World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(REVIEW ARTICLE)

Exercise regulating mechanism for plasticity of aging hippocampus

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World Journal of Biology Pharmacy and Health Sciences, 2024, 19(02), 332–339

Publication history: Received on 02 January 2024, revised on 14 June 2024, and accepted on 03 August 2024

Article DOI: https://doi.org/10.30574/wjbphs.2024.19.2.0500

Abstract

There are a number of characteristics responsible for the loss of vascular as well as metabolic integrity which is associated with the aging progression. These vascular and metabolic integrity losses instigate comprehensive damage in regional, biomarker, and functional areas. Instead, Exercise plays a dynamic role in sustaining a healthy body, consequently support to uphold healthy vascular and cellular integrity to maintain a healthy brain. Although the human brain shrinks with increasing age, reports have hinted that the brain is likewise capable of significant plasticity in individuals with progressive age. In this review, the prospective benefits of exercise that have the ability to modulate the plasticity of the aging brain, particularly the hippocampus will be discussed. This review will further elaborate on how these exercises modulate the plasticity of the aging hippocampus based on previous and current reports.

Keywords: Exercise; Astrocyte; Microglia; Neuroinflammation; Autophagy; Mitochondria; Aging hippocampus; Neuroplasticity

1. Introduction

The hippocampus is a formation in the brain which is slightly curved and plays an important role in the limbic system. The hippocampus plays a vital function in the formation, organization, and storage of novel recalls as well as linking particular sensations and emotions to these recalls. Studies also have shown that diverse sub-regions of the hippocampus play a vital function in particular categories of memory [1]. The actual portion of the hippocampus is intricated in the processing of unique memories. Reports of London cab drivers by Maguire EA et al. discovered that navigating complex measures a large city street is interconnected to the progress of the hippocampal rare region [2]. The hippocampus similarly plays a function in consolidating memories in sleep. Studies by Peigneux P et al. hinted that the more activity of the hippocampus in sleep subsequently after certain training is learning practice leads to healthier recall of the material the next day [3]. Impairment to the hippocampus by illness or injury be able to affect an individual's memories and their capability to form novel memories. Thus, impairment of the hippocampus can especially affect the unique memory or the capability to memorize directions, locations, and orientations. An earlier report stated that impairment to the hippocampus has been noticed upon post-mortem examination of the brains of people with amnesia. Such impairment is interrelated to complications with forming explicit memories e.g. names, dates, and events [4]. The precise influence of impairment can vary depending on which hippocampus has been affected. Investigation on mice suggests that impairment to the left hippocampus disturbs the remembrance of spoken information whereas

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impairment to the right hippocampus affects a problem with visual information [5]. Factors that be able to affect the role of the hippocampus may differ. Studies recommend that age may correspondingly have a main impact on the implementation of the hippocampus. Magnetic resonance imaging (MRI) scans of human brains have discovered that the human hippocampus shrinks by approximately 13% between the ages of 30 and 80 [6]. Reports by Sherwood CC et al. furthermore suggest that individuals who experience such a loss measure substantial declines in memory functioning. Cell degeneration in the hippocampus has similarly existed interrelated to the onset of Alzheimer's disease [7]. An investigation by Duzel E et al. indicates that exercise might aid in protecting the hippocampus from the harmful effects of aging [8]. Hence, we provide a brief review, based on the current state of knowledge, we have conversed the possible benefits of exercise that can regulate the plasticity of the aging hippocampus.

2. Exercise and neuroplasticity/ brain plasticity

For many years, researchers thought that neurogenesis, i.e., the production of new neurons throughout the division of stem cells inside the brain, takes place only thru embryonic development and not after the brain is completely developed. However, in recent decades, experimental evidence by Whitman, M. C et al, and Kempermann, G et al. has publicized that neurogenesis happens likewise in the adult brain in two particular regions: the olfactory bulb, scrambled in the sensitivity of odors, and the hippocampus, mainly involved in memory consolidation [9-10]. In the hippocampus, multipotent undifferentiated neural stem cells, placed in the subgranular zone of the dentate gyrus, give rise to neural progenitor cells. These cells multiply therefore migrate into the granule cell layer then distinguish into neurons, astroglia, or oligodendrocytes [11].

