The Effects of Aerobic Exercise on Cognitive and Neural Decline in Aging and Cardiovascular Disease

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Abstract Aging is characterized by a decline in cognitive functions, particularly in the domains of executive function, processing speed and episodic memory. These age-related declines are exacerbated by cardiovascular disease (CVD) and cardiovascular risk factors (hypertension, diabetes, obesity, elevated total cholesterol). Structural and functional alterations in brain regions, including the fronto-parietal and medial temporal lobes, have been linked to age- and CVD-related cognitive decline. Multiple recent studies indicate that aerobic exercise programs may slow the progression of age-related neural changes and reduce the risk for mild cognitive impairment as well as dementia. We review age- and CVD-related decline in cognition and the underlying changes in brain morphology and function, and then clarify the impact of aerobic exercise on moderating these patterns.

Keywords Aging · Cardiovascular disease · Exercise · Physical activity · Cardiorespiratory fitness · Aerobic fitness ·

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Memory · Declarative memory · Episodic memory · Executive functions · Cognitive control · Attention · Processing speed · MRI · fMRI · Diffusion tensor imaging

Introduction

The older adult population is growing rapidly and it is projected that approximately 20 % of the US population will be greater than 65 years old by the year 2030 [1, 2]. The escalating demographics of population aging are particularly notable with respect to healthcare implications. Aging increases susceptibility to health-related illnesses and places burdens on seniors in terms of their quality of life and independence [3, 4], as well as on families, caregivers and healthcare systems in terms of the costs and liabilities associated with an aging population. In particular, an estimated 40.5 % of the US population is projected to have some form of cardiovascular disease (CVD) by the year 2030, with disproportionate prevalence in the population aged 65 years and older [4]. CVD is associated with loss of functional independence and an estimated \$315.4 billion in total costs [3, 4]. The consequences of CVD will indeed increase as the population of older adults continues to rise.

Neurocognitive sequelae are associated with CVD and may partially underpin poor outcomes and high costs associated with CVD. CVD is an identified risk factor for vascular dementia and Alzheimer's disease [5–7], and mild cognitive impairment can also be found in persons with CVD prior to dementia onset. These findings and the forecasted increase in the older adult population underscore the need to identify modifiable factors that maintain brain health and cognitive function and prolong independence, thereby reducing caregiver burden and healthcare costs.

Cardiorespiratory fitness (CRF) is one factor that has been suggested to benefit cognition and neural integrity in older

adult and CVD populations. CRF is the ability of the circulatory and respiratory systems to supply oxygen to skeletal muscles during sustained physical activity. CRF declines with age and reductions are typically exacerbated by CVD, with effects including diminished brain perfusion as well as systemic physiological changes such as inflammation, oxidative stress, changes in gene expression [8]. However, CRF can also be improved by aerobic exercise and such benefits yield physiological benefits that translate to better cardiovascular and neurocognitive outcomes.

Cognitive and Neural Decline in Aging and CVD

Evidence for age-related cognitive decline is extensive. The cognitive domains most sensitive to aging include executive functions such as planning, inhibition, task switching, maintenance and manipulation of information [9, 10•, 11], processing speed [12] as well as episodic memory (i.e., memory of previous events) [13–15].

Age-related cognitive decline is exacerbated by CVD as well as cardiovascular risk factors (e.g., hypertension, diabetes, obesity, elevated total cholesterol). Impairments in attention, executive function, and processing speed are common in CVD populations [16–21]. Reduced episodic memory performance is also typically found in CVD [21–24]. Data from cross-sectional studies are reinforced by longitudinal analyses showing accelerated cognitive decline in CVD within the domains of executive function and episodic memory [25–29].

Cognitive changes associated with aging and CVD are underpinned by alterations in neural structure and function. With normal aging, neural reductions in gray and white matter volume [30–32], white matter microstructure [33, 34] and alterations in neural functional activity [35–37] are well documented, with the medial temporal lobes and fronto-parietal regions most susceptible to age-related decline. Notably, age-related changes in the medial temporal lobes and fronto-parietal regions have been linked to performance on tasks requiring executive function and episodic memory [9, 38•, 39].

