"The Effect of Mental Stimulation on the Onset of Alzheimer's Later in Life"

An Honors Thesis

by

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ABSTRACT

Alzheimer's disease is a progressive neurodegenerative disease that affects the cognition of an individual. There is currently no cure, but potential treatments, preventions, and risk factors have been identified regarding both genetic and environmental factors. The main objective of the thesis was to identify if a lifetime of mental stimulation affects the onsets of Alzheimer's disease later in life. Various scientific articles were read regarding Alzheimer's disease, neurodegeneration, and research about mental stimulation. Mental stimulation was concretely defined in terms of what this thesis was focused upon. Statistical analyses were also completed to look at any correlations between environmental factors, such as amount of education achieved during an individual's lifetime, and Alzheimer's disease. This work has the potential to identify ways to lessen the chance of developing Alzheimer's disease later in life.

ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is an irreversible neurodegenerative disease that affects the neurons in the brain and becomes worse with incremental changes that occur up to twenty years before symptoms become noticeable (Alzheimer's Association, 2019). The initial symptoms include slight loss in cognitive function, judgement, and visual-spatial orientation (Purves et al., 2018). As the disease progresses, multitudes of neurons can be damaged or destroyed, reaching the point where neurons that enable basic bodily functions and personality are affected (Alzheimer's Association, 2019). The neuronal deaths cause cerebral atrophy, and the third ventricle eventually widens (Sherimon et al., 2021). If the disease progresses enough, it can become fatal (Purves et al., 2018).

The preliminary diagnosis is established by the physical symptoms and characteristics seen, such as recent memory loss and impairment in judgement and language (U.S., 2021). To conclude a more decisive diagnosis, an assortment of approaches must be completed since there is no set way to diagnose AD (Alzheimer's Association, 2019). These approaches include examining family and medical history, completing neurological and physical examinations, administering cognitive tests, utilizing brain imaging instruments, etc. (Alzheimer's Association, 2019). A confirmed diagnosis is determined postmortem through prominent cellular pathology completed on the brain (Purves et al., 2018). Distinguishable histopathological differences can be identified between an average brain and one of AD (Purves et al., 2018). The diseased brain is comprised of three features: dispersed depletion of neurons (Purves et al., 2018), clusters of neurofibrillary tangles or intraneuronal cytoskeletal filaments, and

accumulations of amyloids in senile plaques (Henderson, 2014). These differences are pronounced in pathological scans and are found in the limbic structures, neocortex, and basal forebrain nuclei (Purves et al., 2018).

Most AD cases emerge after the age of 60 and are considered “late-onset” of AD (Spina et al., 2021). However, there are some rare cases of early-onset AD which occurs during the middle stages of life (Purves et al., 2018). This form has more of a uniform neuropathological substrate (Spina et al., 2021) that has been used to help identify potential genetic factors of late-onset AD (Purves et al., 2018).

EARLY-ONSET DISCOVERIES

It was discovered in early-onset forms, (Purves et al., 2018) that the amyloid precursor protein (APP), which is found in the brain at high levels, creates β-amyloid peptide (Aβ) (O'Brien & Wong, 2011). These peptides are the main components of the amyloid plaques (Galvão et al., 2019) that are found during postmortem cellular pathology examinations (Purves et al., 2018). The Aβs can become neurotoxic (O'Brien & Wong, 2011**)** and target synapses of neurons to inhibit long term potentiation, which in turn affects memory formation (Galvão et al., 2019).

This finding sparked the discovery of apolipoprotein E (ApoE) in cerebrospinal fluid of AD patients when Aβ is immobilized (Escott-Price & Schmidt, 2021). This is important because a gene found on chromosome 19 encodes an isoform of ApoE, and some late-onset AD patients have genetic markers also located on chromosome 19 (Purves et al., 2018). From here, three alleles of ApoE, *e2, e3,* and *e4* (Escott-Price & Schmidt, 2021), have been analyzed to detect any correlations they may have with AD

(Purves et al., 2018). It has been determined that the frequency of *e4* is approximately four times higher in late-onset AD patients than that of the general population (Purves et al., 2018). Likewise, 90% of people who have two versions of *e4* develop AD by 75 years of age, while 20% of individuals with no copies of *e4* develop AD by the same age (Purves et al., 2018). It has been concluded that inheritance of the *e4* allele in ApoE put individuals at a greater risk for AD compared to if they do not inherit the allele (Purves et al., 2018).

