EXERCISE ENHANCEMENT OF COGNITIVE RESERVE: PROMOTION OF MENTAL HEALTH IN OLDER AGE?

by
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ABSTRACT

The concept of cognitive reserve is one that quite recently has been discussed in clinical neuroscience literature. Cognitive reserve posits that there is an established amount of supply in the brain that compensates for brain functions during normal age-related decline or when there is pathology present. Many factors contribute to the growth of reserve throughout an individual's life, but one that is seen to be significantly beneficial, even in older adulthood, is aerobic exercise. The focus of this paper is on the promotion of healthy aging through exercise enhancement of cognitive reserve to assist the brain through the normal process of aging. In addition, one of the most prevalent mental illnesses afflicting older adults is depression. Not only is it more prevalent in older adults, but because it manifests differently in older adults, it is more detrimental to overall brain health. It is hypothesized that exercise enhances cognitive reserve, which may prevent or minimize negative aging effects on the brain such as depression, leading an individual to age without decline in quality of life.

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INTRODUCTION

Cognitive reserve is a theoretical construct that proposes the presence of a capacity, or a reserve, that aids in functioning as an individual goes through normal age-related brain changes or disease pathology [Stern, Y, 2007]. Cognitive reserve is divided into two main portions: active and passive reserve [Stern, Y., 2009]. Active reserve refers to the compensation related to cognitive processes in the brain. For example, active reserve would accommodate for any deficiencies by continuing normal cognitive functioning even through experiencing brain trauma. Passive reserve is the structural portion of cognitive reserve and is involved in preventing further deterioration from the normal aging process. The volume of the brain and/or the size, number of neurons, and synapse count, are examples of some structures that passively provide compensation for maintenance of the brain's integrity through trauma or psychopathology.

This thesis will primarily focus on passive reserve because evidence suggests that exercise enhances structural integrity in the brain, and this can be significant in the promotion of mental health, especially in older adulthood [Cheng, S.T., 2016; Christie, G.J., 2017; Colcombe, S.J., 2006; Mora, F., 2013; Craft, L.L. & Perna, F.M., 2004].

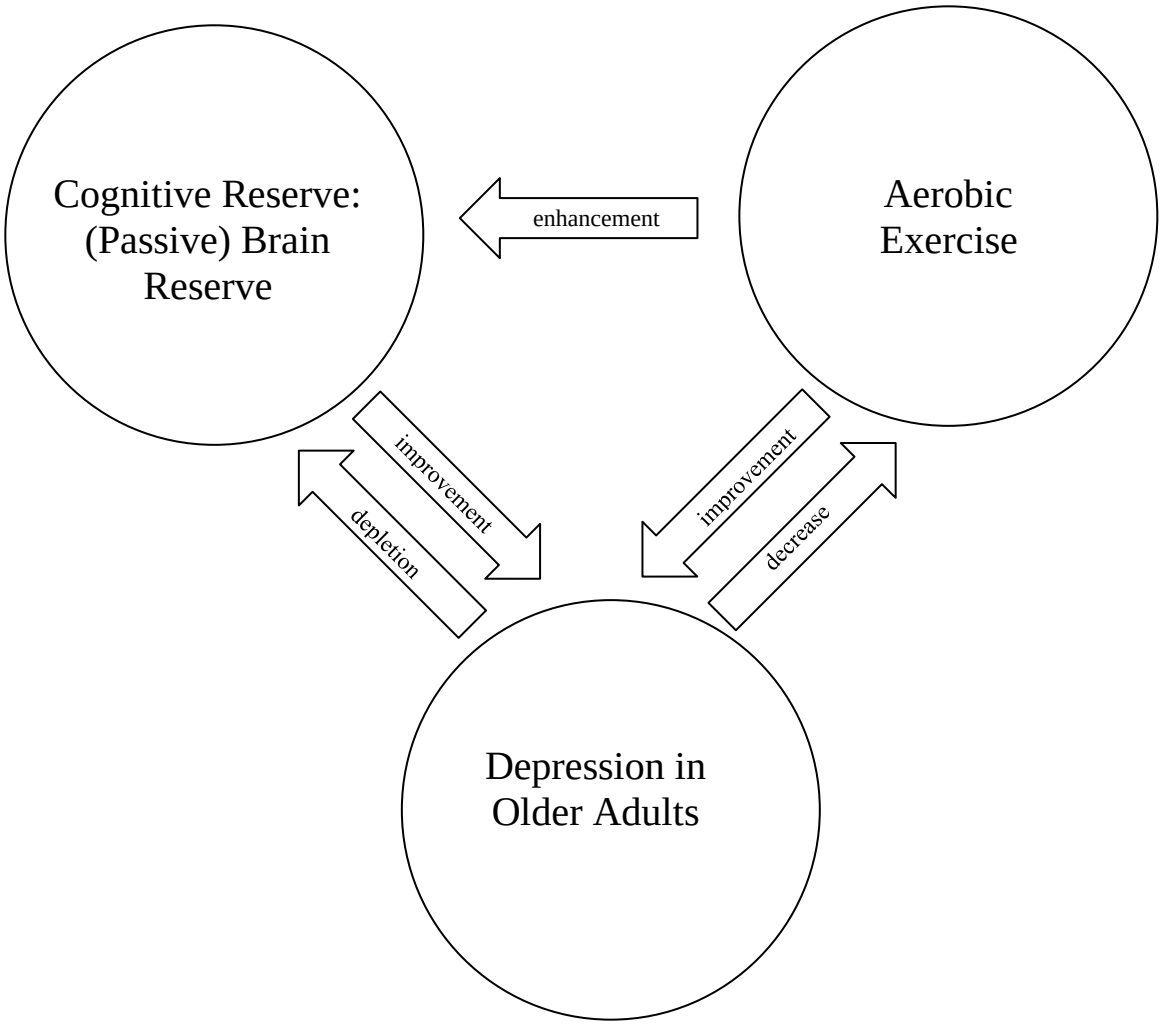
Aerobic exercise is considered to be cardiorespiratory activities such as running and walking. Exercise, specifically aerobic exercise, has demonstrated enhancements in brain mass that lead to better overall brain functioning [Bittner, N. et al., 2019]. Exercise also increases the formation of new neurons in the hippocampus, also known as neurogenesis, and of new connections between neurons in many brain areas, or synaptogenesis [Mora, F., 2013]. Due to its enhancement of brain structures, we can theorize that exercise consequently builds and maintains passive reserve. This leads to the support of higher functioning for a longer period of time as an individual ages. In older adults, depression is a common mental illness, and it presents itself in

many different ways. These include brain structural abnormalities, including the atrophy of brain regions such as the hippocampus, which is important in the storage and formation of memories and emotional regulation [Drevets, W.C., Price, J.L., & Furey, M.L., 2008].

Neurons are the basic working unit of the brain. Neurons contain a cell body that is supplemented with dendrites and axons that transmit signals through synapses, or connections, between cells. The more synapses present in the brain, the stronger and faster the messages between the neurons. The cells will be able to then work more efficiently which allows for increased adaptability to changes within the environment. Neuroplasticity, also known as brain plasticity, is the ability of an individual's brain to be flexible and respond to external stimuli or changes, such as behavioral and environmental changes. Plasticity in areas of the brain such as the hippocampus, may be demonstrated through the process of neurogenesis and synaptogenesis and are directly correlated with cognitive reserve [Zarif, H. et al., 2017].

Therefore, I will provide evidence that *exercise preserves cognitive reserve, and enhances brain plasticity, subsequently reducing depression in older adults.* High cognitive reserve can be demonstrated when an older adult sustains a brain lesion, or early brain disease pathology, but does not exhibit cognitive or mood impairment. While depression is associated with compromised structural integrity, exercise enhances passive reserve, mitigating the effects of depression on an individual's brain. This then leads an individual to stay cognitively intact for a longer period of time, even in the presence of neuropathology [Craft, L.L. & Perna, F.M., 2004].

Figure 1: Exercise enhancement of cognitive reserve: Promotion of mental health in older age?



Although cognitive reserve is the umbrella concept, the specific focus in this paper is on passive reserve. Aerobic exercise is seen to enhance passive reserve and also alleviate depression in older adults. Passive reserve is also seen to alleviate depression because of the structural support that it provides in the support of functioning. Passive reserve also prevents further deterioration of brain structures by psychopathology. Depression is seen to decrease the motivation to exercise that may be reflected by each individual, preventing them from exercising. This is consistent with the relationship between depression and passive reserve as well. As an older adult is seen to have higher prevalence of depression, their passive reserve in turn, deteriorates, thereby detracting from overall mental health.

COGNITIVE RESERVE

Types of Cognitive Reserve

Cognitive reserve is divided up into two main portions of reserve which can be classified as active reserve and passive reserve. If cognitive reserve were to be compared to a computer, active reserve would represent the software of the computer. This includes the coding, applications, and utilities within the computer that are not seen, but perform functions that run the computer. Using this same analogy, passive reserve would represent the hardware of the computer. This includes the hard drive, body of the computer, and motherboard that provide structural integrity to rely on for the proper overall function of a computer.

The concept of neural reserve also encompasses two aspects that are intertwined with active reserve: efficiency and capacity. While efficiency refers to the functionality portion of cognitive reserve, (e.g. neuronal circuit rewiring), capacity is more of the "amount" of reserve there is, as well as how much compensation can be done [Barulli, D. and Stern, Y., 2013]. In some cases of a brain lesion, neuronal networks have to be rewired in order for the brain to keep functioning at the same level as it did before that brain lesion.

The other portion of cognitive reserve is passive reserve, which is also referred to as brain reserve. It accounts for the structural aspects of the brain that contribute to the compensation of normal age-related brain changes. These structural aspects include overall brain volume, head circumference, synaptic count, dendritic count, grey and white matter, and brain-derived neurotrophic factor (BDNF). BDNF is a protein that aids in the growth, maturation, and maintenance of cells. Brain reserve capacity refers to the quantitative measure of structure and volume which aids in protection against normal age-related brain changes or psychopathology.

Although cognitive reserve does maintain cognitive function, there is a certain threshold that each individual maintains, (referred to as the inflection point), that is reflected by brain reserve capacity. Up to the inflection point, cognitive reserve preserves function and prevents the brain from exhibiting significant functional differences due to normal age-related changes [Stern, Y., 2009]. As previously mentioned, in the case of a brain trauma in one area, cognitive reserve would allow the brain to rewire and use a different non-affected area to do the job. Therefore, your brain would not exhibit much difference in overall functioning due to the reserve. Once this inflection point is reached, reserve is overwhelmed by degenerative changes and therefore cognitive impairment becomes apparent. The inflection point pertains directly to individuals who already have degeneration in the brain via a disease such as Alzheimer Disease or another form of dementia (see Figure 2 below).

