

Review

The Structural and Biochemical Organization of Myelin in Health and Pathology

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Abstract

This review examines current understanding of myelin biology and its adaptive roles in health, disease, and aging. We describe the cell populations involved in myelination, demyelination, and remyelination. We discuss the microstructural organization of myelin and its maintenance through complex molecular interactions within the glial microenvironment. We summarize morphological changes in myelin associated with various neurological disorders of the central and peripheral nervous systems. We note the fundamental biochemical differences between central nervous system (CNS) and peripheral nervous system (PNS) myelin and describe potential mechanisms underlying pathological molecular alterations. This review discusses recent and sometimes conflicting evidence on adaptive and maladaptive myelin plasticity, the role of myelin function in aging, the relationship between myelin and the microbiota, and the involvement of myelin in gray matter neurodegeneration. We present relevant data on myelin vulnerability and myelin degradation as potential markers of neurodegeneration in animal models. This review summarizes current understanding of the key cellular and molecular mediators of physiological myelination and pathological demyelination and examines the molecular mechanisms underlying these processes.

Keywords: neurology; neuroinflammation; myelin; brain; neurodegeneration

1. Introduction

According to classical concepts, the formation of the myelin sheath around neuronal axons is provided by oligodendrocytes in the central nervous system (CNS) and Schwann cells in the peripheral nervous system (PNS) [1,2,3]. Despite this, newly obtained data show that myelin production and organization are tightly controlled by different types of neuronal cells. This process begins in early embryonic development and continues throughout the entire life. Current views show that myelination is an active process, not a passive one. It is a complex mechanism of interactions between cellular components that needs to be described in detail.

Recent studies have highlighted the involvement of other cellular elements in myelination, demyelination, and remyelination processes. These include:

(1) *macroglial cells* — *astrocytes* and *ependymocytes* — originating from the neural tube. Astrocytes serve as controllers of myelination, coordinating the process of axonal growth and the growth of oligodendrocyte processes in the correct direction. They also synthesize some neuro-

transmitters [4,5,6]. Ependymocytes provide trophic functions, synthesize various neurotransmitters, and support cellular regeneration [7,8] originating from the neural tube;

(2) *microglial cells* — originating from erythromyeloid precursors in the yolk sac or from hematopoietic stem cells during later stages of ontogenesis (part of the reticuloendothelial system) [9]. In their resting state, they perform protective functions, and upon activation by pathological stimuli, they manage demyelination processes (after fiber injury, etc.) [10,11].

Furthermore, one of the most amazing observations was that, under certain pathological conditions, PNS Schwann cells can participate in CNS axon myelination [12,13,14]. In the PNS, satellite cells of the peripheral nerve ganglia, which develop from the neural crest, can proliferate into sensory and autonomic neurons after injury [15,16] (Figs. 1,2).

The process of myelination (the multi-layered thickening of the compacted cell membrane) is a key regulator of axonal conduction. The tight apposition of the fatty-like membrane of myelinating cells to neuronal axons forms the special myelin sheath. This structure reduces axonal mem-



