

# Exercise as a Way of Capitalizing on Neuroplasticity in Late Adulthood

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The increasing proportion of older adults in the population is expected to lead to an increased prevalence of age-related diseases, including cognitive decline and impairment. It is imperative to find affordable and effective methods for improving cognitive and brain function throughout the life span. Research reviewed in this article suggests that physical activity and exercise have the potential for improving cognitive function and taking advantage of the capacity of the brain for plasticity in late adulthood. Promising evidence from studies examining the effect of physical activity and exercise on brain health indicates the need for further research in this area.

**Key words:** brain, cognition, cortex, exercise, fitness, neuroplasticity, physical activity

There is expected to be a dramatic and global rise, including in the United States, in the number of adults older than 65 years.<sup>1</sup> This increased proportion of older adults may also increase the prevalence of age-related vascular and metabolic diseases, as well as neurocognitive impairments. In fact, the prevalence of cognitive impairment, including mild cognitive impairment (MCI), Alzheimer disease (AD), and other dementias, is expected to parallel the projected increase in the number of adults older than 65 years. Yet, despite the anticipated increase in the prevalence of MCI and dementias, there remains significant variability in the relative risk for experiencing cognitive impairment in late life, the breadth of cognitive decline, and the rate at which cognitive decline occurs. Such individual differences in cognitive decline suggest that unstudied third variables may be influencing the trajectory of cognitive losses throughout the life span.

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If the factors influencing the progression of neurocognitive loss can be identified, interventions targeting these factors may be successful in preventing decline, improving function, or delaying impairment.

One of the fundamental properties of the brain is its capacity to adapt in response to environmental stimulation. In fact, plasticity of brain networks as information is learned or forgotten is the biological analogue of learning and memory. In this context, the concept of neuroplasticity has emerged. Although difficult to define, the term neuroplasticity is usually used in reference to positive or adaptive (rather than maladaptive) changes to brain architecture that is above and beyond its current functioning limits. Hence, the concept of neuroplasticity is different from compensation, which is often used in reference to the ability of the brain, given its current architecture, and may include different strategies or approaches to solve a particular problem or challenge. In general, neuroplasticity is often considered a more protracted neurological process whereas compensation is more ephemeral.

Physical activity has the potential to take advantage of the natural capacity of the brain for plasticity. In fact, moderate-intensity aerobic exercise has emerged as an important modifiable behavior that could improve brain health and function in many different populations, as well as reduce the risk for developing neurological disorders. As is explained later, recent technological advancements in brain imaging have allowed researchers to gain insight into the biological consequences of exercise and to better understand how and under what conditions exercise influences brain structure and function.

## PHYSICAL ACTIVITY AND EXERCISE EFFECTS ON COGNITIVE FUNCTION AND MOOD

Before proceeding, it is important to define what is meant by exercise, fitness, and physical activity. First, physical activity refers to many different activities and behaviors that have some physical component to them. For example, gardening, carpentry, and bowling are all forms of physical activity. On the contrary, exercise is a form of physical activity that is structured with the aim of increasing aerobic capacity or fitness. Brisk walking, tennis, cycling, swimming, and basketball are all physical activities that qualify as

exercise as long as they are done at a level that increases heart rate. Finally, cardiorespiratory fitness is a measure of aerobic capacity in the same way that an IQ test is a measure of intellectual function. Cardiorespiratory fitness can be modified by participation in exercise and physical activities and is often used as an outcome variable or as a metric of the success of an exercise intervention (ie, those people in an exercise intervention should demonstrate increases in cardiorespiratory fitness after completion of the exercise intervention). The distinction between these 3 terms is important to understand since the research described later sometimes uses measures of physical activity and other times uses measures of exercise or fitness.

