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Review

Myelin, aging, and physical exercise

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ABSTRACT

Myelin sheath is a structure in neurons fabricated by oligodendrocytes and Schwann cells responsible for increasing the efficiency of neural synapsis, impulse transmission, and providing metabolic support to the axon. They present morpho-functional changes during health aging as deformities of the sheath and its fragmentation, causing an increased load on microglial phagocytosis, with Alzheimer's disease aggravating. Physical exercise has been studied as a possible protective agent for the nervous system, offering benefits to neuroplasticity. In this regard, studies in animal models for Alzheimer's and depression reported the efficiency of physical exercise in protecting against myelin degeneration. A reduction of myelin damage during aging has also been observed in healthy humans. Physical activity promotes oligodendrocyte proliferation and myelin preservation during old age, although some controversies remain. In this review, we will address how effective physical exercise can be as a protective agent of the myelin sheath against the effects of aging in physiological and pathological conditions.

1. Introduction

The myelin sheath (MS) is an evolutionary trait recently developed among vertebrates. This structure was first reported in jawed fishes of the Devonian period, which occurred around 400 million years ago. As a result of this feature, neural impulses could be transmitted faster, leading to an advantage in predatory and escape behaviors (Zalc et al., 2008). It is noteworthy that the myelin deposition occurs in segments of concentric lipidic lamellae, separated by gaps where voltage-gated sodium channels enable signal propagation along the axon. These gaps are called the nodes of Ranvier (Fig. 1B). The sheath is made by myelinating oligodendrocytes in the central nervous system (CNS) and Schwann cells in the peripheral nervous system (PNS). Besides creating the sheath, both cells provide metabolic support to the axon. Without this supply, the axon would degenerate (Bolino, 2021; Brown et al., 2012; Fünfschilling et al., 2012; Muppirala et al., 2021; Saab et al., 2013; Xin & Chan, 2020).

While in the PNS, each Schwann cell is responsible for only 1 neuron, in the CNS, each oligodendrocyte is responsible for myelinating several neurons (Fig. 1). Due to this arrangement, myelinated axons have some physical properties: reduced transverse capacitance and increased transverse resistances. For that reason, saltatory conductions are facilitated along the axon, and there is a drastic increase in its speed compared to an unmyelinated axon of the same caliber (Zalc et al., 2008; Zalc, Colman, 2000). Achieving these conduction speeds without the sheath would require much greater axonal diameters to be advantageous to the individual (Hartline and Colman, 2007). In addition, conduction speeds are influenced by 2 characteristics of the sheath: (1) its thickness compared to the axon's (*g*-ratios) (Fig. 2) and (2) its internode length and spacing (Fig. 1B). Through decades of experimentation and theories, scientists have established the optimal *g*-ratios and internode length parameters ratios for maximum conduction velocity (Huxley and Stampfli, 1949; Smith and Koles, 1970; Wu et al., 2012).

Abbreviations: AD, Alzheimer's disease; CNS, central nervous system; GM, gray matter; MBP, myelin basic protein; MS, myelin sheath; OPC, oligodendrocytes precursor cell; PLP, proteolipid protein; PNS, peripheral nervous system; TEM, transmission electron microscopy; WM, white matter

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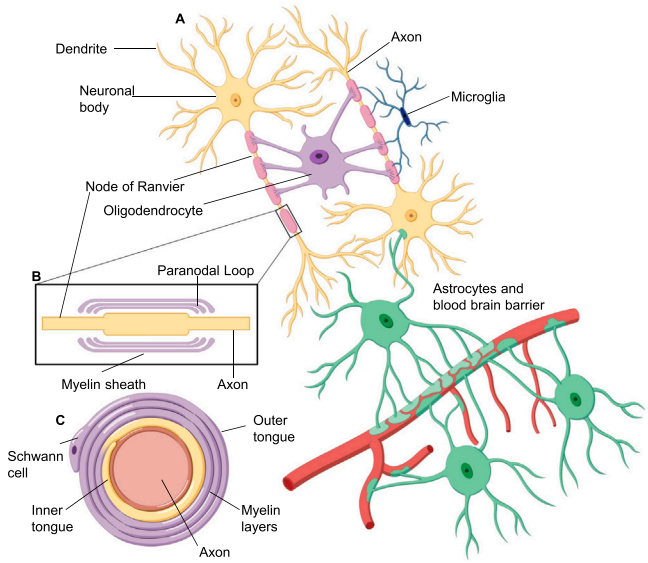

Fig. 1. Neuron myelination. (A) Basic CNS functional unit, presenting an oligodendrocyte myelinating 2 neurons. The astrocytes sustain the neuron and form the blood-brain barrier. The microglia protect the brain from possible threats and debris. (B) Representation of a myelin sheath structure, showing the internode length and node of Ranvier. (C) Formation of the sheath on the peripheral nervous system, highlighting the formation of myelin layers. Figure drawn by Stahr Marr Vasconcelos. Abbreviation: CNS, central nervous system.

1.1. Myelin structure

The MS became the focus of various studies because of 2 main factors: (1) the refinement of Transmission Electron Microscopy (TEM) and (2) the establishment of protocols to physically isolate the sheath from other membranes based on biochemistry (Norton and Poduslo, 1973). After analyzing the MS with TEM, it was possible to identify that myelin is a multilayered stack of uniformly thick membranes alternating between electron-dense and light layers, also named the "major dense line" and the "intraperiod line," respectively. These lines represent adhesion zones that show opposing cytoplasmic and extracellular myelin membrane bilayers. Compacted myelin provides high electrical insulation and low capacitance, vital elements for saltatory impulse propagation. At the edges, the outer layers membranes of myelin lamellae are tightly connected by junctions made of claudin-11 (Gow et al., 1999; Morita et al., 1999). These strands run radially along the myelin, being nominated "radial components" (Fig. 1C). The non-compacted regions of inner and outer periaxonal "lips" of myelin are called paranodal loops (Fig. 1B), with Schmidt–Lanterman incisures present on PNS (Fig. 3). Cytoplasmic channels present on Schmidt–Lanterman incisures can be found in early CNS MSs but largely disappear upon completion (Snaidero et al., 2014).

