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Types of exercise in Relation to the Risk Reduction and Treatment of Alzheimer's Disease

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ABSTRACT

As the world progressed, Alzheimer's Disease (AD), a neurodegenerative disease, became an increasing issue we face. Unfortunately, as there are no current viable results that came from pharmaceutical research, scientists began investigating other factors that could be altered to prevent and even treat AD. Physical and mental exercises were discovered as effective measures to prevent and even a potential intervention within the treatment of AD. Some examples of physical exercise include aerobic exercise and resistance training, whereas mental activity involves leisure activities and learning. The effects of the types of exercise were reviewed in the manuscript. The exercise in relation to aging is discussed. An in-depth discussion over the hippocampal volume, cellular and molecular response and Cognitive Reserve (CR) was taken place. The types of physical activities were reviewed in terms of their effectiveness. We concluded that physical exercise, especially aerobic exercise is beneficial in terms of risk reduction and treatment of AD. However, more research on the types of exercises beneficial for people living with AD, and different factors (sleep, stress management, etc.) could be taken into practice while discussing the implications of exercise on the risk reduction and treatment of AD.

Introduction

Alzheimer's disease (AD) is a neurological illness that mostly affects older people. According to the Alzheimer's Association, an estimated 13 percent of Americans over the age of 65 are diagnosed with AD, with the proportion rising to 45 percent for those aged 85 and older (Alzheimer's Association, 2012). It indicates a deterioration in cognitive performance and memory impairment. Memory loss is one of the most common symptoms of Alzheimer's disease. As Alzheimer's disease progresses, it can lead to a loss of ability to communicate and respond to the surroundings. Parts of the brain that control ideas, memories, and language are affected by dementia. In older adults, a decreased hippocampal volume is noticed, which generates worsened memory performance. (Erickson et al., 2010) The disease is defined by the abnormal buildup of amyloid plaques, which are composed of aggregated β-amyloid protein (Aβ) and neurofibrillary tangles (NFTs) formed from abnormally processed tau protein (Mondragon-Rodriguez et al., 2010). Within the boundaries of the amyloid plaques, Aβ is thought to play an important role that leads the neuronal death within the late stage of AD (Mattson, 2004).

Despite the stress on the concept of providing therapies focused on amyloid, the effectiveness of these therapies remains low within phase 3 human trials. In fact, over 200 research projects had been deserted (Atri, 2019). The accepted clarification for the failures of clinical trials for AD includes the late administration process within the disease development (Gauthier et al., 2015).

Scientists began to look for other ways outside of pharmaceutical therapies and studied other risk factors for potential methods to conduct prevention and intervention toward AD. One of the most well-known risk factors associated with AD is age. However, other risk factors associated with AD are low educational level, diabetes and genetics. In addition, other factors in several studies discovered that obesity, high cholesterol, hypertension, and diabetes are connected with the increased risk of dementia (Kloppenborg, van den Berg, Kappelle, & Biessels, 2008). In addition,

depression and smoking were identified to be risk factors associated with dementia. (Plassman, 2010) This was later affirmed by another review, which found that these risk factors together contributed to an approximation of 50% for all the causes of AD (Barnes & Yaffe, 2011). Exercises began to appeal to themselves as a low-cost and low-risk experiment that could potentially alter the risk of AD (Rolland, Abellan van Kan, & Vellas, 2008).

Evidence suggests the risk reduction for AD is plausible. This takes place from the modifiable risk factors, which are identified as cardiovascular or lifestyle habits (Crous-Bou, Minguillón, Gramunt, & Molinuevo, 2017). In addition, mental exercises such as reading, writing, and artistic creation are considered to be beneficial for the prevention and treatment of AD (Scarmeas, Levy, Tang, Manly, & Stern, 2001). Those who reported a higher engagement within leisure activities are statistically proven to have a lower number of diagnosed with AD (Wilson et al., 2002). Later reports with years of data showed how the risk of AD is higher for those who had fewer years of education (Ott et al., 1999).

One of the most prominent factors discussed within the scope of Alzheimer's Disease is the activities for risk reduction. In this review, we are mainly discussing how physical and mental exercise play into account in AD prevention and treatment.