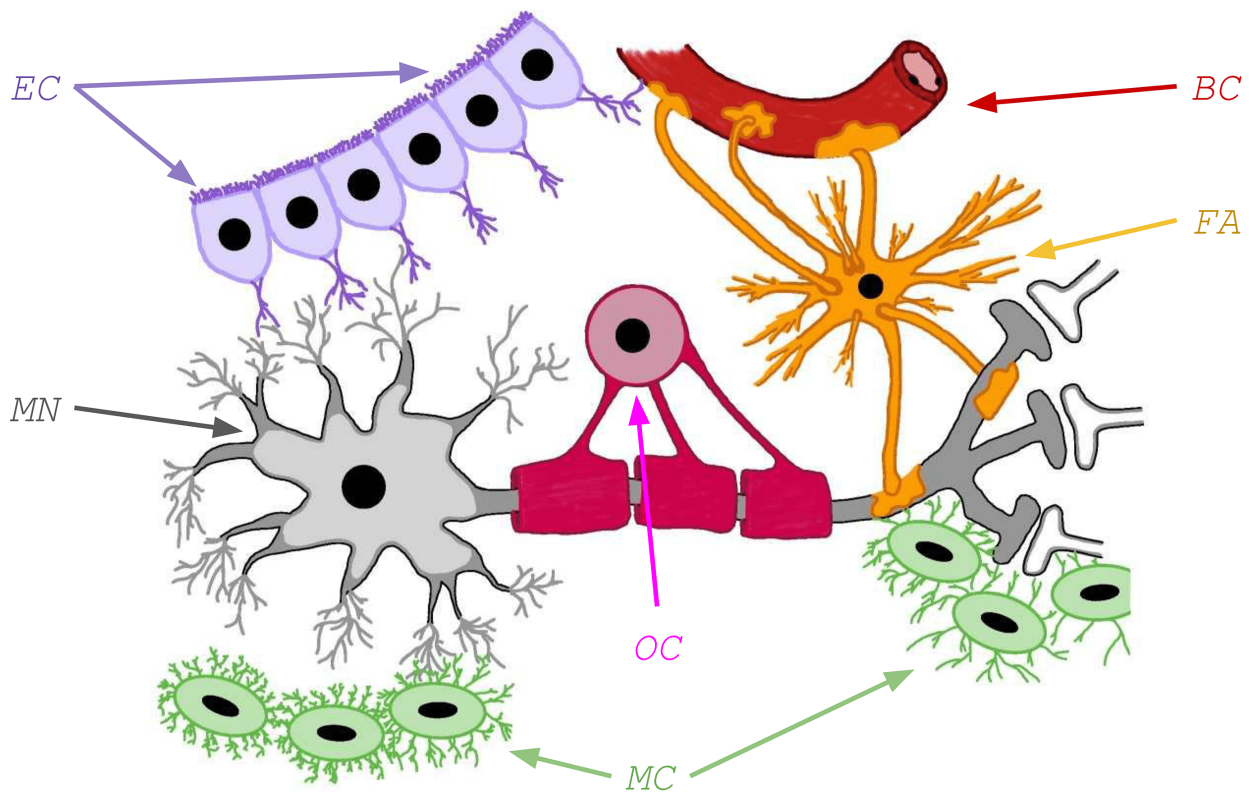


Fig. 1. Organization of myelinating cells in the human central nervous system. EC, ependymal cells (tanycytes); BC, blood capillary; FA, fibrous astrocyte; OC, oligodendrocyte cell; MC, microglial cell; MN, mature neuron. The processes of myelination in the central nervous system are usually provided by oligodendrocytes. Some pathogenetic processes induce demyelination with participation of astrocytes (manifesting astrogliosis) and activation of microglial cells (manifesting microgliosis). Both factors affect the myelination ability of oligodendrocytes and the myelin affinity to neural axons. In remyelination, processes can be involved: cells with a selective ability to proliferate (subspecies of ependymocytes) and stem cells of the central nervous system located in three regions — (1) dentate gyrus of the hippocampus; (2) lateral ventricles of the brain; (3) hypothalamic region.

brane capacitance, provides electrical isolation (ionic impermeability) for nerve fibers, and facilitates saltatory conduction of excitatory potentials [17]. The organization of the myelin sheath, its stability, length, and thickness are strictly regulated by molecular and biophysical signals from the axon and the local cellular microenvironment. Alterations in any of these parameters can affect the speed and accuracy of nerve impulse conduction [18].

Myelinating oligodendrocytes exhibit certain forms of plasticity in adult humans. This plasticity ranges from the generation of entirely new myelinating cells to more subtle alterations in the length, thickness, and distribution of the myelin sheath along axons [18,19,20]. Plasticity is also a feature of PNS cells. Following traumatic injuries or peripheral neuropathies, cells become activated. This process involves changes in their gene expression and the remodeling of their activity and function. This activity manages the regeneration process, the disintegration of damaged axons by macrophagic cells, and demonstrates neuroprotective effects, as well as the redistribution of myelin and axonal outgrowth [21,22,23,24].

Myelination of the human PNS is largely complete within the first two years after birth, while CNS myelination continues intensely until approximately age 40 and then declines in older age. These changes vary across different brain regions [25,26]. Pathology of the myelin sheath is a key factor in the development of neurodegeneration [27,28,29,30].