Myelin is a poorly hydrated structure, with most water being removed during compaction (Stadelmann et al., 2019). About 70%–80% of the MS's dry mass is formed by lipids and a small number of proteins, being most abundant in myelin basic protein (MBP) and proteolipid protein (PLP) (Poitelon et al., 2020). Besides, proteome studies have shown a variety of proteins within purified myelin fractions (Dhaunchak et al., 2010; Ishii et al., 2009; Manrique-Hoyos et al., 2012; Patzig et al., 2011; Werner et al., 2007).

Stability is another feature of the sheath that deserves mentioning, shown when 5000-year-old myelin was dissected from a Tyrolean iceman (Hess et al.,1998). The molecular basis responsible for this stability is probably its lipid composition, with high levels of saturated, long-chain fatty acids and enrichment of glycosphingolipids (20%) and cholesterol (40%) (Coetzee et al., 1996; Montani, 2021; O'brien, 1965). The sheath also comprises a high proportion of plasmalogens with saturated fatty acids (Chrast et al., 2011). Around 20% of the fatty acids have hydrocarbon chains longer than 18 carbon atoms, and only 6% are polyunsaturated. Van der Waals dispersion forces, generated by the interactions between methylene groups of these saturated hydrocarbon chains, significantly contribute to holding the molecules. Also, more than 50% of galactosylceramide and sulfatide are hydroxylated by fatty acid 2-hydroxylase, providing additional hydroxyl groups and increasing the packing density of lipids (Eckhardt et al., 2005; Montani, 2021; Zöller et al., 2008).

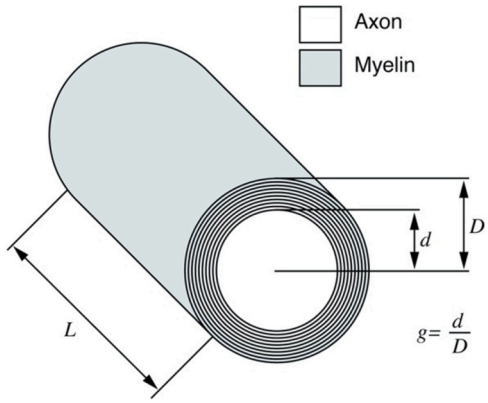

Fig. 2. *g*-Ratio. Representation of an axon and its myelin sheath illustrating *g*-ratios (*g*). *D* represents the fiber diameter, while *d* represents the axon diameter, and *L* represents the length of the myelin sheath (Paus and Toro, 2009).

1.2. The process of myelination

Myelination is a complex process, which can be summarized into some steps: (1) proliferation of oligodendrocytes precursor cells (OPCs) in the white matter (WM); (2) recognition of axons and axon-glia signaling; (3) differentiation of OPCs into myelinating oligodendrocytes; (4) membrane outgrowth and axonal wrapping; (5) transportation of membrane components; and (6) myelin compaction and node formation (Bakhti et al., 2014; Barres and Raff, 1999; Baumann and Pham-Dinh, 2001; Emery, 2010; Freeman and Rowitch, 2013; Miller, 2002; Simons et al., 2012).

The myelination process starts at the end of the gestational period with the large bundles of brain stem fibers ascending to the diencephalic bundles and the posterior portion of the corpus callosum, between the first and third months postnatal, followed by the internal capsule and the remaining corpus callosum between 6 and 8 months old, reaching the WM at the first year of life. At this point, the process continues slowly until puberty (Lent, 2022). Most oligodendrocytes generate between 20 and 60 myelinating processes with lengths of approximately 20–200 μm and up to 100 turns (Chong et al., 2012; Hildebrand et al., 1993; Matthews and Duncan, 1971) and have a surface estimated up to $5–50 \times 10^3$ μm^2 (Baron and Hoekstra, 2010; Pfeiffer et al., 1993).

1.3. Analysis methods

The knowledge of the ultrastructure of the myelin was based on the TEM of glutaraldehyde-fixed and dehydrated membranes commonly associated with the collapse of extracellular space. Fixation-free TEM method using high-pressure freezing has been implemented with enhanced architecture preservation (Möbius et al., 2010), and more recently, Cryogenic electron microscopy (cryo-EM)

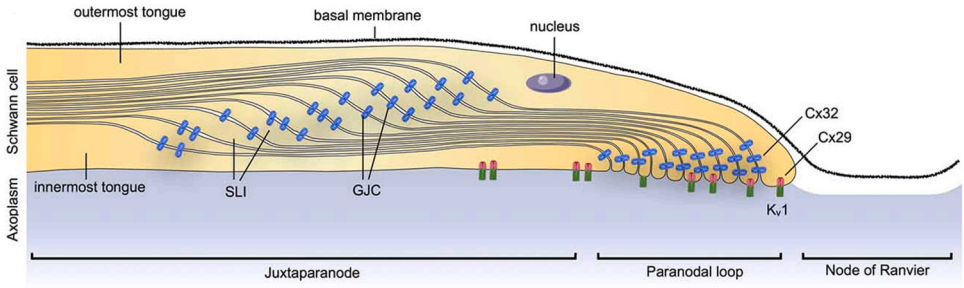

Fig. 3. Representation of a Paranodal loop on the PNS. This longitudinal view shows the different compartments: outmost tongue, innermost tongue, Schmidt–Lanterman incisures (SLI), and connexins (Cxs) forming gap junction (gip) channels and hemichannels, like the Potassium voltage-gated channel subfamily 1 (kv1) (Cisterna et al., 2019). Abbreviation: PNS, peripheral nervous system.

has been more commonly used as a powerful tool for analyzing biological structures (Earl et al., 2017), and utilized in MS investigations (Ma et al., 2022; Ruskamo et al., 2020).