The gold standard of experimental methods to evaluate the effects of exercise on biological outcomes (eg, cognitive function) is randomized exercise interventions. In these interventions, participants are randomly assigned to either a group that receives instructed and monitored exercise (usually brisk walking) for some period (often between 3 months and 1 year) or a control group. Such interventions have been mainly conducted in older adults (>60 years) to examine whether participation in exercise is effective at improving cognitive performance in late life. Meta-analyses of these studies have concluded that aerobic exercise is effective at improving cognitive function across many different cognitive domains, but most extensively in the domain of executive functions.<sup>2,3</sup> Executive functions include selective attention, working memory, planning, and selecting and executing behaviors. Interestingly, executive functions show some of the earliest deficits with increasing age, indicating that remaining physically active may prevent age-related cognitive deficits.

Consistent with this line of reasoning, prospective longitudinal studies have also linked physical activity to better cognitive function. These studies, usually assessing several thousand individuals over the course of several years, have consistently found that greater amounts of physical activity earlier in life are associated with a reduced risk of developing cognitive impairment later in life. In fact, a recent meta-analysis of 15 prospective studies including more than 33 000 nondemented individuals found that participation in physical activity was associated with a 38% reduced risk of cognitive decline.<sup>4</sup> Furthermore, an analysis of modifiable risk factors reported that physical inactivity contributed the greatest percentage of risk for dementia in the United States.<sup>5</sup>

Cumulatively, these studies provide the argument that physical activity is an important factor for reducing the risk for cognitive decline and dementia and that, at least in nondemented individuals, an exercise regimen is effective at improving cognitive function. Unfortunately, only a few studies have examined the potential for physical activity to act as a treatment option for individuals already experiencing cognitive impairment. Lautenschlager et al<sup>6</sup> reported

that individuals with memory problems showed significant improvements in cognitive performance after 24 weeks of exercise. Similarly, Baker et al<sup>7</sup> found that females, but not males, with MCI showed improved executive function after a 6-month randomized exercise intervention. Nagamatsu et al<sup>8</sup> also reported that a 6-month exercise intervention improved verbal and spatial memory functions in adults with MCI. In sum, although there is promising evidence that exercise may improve cognitive functions in persons with MCI or dementia, there are too few published studies to make any firm conclusions.

Exercise is also effective as an augmentation to pharmacotherapy interventions, as it improves mood in depressed populations and reduces the risk of depression in healthy populations. In fact, epidemiological studies have shown that self-reported exercise is associated with fewer depressive symptoms<sup>9-13</sup> and randomized interventions find that participation in physical activity enhances mood in depressed populations.<sup>14-17</sup> The emerging evidence for exercise as a viable intervention for improving mood is far from conclusive, with several studies reporting null effects<sup>18-20</sup> and significant heterogeneity in the quality of randomized interventions examining the therapeutic effects of exercise on mood. Such studies of exercise and mood are highly relevant for the conceptualization of cognitive impairment since depression is a prodromal state for dementia and individuals with dementia often have depressed mood. Hence, exercise could be effective at improving both mood and cognition in older adults or the improvement in mood could be dependent on the improvement in cognitive function.

Exercise influences many different physiological systems that could be influencing cognitive function and/or mood. Many of the different physiological systems affected by exercise include those related to metabolism. For example, an accumulation of metabolic risk factors, known as the metabolic syndrome (MetS), increases the risk for cognitive decline and dementia.<sup>21</sup> The MetS is defined by the presence of at least 3 of the following metabolic disorders: obesity, insulin resistance, hypertension, dyslipidemia, and inflammation. Prospective research has demonstrated that the risk of developing dementia is increased by the presence of individual metabolic risk factors including obesity,<sup>22-24</sup> high blood pressure,<sup>25,26</sup> elevated triglyceride levels,<sup>27</sup> and low high-density lipoprotein cholesterol levels.<sup>25,28</sup> Even in cognitively healthy populations, these metabolic risk factors are related to cognitive decline.<sup>29-32</sup> For example, Elias et al<sup>29</sup> reported reductions in learning and memory performance among nondemented older adults with hypertension or obesity (body mass index  $\geq 30$  kg/m<sup>2</sup>). The combined presence of multiple metabolic risk factors may produce an additive effect, with research indicating that those with the MetS display greater cognitive deficits than those without the MetS.<sup>32,33</sup> Similarly, Yaffe and colleagues<sup>34</sup> found that the