2.1. Effects of Exercise on astrocytes and Neuroplasticity

Astrocytes are vital moderators of numerous aspects of synaptic transmission besides neuroplasticity. Instead, exercise has been exhibited to produce neuroplasticity and synaptic modifying. A preceding narrative review on the function of astrocytes on the outcomes of exercise on intermittent recall function by Loprinzi PD indicates that exercise can rise astrocytic dimension, diminish astroglia degeneration, progress astrocytic aquaporin-4 appearance, and expansion astrocytic transporter intensities. [12]. Another review by Tsai SF et al. implicates lactate as a minimum a supplemental metabolite, besides as an essential molecule tangled in plasticity associated gene expression. While brain lactate metabolism is distorted by mutually aging than exercise, it is essential to tackle whether lactate straightforwardly contributes to the outcomes of aging and exercise on recall function [13]. An investigation by Adam JL et al. showed that exercise amends astrocytes in an exercise then region reliant approach as dignified by GFAP plus SOX9 immunohistochemistry besides morphological examination in male mice. [14]. Another research on exercise intervened astrocytes plus radial glia-like cells by Morgan ES et al. suggests that subsequently exercise, the cleaved caspase3 appearance can aid a non-apoptotic function in these hippocampal astrocytes plus radial glia alike cells. [15]. A study on astrocyte modifying thru controlled exercise in Alzheimer's disease by Irina Belaya et al. disclosed that Controlled bodily exercise regulates the responsive astrocyte state, that might be accompanying through astrocytic BDNF plus PSD-95 to better cognition in 5xFAD hippocampi [16]. According to the study on astrocytes modulate brainstem by Shahriar S et al. signify that astrocytes regulate the pursuit of CNS circuits producing the respiratory rhythm, vitally provide adaptive respiratory responses in circumstances of improved metabolic needs as well as establish the exercise ability [17]. A study by Takashi M et al. on astrocyte glycogen originated lactate suggests that their report specifies straight evidence for the vigorous function of astrocytic glycogen originated lactate in the extensive exercising brain, involving the importance of the level of brain glycogen in durability. Glycogen upheld ATP in the brain is a probable defense mechanism for neurons in the fatigued brain [18]. Several added reports by multiple investigators furthermore suggest that exercise aids recover the modifying of astrocyte morphology or plasticity in mice than humans through different routes in numerous brain-related conditions [19-25].

2.2. Effects of Exercise on microglia and Neuroplasticity

Microglia are a form of glial cell found in the brain and spinal cord. In the past years, it has become obvious that the immune system can disturb the role of the CNS. Noticing aspects that persuade neuroinflammation then examining latent anticipatory treatments is estimated to expose the ways of upholding usual microglial activity in the elderly brain [26]. It is necessary to preserve the brain cognitive function and avoid the maladaptive reactions that arise via illness or injury through maturity and aging [27]. A report by Elisa G. et al. suggests that exercise or CSF1R inhibition avoids damage of innervation in elderly mice via alteration of microglia [28]. Another report raveled that hippocampal aging is cooperative to pro-youth involvements. Revealing fundamental mechanisms of hippocampal aging plus rejuvenation will stipulate the basis for emerging clinically feasible mediations in the aged that can neutralize brain aging and vulnerability to age-associated neurodegenerative disease [29]. A study on elderly mice was carried out by Rachel AK et al recommended that wheel running could mitigate microglia division, therefore, encourage a pro-neurogenic phenotype in elderly mice [30]. Another study by Caroline PB et al. recommends that Low-volume high-intensity

interval exercise established on lactate threshold appears to be further efficient subsequently cerebral ischemia than exertion coordinated moderate-intensity aerobic exercise to progress aerobic fitness then grip strength besides could encourage cerebral plasticity [31]. Research by Sun LN et al. implied that exercise stress-induced neuronal inflammatory reactions in the hippocampus are accompanying HIE-induced cognitive discrepancies, that can be tangled in the upregulation of the JNK/p38/ERK pathway [32]. Another animal model research in clinical sceneries by Martina S et al. implies that the positive outcomes of exercise have been associated with better intensities of neurotrophic factors, raised expression of anti-inflammatory cytokines, plus condensed intensities of pro-inflammatory cytokines, and initiated microglia [33]. Several added studies by various investigators similarly support these investigations [34-40].