The use of dyes is also applied to visualize cytoplasmic channels within myelin, usually by injecting the dye into oligodendrocytes or expressing fluorescent proteins. By using the fluorescent dye Lucifer Yellow, Velumian et al. (2011) managed to observe in slices of isolated spinal cord an extensive network of interconnected cytoplasmic pockets (Velumian et al., 2011). Several histological methods can be used to observe the MS, such as the Luxol Fast Blue, the Weils's Iron Hematein method, Osmium Tetroxide, Swank & Davenport, and Sudan Black B (Evangelou & Gorgoulis, 2017; Kiernan, 2007). Immunohistochemical methods are also commonly used when analyzing MS, usually by using antibodies that target specific MS proteins, such as MBP and PLP (Guo et al., 2018; Payne et al., 2012). These methods are applied in histological sections, and image techniques like the Magnetic resonance imaging (MRI), have been used to investigate the WM in live humans (Bennett and Madden, 2014; Gunning-Dixon et al., 2009; Sexton et al., 2014; Walhovd et al., 2014). By modifying the exam parameters, it is possible to highlight WM images from the rest of the brain, which allows for more in-depth analysis (Walhovd et al., 2014).

The effects of the demyelination process can also be observed using image analysis techniques to provide insight into macro and microstructures (Walhovd et al., 2014). Different image analyses, such as MRI and Positron emission tomography (PET) scans, have quantified WM volumes in the brain and volume or rating in lesions and microstructures. These techniques have been instrumental in determining the characteristics of WM change with aging, detailing the decrease of WM volumes and increase of WM lesions, in severity and volume, with advanced aging (Bennett and Madden, 2014; Gunning-Dixon et al., 2009; Sexton et al., 2014). When observing MRI exams of older patients, hyperintensity can be observed in the WM, which reflects the increased load of lesions as age increases (Yoshita et al., 2006).

2. Myelin degeneration and aging

Numerous modifications happen to the body during aging, and in the nervous system, they are not mainly related to the loss of neurons or changes in the synapses. They consist of changes in the myelinated nervous fibers morphology, as first shown by Feldman and Peters (1998) and other more recent published data (Ahn et al., 2022; Butt et al., 2022; Pannese, 2021).

Over time, a substantial amount of sheaths start to exhibit degenerative properties. The most common alteration observed is splitting at major dense lines, resulting in an accumulation of cytoplasm with vesicular intrusions (Feldman and Peters, 1998). Another aging-related change is the formation of "balloons." When observed via light microscopy, these balloons appear to be holes, and electron microscopy shows that they arise from the inter-period lines of the myelin, causing the sheath to bulge out. Moreover, the out folding of compacted myelin lamellae is another feature observed in aged macaques' brains. Fragments of myelin lamellae are also observed in the brain of aging mice (Hill et al., 2018; Safaiyan et al., 2016). Some of these fragments represent myelin out folding, while others are engulfed by microglia.

In addition, the brain of aged mice suffers a significant numerical increase in microglia with expanded lysosomal compartments, besides an accumulation of auto-fluorescent material reminiscent of lipofuscin. Lipofuscin contains nondegradable oxidized lipids, some of which are indigestible myelin. Thus, the extra/heavier burden of cleaning the damaged myelin in the old brain may not only lead to an increase in microglia with lysosomal inclusion but could also contribute to worsening microglial dysfunction (Safaiyan et al., 2016).

Chronic, sterile, low-grade inflammation has recently been studied as a possible mechanism related to age-related diseases in the aging organism, also known as "inflammaging" (Franceschi et al., 2018). Contrary to acute inflammation, which is a short-term defense mechanism (Mittal et al., 2014), this low-grade inflammation is a long-term process, which causes negative effects on the organism (Nathan and Ding, 2010), and has the brain as one of its major target (Grammatikopoulou et al., 2023). This process also includes metabolic pathway changes and adaptation to stress. This self-perpetuating state can spread from cell to cell due to Micro RNA, in particular 3 molecules, MiR21, MiR162, and MiR146a, which are known as inflammo-micro-ribonucleic acid (miRs), with MiR21 being used as an important biomarker of inflammaging (Olivieri et al., 2012). In the nervous system, this phenomenon manifests by hyperactivation of microglia cells, leading to inflammation, significant decreases in dendritic and axonal arborization, dendritic spines, post-synaptic densities, presynaptic markers, synapse, and cortical volume, as well as a reduction of specific neuronal population (Yankner et al., 2008), and is being studied as a factor in diseases such as Alzheimer's disease (AD) (Onyango et al., 2021) and atherosclerotic vascular disease (Cicolari et al., 2021).