risk of developing cognitive impairment increased 23% for every unit increase in the number of MetS components. Cerebral hypoperfusion, inflammation, and alterations in the deposition or clearance of amyloid- $\beta$  may be some of the pathophysiological mechanisms by which metabolic risk factors impair cognition.

Physical activity reduces the risk for development or progression of metabolic risk factors and may also mitigate the cognitive consequences of these conditions. Intervention and cross-sectional studies have found that increased physical activity favorably affects blood pressure,<sup>35</sup> visceral fat,<sup>36</sup> and cholesterol and triglyceride levels.<sup>37,38</sup> Randomized controlled trials have also demonstrated that moderate to vigorous physical activity may be protective against the development of the MetS.<sup>39</sup> Furthermore, physical activity may combat some of the pathophysiological consequences of metabolic risk factors. For example, higher levels of physical activity have been associated with lower plasma levels of inflammatory markers<sup>40,41</sup> and reduced brain amyloid burden.<sup>42</sup> The modifiable capacity of these risk factors suggests that the cognitive changes initiated by metabolic risk factors may be attenuated by physical activity. However, despite the scientific literature on the link between physical activity and the MetS, we can only speculate at this time about whether changes in metabolic factors contribute to improvements in cognitive and brain health.

## **CARDIORESPIRATORY FITNESS LINKS TO BRAIN STRUCTURE IN CROSS-SECTIONAL STUDIES**

Beginning in the early 2000s, magnetic resonance imaging (MRI) technology has been used to examine whether there are any discernible associations between higher cardiorespiratory fitness levels and brain volume. Metrics of total or regional brain volume are important because they provide a biological basis for understanding the associations between physical activity and cognitive function. This is especially important when considering cognitive impairment, as brain volume typically atrophies prior to the onset of behavioral cognitive symptoms.<sup>43</sup> Overall, the studies examining associations between fitness and brain structure have shown strikingly similar patterns such that higher fitness levels are routinely associated with greater brain volume throughout many different areas of the brain, but most consistently in the prefrontal cortex and hippocampus. The prefrontal cortex has many different functions, some of which include executive functions, which, as discussed earlier, are influenced by participation in exercise. The hippocampus has long been associated with memory functions, and deterioration of this structure is strongly predictive of developing dementia. Since the brain shrinks during late adulthood and loss of volume is predictive of dementia, greater gray matter volume in relation to cardiorespiratory fitness could be one pathway by which

physical activity is linked to better cognitive performance and reduced risk for dementia.

In a study examining the association between fitness levels and brain volume in nondemented older adults, increased age was associated with reduced volume throughout much of the cortex including the prefrontal and parietal lobes.<sup>2</sup> However, higher cardiorespiratory fitness levels mitigated the age-related decrease in volume in many of the same brain areas. As a follow-up to this study, Erickson et al<sup>44</sup> reported in a sample of 165 nondemented older adults that higher fitness levels were associated with larger hippocampal volumes and that larger hippocampal volumes were associated with better memory performance. Similar associations have been found in other populations. For example, in a sample of early-stage AD patients, higher cardiorespiratory fitness levels were associated with larger hippocampal volumes relative to their less-fit peers.<sup>45</sup> In cognitively healthy, obese, older adults, higher fitness levels were associated with larger hippocampal volumes.<sup>46</sup> Even in adolescents<sup>47</sup> and children,<sup>48</sup> higher fitness levels have been associated with greater hippocampal volume.

