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Physical Activity, Brain Plasticity, and Alzheimer's Disease

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Abstract

In this review we summarize the epidemiological, cross-sectional, and interventional studies examining the association between physical activity and brain volume, function, and risk for Alzheimer's disease. The epidemiological literature provides compelling evidence that greater amounts of physical activity are associated with a reduced risk of dementia in late life. In addition, randomized interventions using neuroimaging tools have reported that participation in physical activity increases the size of prefrontal and hippocampal brain areas, which may lead to a reduction in memory impairments. Consistent with these findings, longitudinal studies using neuroimaging tools also find that the volume of prefrontal and hippocampal brain areas are larger in individuals who engaged in more physical activity earlier in life. We conclude from this review that there is convincing evidence that physical activity has a consistent and robust association with brain regions implicated in age-related cognitive decline and Alzheimer's disease. In addition to summarizing this literature we provide recommendations for future research on physical activity and brain health.

Introduction

The proportion of the world and of the U.S. population >65 years of age is expected to inflate over the next 40 years. It is anticipated that this growth will result in an increase in the prevalence of age-related diseases and impairments that will, in turn, lead to a rise in health care costs and family and caregiver distress. Alzheimer's disease (AD), or cognitive impairment more generally, is one of the more alarming age-related diseases leading to loss of personal identity and increased dependence on caregivers. Unfortunately, pharmaceuticals have been unsuccessful at preventing or treating dementia, prompting the search for nonpharmaceutical approaches such as cognitive engagement, dietary supplements, and physical activity.

Modifiable risk factors including education, smoking, mid-life obesity, hypertension, diabetes, depression, and physical inactivity contribute significantly to the risk of AD and only a 10–25% reduction in these factors could prevent as many as 3 million cases of AD worldwide (1). Unfortunately, the historic trend in AD prevention and treatment has been to be relatively dismissive of so-called nonpharmacological methods with the hope that there

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would be a pharmaceutical approach to prevention or treatment in the near future. In fact, large-scale interventions intending to examine the disease-modifying potential of nonpharmacological approaches are rarely conducted to the extent, breadth, or rigor of pharmaceutical trials. This may reflect a cultural (and human) desire for a magic pill to treat cognitive decline in addition to a misunderstanding of the complexity of the pathways by which lifestyle factors (e.g., physical activity) exert their effects on the endogenous pharmacology of the brain.

Because of the growing recognition of the importance of nonpharmaceutical approaches, there has been interest in delineating the role of physical activity to either prevent or delay the emergence of cognitive symptoms of AD. However, the continued skepticism that physical activity could have any lasting or important impact on brain health has led to confusion on the part of both scientists and clinicians. There is confusion about the strength and consistency of the effects of physical activity and also where the current gaps in knowledge are that need to be addressed by future research. In this review, we summarize the research examining the effect of physical activity and exercise on cognitive and brain outcomes in late life, the epidemiological evidence that links physical activity to dementia, and the pathways and moderators of the effect of physical activity on brain health. Our objective is to describe the evidence in favor of the promising effects of physical activity in addition to highlighting the need for future research.

Physical Activity and Dementia: Epidemiological Results

Epidemiological research shows a consistent relationship between higher physical activity levels and a reduced risk of developing dementia (2–4). In a meta-analysis of 16 prospective, epidemiological studies on the incidence of neurodegenerative disease, engaging in more baseline physical activity reduced the risk of developing all-cause dementia by 28% and of developing AD by 45%, even after controlling for confounding variables (5). Physical activity was not found to protect against incidence of Parkinson's disease, although only three such studies were included in the analysis.

Epidemiological studies differ widely in the length of follow-up for the assessment of dementia onset. For instance, in the aforementioned meta-analysis, the studies varied in follow-up from 3–30 years with the majority examining dementia incidence within 10 years of baseline. However, there has been increased interest in examining whether earlier engagement in physical activities more strongly protects cognition than beginning an exercise regimen later in life. Middleton and colleagues (6) investigated the relationship between late-life cognitive impairment and self-reported physical activity across the lifespan in a multicenter, prospective, observational study of women aged 65 and older.