During low-grade inflammation characteristic of the inflammaging process, microglia activation, which is a carefully controlled process, is fundamentally different from its acute high-grade counterpart (Holtman et al., 2015), with an upregulation of pathways related to the phagosome, lysosome, or antigen presentation, inducing the senescent microglia phenotype. During inflammaging, proinflammatory markers are also expressed, such as Interleukin-1 beta (IL-1β), Tumor Necrosis Factor Alpha (TNFα), Interleukin-6 (IL-6), and major histocompatibility complex II (MHC-II) (Wolf et al., 2017). Combined with this phenotype change, there is a total reduction of microglia cells (Cerbai et al., 2012; Damani et al., 2011), as well as a severe decrease in mobility (Krabbe et al., 2013), which results in a diminished neuroprotective efficiency. This decrease in mobility allows for the accumulation of degenerating neurons and

proinflammatory debris, thus accelerating the aging process (Krabbe et al., 2013).

2.1. Degeneration in pathological conditions

Some diseases, however, can accelerate the rate of these changes, resulting in acute loss of brain function and worsening the individual's life quality. AD, for example, has been typically associated with the brain's gray matter due to the distribution of this pathology and the neurodegeneration associated with it (Selkoe and Hardy, 2016) and is one of the most common age-related diseases, affecting 10% of the older population in the United States (Alzheimer's Association, 2022). According to the World Health Organization (2022), 55 million people have dementia worldwide. However, neuroimaging studies that can identify neurodegenerative processes have accused micro and macrostructural damages in WM in the risk and progression of AD, suggesting that, in addition to the neuronal loss characteristic of the disease, WM degeneration and demyelination can be a defining pathophysiological characteristic of the disease. Myelin loss and the inability of the oligodendrocytes to repair the damage are features of AD (Bartzokis, 2011; Matute, 2010; Matute et al., 2007; Pak et al.,2003). Due to the role of these cells in producing and maintaining the MS, changes in their numbers of functionality can affect the sheath's integrity, therefore being potentially implicated in AD pathology (Desai et al., 2009).

The notion that myelin degeneration might be associated with AD is relatively new. As previously mentioned, the myelin becomes more susceptible to insults with age, resulting in its breakdown, and underlines cognitive loss from dementia and AD (Bartzokis, 2011). In vivo, AD models show significant alteration in overall myelination and oligodendrocyte status before the development of classic AD signs amyloid and tau pathologies (Desai et al., 2009, 2010). However, those alterations can alter depending on the mutation of the AD model. In the amyloid precursor protein/presenilin 1 (APP/PS1) mouse model of AD, it is consistent that myelination commonly occurs until 3–6 months of age (Games et al., 1995; Oddo et al., 2003; Radde et al., 2006).

Myelin breakdown is also hypothesized to be a significant factor in toxic β amyloid deposits, as the process promotes the buildup of fibrils and enhances the formation of amyloid plaques (Bartzokis, 2011; Bartzokis et al., 2007a). These plaques and tau deposits are potent inductors of cell senescence. Myelin breakdown in late myelin regions may release iron, promoting, Aβ pathology development (Bartzokis et al., 2007a, 2007b).

Mito et al. (2018) compared MRI data from patients with AD or mild cognitive impairment with healthy older control participants and whole-brain analysis. The study showed significant loss of myelin in AD patients, while mild cognitive impairment patients only showed a loss in specific WM tracts. Another study (Caso et al., 2015) compared groups with different types of dementia, including an atypical form of AD, with healthy control groups through MRI imaging. Patients with atypical AD presented a more severe and widely distributed WM damage than the other forms of dementia, indicating that MRI scanning might be an early indicator of AD before significant cognitive damage can occur. Walsh et al. (2021) compared groups with early and late mild cognitive impairment, as well as AD groups, with control groups, showing an increase of hyperintensity in WM volumes of the afflicted patients compared with the control group.

Myelin degeneration also occurs in other pathologies. Zarkali et al. (2020) showed a possible correlation between Parkinson's hallucinations and visual dysfunctions with WM degeneration of the post-hypothalamic tract. WM degeneration is also a critical diagnostic tool for multiple sclerosis (Hunter, 2016).

Oligodendrocytes, responsible for MS, are the focus of studies involving myelin and its degeneration. Several studies in humans and animals have investigated oligodendrocyte changes in AD. A survey with APP/PS-1 mice showed an increase in OPC, while olig2+ numbers decreased (Behrendt et al., 2013). Another study revealed a higher number of microtubule-associated protein-2 positive remyelinating oligodendrocytes adjacent to WM lesions and a higher number of platelet-derived growth factor receptor α positive OPCs in those lesions (Simpson et al., 2007). In a PS-1 knock-in mouse model, increased vulnerability of glutamate and Aβ (amyloid-β-peptide) was demonstrated, and these cells showed a deficit in calcium regulation, suggesting that the abnormalities observed on oligodendrocytes in the presence of PS1 mutation could be an early event in the disease course (Pak et al., 2003).

One frequently accepted theme related to oligodendrocyte damage in AD is that these cells suffer from oxidative stress, which can produce several factors affecting their function. OPCs in the CNS can be mobilized to differentiate into myelinating oligodendrocytes (Baumann and Pham-Dinh, 2001). Oxidative stress impairs the differentiation of the OPCs by decreasing the expression of genes that promote the process (French et al., 2009).

Iron, as mentioned previously, also contributes to degeneration, increasing with age and AD. In this sense, it is essential to note that oligodendrocytes are the cell type with the highest iron contents (Bartzokis, 2011). That, combined with low amounts of antioxidants and half the activity of glutathione reductase (Juurlink et al., 1998), makes the oligodendrocytes one of the most vulnerable cell classes to oxidative stress in the CNS. Besides, increased oxidative stress due to age may lead to cellular damage (Tse and Herrup, 2017).