CVD-related neural changes are similar to those observed in aging. CVD has also been associated with structural and functional alterations in the fronto-parietal and medial temporal lobe regions, including reduced brain volume [40–42], decreased white matter integrity [43, 44], reductions in cerebral blood flow [45, 46] and altered fMRI activity in the hippocampus, cingulate gyrus and fronto-parietal regions during memory [47, 48] and executive function tasks [49–52]. Structural and functional brain alterations associated with aging and CVD induce predictable cognitive impairments such as deficits in episodic memory and executive dysfunction [53–55].

Aging and CVD most profoundly impact executive function, processing speed and episodic memory as well as brain

regions that mediate these mental abilities, including fronto-parietal regions and the medial temporal lobes. Aerobic exercise represents a behavioral intervention that may alter the trajectory of age- and CVD-related cognitive and neural decline. Below we review existing evidence that demonstrates the positive impact of aerobic exercise on cognition and the brain in aging and CVD populations.

Impact of Aerobic Exercise on Cognitive Function

Aging

A landmark meta-analysis elucidated the positive impact of aerobic exercise on cognitive function in older adults [56]. The results highlight the utility of aerobic training in improving performance in multiple cognitive domains [e.g., processing speed (simple response time tasks, finger tapping), spatial processing (mental transformation of figures or memory for spatial information)] with effects that are largest for tasks requiring executive functions (e.g., planning, inhibition). A more recent meta-analysis further supports the beneficial effects of aerobic exercise on cognition, as aerobic exercise training is positively associated with performance on tasks requiring attention and processing speed, executive functions and episodic memory [57] (see [58]), although the reported effect sizes were similar across cognitive domains [57].

The positive impact of aerobic exercise training has recently been extended to frail older adults [59]. Frail older adults exhibited improvements in measures of processing speed, executive functions and working memory following completion of a 12-week (1-hour session, 3 days/week) aerobic exercise training program relative to a wait-list control group. This preliminary evidence suggests that the benefits of aerobic exercise on cognitive function generalize to older, frail populations.

Cardiovascular Disease

Poor physical fitness accompanies CVD [60] due to limits induced in part by abnormal cardiovascular physiology, but also due to sedentary behaviors that compound exercise limitations [61, 62]. Reduced fitness exacerbates negative outcomes in CVD patients (e.g., premature death). Cognitive impairments are also worse in sedentary CVD patients [63–65] and likely compound CVD risks. For example, reduced fitness has been associated with impaired performance on tasks reflecting attention, executive function and episodic memory in patients with CVD [65].

Fortunately, exercise training is an integral treatment component in the management of CVD [66, 67]. In fact, exercise training is a key component of cardiac rehabilitation, a

standard of CVD management. However, in addition to the acknowledged benefits of exercise training on cardiovascular parameters, the exercise benefits on cognitive gains in CVD are less well promulgated [68]. In multiple analyses of 12- to 18-week structured exercise (provided as cardiac rehabilitation programming) among heterogeneous CVD patients, exercise programs were associated with improved performance on tasks of attention, executive function, psychomotor speed and episodic memory [68–70]. Improvements in global cognition, attention and executive functions have also been observed among post-stroke survivors with high sample rates of CVD six months after combined aerobic and resistance exercise training [71]. Furthermore, there is evidence that cognitive gains in attention, executive function and memory are maintained nine months after the completion of a 12-week cardiac rehabilitation program [72], raising the possibility that exercise may attenuate accelerated cognitive decline and perhaps even reduce risk of dementia among CVD patients. Other studies suggest that even daily physical activity in persons with CVD may lead to better cognitive function [73, 74].

Aerobic Exercise and Cognition Summary

Overall, the extant evidence suggests that exercise confers cognitive benefits that may offset the insidious declines associated with aging and CVD. Cognitive gains achieved with exercise training are most prominent in the domains sensitive to the adverse effects of aging and/or CVD, including

executive functions, processing speed and episodic memory. Given these cognitive domains are critical for optimal performance of daily living activities, exercise may serve as one potential behavioral intervention that can preserve functional independence via attenuation of age- and disease-related cognitive decline.