Our knowledge and understanding of myelin biology have increased significantly over the last decades. However, many unsolved questions and controversies remain. The physiological changes in myelin that dynamically influence axon function and neural circuitry stay unclear. We do not fully understand the relationship of these mechanisms with learning, memory, and cognitive function [18,22]. There is no reliable information about the evolutionary origin of myelinating cells in the vertebrate nervous system. Multipotent cells in the PNS that are homologous to glial progenitors in the CNS have not been fully described [22], and the regenerative and proliferative potential of satellite glial cells [15,16] and their involvement in different CNS disorders [12,13,14] remain unclear.

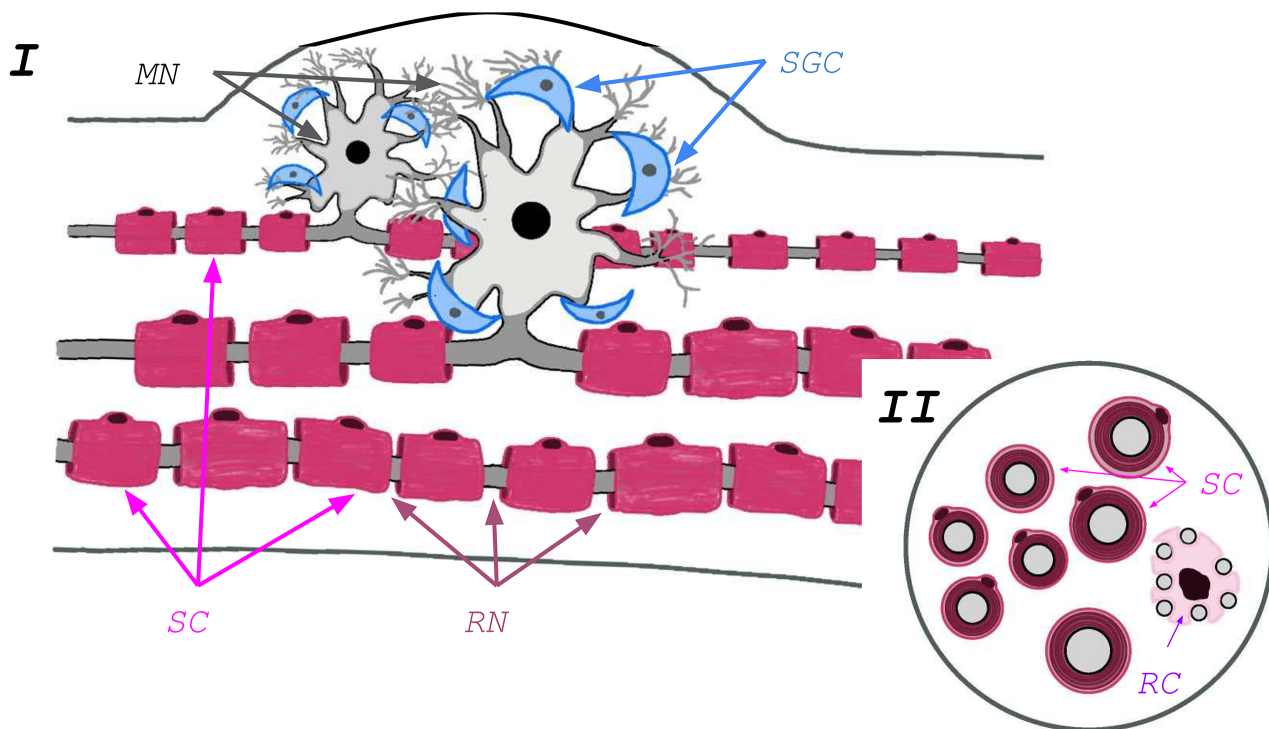


Fig. 2. Organization of myelinating cells in the human peripheral nervous system. I — schematic picture of peripheral ganglion; II — schematic picture of peripheral nerve (transverse section). MN, mature neuron (pseudounipolar); SGC, Satellite Glial Cells; SC, Schwann cells; RC, Remak cells. Each Schwann cell wraps a section of only one axon. These cells are separated from each other by nodes of Ranvier (RN) — a distinctive feature of higher vertebrates. This promotes the saltatory transmission of nerve impulses along the fiber (similar to the myelinated oligodendrocyte fiber of the CNS). Satellite glia cells express several markers of Schwann cell precursors and mature Schwann cells, showing the ability to differentiate in them. SGC also form a unified functional structure with sensitive/autonomic neurons, provide various molecular interactions. Non-myelinating forms of lemmocytes (Remak cells and bundles) are also present in the PNS, performing trophic and supportive functions.