Physical exercise in relation to Physiologic brain aging

Lifestyle changes include physical activity and socialization as factors that contribute to the prevention of AD (Jedrziewski, Ewbank, Wang, & Trojanowski, 2014). Throughout history, Physical exercise has been connected with increased cognitive function. One of the first studies that discovered the beneficial relationship between exercise and cognitive function was in 1978 when older active males were proven to report a much healthier result than their sedentary counterparts, including cognition (Spirduso & Clifford, 1978). In 2011, evidence showed how aerobic exercise was demonstrated to be able to increase the size of the hippocampus and significantly ameliorate memory (Erickson et al., 2011).

An analysis created by Hamer & Childa explained how there are three different factors of which exercise provides a neuroprotective effect. The same meta-analysis concluded with more than 16 studies, with over 160,000 participants finding a reduction of 45% due to regular physical exercise (Hamer & Chida, 2008). A later meta-analysis in 2019 discovered that there is a positive correlation between increased cognitive function and physical activity and exercise. The analysis found that intervention toward exercise for up to 2 h per week with no more than 30 min per time showed a greater effect on improving cognition (Jia, Liang, Xu, & Wang, 2019).

However, some criticism related to these studies is inclusiveness. The majority of the meta-analyses analyzed were limited to English and Chinese. Other studies from different languages were not captured, which could have information that may change the conclusion of the meta-analyses. In addition, there were no clear standards for what type of activities were conducted during the experiments. For instance, it was pointed out how in the 13 included studies of the analysis made by Jia, Liang, Xu & Wang, only one carried out moderate-to-high-intensity, and 11 studies are aerobic exercises. However, there was no clear distinction as to what extent the aerobic and anaerobic exercises and the difference between the low, moderate and high-intensity exercises contribute to cognitive function improvement within the conclusion.

Despite the criticism, the point made by the studies was clear in its conclusion. The exercise programs generally consist of low-moderate-exercise, that are conducted for around 30-45 minutes at around 2 hours per week to create a benefit in terms of cognitive function for older adults.

In addition, aerobic exercises were proven to be the most beneficial cognitive function. A study in 2015 researched volunteers aged 50-80 years with cognitive impairment. The aerobic group was treated with cycling training with 70% of maximal intensity for 40 min per day, and 3 days per week for 3 months. The results had shown significant improvement for the aerobic group, with the Quality-of-Life Alzheimer's Disease score and the plasma Apo-a1 level significantly increased ($P<0.05$) (Yang et al., 2015).

Mental exercise in relation to Physiologic brain aging

Participation in intellectually challenging activities demonstrated a lessened decline over time for older adults without dementia (RA;, 2012). Another research developed in 2003 discovered that those who have music, board games, reading and dancing as a hobby are generally at lower risk for dementia (Verghese et al., 2003). These findings support the theory that cognitively stimulating activities protect people from age-related decline, where the subjects who scored high on cognitive activities had a 63% lower risk of dementia than other subjects (Verghese et al., 2003).

Education is also measured to be a component of mental exercise that influences the risk of dementia. Studies reveal that a higher level of education shows a lower correlation within the buildup of Aβ, which led to conclusions about how increased education develops brain resistance again the Aβ pathology (Gonneaud et al., 2020).

Despite the number of studies proving the positive correlation between activities that involve thinking and brain usage, there's no clear justification as to which part of the brain helps alleviate or even reverse the physiologic brain aging. One of the potential factors could be the lack of animal model experiments to prove the theories - it's virtually impossible to involve animals to read/play music, which are some examples of mental exercise.

In addition, despite the stress on the mental exercises for physiologic brain aging, there's no engagement on the specific types of leisure activities/mental exercises within the studies. For instance, in some studies, music playing, reading, and knitting are included, whereas other activities such as crossword puzzles are encouraged within other studies. There are potential factors where music and crossword puzzles influence different parts of the brain towards the prevention and treatment of dementia, but they are included within the category of mental exercise.

Mechanisms of activation within the exercises

Hippocampal Circuits

Hippocampal volumes are connected with improved cognitive functioning. The physical exercises had shown an improvement in the hippocampal volumes (Erickson et al., 2011). Both the mouse model and human studies demonstrated the effectiveness of physical exercise on the hippocampal volume. While analyzing the research, the left hippocampal volume significantly increases in comparison to the control groups in the research (Firth et al., 2018). On the activation within the exercise, circulation is encouraged from the skeletal muscle, which enacts the brain. The FNDC5 is expressed within the brain, which demonstrates the increase in the response of the hippocampal gene expression (Wrann et al., 2013). In addition, running-induced exercises were demonstrated to be helpful toward the pattern separation of the brain.