Participants were asked about the frequency of low-, moderate-, or high-intensity physical activity using a modified Paffenbarger questionnaire, a valid and reliable questionnaire of engagement in physical activities that assesses activities such as walking, gardening, playing tennis, or dancing. Physical activity was retrospectively reported for teenage, age 30, age 50, and late-life frequencies. This study found that physical activity at all four timepoints was associated with reduced odds of developing cognitive impairment, defined by a score of at least 1.5 standard deviations below the mean on the modified Mini-Mental State Examination (mMMSE), a measure of global cognitive ability. When all timepoints were analyzed together, physical activity as a teenager was associated with the lowest odds of cognitive impairment. However, women who were physically inactive as teenagers but who then became active in midlife had lower odds of developing cognitive impairment than those women who remained inactive into late-life. These data suggest that engagement in physical activity earlier in life has the strongest effect on global measures of cognitive health, but

increased engagement in physical activity later in life can still mitigate the risk for cognitive impairment.

The majority of studies agree that engaging in more activities reduces the risk of developing dementia. However, many of these studies are limited in that they utilize self-report assessments of physical activity. Self-report measures often correlate at only low to moderate levels with objective measures of total daily physical activity (7). Self-report assessments may be less accurate because they may fail to capture nonintentional activity throughout the day such as fidgeting, pacing, and other low-intensity activities. Self-report measures are also prone to social desirability biases, which could artificially inflate the rates of participation in physical activity and thereby increase noise in the data. It is likely that correlations between self-reported physical activity and objective measures are even worse in cognitively impaired populations.

In order to compensate for this measurement limitation, researchers are now employing objective measures such as actigraphy to assess physical activity. Actigraphs are worn on the wrist, waist, or ankle, are similar to a watch, and are relatively easy to utilize in a research setting. One such study by Barnes and colleagues (8) used actigraphy in a cross-sectional study of older women. As compared to women in the lowest movement quartile, those in the highest quartile performed better on both a global cognitive test (MMSE) and a measure of executive control, even after controlling for health behaviors and physical ability. Interestingly, self-reported blocks walked only modestly correlated with actigraphy data ($r = 0.26$). In another study using actigraphy, Buchman and colleagues (4) found that persons with the lowest baseline physical activity had more than a 2-fold increased risk of developing AD 3.5 years later as compared to those engaging in the highest level of physical activity. This relationship remained even after adjusting for self-reported physical, social, and cognitive activities. Similar patterns emerged when using the gold standard objective measure of physical activity, activity energy expenditure (AEE) as measured by doubly labeled water (9). In this prospective study of incident cognitive impairment, participants in the highest tertile of AEE exhibited the lowest odds of developing cognitive impairment at the 5-year follow-up. When using self-reported physical activity, which only correlated slightly with AEE ($r = 0.19$), there was no difference in odds of developing cognitive impairment between the tertiles of activity groups. Even simpler objective measures such as assessing physical fitness via balance have been found to predict development of mild cognitive impairment (MCI) and AD after 12 years, whereas self-reported physical activity did not show the same predictive power (3). In sum, objective measures of physical activity are more sensitive to long-term changes in cognitive status than self-report questionnaires and show a strong relationship between higher physical activity and a reduced risk for cognitive impairment.

Although it appears that physical activity may have the capacity to moderate the trajectory of cognitive impairment, the role of physical activity in persons already experiencing pathological impairment is less clear. Preliminary studies show that obtaining objective measures of physical activity in cognitively impaired populations is feasible (10). For instance, fitness levels positively relate to whole-brain and white matter volume in patients with early-stage AD (10). In one of the few randomized, controlled trials conducted on cognitively impaired participants, 24 weeks of physical activity led to improvements in global cognitive functioning as compared to a usual care control group (11). This improvement even manifested in MCI patients already experiencing cognitive decline. Interestingly, participants who were noncarriers of the apolipoprotein epsilon 4 (Apoε4) allele improved the most over the 24 weeks. These benefits persisted for 6 months after the trial had finished, showing a long-term effect of the exercise intervention. Although this field is in its infancy, it appears that physical activity may be a feasible way to treat

cognitive decline in the face of pathology. Continued research on the strength, consistency, and dose-response relationship is needed in order to safely disseminate physical activity as a treatment for cognitive impairment.

Physical Activity and Brain Aging: Neuroimaging Results

The extensive and compelling epidemiological literature described above argues that increased physical activity may be an effective method for reducing the risk for cognitive impairment. Because there appears to be a consistent and robust effect of physical activity on risk for AD, it is reasonable to predict that physical activity may also have a noticeable effect on biomarkers associated with cognitive decline and AD including *in vivo* neuroimaging measures. Such a finding would strengthen the argument for a link between physical activity and AD but would also provide a lower-level biological platform for understanding the pathways by which physical activity exerts its effects on cognitive function.