POTENTIAL WAYS TO MINIMIZE AD RISK

Among all adults, AD is the sixth leading cause of death (U.S., 2021) and accounts for approximately 70% of dementia cases (Purves et al., 2018). Overall, approximately 1.6% of the population in the United States of America that is over 65 years of age has AD and related dementias (Matthews et al., 2018). The risk of AD generally doubles every five years after a person reaches the age of 65 (Galvão et al., 2019).

AD is an extremely complex disease that may incorporate a plethora of different cellular and molecular abnormalities (Purves et al., 2018). Although some genetic factors have been identified from early-onset AD, there are also other factors that may inhibit the late-onset form (Lindsay et al., 2002). In other words, there is no one common cause that has been identified to be the primary source. Genetic and environmental factors, such as family history and highest education level achieved, are both capable of increasing the risk of the onset of AD (Lindsay et al., 2002).

There is currently no cure for AD (Sherimon et al., 2021), however, continual research focused on treatment is being conducted to potentially alleviate some of the symptoms (Desai & Grossberg, 2005). Treatments are targeted towards several different areas (Shah et al., 2008) and lie in the realms of medications and non-pharmacologic therapies to improve and maintain cognitive performance (Alzheimer's Association, 2019). The medicinal route focuses on inhibitors of acetylcholinesterase (Scarpini, Schelterns, & Feldman, 2003), while the non-pharmacologic course of action involves cognitive therapy and memory training (Alzheimer's Association, 2019).

Preventative techniques associated with non-pharmacologic therapy have also been identified (Zahs & Ashe, 2010). One that is being investigated is the use of mental stimulation throughout an individual's lifetime (Wilson, 2011). The question then becomes: can mental stimulation throughout a person's life have any impact on the onset of AD later in life?

MENTAL STIMULATION

Mental stimulation (MS) is defined as interventions to improve cognitive functions and wellbeing (Sánchez-Nieto et al., 2019), especially in older individuals, through the use of increasing amounts of mentally stimulating activities (Kelly et al., 2014). These activities must support new ideas and modify the task's difficulty in order for the individual to execute a more advanced cognitive function (Sánchez-Nieto et al., 2019). Some activity examples are reading, playing chess, preforming music, utilizing the Internet, learning a new topic such as a language, exceeding various levels of education, or completing puzzles.

As individuals grow older, regardless of indications of AD, the synaptic connections become weaker and cause a gradual deterioration of cognitive connections and memories (Craik, 2002). This means that there is an inevitable loss of some memory. However, the severity of the memory loss may be lessened through MS (Grotz et al., 2018). This theory is similar to the idea of exercising on a regular basis to lessen the deterioration process in the neuromuscular system (Purves et al., 2018). The more activity that utilizes declarative and non-declarative memory to strengthen the nervous system, similar to physically exercising to strengthen the neuromuscular system, the lower the probability of experiencing neural deterioration with age (Purves et al., 2018).

It should be noted, though, that some early neural changes have the possibility to lead to the lack of interest in MS activities. In other words, some individuals do not enjoy doing certain MS activities, such as puzzles, due to early neural changes. This is due to the early neural changes that could occur up to twenty years before symptoms of AD become noticeable (Alzheimer’s Association, 2019). These individuals would not be as likely to partake in MS activities during their lifetime to prevent the onset risk of AD later in life**.**

The use of MS is capable of enhancing brain plasticity and overall cognitive function to improve the well-being of the nervous system (Shaw, Cronje, & Shaw, 2021). In other words, utilizing MS daily produces better overall cognitive function and reduces the onset of AD and other related dementias (Wilson, 2011). Thus, it has been hypothesized that people can benefit from partaking in MS throughout their lifetimes to potentially reduce the onset risk of AD (Shaw, Cronje, & Shaw, 2021). Likewise, it has

been hypothesized that AD patients are able to alleviate their symptoms through MS (Shaw, Cronje, & Shaw, 2021). It has been shown, though, that people already diagnosed with AD must be engaged in the MS consistently to show any signs of improvement (Shaw, Cronje, & Shaw, 2021).

