EXERCISE & SPORT NUTRITION REVIEWS

EXERCISE & SPORT NUTRITION LABORATORY
TEXAS A&M UNIVERSITY

Article

Exercise and its role in treating neurodegenerative diseases: a scientific review

Lacey Wert[1,*]

[1] Exercise & Sport Nutrition Lab, Department of Health & Kinesiology, Human Clinical Research Facility, College Station, Texas, USA, 77843-4253

* Correspondence: laceynwert@gmail.com

Received: April 1, 2019; Accepted: May 15, 2019; Published: July 28, 2019

Abstract: Neurodegenerative diseases afflict many people causing the patients and their families to suffer. Diseases such as Parkinson's Disease, Alzheimer's Disease, and Multiple Sclerosis are progressive degenerative disorders for which, as of now, there is no definitive cure. Recent research has focused on the effect of exercise on neurodegenerative diseases. It is well known that exercise has many essential health benefits but, can exercise be used to combat mental diseases? More specifically, what is the role of exercise in treating neurodegenerative diseases? This review describes all the current research regarding exercise and its therapeutic role in treating Parkinson's Disease, Alzheimer's Disease, and Multiple Sclerosis.

Keywords: Exercise, Neurodegenerative, Parkinson's Disease, Alzheimer's Disease, Multiple Sclerosis

1. Introduction

The human brain is a complex organ. It holds great responsibility. The brain must regulate heart rate, breathing, digestion, hormone levels, skeletal movement, and blood chemistry. It must also take life experiences and learned materials and store them as memory. All the while, our brain is regulating our emotions and organizing thoughts thereby producing our mood and personality. Neurons are the primary cell type in the brain; the fundamental unit. The brain communicates with itself, other parts of the body, and the environment through the synaptic connections of neurons. Each neuron, or nerve cell, can form thousands of these connections and transmit signals across a synapse to the next neuron, and the next, and so forth. At birth, we are born with a certain number of synaptic connections. As we grow and learn and move, we form more neural connections. The brain's ability to form new connections is called neuroplasticity. Without neuroplasticity, humans would not be able to learn or adapt to our environment. What we do on a day to day basis effects the plasticity of our brains, including exercise. Studies have shown that exercise can be beneficial, even instrumental, in the neuroplasticity of the brain.

The Center for Disease Control (CDC) recommends that an adult should get at least 150 minutes of moderate-intensity aerobic exercise each week. Further health benefits develop when strength conditioning is implemented at least 2 days a week working all major muscle groups (*Physical Activity Guidelines for Americans* 2018). Regular exercise is shown to decrease the risk of cardiovascular disease, type 2 diabetes, and various types of cancer. Doctors will even prescribe exercise as treatment to some patients suffering from disorders like depression, osteoporosis, and diabetes. A study by Xu and colleagues shows that a resistance exercise program can preserve, or even improve, bone density in patients with osteoporosis (Xu, Lombardi, Jiao, & Banfi, 2016). Clearly, exercise has a plethora of physical health benefits. What about mental health benefits?

Recent studies have shown that the role of exercise in neuroplasticity may indicate a therapeutic role of exercise in slowing onset of neurodegenerative diseases. Exercise is even shown to decrease the side effects of certain neurodegenerative diseases. Unfortunately, many people battle a neurodegenerative disease later in life where neurons in the brain become permanently damaged. These are progressive diseases for which, as of now, there is no cure.

The purpose of this review is to consolidate the literature on the impact that exercise has on neurodegenerative diseases. I have reviewed all research and have formulated exercise's overall benefit on brain health. The evidence presented in this review provides hope to those suffering from neurodegenerative diseases.

2. Methods

A comprehensive review of literature was conducted by searching the PubMed database of the US National Library of Medicine of the National Institutes of Health. This search was made in EndNote, a reference management software, by searching keywords such as, neuroplasticity, exercise, rehabilitation, Parkinson's, Alzheimer's, and neurodegenerative. A database of over 200 articles were considered for this review. Data from a smaller subset of 20 articles is included in this review.

