Exercise-induced Neuroplasticity: A Therapeutic Strategy for Alzheimer's Disease, Parkinson's Disease, and Stroke Recovery

Erin M. Welby[1*‡], Jasleen Kaur[1*‡], Brooke A. Ostrander[1*‡], and Sadana R. Padmanabhan[1*‡]
[1]Geisinger Commonwealth School of Medicine, Scranton, PA 18509
*Master of Biomedical Sciences Program
‡Authors contributed equally
Correspondence: erinmwelby@gmail.com

Abstract

Neurodegenerative disorders include multiple disease types characterized by a progressive loss of function or death of cells, leading to varying symptoms such as decreased coordination, cognition, or sensation. The development of neurodegenerative diseases has been linked to the natural process of aging. Neuroplasticity is the brain's ability to modify the connectivity of its neurons throughout an individual's life. This is an especially important topic of research for those impacted by neurological diseases that depend upon mechanisms of neuroplasticity for recovery. Current research is focused on aging, its effects on neuroplasticity, and treatments aimed to promote neuroplasticity. Neurotrophins, such as BDNF, IGF-1, and VEGF, are present with physical exercise and are recognized as influencing and enabling neuroplasticity. Therefore, physical exercise is being explored as both a cognitive repair technique after stroke and a neuroprotective mechanism for Parkinson's disease and Alzheimer's disease. Furthermore, various exercise types have been shown to produce different neuroplastic outcomes. The purpose of this literature review was to examine current information regarding the potential role of physical exercise-induced neuroplasticity in stroke rehabilitation, as well as in the treatment and prevention of Parkinson's disease and Alzheimer's disease.

Introduction

Neuroplasticity is the central nervous system's ability to adapt or recover following injury, aging, or other impactful occurrences by reorganizing its structure, connections, and functions throughout life (1, 2). More specifically, it involves neurogenesis, reorganization of neural networks, and synaptogenesis to persevere and prosper after or through acute and long-term transformative events (1, 2). Intrinsically, aging generates neuroplasticity, as it induces decreased cognition and memory, in addition to genome, oxidative, and DNA damage, consequently increasing the susceptibility to developing neurodegenerative diseases (3–5). Recent experimentation has focused on the potential neurobiological paths associated with aging, ways to improve preservation, the human experience with this, and the subsequent neurodegenerative diseases and disorders (1,4). Physical exercise (PE) may be a neuroprotective mechanism for Parkinson's disease (PD) and Alzheimer's disease (AD) (6–10). PE may also be a promising rehabilitation method to improve brain function following stroke (11–14).

The idea of PE having a major impact on preventing a significant decline in cognition has been a topic of much research (4). Not only does PE help manage weight, strengthen the body, and assist in combating illness, it positively impacts the brain's ability to rearrange and restore itself (15, 16). There remains uncertainty in the scientific community regarding the specific biochemical mechanism behind the relationship between neuroplasticity and PE. It is important to further investigate the mechanism responsible for this relationship to understand how to utilize it clinically in the treatment of neurodegenerative disorders and neurological damage (15). The hippocampus is linked to spatial memory, consolidation, and a high degree of plasticity (1). Therefore, many investigations have focused on this area when exploring the effects of exercise-induced neuroplasticity (1, 3, 17). Although the PE-induced neuroplasticity biological process remains primarily undetermined, it is believed that neurotrophins produced during and after exercise facilitate neuroplasticity through neurogenesis, angiogenesis, and synaptogenesis, in addition to increasing cerebral blood flow (3, 16, 18–20). Neurogenesis (when new neurons in the brain are formed) improves spatial learning, memory, and cognition (1, 21). Angiogenesis, when new blood vessels are formed, is vital in neurorepair and takes place following PE (1).

Several different neurotrophins are consistently identified in mediating, regulating, and otherwise impacting neuroplasticity (Table 1). Brain-derived neurotrophic factor (BDNF) is an important modulator of plasticity and increases cell survival with respect to learning and memory (1, 3, 19, 22). Exercise

Neurotrophin	Function in Neuroplasticity	Effect of Exercise
BDNF	Increases cell survival (1,3,19,22)	Increased transport and production (1,3)
Lactate	Associated with increased BDNF; neuro-benefits (19,23,24)	Increased levels (19,23,24)
IGF-1	Supports cognition (1,15,22)	Increased levels, particularly after resistance training (1)
VEGF	Neurogenesis and cognition (1,25,26)	Increased levels, released by skeletal muscle (1,25,26)
PKC	Mediates inflammation and immunity; cell differentiation, survival, and development; improves learning and memory (3,15)	Increased levels (3,15)
NMDA Receptors	Glu receptor, learning and memory (1,3)	Increased expression (1,27)