Several neuroimaging studies have taken an epidemiological perspective to examining the association between physical activity and brain health and have found that greater amounts of self-reported physical activity earlier in life are associated with greater brain volume later in life (12,13). For example, in 1989– 1990 the Cardiovascular Health Study conducted in Pittsburgh, Pennsylvania recruited 1,479 ambulatory adults >65 years of age into a longitudinal study on the prevalence and incidence of cardiovascular disease. In this study, information about lifestyles, habits, and physical function were collected including self-reported measures of physical activity. One of the measures of physical activity was the number of blocks walked on average per week. Approximately 9 years after this initial testing session, these same subjects were recruited to participate in a brain magnetic resonance imaging (MRI) study in which high-resolution brain images were collected and details about regional gray matter volume were calculated. Of the original sample of 1,479 participants, 516 returned for a follow-up MRI and 299 of those were cognitively normal based on a neuropsychological evaluation. The brain images from these 299 cognitively normal adults were then used in an analysis to determine whether participation in greater amounts of physical activity 9 years earlier would be predictive of regional estimates of gray matter volume later in life (12). It was found that greater amounts of walking was associated with greater gray matter volume 9 years later in several brain areas such as the frontal cortex, parietal cortex, and temporal cortex including the hippocampus. The hippocampus is important in memory formation and is a region intimately linked to memory impairments and AD. Hence, it was reasoned that greater gray matter volume in the hippocampus may be associated with a reduced risk of AD. To test this hypothesis, the 299 participants returned 4 years later and received another neuropsychological evaluation. From this sample, 183 remained cognitively normal, whereas 116 were diagnosed with either MCI or dementia. It was found that greater gray matter volume in several brain areas including the hippocampus were associated with a reduced risk of cognitive impairment.

Therefore, greater amounts of physical activity were associated with greater gray matter volume 9 years later which, in turn, was associated with a 2-fold reduced risk of developing cognitive impairment 4 years later. These results remained significant even after controlling for several potentially confounding variables such as age, mobility, and hypertension. The importance of these results, and their consistency with the epidemiological literature described above, are important in that they linked for the first time the association between physical activity and risk for AD with greater gray matter volume.

This study and others (13,14) suggest that even modest amounts of physical activity may modify the size of brain areas that typically atrophy and shrink in late life, thereby delaying the onset or prevention of AD. Yet, one limitation of the studies described above is the use

of subjective, self-reporting instruments to measure physical activity. As described in the section on epidemiological findings, self-report assessments of physical activity have a limited scope and are subject to social desirability biases that could confound interpretations and significantly reduce effect sizes. Objective measures of physical activity and aerobic fitness may be better suited to capture associations with AD or brain atrophy. For example, one study objectively measured aerobic fitness levels in 165 adults between 59 and 81 years of age and used high-resolution MRI scans to quantify the size of the hippocampus (15). It was found that individuals with higher aerobic fitness levels had larger hippocampal volumes even after controlling for variance associated with age, gender, and years of education. Furthermore, higher fit individuals performed better on a spatial memory task that was also associated with the size of the hippocampus. Using a statistical modeling approach to assess the associations between variables, the authors found that the link between aerobic fitness and better memory performance was mediated by the size of the hippocampus, indicating a direct role of the hippocampus in enhanced memory function associated with higher fitness levels.

Several other studies have also reported that objectively measured aerobic fitness is associated with brain volume measures in populations already experiencing cognitive decline. For example, higher aerobic fitness levels were associated with larger total gray matter volumes (10) and greater medial temporal lobe volume in aerobically fit older adults in the early stages of AD (16). These results highlight several key principles on the influence of physical activity and aerobic fitness on the aged brain: a) it appears that regions susceptible to age-related atrophy and that lead to AD are larger in individuals engaging in more physical activity or who have higher fitness levels, b) the links between higher cardiorespiratory fitness levels and elevated cognitive function are mediated by greater gray matter volume, and c) adults experiencing normal age-related cognitive decline and those experiencing more precipitous rates of decline (e.g., early AD) both show associations between physical activity, fitness, cognitive function, and brain volume. These key principles beg the following question: could a randomized exercise intervention increase the size of brain regions implicated in memory function and AD?