Impact of Aerobic Exercise on Neural Structure and Function

Aging

Prominent literature now centers on the use of MRI and other imaging techniques to assess the neurological mechanisms underlying cognition. We reviewed the literature and found seven studies that used an aerobic exercise intervention and pre- and post-intervention MRI in older adults (see Table 1). All studies used walking (with varying duration and intensity levels) as the primary type of exercise training in at least one study group, targeting enhanced CRF as the main training effect. In each study sedentary subjects (e.g., not more than two bouts of physical activity >30 min in the previous six months) were recruited on the assumption that improvements in CRF associated with aerobic exercise intervention would be most prominent in respect to baseline sedentary behaviors and presumably in respect to the most prominent neurologic changes as well.

Table 1 Exercise intervention studies examining the relationship between cardiorespiratory fitness (CRF) and the brain. CON = control group; DTI = diffusion tensor imaging; Func = functional

study; fMRI = functional Magnetic Resonance Imaging; INVN = intervention group; ROI = regions of interest; Struct = structural study; T1 = T1-weighted imaging

Author	Year	Study Focus	Imaging Type	Analysis	Fitness Measure	# of Subjects (# females)	Mean Age (years)
Colcombe et al.	2006	Aging	Struct (T1)	Whole Brain	VO ₂ peak	59	66
Erickson et al.	2011	Aging	Struct (T1)	ROI	VO ₂ max	120	55–80
Ruscheweyh et al.	2011	Aging	Struct (T1)	Whole Brain	Ergometer test, questionnaire, lactate step test	62 (43)	60
Voss et al.	2012	Aging	Struct (DTI)	ROI	Composite score: VO ₂ max, Rockport 1 mile walk	70 (45)	65
Colcombe et al.	2004	Aging	Func (fMRI)	Flanker Task (Executive Function)	VO ₂ peak	29	58–77
Voelcker-Rehage et al.	2011	Aging	Func (fMRI)	Flanker Task (Executive Function)	Composite score: VO ₂ peak, action speed, reaction speed, & balance	44 (28)	70
Voss et al.	2010	Aging	Func (fMRI)	Passive Viewing Task	VO ₂ max	CON: 35 INVN: 30	65 67
Anazodo et al.	2013	CVD	Struct (T1)	ROI	VO ₂ max	CON: 21 (10) INVN: 39 (11)	59 59
*Kooistra et al.	2014	CVD	Struct (T1; FLAIR)	Whole brain; visual assessment	Metabolic Equivalents via physical activity questionnaire	1,232 (246)	59

*Longitudinal study that did not implement formal exercise training.

These intervention studies demonstrated that aerobic exercise significantly impacted brain structure. In one study, increased volume of the anterior cingulate cortex, supplementary motor cortex, right inferior frontal gyrus, left superior temporal gyrus and anterior corpus callosum was reported in the aerobic training group (exercising at up to 70 % of their heart rate reserve; 16.1 % training increase in peak VO_2) relative to a non-aerobic stretching control group (5.3 % training increase in peak VO_2) [75]. Another study showed that improvements in physical activity (assessed with a questionnaire) that resulted from exercise training over a six-month period were associated with gray matter volume increases in the cingulate gyrus (including the anterior and posterior cingulate cortex), the left superior frontal gyrus, the left medial parietal cortex and regions of the occipital cortex [76]. Likewise, in a study focusing on the medial temporal lobes [77] improvements in CRF were positively associated with hippocampal volume. Aerobically trained older adults demonstrated an approximately 2 % increase in hippocampal volume, whereas a *decrease* of roughly 1.4 % was observed in the stretching control. These data are particularly striking given that the volumetric increases more than offset the annualized age-related medial temporal lobe volume loss of 1–2 % in this age group [32, 78].

Three intervention studies used functional Magnetic Resonance Imaging (fMRI) to assess the impact of aerobic exercise training on brain function (see Table 1). Colcombe et al. [79] were the first to demonstrate functional brain changes associated with exercise training. Training consisted of a six-month aerobic exercise intervention (walking) with training at up to 70 % of heart rate reserve, and observed a 10.2 % increase in peak VO_2 relative to a 2.9 % increase in a stretching control group. They observed increased fMRI activity in lateral fronto-parietal regions and decreased activity in the anterior cingulate cortex (associated with response conflict monitoring) during flanker task performance (a task of executive function) in a group of aerobically-trained older adults relative to a stretching control group. CRF was also linked to performance on the flanker task.