2.3. Effects of Exercise on autophagy and Neuroplasticity

Autophagy is a vital portion of growth directive and the preservation of homeostasis in multicellular organisms. Mitophagy has been detected as selective autophagy in numerous functional processes and illnesses [41-42]. On the other hand, autophagy and neurogenesis play a crucial function in upholding cellular homeostasis of neurons in the brain. [43]. A recent report on the influence of exercise on lysosomal functions in the brain by Jun H et al found that exercise encouraged the nuclear translocation of TFEB in the cortex that upregulated accompanying autophagy then lysosome. Exercise straightforwardly triggered the autophagy or lysosome procedure through the upregulating of AMPKSIRT1 signaling. These outcomes indicate that running exercise stimulates a lysosomal utility in the brain across the AMPK-SIRT1-TFEB pathway [44]. Prior research on Bodily exercise alleviates doxorubicin persuaded brain cortex by Marques-Aleixo I et al have established that the amendments in mitochondrial biogenesis, dynamics and autophagy indicators persuaded via exercise accomplished before plus during therapy can provide to the spotted protecting brain cortex and cerebellum mitochondrial phenotype that is further unaffected to oxidative injury and apoptotic signaling in sub persistently DOX cured animals [45]. Another research on Parkinson's disease by Koo JH et al established that TE can lessen α-Syn intensities thru refining mitochondrial role and aggregate autophagic flux, thus ameliorating chronic MPTP/P persuaded motor discrepancies in mice with PD [46].

2.4. Effects of Exercise on mitochondria and Neuroplasticity

Mitochondria form a broad network in numerous cells upheld by an obscure equalize amongst fission and fusion, mitochondrial biogenesis, and mitophagy [47-48]. A study on elderly mice by Aaron M et al suggest that exercise training in aged mice be able to progress brain mitochondrial role throughout outcomes on electron transport chain utility then mitochondrial dynamics deprived of aggregate mitochondrial biogenesis [49]. Another study on mice by Aguiar AS et al revealed that exercise seems to occupy mitochondrial pathways and to potentiate neuroplasticity and could be related to mood perfection [50]. Research by Luo L et al suggests that maintenance of cognitive function by longstanding exercise is related to the expansion of mitochondrial property control in the elderly hippocampus and that lysosomal degradation is essential for this progression. Their findings suggest that it might be efficient approaches for decelerating down age-associated cognitive decline [51]. Another prior research report by Teresita LB et al recommends a connection concerning behavioral exercise and synaptic plasticity in the section adjoining to the injury and metabolic link of this synaptic plasticity is an enlarged quantity of mitochondria at synaptic axon terminals [52]. Nonetheless, a study by Park HS et al on physical exercise and hippocampal neuroplasticity and mitochondrial function indicated that low-intensity exercise can support in avoiding cognitive dysfunction while chemotherapy in patients with numerous cancers [53]. A recent research report by Park SS et al also indicated that bodily exercise stimulated dorsal raphe nucleus (DRN) roles, thus lessening mood disorders. Hence, the study outcomes propose that exercise can avoid mood disorders triggered by early-life stress. [54]. Researches by some other academics likewise suggested the effectiveness of bodily exercise on mitochondrial role thus improving the neuroplasticity in different diseases [55-57].

2.5. Effects of Exercise on neuroinflammation and Neuroplasticity

Exercise and its influence are satisfactorily proven in modern-day society [33]. Research on elderly rats by Gomes da Silva S et al. indicated that a promising outcome of physical exercise in the poise between hippocampal pro-inflammatory and anti-inflammatory in aging [58]. Another research on mice by Liu Y et al indicated that temporary resistance exercise enhanced cognitive function in 3xTg mice, and deliberated favorable outcomes on neuroinflammation, amyloid, tau pathology, and synaptic plasticity. Resistance exercise can characterize an alternate exercise approach for delaying disease advancement in AD [59]. A recent study by Martha PD et al. correspondingly stipulates evidence concerning the function of neuroinflammation and bodily exercise in the alteration of adult hippocampal neurogenesis with prominence on the initiation of development from adult neural stem cells to lineage-committed progenitors to their posterity primarily in murine models [60]. Another study by Hueston CM et al indicated that youth characterizes a crucial phase of the lifespan throughout which external features e.g. stress and exercise be able to affect hippocampal maturity and can modify the reaction to challenges e.g. neuroinflammation in later life [61]. Other researchers subsequently confirm the exercise benefits for neuroinflammation and neuroplasticity [62-63].