3. Exercise and its Effect on Parkinson's Disease

Parkinson's Disease (PD) is a common neurodegenerative disorder that affects over 1.5 million Americans every year (Alberts, Linder, Penko, Lowe, & Phillips, 2011). The disorder is characterized by many motor deficits such as tremors, postural instability, gait problems, slow movement, and immobility (Mak, Wong-Yu, Shen, & Chung, 2017). These motor deficits are caused by a loss of dopamine production in the brain. Parkinson's Disease is classified as a neurodegenerative disorder because it leads to the degeneration of substantia nigra neurons – neurons that produce dopamine (Petzinger et al., 2010). Dopamine plays a vital role in the generation of movement and the control of movement (Meder D, 2018). Thus, PD is associated with muscle tremors; the lack of dopamine leads to less control of muscle movement (see Figure 1.). There is no known cure for PD yet, however, exciting new research suggests that exercise may promote brain repair in those suffering from this disorder.

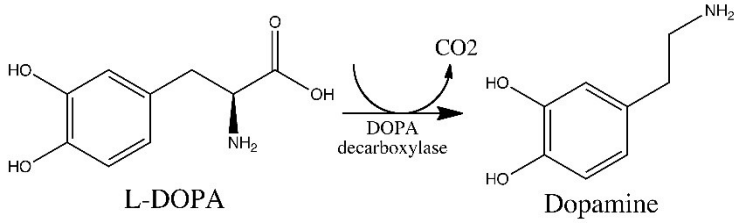

Figure 1. Levodopa Metabolic Pathway (from (harma, 2016)

3.1. Exercise on Dopaminergic Neurotransmission

One bout of exercise can impact overall brain health by reducing inflammation, stabilizing calcium homeostasis, releasing endogenous endorphins, and stimulating nerve growth factor (Hirsch & Farley, 2009). More importantly for PD patients, exercise induces changes in dopaminergic neurotransmission (Petzinger et al., 2010). Following an acute bout of exercise, there is evidence of increased dopamine synthesis in the brain (King & Horak, 2009). King and colleagues performed a study on the benefit of treadmill training and walking programs for people with Parkinson's Disease. Their results explain that exercise combats PD by improving the brain's ability to produce levodopa, a biological precursor to dopamine. The more levodopa available, the more dopamine can be produced thus decreasing motor deficits of the disease. Additionally, Fisher, Petzinger, and colleagues performed a study in 2013 confirming the results of King's and Horak's study. They found that PD patients participating in an exercise program showed an 81% to 98% increase in dopamine availability. Moreover, 23% of patients not participating in an exercise program showed a decrease in dopamine availability (Fisher et al., 2013). As previously mentioned, PD brings with it a multitude of mobility dysfunctions. Since dopamine plays a major role in motor control, the absence of dopamine leads to poor coordination, reduced motor function, bradykinesia (slow movement), decreased range of motion, and an increased risk of falls. By increasing the amount of dopamine available in the brain, many motor deficits caused by PD will decrease or subside altogether.

3.2. Exercise and the Release of Neurotrophins

Exercise has also been shown to have neuroprotective effects in the brain. Even more so, inactivity is thought to be prodegenerative (Hirsch & Farley, 2009). Hirsch and Farley claim that not only is inactivity a precursor to a PD diagnosis, but lack of exercise can also exacerbate certain motor deficits. In their review, Hirsch and Farley focus on the ability of exercise to release neurotrophins: brain-derived neurotropin (BDNF), glia-derived neurotrophin (GDNF), nerve growth factor (NGF), and galanin. A separate study conducted by Hirsch and colleagues' states that BDNF can regulate the survival and activity level of dopaminergic neurons. Hirsch states that BDNF is a "powerful inhibitor" of dopaminergic neuronal death. An experiment conducted in Japan by Tajiri and associates proved that exercise upregulates both BDNF and GDNF. They also found that exercise protects a part of the brain that houses dopaminergic neurons, the striatum (Tajiri et al., 2010). To perform this