A recent study [80] replicated Colcombe et al.'s finding of decreased activation in the anterior cingulate cortex subsequent to aerobic training. Additional reductions in activation were prominent in the left middle frontal gyrus, left parahippocampal gyrus and left middle and superior temporal gyrus among the training group, while controls showed increased activation in these same regions following the stretching/relaxation intervention. The authors explained these unexpected findings by suggesting that the decreased prefrontal activation observed in aerobic training reflected “a reduced need for compensation or increased cognitive control.” This explanation highlights one of the primary challenges associated with functional brain imaging; i.e., it is not

clear whether increased or decreased activation represents an optimal pattern of neural functioning.

In another study, Voss et al. [81] examined aerobic exercise-associated changes in functional connectivity in multiple neural networks (the default network and two executive control networks: a frontal-insular network and a frontal-parietal network). They examined functional connectivity in older adults during passive viewing tasks at baseline, following six months and following 12 months of aerobic exercise training (walking) or flexibility, toning and balance training. In comparison to non-aerobic training, 12 months of aerobic training led to increased connectivity in medial temporal lobe, parietal and frontal regions including enhanced functional connectivity between parahippocampal gyri and the middle temporal gyrus, the parahippocampal gyri and bilateral inferior parietal cortex, and the left middle frontal gyrus and middle temporal gyri.

Cardiovascular Disease

There is also evidence that exercise promotes neural integrity in adults with CVD. Reduced physical fitness is associated with brain alterations in CVD populations, including reductions of cerebral blood flow [82•], an increase in white matter lesions [83], and a thinner cortex and smaller total and regional (e.g., hippocampus, cingulate gyrus) gray matter volume [83, 84]. These data suggest that exercise may attenuate adverse brain changes in CVD through improvements in physical fitness and subsequent cerebrovascular benefits, particularly increased cerebral perfusion [82•, 85, 86].

According to our review, only one study to date has examined the impact of exercise intervention using pre- and post-intervention MRI in older adults with CVD in comparison to a healthy control group [87••]. Brain volume was assessed in this study using voxel-based morphometry in patients with CVD and age-matched controls to elucidate the impact of exercise training on brain structure. Prior to the exercise intervention CVD patients exhibited smaller gray matter volume of the superior, medial and inferior frontal gyrus, superior and inferior parietal gyrus, middle and superior temporal gyrus and the posterior cerebellum relative to controls. Lower peak VO_2 was shown to contribute to the reduced gray matter volume in persons with CVD. However, after completion of a six-month cardiovascular rehabilitation intervention, CVD patients exhibited gray matter recovery of the superior frontal gyrus, superior temporal gyrus and posterior cerebellum, in addition to gray matter increases in supplementary motor areas.

Daily physical activity may also promote greater brain volume in persons with CVD. Kooistra et al. [88•] examined the effects of leisure time physical activity on the brain among a large sample of patients with vascular disease (baseline $n=1,232$; follow-up $n=663$). Increased metabolic equivalents at

baseline (as assessed by a self-reporting physical activity questionnaire) correlated with larger total brain volume and a trend for smaller ventricular volume and decreased risk of brain infarcts. However, there was no longitudinal association between daily physical activity and brain changes.

Self-reported physical exercise has also been linked with white matter microstructural integrity in a sample of 440 older adults with cerebral small-vessel disease, a disease that is often a manifestation of CVD-related conditions [89•]. Lastly, although past work in stroke patients demonstrates post-exercise improvements in functional brain activation [90], to our knowledge there are no fMRI studies to more definitively assess exercise benefits on brain function among stroke patients.