3. Discussion

For a long period, it has been presumed that brain plasticity peaks at an early age, then steadily declines with age. This is similarly highlighted by the countenance that is denoting that individuals who became familiar with doing things in a certain method will not simply unrestraint their conduct and amendment their behavior. Credits to wonderful developments in imaging techniques for assessment of brain structure and function, increasing evidence for enduring brain plasticity has been made over the previous years. Training leads to upgrading in and modification of implementation on motor tasks then the vigorous behavioral course is linked with transformed brain pursuit, happening in a related manner in youthful and elderly adults. Moreover, efficient brain modifications, training additionally encourages fundamental modifications, e.g. modifications in regional brain grey and white matter arrangements that are usually engaged throughout task implementation. [64]. Aging of the brain is an extremely multifaceted biological procedure linked with decreases in sensory, motor, and cognitive functions. Nevertheless, aging is not an illness. Aging is a usual physiological course that be able to progress without the presence of simultaneous illnesses. Nonetheless, with increasing age, the probability of people suffers from dementia, as a result of that physiological course of aging, has been assumed. Moreover, it has been recommended that at approximately 120 years of age, deprived of simultaneous illnesses, the people of neocortical synapses can drop to the level discovered in AD, with damage of intracerebral connectivity of approximately 40%. This damage can consequence in exact principal senile dementia without the existence of the plaques and tangles that depict AD. While this information is open to discussion and refers to an extremely longstanding age, which is at the upper boundary of human longevity, they yet uncover the bosom connection concerning age and disease [65]. For over two decades, there have been widespread researches of practice-centered neural plasticity investigating efficient uses of brain plasticity for cognitive and motor improvement. The study implies that human brains constantly endure through structural reform and functional modifications in reaction to stimuli or exercise. The idea of lifespan brain plasticity has been prolonged to elder adults in relation to the aids of cognitive exercise and physical treatment. It was presented that the idea of neural plasticity from a progressive viewpoint. Then, it was noticed that motor learning frequently denotes thoughtful exercise and the subsequent presentation improvement and adaptableness. As discussed, the adjacent interaction amongst neural plasticity, motor learning plus cognitive aging. Afterward, it was studied investigation on motor ability attainment in elder adults with or without, damages comparative to aging-associated cognitive deterioration. It was then emphasized the consequences of neural plasticity in abilities learning and cognitive therapy for aging people [66]. A prior review suggests that the plasticity of nerve cells is nearly entirely dissolved throughout aging. They have recommended that aging is a bodily course that happens asynchronously in diverse parts of the brain and that the degree of that course is regulated by environmental aspects and linked to the neuronal-synaptic molecular substrates of the respective region. They highpoint the outcomes after their specific laboratory on the crescendos of neurotransmitters in diverse regions of the brain. Precisely, they have studied first the consequences of aging on neurons, dendrites, synapses, as well as on molecular and efficient plasticity. Then, the consequences of environmental enhancement on the brain of early and aged animals. Afterward, the outcomes of an augmented environment on the age-associated fluctuations in neurogenesis and the extracellular absorptions of glutamate and GABA in the hippocampus, and dopamine, acetylcholine, glutamate, and GABA under a state of acute mild stress in the prefrontal cortex [67]. A recent study stated that aging in humans and animals is linked with steady and inconstant modifications in certain cognitive tasks, nevertheless the reasons and elucidates specific discrepancies remain uncertain. Hydration declines with aging however whether dehydration donates to cognitive dysfunction is not identified. The brain hydration of aging mice was resolute by colloid osmotic-pressure titration. Dehydration raised with age or a progressive loss of brain water although appeared to level off subsequently. When regulated dehydration in hippocampal portions of <8-week-old mice to the intensities perceived in mice 40 weeks and elder, their basal synaptic responses remained augmented at all incentive voltages examined, although initiation of late-stage long period potentiation was decreased. Their consequences document progressive brain dehydration with age in congenital mice to intensities at which in vitro synaptic plasticity seems dysregulated. They furthermore recommended that dehydration donates to certain of the fluctuations in synaptic plasticity perceived with aging, maybe due to changes in neuronal excitation mechanisms [68]. Another study on mice was done by Shanshan Ren et al. to study the consequences and mechanisms of exercise on resisting brain aging after the phase of synaptic plasticity. They have discovered that in the Morris water maze examination, brain aging mice exhibited a substantial lengthier emission expectancy than the usual control mice. Brain aging mice and training showed a significantly shorter EL than brain aging mice, but no difference was found when compared with usual control mice. There was no statistical distinction in EL amongst the controls and exercise groups. The number of synaptosomes in brain aging mice plus exercise remained fewer than individuals in non-brain aging mice. The number of synaptosomes in brain aging mice plus exercise was more than brain aging mice. There was no statistical variance in the number of synaptosomes between the controls and exercise cluster. Membrane fluidity of synaptosomes: the viscosity of membrane in the brain aging cluster was higher than in the non-brain aging cluster and higher than the brain aging plus exercise cluster. There was no statistical variance in viscosity of membrane amongst brain aging cluster and non-brain aging cluster, besides amongst the controls and exercise cluster. The AChE activity in brain aging and brain aging plus exercise cluster were