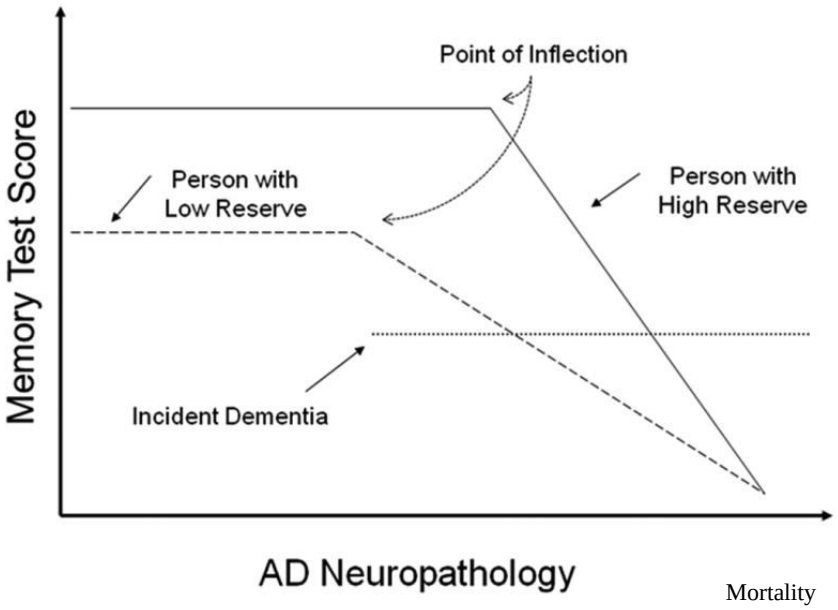


Figure 2: Point of Inflection

In this graph, memory test score is the proxy measure that is quantifying cognitive reserve. The x-axis represents deterioration of the brain over time through Alzheimer Disease neuropathology. High cognitive reserve is indicated when the pathology of Alzheimer or dementia is present, but there is still high cognitive functioning in the individual because of the availability of reserve [Stern, Y., 2009].

As displayed in Figure 2, mortality is not delayed and theoretically remains the same when comparing the two individuals who differ in reserve capacities. The difference is that a

high reserve individual is able to maintain high cognitive control for a longer period of time despite the presence of neuropathology of Alzheimer Disease or dementia. An individual who has low reserve accompanied by neuropathology would have a point of inflection come earlier, thus resulting in lower cognitive functioning.

The person with higher reserve maintains normal functioning for a longer period of time, but then experiences a steeper deterioration rate to incident dementia once the point of inflection is reached. While overall brain functioning is sustained, the neuropathology eventually starts affecting an individual at the threshold point (i.e. inflection point). This is due to cognitive reserve being depleted which results in a sharper decline in overall brain function and a shorter time until mortality is reached, compared to an individual with lower cognitive reserve [Stern, Y. et al., 1994]. The result of higher reserve is the expression of clinical symptoms past the inflection point, after brain trauma cannot be sustained by brain reserve capacity any longer. This is consistent with quantitative threshold models that illustrate the existence of a capping point to a certain behavior or a function. The threshold model is important in the context of brain reserve capacity, because it clarifies its quantitative component [Katzman, R., 1993; Satz, P. & Butters, N., 1993]. Ultimately, cognitive reserve absorbs both normal age-related brain changes as well as any brain trauma that an individual might face throughout their life. The effects of brain degeneration are suppressed by the brain's continued normal functioning and delayed onset of any cognitive deficits [Cheng, S.T., 2016].

Table 1: Types of Cognitive Reserve

Cognitive Reserve	The theoretical concept of a supply in an individual's brain that allows for continuation of brain functioning through the presence of psychopathology or brain lesions.
⇒ **Active Reserve**	The portion of reserve that serves to aid in cognitive processes and compensation at the functional level. If cognitive reserve were a computer, active reserve would be the software.
○ **Neural Reserve**	The efficiency and capacity functions at the neural level of active reserve that aid in maintenance of overall brain functioning.
⇒ **Passive Reserve**	The portion of reserve that serves to aid in the support of compensation through structural integrity. If cognitive reserve were a computer, passive reserve would be the hardware.
○ **Brain Reserve Capacity**	The quantitative representation of reserve through passive compensation in structural components of the brain.

Measures of Cognitive Reserve

There are many different measures for both active and passive reserve. Active reserve is measured through proxy measures such as socioeconomic status, including income and occupational attainment, educational attainment, and in some cases, leisure activity. Task demand is another proxy measure used in determining the amount of active reserve that an individual has. One specific example is the Letter and Shape Sternberg Task, which assigns 1, 3, or 6 letters for 3 seconds, which is then followed by a 7 second retention period. The participants are then given a single letter and asked to identify whether that letter is part of the studied set. The same process is done with a shape that is specifically designed to be difficult to verbally decipher. The main behavioral measure taken from the tasks is the reaction time that is associated with making a decision as the number of letters/shapes given, increases [Stern, Y., 2009]. This is more helpful in determining differences between the young and the older adults when it comes to active reserve, which will be discussed later.

Additionally, active reserve can be determined through cerebral blood flow, the blood supplied directly to the brain, measured directly in a given period of time through imaging

technology such as single-photon emission computed tomography (SPECT), positron emission tomography (PET), or magnetic resonance imaging (MRI), among others. High levels of cerebral blood flow have been associated with high cognitive function as well as brain efficiency. It also declines with normal aging processes, and lower cerebral blood flow correlates subsequently, with lower cognitive functioning [Ainslie, P.N. et al., 2008; Bertsch, K. et al., 2009]. Lower cerebral blood flow also indicates more advanced Alzheimer-associated pathology [McGeer, P.L. et al., 1986; Hoffman, J.M. et al., 2000]. Therefore, it can be argued that because cognitive decline through Alzheimer Disease pathology is negatively associated with cerebral blood flow measures of active reserve, it must be negatively associated with active reserve as well [Stern, Y., 2009]. These findings support the hypothesis that individuals with higher active reserve are able to handle brain changes attributed to pathology or trauma at a greater level than individuals with lower reserve.

Epidemiological evidence suggests proxy measures accurately estimate active reserve because the idea of active reserve, compared to passive, relates to functionality and is harder to be seen through imaging technology such as PET or MRI. Proxy measures are forms of measurement that are indirectly, but strongly, related to what is being measured. In this case, it is theorized that certain variables such as diet, lifestyle activities, and occupational and educational attainment can have an increasing effect on the amount of reserve that an individual possesses. Thus, such measures are used as indirect measures of active reserve. Educational and occupational attainment are important correlates of reserve because they are negatively associated with overall brain deterioration. Individuals with fewer years of education consistently have faster cognitive decline, and those with more years of formal education were found to have slower cognitive decline [Evans, D. et al., 1993]. It is also an indication that measures such as

years of education are seen to be positively correlated with active reserve and, thus, negatively correlated with cognitive decline or psychopathology [Mortel, K.F. and Meyer, J.S., 1995; Rocca, W.A. et al., 1990].

Specifically, the complexity of occupation combined with the number of jobs and the years on those jobs, were negatively associated with whole brain atrophy, especially in the hippocampus [Boots, E. et al., 2015]. A more complex occupation, for example, was correlated with reduced brain atrophy. In another major study, a systematic review of twenty-two cohort studies of the relationship between the effects of education, occupation, premorbid IQ, mental activities and cognitive decline, showed that increased complex activities in late adulthood were closely associated with lower rates of cognitive decline [Velenzuela, M.J. and Sachdev, P., 2006]. The consistency in the studies from the review strongly supported the hypothesis of educational attainment, occupational attainment, and premorbid IQ being negatively correlated with cognitive decline and thus being positively correlated with active reserve

In some cases, educational attainment is replaced by degree of literacy and is seen as a better measure of the capacity for compensation as a result of brain damage. Literacy levels can be a better measure compared to years of education. This is because individual motivations to gain knowledge and/or apply that knowledge can be demonstrated with literacy levels, and this is best represented through longitudinal studies. After accounting for age and years of education, one study showed low literacy levels were associated with a sharper decline in memory recall, when compared to individuals with higher literacy levels [Manly, J.J. et al., 2003]. Another study by the same authors assessed a cohort of ethnically diverse English-speaking individuals who were cognitively and functionally normal at baseline. It was found that literacy level seemed to

be a better predictor of decline in memory, executive function, and language skills when compared with the years of education [Manly, JJ. et al. 2005].

Passive reserve, on the other hand, is measured using structural measures such as volume or mass of the brain, grey and white matter count, synaptic and dendritic count, and the number of neurons. Some imaging studies are also used to understand an expected clinical outcome or brain trauma or brain changes that come with normal aging. Brain scans are used to determine visible differences when two individuals are compared to each other, with regard to demonstrating brain reserve capacity [Stern, Y., 2012].

Brain reserve capacity that is measured through imaging, shows that structural markers in different areas of the brain (e.g. hippocampus, lateral ventricles, etc.) demonstrate white and grey matter brain volume are important. One study concluded that these structural markers, specifically in the right/left hippocampal volume and white matter lesion load, can give information regarding brain reserve capacity of each individual [Cavedo, E. et al., 2012].

Cognitive Reserve in Older vs. Younger Adulthood

Efficiency and compensation are seen in both younger and older adults. Compensation relates to cognitive reserve because it is seen most in those with higher reserve. In one study, better performing elders were seen, through PET (Positron Emission Tomography) and fMRI (functional Magnetic Resonance Imaging) scans, to use additional brain areas, especially in the contralateral hemisphere, when compared to younger subjects. The tasks that were used were the Wechsler Memory Scale-Revised and the Long-Delay Cued Recall from the California Verbal Learning Test. The tasks were selected specifically to distinguish older adults with low and high mnemonic functioning, which is the demonstration of retrieval of information and learning through a mnemonics task. Although the young and old adults were performing the same tasks,

the elders who kept up with the young adults were the ones who utilized additional brain areas in order to keep up [Cabeza, R. et al., 2002].

One way to expose differences between young and older adults is by looking at neuroimaging scans from task demand activation. Brain plasticity, as it relates to cognitive reserve, is presented differently in older adults as opposed to young adults, when looking at scans. This is because of the implementation of plasticity in older adulthood leading to higher activation in certain brain areas. It is hypothesized that when plasticity is being implemented, there is increased activity that is concentrated in the prefrontal cortex while decreased brain activity is observed in the posterior brain regions in older adults, when compared with young adults [Lovden, et al., 2010]. In the same study, flexibility, functional capacity, brain functioning, and experiences shape cognition and lead to higher brain plasticity (i.e. more flexibility in experiencing change). Brain plasticity in older adults represents the ability to be flexible in the adaptation of behaviors or environmental changes that affect the structure of the brain. In the normal aging process, or when lesions affect cognition, greater activation would be present because the use of higher function would be necessary in older adulthood as opposed to young adulthood.