experiment, Tajiri and colleagues acquired 60 rats and lesioned (purposefully injured) their right striatum to mimic PD. All rats were then introduced to a treadmill program where they ran 30 minutes a day, 5 days a week for 4 weeks. At the end of the training program, the rats were euthanized to further inspect the physiological effects. Additionally, a nonexercise control group was studied to compare the effect of the exercise training program on inactivity. Further physiological examination showed preservation of the nigrostriatal dopaminergic fibers of the striatum in the exercising group. Essentially, the rats that participated in the exercise program showed less neurodegeneration of their dopamine neurons. The results showed that BDNF was significantly increased in the brains of the exercising rats compared to the non-exercising rats. A similar study was conducted by Marusiak and colleagues using stationary bikes. Eleven adults with moderate PD participated in an interval cycling training program. The results from this study also indicated an increase in BDNF levels. Since this was a study conducted on humans, they were able to directly see the effect of exercise on the motor deficits associated with PD. The increase in BDNF correlated with less muscle rigidity and a decrease in tremor frequency (J. Marusiak, 2015). All current research suggests that exercise increases the BDNF levels of the brain. Since BDNF is associated with inhibiting dopaminergic cell death, one can conclude that exercise protects the brain from degeneration of dopamine-producing neurons. Table 1 summarizes results of these studies.

Table 1. Summary of Results Regarding BDNF.

	BDNF (exercise group)	BDNF (non-exercise group)
Tajiri et al.	0.87 ± 0.21	0.55 ± 0.12
Marusiak et al.	34% increase (p=0.035)	No increase in BDNF

3.3. Future Implications

This new research provides hope for many PD patients and their caregivers. Exercise can greatly reduce the mobility disabilities in Parkinson's patients because it targets higher centers in the brain. The increase in BDNF, dopamine, and levodopa is the perfect "drug" for many PD brains.

4. Exercise and its Effect on Alzheimer's Disease

Alzheimer's Disease (AD) is the leading cause of dementia among the elderly population. AD is an irreversible, progressive disease that affects the hippocampus and causes memory deficits. Globally, over 26 million people suffer from the adverse effects of this disease (Dao, Zagaar, & Alkadhi, 2015). One study conducted in China claims that AD is becoming the fifth leading cause of death in people over the age of 65 (Cui, Lin, Sheng, Zhang, & Cui, 2018).

4.1. Exercise and the Release of Neurotrophins

Exercise leads to an increase in synaptogenesis, neurogenesis, and the release of neurotrophins (Hotting & Roder, 2013). Some of the same benefits of exercise for Parkinson's Disease apply to Alzheimer's Disease. For example, the neurotrophic factor, BDNF, promotes neurogenesis in AD patients (Foster, Rosenblatt, & Kuljis, 2011). Foster, Rosenblatt, and Kuljis noted in their review on exercise induced cognitive plasticity that there is an age-related decline in BDNF. Reduced levels of BDNF are associated with a smaller hippocampus which precedes a multitude of memory deficits. The size of the hippocampus is directly correlated with spatial memory capability (Erickson, 2011). Data presented by Dao and associates from the study on moderate treadmill exercise confirms that BDNF is significantly upregulated by exercise (Dao et al., 2015). For this experiment, Dao and his team obtained rats to test the effects of a treadmill exercise program on AD. Some rats were subjected to an amyloidogenic Aβ1–42 peptide infusion to mimic AD. The remaining rats did not undergo infusion, therefore acting as a control group. All rats participated in a 4-week treadmill training program where they ran twice a day for 15 minutes each session. The experiment hosted 4 groups: control group, Alzheimer's sedentary group (nonexercised), exercise group (non-Alzheimer's), and an Alzheimer's exercise group. After the four weeks of training, both the exercise group (non-Alzheimer's) and the Alzheimer's exercise group showed an increase in BDNF. Additionally, the Alzheimer's exercise group showed similar BDNF levels as the Non-Alzheimer's exercise group. These findings suggest two things: (1) exercise increases BDNF levels in both an AD afflicted brain and a healthy brain and (2) the increase in BDNF is significant enough in the AD brain to

match that of the non-AD brain. BDNF is important for neuronal development, maintenance of the hippocampus, and synaptic plasticity. Therefore, increasing its availability in the brain through exercise can help curtail the degenerative effects of AD. Exercise has a beneficial impact on PD by diminishing motor deficits, whereas, exercise manifests its beneficial impact on AD through an improvement in cognitive abilities. Exercise leads to an increase in synaptogenesis, neurogenesis, and the release of BDNF (see Table 2). Through these processes, an improvement in cognition occurs. In healthy brains, cognition is refined by exercise. In brains afflicted with AD, exercise can slow the onset of cognitive impairments (Cui et al., 2018).