higher than individuals in the control and exercise cluster. There was no statistical variance in AChE activity among the controls and exercise cluster. These findings suggest that exercise can efficiently safeguard in contradiction of a deterioration in the capability of learning and recall in brain aging mice [69]. Nonetheless, another review on brain plasticity and neural recovery stated that lifetime devotion to a least commended physical activity appears to be linked with indicators of cognitive function plus neuronal integrity in later age [70]. In our review, an overall discussion was made based on the current state of knowledge on how exercise regulates the plasticity of the aging hippocampus.

4. Conclusion

The hippocampus plays a vital role in the formation, organization and storage of novel memories. Factors that be able to disturb the role of the hippocampus can differ. Reports indicate that age can correspondingly have a key influence on the performance of the hippocampus and various mechanisms have been proposed. Therefore, in this article, we presented a brief review of the exercise that aids modulating the plasticity of the aging brain particularly the hippocampus in a multifactorial manner, consisting of astrocytes, microglia, autophagy, mitochondria and neuroinflammation.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] Tyng CM, et al. The Influences of Emotion on Learning and Memory. Front Psychol. 2017; 8:1454. doi:10.3389/fpsyg.2017.01454

[2] Maguire EA, et al. Navigation-related structural change in the hippocampi of taxi drivers. Proc Natl Acad Sci U S A. 2000; 97(8):4398-4403. doi:10.1073/pnas.070039597

[3] Peigneux P, et al. Are Spatial Memories Strengthened in the Human Hippocampus During Slow Wave Sleep? Neuron. 2004; 44(3):535-545. doi:10.1016/j.neuron.2004.10.007

[4] Clark IA, et al. Remembering Preservation in Hippocampal Amnesia. Annu Rev Psychol. 2016; 67:51-82. doi:10.1146/annurev-psych-122414-033739

[5] Shipton OA, et al. Left-right dissociation of hippocampal memory processes in mice. Proc Natl Acad Sci USA. 2014; 111(42):15238-15243. doi:10.1073/pnas.1405648111

[6] Sherwood CC, et al. Aging of the cerebral cortex differs between humans and chimpanzees. Proc Natl Acad Sci USA. 2011; 108(32):13029-13034. doi:10.1073/pnas.1016709108

[7] Anand KS, et al. Hippocampus in health and disease: An overview. Ann Indian Acad Neurol. 2012; 15(4):239-246. doi:10.4103/0972-2327.104323

[8] Duzel E, et al. Can physical exercise in old age improve memory and hippocampal function? Brain. 2016; 139(3):662-673. doi:10.1093/brain/awv407

[9] Whitman MC, et al. Adult neurogenesis and the olfactory system. Prog. Neurobiol. 2009; 89, 162–175. doi:10.1016/j.pneurobio.2009.07.003

[10] Kempermann G, et al. Neurogenesis in the adult hippocampus. Cold Spring Harb. Perspect. Biol. 2015; 7:a018812. doi:10.1101/cshperspect.a018812

[11] Gage FH. Mammalian neural stem cells. Science 2000; 287, 1433–1438. doi:10.1126/science.287.5457.1433

[12] Loprinzi PD. The role of astrocytes on the effects of exercise on episodic memory function. Physiology International, 2019; 106(1), 21–28. doi:10.1556/2060.106.2019.04

[13] Tsai S-F, et al. Exercise Counteracts Aging-Related Memory Impairment: A Potential Role for the Astrocytic Metabolic Shuttle. Front. Aging Neurosci, 2016; 8:57. doi: 10.3389/fnagi.2016.00057

[14] Lundquist AJ, et al. Exercise induces region-specific remodeling of astrocyte morphology and reactive astrocyte gene expression patterns in male mice. J Neuro Res. 2019; 97:1081–1094. doi:10.1002/jnr.24430