MENTAL STIMULATION HYPOTHESES

Three hypotheses have been identified as to why it is concluded that MS affects the probability of the onset of AD (Wilson, 2011). The first hypothesis is called the reverse causality hypothesis, and states that the amount of MS completed is a result of a preexisting disease (Wilson, 2011). Another idea indicates that the cognitive function and activity are associated with another related variable (Wilson, 2011), such as education or occupation (Karp et al., 2009). The third hypothesis is called the brain reserve hypothesis, where brain reserve is defined as the capability to modify to neuropathological damage (Wilson, 2011). This hypothesis demonstrates that MS is capable of modifying the structure, and ultimately the function, of the neural systems that entail cognition and memory (Wilson, 2011).This means that these specific neural systems are able to adjust to changes, especially neurodegenerative changes that come with aging (Wilson, 2011). In other words, MS is potentially capable of increasing the brain reserve and, thus, able to perhaps prevent a greater risk of impairment, specifically AD or other related dementias (Wilson, 2011). One downside to this hypothesis, though, is that there is a set point for AD where the brain reserve is no longer defensive in cognitive decline (Wilson, 2011).

All three hypotheses encompass the idea that the more MS, the less cognitive diminishment there will be during aging. However, there is a difference between them all,

specifically with the reverse causality and brain reserve hypotheses. The reverse causality hypothesis states that the onset of AD is delayed through MS throughout one's lifetime, but eventually creates a rapid reduction once the onset begins (Wilson, 2021). On the other hand, the brain reserve hypothesis describes the association between rapid cognitive and memory decline after symptoms begin to appear and the MS conducted before signs of AD (Wilson, 2011). Although these hypotheses are slightly different in manner, they both indicate that MS may have an effect on the onset of AD later in life.

BUILD UP OF BRAIN RESERVE

Neuroimaging studies, which have undergone massive breakthroughs in recent years (Belenguer-Llorens et al., 2022), have given some indications as to how brain reserve may be enhanced by MS (Wilson, 2011). One theory is that continuous mental stimulation plays a part in the nervous system, specifically with its neural adaptability and efficiency, in terms of underlying cognition (Wilson, 2011). This can be seen through increasing volumes of the brain in various regions (Wilson, 2011), such as the neocortex and hippocampus (Draganski et al., 2004).

All in all, these findings suggest that by training with a greater amount of mental stimulation in a person's lifetime, an individual's cognitive health in their elder years has the opportunity to be better than those who do not utilize MS regularly (Wilson, 2011). There have been some issues, though, with the training process during one's lifetime since they are specific and typically are not transferrable with related tasks (Wilson, 2011). However, there have been some proposals that jump around this issue (Wilson, 2011).

The first approach is distinct (Wilson, 2011) and employs the advancement in the realm of ability rather than the task spectrum by looking at particular target processes as the control (Takeuchi et al., 2010), which include working memory (Wilson, 2011). Hypotheses have been introduced from this approach that state there is an increase in myelination due to the training involved (Lövdén et al., 2010). The second approach is more generalized, on the other hand, where individuals complete diverse complex activities that challenge the particular control target processes (Wilson, 2011). Much like the first approach this idea has brain alterations, such as the myelination increase, due to the training the individual undergoes (Lövdén et al., 2010).

TRAININGS OF MS

The training individuals with AD undergo is defined as non-pharmacological mentally stimulating activities that may increase brain function and cognition (Mayor, 2017). These activities may include reading, playing games, using the Internet, partaking in social activities, and much more (Mayor, 2017). Obtaining an education is also considered a factor that may increase MS (Wilson et al., 2009). According to Mayor (2017), individuals who frequently engage in mentally stimulating activities showed signs of reduced risk of the onset of AD and other related dementias.