Table 2: Summary of Exercise and BDNF Data (Dao et al., 2015)

	Alzheimer's (Aβ) non-exercise	Alzheimer's (Aβ) exercise	Non-Alzheimer's exercise	Non-Alzheimer's non-exercise (control)
BDNF levels	0.9145±0.1682	1.806±0.6664	1.758 ±0.512	1.0±0.1601

4.2. Exercise as Early Intervention

Alzheimer's Disease is a hereditary disease. Most people with AD have been genetically predisposed. In the 1990s, Saunders and his colleagues conducted a study and found that the allele for apolipoprotein E type 4 (epsilon 4) is found in many people suffering from late-onset AD (Saunders AM1, 1993). More recent studies have confirmed their findings. The allele, epsilon 4 (ε4), is present in 40-50% of all late-onset AD cases (Kathryn Nichol, 2006). Nichol and colleagues say that "ε4 is neither necessary nor sufficient for the development of AD." However, ε4 is a substantial risk factor for AD. Research has shown that exercise may play an important role in preventing the onset of Alzheimer's in people that are genetically (ε4) predisposed. A long study lasting 6 years conducted by Larson and colleagues proved that exercise is associated with a dramatic risk reduction in carriers of the ε4 gene. The incidence of Alzheimer's in ε4 carriers was less in those who exercised more than 3 times a week (Larson EB1, 2006).

To test this theory, Nichol and her colleagues obtained 15 transgenic mice (mice who were bred to carry the ε4 gene). They were split into two groups: exercising (RUN) group and sedentary (SED) group. Each mouse in the RUN group was provided with a running-wheel in their cage. After 6 weeks, the rats underwent cognitive testing. Researchers confirmed differences in training between the two groups by analyzing oxidative enzyme levels, such as citrate synthase, in the rats' blood. Rats in the exercising group had high levels of citrate synthase indicating a high oxidative capacity due to their aerobic training. Rats were tested on cognitive tasks such as object learning, place learning, spatial learning, and memory. All exercising mice in the experiment showed improved cognitive performance while sedentary mice showed impaired cognitive performance. These findings are important because they suggest that exercise can improve cognition in brains at risk for AD. Modern genetic testing can give an individual a lot of information about their biological makeup. If a person finds out he/she has the ε4 gene and are at risk of Alzheimer's, regular aerobic exercise would greatly benefit them. Exercise can improve their cognitive function and delay/prevent the onset of AD.

4.3. Future Implications

The research suggesting the therapeutic role of exercise in treating/preventing Alzheimer's is exciting. It provides hope to those suffering from AD. It provides hope to those caring for their loved ones with AD. And it provides hope to those living in fear because they are genetically predisposed to AD. An exercise program can be greatly beneficial in combatting this disease. Further research is needed, however. It is unknown as to why there is a decrease in BDNF levels with age. Discovering the reason for BDNF decrease could have big implications. It would open the door to understanding why there is a decrease in hippocampal volume which could lead to more productive research; hopefully, research that could cure AD.

5. Exercise and its Effect on Multiple Sclerosis

Multiple Sclerosis (MS) is an autoimmune neurodegenerative disorder in which the protective sheath, called myelin, around your nerves begins to degrade (Society, 2019). Myelin provides insulation and protection to the axons of nerves within the central and peripheral nervous systems. It also allows neural impulses to be transmitted quickly and efficiently down the axon. Without myelin, your nerves do not work as they should.

This causes the manifestation of symptoms such as numbness, pain, fatigue, ambulation difficulties, and weakness. Exercise as a treatment for MS has not always been considered due to safety concerns. Exercise was once considered dangerous for MS patients because of the motor defects and risk of exacerbating symptoms (relapse). However, a systematic review conducted by Pilutti and colleagues refuted this argument (Pilutti LA, 2014). They searched multiple data bases to find experiments conducted on the effect to exercise on Multiple Sclerosis and calculated the risks from each experiment. The results indicate that there is no increased rate of relapse or other adverse effects caused by exercise. Exercise is completely safe for MS patients.