When comparing both groups, task demand activation is also important because it shows differences in brain processes between the two groups. Activation tasks are used to determine the response to a certain task given, which the results can then be analyzed for efficiency and capacity, and overall cognitive reserve. If the task given is a 5-word memory task, then it would naturally be harder for an older adult to perform this task than it would be for a young adult. Therefore, the older adult would show more activation because of the greater capacity at which the older individual's brain is being used. However, when given a 20-word memory task, this

would be difficult for both older and young adult. That young adult would show the same high level of activation in a 20-word task that an older adult might have shown when given the 5-word memory task. The capacity of both is around the same for this task. Efficiency comes in when comparing these results to determine cognitive reserve. It is hypothesized that the more efficient the brain is in performing activation tasks, the more cognitive reserve present [Stern, Y., 2009].

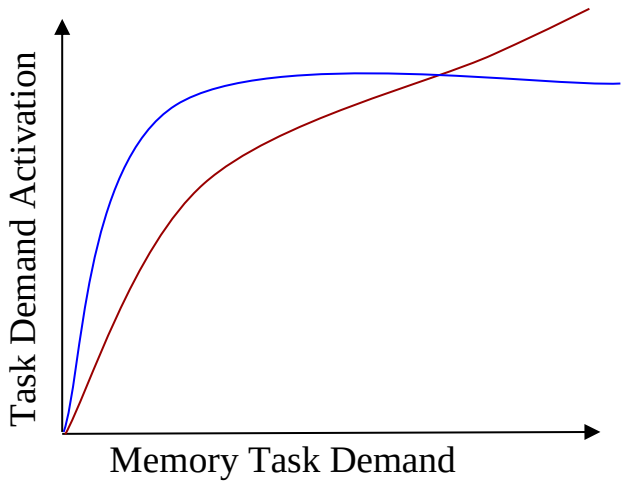


Figure 3: Task Demand in Older vs. Young Adulthood

The blue line represents older adults in a memory task while the red line represents the younger. Based on Stern's findings, the older adult starts off high but levels out, which the young adult goes at a steadier pace, and activation gets higher as the task demand is higher as well.

Passive Reserve: Brain Reserve Capacity

As mentioned, intracranial brain volume is a very common measure for passive reserve, and it is considered an accurate measure of passive reserve when controlling for pathology [van Loenhoud, A. et al., 2018]. Although overall brain volume is important in determining brain reserve capacity, complexity of cognitive activities is important as well and a strong indicator of overall cognitive reserve and brain plasticity. Some of these complex activities include playing chess, puzzles, and other hobbies that require more intellectual functioning by the brain. These

cognitive activities require higher functioning and brain engagement, and therefore are hypothesized to build brain reserve capacity [Lovden, M. et al., 2010]. Plasticity contributes to the development of passive reserve as well because of its enhancement of functioning and capacity for the brain to not fall susceptible to age-related brain changes.

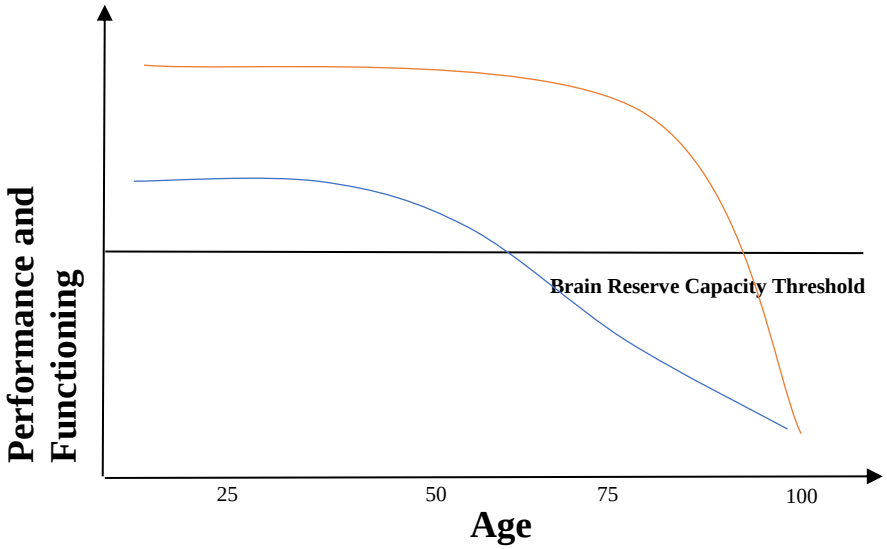


Figure 4: Brain Functionality and Age

Person 1, represented by the blue line, has lower over performance and functioning and therefore reserve and gradually declines while they age. Person 2, represented by the red line, starts at a higher level of performance and functioning and because they have more plasticity and reserve, start deteriorating later. [Lovden, M. et al., 2010].

The proxy measures that cognitive reserve is strongly associated with are the same that contribute to the enhancement of individual reserve. For example, negative effects of aging and dementia can be slowed by the stimulation of the brain through cognitive activities. Previous research has expressed that individuals with a higher IQ tend to display lower, and more efficient brain activation, as measured by PET scans while performing cognitive tasks [Haier, R.J. et al., 1988]. More recently, studies have been conducted examining the effects of complex mental activities on overall cognitive functioning. In one study, complex mental activities were associated with a greater ability to handle brain trauma [Valenzuela, M, Breakspear, M., and Sachdev, P., 2007]. Complex mental activities also lead to greater brain plasticity and greater

resistance to age-related brain changes. Plasticity can also be defined as a reactive brain process. The more plasticity there is, consistent with passive reserve, the more an individual is likely to continue normal function after a brain lesion or trauma. An individual with higher levels of plasticity is theorized to sustain the optimal performance of brain tasks for a longer period of time when compared with an individual of lower plasticity, up until the threshold is met. However, this is true up to the point of inflection for brain reserve capacity.

Cognitive reserve is built over a lifetime and many factors contribute to its structure. Brain reserve capacity is demonstrated through increased plasticity in the brain where an individual will continue with high cognitive functioning despite the presence of disease pathology. Neuroplasticity is an umbrella term that includes neural functioning, efficiency, and compensation. Neural mechanisms linked to cognitive reserve are enhanced with neuroplasticity. Lifetime exposures, some short-term and some long-term, increase neurogenesis in areas of the brain [Xu, W., Yu, J., & Tan, L., 2015]. One area of the brain specifically that contains and contributes to passive reserve is the hippocampus.

We have now looked at the importance of passive reserve in the maintenance of brain functioning as individuals age. An important component of passive reserve that was emphasized was brain reserve capacity, which demonstrates the plasticity that is built in the brain. Next, it is important to focus on how it is built and where. Neurogenesis in the hippocampus may be stimulated by lifestyle factors such as diet, socializing, complex cognitive leisure activities, and exercise. Throughout the lifetime of an individual, neurogenesis occurs in the hippocampus specifically that is correlated positively with passive reserve [van Loenhoud, A.C. et al., 2018]. Aerobic exercise is most closely linked with neurogenesis in the dentate gyrus of the

hippocampus, specifically, hence improving memory and mood function [van Praag, H. et al., 1999].

AEROBIC EXERCISE

Exercise is considered to be activity associated with movements of the body that relate to higher cardiovascular output compared to baseline activity. Studies have shown that exercise, particularly aerobic and long-term exercise, is a protective factor in aging of the brain [Cotman, C.W. and Berchtold, N.C., 2002]. In the context of brain reserve capacity, exercise, especially aerobic exercise, is seen as a protective factor for cognitive decline. Aerobic exercise is the stimulation of exercise through oxygen and cardiovascular conditioning and can be low or high intensity. Not only does frequent aerobic exercise maintain brain health and plasticity, but it is also seen to stimulate neurogenesis in the hippocampus and have neuroprotective properties. Aerobic exercise also aids in increasing neurogenesis in the hippocampus that subsequently leads to higher overall functioning [Barullli, D. and Stern, Y., 2013]. It is also associated with less age-related gray and white matter loss and the maintenance of neuronal structure and brain volume [Norton, S. et al., 2014]. In one longitudinal study, cognitive decline in older adulthood was strongly negatively correlated with exercising, after controlling for risk factors [Hamer, M. and Chida, Y., 2008].

Some of these neuroprotective factors include the increase in brain-derived neurotrophic factor (BDNF) and glial derived neurotrophic factor (GDNF), especially in the hippocampus [Colcombe, S. and Kramer, A.F., 2003; Hillman, C.H. et al., 2008]. Some studies have also suggested that because exercise is seen to enhance hippocampal structure, stimulate memory and

mood functioning, in turn increase plasticity in the brain, this leads to higher cognitive functioning [Mahncke, H. et al., 2006].

Exercise in Specific Areas of the Brain

Epidemiologic studies suggest that there is a correlation between physical activity and improved cognition in dementia or Alzheimer patients [Smith, J.C. et al., 2012, Gómez-Pinilla, F., So, V., & Kesslak, J.P., 1998]. Individuals with neuropathology such as Alzheimer Disease are commonly studied in determining the trajectory to cognitive impairment because impairments are prominent and clearly defined. This helps to conceptualize the trajectory to cognitive impairment and answers questions such as: "What factors are less or more likely to lead an individual to brain deterioration faster?" and "Do certain lifestyle factors play protective roles in aging?" One prospective cohort study followed 1740 individuals who were older than 65 but did not have cognitive impairment [Larson et al., 2006]. In that study, participants reported the amount that they exercised, mental health, lifestyle characteristics, and potential risk factors for the development of dementia and Alzheimer Disease. When following up with these individuals after 6.2 years, 158 participants had developed dementia and another 107 had developed Alzheimer Disease. After specifically taking into consideration the predisposition, the conclusion was that frequent exercise was associated with a delay in onset of these brain diseases.

Findings from other studies that investigate the relationship between exercise and cognitive impairment also find that exercise delays cognitive impairment [Podewils et al. 2005, etc.; Tomprowski, P.D., 2003; Yaffe et al., 2001; Weuve J. et al., 2004; Yamada, M. et al., 2003]. Although the studies mentioned focused mainly on self-reported exercise, one study conducted by Barnes and colleagues measured the self-report of exercise as well as oxygen

consumption in a cohort of 349 individuals [Barnes et al., 2003]. The results from this particular study concluded that there is an inverse relationship between exercise and cognitive decline. The study also emphasized the importance of aerobic exercise in relation to cognition, where aerobic exercise was seen to have a significant positive effect on an individual's cognitive abilities.

Aerobic exercise is seen to have enhanced effects on cognition especially in older adults. Colcombe and Kramer conducted a meta-analytic study on the effects of exercise on the cognitive functioning of older adults [Colcombe, S. & Kramer, A., 2003]. The differentiating factor of this study was that it focused on aerobic exercise effects in isolation along with combined aerobic and strength training exercise. Previous studies in animal models showed that exercise does increase cognitive performance. This study affirmed the conclusion by providing evidence in humans. Aerobic exercise was seen to increase cognitive performance in older adults, specifically in the prefrontal cortex with executive functioning [Colcombe, S. & Kramer, A., 2003].