A persistent question emerging from this literature is the extent to which volumetric associations with fitness levels are linked to cognitive function. In other words, are larger brain volumes a meaningless consequence of higher fitness levels or are larger brain volumes associated with better cognitive function? Although only a few studies have carefully examined these links, the evidence suggests that the volumetric associations with fitness are not meaningless by-products but, rather, are important pathways in elevated cognitive function. For example, Weinstein et al<sup>49</sup> found that higher cardiorespiratory fitness levels were associated with greater gray matter volume in the prefrontal cortex in a sample of 142 nondemented older adults. Furthermore, greater gray matter volume in the prefrontal cortex mediated the association between fitness levels and cognitive performance. In another study examining the association between fitness and the volume of the striatum (a bundle of structures located in the middle of the brain involved in cognitive function, reward, and movement), higher fitness levels were associated with greater volume in 2 locations in the striatum, and this, in turn, mediated the fitness association with executive function.<sup>50</sup> These studies indicate that greater gray matter volume may be an important contributor to better cognitive function in higher-fit individuals.<sup>46</sup>

Recently, several studies have also started to investigate associations between cardiorespiratory fitness and white matter integrity. White matter is made of myelinated axons, which are the primary connections of the brain and allow different brain areas to rapidly communicate with one another. Unfortunately, with increasing age, there is a decrease in the integrity of these pathways, but several

studies have now reported that higher fitness levels may attenuate age-related decline in some white matter tracts. For example, Johnson et al,<sup>51</sup> using an MRI scan of white matter integrity called diffusion tensor imaging, found that higher-fit and nondemented older adults had greater integrity of white matter circuits throughout several different brain areas.<sup>52,53</sup> Similarly, in a 12-month exercise intervention with nondemented older adults, greater improvements in cardiorespiratory fitness levels were associated with increased white matter integrity as measured by diffusion tensor imaging.<sup>54</sup> In another study with older adult athletes, Tseng et al<sup>55</sup> reported that the athletes had greater white matter integrity and fewer white matter lesions than their more sedentary counterparts.<sup>56</sup>

In summary, cross-sectional research indicates that fitter older adults have greater gray matter volume and greater white matter integrity in several brain areas. These results parallel the research on the effects of exercise and physical activity on cognitive function and risk for developing dementia. Such volumetric differences are important in an age range when brain atrophy is common and when the risk for dementia increases. Yet, despite the provocative findings reported earlier, we have yet to discuss whether participation in exercise or physical activity is associated with increased volume or reduced decline over a longitudinal period. We describe these patterns in the next section.

## **EFFECTS OF EXERCISE INTERVENTIONS AND LONGITUDINAL ASSESSMENTS OF PHYSICAL ACTIVITY ON BRAIN STRUCTURE**

In the studies described earlier, cardiorespiratory fitness was used as a cross-sectional measure of overall physical health that can be influenced by participation in physical activity. The next step in this research is to determine whether randomized controlled interventions of exercise participation are able to modify the size of brain areas.

In one study, Colcombe et al<sup>57</sup> reported in a sample of cognitively normal older adults that those who participated in 6 months of moderate-intensity exercise (walking) exhibited significant increases in the size of gray matter in the prefrontal cortex and temporal lobes relative to a stretching and toning control group. The results from this study are important, as it was the first to demonstrate that participation in only moderate amounts of exercise was sufficient for changing the morphology of the brain in an age range when the brain is normally shrinking. As such, this was compelling evidence in support of the argument that exercise takes advantage of neuroplasticity in late life and promotes neural, regional, and possibly total brain growth.<sup>58</sup>

As previously described, cross-sectional studies have reported that volume of the medial temporal lobe, including the hippocampus, is positively associated with cardiorespiratory fitness<sup>44</sup> and physical activity<sup>59</sup> in older adults.