5.1 Exercise and the Alleviation of Symptoms

An experiment conducted by Feys and associates published in the *Multiple Sclerosis Journal* outlines the benefit exercise has on improving the symptoms of MS (Feys et al., 2017). Participants in the aerobic exercise training program showed less fatigue and greater functional mobility. For the experiment, 42 adults with MS were randomly assigned to either the exercise training group or to a control group. The exercising group was trained 3 times a week for 12 weeks. After 12 weeks, they were tested on both physical and cognitive ability. Physical tests that were performed include testing VO_{2max}, a sit-to-stand test, and a 6-minute walking test. Cognitive tests include several standardized assessments. The results indicate substantial improvements in both physical and cognitive abilities. For example, pre-training results for the 6-minute walking test indicated that participants walked on average a length of 576 meters in 6 minutes. After training, that length increased by 14 meters. Furthermore, participants in the training program scored higher on all standardized cognitive assessments than the control group. Clearly, exercise can benefit MS patients by alleviating both cognitive and physical symptoms.

Another study conducted by Rampello and colleagues had similar findings (Rampello A, 2007). This study focused on the physical benefits of exercise; more specifically, exercise tolerance and walking capacity. For this experiment, 19 adults with mild to moderate MS participated in an 8-week aerobic training program. After training, the subjects showed a greater walking distance and were able to work at a higher capacity (measured by VO_{2max}). Furthermore, results showed that subjects with more severe MS improved at a greater rate than subjects with a milder case. These findings indicate that exercise can benefit any persons with MS regardless of how far it has progressed. The ability of exercise to improve cognitive and physical capability is exciting because it can lead to an overall improvement in quality of life.

5.2 Exercise and Quality of Life

Multiple Sclerosis has the youngest average age of diagnosis out of all neurodegenerative diseases (Staff, 2019). The average age of diagnosis for MS is anywhere between 16-55. The average age of diagnosis for AD and PD is around 70 years of age. Therefore, improving quality of life in MS patients is a big focus of research for MS. The experiment by Feys and colleagues previously mentioned found that participants in a training program showed a decrease in feelings of anxiety and/or depression. This is significant. Not only can exercise alleviate adverse motor and cognitive effects of MS, but it can also improve mood. People with a multiple sclerosis diagnosis know they have a long road ahead. Many people live with MS for decades while raising a family, competing in the corporate ladder, or accomplishing whatever goal they have in mind. The role that exercise plays in improving mood can have an immense positive influence on how patients with MS handle life and achieve their goals.

5.3 Future Implications

Exercise as part of the treatment plan to combat MS has many benefits. All research suggests that people afflicted with MS should participate in a regular exercise training program. This will improve motor ability, cognition, and will fight anxiety/depression associated with MS.

6. Summary and Practical Applications

To conclude, exercise can play a crucial role in the treatment of neurodegenerative disorders because of its neuroplastic properties. Exercise improves cognitive functions by improving the function of the most fundamental cell in the brain, the neuron. The ability of exercise to increase neurotrophin levels in the brain has therapeutic effects on both Parkinson's Disease and Alzheimer's Disease. Brain-derived neurotrophin protects dopaminergic neurons, enhances neural functioning, and promotes neurogenesis. In PD, maintaining dopaminergic neurons is vital to decreasing the negative motor deficits of the disease. Maintaining neural functioning and promoting neurogenesis are important processes in combatting all neurodegenerative

disorders. Exercise has a direct biological benefit. It effects chemicals in the brain and promotes neural mechanisms that have neuroprotective effects. However, the most important effect of exercise may be its ability to improve the standard of living in patients battling neurodegenerative diseases.

Many people live in fear that they will be subjected to a neurodegenerative disease later in life, especially if they've witnessed their loved ones battle an illness. Parkinson's Disease, Alzheimer's Disease, and Multiple Sclerosis are devastating diseases that can cause heartache for families. Watching a loved one forget who you are, struggle to walk because of motor deficits, or suffer from anxiety/depression because of their diagnosis is too difficult to put into words. Their sorrow often becomes fear that they too will suffer from the adverse effects of a neurodegenerative disease. Alzheimer's has a genetic component (ε4) that predisposes many people to the disease. However, exercise provides hope. Research shows that an exercise program for those predisposed to a disease can prevent the onset of neurodegeneration. Moreover, it has been shown that exercise improves mood. In people suffering from a disease, exercise can act as a prescription for anxiety and depression associated with battling a progressive disorder. Exercise improves quality of life.