The prefrontal cortex is an area of the brain that functions in decision making, flexibility, and planning. It also plays a role in short term memory. It can be deemed as the control center of thoughts and actions, or more commonly known as the center for executive functioning. The prefrontal cortex's role in aging is such that it provides inhibitory control and proper order in an individual's brain. Damage to this area can result in major cognitive deficiencies. A normal process of aging is brain volume loss, especially in areas of the brain such as the prefrontal cortex. Lower brain volume would result in lower cognitive functioning as well as lower passive reserve. Kramer and colleagues conducted a study on older adults and had them participate in a six-month aerobic exercise program, in order to determine changes in cognitive functioning. Results showed that even after a short-term exercise program, areas of the brain such as the

frontal cortex and the temporal lobe, showed significant increases in grey matter volume [Kramer, A.F. et al., 2006]. These, and other findings show that aerobic exercise can restore the loss of brain volume by increasing grey and white matter in the prefrontal cortex [Rosano, C. et al., 2010].

Another area of the brain that is significantly enhanced due to exercise is the hippocampus. The hippocampus is located in both the right and left temporal lobes of the brain and it functions in learning, memory capacity, and emotion. The hippocampus, consistent with other brain areas, shrinks as an individual gets older. The loss of brain volume in the hippocampus results in impaired memory and learning, as well as emotional discrepancies. The shrinking hippocampus is implicated in the onset of dementia and Alzheimer Disease, given its role in memory and learning [Jack, C.R. et al., 2010]. A specific area in the hippocampus, called the dentate gyrus, functions as the control center of the hippocampus and is where input comes through in order to be processed. It is an area where neurogenesis occurs as a result of exercise and aids in the maintenance of optimal function of the hippocampus. BDNF aids in neurogenesis because it is a protein that supports the survival of new cells and maintains the growth of these cells. Thus, greater levels of BDNF are associated with neurogenesis. Erikson and colleagues found that aerobic exercise worked to decrease the effects of hippocampal shrinking in a trial of 120 older adults. Increased hippocampal volume was also associated with greater levels of BDNF, which was mediated by neurogenesis in the dentate gyrus of the hippocampus [Erikson et al., 2011]. These findings are consistent with previous studies that examine roles of BDNF and hippocampal neurogenesis that lead to better memory functioning [Kim, Y., et al., 2003; Pang, P.T. & Lu, B., 2004; Rasmussen, P. et al., 2009].

Looking at the overall hippocampus, behavioral studies conducted in rats have also shown significant increases in learning and memory capacity due to exercise. Wheel running especially was seen to increase performance in spatial-learning tasks that are specialized to the hippocampus [Fordyce, D.E. & Wehner, J.M., 1993]. Fordyce and Wehner measured learning performance by running rats on wheels and having them perform spatial learning. Results were then compared with those of sedentary rats, and it was found that the exercised group of rats' spatial navigation performance was significantly improved due to exercise. Other studies have shown similar findings and included evidence of exercise enhancing fibroblast growth factor in the hippocampus, which was also accompanied by an increase in density in the hippocampus [Garza, A.A. et al., 2003; Gomez-Pinilla, F., So, V., & Kesslak, J.P., 1998].

Effects of Acute vs. Long-Term Exercise

The main difference between effects of acute exercise versus long-term exercise is in the area of the brain that it influences. Acute exercise has been shown to have significant effects on prefrontal cortex functioning but not hippocampal functioning [Basso, J.C. et al., 2015; Coles, K. & Tomporowski, P.D., 2008]. Basso and colleagues conducted a randomized control study with 85 participants who were either assigned to an intense acute aerobic exercise group, or a control sedentary group that comprised of watching videos. Based on the measures after exercise intervention or video-watching, the results showed that those who were assigned to the aerobic exercise group improved in tasks that were prefrontal cortex functions, but not in the hippocampus-dependent functions.

Studies done in young adult populations show that exercise increases BDNF levels in the hippocampus after 5 weeks of aerobic exercise intervention. Although this is considered short-term and the enhancements show in the hippocampus, the result may be attributed to the

difference of baseline BDNF levels in younger versus older adults [Griffin, E.W. et al., 2011]. We can attribute this minor discrepancy to the differences in brain capacity of young versus older adults, as other studies confirm the results of Basso and colleagues [Brisswalter, J. Collardeau, M. & René, A., 2002; Etnier, J.L. et al., 2016; Smith, M. et al., 2016]. It is difficult to determine the effects of exercise trajectory on the developing brain because of factors such as incremental inactivity, frequency, and intensity, that are paired with development. We can conclude that exercise is shown to have significant effects on cognition in the developing brain, thus increasing brain reserve capacity. Although more research is needed to determine the extent to which and how significant the effects of long-term exercise are on brain plasticity and overall cognitive functioning, the basic enhancements are significant [Perez, E. et al., 2019].

Exercise Effects on Passive Reserve

From these findings, we can conclude that frequent aerobic exercise plays a major role in delaying the onset of cognitive impairment. Exercise is shown to enhance areas of the brain and increase plasticity in the sensorimotor cortex, prefrontal cortex, and the hippocampus. Additionally, exercise increases neurogenesis in the hippocampus. Higher cognitive control and increases of volume translate to the ability to perform cognitive tasks efficiently and without disruption for a longer period of time. Brain volume loss is important in determining the amount of passive reserve that an individual has due to its correlations with cognition and control. The higher amount of passive reserve that an individual contains, the more likely they are to stay cognitively aware for longer and age more ‘successfully’. Normal aging is associated with volume loss in the brain overall, but exercise is seen to restore these losses and provide more plasticity. From this, we can conclude that exercise enhances passive reserve due to its ability to build more volume in areas that are responsible for cognitive control.

The second major function of the hippocampus is emotional regulation and emotional processing. The majority of research that has been done on exercise and the hippocampus demonstrates that exercise increases structure, therefore increasing mood function and reducing negative emotions [Arent, S.M., Landers, D.M., & Etnier, J.L., 2000; Berger, B.G. & Motl, R.W., 2008; Bittle, S.J.H., 2003; Reed, J. & Ones, D.S., 2005]. The clinical implications of determining the role of the hippocampus in emotion is that interventions that target the hippocampus can be used to treat mental illnesses such as major depressive disorder (MDD) and anxiety disorders. Using fMRI technology, one study elicited activations in the hippocampus by inducing emotions through recall of autobiographical memories [Zhu, Y. et al., 2019]. The control group was scanned at a resting state while the manipulated group was asked to recall autobiographical memories. The study found that the hippocampus in the brain was activated in the manipulated group. The figure below illustrates the differences between the manipulated and control group.

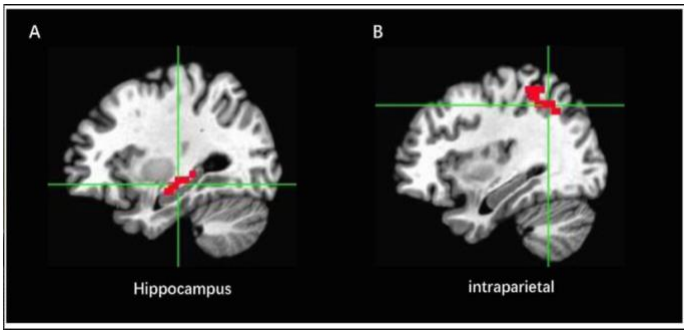


Figure 5 Brain Activation between Manipulated Group and Control Group

A represents the manipulated group that was required to recall an autobiographical memory while B represents the control group. As shown in the figure, group A had activation in the hippocampus while inducing emotion, and group B was at a resting state while taking the scan [Zhu, Y. et al., 2019].

DEPRESSION

Major Depressive Disorder

The most common form of depression is MDD. Individuals with this diagnosis present with 5 or more of the following criteria during the same two-week period: depressed mood, loss of interest/pleasure (anhedonia), weight loss or gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive/inappropriate guilt, decreased ability to think/concentrate or indecisiveness, and/or recurrent thoughts of death/suicide (American Psychiatric Association, 2013). Although the diagnostic criteria for major depressive disorder is the same in younger and older adults, symptoms of depression in older adults present differently. In older adults the presence of apathy is more common as opposed to intense feelings of sadness and sorrow.

Depression in Older Adults

Depression in older adults is generally underdiagnosed for several reasons. One specific reason for this is that older adults are less likely to go to their physicians and discuss their emotional and mental wellbeing because they do not view their doctor as one who can diagnose mental disorders, but rather only physiological health. Additionally, depression in older adults is often ignored because of the inaccurate assumption that the symptoms of depression presented are a normal part of aging. The elderly population is more difficult to treat because medications affect the geriatric population differently due to slower metabolism when compared to young adults.

Although it looks different in everyone, the key components of depression are similar in most cases. For older adults, depression affects individuals more cognitively rather than in mood impairments that is common with younger adults. Because of a lower level of plasticity and other

factors caused by normal aging, there is already a predisposition for older adults to have depression. Depression in older adults is linked to increased risk of mortality, suicide ideations or acts, and decreased cognitive and social functions compared to non-depressed individuals [Fiske, A., Wetherell, J.L., & Gatz, M., 2009]. Not only is it under-diagnosed, but it is also harder to treat in older adults because of factors such as compliance and side effects of medication that older adults have. Epidemiology suggests higher stress, lack of physical activity, lack of socialization, and genetic predisposition as some of the causes of depression in older adults [Pocklington, C. 2017].

Depression and Passive Reserve

Focusing specifically on the cognitive deficiencies that are more commonly found in older adults, the hippocampus plays a major role in the outlook of depression for many reasons. The first is that in depressed individuals, the hippocampal volume is decreased. As previously stated, the hippocampus plays a major role in not just memory and learning, but also emotion. There have been numerous studies that associate MDD with smaller hippocampal volumes, but it is not clear if hippocampal volume leads to depression, or if depression leads to smaller hippocampal volume [Sheline, Y.I., 2011]. A smaller hippocampus also assumes decreased cognitive stimulation such as neurogenesis, or synaptogenesis. Atrophy could also correlate with the decrease of structural components such as BDNF, and grey and white matter, that ultimately lead to deficits in overall hippocampal functioning.

There have been studies that are consistent with this hypothesis. One study examined the results of a smaller hippocampus leading to depression, but others have shown there is a bidirectional relationship between depression and the hippocampus [MacQueen, G. & Frodl, T., 2011; Sheline, Y.I. et al., 1996; Sheline, Y.I. et al., 1999]. One study suggests that BDNF

determines plasticity, neurogenesis, and synaptogenesis in the hippocampus, and lower levels of BDNF are correlated with smaller hippocampal volume, as well as with the presence of depression [Frodl, T. et al., 2007; Joffe, R.T. et al., 2009]. Conversely, depression may deplete these incremental resources [MacQueen, G. & Frodl, T., 2011].