[15] Stevenson ME, et al. Astrocytes and radial glia-like cells, but not neurons, display a nonapoptotic increase in caspase-3 expression following exercise. Brain Behav. 2018; e01110. doi:10.1002/brb3.1110

[16] Irina B, et al. Astrocyte remodeling in the beneficial effects of long-term voluntary exercise in Alzheimer's disease. Journal of Neuroinflammation, 2020; 17:271. doi:10.1186/s12974-020-01935-w

[17] Shahriar S, et al. Astrocytes modulate brainstem respiratory rhythm-generating circuits and determine exercise capacity. Nature communications, 2018; 9:370. doi:10.1038/s41467-017-02723-6

[18] Takashi M, et al. Astrocytic glycogen-derived lactate fuels the brain during exhaustive exercise to maintain endurance capacity. PNAS Early Edition, 2017, 1-6. doi:10.1073/pnas.1702739114

[19] Lundquist AJ, et al. Exercise induces region-specific remodeling of astrocyte morphology and reactive astrocyte gene expression patterns in male mice. J Neuro Res. 2019; 97:1081–1094. doi:10.1002/jnr.24430

[20] Morgan E, et al. Exercise pattern and distance differentially affect the hippocampal and cerebellar expression of FLK-1 and FLT-1 receptors in astrocytes and blood vessels. Behavioural Brain Research 337, 2018, 8–16. doi:10.1016/j.bbr.2017.09.037

[21] Jing Z, et al. Long-term treadmill exercise attenuates Aβ burdens and astrocyte activation in APP/PS1 mouse model of Alzheimer's disease, Neuroscience Letters, 2017, doi:10.1016/j.neulet.2017.12.025

[22] Atoossa F, et al. Physical exercise induces structural alterations in the hippocampal astrocytes: exploring the role of BDNF-TrkB signaling. Brain Struct Funct, 2016, doi:10.1007/s00429-016-1308-8

[23] Marina L, et al. Physical exercise promotes astrocyte coverage of microvessels in a model of chronic cerebral hypoperfusion. Journal of Neuroinflammation, 2020, 17:117. doi:10.1186/s12974-020-01771-y

[24] Tatsumi K, et al. Voluntary Exercise Induces Astrocytic Structural Plasticity in the Globus Pallidus. Front. Cell. Neurosci, 2016; 10:165. doi:10.3389/fncel.2016.00165

[25] He X, et al. Voluntary Exercise Promotes Glymphatic Clearance of Amyloid Beta and Reduces the Activation of Astrocytes and Microglia in Aged Mice. Front. Mol. Neurosci, 2017; 10:144. doi:10.3389/fnmol.2017.00144

[26] Rachel A. Aging Microglia: Relevance to Cognition and Neural Plasticity. In Book: Qing Yan (ed.), Psychoneuroimmunology: Methods and Protocols, Methods in Molecular Biology, 2012; 934, doi:10.1007/978-1-62703-071-7_11

[27] Jorge V, et al. Lifestyle shapes the dialog between environment, microglia, and adult neurogenesis. ACS Chem. Neurosci., 2016. doi:10.1021/acschemneuro.6b00009

[28] Elisa G, et al. Modulation of Microglia by Voluntary Exercise or CSF1R Inhibition Prevents Age-Related Loss of Functional Motor Units. Cell Reports, 2019; 29, 1539–1554. doi:10.1016/j.celrep.2019.10.003

[29] Xuelai F, et al. Mechanisms of Hippocampal Aging and the Potential for Rejuvenation. Annu. Rev. Neurosci, 2017; 40:251–72. doi:10.1146/annurev-neuro-072116-031357

[30] Rachel A. et al. Wheel running attenuates microglia proliferation and increases expression of a pro neurogenic phenotype in the hippocampus of aged mice. Brain, Behavior, and Immunity, 2012; 26, 803–810. doi:10.1016/j.bbi.2011.10.006

[31] Caroline P, et al. Effects of High- Versus Moderate-Intensity Training on Neuroplasticity and Functional Recovery After Focal Ischemia. Stroke, 2017; 48:00-00. doi:10.1161/STROKEAHA.117.017962.