Table 1. Select Neurotrophins and Their Effect in Neuroplasticity. A list of selected neurotrophins, their known function in the mechanism underlying neuroplasticity, and the effect that exercise has on their expression in the human body.

increases BDNF transport and production (1, 3). Lactate, essential for the brain's metabolism, has been associated with greater BDNF levels and may play a role in exercise neuro-benefits (19, 23, 24). Insulin-like growth factor 1 (IGF-1), a hormone involved in many functions including neurogenesis, is suggested to be another mediator of neuroplasticity, and seems to support cognitive function (1, 15, 22). Previous research has identified increased IGF-1 post-exercise, particularly in resistance training (1). Several other growth factors, such as vascular endothelial growth factor (VEGF), appear to contribute to neurogenesis and cognitive improvement as well (1, 25, 26). Protein kinase C (PKC), known for mediating inflammation and immunity in various ways and is part of differentiation, survival, and development, has also shown better memory and learning with direct involvement (3, 15). N-methyl-D-aspartate (NMDA) receptors are a glutamate receptor family integral for learning, memory, and excitation (1, 3). Higher expression of some NMDA receptors has been reported after exercise, with the possibility of more remarkable plasticity at glutamatergic synapses (1, 27).

Presently, it has been shown that there are differences in the effect on neuroplasticity among exercise types. One study determined that the longer duration of exercise produced elevated BDNF (20), while another determined that high-intensity interval training (HIIT) did the same as continuous exercise (23). Aerobic exercise regulates cellular redox homeostasis, improves memory, cognition, and learning, and increases synaptic plasticity and corticospinal excitability (22, 23, 28). Aerobic and strength training both have exhibited neuroplasticity and facilitated better memory (15). However, more research is needed focusing on strength and resistance training regarding its relation to exercise-induced neuroplasticity specifically (1, 3). This review aims to determine if, based on all available research, PE can be an effective treatment in neurological damage caused by AD, PD, and stroke.

Methods

A thorough literature search was conducted utilizing databases including Google Scholar and PubMed. A combination of search terms including aging, stroke, exercise, aerobic exercise, Parkinson's disease, and Alzheimer's disease were utilized to select sources. We only examined relevant articles published within the past 25 years, with a specific focus on exploring exercise as a therapeutic strategy for the treatment of neurological degeneration specifically due to stroke, AD, and PD. In order to ensure the reliability of included studies, we selected articles that were published in peer-reviewed journals and sourced from reputable databases.

Discussion

Benefits of Exercise for Stroke Recovery

Stroke is one neurological disease that remains a major concern and a prominent area of investigation, and the role of PE as a therapeutic tool for stroke has continued to spark great interest. It is a leading cause of death and long-term disability in the United States (U.S.) (29). Every year, over 795,000 people have a stroke, with the most common type of stroke being ischemic (29). In this type of stroke, blood flow to cerebral tissue is substantially reduced causing a time-sensitive cascade of events (30). First, there is a loss of tissue function because of disturbances in normal electrical and membrane functioning (30). These disturbances can eventually lead to reactive oxygen species (ROS) generation, and eventually, cell lysis and neuronal death (30). The excessive production of ROS has been linked to severe functional deficits by causing oxidative stress and, consequently, neuronal damage (31). Moreover, the loss of these neurons is one of the most direct causes of neuronal injuries observed after stroke (32). Thus, neuronal regeneration and neuronal protection are key areas worth investigating to prevent cerebral functional deficits (33). PE is believed to help with post-stroke recovery by increasing the expression of proteins involved with neuroplasticity and serving as a neuroprotective mechanism against neuronal damage (13).

A recent study investigated the ways in which rehabilitation exercises improved neurological function in rats that had undergone middle cerebral artery occlusion (MCAO). The results indicated that treadmill exercise 24 hours after MCAO increased the expression of VEGF (34). The increased VEGF expression by endothelial cells was linked to promoting neurological functioning by stimulating angiogenesis and reducing apoptosis (25, 26). In another report, the neuroprotective effects of PE in rats following an ischemic stroke were analyzed, and similar effects were observed (35). However, compared to the previous study mentioned (34), this investigation revealed a different molecular pathway and mechanism for neuroprotection (35). Post-stroke treadmill exercise increased oxaloacetate, as well as decreased glucose and phosphoenolpyruvic acid (PEP) in rats (35). During ischemic injury, the switch to gluconeogenesis due to impaired mitochondrial oxidative phosphorylation, leads to excess PEP and lactic acidosis activity, contributing to ROS production and cell death (35–37). Therefore, the researchers suggested that the process of gluconeogenesis in these rats was suppressed because of the PE, and consequently, helped protect against neuronal death (38).