Along with volumetric differences between depressed and non-depressed individuals, studies confirm that there is also decreased neurogenesis in the dentate gyrus of the hippocampus in depressed individuals. Additionally, there is loss of glial cells that are important in proper mood functions, that can be associated with the presence of depression in the brain [Arnone, D. et al., 2013; Campbell, S. & MacQueen, G. 2004; Frodl, T. et al., 2002; MacQueen, G.M. et al., 2003; Sapolsky, R.M., 2001; Steffens, D.C. et al., 2000]. There are several other lines of evidence for BDNF level associations with depression and hippocampal atrophy. One of these involves postmortem examinations of depressed patients and suicide victims. They were both found to have decreased levels of BDNF in different brain areas including the hippocampus and the prefrontal cortex [Duman, R.S. & Monteggia, L.M., 2006].

Regardless of the age of MDD onset, these volumetric differences have been seen to contribute to Alzheimer Disease as well as dementia in older adulthood, indicating that they have effects on cognitive decline, and possibly brain reserve capacity as well [Jorm, A.F. et al., 1991; Opel, N. et al., 2014; Speck, C.E. et al., 1995; Steffens, D.C. et al., 1997]. This is important in understanding the role that passive reserve plays in enhancing cognitive functioning.

Depression and Aerobic Exercise

Although medication and psychotherapy have been shown to improve the outlook of MDD, it is also important to look at preventative and reversing methods, such as exercise intervention. There are many outlined benefits to exercise for depression, including the

improvement of mood [Craft, L.L. & Perna, F.M., 2004], overall well-being [Bartholomew, J.B., Morrison, D., & Ciccolo, J.T., 2005], and an increase of neurogenesis, synaptogenesis, as well as an increase in BDNF specifically in the hippocampus [Erikson, K.I. et al., 2011].

Erikson and colleagues focused on the findings of BDNF and the relationships between the hippocampus, exercise, and depression. BDNF is found in high concentrations in the hippocampus and is critical in understanding hippocampal atrophy. BDNF supplements neurogenesis, synaptogenesis, and cell survival. Lower levels of BDNF indicate a greater chance of atrophy being present in that region. In the hippocampus specifically, reduced grey and white matter in that region explains why lower BDNF levels are associated with hippocampal atrophy and depression in an individual. BDNF can also be measured with cerebrospinal fluid (CSF), which is also seen to be associated with cognitive decline and neuropathology [Soldan, A. et al., 2013].

Although animal studies have shown cell proliferation in the dentate gyrus of the hippocampus, neurogenesis and the other preventative action for age-related decline, [Kronenberg, G. et al., 2005; van Praag et al., 2005] clinical studies are more complex. One study done recruited 165 older adults without dementia. After controlling for possible confounding variables, the results were consistent with animal studies in that aerobic exercise was associated with greater hippocampal volume. This finding was mediated by performance on a spatial memory task [Erikson, K.I. et al., 2009]. Another study demonstrated similar results and found that moderate-intensity endurance training also increased BDNF levels, neuronal growth, and plasticity in humans [Zoladz, J.A. et al., 2008].

Based on these findings it can be concluded that exercise enhances brain functioning in the hippocampus and prefrontal cortex, specifically. Furthermore, exercise can then be

determined to enhance passive reserve, leading an individual to live a longer healthier life with a reduced likelihood of developing depression.

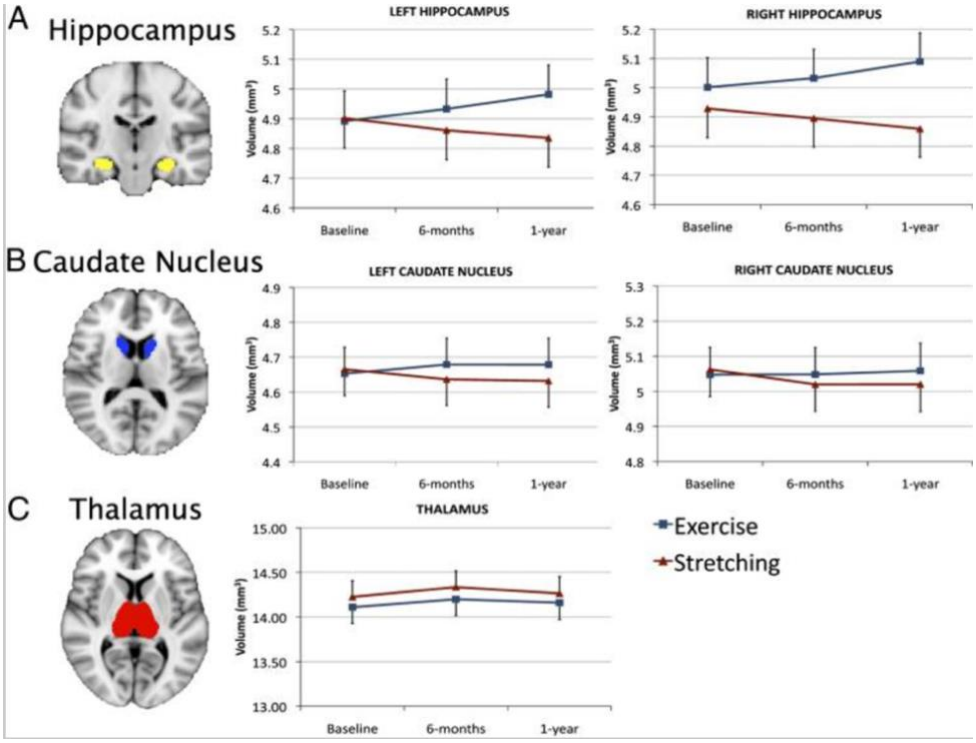


Figure 6: Significance of Exercise in the Hippocampus

Erikson and colleagues conducted a 1-year exercise intervention measuring both aerobic exercise and stretching effects in three areas of the brain. The most significant results occurred in the hippocampus as demonstrated by the graph title "A". [Erikson, K.I. et al., 2011].

CONCLUSION

The two components of cognitive reserve, passive and active reserve, make up the brain's resistance to normal age-related brain changes as well as any damage created by brain lesions or disease-related pathology. The structural component of cognitive reserve, represented by brain reserve capacity, is shown to be enhanced by lifestyle factors such as aerobic exercise. Aerobic exercise in early, middle, and older adulthood contributes to the growth of brain mass in areas such as the hippocampus and prefrontal cortex [Chen, F.T. et al., 2020]. The important functions of the hippocampus are enhanced with the presence of exercise. A greater amount of consistent

exercise leads to greater cognitive functioning and brain reserve capacity. This provides an increased ability to resist brain trauma and psychopathology [Cheng, S.T., 2016].

Normal age-related brain changes cause atrophy in brain structures such as the hippocampus and prefrontal cortex. Aerobic exercise is seen to protect against this growth, reverse negative effects, and increase volume [Erikson, K.I. et al., 2011]. Smaller hippocampal structures are also noticed in individuals with depression, making older adults more susceptible to depression [Raz, N. et al., 2005; Sapolsky, R.M., 2001]. The role of exercise in depression is enhancement of brain structure as well. Exercise's ability to build mass through neurogenesis, synaptogenesis, increase of BDNF in the hippocampus, and the increase of grey and white matter, can then lead to higher functioning in the brain structure. This heightened functioning in the hippocampus subsequently leads to improved mood regulation and memory/learning capacity. This could reduce the presence or even onset of depression, even as individuals age.

The focus of this thesis is on the passive reserve component of cognitive reserve which can be represented by brain reserve capacity. It has been demonstrated that aerobic exercise has a clear connection with the enhancement of brain reserve capacity through the increase in brain mass, specifically in areas such as the hippocampus and prefrontal cortex. Passive reserve can also be differentiated when comparing how different brain areas are affected by depression. Exercise increases neurogenesis and neurotrophic levels specifically in the hippocampal area. Therefore, it can be concluded that exercise reduces the incidence of depression as an individual ages [Cheng, S.T., 2016; Colcombe, S.J., 2006; Mora, F., 2013]. Following the cognitive reserve theory, due to these brain structures staying intact, other normal age-related changes would not impact an older individual's functioning or brain processes. The aerobic exercise enhancement of the hippocampus specifically includes the enhancement of structure and thus overall functioning

by neurogenesis, synaptogenesis, and the increase of BDNF, thereby reducing and even possibly preventing the development of depression. Consequently, exercise may lead an individual to age successfully with the increased passive reserve capacity available to combat experienced changes and reduce the likelihood of the onset of depression.

Implications

The findings from this thesis can further be used to design interventions for the treatment of depression in older adults, specifically through exercise. Compared with young adulthood, depression in older adulthood is presented and medicated differently, making it more challenging to treat. However, exercise is one consistent intervention that is effective in the treatment and possible prevention of depression in both younger and older adults. It is important to note that starting aerobic exercise late in older adulthood is still able to have reversible effects on atrophy in brain structures such as the hippocampus and prefrontal cortex. This is significant because this means that even in middle and older adulthood, passive reserve can be built and used to fight brain deterioration, normal age-related brain changes, and even the onset of psychopathology such as depression or dementia [Arent, S. et al., 2000; Rovio, S. et al., 2005].

Additionally, exercise can be a continuous enhancement of brain reserve capacity in young adulthood as well. The findings of acute vs. long-term exercise demonstrated that long-term exercise was seen to increase and sustain cognitive functioning through the building of brain reserve capacity. Given this knowledge, beginning exercise interventions in younger and older adulthood can prevent rapid cognitive decline associated with aging and even the onset of psychopathology.

REFERENCES

Ainslie, P. N., Cotter, J. D., George, K. P., Lucas, S., Murrell, C., Shave, R., Thomas, K. N., Williams, M. J. A., & Atkinson, G. (2008). Elevation in cerebral blood flow velocity with aerobic fitness throughout healthy human ageing. *The Journal of Physiology*, *586*(Pt 16), 4005–4010. https://doi.org/10.1113/jphysiol.2008.158279

Alexander, G. E., Furey, M. L., Grady, C. L., Pietrini, P., Brady, D. R., Mentis, M. J., & Schapiro, M. B. (1997). Association of premorbid intellectual function with cerebral metabolism in Alzheimer's disease: Implications for the cognitive reserve hypothesis. *The American Journal of Psychiatry*, *154*(2), 165–172. https://doi.org/10.1176/ajp.154.2.165

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Arlington, VA

Arent, S. M., Landers, D. M., & Etnier, J. L. (2000). The Effects of Exercise on Mood in Older Adults: A Meta-Analytic Review. *Journal of Aging & Physical Activity*, *8*(4), 407.