The studies described above have been either cross-sectional or longitudinal in nature. Such studies can be informative about the presence or absence of associations, but lack the ability to make strong causal claims between physical activity, fitness, and brain health. That is, these prior studies fail to address the following question: could starting an exercise regimen alter the size of brain regions (e.g., hippocampus) and reduce the risk of developing AD? Fortunately, several recent studies provide some answer to the question of whether the size of brain regions can be modified by participation in physical activity. For example, results from one study suggest that modest amounts of moderate intensity exercise for 1 year is effective at increasing the size of the anterior portions of the hippocampus (17), indicating a causal link between aerobic exercise and hippocampal volume. In this study, 120 adults were randomized to either a walking group or to a stretching and toning control group. These groups were identical except that the walking group participated in moderate intensity walking for about 30–45 min per day, 3 days per week, whereas the stretching and toning control group participated in low-impact toning exercises for the same amount of time as the walking group. Both groups received the same amount of social interaction and the same amount of health instruction from a trained exercise physiologist so that the primary manipulation was the walking component of the intervention. High-resolution brain MRI scans were conducted before randomization, after 6 months, and again after completion of the 1 year trial. An automated segmentation algorithm was used to identify the size and shape of the hippocampus at all timepoints. Although the walking and stretching and toning groups began the intervention with comparable volumes of the hippocampus, the stretching and toning control group showed about a 1.5% decline in the size of the structure over the 1-

year period. This rate of decline is consistent with other longitudinal studies of aging indicating that there is between a 1 and 2% annual rate of decline in the size of the hippocampus in nondemented individuals >50 years of age (18). On the other hand, individuals in the walking group demonstrated a significant 2% increase in the size of the hippocampus and this effect appeared to be isolated to the anterior portions of the hippocampus. In summary, this study finds that beginning an exercise regimen in late life is capable of altering the size of the hippocampus, a brain structure implicated in AD and memory impairment, and demonstrates the modifiability and plasticity of this structure even in late adulthood.

The results described above on physical activity, fitness, and brain health are strikingly similar to one another and indicate that not only does the brain remain plastic throughout the lifespan, but that the hippocampus in particular is sensitive to the effects of fitness and physical activity. Research, however, has also found that brain areas other than the hippocampus are also associated with physical activity and cardiorespiratory fitness. For example, the size of the prefrontal cortex is increased in older adults after 6 months of participation in an exercise intervention (19). Cross-sectional research using objective measures of cardiorespiratory fitness also finds that higher fitness levels are associated with greater prefrontal cortex volume (20) and that greater prefrontal cortex volume mediates the link between higher fitness levels and elevated executive function (21). These associations and effects of physical activity are consistent with the longitudinal study described earlier demonstrating that participation in greater amounts of walking earlier in life was associated with greater prefrontal cortex volume later in life (12). Together this literature suggests that the prefrontal cortex, like the hippocampus, is sensitive to the effects of physical activity, cardiorespiratory fitness, and exercise throughout the lifespan.

Several studies have also reported that the functional dynamics of the brain are affected by participation in randomized exercise interventions. For example, a group of older adults were given a selective attention task while being scanned in an MRI and brain activation patterns were assessed as a function of cardiorespiratory fitness levels and participation in a 6-month randomized physical activity trial (22). It was found that both higher fit adults and adults participating in the walking arm of the intervention showed increased activity in brain areas that support selective attention processes such as the prefrontal and parietal cortices, which was accompanied by better performance on the task.

Similarly, continued participation in physical activity appears to have long-term consequences on age-related brain activity patterns. For example, in a follow-up of a randomized trial of physical activity, those older adults who retained their physical activity routines had greater activity patterns in the prefrontal cortex compared to adults failing to retain their participation in physical activity (23). Yet, other studies have focused on the connectedness and cohesiveness of the brain activation patterns. Although older adults often show impaired or reduced brain connectivity, physical activity increases the connectivity between frontal and hippocampal regions (24–26). In short, there is an emerging consensus that task-evoked activation patterns (27), intrinsic functional connectivity (24–26), and hippocampal blood flow (28) are influenced by participation in physical activity and could be directly reducing the risk of developing cognitive impairment or AD.

There is also emerging evidence that physical activity influences more than just the brain's vascular system in late life. For example, in a group of older adults, an objective measure of cardiorespiratory fitness was acquired along with an *in vivo* measure of N-acetylaspartate (NAA), a putative measure of neuronal viability and metabolism. NAA is important because it is considered to be a direct measure of the central nervous system that is independent of the brain's circulatory system, minimizing the possibility that an association between fitness

and NAA is attributable to differences in brain vascularization. In addition, there are age-related reductions in the concentrations of NAA throughout late life that are especially prevalent in AD. Interestingly, in this study, higher aerobic fitness levels offset the age-related reduction in NAA levels (29) and higher NAA levels were associated with better working memory performance. This indicates that higher NAA levels in more aerobically fit individuals may have functional consequences for cognitive function in late adulthood.