However, there is an issue with exercise as a treatment for neurodegenerative disorders. Many neurodegenerative disorders occur in the elderly. If the elderly afflicted with these diseases have been previously physically handicapped, exercise as a treatment might not be effective. Furthermore, research indicates that exercise may only be effective before a certain point in the neurodegenerative process (Feys et al., 2017). Feys and associates claims exercise is most beneficial as a treatment when implemented early in the diagnosis. More research is needed. Current research focuses on aerobic training exercise programs such as running, walking, or biking. Little research is published on the effect of weight lifting programs, plyometric training, or interval training. An experiment on the effect of non-aerobic exercise (weight training, yoga, etc.) could provide more training options for patients.

Exercise benefits everyone, especially people suffering from a neurodegenerative disorder. Exercise can be used as treatment because it increases neurotrophin levels in the brain, prevents dopaminergic neuron degeneration, delays the onset of disease, alleviates symptoms, and improves mood to prevent anxiety and depression. The research is clear, exercise is a safe and effective way to combat Parkinson's Disease, Alzheimer's Disease, and Multiple Sclerosis.

Acknowledgments: I would like to thank Dr. Richard Kreider for providing the education and resources to complete this paper. I would also like to thank my peers, Christian Vasquez, Helen Morrow, and Megan Thomas for their helpful editing contributions. Lastly, I would like to thank Logan Voss for assisting with technical difficulties experienced while writing this review.

Author Contributions: LW, RK; Methodology, LW; Formal Analysis, LW; Writing – Original Draft Preparation, LW; Writing – Review & Editing, LW, RK, CV, HM. All authors read and approved the final manuscript.

Conflicts of Interest: Authors have no competing interests to declare. Comments and conclusions drawn do not constitute endorsement by the authors and/or the institution. Authors independently reviewed, analyzed and interpreted the results from this review and have no financial interests in the results of this study.

References

1. Alberts, J. L., Linder, S. M., Penko, A. L., Lowe, M. J., & Phillips, M. (2011). It is not about the bike, it is about the pedaling: forced exercise and Parkinson's disease. Exerc Sport Sci Rev, 39(4), 177-186. doi:10.1097/JES.0b013e31822cc71a

2. Cui, M. Y., Lin, Y., Sheng, J. Y., Zhang, X., & Cui, R. J. (2018). Exercise Intervention Associated with Cognitive Improvement in Alzheimer's Disease. Neural Plast, 2018, 9234105. doi:10.1155/2018/9234105

3. Dao, A. T., Zagaar, M. A., & Alkadhi, K. A. (2015). Moderate Treadmill Exercise Protects Synaptic Plasticity of the Dentate Gyrus and Related Signaling Cascade in a Rat Model of Alzheimer's Disease. Mol Neurobiol, 52(3), 1067-1076. doi:10.1007/s12035-014-8916-1

4. 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.,and Kramer,A. F. . (2011). Exercise Training Increases Size of Hippocampus and Improves Memory. doi:https://doi.org/10.1073/pnas.1015950108

5. Feys, P., Moumdjian, L., Van Halewyck, F., Wens, I., Eijnde, B. O., Van Wijmeersch, B., . . . Van Asch, P. (2017). Effects of an individual 12-week community-located "start-to-run" program on physical capacity, walking, fatigue, cognitive function, brain volumes, and structures in persons with multiple sclerosis. Mult Scler, 1352458517740211. doi:10.1177/1352458517740211

6. Fisher, B. E., Li, Q., Nacca, A., Salem, G. J., Song, J., Yip, J., . . . Petzinger, G. M. (2013). Treadmill exercise elevates striatal dopamine D2 receptor binding potential in patients with early Parkinson's disease. Neuroreport, 24(10), 509-514. doi:10.1097/WNR.0b013e328361dc13

7. Foster, P. P., Rosenblatt, K. P., & Kuljis, R. O. (2011). Exercise-induced cognitive plasticity, implications for mild cognitive impairment and Alzheimer's disease. Front Neurol, 2, 28. doi:10.3389/fneur.2011.00028

8. Hirsch, M. A., & Farley, B. G. (2009). Exercise and neuroplasticity in persons living with Parkinson's disease. Eur J Phys Rehabil Med, 45(2), 215-229.