Moreover, a type of exercise known as skilled reaching training (SRT) had positive effects on the cognitive function of transient MCAO rats (39). Specifically, it upregulated BDNF and stimulated gray and white matter plasticity (39, 40). Furthermore, antisense BDNF oligonucleotide was injected into the contralateral lateral ventricle of rats after ischemic stroke to determine the role of this molecule in improving cognitive performance. The blocked production of BDNF mRNA due to the injected oligonucleotide resulted in the ineffectiveness of the rehabilitation on the recovery (41). Thus, this study further emphasized the importance of increased BDNF in synaptic plasticity resulting from PE therapy post-stroke. PE may serve as an important non-invasive therapeutic tool for ischemic stroke by modulating synaptic plasticity.

Benefits of Exercise in the Treatment of Parkinson's Disease

PD is the second-most common neurodegenerative disorder diagnosed in North America, currently affecting about 1 million Americans (42). A new study has shown that PD has an incidence rate of nearly 90,000 diagnoses each year, which is about 50% higher than current estimates (43). PD incidence increases with age of 65 or older and is higher in males at all ages (43). Incidence of PD is higher in certain geographical

regions, including the "Rust Belt," southern California, southeastern Texas, central Pennsylvania, and Florida (43). PD has an annual economic burden of $52 billion in the U.S. (44).

Pathologically, PD is characterized by the loss of nigrostriatal dopaminergic innervation, but neurodegeneration seen in the disease is not limited to just these neurons (45). PD has a very widespread pathology, so reliable diagnostic tests are not available yet (45). Diagnosis is based on clinical symptom presentation (45). Diagnosis requires the presence of two clinical features: resting tremor, bradykinesia, rigidity, and/or postural instability (45). These criteria can only diagnose probable PD (45). True diagnosis requires histopathology testing to identify alpha-synuclein-containing Lewy bodies (45). The pathogenesis of PD involves alpha-synuclein misfolding and aggregation (46), mitochondrial dysfunction (47), and dysfunctional protein clearance (45).

Treatment of PD includes increasing levels of dopamine in the brain (48). The current first-line treatment for the motor symptoms of PD is levodopa (48). Levodopa (or L-dopa) is a dopamine precursor (49). L-dopa is usually used in combination with carbidopa, which inhibits aromatic-L-amino-acid decarboxylase, the enzyme responsible for the breakdown of dopamine (49). These drugs both work to increase the levels of dopamine in the synapses (49). This treatment does not modify the course of neurodegeneration, but it is very effective at treating the motor symptoms of the disease (49). Drugs like carbidopa-levodopa extended-release capsules, also called IPX066, have been shown to have an increased efficacy and improved patient compliance (50).

Although these treatments can manage the symptoms of PD, there is currently no cure for this debilitating disease. In a recent study that evaluated 114 countries from 1994-2019, it was estimated that there were 1,064,753 deaths due to PD globally (51). Throughout this period, the mortality rate in both men and women increased substantially (51). Overall, PD is the second-most prevalent neurodegenerative disease in the U.S. for which there is no current cure. Current treatment methods need improvement to reduce PD-related morbidity and mortality.

There is widespread evidence of the beneficial effects of aerobic exercise on inducing neuroplasticity and improving cognition (52–57). Specifically, it has been shown that exercise reduces atrophy in the motor systems of aging individuals and induces neuroplasticity, which preserves motor function and promotes the relearning of motor skills (53). PE has been linked to improved motor function which includes increased gait speed, balance, and coordination (53). Due to these results, the effects of aerobic exercise have recently been studied in PD to determine if this could be an effective addition to current treatment options. The substantia nigra, the main area affected by PD-related neurodegeneration, can produce new neurons throughout adulthood (58). Due to this, and the ability of exercise to induce neuroplasticity, it has been thought that exercise may improve the symptoms of and possibly protect from the progression of PD. More recent studies have shown that exercise induces alterations in dopaminergic and glutamatergic neurotransmission, which diminishes the cortically driven hyperexcitability present in the basal ganglia of PD patients (27). Studies of PD-specific goal-based motor training and aerobic exercise have shown the potential to improve the cognitive and autonomic components of motor control in mild to moderate PD (10). More research is needed to fully understand the circuitry involved in exercise-induced neuroplasticity and how it can improve motor function in PD patients before it is recommended as a therapeutic intervention. Furthermore, additional study is warranted to evaluate the ideal amounts of exercise in order to mitigate injury and maximize the impact of its use.