3. Myelin and physical exercise

Considering the above information concerning MS during aging and AD, how might exercise be protective against MS degeneration? Studies have been conducted for nearly 2 decades to understand how physical activity can improve neural function (Cassilhas et al., 2016; Meeusen, 2005). Animal studies have indicated a relationship between voluntary physical exercise and improvement in the memory task, which has been associated with a higher survival rate of hippocampal neurons (van Praag et al., 1999a, 1999b), an increase in neurogenesis, cell proliferation (Stranahan et al., 2006; van Praag et al., 1999b, 2005), and dendritic branching (Eadie et al., 2005; Stranahan et al., 2007).

Exercise also modulates the neurotransmitter systems (Meeusen, 2005; Moon, van Praag, 2014; Arida et al., 2015; Chaouloff, 1989; Farmer et al., 2004; Hill et al., 2010; Molteni et al., 2002; Vasuta et al., 2007), such as increased expression of specific subunits of N-methyl-D-aspartate (NMDA) receptors, which are essential for the excitatory neurotransmission by glutamate. The increase in these subunits demonstrates enhanced synaptic plasticity and the generation of new neurons (Vivar et al., 2013; Nácher et al., 2007). Other plausible mechanisms include the action of growth factors in the brain, such as brain derived neurotrophic factor (BDNF) (van Praag et al., 2005; Vaynman, Gomez-Pinilla, 2005; Vaynman et al., 2004) and insulin growth factor (IGF-1) (Ding et al., 2006; Trejo et al., 2001; Ye et al., 1995).

3.1. Physical exercise and MS in animals

Concerning the role of exercise on the MS, clinical and pre-clinical investigations have reported optimist findings (Fig. 4). Recent animal studies have demonstrated that exercise can protect or minimize MS degeneration (Chao et al., 2018; Xiao et al., 2018). For instance, according to Xiao et al. (2018), a group of rats submitted to a protocol of depression presented a reduction in the length and volume of myelinated fibers and a reduction of the volume and thickness of the MSs compared to the control and exercise groups. Interestingly, these parameters were significantly improved after

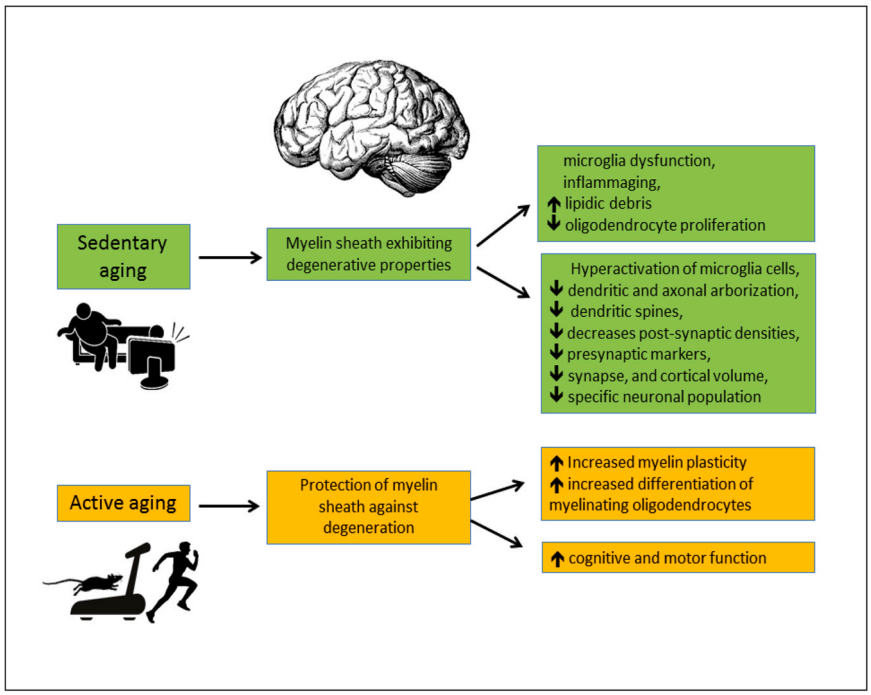

Fig. 4. Brief summary of the effects of aging on the brain, and the effects of an active lifestyle during aging on the myelin sheath. Although conflicting results have been demonstrated in scientific literature, most studies reported optimistic findings. Figure made using PowerPoint.

exercise. These findings have also been observed in AD animal models. Chao et al. (2018) quantified the recovery of WM degeneration after an exercise protocol in a group of AD mice. They observed that the increase in learning, spatial memory, and volume of the CA1 hippocampal region of AD animals submitted to exercise was associated with a significantly greater volume of the MSs in the cornu Ammonis 1 (CA1) field compared to their AD control counterparts. These findings support that exercise may protect MS from degeneration.