9. J. Marusiak, J. M., E. Zeligowska, J. Mencel, K. Kisiel-Sajewicz, J. Majerczack, J.A. Zoladz, A. Jaskolski (2015). Interval training-induced alleviation of rigidity and hypertonia in patients with Parkinson's Diseases is accompanied by increased basal serum brain-derived neurotrophic factor

10. Kathryn Nichol, a., * Sean P. Deeny,a Joseph Seif,b Kevin Camaclang,b and Carl W. Cotman. (2006). Exercise improves cognition and hippocampal plasticity APOE ε4 mice doi:https://dx.doi.org/10.1016%2Fj.jalz.2009.02.006

11. King, L. A., & Horak, F. B. (2009). Delaying mobility disability in people with Parkinson disease using a sensorimotor agility exercise program. Phys Ther, 89(4), 384-393. doi:10.2522/ptj.20080214

12. Larson EB1, W. L., Bowen JD, McCormick WC, Teri L, Crane P, Kukull W. (2006). Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older.

13. Mak, M. K., Wong-Yu, I. S., Shen, X., & Chung, C. L. (2017). Long-term effects of exercise and physical therapy in people with Parkinson disease. Nat Rev Neurol, 13(11), 689-703. doi:10.1038/nrneurol.2017.128

14. Meder D, H. D., Rowe JB, Lehericy S, Siebner HR. (2018). The role of dopamine in the brain - lessons learned from Parkinson's Disease doi: 10.1016/j.neuroimage.2018.11.021

15. Petzinger, G. M., Fisher, B. E., Van Leeuwen, J. E., Vukovic, M., Akopian, G., Meshul, C. K., . . . Jakowec, M. W. (2010). Enhancing neuroplasticity in the basal ganglia: the role of exercise in Parkinson's disease. Mov Disord, 25 Suppl 1, S141-145. doi:10.1002/mds.22782

16. Physical Activity Guidelines for Americans (2018). Washington, DC Retrieved from https://health.gov/paguidelines/second-edition/pdf/Physical_Activity_Guidelines_2nd_edition.pdf

17. Pilutti LA, P. M., Motl RW, Latimer-Cheung AE. (2014). The Safety of Exercise Training in Multiple Sclerosis: a systematic review. J Neurol Sci. doi:https://doi.org/10.1016/j.jns.2014.05.016

18. Rampello A, F. M., Piepoli M, Antenucci R, Lenti G, Olivieri D, Chetta A. (2007). Effect of Aerobic Training on Walking Capacity and Maximal Exercise Tolerance in Patients with Multiple Sclerosis: a Randomized Crossover Controlled Study doi:https://doi.org/10.2522/ptj.20060085

19. Saunders AM1, S. K., Breitner JC, Benson MD, Brown WT, Goldfarb L, Goldgaber D, Manwaring MG, Szymanski MH, McCown N, et al. (1993). Apolipoprotein E epsilon 4 allele distriutions in late-onset Alzheimer's Disease and in other amyloid-forming diseases.

20. Sharma, S. (2016). L-DOPA. Retrieved from https://hvmn.com/biohacker-guide/nootropics/l-dopa

21. Society, N. M. S. (2019). Retrieved from https://www.nationalmssociety.org/About-the-Society

22. Staff, M. C. (2019). Multiple Sclerosis. Retrieved from https://www.mayoclinic.org/diseases-conditions/multiple-sclerosis/symptoms-causes/syc-20350269

23. Tajiri, N., Yasuhara, T., Shingo, T., Kondo, A., Yuan, W., Kadota, T., . . . Date, I. (2010). Exercise exerts neuroprotective effects on Parkinson's disease model of rats. Brain Res, 1310, 200-207. doi:10.1016/j.brainres.2009.10.075

24. Xu, J., Lombardi, G., Jiao, W., & Banfi, G. (2016). Effects of Exercise on Bone Status in Female Subjects, from Young Girls to Postmenopausal Women: An Overview of Systematic Reviews and Meta-Analyses. Sports Med, 46(8), 1165-1182. doi:10.1007/s40279-016-0494-0