Playing games at least once a week lowers the risk of developing cognitive impairments by 22% compared to playing games about once a month (Mayor, 2017). Likewise, participating in other mentally stimulating activities have proven to reduce the risk when partaken in routinely rather than scarcely (Mayor, 2017). These other activities include crafts, partaking in social activities, reading books, or using a computer (Mayor,

2017). As stated prior, there may be a lack of interest in MS activities due to the early neural deterioration that may arise prior to symptoms.

STATISTICAL ANALYSIS

It has been a challenge to correctly study MS on a level playing field in humans since every individual is different in a multitude of aspects (Thoft et al., 2021). The most typical technique used is collection of self-reported data, indicated by the participants, on the levels of mentally stimulating activities partaken in (Wilson, 2011). Data is collected during at least the pre- and post-study, with some mid-study collections also being completed (Thoft et al., 2021). The participants in each study state their amounts of participation in specific activities that involve MS (Wilson, 2011). The results are then analyzed in various ways depending on what the specific study is researching (Wilson, 2011).

One way to look at the effects of MS within elderly individuals is to look at levels of education completed during their younger years. Using the data, published by Tennstedt et al. (2010), a correlational statistical analysis was completed on 2800 people, ages 65 to 94, from six metropolitan areas in the United States. These individuals were at risk of losing functional independence but were noninstitutionalized (Tennstedt et al., 2010). The correlation studied was the highest level of education achieved versus the total score on the Mini Mental Status Exam (MMSE). The MMSE is a clinical test to determine mental status (Milman et al., 2018) and cognitive impairment based on cognitive abilities (Torabinikjeh et al., 2022) through 30 various tasks (Stein et al., 2015). This assessment is designed for individuals with normal cognition to easily achieve a

perfect score of 30 points, while lower scores indicate a presence of some type of cognitive impairment. The MMSE used for the statistical analysis in this study consisted of 12 tasks (Tennstedt et al., 2010).

Originally, the study consisted of 2832 individuals, but if the participant was deemed ineligible at any given point before the MMSE was started, they were immediately taken out of the study (Tennstedt et al., 2010) and were not accounted for within the statistical tests run. Thus, 2800 people were considered eligible and their data was utilized to complete the statistical analysis. The MMSE examines various factors of an individual's cognitive functions, such as short-term memory and recall ability, to showcase any signs of cognitive impairment (Tennstedt et al., 2010). This exam is split into two segments: memory-related inquiries and reading and writing questions (Tennstedt et al., 2010).

First, the highest grade level achieved was looked at. The levels involved No School, Grades 1-12/GED, Vocational Training or Some College, Associate Degree, Bachelor's Degree, Some Professional School, Master's Degree, and Doctoral Degree (Tennstedt et al., 2010). Each level was assigned a number. For instance, No School was categorized as 00, Grade 1 was labelled 01, Vocational Training or Some College was 13, Associate Degree was 14, Bachelor's Degree was 16, Some Professional School was 17, Master's Degree was 18, and Doctoral Degree was 20 (Tennstedt et al., 2010). The total MMSE score, which was gathered from summing the points for each completed question and task (Tennstedt et al., 2010), was then observed for each individual participant. A score of at least 23 deemed the individual as eligible and could continue on into the rest

of the study (Tennstedt et al., 2010). A score of 23 indicated that there was a presence of some cognitive impairment, but not enough to deem the individual incompetent.

A correlational analysis was completed on the data retrieved from the database since the data was categorical. A Spearman's Rank-Order Correlation analysis was preformed, using SPSS software. This provided a correlation coefficient of 0.280 (p-value<0.001). It was determined that there is a significant relationship, or correlation, between the highest level of education achieved and the total MMSE score.

Using the raw data, the average total score of the MMSE was calculated based on each grade level achieved. The standard deviations were then also calculated for the total MMSE score on the same basis of education level. From this data, a scatterplot was made (Figure 1), which showed a slight positive correlation. It was concluded that the higher the education level achieved, the greater the total MMSE score was.

This study was partially biased due to the data used. The study that the data was gathered from looked primarily at individuals who were aged 65 to 94 in a specific location and were at some risk of losing functional independence but were noninstitutionalized (Tennstedt et al., 2010). The original study looked at 2832 individuals, but only 2800 were eligible for forthgoing in the study (Tennstedt et al., 2010). The other 32 participants' answers were not recorded in the database since they were not considered eligible before the MMSE was completed (Tennstedt et al., 2010).