Many of the successful instances involve aerobic training. The majority of the research discussed running and fast-paced walking. Under normal physiological settings, adult hippocampus neurogenesis (AHN) has been linked to cognitive processes like learning, memory, pattern separation, and cognitive flexibility. Hippocampal neurogenesis is increased upon exercise, in which novel neurons were produced continuously within the hippocampal dentate gyrus (van Praag, Christie, Sejnowski, & Gage, 1999). AHN enhanced by exercise is linked to the development of the hippocampal function, which ultimately benefits memory and beyond (Marlatt, Potter, Lucassen, & van Praag, 2012). Because they have a functional synaptic connection with the current neural circuit and specific morphological properties of the dendritic spine for promoting synaptic potentiation, newly formed mature neurons are thought to play a role in memory formation. Evidence that the neurons are selectively engaged during hippocampal-dependent behavioural tasks supports their crucial role in memory processing (Kee, Teixeira, Wang, & Frankland, 2007).

Cellular and molecular response

Postexercise concentrations of peripheral blood were connected to improvements within the executive functioning of the brain following resistance to physical exercise (Tsukamoto et al., 2016). Because it can cross the BBB with the help of monocarboxylate transporters, peripherally (e.g., in the muscles) produced lactate is expected to be used as 'fuel' for cognitive processes. Furthermore, the release of serum BDNF may be triggered by peripheral lactate, but this link appears to be highly dependent on the proper selection of resistance exercise variables. BNDF is proven to be significantly contributing to changes in cognition and performance (Leckie et al., 2014).

Cognitive Reserve (CR)

Within the scope of education, cognitive reserve is a term explaining the size of the brain, and the synaptic density in the cortex. Evidence suggests that while having a greater cognitive reserve, there's proven to be a reduced risk of AD. It is impossible to directly detect cognitive reserve since it is a theoretical concept. As a result, proxy variables that are descriptive of lifetime experiences, such as educational and vocational accomplishment, intellect, and level of interest in lifestyle or leisure activities, are most typically used to quantify it (e.g., socially, physically, and cognitively stimulating activities) (Richards & Deary, 2005). Reviews suggest that the CR impacted within the years of education. In addition, CR shows the relationship between the neural reserve and AD biomarkers (Pettigrew & Soldan, 2019). Current evidence suggests that CR heavily influences the brain volume, and white matter integrity, which are direct insights of AD (Solé-Padullés et al., 2009).

Types of physical and mental exercises engaged with risk reduction and intervention Ideas

Physical Training

Aerobic exercise

As aerobic exercises are slowly considered to be an effective measurement, many studies began to evaluate the validity of aerobic exercises. A study conducted in 2017 looked if aerobic exercise will benefit ability. The study was a 26-week random trial that compared aerobic exercise vs. non-aerobic exercise. It concluded that exercise-related improvements in cardiorespiratory fitness were linked to better memory and less hippocampus atrophy, implying that cardiorespiratory fitness improvements are significant in promoting brain benefits. (Morris et al., 2017) Many more studies ensue, which all suggest the positive correlation between the increased hippocampal volume, and in some cases, reversing hippocampal atrophy in older adults (ten Brinke et al., 2014) (Erickson et al., 2011) (Baker et al., 2010).

One of the significant aerobic exercises is the treadmill or running exercise. Within the research on the animal model of AD, in a study made in 2017, Lu took the mouse models of AD, and underwent treadmill exercise, which was 30 min a day and 5 days per week for 4 weeks. Lu found that the treadmill exercise strongly maintained hippocampal-dependent cognitive functioning. In addition, the amyloid-β accumulation and tau phosphorylation was suppressed. The same exercise also suppressed oxidative damage and oxidized DNA damage (Lu et al., 2017). Another article concluded that running-induced changes provide beneficial effects on the hippocampus, where factors such as neural circuitry, neurotransmitters, and vasculature were ameliorated (Cooper, Moon, & van Praag, 2017). This claim was further supported by Cho in 2015, where the 12-week treadmill running for the mouse reversed the cognitive declines and improved the tau pathology, in addition to the suppression of the PSD-95 in the hippocampus. (CHO et

al., 2015). It is proven that higher levels of training increase hippocampal volume and alleviate hippocampal decay, which correlates to superior memory function.

