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Role of exercise in the brain: focus on oligodendrocytes and remyelination

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The phrase "Mens sana in corpore sano" taken from Juvenal's Satires (127 a. C.) represents one of the best-known and most used sentences of all time, whose meaning in the modern age refers to the importance of physical activity for mental health and wellbeing. Robust literature demonstrated the positive role of exercise in counteracting several diseases, such as diabetes, cardiovascular diseases, neurodegenerative diseases, cancers and age-related disorders including muscle atrophy, the reduction of aerobic capacity, bone and cartilage loss. Moreover, physical exercise ensures brain health and acts as a key player in preventing cognitive decline related to aging. Exercise represents a promising strategy to ensure optimal aging, whose benefits in healthy adults were observed in attention, processing speed, memory, and executive functions. Studies performed on human and animal models showed the ability of physical activity to increase the volume of different brain regions and enhance brain plasticity and neurogenesis through the stimulation of neural progenitor cell proliferation and the sustainment of the developing neurons. Interestingly, the systemic administration of blood plasma derived from exercised mice on aged animals increased the number of newly born neurons in the dentate gyrus region, ameliorating the impaired neurogenesis and cognition in the aged hippocampus (Horowitz et al., 2020). The strict association between physical exercise and neurogenesis was recently confirmed in adult zebrafish. Here, in a spinal cord injury model, the exercise showed to activate the nicotinic-ACh receptors and inhibit the $GABA_A$ receptors, by increasing the number of newborn neurons and promoting motor function restoration (Chang et al., 2021). This evidence also corroborates previous results showing the positive role of exercise to enhance motor and sensory functions in spinal cord injury-affected patients as well as axonal regeneration and sprouting in rodent models. The positive relationship between exercise and neurogenesis is also due to the ability of physical activity to increase the expression levels and the secretion of neurotrophic and growth factors, including brain-derived neurotrophic factor, insulin-like growth factor-1, nerve growth factor and vascular endothelial growth factor. Brain-derived neurotrophic factor plays a key role in cognition, neuroplasticity, and angiogenesis. It promotes neural connectivity and is involved in the development of learning and memory. Insulin-like growth factor-1 is a neuroprotective factor, which supports brain development, neural survival and vasculature. Nerve growth factor is considered to play an essential role in mediating neuronal development and survival, and its treatment inverts the effects of lesions and age-related degeneration. Exercise also stimulates the release of vascular endothelial growth factor, which through angiogenesis also directly enhances neurogenesis and synaptic function.

The benefits of exercise on the brain can be explained as a combination of effects that occur not only on neurons but also on glial cells (**Figure 1**). Several studies described elsewhere (Maugeri et al., 2021) show how exercise, through different biological mechanisms, protects neuronal function via the adaptation of astrocytes. These cells, representing the most numerous glial cells in the brain, are involved in glutamate uptake, the release of trophic factors, the maintenance of basal levels of catecholamine, and the coverage of cerebral blood vessels. Exercise modulates microglia, the major cell type implied in orchestrating inflammatory events in the brain, and also acts on ependymal cells, representing an important source of endogenous neural stem cells in the adult spinal cord. In particular, exercise increases their proliferation while improving functional recovery.

The influence of physical exercise on glial cells includes also oligodendrocytes (OLs). OLs are multipolar glial cells developing from oligodendrocyte precursor cells (OPCs), which arise from the restricted region of the ventricular zone of the central nervous system. As OPCs mature, they obtain lipids and express specific myelin proteins until the expression in the mature OLs of the major myelin proteins, including myelin basic protein, proteolipid protein, myelin-associated glycoprotein, and myelin oligodendrocyte glycoprotein. OLs form multiple myelin sheaths spirally wrapped around axons which increase nerve conduction velocity through saltatory impulse propagation. Apart from their myelinating function, OLs ensure nutritionally and metabolically support to neurons and are required for proper motor and cognitive function in the nervous system. Damage of central nervous system myelin has been associated with various diseases, such as multiple sclerosis, spinal cord injuries, Alzheimer's disease, amyotrophic lateral sclerosis and other neurodegenerative diseases. Moreover, the aging brain shows faint but widespread structural deterioration of myelin, which can be counteracted with efficient remyelination. Remyelination is an endogenous regenerative program, which occurs in distinct phases: activation and recruitment of OPCs; migration of OPCs to areas of demyelination; OPCs proliferation and differentiation in OLs; myelin deposition around demyelinated axons. This complex process is regulated not only by intrinsic cues but also extrinsic factors, and exercise appears to enhance remyelination. In accord, in mice treated with cuprizone, which induces demyelination and brain inflammation, the voluntary running wheel improved neuromuscular function and motor coordination, by reducing the loss of myelin basic protein and 2′,3′-cyclic-nucleotide 3′-phosphodiesterase in the striatum and the corpus callosum (Mandolesi et al., 2019). Similarly, preconditioning exercise consisting of free swimming for 40 minutes per 3 weeks, showed improved areas of remyelination, increased expression of myelin basic protein and brain-derived neurotrophic factor and reduced GFAP expression in the corpus callosum (Begum et al., 2022). In the same model of demyelination, Bacmeister et al. (2020) showed that motor learning enhanced the remyelination process through cortical oligodendrogenesis and myelin sheath formation by surviving OLs. Moreover, voluntary running promoted an endogenous brain repair mechanism leading to an increase in oligodendrogenesis, myelination and lifespan of ataxic mice (Alvarez-Saavedra et al., 2016). The mechanistic role through which short bouts of exercise influence both naïve mice and animals following lysolecithin-induced spinal cord demyelination was analyzed through quantitative shotgun proteomics (Lozinski et al., 2021). The study showed that acute amounts of physical exercise are enough to significantly modify