[32] Li-na S. et al. High-intensity Treadmill Running Impairs Cognitive Behavior and Hippocampal Synaptic Plasticity of Rats via Activation of Inflammatory Response. Behavior, Cognition and Synaptic Plasticity. Journal of Neuroscience Research, 2016; doi:10.1002/jnr.23996

[33] Martina S. et al. Effects of Physical Exercise on Neuroinflammation, Neuroplasticity, Neurodegeneration, and Behavior: What We Can Learn from Animal Models in Clinical Settings. Neurorehabilitation and Neural Repair, 2014; 1–13. doi:10.1177/1545968314562108

[34] Virginia M. et al. Exercise-induced re-programming of age-related metabolic changes in microglia is accompanied by a reduction in senescent cells. Brain, Behavior, and Immunity, 2020. doi:10.1016/j.bbi.2020.01.012

[35] Andoh M, et al. Exercise, microglia, and beyond – workout to communicate with microglia. Neural Regen Res, 2020; 15(11):2029-2030. doi:10.4103/1673-5374.282241

[36] Kami K, et al. Histone acetylation in microglia contributes to exercise-induced hypoalgesia in neuropathic pain model mice, Journal of Pain, 2016; doi:10.1016/j.jpain.2016.01.471.

[37] Gong Y. et al. Zhang, Infant nerve injury induces delayed microglial polarization to the M1 phenotype, and exercise reduces delayed neuropathic pain by modulating microglial activity, Neuroscience, 2017; doi:10.1016/j.neuroscience.2017.02.051

[38] Xiong JY. et al. Long-term treadmill exercise improves spatial memory of male APPswe/PS1dE9 mice by regulation of BDNF expression and microglia activation. Biol Sport, 2015; 32(4):295–300.

[39] Jiang T. et al. Physical Exercise Improves Cognitive Function Together with Microglia Phenotype Modulation and Remyelination in Chronic Cerebral Hypoperfusion. Front. Cell. Neurosci, 2017; 11:404. doi:10.3389/fncel.2017.00404

[40] Zhang X. et al. Treadmill Exercise Decreases A Deposition and Counteracts Cognitive Decline in APP/PS1 Mice, Possibly via Hippocampal Microglia Modifications. Front. Aging Neurosci, 2019; 11:78. doi:10.3389/fnagi.2019.00078

[41] Kelekar A. et al. Ann N Y Acad Sci, 2005; 1066:259-71. doi:10.1196/annals.1363.015.

[42] Wang N. et al. Effects of Mitophagy on Regulatory T Cell Function in Patients with Myasthenia Gravis. Front. Neurol, 2020; 11:238. doi:10.3389/fneur.2020.00238

[43] Yongchul Jang. Endurance exercise-induced expression of autophagy-related protein coincides with anabolic expression and neurogenesis in the hippocampus of the mouse brain. Neuro Report, 2020; 31:442–449. doi:10.1097/WNR.0000000000001431

[44] Huang J. et al. Exercise activates lysosomal function in the brain through the AMPK-SIRT1-TFEB pathway. CNS Neurosci Ther, 2019; 00: 1–12. doi:10.1111/cns.13114

[45] Marques-Aleixo I. et al. Physical exercise mitigates doxorubicin-induced brain cortex and cerebellum mitochondrial alterations and cellular quality control signaling. Mitochondrion, 2016; 26:43–57. doi:10.1016/j.mito.2015.12.002

[46] Jung-Hoon K. et al. Treadmill Exercise Attenuates α-Synuclein Levels by Promoting Mitochondrial Function and Autophagy Possibly via SIRT1 in the Chronic MPTP/P-induced Mouse Model of Parkinson's Disease. Neurotox Res, 2017. doi:10.1007/s12640-017-9770-5

[47] Hoitzing H. et al. What is the function of mitochondrial networks? A theoretical assessment of hypotheses and proposal for future research. Bioessays, 2015; 37(6):687–700. doi:10.1002/bies.201400188

[48] Herst PM. et al. Functional Mitochondria in Health and Disease. Front. Endocrinol. 2017; 8:296. doi:10.3389/fendo.2017.00296

[49] Gusdon. et al. Exercise increases mitochondrial complex I activity and DRP1 expression in the brains of aged mice, Experimental Gerontology, 2017. doi:10.1016/j.exger.2017.01.013

[50] Aguiar A. et al. Effects of Exercise on Mitochondrial Function, Neuroplasticity and Anxio-Depressive Behavior of Mice. Neuroscience, 2014; 271:56–63. doi:10.1016/J.Neuroscience.2014.04.027

[51] Li Luo. et al. Lysosomal Proteolysis Is Associated with Exercise-Induced Improvement of Mitochondrial Quality Control in Aged Hippocampus. J Gerontol A Biol Sci Med Sci, 2017; 1–10. doi:10.1093/gerona/glw242