To examine whether exercise participation alters the size of the hippocampus, Erickson et al<sup>60</sup> conducted a 12-month randomized exercise intervention among 120 older adults. Using MRI techniques before and after the intervention, they found that the exercise group showed a significant 2% increase in the size of the hippocampus, or roughly the reversal of about 1 to 2 years of age-related loss in hippocampal volume. In contrast, the stretching and toning control group showed a loss in volume of about 1.5% over the 12-month interval, consistent with age-related atrophy. Furthermore, within the control group, higher fitness levels at baseline were indicative of less volume loss over the 1-year interval, indicating that higher fitness levels may be neuroprotective against tissue loss. Overall, this study indicates that the hippocampus, a brain region critically involved in memory formation and an important area implicated in AD, can increase in volume with only modest amounts of exercise over the course of 1 year.

Although randomized exercise interventions are the gold standard for determining causality between exercise and neurocognitive health, observational longitudinal studies are also useful for determining the trajectory of brain atrophy and the potential for physical activity or exercise to mitigate the loss in tissue. In one such study,<sup>61</sup> self-reported physical activity was assessed by the number of blocks walked per week in 1479 adults older than 65 years in the greater Pittsburgh community. Nine years after the physical activity assessment, 299 cognitively healthy individuals returned to the laboratory for an MRI scan of their brain. Erickson et al<sup>61</sup> examined whether greater self-reported walking at baseline would be associated with greater gray matter volume at the 9-year follow-up. In support of their hypothesis, older adults who reported walking at least 72 blocks per week (~1 mile per day) had greater gray matter volume in the frontal, parietal, and temporal lobes, including the hippocampus. Furthermore, a follow-up of these subjects 4 years after the MRI scan (13-year follow-up) revealed that greater volume in the hippocampus and frontal cortex was associated with a 2-fold reduced risk of developing cognitive impairment (MCI or dementia). Hence, this was the first study that linked physical activity and reduced risk for dementia with greater gray matter volume.<sup>62</sup>

In summary, results from both randomized controlled trials of exercise and observational longitudinal studies of brain morphology are consistent with the cross-sectional literature of fitness effects on the brain. All of these studies have shown that exercise influences brain morphology in the prefrontal cortex and hippocampus. Further studies are needed to replicate these effects, to extend them to populations with neurological or psychiatric conditions, and to clarify the mechanisms by which they influence cognitive function and mood (ie, depression).



## MOLECULAR AND FUNCTIONAL BRAIN IMAGING AND POTENTIAL MODERATORS

As previously stated, there is convincing evidence that gray matter volume varies as a function of cardiorespiratory fitness level and may change after participation in an exercise intervention. In addition to this body of research, several studies have examined whether exercise or physical activity is associated with altered and/or improved brain function. Using a technique called functional MRI, changes in blood flow to different brain areas can be traced and examined as a function of an exercise intervention or fitness levels. Using this technique, Colcombe et al<sup>65</sup> reported that participation in 6 months of exercise increased brain function in the prefrontal cortex during an attentionally demanding task. Consistent with these findings, Prakash et al<sup>64</sup> reported that higher cardiorespiratory fitness levels were associated with greater activation in the prefrontal cortex during an executive functioning task. Similar results have been reported in other studies of physical activity, fitness, and exercise.<sup>65-70</sup>

Another brain imaging technique called positron emission tomography uses an injection of a marker that binds to certain molecules in the brain. The concentration of that marker can then be assessed in relation to physical activity or fitness levels. In one such study, Liang et al<sup>71</sup> reported that more physically active older adults had lower concentration of amyloid plaques than their less-fit peers. Amyloid plaque is a putative marker for AD, where higher levels are thought to indicate a greater risk for memory impairment and dementia. Lower concentration of amyloid plaques in more physically active individuals suggests that physical activity may reduce the risk for AD by altering the deposition of amyloid in the brain. In a follow-up to this study, Head et al<sup>72</sup> examined whether greater amounts of physical activity would moderate the genetic risk for AD by examining amyloid concentrations using positron emission tomography. Consistent with their predictions, greater amounts of physical activity mitigated the buildup of amyloid, but did so primarily in individuals who were at a genetically heightened risk of developing AD.<sup>70</sup> This interesting finding suggests that other genetic factors may also moderate the effect of exercise on neurocognitive function.