Thus, we have briefly described the cellular types involved in the processes of myelination, demyelination, and remyelination. Even these materials have important clinical significance: the treatment of neurological diseases associated with myelin damage must consider all of these complex cellular interactions and molecular mechanisms. This is one of the major reasons why many neurological diseases remain idiopathic and incurable (with only symptomatic therapy available).

2. Results

2.1 Embryogenesis and Cell Lineages of the Principal Myelinating Cells

From a certain evolutionary perspective, the myelin sheath is an adaptive structure [31,32]. Comparative research on myelin in vertebrates and invertebrates has had a great impact on advancing our relevant knowledge [33,34]. Due to this, we underline that myelin development is connected to the phylogeny of all vertebrates and plays a crucial role in the development of human cognitive, sensory, motor, and intellectual abilities.

The organization of myelin in vertebrates follows several general principles, revealed by electron microscopy. These include the multiplicity of lipid membranes, their condensation and compaction, specialized marginal densities, and the formation of nodes [35]. At the same time, myelinating glia are the last type of neural cell to appear during the evolution of the vertebrate nervous system [36]. Consequently, these cellular structures and their derivatives can influence the development of higher nerve centers in humans and provide special cognitive functions, memory, and adaptation in learning. Numerous studies describe the cellular differentiation and maturation of glial cells, including myelinating cells [37,38,39]. However, the specifics of interactions between genetic and epigenetic factors, their paracrine and immune regulation, and relationships with the surrounding microenvironment (with other cells and the extracellular matrix) remain debatable.

According to general concepts:

Oligodendrocyte precursors originate from neural stem cells of the radial glia. Radial glia migrate along the neural tube throughout the CNS (a process known as “migration waves”) [40,41]. As a result, some cells transform

into pre-myelinating oligodendrocytes (PMOs). However, the majority of other cells do not differentiate until they reach maturity [37,39]. It is precisely these PMOs that are supposed to transform into mature myelinating forms. But only about 1/4 manage to do so, while the remaining cells apparently fail to do so in time and undergo apoptosis [37,42].

The genetic and proteomic factors of differentiation and maturation are next:

(1) *Arx*, *Cebpb*, *Egr1*, *Id2*, *Klf4*, *Klf10*, *Sox11* [43], *PAX6*, *Musashi*, and the genes expressing vimentin and nestin — in neural stem cells [44];

(2) *PDGFR-α*, *A2B5*, *Ng2*, *Olig1-2*, *Sox10*, *Nkx2-2* — in oligodendrocyte precursors [44,45];

(3) *MRF*, *Krox20* [46], *Cnp*, *Galc*, *Plp1*, and *Mbp* — in mature oligodendrocytes [44]. Meanwhile, the expression of *ERBB4* and *SORL1* increased during the transition from stem cells to mature ones [44].

Lemmocyte's cell precursors originate from neural crest cells [47,48]. They migrate dorsally under the skin or ventrally through the somites. After that, they translocate segmentally through the rostral halves of the sclerotomes and populate associated regions of the trunk [49,50].

Their cell lineage is represented by the following chain: neural crest cells → Schwann cell precursors → immature cells → mature forms [51,52]. Mature forms go 2 main directions [53,54]:

(1) *myelinating lemmocytes (Schwann cells)* typically myelinate only peripheral axons with a diameter greater than 1 μm [12];

(2) *non-myelinating lemmocytes*, which include:

(a) Presynaptic gliocytes (terminal Schwann cells) — associated with axons of neuromuscular synapses and possibly participating in regulating synaptic activity. After injury, they phagocytose the remnants of axon terminals, preparing them for remodeling (participating in remyelination) [55].