Resistance training

Equipment was used for resistance training. One of the most used pneumatic resistance machines is Keiser Sports Health Equipment, used in high-intensity training. (Broadhouse et al., 2020)
The study, which was conducted in 2014, found positive outcomes for resistance training and cognitive function. With the ADAS-Cog increased at 6 months, Normal ADAS-Cog scores at 48% compared to 27% pre-resistance training (Fiatarone Singh et al., 2014).

Changes in muscle strength are closely linked to brain functions. For instance, Nakamoto et al., 2011 discovered how the strength of the knee extensors has a positive correlation with cognitive function in elderly men. (Nakamoto et al., 2011) Findings further affirmed how factors such as lower limb power have a positive cognitive change in the normal population (Steves, Mehta, Jackson, & Spector, 2015).

Sets and frequency were recommended for resistance training. Resistance training should be done three times a week, which was proven to be more efficient than two times a week (Herold, Törpel, Schega, & Müller, 2019).

Cognitive Exercise

Within the studies analyzed, the majority of the leisure activities consisted of the following 12 methods: Physical conditioning, going to movies, restaurants, sporting events, reading magazines, newspapers, or books, watching television or listening to the radio, doing unpaid community volunteer work, playing cards, games, or puzzles, going to a club or centre, and going to church, synagogue, or temple. There is no current research on the particular format of leisure activities that contribute to AD the most. In addition, the twelve variables are not used together, where some studies only included cards, books and puzzles, and others even included social interactions as a type of leisure activity.

Conclusion

Changes in lifestyle are needed for the prevention and treatment of AD. The changes could be administered in both mental activities, which include leisure exercises and education, and physical activities, which include aerobic exercises and resistance training. For now, there's little evidence on how leisure exercises specifically influence the prevention of AD, though multiple research affirmed the link between the two subjects. However, physical and mental activities are proven to have positive outcomes. Overall, current evidence shows that efforts to increase social and educational opportunities can have a positive impact on cognitive and brain health in the elderly. For example, policies that provide learning opportunities for the elderly community (adult classes, lifelong learning classes, local libraries, etc.) and promote social connections and physical activity (green areas, pools, sidewalks, bicycle lanes, etc.) can support cognitive well-being. Not only these opportunities could be given to the elderly, but to those who wish to hinder or reduce the risk for AD. This is affirmed by Brookmeyer, where these social and educational factors could delay the onset of dementia by 50%. (Brookmeyer, Gray, & Kawas, 1998).

Despite the positive correlation between exercises overall and AD, there are no studies to recommend specific exercises to patients living with AD. The current research on AD is still limited outside of traditional medicine. AD will continue to be a challenge for the field of medicine. As the shift of viewpoint on potential therapies and preventions of AD changes, exercise will continue to become a valid option for many.

Further Directions

It is crucial to continue understanding the mechanics of brain activation. There's a lack of research on mental exercises in the status quo, many studies involve a link between mental practice and reduced signs of AD. In addition, there's a lack of understanding relating to the application of the physical and mental exercises to the brain of the patients living with AD. For instance, within each research indicator, the social-behavioural and neurobiological drivers for each experiment may be different, which could result in inconsistency of data. Different factors for future studies could be taken into account. For instance, sufficient and quality sleep, stress management, mood and anxiety are all factors that are directly or indirectly influenced by the mental exercise, which could ultimately lead to the reversal or prevention of the development of AD (Musiek, Xiong, & Holtzman, 2015) (Knopman et al., 2021). Another issue pointed out in studies revolving around leisure activities, is that the low leisure activity could potentially be preset for early dementia (Scarmeas, Levy, Tang, Manly, & Stern, 2001). Further studies could eliminate studies with low dementia scores.

Physical exercises are also in need of comprehension of the status quo. It is important to understand the methods of intervention and physical activities that would best work on the hippocampal volume of the individual living with AD. For instance, load, sets, frequency, time and other factors that could influence the functional brain changes and cognitive function. In addition, longitudinal studies are required to look at the prevention of AD. Studies could track groups where people exercise (eg. aerobic, resistance exercise) regularly and the cognitive level over a period of time, and compare the statistics towards the other group, which are within a normal setting to judge the impact physical exercises have on the prevention of AD.

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