In the gene that encodes brain-derived neurotrophic factor (BDNF), a single-nucleotide polymorphism alters the structure of the BDNF protein and influences the secretion of the molecule from the cell. Because exercise has been shown to upregulate BDNF gene expression, Erickson et al<sup>73</sup> hypothesized that physical activity may influence cognitive function differentially in individuals with one variant of the BDNF gene compared with the other variant. Consistent with their predictions, the risk genotype (Met carriers) showed greater improvements in working memory with physical activity than those in the nonrisk genotype (Val homozygotes). In essence, these

studies suggest that physical activity may have the capacity to mitigate some genetic effects on brain and cognition.<sup>74</sup>

In sum, there is a growing literature demonstrating that fitness and exercise are associated with improved brain function, primarily in the frontal cortex of older adults. These effects extend to individuals with a genetic risk for dementia, but there is a dearth of research examining functional or molecular effects of exercise in individuals with MCI or dementia or individuals with mood disorders. It is clear that other lifestyle and genetic factors are moderating the benefits of exercise on cognitive and brain function, but this field is in its infancy and more research is needed to determine which factors are most important in modifying the effects of exercise on neurocognitive function.

## CONCLUSION

The aging brain retains its capacity for neuroplasticity, and the existing evidence suggests that only modest amounts of physical activity or exercise are required to take advantage of this basic principle of the brain. There are several fundamental principles that emerge from the research described earlier. First, starting to exercise in late life is not futile. Even sedentary older adults can engage in physical activity and reap the cognitive and neural benefits of an active lifestyle. Second, exercise and physical activity can alter the brain in several ways, including the overall structure or morphology, functioning, and molecules associated with dementia. Third, only modest amounts of exercise are sufficient for detecting these effects. Brisk walking is the most common exercise in the studies described earlier, and these activities were only done for several months with significant effects. Finally, not all brain regions are affected equally by exercise. There appears to be regionally specific effects, with the prefrontal cortex and hippocampus being especially sensitive to physical activity.

Despite these basic principles that can be extrapolated from the research conducted thus far, many unanswered questions remain for future research to pursue. For example, we have yet to understand the persistence of the effects. That is, we do not know whether increased gray matter volume or improved white matter integrity persists after the completion of the exercise intervention or after some period of inactivity. It will be important for future research to conduct follow-up assessments to determine whether the effects dissipate or are retained after some interval. A second remaining question involves the types of exercise. Most of the studies described used brisk walking as the method of exercise; would similar effects be found with other forms of activity such as tennis, swimming, cycling, or resistance training? It is likely that the effects would be similar as long as the activity was aerobically engaging, but empirical data have yet to support or refute this claim. We also have a poor understanding of what age is optimal to start exercising. Although starting to exercise

in late life is not futile, there may be significantly larger effects maintained for longer periods if a habitual exercise routine is started earlier in life and maintained through late life. However, studies have yet to closely examine this question. Finally, although great strides have been made in understanding the link between exercise and neurocognitive function in cognitively normal adults, we have yet to fully understand its effects in cognitively impaired populations including persons with AD, depression, and Parkinson's disease. Translating the effects from the studies described earlier to a sample with clinically defined symptoms and disorders is necessary for prescribing exercise as a nonpharmaceutical method for improving brain health.

In sum, we can conclude from this review that exercise and physical activity hold great potential as inexpensive and effective methods of elevating cognitive function, improving brain health, and restoring brain function after atrophy or disease. The research described here is evidence that the aged brain retains its capacity for plasticity and that exercise is a potent modifiable lifestyle factor that could influence many different neurological and psychiatric conditions throughout the life span.

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