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The effect of exercise on cognition and memory and its applications to Alzheimer's Disease

Christopher S Lozano[1], BSc

1. The Royal College of Surgeons in Ireland, 123 St Stephen's Green, Dublin 2, Ireland

The benefits of exercise, particularly for cardiovascular disease are well-established. Recently, there has been much interest in the mainstream media about the use of exercise as both a treatment and preventative measure for neurodegenerative diseases that affect learning and memory, including Alzheimer's Disease. This mini-review serves to explore whether or not exercise can be used as a preventative measure and/or treatment to improve memory, especially in the context of Alzheimer's Disease. A literature search was conducted for both animal and human studies, which investigated the effects of exercise on cognitive measures. The evidence found does not provide a definitive conclusion. Animal studies show a strong relationship between exercise and memory performance and this is associated with increased neurogenesis in regions of the brains implicated in memory. Human studies have been less consistent; some studies have found modest improvements in cognitive measures like memory, particularly with aerobic exercise, while others have failed to show any effect at all. In the treatment of Alzheimer's Disease, again, studies of animal models have shown good evidence for a benefit of exercise, but this has not translated into humans. Nevertheless, large observational studies indicate that physical activity reduces the risk of developing Alzheimer's disease. The reason for the inconsistencies in humans is likely multifactorial and will require further research to investigate what modality of exercise is optimal, for how long, when it should be administered, and for which patient population aerobic exercise is most effective.

Introduction

An immense economic burden is placed on the global health care system due to neurodegenerative diseases. Collectively, diseases that affect cognition and memory are estimated to have had worldwide costs of over US$800 billion in 2015 and this figure is expected to breach US$1 trillion in 2018 (1). Diseases like Alzheimer's Disease (AD) are strongly linked to age and given the rise of the aging global population it is expected that the burden from these diseases will increase tremendously over time.

Disorders of learning and memory affect a region of the brain known as the hippocampus (2). The hippocampus is thought to be implicated in the formation and retrieval of memory.

Corresponding Author Christopher S Lozano 123 St Stephen's Green, Dublin 2, Ireland +353 (89) 606 1930 Christopherlozano@rcsi.com. **Keywords**: aerobic exercise, Alzheimer's Disease, learning, memory, novel treatments, resistance exercise
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Specifically, the hippocampus is thought to be involved in declarative forms of memory, which match a stimulus with a particular context, such as a location or behaviour (3). In a process known as neural replay, the hippocampus plays a role in the consolidation of short-term memory into long term storage in other regions of the bran (4). In AD, there is global atrophy of the brain, compared to age-matched controls and the hippocampus appears to be particularly affected (5). The aetiology of AD is complex and many theories exist. Some of these theories include the formation of toxic amyloid-beta and tau protein aggregates, and neuronal calcium dysregulation and lysosomal dysfunction, all of which contribute to neuronal death (2). The clinical consequence of this global and targeted atrophy in AD is cognitive impairment including deficits in working and long-term memory.

Currently, there is no cure for AD and other dementia-related conditions. While many new drugs to treat these conditions are on the horizon, many of them have failed to extend to the clinical trial stage (6). Perhaps it is time to look into alternatives to traditional therapies. Physical activity such as running, walking, and resistance training have all been proposed as either preventative measures or treatments to fill this gap. Not only would this approach be inexpensive and highly accessible, but it would also promote cardiovascular health. While physical activity has shown consistent benefits in animal models, the evidence is less conclusive in human trials. This mini-review explores the current state of research for the use of physical activity to enhance learning and memory with a focus on the prevention and treatment of AD.

Physical Activity in Animals

Exercise is known to influence many factors that are thought to be involved in learning and memory and this has been extensively studied in animals. Animal studies of physical activity have documented a correlation between physical activity and proliferative brain factors such as brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF) and Insulin-like growth factor-1 (IGF-1). In turn, these factors boost neuronal survival and enhance synaptic connections which have correlated with improved learning and memory (7). In recent years, research has shifted its focus towards refining which type of physical activity is most potent to stimulate these effects. One study compared the effect of voluntary versus controlled exercise in mice, finding that both lead to an increase in hippocampal neurogenesis in a dose-dependent manner and lead to improvement of spatial memory performance at a moderate level of exercise volume (8). These findings are consistent with an earlier study that found aged mice learned and retained a memory task better when they had access to a wheel for voluntary running, compared to age-matched controls (9). Furthermore, the aged mice who were able to exercise had an increase in neurogenesis and these newly-formed neurons morphologically resembled those of young mice. It is important to note, however, that not all types of exercise can convey these effects. A recent study of male rats compared the effect of various types of exercise on hippocampal neurogenesis and found that consistent with the prior studies, aerobic exercise such as running resulted increased neurogenesis. In the same study, higher intensity exercise styles such as high-intensity interval training (HIIT) and resistance exercise resulted in little to no effect (10).