Benefits of Exercise in the Treatment of Alzheimer's Disease

The clinical impact of PE extends beyond neuroplasticity to benefit patients diagnosed with dementia and, specifically, AD. This disease is characterized by cognitive decline, memory loss, and disorientation and affects a large percentage of the world population, specifically individuals 65 years of age and older (59, 60). Based on the World Alzheimer Report, as of 2016, 47 million people across the world live with dementia, and nearly 70% of them are eventually diagnosed with Alzheimer's (7). Due to the irreversibility of AD and the absence of successful pharmacological treatments, the number of patients with AD is continuing to increase and is projected to be four times higher by 2050 (7, 61). This disease explicitly affects the more complex parts of the brain connected to memory, such as the hippocampus and neocortex (61). At the cellular level, patients with AD present with an increased level of amyloid plaques, composed of Aß peptides and neurofibrillary tangles, which are connected to the deterioration of cognitive functions (7, 59, 61). Simultaneously, a low count of BDNF also accounts for the neurocognitive decline of patients with dementia (62). Along with these pathophysiological features that characterize Alzheimer's, risk factors that contribute to worsening and expedited symptoms of this disorder include diabetes, hypertension, obesity, and a sedentary lifestyle (8, 60, 63, 64).

Engaging in PE has been shown to reduce a patient's risk of AD by 45% by impacting the individual at a behavioral, cellular, and molecular level by enhancing blood flow, improving brain plasticity, and conserving brain tissue (7, 9). In a 2011 meta-analysis, patients with dementia scored higher on cognitive tests following 6 to 12 months of exercise versus a sedentary lifestyle. Moreover, the patients that took part in PE had improved spatial memory and larger hippocampus volumes (8). This is parallel to the neurotrophic hypothesis, which emphasizes that improved cognition is tied to the increase in growth factors and neurotrophins induced by PE (59). In a follow-up investigation in 2020, high levels of Aß in rats were reversed by physical and cognitive exercise, which further reversed damages done to the hippocampus brought on by neurotoxicity (65). PE also increased BDNF levels which can further slow the progression of AD symptoms and reduce the risk of developing Alzheimer's in healthy older individuals (61).

While other forms of treatment to slow down the development of Alzheimer's are being studied, such as the impact of a healthy diet with low fat intake and drugs, PE is the most promising. Is has been shown to slow the spread and low-cost intervention to treating and lowering the risk of patients with AD (62, 66, 67). In a 2022 study, the benefits of a Mediterranean diet combined with PE resulted in higher BDNF levels compared to a Western diet and a sedentary lifestyle (62). Non-pharmacological interventions such as PE are thought to have a better success rate in slowing AD compared to pharmaceutical

drug treatments (68). For example, it is hypothesized that NSAIDs can reduce the risk of AD due to the anti-inflammatory component; however, there is limited research to prove this to be as successful as PE (69). Similarly, intranasal insulin, omega-3 fatty acids, and vitamin B12 are being studied. These are also more costly than maintaining a healthy diet and PE (63, 70). Moreover, even with the medications that are currently available, the growth of AD as a leading cause of morbidity in the U.S. and the lack of clinical trials, with a current 0.4% success rate, points toward the need for a better understanding of the progression of this disease (69, 71, 72). Since pharmaceutical treatments for AD are expensive to develop and test, the success of PE as a preventative measure points to its benefits as a cheaper alternative while searching to find a cure (7–9).

Conclusion

Neurodegenerative diseases remain a persistent issue in healthcare since they are often challenging to treat due to the brain's complex circuitry. Thus, therapies that help prevent the onset and progression of these diseases continue to draw attention in neurology. PE is one noninvasive therapy that can serve to reduce the burden of these diseases by inducing neuroplasticity in the hippocampus, an area of the brain linked to exhibiting high instances of plasticity and memory consolidation (1). Particularly, neurotrophins produced during and after exercise improve cognitive function by supporting cell growth, proliferation, and the processes of neurogenesis and angiogenesis (1, 3, 16, 18–21, 73). Numerous studies have found elevated BDNF, VEGF, and IGF-1 after exercise (1, 20, 34, 39–41, 61, 62). The upregulation of these molecules is associated with increased cognitive functioning in experiments involving rat models with different diseases, such as ischemic stroke, AD, and PD (10, 34, 39–41, 61, 62). Aerobic exercise, particularly, improves memory and cognition via neuroplasticity (74). PE positively influences neuroplasticity, neurorepair, and rehabilitation of Alzheimer's disease, Parkinson's disease, and stroke (28).