Arnone, D., McKie, S., Elliott, R., Juhasz, G., Thomas, E. J., Downey, D., Williams, S., Deakin, J. F. W., & Anderson, I. M. (2013). State-dependent changes in hippocampal grey matter in depression. *Molecular Psychiatry*, *18*(12), 1265–1272. https://doi.org/10.1038/mp.2012.150

Barnes, D. E., Yaffe, K., Satariano, W. A., & Tager, I. B. (2003). A longitudinal study of cardiorespiratory fitness and cognitive function in healthy older adults. *Journal of the American Geriatrics Society*, *51*(4), 459–465. https://doi.org/10.1046/j.1532-5415.2003.51153.x

Bartholomew, J. B., Morrison, D., & Ciccolo, J. T. (2005). Effects of Acute Exercise on Mood and Well-Being in Patients with Major Depressive Disorder. *Medicine & Science in Sports & Exercise*, *37*(12), 2032–2037. https://doi.org/10.1249/01.mss.0000178101.78322.dd

Barulli, D., & Stern, Y. (2013). Efficiency, capacity, compensation, maintenance, plasticity: Emerging concepts in cognitive reserve. *Trends in Cognitive Sciences*, *17*(10), 502–509. https://doi.org/10.1016/j.tics.2013.08.012

Basso, J. C., Shang, A., Elman, M., Karmouta, R., & Suzuki, W. A. (2015). Acute Exercise Improves Prefrontal Cortex but not Hippocampal Function in Healthy Adults. *Journal of the International Neuropsychological Society: JINS*, *21*(10), 791–801. https://doi.org/10.1017/S135561771500106X

Basso, J. C., & Suzuki, W. A. (2017). The Effects of Acute Exercise on Mood, Cognition, Neurophysiology, and Neurochemical Pathways: A Review. *Brain Plasticity*, *2*(2), 127–152. https://doi.org/10.3233/BPL-160040

Berger, B. G., & Motl, R. W. (2000). Exercise and mood: A selective review and synthesis of research employing the profile of mood states. *Journal of Applied Sport Psychology*, *12*(1), 69–92. https://doi.org/10.1080/10413200008404214

Bertsch, K., Hagemann, D., Hermes, M., Walter, C., Khan, R., & Naumann, E. (2009). Resting cerebral blood flow, attention, and aging. *Brain Research*, *1267*, 77–88. https://doi.org/10.1016/j.brainres.2009.02.053

Biddle, S. J. H., Fox, K., & Boutcher, S. (2003). *Physical Activity and Psychological Well-Being*. Routledge.

Boots, E. A., Schultz, S. A., Almeida, R. P., Oh, J. M., Koscik, R. L., Dowling, M. N., Gallagher, C. L., Carlsson, C. M., Rowley, H. A., Bendlin, B. B., Asthana, S., Sager, M. A., Hermann, B. P., Johnson, S. C., & Okonkwo, O. C. (2015). Occupational Complexity and Cognitive Reserve in a Middle-Aged Cohort at Risk for Alzheimer's Disease. *Archives of Clinical Neuropsychology*, *30*(7), 634–642. https://doi.org/10.1093/arclin/acv041

Brisswalter, J., Collardeau, M., & René, A. (2002). Effects of acute physical exercise characteristics on cognitive performance. *Sports Medicine (Auckland, N.Z.)*, *32*(9), 555–566. https://doi.org/10.2165/00007256-200232090-00002

Cabeza, R., Anderson, N. D., Locantore, J. K., & McIntosh, A. R. (2002). Aging Gracefully: Compensatory Brain Activity in High-Performing Older Adults. *NeuroImage; Amsterdam*, *17*(3), 1394–1402. http://dx.doi.org.ezproxy.lib.uh.edu/10.1006/nimg.2002.1280

Cavedo, E., Galluzzi, S., Pievani, M., Boccardi, M., & Frisoni, G. B. (2012). Norms for Imaging Markers of Brain Reserve. *Journal of Alzheimer's Disease*, *31*(3), 623–633. https://doi.org/10.3233/JAD-2012-111817

Chen, F.-T., Hopman, R. J., Huang, C.-J., Chu, C.-H., Hillman, C. H., Hung, T.-M., & Chang, Y.-K. (2020). The Effect of Exercise Training on Brain Structure and Function in Older Adults: A Systematic Review Based on Evidence from Randomized Control Trials. *Journal of Clinical Medicine*, *9*(4). https://doi.org/10.3390/jcm9040914

Cheng, S.-T. (2016). Cognitive Reserve and the Prevention of Dementia: The Role of Physical and Cognitive Activities. *Current Psychiatry Reports*, *18*(9), 85. https://doi.org/10.1007/s11920-016-0721-2

Chida, Y., & Hamer, M. (2008). Chronic psychosocial factors and acute physiological responses to laboratory-induced stress in healthy populations: A quantitative review of 30 years of investigations. *Psychological Bulletin*, *134*(6), 829–885. https://doi.org/10.1037/a0013342

Christie, G. J., Hamilton, T., Manor, B. D., Farb, N. A. S., Farzan, F., Sixsmith, A., Temprado, J.-J., & Moreno, S. (2017). Do Lifestyle Activities Protect Against Cognitive Decline in Aging? A Review. *Frontiers in Aging Neuroscience*, *9*. https://doi.org/10.3389/fnagi.2017.00381

Colcombe, S. J., Erickson, K. I., Scalf, P. E., Kim, J. S., Prakash, R., McAuley, E., Elavsky, S., Marquez, D. X., Hu, L., & Kramer, A. F. (2006). Aerobic Exercise Training Increases Brain Volume in Aging Humans. *The Journals of Gerontology: Series A*, *61*(11), 1166–1170. https://doi.org/10.1093/gerona/61.11.1166

Colcombe, S., & Kramer, A. F. (2003). Fitness Effects on the Cognitive Function of Older Adults: A Meta-Analytic Study. *Psychological Science*, *14*(2), 125–130. https://doi.org/10.1111/1467-9280.t01-1-01430

Coles, K., & Tomporowski, P. D. (2008). Effects of acute exercise on executive processing, short-term and long-term memory. *Journal of Sports Sciences*, *26*(3), 333–344. https://doi.org/10.1080/02640410701591417

Cotman, C. W., & Berchtold, N. C. (2002). Exercise: A behavioral intervention to enhance brain health and plasticity. *Trends in Neurosciences*, *25*(6), 295–301. https://doi.org/10.1016/S0166-2236(02)02143-4

Craft, L. L., & Perna, F. M. (2004). The Benefits of Exercise for the Clinically Depressed. *Primary Care Companion to The Journal of Clinical Psychiatry*, *6*(3), 104–111.

Drevets, W. C., Price, J. L., & Furey, M. L. (2008). Brain structural and functional abnormalities in mood disorders: Implications for neurocircuitry models of depression. *Brain Structure & Function*, *213*(1–2), 93–118. https://doi.org/10.1007/s00429-008-0189-x

Duman, R. S., & Monteggia, L. M. (2006). A Neurotrophic Model for Stress-Related Mood Disorders. *Biological Psychiatry*, *59*(12), 1116–1127. https://doi.org/10.1016/j.biopsych.2006.02.013

Erickson, K. I., Prakash, R. S., Voss, M. W., Chaddock, L., Hu, L., Morris, K. S., White, S. M., Wójcicki, T. R., McAuley, E., & Kramer, A. F. (2009). Aerobic Fitness is Associated With

Hippocampal Volume in Elderly Humans. *Hippocampus*, *19*(10), 1030. https://doi.org/10.1002/hipo.20547

Erickson, K. I., Voss, M. W., Prakash, R. S., Basak, C., Szabo, A., Chaddock, L., Kim, J. S., Heo, S., Alves, H., White, S. M., Wojcicki, T. R., Mailey, E., Vieira, V. J., Martin, S. A., Pence, B. D., Woods, J. A., McAuley, E., & Kramer, A. F. (2011). Exercise training increases size of hippocampus and improves memory. *Proceedings of the National Academy of Sciences*, *108*(7), 3017–3022. https://doi.org/10.1073/pnas.1015950108

Etnier, J. L., Wideman, L., Labban, J. D., Piepmeier, A. T., Pendleton, D. M., Dvorak, K. K., & Becofsky, K. (2016). The Effects of Acute Exercise on Memory and Brain-Derived Neurotrophic Factor (BDNF). *Journal of Sport & Exercise Psychology*, *38*(4), 331–340.

Evans, D. A., Beckett, L. A., Albert, M. S., Hebert, L. E., Scherr, P. A., Funkenstein, H. H., & Taylor, J. O. (1993). Level of education and change in cognitive function in a community population of older persons. *Annals of Epidemiology*, *3*(1), 71–77. https://doi.org/10.1016/1047-2797(93)90012-S

Fiske, A., Wetherell, J. L., & Gatz, M. (2009). Depression in Older Adults. *Annual Review of Clinical Psychology*, *5*, 363–389. https://doi.org/10.1146/annurev.clinpsy.032408.153621

Fjell, A. M., Walhovd, K. B., Fennema-Notestine, C., McEvoy, L. K., Hagler, D. J., Holland, D., Brewer, J. B., & Dale, A. M. (2009). One-Year Brain Atrophy Evident in Healthy Aging. *The Journal of Neuroscience*, *29*(48), 15223–15231. https://doi.org/10.1523/JNEUROSCI.3252-09.2009

Frodl, T., Meisenzahl, E. M., Zetzsche, T., Born, C., Groll, C., Jäger, M., Leinsinger, G., Bottlender, R., Hahn, K., & Möller, H.-J. (2002). Hippocampal Changes in Patients With a First Episode of

Major Depression. *American Journal of Psychiatry*, *159*(7), 1112–1118. https://doi.org/10.1176/appi.ajp.159.7.1112

Frodl, T., Schüle, C., Schmitt, G., Born, C., Baghai, T., Zill, P., Bottlender, R., Rupprecht, R., Bondy, B., Reiser, M., Möller, H.-J., & Meisenzahl, E. M. (2007). Association of the Brain-Derived Neurotrophic Factor Val66Met Polymorphism With Reduced Hippocampal Volumes in Major Depression. *Archives of General Psychiatry*, *64*(4), 410–416. https://doi.org/10.1001/archpsyc.64.4.410

Garza, A. A., Ha, T. G., Garcia, C., Chen, M. J., & Russo-Neustadt, A. A. (2004). Exercise, antidepressant treatment, and BDNF mRNA expression in the aging brain. *Pharmacology Biochemistry and Behavior*, *77*(2), 209–220. https://doi.org/10.1016/j.pbb.2003.10.020

Gómez-Pinilla, F., So, V., & Kesslak, J. P. (1998). Spatial learning and physical activity contribute to the induction of fibroblast growth factor: Neural substrates for increased cognition associated with exercise. *Neuroscience*, *85*(1), 53–61. https://doi.org/10.1016/s0306-4522(97)00576-9

Griffin, É. W., Mullally, S., Foley, C., Warmington, S. A., O'Mara, S. M., & Kelly, Á. M. (2011). Aerobic exercise improves hippocampal function and increases BDNF in the serum of young adult males. *Physiology & Behavior*, *104*(5), 934–941. https://doi.org/10.1016/j.physbeh.2011.06.005

Haier, R. J., Siegel, B. V., Nuechterlein, K. H., Hazlett, E., Wu, J. C., Paek, J., Browning, H. L., & Buchsbaum, M. S. (1988). Cortical glucose metabolic rate correlates of abstract reasoning and attention studied with positron emission tomography. *Intelligence*, *12*(2), 199–217. https://doi.org/10.1016/0160-2896(88)90016-5

Hillman, C. H., Erickson, K. I., & Kramer, A. F. (2008). Be smart, exercise your heart: Exercise effects on brain and cognition. *Nature Reviews Neuroscience*, *9*(1), 58–65. https://doi.org/10.1038/nrn2298

Hoffman, J. M., Welsh-Bohmer, K. A., Hanson, M., Crain, B., Hulette, C., Earl, N., & Coleman, R. E. (2000). FDG PET imaging in patients with pathologically verified dementia. *Journal of Nuclear Medicine: Official Publication, Society of Nuclear Medicine*, *41*(11), 1920–1928.