(b) Remak cells — typically associated with smaller-diameter axons. They enclose and separate several small axons in shallow grooves on their surface and wrap them into a single bundle (a non-myelinating Remak bundle). According to some data, this allows them to perform a trophic and metabolic support function [12,37,56].

(c) Enteric glia [57] — involved in maintaining the homeostasis of the neuronal microenvironment and in neuroeffector reactions of the hollow organs of the gastrointestinal tract [58,59].

After injury, intermediate forms that can transform into both subtypes are observed between Schwann cells and Remak cells [51].

The genetic and proteomic factors of differentiation and maturation are next:

(1) *Ap2α*, *Pax3*, *Sox2* — in Schwann cell precursors [60];

(2) *Nrg1* [54,61], *ErbB2*, *Krox20*, *Oct6* [60], *Pou3f1* and *Pou3f2* [62] — in immature cells (upon interaction with other factors, they initiate the synthesis of *MPZ* and *S100b* [60,62]);

(3) *CNTF*, *Sox10*, *Krox20* [60], *TGFβ* *STAT3* [63] — in mature cells (upon interaction with other factors lead to expression of *p75NTR*, *S100b*, *Gap43*, *GFAP*, *Mbp*, *Pmp22* [60], *LICAM* [64]).

Three main signaling pathways (Wnt, FGF, BMP) ensure the normal process of cell induction and their migration from the neural crest, while the Notch signaling pathway suppresses neurogenesis [60]. Another signaling pathway, mediated by *Nrg1*, prevents excessive myelination, which in the adult organism can cause reactive myelin degeneration [54]. Other regulatory mechanisms and molecular pathways are also under discussion [65].

Overall, the Schwann cell lineage is more plastic compared to oligodendrocytes, allowing them to regenerate more effectively [37]. Consequently, these features can partially explain the increased regenerative capacity of PNS cells relative to CNS cells, as well as the higher stability of PNS myelin, which is maintained over time [66].

Thus, we are beginning to understand the complex genetic and molecular mechanisms of myelinating cell development. This provides us with an opportunity to explore the treatment of hereditary myelopathies. It also offers a chance to investigate the regenerative potential of some cells for use in adult degeneration, etc. More detailed description of cell populations is provided in Table 1 (Ref. [3,4,5,7,8,9,10,12,15,37,42,56,57,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108]).

2.2 Cell Populations Involved in Myelination, De- and Remyelination

The functional significance and differentiation of subtypes are presented in Table 1.

2.2.1 Oligodendrocytes of Macrogliia

They originate primarily from a population of resident precursor cells (radial glia with an *Ng2* marker). These cells migrate from the subventricular zone of the neural tube, have a diffuse distribution in the CNS, and are present in the adult brain [18,41].

Morphological varieties are represented by the following forms [67,68]:

(1) *type I* — have small, round cell bodies with a large number of processes; generally located in gray and white matter of the CNS;

(2) *type II* — have polygonal-shaped cell bodies; generally located in white matter of CNS;

(3) *type III* — have large cell bodies, outlining myelin sheaths; selectively ensheath large-caliber axons in the white matter;

(4) *type IV* — have elongated cell bodies; selectively located in white matter of the brainstem and spinal cord;

(5) *small process-bearing cells* — discovered in the frontal lobes of mice [109];

(6) *branched, stellate, smooth cells* — discovered in the hippocampus of mice [110].

Studies of gene expression profiles and molecular markers distinguish approximately 6 variants of mature oligodendroglia cells [67] and approximately 12 variants (in mice), including immature oligodendrocytes [111]. Modern techniques provide single-cell RNA-sequencing (scRNA-seq) to observe specific cell populations according to gene patterns. In mice, 14 clusters were explored, including several types of immuno-active oligodendrocytes induced in encephalomyelitis [112].

2.2.2 Astrocytes of Macroglia

They originate primarily from the neuroectoderm (radial glial precursor cells), are fundamentally similar to oligodendrocytes, and have a diffuse distribution in the CNS. They are the most numerous population of macroglial cells [69,113].