Due to the costly nature of studies centered around human participants and the availability of current research, there are limitations on the ability to conduct research on human subjects with neurodegenerative diseases such as AD and PD (1, 15, 66). Future studies should explore different exercise protocols for comparison, including more resistance studies or varying intensity, and more human and animal studies for a more generalized interpretation (1, 11, 15, 19). Multiple studies have discussed the idea of utilizing pharmaceuticals to administer the beneficial exerkines, especially considering some individuals experiencing the effects of aging, AD, PD, and stroke may be unable to complete PE (20, 23).

Acknowledgments

We would like to thank Iris Johnson for technical support and Gabrielle Verbeke O'Boyle, MBS, and Brian Piper, PhD, for feedback and editing.

Disclosures

The authors have no relevant disclosures.

References

1. Cassilhas RC, Tufik S, de Mello MT. Physical exercise, neuroplasticity, spatial learning and memory. *Cell Mol Life Sci*. 2016;73:975-83.
2. Gulyaeva NV. Molecular mechanisms of neuroplasticity: An expanding universe. *Biochemistry (Mosc)*. 2017;82:237-42.
3. Vilela TC, Muller AP, Damiani AP, Macan TP, da Silva S, Canteiro PB, et al. Strength and aerobic exercises improve spatial memory in aging rats through stimulating distinct neuroplasticity mechanisms. *Mol Neurobiol*. 2017;54(10):7928-37.
4. Gutchess A. Plasticity of the aging brain: New directions in cognitive neuroscience. *Science*. 2014;346(6209):579-82.
5. Anderson ND. Cognitive neuroscience of aging. *J Gerontol B Psychol Sci Soc Sci*. 2019;74(7):1083-5.
6. Johansson H, Hagströmer M, Grooten WJ, Franzén E. Exercise-induced neuroplasticity in Parkinson's disease: A metasynthesis of the literature. *Neural Plast*. 2020.
7. Lin TW, Tsai SF, Kuo YM. Physical exercise enhances neuroplasticity and delays Alzheimer's disease. *Brain Plast*. 2018;4(1):95-110.
8. Ahlskog JE, Geda YE, Graff-Radford NR, Petersen RC. Physical exercise as a preventive or disease-modifying treatment of dementia and brain aging. *Mayo Clin Proc*. 2011;86(9):876-84.
9. Huuha AM, Norevik CS, Moreira JB, Kobro-Flatmoen A, Scrimgeour N, Kivipelto M, et al. Can exercise training teach us how to treat Alzheimer's disease? *Ageing Res Rev*. 2022;75:101559.
10. Petzinger GM, Fisher BE, McEwen S, Beeler JA, Walsh JP, Jakowec MW. Exercise-enhanced neuroplasticity targeting motor and cognitive circuitry in Parkinson's disease. *Lancet Neurol*. 2013;12(7):716-26.
11. Penna LG, Pinheiro JP, Ramalho SH, Ribeiro CF. Effects of aerobic physical exercise on neuroplasticity after stroke: Systematic review. *Arq Neuropsiquiatr*. 2021;79:832-43.
12. Crozier J, Roig M, Eng JJ, MacKay-Lyons M, Fung J, Ploughman M, et al. High-intensity interval training after stroke: An opportunity to promote functional recovery, cardiovascular health, and neuroplasticity. *Neurorehabil Neural Repair*. 2018;32(6-7):543-56.
13. Nie J, Yang X. Modulation of synaptic plasticity by exercise training as a basis for ischemic stroke rehabilitation. *Cell Mol Neurobiol*. 2017;37(1):5-16.
14. Xing Y, Bai Y. A review of exercise-induced neuroplasticity in ischemic stroke: Pathology and mechanisms. *Mol Neurobiol*. 2020;57(10):4218-31.
15. Liang J, Wang H, Zeng Y, Qu Y, Liu Q, Zhao F, et. al. Physical exercise promotes brain remodeling by regulating epigenetics, neuroplasticity and neurotrophins. *Rev Neurosci*. 2021;32(6):615-29.
16. Gourgouvelis J, Yielder P, Murphy B. Exercise promotes neuroplasticity in both healthy and depressed brains: An fMRI pilot study. *Neural Plast*. 2017;2017:8305287.