Physical Activity in Humans

The benefit of exercise on cognitive performance and memory is well documented. A meta-analysis of 29 randomized controlled trials of aerobic exercise conducted between 1966 and 2009 found that participants on various aerobic exercise

protocols experienced improvements in attention, processing speed as well as memory, although the effects on short-term memory are not consistent (11). The studies analysed in this meta-analysis must have had adult (>18 years old) participants that were on a supervised aerobic exercise program (such as brisk walking or biking), a duration of treatment greater than one month and a non-aerobic exercise control group. An important caveat of this paper was that it only included three studies in which participants had cognitive impairment (all others included healthy adults only) and as such, its conclusions may not be generalizable to patients with cognitive disorders. An even more extensive meta-analysis with 29 acute and 21 long-term exercise studies of various designs found that both acute and long-term exercise had modest positive effects on short term-memory, although the effect was larger in the acute exercise studies (12). They also found that acute exercise had a moderate positive effect on long-term memory, while long-term exercise had no significant effect. The authors hypothesize that acute and long-term exercise, therefore, affect memory in two distinct mechanisms. The analysis was restricted to controlled trials with subjects greater than 18 years old participating in aerobic exercise at least twice per week for a minimum duration of at least 4 weeks. Unlike the other meta-analysis, however, none of the studies analysed had participants with a known history of cognitive impairment disorders.

Recent strong evidence for the link between exercise and cognition and memory comes from Erickson et al., who performed a randomized controlled trial of aerobic exercise versus stretching in men and women in their sixties with and without dementia (13). Participants were put on a one-year program involving either walking or non-aerobic stretching. Before the intervention, all patients received structural magnetic resonance imaging (MRI) scans of their brain as well as a baseline assessment of their spatial memory. The participants received follow-up MRI scans and the same spatial memory task at six months and one year into the intervention. This study found that those in the aerobic exercise group experienced an increase in the size of their anterior hippocampus on average and this correlated with improvements on the spatial memory. Greater improvements in fitness (VO2 max) also correlated with greater increases in hippocampal volume. This study is particularly valid because it cross-examines and demonstrates a correlation between several relevant factors. Not only did exercise correlate with improved memory performance and hippocampal growth, but these changes occurred with increased serum levels of BDNF, a factor that is important for triggering neuronal growth and proliferation in the hippocampus, suggesting that BDNF could be one of the underlying factors involved in these changes. Indeed, animal studies have demonstrated that factors released during exercise trigger BDNF expression (14) and that some of these factors also correlate with memory function in humans (15). In animals, it has been demonstrated that just one bout of exercise is enough to cause BDNF expression and this effect can be enhanced with long term regular exercise (16).

Exercise and Alzheimer's Disease

There is a well-established body of literature demonstrating the benefits of exercise in treatment of AD in animal models. These studies, which use transgenic mice carrying one of the mutations found in familial forms of AD such as amyloid precursor protein and presinilin-1, have demonstrated that aerobic exercise has delayed the signs of disease progression (17) and rescued animals from spatial memory deficits (18). The extension of these benefits to humans is unclear. On one hand, observational studies suggest that physical activity reduces the risk of developing

developing AD (19). Similarly, evidence suggests that physical inactivity is a risk factor for developing AD (20). What is still unclear from these studies, however, is whether or not physical activity is the key factor involved or if a confounding variable is implicated. It is likely that those who have higher physical activity tend to lead healthier lifestyles in general. Conversely, physical inactivity can exacerbate existing neurovascular pathologies - interplaying with hypertension, hypercholesteremia and diabetes, potentially contributing to neurodegeneration. In any case, the evidence shows that people who are physically active have a reduced risk of developing AD, but what about using exercise as a treatment in existing AD? A 2016 randomized controlled trial of exercise in patients with Alzheimer's disease failed to show a positive effect on cognition and quality of life (21). Similarly, a study conducted in 2017 investigated a 26-week protocol of aerobic exercise in early-AD patients failed to show a significant effect on memory function, however it did show a modest improvement in functional ability (Disability Assessment for Dementia) and depressive symptoms (Cornell Scale for Depression in Dementia) in these patients (22).

Additional considerations

It appears that not all exercise conveys the same effects. For example, there is conflicting evidence as what effect resistance-type exercise has. In one study of AD patients, a 16-week resistance training protocol resulted in no improvement in cognitive function as quantified on a mini-mental state exam (23). On the other hand, a six-month study of medium - and high-intensity resistance exercise in an elderly group found modest improvements in cognition as quantified by a different scale, the Stroop Test (24). To support the idea that resistance exercise may be protective for AD, a review by Balsamo et al. found multiple instances of studies in which muscular strength correlated with cognitive and memory performance (25). In a cohort of approximately 900 elderly people, baseline muscle strength was significantly associated with a decreased risk in developing AD (26).

There is yet to be a consensus in the literature as to what form of exercise and what kind of regimen is most effective for the prevention and treatment of cognitive disorders (27). Efficacy must also be weighed against the practicality of such interventions. Exercise protocols that are intense or take up a lot of time may not feasible, especially in the case of AD where patients are elderly. One activity type that appears to carry a benefit while remaining feasible in older patients is the simple of act of walking (28, 29).

Another important consideration to make is the cost of treatments for diseases like AD. An exercise-based treatment could lessen the economic burden if it could prove to be effective. Current treatments are both expensive and have variable efficacy, but more importantly are largely symptomatic treatments only; these medications fail to stop the progression of the disease (30). There are disease-modifying agents on the horizon, though it is estimated that these drugs will not be on the market for about another decade (31). Furthermore, the cost of developing these types of drugs is steep. For these reasons, it would be prudent to develop an exercise-related treatment that could be both cost-effective and highly accessible. If not a treatment, surely exercise could be incorporated as a preventative measure. Several studies have noted that mid-life exercise does decrease the risk of cognitive impairment later in life (32–34).

Conclusion

There has been extensive research on the use of physical activity to enhance learning and memory.

While there is a clear link between these factors in animal studies, human studies have shown only modest results. Any form of physical activity will likely impart some benefit, although further research will be required to fine tune exercise protocols before they can be used an effective treatment for AD.

Author Disclosures

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