Interplay between brain-derived neurotrophic factor and signal transduction modulators in the regulation of the effects of exercise on synaptic-plasticity. (2003). *Neuroscience*, *122*(3), 647–657. https://doi.org/10.1016/j.neuroscience.2003.08.001

Jack, C. R., Wiste, H. J., Vemuri, P., Weigand, S. D., Senjem, M. L., Zeng, G., Bernstein, M. A., Gunter, J. L., Pankratz, V. S., Aisen, P. S., Weiner, M. W., Petersen, R. C., Shaw, L. M., Trojanowski, J. Q., Knopman, D. S., & Initiative, the A. D. N. (2010). Brain beta-amyloid measures and magnetic resonance imaging atrophy both predict time-to-progression from mild cognitive impairment to Alzheimer's disease. *Brain*, *133*(11), 3336–3348. https://doi.org/10.1093/brain/awq277

Joffe, R. T., Gatt, J. M., Kemp, A. H., Grieve, S., Dobson-Stone, C., Kuan, S. A., Schofield, P. R., Gordon, E., & Williams, L. M. (2008). Brain derived neurotrophic factor Val66Met polymorphism, the five factor model of personality and hippocampal volume: Implications for depressive illness. *Human Brain Mapping*, *30*(4), 1246–1256. https://doi.org/10.1002/hbm.20592

Jorm, A. F., Group, A. H. for the E. R. F. R., Van Duijn, C. M., Group, A. H. for the E. R. F. R., Chandra, V., Group, A. H. for the E. R. F. R., Fratiglioni, L., Group, A. H. for the E. R. F. R., Graves, A. B., Group, A. H. for the E. R. F. R., Heyman, A., Group, A. H. for the E. R. F. R., Kokmen, E., Group, A. H. for the E. R. F. R., Kondo, K., Group, A. H. for the E. R. F. R.,

Mortimer, J. A., Group, A. H. for the E. R. F. R., Rocca, W. A., … Group, A. H. for the E. R. F. R. (1991). Psychiatric History and Related Exposures as Risk Factors for Alzheimer's Disease: A Collaborative Re-Analysis of Case-Control Studies. *International Journal of Epidemiology*, *20*(Supplement_2), S43–S47. https://doi.org/10.1093/ije/20.Supplement_2.S43

Katzman, R. (1993). Education and the prevalence of dementia and Alzheimer's disease. *Neurology*, *43*(1), 13–20. https://doi.org/10.1212/WNL.43.1_Part_1.13

Kesler, S. R., Tanaka, H., & Koovakkattu, D. (2010). Cognitive reserve and brain volumes in pediatric acute lymphoblastic leukemia. *Brain Imaging and Behavior*, *4*(3), 256–269. https://doi.org/10.1007/s11682-010-9104-1

Kim, Y.-P., Kim, H., Shin, M.-S., Chang, H.-K., Jang, M.-H., Shin, M.-C., Lee, S.-J., Lee, H.-H., Yoon, J.-H., Jeong, I.-G., & Kim, C.-J. (2004). Age-dependence of the effect of treadmill exercise on cell proliferation in the dentate gyrus of rats. *Neuroscience Letters*, *355*(1–2), 152–154. https://doi.org/10.1016/j.neulet.2003.11.005

Kramer, A. F., Erickson, K. I., & Colcombe, S. J. (2006). Exercise, cognition, and the aging brain. *Journal of Applied Physiology*, *101*(4), 1237–1242. https://doi.org/10.1152/japplphysiol.00500.2006

Kronenberg, G., Bick-Sander, A., Bunk, E., Wolf, C., Ehninger, D., & Kempermann, G. (2006). Physical exercise prevents age-related decline in precursor cell activity in the mouse dentate gyrus. *Neurobiology of Aging*, *27*(10), 1505–1513. https://doi.org/10.1016/j.neurobiolaging.2005.09.016

Lam, R. W., Kennedy, S. H., McIntyre, R. S., & Khullar, A. (2014). Cognitive Dysfunction in Major Depressive Disorder: Effects on Psychosocial Functioning and Implications for Treatment. *Canadian Journal of Psychiatry. Revue Canadienne de Psychiatrie*, *59*(12), 649–654.

Larson, E. B., Wang, L., Bowen, J. D., McCormick, W. C., Teri, L., Crane, P., & Kukull, W. (2006). Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. *Annals of Internal Medicine*, *144*(2), 73–81. https://doi.org/10.7326/0003-4819-144-2-200601170-00004

Lövdén, M., Bäckman, L., Lindenberger, U., Schaefer, S., & Schmiedek, F. (2010). A theoretical framework for the study of adult cognitive plasticity. *Psychological Bulletin*, *136*(4), 659–676. https://doi.org/10.1037/a0020080

MacQueen, G., & Frodl, T. (2011). The hippocampus in major depression: Evidence for the convergence of the bench and bedside in psychiatric research? *Molecular Psychiatry*, *16*(3), 252–264. https://doi.org/10.1038/mp.2010.80

MacQueen, G. M., Campbell, S., McEwen, B. S., Macdonald, K., Amano, S., Joffe, R. T., Nahmias, C., & Young, L. T. (2003). Course of illness, hippocampal function, and hippocampal volume in major depression. *Proceedings of the National Academy of Sciences of the United States of America*, *100*(3), 1387–1392. https://doi.org/10.1073/pnas.0337481100

Mahncke, H. W., Connor, B. B., Appelman, J., Ahsanuddin, O. N., Hardy, J. L., Wood, R. A., Joyce, N. M., Boniske, T., Atkins, S. M., & Merzenich, M. M. (2006). Memory enhancement in healthy older adults using a brain plasticity-based training program: A randomized, controlled study. *Proceedings of the National Academy of Sciences*, *103*(33), 12523–12528. https://doi.org/10.1073/pnas.0605194103

Manly, J. J., Schupf, N., Tang, M.-X., & Stern, Y. (2005). Cognitive Decline and Literacy Among Ethnically Diverse Elders. *Journal of Geriatric Psychiatry and Neurology*, *18*(4), 213–217. https://doi.org/10.1177/0891988705281868

Manly, J. J., Touradji, P., Tang, M.-X., & Stern, Y. (2003). Literacy and Memory Decline Among Ethnically Diverse Elders. *Journal of Clinical and Experimental Neuropsychology*, *25*(5), 680–690. https://doi.org/10.1076/jcen.25.5.680.14579

McGeer, P. L., Kamo, H., Harrop, R., Li, D. K., Tuokko, H., McGeer, E. G., Adam, M. J., Ammann, W., Beattie, B. L., & Calne, D. B. (1986). Positron emission tomography in patients with clinically diagnosed Alzheimer's disease. *CMAJ: Canadian Medical Association Journal = Journal de l'Association Medicale Canadienne*, *134*(6), 597–607.

Mortel, K. F., Meyer, J. S., Herod, B., & Thornby, J. (1995). Education and Occupation as Risk Factors for Dementias of the Alzheimer and Ischemic Vascular Types. *Dementia and Geriatric Cognitive Disorders*, *6*(1), 55–62. https://doi.org/10.1159/000106922

Mortimer, J. A., Snowdon, D. A., & Markesbery, W. R. (2003). Head Circumference, Education and Risk of Dementia: Findings from the Nun Study. *Journal of Clinical and Experimental Neuropsychology*, *25*(5), 671–679. https://doi.org/10.1076/jcen.25.5.671.14584

Neeper, S. A., Góauctemez-Pinilla, F., Choi, J., & Cotman, C. (1995). Exercise and brain neurotrophins. *Nature*, *373*(6510), 109–109. https://doi.org/10.1038/373109a0

Norton, S., Matthews, F. E., Barnes, D. E., Yaffe, K., & Brayne, C. (2014). Potential for primary prevention of Alzheimer's disease: An analysis of population-based data. *The Lancet Neurology*, *13*(8), 788–794. https://doi.org/10.1016/S1474-4422(14)70136-X

Opel, N., Redlich, R., Zwanzger, P., Grotegerd, D., Arolt, V., Heindel, W., Konrad, C., Kugel, H., & Dannlowski, U. (2014). Hippocampal Atrophy in Major Depression: A Function of Childhood Maltreatment Rather than Diagnosis? *Neuropsychopharmacology*, *39*(12), 2723. https://doi.org/10.1038/npp.2014.145

Pang, P. T., & Lu, B. (2004). Regulation of late-phase LTP and long-term memory in normal and aging hippocampus: Role of secreted proteins tPA and BDNF. *Ageing Research Reviews*, *3*(4), 407–430. https://doi.org/10.1016/j.arr.2004.07.002

Perneczky, R., Drzezga, A., Diehl-Schmid, J., Schmid, G., Wohlschläger, A., Kars, S., Grimmer, T., Wagenpfeil, S., Monsch, A., & Kurz, A. (2006). Schooling mediates brain reserve in Alzheimer's disease: Findings of fluoro-deoxy-glucose-positron emission tomography. *Journal of Neurology, Neurosurgery, and Psychiatry*, *77*(9), 1060–1063. https://doi.org/10.1136/jnnp.2006.094714

Pocklington, C. (2017). *Depression in older adults*. *10*(1), 7.