17. Nauer RK, Dunne MF, Stern CE, Storer TW, Schon K. Improving fitness increases dentate gyrus/CA3 volume in the hippocampal head and enhances memory in young adults. *Hippocampus*. 2020;30(5):488-504.
18. Halliday MR, Abeydeera D, Lundquist AJ, Petzinger GM, Jakowec MW. Intensive treadmill exercise increases expression of hypoxia-inducible factor 1α and its downstream transcript targets: A potential role in neuroplasticity. *Neuroreport*. 2019;30(9):619-27.
19. Müller P, Duderstadt Y, Lessmann V, Müller NG. Lactate and BDNF: Key mediators of exercise induced neuroplasticity?. *J Clin Med*. 2020;9(4):1136.
20. Vints WA, Levin O, Fujiyama H, Verbunt J, Masiulis N. Exerkines and long-term synaptic potentiation: Mechanisms of exercise-induced neuroplasticity. *Front neuroendocrinol*. 2022;66:100993.
21. Li C, Liu T, Li R, Zhou C. Effects of exercise on proactive interference in memory: Potential neuroplasticity and neurochemical mechanisms. *Psychopharmacology (Berl)*. 2020;237:1917-29.
22. El-Sayes J, Turco CV, Skelly LE, Nicolini C, Fahnestock M, Gibala MJ, et al. The effects of biological sex and ovarian hormones on exercise-induced neuroplasticity. *Neuroscience*. 2019;410:29-40.
23. Huang Z, Zhang Y, Zhou R, Yang L, Pan H. Lactate as potential mediators for exercise-induced positive effects on neuroplasticity and cerebrovascular plasticity. *Front Physiol*. 2021;12:1006.
24. Sungjun L, Yonghyun C, Eunseo J, Jongjun P, Jiwon K, Masayoshi T, et al. Physiological significance of elevated levels of lactate by exercise training in the brain and body. *J Biosci Bioeng*. 2023;135:167-175
25. Oshikawa M, Okada K, Kaneko N, Sawamoto K, Ajioka I. Affinity-immobilization of VEGF on laminin porous sponge enhances angiogenesis in the ischemic brain. *Adv Healthc Mater*. 2017;6:1700183
26. Hatakeyama M, Ninomiya I, Kanazawa M. Angiogenesis and neuronal remodeling after ischemic stroke. *Neural Regen Res*. 2020;15:16–19.
27. Petzinger GM, Fisher BE, Van Leeuwen JE, Vukovic M, Akopian G, Meshul CK, et al. Enhancing neuroplasticity in the basal ganglia: The role of exercise in Parkinson's disease. *Mov Disord*. 2010;1(1):S141-5.
28. Mu L, Cai J, Gu B, Yu L, Li C, Liu QS, et al. Treadmill exercise prevents decline in spatial learning and memory in 3× Tg-AD mice through enhancement of structural synaptic plasticity of the hippocampus and prefrontal cortex. *Cells*. 2022;11(2):244.
29. Tsao CW, Aday AW, Almarzooq ZI, Alonso A, Beaton AZ, Bittencourt MS, et al. Heart disease and stroke statistics- 2022 update: A report from the American Heart Association. *Circ Journal*. 2022;145(8):e153-e639.
30. Feske SK. Ischemic stroke. *Am J Med*. 2021;134(12):1457-1464.