CONCLUSION

There is still so much unknown about the impact MS may have on the onset of AD. In fact, there is a lot to learn about AD in general. Various studies have indicated that MS should be used during an individual's everyday life to delay and minimize the severity of the onset of AD in elderly years (Wilson, 2011). MS activities can be started at any point in an individual's lifetime and have some effect on the onset risk, as long as the onset of AD and other related dementias have not already begun (Mayor, 2017). Additional studies need to be conducted to create more concrete conclusions regarding the matter. However, through the data found, the research already conducted has concluded that MS does in fact have an effect on Alzheimer's disease later in life (Wilson, 2011).

FIGURES AND GRAPHS

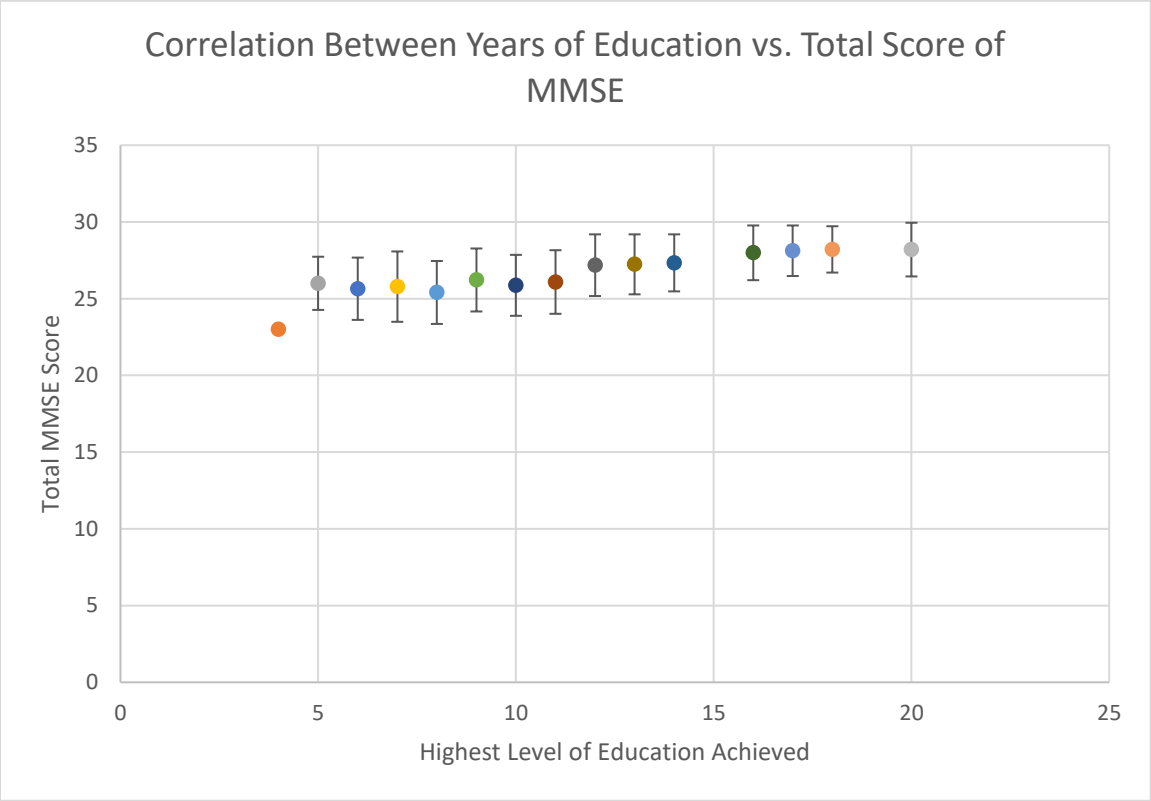

Figure 1. Correlational statistical analysis completed on a database from Tennstedt et al. (2010) on the highest level of education completed and the corresponding total MMSE score. The level of education is described in the text on page 11 and 12.

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