[52] Teresita L. et al. Changes in number of synapses and mitochondria in presynaptic terminals in the dentate gyrus following cerebral ischemia and rehabilitation training. Brain Research, 2005; 1033:51– 57. doi:10.1016/j.brainres.2004.11.017

[53] Hye-Sang P. et al. Physical exercise prevents cognitive impairment by enhancing hippocampal neuroplasticity and mitochondrial function in doxorubicin-induced chemobrain. Neuropharmacology, 2018; 133:451e461. doi:10.1016/j.neuropharm.2018.02.013

[54] Sang-Seo P. et al. Exercise attenuates maternal separation-induced mood disorder-like behaviors by enhancing mitochondrial functions and neuroplasticity in the dorsal raphe. Behavioural Brain Research, 2019; 372:112049. doi:10.1016/j.bbr.2019.112049

[55] Bernardo TC. et al. Physical exercise and brain mitochondrial fitness: the possible role against Alzheimer's disease. Brain Pathology, 3016. doi:10.1111/bpa.12403

[56] Marques-Aleixo A. et al. Physical Exercise Improves Brain Cortex and Cerebellum Mitochondrial Bioenergetics and Alters Apoptotic, Dynamic and Auto (Mito) Phagy Markers. Neuroscience, 2015; 301:480–495. doi:10.1016/j.neuroscience.2015.06.027

[57] Jin-Hee S. et al. Physical exercise ameliorates psychiatric disorders and cognitive dysfunctions by hippocampal mitochondrial function and neuroplasticity in post-traumatic stress disorder. Experimental Neurology, 2019; 322:113043. doi:10.1016/j.expneurol.2019.113043

[58] Gomes da S. et al. Exercise-induced hippocampal anti-inflammatory response in aged rats. Journal of Neuroinflammation, 2013; 10:61. doi:10.1186/1742-2094-10-61

[59] Yan L. et al. Short-term resistance exercise inhibits neuroinflammation and attenuates neuropathological changes in 3xTg Alzheimer's disease mice. Journal of Neuroinflammation, 2020; 17:4. doi:10.1186/s12974-019-1653-7

[60] Martha PD, et al. Tovar-y-Romo and Angélica Zepeda*. Neuroinflammation and physical exercise as modulators of adult hippocampal neural precursor cell behavior. Rev. Neurosci, 2017; aop. doi:10.1515/revneuro-2017-0024

[61] Hueston CM. et al. Adolescent social isolation stress unmasks the combined effects of adolescent exercise and adult inflammation on hippocampal neurogenesis and behavior. Neuroscience, 2017. doi:10.1016/j.neuroscience.2017.09.020

[62] Harra R. Sandrow-Feinberg, John D. Houlé, Exercise after spinal cord injury as an agent for neuroprotection, regeneration and rehabilitation, Brain Research, 2015. doi:10.1016/j.brainres.2015.03.052

[63] Alita S. et al. Effects of exercise on adolescent and adult hypothalamic and hippocampal neuroinflammation. Hippocampus, 2016. doi:10.1002/hipo.22620

[64] Lisa P. et al. Aging and brain plasticity. Aging, 2018; 10(8):1789-1790.

[65] Francisco M. Successful brain aging: plasticity, environmental enrichment, and lifestyle. Dialogues Clin Neurosci, 2013; 15:45-52.

[66] Liuyang C. et al. Brain plasticity and motor practice in cognitive aging. Frontiers in Aging Neuroscience, 2014; 6:31. doi:10.3389/fnagi.2014.00031

[67] Francisco M. et al. Aging, plasticity and environmental enrichment: Structural changes and neurotransmitter dynamics in several areas of the brain. Brain research reviews, 2007; 5 5:7 8 – 8 8. doi:10.1016/j.brainresrev.2007.03.011

[68] Anirudh V. et al. Age-dependent changes in brain hydration and synaptic plasticity. Brain Research, 2018; 1680:46–53. doi:10.1016/j.brainres.2017.12.006

[69] Shanshan R. et al. Effects of exercise on spatial learning and hippocampal synaptic plasticity in brain aging mice. Wei Sheng Yan Jiu, 2010; 39(2):239-41.

[70] Tobias E. et al. Lifespan leisure physical activity profile, brain plasticity and cognitive function in old age, Aging & Mental Health, 2018. doi:10.1080/13607863.2017.1421615