Thus far, we have summarized the extant literature finding associations between physical activity and cardiorespiratory fitness with risk for dementia, brain atrophy, and brain function. However, in addition to the association between cardiorespiratory fitness and NAA described above, there have been several other studies demonstrating that physical activity offsets genetic risk factors for AD (30). For example, in a functional MRI study using a semantic memory paradigm, older adults were categorized into groups who were genetically at high risk for developing AD or at a genetically lower risk for developing AD. These genotype groups were then subdivided into groups who reported engaging in either higher amounts of physical activity or lesser amounts. They found that higher amounts of physical activity were more strongly associated with brain activation in individuals at the highest genetic risk for AD than those at a lower genetic risk. Hence, participation in greater amounts of physical activity may offset the genetic risk associated with AD, at least for brain activation outcomes. However, other recent evidence suggests that this same moderating effect of physical activity on risk for AD may also extend to *in vivo* measures of amyloid deposition using Pittsburgh Compound B, a radioactive tracer that binds to β-amyloid (Aβ), a putative cause of AD (31,32). For example, although greater amounts of self-reported physical activity are associated with reduced levels of Aβ (32), the effect of physical activity is greater in individuals with a genetic susceptibility for AD (31). In sum, it appears that the benefits of physical activity on brain health may be greater in individuals at a heightened risk for AD.

Finally, there is emerging research on the molecular pathways by which greater amounts of physical activity lead to improved brain health and elevated cognitive function. For example, brain-derived neurotrophic factor (BDNF) is a molecule produced and secreted in several brain areas and is involved in long-term memory formation. Physical activity increases BDNF levels (33) and, in at least one study, increased hippocampal volume with exercise was associated with increases in serum-derived BDNF (17). Although speculative at this time, it is possible that physical activity is increasing the production of BDNF, which enhances memory formation by influencing the integrity of the neural circuitry in the hippocampus. This pathway is especially alluring given that BDNF levels decrease in later ages and with AD (33). It is possible that increased BDNF is at least partially mediating the cognitive benefits that emerge from physical activity in humans.

Conclusions and Recommendations for Future Research

There is now a convincing body of evidence suggesting that physical activity reduces the risk for AD and age-related cognitive decline more generally. Furthermore, neuroimaging studies suggest that physical activity may reduce the risk for cognitive impairment by increasing the size of brain areas involved in memory formation, increasing functional brain activity in frontal and hippocampal brain regions and by offsetting the genetic and molecular risk factors associated with AD such as elevated levels of Aβ and lower levels of NAA. Overall, this research provides some compelling arguments for the effectiveness of physical activity to improve brain health throughout the lifespan and especially in late life when the risk for cognitive impairment is at its peak.

A review of this literature allows us to make some general claims: a) the brain retains its natural capacity for plasticity well into late adulthood and participation in physical activity

can take advantage of this characteristic of the brain, b) relatively modest amounts of physical activity is sufficient for improving cognitive function and increasing the size and function of different brain areas, and c) even in individuals at a higher risk for developing cognitive impairment, greater amounts of physical activity are associated with a reduced risk for AD and a reduction in pathological symptoms associated with AD. Despite these well-established associations, there remain many unanswered questions that future research needs to address. First, there needs to be multisite physical activity interventions that continue for several years in a large sample of older adults to assess whether the *incidence* of AD is reduced by participation in physical activity. In this review it is clear that the evidence suggests that physical activity might be effective at reducing incident rates, but well-controlled randomized intervention studies have not yet been conducted to formally address this question. Second, there is little evidence about how much physical activity is necessary to observe long-term consequences on cognitive and brain health. In the studies described above, 6 months–1 year was sufficient for finding effects, but this amount may be dependent on the intensity of the exercise, type of exercise, population being studied, and particular outcomes of interest. In short, we still understand very little about the dose-response effects of physical activity on cognitive and brain outcomes. Finally, although animal research has outlined many of the possible molecular pathways by which physical activity exerts its effects on brain function, we know very little about the pathways by which physical activity reduces the risk for AD in human populations. These pathways may include changes in vascular markers, increases in growth factors, or changes in inflammatory pathways. Future research on physical activity would benefit from including these measures in their studies to better link the possible molecular pathways with functional and diagnostic outcomes in persons at risk for AD.

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