Aerobic Exercise and Neural Integrity Summary

Although there are few exercise training and brain MRI studies in older adults reported to date, there is consistency in the brain regions that benefit from aerobic training [91••]. These regions include the anterior cingulate cortex, lateral prefrontal regions and lateral parietal regions and were evident in both structural and functional MRI studies. A relationship between aerobic exercise and the medial temporal lobes was observed in structural MRI studies, but was less apparent in the fMRI studies. This discrepancy may be attributable to the lack of tasks implemented during the fMRI that would be expected to elicit activation in medial temporal lobe regions.

The number of studies implementing exercise interventions in older CVD patients with pre- and post-exercise intervention MRI remains relatively limited. Nevertheless, when one also considers longitudinal data linking physical activity and the brain in CVD, there is accumulating evidence suggesting physical activity may improve neurocognitive outcomes in this population. Older adults with CVD showed a positive relationship between physical activity and brain regions including frontal and lateral temporal lobes, while those at-risk for CVD exhibited similar associations as well evidence of a positive relationship between physical activity and the medial temporal lobes.

Conclusions

Data linking CRF to cognition in aging and CVD are compelling. The cognitive domains most adversely affected by aging and CVD, including executive functions, processing speed and memory, are the same cognitive functions that benefit from aerobic exercise training. Clinical implications include improved health and well-being, as well as better clinical outcomes. While fewer MRI studies are available to corroborate neural correlations and clarify causal

relationships, those that are available reinforce a conclusion that aerobic exercise positively impacts neural structural integrity, with relatively consistent effects in fronto-parietal and lateral temporal regions, as well as the medial temporal lobes (although less evidence is available for older adults with CVD).

While there are multiple studies assessing pre- and post-exercise intervention with brain MRI, these studies have spanned multiple imaging modalities that are sensitive to distinct indicators of neural integrity (T-1 weighted imaging to assess brain volume or gray matter density, diffusion tensor imaging to examine white matter microstructure, and fMRI to examine neural activation). Thus, to date there is minimal evidence for replication and precise neuroanatomical localization of the reported effects, yet there is still a compelling array of neural effects that have been associated with aerobic exercise or enhanced CRF. For instance, in addition to increases in gray and white matter volume described above, aerobic exercise and enhanced CRF have also been linked to increases in cerebral blood volume and hippocampal neurogenesis [92], cerebral perfusion [93], reductions in white matter hyperintensities [94], enhanced white matter microstructure [95, 96] and enhanced functional connectivity within neural networks that determine executive function and episodic memory [81]. Likewise, animal studies have linked aerobic exercise (wheel-running) to enhanced neurogenesis, synaptogenesis and angiogenesis (formation of new neurons, synapses, and blood vessels, respectively), as well as to growth factors that support these processes (e.g., brain derived neurotrophic factor, vascular endothelial growth factor), often attenuating age-related reductions [97, 98].

Overall, there is a complex neurobiological cascade that underpins associations between aerobic exercise and cognition. Cardiorespiratory benefits span from the cellular level to the systems level and have engendered substantial enthusiasm to further assess benefits of aerobic training to attenuate age- and CVD-related cognitive decline (although the specific mechanisms remain unclear). The clinical value of aerobic exercise to mitigate age- and CVD-related decline is appealing for a variety of reasons. For example, aerobic activities (walking, jogging, etc.) are inexpensive, convenient and could potentially improve quality of life by delaying cognitive decline and prolonging independent function.

Although this review focused on aerobic exercise, recent reports have indicated that resistance training may positively impact cognitive performance and brain function [99, 100] and suggest that different types of exercise training may impact different cognitive functions and distinct brain regions [101]. Indeed, aerobic activities that rely more heavily on coordination such as ballroom dancing or water aerobics or that also implement strength training may confer additional cognitive and neural benefits. Additional research is needed to clarify issues regarding the impact of specific exercise

programs (e.g., strength, aerobic or combined training), dose of exercise (frequency, intensity, duration) and combined training on a range of cognitive functions. Furthermore, while we have focused on the impact of aerobic exercise targeting enhanced CRF, it has also been suggested that simply avoiding sedentary behavior and its deleterious effects may also positively impact cognition and the brain.

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Compliance with Ethics Guidelines

Conflict of Interest Scott M. Hayes, Michael L. Alosco, and Daniel E. Forman declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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