31. Hu X, Wu D, He X, Zhao H, He Z, Lin J, et al. CircGSK3ß promotes metastasis in esophageal squamous cell carcinoma by augmenting ß-catenin signaling. *Mol Cancer*. 2019;18:160
32. Chen YC, Ma NX, Pei ZF, Wu Z, Do-Monte FH, Keefe S, et al. A neuroD1 AAV-based gene therapy for functional brain repair after ischemic injury through in vivo astrocyte-to-neuron conversion. *Mol Ther*. 2020;28:217–234.
33. Zhao Y, Zhang X, Chen X, Wei Y. Neuronal injuries in cerebral infarction and ischemic stroke: From mechanisms to treatment. *Int J Mol Med*. 2022; 49(2):15.
34. Geng H, Li M, Tang J, Lv Q, Li R, Wang L. Early rehabilitation exercise after stroke improves neurological recovery through enhancing angiogenesis in patients and cerebral ischemia rat model. *Int J Mole Sci*. 2022;23(18):10508.
35. Geng X, Li F, Yip J, Peng C, Elmadhoun O, Shen J, et al. Neuroprotection by chlorpromazine and promethazine in severe transient and permanent ischemic stroke. *Mol Neurobio*. 2017;54(10):8140–8150.
36. Rabinowitz JD, Enerback S. Lactate: The ugly duckling of energy metabolism. *Nat Metab*. 2020;2(7):566–571.
37. Wu KC, Cheng KS, Wang YW, Chen YF, Wong KL, Su TH, et al. Perturbation of Akt signaling, mitochondrial potential, and ADP/ATP ratio in acidosis-challenged rat cortical astrocytes. *J Cell Biochem Suppl*. 2017;118(5):1108–1117.
38. Li F, Geng X, Ilagan R, Bai S, Chen Y, Ding Y. Exercise postconditioning reduces ischemic injury via suppression of cerebral gluconeogenesis in rats. *Brain Behav*. 2023;13(1):e2805.
39. Yong MS, Hwangobo K. Skilled reach training influences brain recovery following intracerebral hemorrhage in rats. *J Phys Ther Sci*. 2014;26:405–407.
40. Li C, Sun R, Chen J, Hong J, Sun J, Zeng Y, et al. Different training patterns at recovery stage improve cognitive function in ischemic stroke rats through regulation of the axonal growth inhibitor pathway. *Behav Brain Res*. 2022;421:113730.
41. Ploughman M, Windle V, MacLellan CL, White N, Doré JJ, Corbett D. Brain-derived neurotrophic factor contributes to recovery of skilled reaching after focal ischemia in rats. *J Stroke*. 2009;40(4):1490-5.
42. Kalia LV, Lang AE. Parkinson's disease. *Lancet*. 2015;386(9996):896–912.
43. Willis AW, Roberts E, Beck JC, Fiske B, Ross W, Savica R, et al. Incidence of Parkinson disease in North America. *NPJ Parkinsons Dis*. 2022;8(1):170.
44. Yang W, Hamilton JL, Kopil C, Beck JC, Tanner CM, Albin RL, et al. Current and projected future economic burden of Parkinson's disease in the U.S. *NPJ Parkinsons Dis*. 2020;6:15.
45. Kouli A, Torsney KM, Kuan WL. Parkinson's disease: Etiology, neuropathology, and pathogenesis. *Exon Publications*. 2018:3-26.