Podewils, L. J., Guallar, E., Kuller, L. H., Fried, L. P., Lopez, O. L., Carlson, M., & Lyketsos, C. G. (2005). Physical activity, APOE genotype, and dementia risk: Findings from the Cardiovascular Health Cognition Study. *American Journal of Epidemiology*, *161*(7), 639–651. https://doi.org/10.1093/aje/kwi092

Rasmussen, P., Brassard, P., Adser, H., Pedersen, M. V., Leick, L., Hart, E., Secher, N. H., Pedersen, B. K., & Pilegaard, H. (2009). Evidence for a release of brain-derived neurotrophic factor from the brain during exercise. *Experimental Physiology*, *94*(10), 1062–1069. https://doi.org/10.1113/expphysiol.2009.048512

Raz, N., Lindenberger, U., Rodrigue, K. M., Kennedy, K. M., Head, D., Williamson, A., Dahle, C., Gerstorf, D., & Acker, J. D. (2005). Regional Brain Changes in Aging Healthy Adults: General Trends, Individual Differences and Modifiers. *Cerebral Cortex*, *15*(11), 1676–1689. https://doi.org/10.1093/cercor/bhi044

Roca, M., Parr, A., Thompson, R., Woolgar, A., Torralva, T., Antoun, N., Manes, F., & Duncan, J. (2010). Executive function and fluid intelligence after frontal lobe lesions. *Brain*, *133*(1), 234–247. https://doi.org/10.1093/brain/awp269

Rocca, W. A., Bonaiuto, S., Lippi, A., Luciani, P., Turtù, F., Cavarzeran, F., & Amaducci, L. (1990). Prevalence of clinically diagnosed Alzheimer's disease and other dementing disorders: A door-to-door survey in Appignano, Macerata Province, Italy. *Neurology*, *40*(4), 626–631. https://doi.org/10.1212/wnl.40.4.626

Rosano, C., Venkatraman, V. K., Guralnik, J., Newman, A. B., Glynn, N. W., Launer, L., Taylor, C. A., Williamson, J., Studenski, S., Pahor, M., & Aizenstein, H. (2010). Psychomotor Speed and Functional Brain MRI 2 Years After Completing a Physical Activity Treatment. *The Journals of Gerontology: Series A*, *65A*(6), 639–647. https://doi.org/10.1093/gerona/glq038

Rovio, S., Kåreholt, I., Helkala, E.-L., Viitanen, M., Winblad, B., Tuomilehto, J., Soininen, H., Nissinen, A., & Kivipelto, M. (2005). Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease. *The Lancet. Neurology*, *4*(11), 705–711. https://doi.org/10.1016/S1474-4422(05)70198-8

Sapolsky, R. M. (2001). Depression, antidepressants, and the shrinking hippocampus. *Proceedings of the National Academy of Sciences of the United States of America*, *98*(22), 12320–12322. https://doi.org/10.1073/pnas.231475998

Satz, P. (1993). Brain reserve capacity on symptom onset after brain injury: A formulation and review of evidence for threshold theory. *Neuropsychology*, *7*(3), 273–295. https://doi.org/10.1037/0894-4105.7.3.273

Schofield, P. W., Tang, M., Marder, K., Bell, K., Dooneief, G., Chun, M., Sano, M., Stern, Y., & Mayeux, R. (1997). Alzheimer's disease after remote head injury: An incidence study. *Journal of Neurology, Neurosurgery & Psychiatry*, *62*(2), 119–124. https://doi.org/10.1136/jnnp.62.2.119

Sheline, Y I, Wang, P. W., Gado, M. H., Csernansky, J. G., & Vannier, M. W. (1996). Hippocampal atrophy in recurrent major depression. *Proceedings of the National Academy of Sciences of the United States of America*, *93*(9), 3908–3913.

Sheline, Yvette I., Sanghavi, M., Mintun, M. A., & Gado, M. H. (1999). Depression Duration But Not Age Predicts Hippocampal Volume Loss in Medically Healthy Women with Recurrent Major Depression. *The Journal of Neuroscience*, *19*(12), 5034. https://doi.org/10.1523/JNEUROSCI.19-12-05034.1999

Smith, J. C., Nielson, K. A., Woodard, J. L., Seidenberg, M., Verber, M. D., Durgerian, S., Antuono, P., Butts, A. M., Hantke, N. C., Lancaster, M. A., & Rao, S. M. (2011). Does Physical Activity Influence Semantic Memory Activation in Amnestic Mild Cognitive Impairment? *Psychiatry Research*, *193*(1), 60–62. https://doi.org/10.1016/j.pscychresns.2011.04.001

Smith, M., Tallis, J., Miller, A., Clarke, N. D., Guimarães-Ferreira, L., & Duncan, M. J. (2016). The effect of exercise intensity on cognitive performance during short duration treadmill running. *Journal of Human Kinetics*, *51*, 27–35. https://doi.org/10.1515/hukin-2015-0167

Soldan, A., Pettigrew, C., Li, S., Wang, M.-C., Moghekar, A., Selnes, O. A., Albert, M., & O'Brien, R. (2013). Relationship of cognitive reserve and CSF biomarkers to emergence of clinical symptoms in preclinical Alzheimer's Disease. *Neurobiology of Aging*, *34*(12). https://doi.org/10.1016/j.neurobiolaging.2013.06.017

Speck, C. E., Kukull, W. A., Brenner, D. E., Bowen, J. D., McCormick, W. C., Teri, L., Pfanschmidt, M. L., Thompson, J. D., & Larson, E. B. (1995). History of Depression as a Risk Factor for Alzheimer's Disease. *Epidemiology*, *6*(4), 366–369. JSTOR.

Steffens, D. C., Byrum, C. E., McQuoid, D. R., Greenberg, D. L., Payne, M. E., Blitchington, T. F., MacFall, J. R., & Krishnan, K. R. R. (2000). Hippocampal volume in geriatric depression. *Biological Psychiatry*, *48*(4), 301–309. https://doi.org/10.1016/S0006-3223(00)00829-5

Steffens, D. C., Plassman, B. L., Helms, M. J., Welsh-Bohmer, K. A., Saunders, A. M., & Breitner, J. C. S. (n.d.). *A Twin Study of Late-Onset Depression and Apolipoprotein E e4 as Risk Factors for Alzheimer' s Disease*. 6.

Stern, Y., Alexander, G. E., Prohovnik, I., Stricks, L., Link, B., Lennon, M. C., & Mayeux, R. (1995). Relationship between lifetime occupation and parietal flow: Implications for a reserve against Alzheimer's disease pathology. *Neurology*, *45*(1), 55–60. https://doi.org/10.1212/wnl.45.1.55

Stern, Yaakov. (2009). Cognitive Reserve. *Neuropsychologia*, *47*(10), 2015–2028. https://doi.org/10.1016/j.neuropsychologia.2009.03.004

Stern, Yaakov. (2012). Cognitive reserve in ageing and Alzheimer's disease. *The Lancet Neurology*, *11*(11), 1006–1012. https://doi.org/10.1016/S1474-4422(12)70191-6

Stern, Yaakov, Gurland, B., Tatemichi, T. K., Tang, M. X., Wilder, D., & Mayeux, R. (1994). Influence of Education and Occupation on the Incidence of Alzheimer's Disease. *JAMA*, *271*(13), 1004–1010. https://doi.org/10.1001/jama.1994.03510370056032

Valenzuela, M. J., & Sachdev, P. (2006). Brain reserve and dementia: A systematic review. *Psychological Medicine*, *36*(4), 441–454. https://doi.org/10.1017/S0033291705006264

Valenzuela, M. J., & Sachdev, P. (2007). Assessment of complex mental activity across the lifespan: Development of the Lifetime of Experiences Questionnaire (LEQ). *Psychological Medicine*, *37*(7), 1015–1025. https://doi.org/10.1017/S003329170600938X

van Loenhoud, A. C., Groot, C., Vogel, J. W., van der Flier, W. M., & Ossenkoppele, R. (2018). Is intracranial volume a suitable proxy for brain reserve? *Alzheimer's Research & Therapy*, *10*(1), 91. https://doi.org/10.1186/s13195-018-0408-5

van Praag, H., Kempermann, G., & Gage, F. H. (1999). Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nature Neuroscience*, *2*(3), 266–270. https://doi.org/10.1038/6368

van Praag, H., Shubert, T., Zhao, C., & Gage, F. H. (2005). Exercise Enhances Learning and Hippocampal Neurogenesis in Aged Mice. *The Journal of Neuroscience*, *25*(38), 8680. https://doi.org/10.1523/JNEUROSCI.1731-05.2005

Vaynman, S., Ying, Z., & Gomez-Pinilla, F. (2004). Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. *European Journal of Neuroscience*, *20*(10), 2580–2590. https://doi.org/10.1111/j.1460-9568.2004.03720.x

Weuve, J., Kang, J. H., Manson, J. E., Breteler, M. M. B., Ware, J. H., & Grodstein, F. (2004). Physical activity, including walking, and cognitive function in older women. *JAMA*, *292*(12), 1454–1461. https://doi.org/10.1001/jama.292.12.1454

Xu, W., Yu, J.-T., Tan, M.-S., & Tan, L. (2015). Cognitive Reserve and Alzheimer's Disease. *Molecular Neurobiology*, *51*(1), 187–208. https://doi.org/10.1007/s12035-014-8720-y

Yaffe, K., Barnes, D., Nevitt, M., Lui, L.-Y., & Covinsky, K. (2001). A Prospective Study of Physical Activity and Cognitive Decline in Elderly Women: Women Who Walk. *Archives of Internal Medicine*, *161*(14), 1703–1708. https://doi.org/10.1001/archinte.161.14.1703

Yamada, M., Kasagi, F., Sasaki, H., Masunari, N., Mimori, Y., & Suzuki, G. (2003). Association Between Dementia and Midlife Risk Factors: The Radiation Effects Research Foundation Adult Health Study. *Journal of the American Geriatrics Society*, *51*(3), 410–414. https://doi.org/10.1046/j.1532-5415.2003.51117.x

Zarif, H., Nicolas, S., Petit-Paitel, A., Chabry, J., & Guyon, A. (2017). How Does an Enriched Environment Impact Hippocampus Brain Plasticity? *The Hippocampus - Plasticity and Functions*. https://doi.org/10.5772/intechopen.71426

Zhu, Y., Gao, H., Tong, L., Li, Z., Wang, L., Zhang, C., Yang, Q., & Yan, B. (2019). Emotion Regulation of Hippocampus Using Real-Time fMRI Neurofeedback in Healthy Human. *Frontiers in Human Neuroscience*, *13*. https://doi.org/10.3389/fnhum.2019.00242

Zoladz, J. A., Pilc, A., Majerczak, J., Grandys, M., Zapart-Bukowska, J., & Duda, K. (2008). Endurance training increases plasma brain-derived neurotrophic factor concentration in young healthy men. *Journal of Physiology and Pharmacology: An Official Journal of the Polish Physiological Society*, *59 Suppl 7*, 119–132.