In a more recent investigation (Zheng et al., 2019), increased myelination in the motor cortex and differentiation of OPCs was observed in mice exposed to voluntary wheel running. An enhanced recuperation of MS in ischemic Mongolian gerbils was also noted after 4 weeks of exercise (Ahn et al., 2016). Another study exploring the interplay between exercise and diet demonstrated the promotion of myelination under a high dietary fat by increasing the major myelin proteins PLP and MBP. Besides that, high lipid diet associated with a physical exercise program induced increased myelin plasticity through insulin-like growth factor 1-AKT kinase (IGF-1-AKT) signaling (Yoon et al., 2016). The analysis of oligodendrocyte lineage cells of mice submitted to voluntary wheel running showed that following 3, 7, and 14 days, not only the pro-remyelination pathways were stimulated, but they were also working in parallel with remyelinating medication clemastine, which was administered after toxin-induced lesion (Jensen et al., 2018). Aerobic exercise also increased cognitive functions in aging mice by regulating the Rho-kinase signal pathway, which is associated with age-related demyelination (Bao et al., 2021). Huang et al. (2022) reported the benefic effects of a 4-month treadmill exercise regimen in Dawley rats, showing an increase in the total length of microvessels in the WM; however, only the female group demonstrated improved performance in the Morris Water Maze Test. In addition, a positive association between long-term aerobic exercise and delay in the loss of myelinated fibers and oligodendrocytes, as well as the prevention of capillary degradation within WM have been observed (Chen et al., 2020). In line with the above findings, a systematic review and meta-analysis (Feter et al., 2017), which analyzed 21 pre-clinical studies, pointed out the positive impact of moderate regular exercise and MS regeneration.

In addition to the beneficial effects on the CNS, exercise positively impacts the peripheral nerves. Trained young and mature rats with peripheral nerve lesions showed a significant increase in motor functions and myelin recovery (Cunha et al., 2011). Neuromuscular recovery has also been reported after crush damage. Treadmill running of medium intensity (10 m/min) accentuated nerve regeneration, accelerated functional recovery, and prevented muscular atrophy in rats. On the other hand, an increase in running intensity to 17 m/min showed undesirable effects (Ferreira et al., 2019). Characteristics of animal studies selected for this review are presented in Table 1.

3.2. Physical exercise and MS in humans

Similar to what occurs with animals, physical exercise can also induce positive effects on the MS of humans. For instance, a comparison between sedentary older adults with older athletes who were engaged in life-long physical exercise programs and elite-level competitions demonstrated a decrease in WM hyperintensity depth in sedentary adults and fewer lesions in the WM in older athletes (Tseng et al., 2013). Many other studies have reported the positive effects of exercise on WM. Increased MRI signals T1w/T2w for WM plasticity were observed in older adults submitted to an aerobic exercise and dancing program for 24 weeks (Mendez Colmenares et al., 2021). An association between cardiorespiratory fitness with WM integrity in older volunteers was also noted, although these effects were most observed in motor areas (Mace et al., 2021). Corroborating with these findings, Wanigatunga et al. (2021) analyzed the intrinsic connection between physical activity and brain morphometry by comparing the volume of WM in older individuals with different intensities of physical activity. Their findings demonstrated higher volumes of WM in individuals with higher ratings of physical exercise. An analysis of a sizeable narrow-age sample of older adults from a UK biobank found that regular physical

Table 1
Summary of the animal studies involving exercise analyzed in this review

Author	Subject	Age	Type of exercise	Period	Condition	Analysis method	Result
Xiao et al. (2018)	Rats	Not informed	Treadmill exercise	4 wk	Depression	Electron microscopy	MS volume and thickness increase
Chao et al. (2018)	Mice	6 mo	Treadmill exercise	4 mo	Alzheimer disease	Morris water maze and electron microscopy	WM degeneration recovery
Zheng et al. (2019)	Mice	Not informed	Wheel running exercise	2 wk	None	Western blot, Real-Time Quantitative Reverse Transcription - polymerase chain reaction (qRT-PCR), immunohistochemical staining, and electron microscopy	Increased myelination and differentiation of OPCs
Ahn et al. (2016)	Mongolian gerbil	22–24 mo	Treadmill exercise	4 wk	Ischemic stroke	Immunohistochemical staining and western blot	Enhanced recuperation of myelin sheath
Yoon et al. (2016)	Mice	9 wk	Wheel running exercise	7 wk	None	Western blot, PCR, and immunohistochemical staining	Promotion of myelination and increased myelin plasticity
Jensen et al. (2018)	Mice	8–12 wk	Wheel running exercise	3, 7, and 14 d	Induced demyelination	Immunohistochemical staining, oil red O staining, electron microscopy, and RNA sequencing	Pro-remyelination paths stimulation
Bao et al. (2021)	Mice	19 mo	Treadmill exercise	6 wk	None	Novel object recognition, morris water maze, luxol fast blue staining, transmission electron microscopy, and western blot	Regulation of demyelination-associated pathways
Huang et al. (2022)	rats	14 mo	Treadmill exercise	4 mo	None	Morris water maze and immunohistochemical staining	Increased microvessel length
Chen et al. (2020)	Rats	14 mo	Treadmill exercise	14 mo	None	Morris water maze, immunohistochemical staining, and enzyme-linked immunosorbent assay (ELISA)	Delay in the loss of myelinated fibers and oligodendrocytes, prevention of capillary degradation
Feter et al. (2017)	Papers		Aerobic exercise		None	Meta-analysis	Positive impact on myelin regeneration
Trigiani et al. (2020)	Mice	3–4 mo	Wheel running exercise	4–6 mo	Vascular cognitive impairment and dementia	Morris water maze, novel object recognition, spontaneous alternation Y-maze, flowmetry, blood pressure and glucose tolerance test, autoradiography, fluorescent-activated cell sorting, electrophysiology, western blot, and immunohistochemistry	Prevention of cognitive damage and WM injury
Zhou et al. (2018)	Mice	6–10 mo	Treadmill exercise	4 mo	Alzheimer disease	Morris water maze and transmission electron microscopy	Cognitive and MS preservation, increased exercise efficiency in females
Cassilhas et al. (2012)	Rats	90 d	Treadmill and vertical ladder exercise	8 wk	None	Morris water maze, immunoradiometric assay, ELISA assay, and western blot	Improved learning and spatial memory, presenting different signal pathways

Key: MS, myelin sheath; OPC, oligodendrocytes precursor cell; WM, white matter.