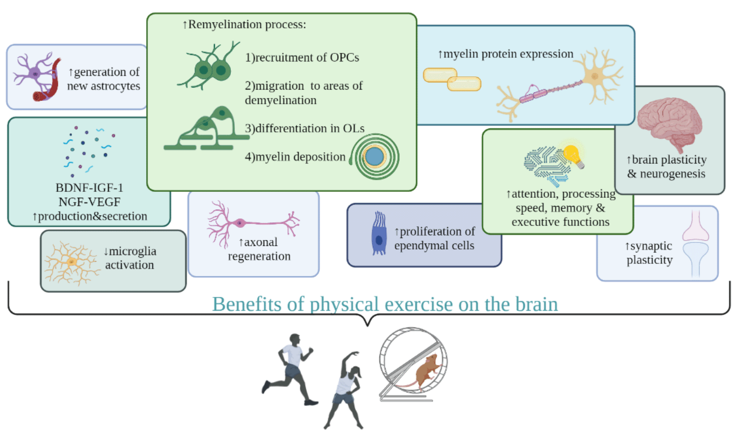

Figure 1 | Positive impact of physical exercise on brain health.
BDNF: Brain-derived neurotrophic factor; IGF-1: insulin-like growth factor-1; NGF: nerve growth factor; OLs: oligodendrocytes; OPCs: oligodendrocyte precursor cells; VEGF: vascular endothelial growth factor; ↑: increase; ↓: decrease. Created with BioRender.com.

the proteome of the spinal cord and serum in both naïve and lysolecithin demyelinated mice. Noteworthy, voluntary running wheel activity over four days significantly altered the expression level of proteins involved in oxidative stress, metabolism, neurotransmission and proteolytic remodeling of the extracellular matrix both in healthy and demyelinated mice (Lozinski et al., 2021). Physical exercise immediately following a demyelinating insult in young mice directly increased the subsequent regeneration of myelin by increasing the proliferation of OPCs. Furthermore, the authors demonstrated that exercise acts in parallel with the remyelinating medication clemastine to induce full remyelination of lesions (Jensen et al., 2018). Very recently, a mouse model of spinal cord injury was used to investigate the effects of the combination of bone marrow mesenchymal stem cell transplantation and exercise training on functional restoration. The *in vivo* results showed that the combination of mesenchymal stem cell transplantation and exercise induced a better therapeutic response on motor function than the single treatments (Sun et al., 2023). On the other hand, the success of the combination of activity-based rehabilitation approaches and biological regenerative therapy was previously demonstrated by Hwang et al. (2014). In fact, the synergy between transplantation of neural stem cells and treadmill training significantly induced neural stem cells graft survival and differentiation more into neurons and OLGs, promoting myelination via insulin-like growth factor-1 in a rat model of spinal cord injury. These data support proof of the principle that physical exercise in combination with appropriate therapy actively enhances the regeneration of myelin, coining the new term MedXercise (Medication + eXercise) (Wuerch et al., 2021).

Whether the physical activity is able to improve remyelination in humans is still unknown. The reported studies demonstrated a positive role of exercise to counteract the damage of myelin and promote remyelination. However, the different types of injury applied and the heterogeneity of the exercise protocols, affect the strength of the results leaving many unanswered questions and requiring further exploration. On the other hand, investigations on humans will be indispensable in the attempt to identify the best protocols to be applied to the patients, considering that each individual differently responds to physical exercise programs and intensities.

Beyond any doubt, exercise has an important role in human brain health and is recommended as a non-pharmacologic approach for different diseases and to counteract aging-related problems. According to World Health Organization 2020 guidelines, adults should perform 150–300 minutes of moderate-intensity, 75–150 minutes of vigorous-intensity physical activity, or some equivalent combination of moderate-intensity and vigorous-intensity aerobic physical activity per week. Among children and adolescents, an average of 60 minutes/day of moderate-vigorous-intensity aerobic physical activity across the week provides health benefits. These guidelines recommend regular physical activity, such as walking, cycling, wheeling, and doing sports, that supports the physical and mental wellness of everyone, regardless of age, ability, and health conditions. Notably, we are now in the Metaverse era, which is an immersive virtual world that users can access through a virtual reality system. Importantly, the Metaverse could be useful for the elders, for patients with compromised motor functions and for individuals who needed rehabilitation, which could perform adapted exercises interacting with each other.

Exercise is a revolutionary tool for the well-being of our brains. A single workout immediately increases the levels of neurotransmitters such as dopamine, serotonin and norepinephrine. Exercise increases attention and concentration and improves reaction time. One of the most astounding things that exercise does is its protective effects on the brain also by increasing the volume of both the hippocampus and the prefrontal cortex. Why is it so important? As the prefrontal cortex and hippocampus are due areas that are more susceptible to neurodegenerative diseases and therefore are associated with normal cognitive decline in aging. So, with an increase in physical activity throughout our lifetime, we are not going to cure dementia or Alzheimer's disease, but what we are going to do is to improve the functionality of the hippocampus and the prefrontal cortex to prevent in part these diseases.

In conclusion, we prompt physicians to encourage patients to perform adapted physical activity. Considering that a single treatment strategy alone is unlikely to be sufficiently effective, the combination with exercise could be the key to achieving clinically meaningful functional improvement for patients. Moving is always better than not moving!

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