46. Baba M, Nakajo S, Tu PH, Tomita T, Nakaya K, Lee VM, et al. Aggregation of alpha-synuclein in Lewy bodies of sporadic Parkinson's disease and dementia with Lewy bodies. *Am J Pathol*. 1998;152(4):879–84.
47. Moon HE, Paek SH. Mitochondrial dysfunction in Parkinson's disease. *Exp Neurobiol*. 2015;24(2):103–16.
48. NIA. Parkinson's disease: Causes, symptoms, and treatments [Internet]. Bethesda, MD; *NIH*;2022. https://www.nia.nih.gov/health/parkinsons-disease
49. Siegel A, Sapru HN. *Essential neuroscience*. Lippincott Williams & Wilkins; 2006.
50. Müller T, Möhr JD. Efficacy of carbidopa-levodopa extended-release capsules (IPX066) in the treatment of Parkinson disease. *Expert Opin Pharmacother*. 2018;19(18):2063-71.
51. Lampropoulos IC, Malli F, Sinani O, Gourgoulianis KI, Xiromerisiou G. Worldwide trends in mortality related to Parkinson's disease in the period of 1994–2019: Analysis of vital registration data from the WHO Mortality Database. *Front Neurol*. 2022;13.
52. Hötting K, Röder B. Beneficial effects of physical exercise on neuroplasticity and cognition. *Neurosci Biobehav Rev*. 2013;37:2243-2257.
53. Nicolini C, Fahnestock M, Gibala MJ, Nelson AJ. Understanding the neurophysiological and molecular mechanisms of exercise-induced neuroplasticity in cortical and descending motor pathways: Where do we stand? *Neuroscience*. 2021;457:259-282.
54. El-Sayes J, Harasym D, Turco CV, Locke MB, Nelson AJ. Exercise-induced neuroplasticity: A mechanistic model and prospects for promoting plasticity. *Neuroscientist*. 2019;25(1):65-85.
55. Rogge A-K, Röder B, Zech A, Hötting K. Exercise-induced neuroplasticity: Balance training increases cortical thickness in visual and vestibular cortical regions. *Neuroimage*. 2018;179:471-9.
56. Vilela TC, Muller AP, Damiani AP, Macan TP, da Silva S, Canteiro PB, et al. Strength and aerobic exercises improve spatial memory in aging rats through stimulating distinct neuroplasticity mechanisms. *Mol Neurobiol*. 2017;54(10):7928-37.
57. Kuhne LA, Ksiezarczyk AM, Braumann KM, Reer R, Jacobs T, Röder B, et al. Cardiovascular exercise, learning, memory, and cytokines: Results of a ten-week randomized controlled training study in young adults. *Biol Psychol*. 2022;176:1-14.
58. Steiner B, Winter C, Hosman K, et al. Enriched environment induces cellular plasticity in the adult substantia nigra and improves motor behavior function in the 6-OHDA rat model of Parkinson's disease. *Exp Neurol*. 2006;199(2):291-300.
59. Llorens-Martín M. Exercising new neurons to vanquish Alzheimer disease. *Brain Plast*. 2018;4(1):111-26.
60. Bernardo TC, Marques-Aleixo I, Beleza J, Oliveira PJ, Ascensao A, Magalhaes J. Physical exercise and brain mitochondrial fitness: The possible role against Alzheimer's disease. *Brain Pathol*. 2016;26(5):648-63.
61. De la Rosa A, Olaso-Gonzalez G, Arc-Chagnaud C, Millan F, Salvador-Pascual A, García-Lucerga C, et al. Physical exercise in the prevention and treatment of Alzheimer's disease. *J Sport Health Sci*. 2020;9(5):394-404.
62. Xue B, Waseem SM, Zhu Z, Alshahrani MA, Nazam N, Anjum F, et al. Brain-derived neurotrophic factor: A connecting link between nutrition, lifestyle, and Alzheimer's disease. *Front Neurosci*. 2022;16:925991.
63. Pronk NP. Neuroplasticity and the role of exercise and diet on cognition. *Am J Clin Nutr*. 2021;113(6):1392-3.
64. Foster PP, Rosenblatt KP, Kuljiš RO. Exercise-induced cognitive plasticity, implications for mild cognitive impairment and Alzheimer's disease. *Front Neurol*. 2011;2:28.
65. Dare LR, Garcia A, Soares CB, Lopes L, Neves BH, Dias DV, et al. The reversal of memory deficits in an Alzheimer's disease model using physical and cognitive exercise. *Front Behav Neurosci*. 2020;14:152
66. Voss MW, Vivar C, Kramer AF, van Praag H. Bridging animal and human models of exercise-induced brain plasticity. *Trends Cogn Sci*. 2013;17(10):525-44.
67. Raefsky SM, Mattson MP. Adaptive responses of neuronal mitochondria to bioenergetic challenges: Roles in neuroplasticity and disease resistance. *Free Radic Biol Med*. 2017;102:203-16.
68. Tan ZX, Dong F, Wu LY, Feng YS, Zhang F. The beneficial role of exercise on treating Alzheimer's disease by inhibiting ß-amyloid peptide. *Mol Neurobiol*. 2021;58(11):5890-906.
69. Kelly AM. Exercise-induced modulation of neuroinflammation in models of Alzheimer's disease. *Brain Plast*. 2018;4(1):81-94.
70. Esiri MM, Chance SA. Cognitive reserve, cortical plasticity and resistance to Alzheimer's disease. *Alzheimers Res Ther*. 2012;4(2):1-8
71. Bhattacharjee S, Patanwala AE, Lo-Ciganic WH, Malone DC, Lee JK, Knapp SM, et al. Alzheimer's disease medication and risk of all-cause mortality and all-cause hospitalization: A retrospective cohort study. *Alzheimers Dement (NY)*. 2019;5:294-302.
72. Casey DA, Antimisiaris D, O'Brien J. Drugs for Alzheimer's disease: Are they effective?. *PT*. 2010;35(4):208.
73. de Sousa Fernandes MS, Ordônio TF, Santos GC, Santos LE, Calazans CT, Gomes DA, et al. Effects of physical exercise on neuroplasticity and brain function: A systematic review in human and animal studies. *Neural Plast*. 2020;2020.
74. Penna LG, Pinheiro JP, Ramalho SH, Ribeiro CF. Effects of aerobic physical exercise on neuroplasticity after stroke: Systematic review. *Arq Neuropsiquiatr*. 2021;79:832-43.