Table 2
Summary of the human studies involving exercise selected for this review

Author	Method	Results
Tseng et al. (2013)	Comparison between sedentary older adults with older athletes who were engaged in lifelong physical exercise programs and elite-level competitions	Reduction of WM lesions
Mendez Colmenares et al. (2021)	Older adults submitted to an aerobic exercise and dancing program for 24 wk	Increased MRI signals T1w/T2w for WM plasticity
Mace et al. (2021)	Analysis of community-dwelling adults of various ages with bike test and diffusion tensor imaging data of global and local WM microstructure	Positive cardiorespiratory fitness-WM integrity association
Wanigatunga et al. (2021)	Comparing the volume of WM in older individuals with different intensities of physical activity	Higher volumes of WM in individuals with higher ratings of physical exercise
Raichlen et al. (2020)	Analysis of samples from older adults from a UK biobank	Elation between regular exercise and reduced lesion load
Eisenstein et al. (2022)	Analysis of lifestyle, cardiorespiratory fitness, structural and diffusion MRI, and memory evaluation of 50 older participants	Positive association between an active lifestyle, cardiorespiratory fitness, and episodic memory
Strömmer et al. (2020)	Analysis of groups of older volunteers' self-reported physical activity levels	Positive impact on myelin loss
Franchetti et al. (2020)	MRI scan of older volunteers with different levels of self-reported fitness	Positive impact of higher levels of fitness on myelin loss
Johnson et al. (2020)	Maximal graded exercise test and structural brain imaging of community-dwelling older adults	Positive impact on myelin loss
Fleischman et al. (2015)	Measurement of total daily activity and brain MRI of older adults	Higher levels of physical activity may reduce the effect of White matter hyperintensities (WMH) burden on motor function in healthy older adults
Burzynska et al. (2014)	Accelerometry assessment of physical activity and brain MRI analysis	Hyperintensity volume reduction and lower volume of WM lesions
Gogniat et al. (2021)	Accelerometry assessment of physical activity and brain MRI analysis	Association between physical exercise and motor function in older adults, as well as myelin preservation
Sexton et al. (2016)	Systematic review	Positive relation between physical activity and WM, although a significant amount of studies could not report significant results
Intzandt et al. 2021	Systematic review	Reported substantial changes in brain MRI, highlighting activity length as an important factor
Dawe et al. (2021)	Assessment of cognition, total daily activity, motor abilities and post-mortem MRI brain analysis, and brain neuropathology assessment	Partial validation of positive relations between physically active older adults and cognition
Ding et al. (2018)	VO_2 max test, diffusion tensor imaging assessment of WM fiber integrity and neurocognitive assessment of older adults, and mild cognitive impairment patients	Association between higher levels of cardiorespiratory fitness and WM integrity
Boa Sorte Silva et al. (2023)	Cross-sectional data analysis and MRI scanning of individuals with small vessel disease and mild cognitive impairment	Positive relation between MS and physical activity
Tarumi et al. (2020)	1-y Randomized controlled trial of aerobic exercise in amnestic mild cognitive impaired participants	No significant change in WM lesion volume, improved WM tract integrity of prefrontal cortex
Venkatraman et al. (2020)	Older adults submitted to a 24-mo physical exercise program	No significant changes in WM lesions
Arild et al. (2022)	MRI scans across the 5-y exercise intervention	No attenuation of WM hyperintensity growth
Pani et al. (2022)	MRI scans across the 5-y exercise intervention	Cardiorespiratory fitness and exercise intensity are associated with WM microstructural organization in aging
Bolandzadeh et al. (2015)	MRI scan of older females submitted to a resisted training protocol	Reduction of WM lesions
Predovan et al. (2021)	MRI analysis of patients with different ages after a 6-mo exercise program	No significant benefits to WM microstructure
Voss et al. (2013)	MRI analysis of older adults during a 1-y protocol of physical exercise or stretching	No change in WM integrity, executive function, or short-term memory, however the walking program was associated with the change in WM integrity in the frontal and temporal lobes
Clark et al. (2019)	Diffusion tensor imaging before and after 6-mo aerobic exercise intervention	No improvements in WM microstructure

Key: MS, myelin sheath; WM, white matter.

activity was related to reduced WM lesions load (Raichlen et al., 2020).

A healthy lifestyle combined with better fitness can also exert an influence on WM. Eisenstein et al. (2022) suggested a positive association between an active lifestyle, cardiorespiratory fitness, and episodic memory by analyzing myelin lesions and pathways, especially in the hippocampus. Strömmer et al. (2020) demonstrated that a healthy lifestyle could positively impact WM loss by comparing groups of older volunteers' self-reported physical activity levels. Their findings are corroborated by Franchetti et al. (2020) and Johnson et al. (2020) studies, reporting similar results. A correlation was also observed between higher levels of physical activity and motor function with a decrease in WM lesions (Fleischman et al., 2015). Following this trend, a human study showed that greater moderate to vigorous physical activity was associated with WM hyperintensity volume reduction and lower volume of WM lesions (Burzynska et al., 2014). However, their findings did not support a significant relationship between cardiorespiratory fitness and WM in frontal brain regions.

Alteration in WM has also been analyzed with the intensity of physical activity. In Gogniat et al. (2021) study, a positive relationship between the short-term physical exercise of variable intensity and the preservation of MS in numerous brain areas, including the cingulum and fornix.

