cerebrovascular reserve” via increasing neurotrophic factors, angiogenesis, vascular function, and neurovascular coupling. This would result in greater neurogenesis, cognitive performance, and cognitive reserve (14).

Exercise and Cognitive Function

The results of several animal studies have consistently demonstrated that aerobic exercise is effective in improving memory and cognition. However, the data in humans are less straightforward and not all results are consistent. The majority of studies have shown that, throughout their lifespan, from young children to the elderly, higher levels of fitness are associated with better performance on cognitive tasks. For example, children of 9–10 yr of age completed cognitive tests and were compared with young adults (between 18 and 30 yr of age). Children with the highest levels of aerobic fitness were statistically similar to young adults, whereas lower levels of fitness corresponded to lower accuracy and slower response speed (57). The more fit children also demonstrated different brain activation patterns, as measured by functional MRI, compared with less fit children, reinforcing the idea that exercise and physical activity are potent modulators of brain structure and function at early ages. In a randomized control trial (FITKids), children aged 7–9 yr of age were randomly assigned to a 9-mo physical activity program or a waitlist. Children in the exercise group demonstrated greater executive control compared with children in the waitlist group (25). Moreover, the improvements in cognitive function were positively correlated with intervention attendance (25).

The level of fitness or amount of physical activity during childhood and young adult years likely exerts lasting effects on the future risk of cognitive impairment. A recent study by Nyberg et al. (38) demonstrated that fitness levels (low, me-

Fig. 4. There is a disconnect between AD pathology and clinical cognitive severity, which is moderated by cognitive reserve. Cognitive reserve is the idea that the brain tolerates structural AD pathology without a significant change in cognitive function. AD pathology ranges from mild to moderate. Individuals with high cognitive reserve may have moderate AD pathology, but they have not yet reached the diagnostic threshold to be considered demented. On the other hand, individuals with low cognitive reserve may be beyond the diagnostic threshold, despite mild AD pathology. MCI, mild cognitive impairment.

Fig. 5. The potential interactions and ideas of how variables associated with aging may interact to affect cognition and how exercise may inhibit this process. The solid arrows indicate interactions backed by research, and the dotted arrows indicate potential interactions with less research focused on the association. CVD, cerebrovascular disease.
diurn, or high) at the age of 18 yr old predicted the risk of MCI and dementia 42 yr later in men. These results were true even when the intelligence quotient was considered and after adjustment for traditional risk factors for MCI. Therefore, low aerobic fitness at the age of 18 yr old emerges as a potential risk factor for future cognitive deficits.

While such data does not yet exist in older women, there is a positive association between aerobic fitness and overall cognitive function after controlling for risk factors. When divided into sedentary versus fit women, there was a significant difference in cognitive scores between the two groups, with fit women having better cognition (10). Additionally, higher aerobic fitness was associated with greater cerebral blood flow, as measured by transcranial Doppler in these older women. This was the first study to link aerobic fitness to both cerebrovascular function and cognition, indicating that blood flow regulation may be a key mechanism underlying the beneficial effects of exercise on cognition.

These associations are not just apparent in healthy adults. Baker et al. (5) enrolled MCI patients into a 6-mo trial of either stretching or aerobic exercise. Women in the aerobic training group improved their cognitive scores relative to the stretching control group. However, there was no difference between exercise groups in men. The study by Baker et al. investigated two forms of exercise, aerobic and stretching, and found aerobic exercise to be superior. This brings up the question concerning what exercises are beneficial for improving cognitive function.

Are Some Exercises More Effective at Improving Cognition?

To date, there are not many studies comparing the effects of different modes of exercise on cognition. Liu-Ambrose et al. (33) compared resistance training to balance training and found that resistance training induced a greater increase in perfusion during some cognitive tasks. Along these lines, when regional brain perfusion was measured in older adults, women who performed strength training at least once per week demonstrated greater cerebral perfusion than those who did not (59). Furthermore, there were no differences in perfusion if groups were stratified by other modes of exercise.

It is likely that a single exercise mode will not be as beneficial as a multicomponent exercise program that builds aerobic fitness, muscular strength, balance, and flexibility. A recent study investigated the effects of 6 mo of multicomponent exercise (aerobic, strength, and balance) in MCI patients. This 2-day/week program was effective in improving logical memory and cognitive function and maintained brain atrophy rates compared with the control group (51).

One issue when evaluating the effectiveness of an exercise intervention is that an intervention usually does not replicate all of the beneficial effects of exercise reported from cross-sectional studies in exercise-trained individuals. Is there a difference in cognitive demand between exercise intervention studies (often using standard indoor gym equipment) and the physical activity performed by exercise-trained individuals? In other words, is there a difference in the cognitive benefits in “disconnected” (typical exercise prescription programs) and “engaged” (outdoor exercise, fitness classes, sports) exercise? To maximize the cognitive benefits of exercise, perhaps including exercise modes that involve learning, coordination, multiple muscle groups, and continuous cognitive stimulation is necessary. While the evidence directly testing this hypothesis is weak, there are several studies emerging that examined combined exercise and cognitive tasks in older adults. One such study by Anderson-Hanley et al. (3) evaluated 3 mo of stationary cycling compared with virtual reality enhanced interactive cycling and found better executive function in the latter group. Future studies are needed to determine how to optimize or even accelerate the cognitive benefits of exercise.

Summary

The medical, psychosocial, and economic consequences of cognitive impairment combined with the growing population of people over 65 yr of age will require multidimensional solutions. Aging is associated with cardiovascular disease risks, vascular dysfunction, and increasing AD pathology, which will affect cerebral vascular function, perfusion, and brain atrophy rates. Clinically, these will present as reduced cognitive function, neurodegeneration, and the onset of dementia. Regular exercise improves cognitive function, and we hypothesize that this occurs through modifications in vascular physiology. Less is known regarding the effects of exercise on AD pathology, but many related studies are in progress. This review highlights the potential interactions and ideas of how the age-associated variables may affect cognition, as shown in Fig. 5.

A 2011 scientific statement from the American Heart Association concluded from a large-scale meta-analysis that physical activity protects against cognitive decline (22). Furthermore, the authors suggested that there is a complex interaction between vascular physiology and AD pathology and that interventions in midlife will be necessary for the prevention or delay of cognitive impairment in the aging. Understanding these interactions will be important for future medical professionals and policy makers to identify solutions and inform decisions.

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Author contributions: J.N.B. conception and design of research; J.N.B. performed experiments; J.N.B. analyzed data; J.N.B. interpreted results of experiments; J.N.B. prepared figures; J.N.B. drafted manuscript; J.N.B. edited and revised manuscript; J.N.B. approved final version of manuscript.

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