Interestingly, in a systematic review, conflicting results were reported (Sexton et al., 2016). While the studies analyzed presented positive findings, a considerable amount of them could not confirm these impacts due to not finding enough significant results. Another

systematic review by Intzandt et al. (2021) comparing cognitive and exercise training reports more substantial changes in brain MRI with exercise. However, it highlights that the length of the intervention might be an essential factor when studying the effects of exercise in humans and advise that a combination of cognitive and exercise training might be an efficient intervention method. In this line, Dawe et al. (2021) partially validated positive relations between physically active older participants and cognition using MRI-based signals in volunteers and post-mortem participants. Characteristics of human studies selected for this review are presented in Table 2.

3.3. Physical exercise in pathological conditions

Physical exercise also exerts a beneficial impact on neurological diseases, such as the reduction of mood disorders (Lawlor and Hopker, 2001) and anxiety (Peluso and Guerra de Andrade, 2005), as well as it can minimize the progression of diseases such as Alzheimer's (Farina et al., 2014), Epilepsy (Arida et al., 2010; Gomes da Silva et al., 2011), Schizophrenia (Malchow et al., 2013), Parkinson's disease (Earhart and Falvo, 2013), and other disorders (de Almeida et al., 2012; Wolff et al., 2011), and more recently its effects on MS have been explored.

While the association between neuropathological conditions and exercise is widely investigated, only some of these studies have MS as their focus. Although few, these studies have shown positive outcomes. Trigiani et al. (2020) reported a positive effect of running exercise in mice with vascular cognitive impairment and dementia, preventing cognitive damage and WM injury. Zhou et al. (2018) investigated the effects of physical exercise on AD in both male and female transgenic mice, reporting not only cognitive protection and MS preservation but also increased exercise efficiency in females. Zhang et al. (2017) corroborate these findings, reporting similar results on the hippocampus of AD mice.

With humans, studies analyzing neuropathology, exercise, and WM are scarce. This is due to the difficulties entailed when working with affected individuals, especially when cognitive-impairing diseases are involved. Nevertheless, studies are tackling the question. For instance, Ding et al. (2018) reported an association between higher levels of cardiorespiratory fitness and WM integrity in Mild cognitive impairment patients. Boa Sorte Silva et al. (2023) showed a positive relation between MS and physical activity in cerebral small vessel disease and mild cognitive impairment-afflicted older adults, linking higher myelin content with more significant physical activity. Tarumi et al. (2020) realized a 1-year randomized controlled trial of aerobic exercise in amnestic mild cognitive impaired participants. While there was no significant change in WM lesion volume between control and exercise groups, individual cardiorespiratory fitness gains were associated with improved prefrontal cortex WM tract integrity. However, null result has been reported. Venkatraman et al. (2020) demonstrated no significant changes in WM lesions or hippocampal volume in a 24-month physical activity program. The need for studies in this field brings into question the efficiency of physical exercise in pathological conditions. Thus, more investigation in the area should be considered.

4. Contradictions

Despite many studies indicating positive relations between physical exercise and WM preservation, some cannot find evidence of this relationship. Conflicting results have been observed in this field of research. Predovan et al. (2021) could not find evidence for the benefits of physical exercise on WM microstructures, although limitations in the study were observed. These findings align with other studies (Clark et al., 2019; Tarumi et al., 2020; Voss et al., 2013), which have shown similar results. Arild et al. (2022) reported no improvements in WM during 5-year physical exercise intervention in older adults, and Pani et al. (2022) found correlations between physical activity and cardiovascular fitness with WM improvements, although with different levels of benefit, in the same time frame of 5 years. This remarkable contradiction leaves a gap in long-term studies of physical exercise intervention in older adults, and more studies are required.

Although the above information is related to the impact of aerobic exercise on MS, little is known about whether other types of exercise can exert the same positive effects. Only 1 study in animals addresses aerobic and resistance training differences (Cassilhas et al., 2012), and only study in humans has used a protocol of resistance training in this context, in which a reduction in WM lesions was observed in older women submitted to 12 months of intervention (Bolandzadeh et al., 2015).

Table 3
Summary of sedentary/senile and active aging findings in this review

Parameter	Sedentary/senile aging	Active aging
Myelin plasticity	Decreased	Increased
Myelin degeneration	Increased	Decreased
Myelin volume	Decreased	Increased
White matter lesions	Decreased	Increased
Microglial dysfunction	Increased	Decreased
Oligodendrocyte	Damaged	Stimulated
Neuronal and synaptic plasticity	Decreased	Increased
Cognitive and motor function	Decreased	Increased

5. Conclusion and future directions

The MS is vital for the propagation of signals quickly and efficiently in both the central and PNS, formed and maintained by oligodendrocytes and Schwann cells, respectively. Various factors, such as aging and sedentarism, may cause a severe decline in cognitive function due to myelin degradation. The present review has outlined physical exercise's potential role in counteracting aging effects (an overall summary of findings is presented in Table 3). Considerable research has documented that physical activity positively influences the brain, especially as therapy and prophylaxis against myelin breakdown. Despite that, there are still questions to be answered. Currently, several studies are exploring the benefits of aerobic exercise on MS; however, there is a remarkable lack of information regarding other types of physical activity, such as resistance (strength) exercise, which could contribute to improving the quality of life of the older population by increasing the physical capabilities and promoting independence. Another issue in this field of study is the presence of conflicting results, which might be caused by the studies' limitations or external factors. Besides, factors such as which intensity and duration of physical exercise are ideal for maximum benefit are still undetermined.

Disclosure statement

The authors have no actual or potential conflicts of interest.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Fig. 1 drawn by Stahr Mar Vasconcelos.

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