Morphological varieties are represented by the following forms [114]:

(1) *fibrous astrocytes* — possess several thin, long, poorly branching processes; generally distributed in the white matter of CNS [115];

(2) *protoplasmic astrocytes* — possess several main branches with numerous short, highly branching processes; generally distributed in the gray matter of CNS [116].

(3) types of astrocytes are distinguished in the human cerebral cortex [70].

Studies of gene expression profiles and molecular markers distinguish approximately 5 variants of astroglia cells [117]. ScRNA-seq of primary neonatal cortical astrocytes demonstrated 3 clusters, with one unique cluster showing the potential to transform into neurons [118].

2.2.3 Ependymocytes of Macroglia

They originate primarily from the neuroectoderm (radial glial precursor cells) and are fundamentally similar to oligodendrocytes and astrocytes [71,72].

Morphological varieties are represented by the following forms [67]:

(1) *ciliated (typical ependymocytes)* — cells of a cuboidal/columnar shape with multiple short cilia on the apical surface [119]; they form the lining of the brain ventricles and the central canal of spinal cord [73,119];

(2) *process-bearing (tanycytes)* — cells of a cuboidal shape, possessing a long process and 0–2 cilia [71]. They are located among the layer of ciliated cells, line the lateral wall and floor of the 3rd ventricle. Also presented in the circumventricular organs [71,73,74].

Some authors report 2 additional subtypes: poorly differentiated non-ciliated ependymocytes and choroidal ependymocytes [7].

Studies of gene expression profiles and molecular markers distinguish approximately 5 variants of ependymal glial cells (for ciliated cells — 1 variant; for tanycytes — 4 variants: $\alpha 1$, $\alpha 2$, $\beta 1$, $\beta 2$) [71,74]. ScRNA-seq demonstrated 17 clusters in human ependymoma, including immuno-active patterns, neuronal stem cell patterns and others [120].

2.2.4 Macrophages of Microglia And Microglia-Like Cells

They originate primarily from erythromyeloid precursors of the yolk sac or from hematopoietic stem cells [9,121].

Morphological varieties are represented by the following forms [122]:

(1) *branched (ramified)* — have a small cell body and numerous thin processes [10,122];

(2) *amoeboid* — cells with a rounded morphology, a large nucleus, and several short, broad processes [10,122];

(3) *reactive* — have the largest cell body among the microglial subtypes, with shorter, fewer, and thicker branchings of the processes [75,122];

(4) *specialized (including Kolmer's cells)* — polymorphic cells [123], possess straight thin or tortuous processes, located in the choroid plexuses [124];

(5) *rod-shaped* — have a narrow, flattened cell body and two poorly branching processes extending from the poles of the cell body (associated with typhus and syphilis infections) [75,76].

There is a possibility of transformation between amoeboid and branched glia [10,76].

Studies of gene expression profiles and molecular markers distinguish approximately 7 variants of microglia cells [77,121]. ScRNA-seq has demonstrated over 200 clusters, categorized into three main groups associated with age, region, and disease. Aged microglia seem to share similar gene expression profiles with microglia detected in disease conditions [125].

2.2.5 Lemmocytes of PNS

They originate primarily from migrating neural crest cells [47,48].

Morphological varieties are represented by the following forms:

(1) *myelinating (Schwann cells)* — before contact with an axon, they have a bipolar morphology with elongated processes [126]. After contact, they spirally envelop the axon, condense by extruding water from the cytoplasm, and their processes unite together forming mesaxon [127];

(2) *non-myelinating (Remak cells)* — are fundamentally similar in organization to Schwann cells but have more processes that envelop several axons [127,128]. They do not form myelin isolation but also form mesaxons [55,56].

Studies of gene expression profiles and molecular markers distinguish approximately 4 variants of Schwann cells [129,130,131]. ScRNA-seq demonstrated over 6

Table 1. Functional description of the main types of glial cells.

Type of Cell	Morphofunctional subpopulation		Function	
		<i>Specific</i>	<i>General</i>	
<i>Oligodendrocytes</i>	type I	• responsible only for forming the myelin sheath around small-diameter axons (typically $0.6 \pm 0.1 \mu\text{m}$) [67,68]	can myelinate several axons of different diameters [3] (forming thicker myelin around the larger axon [80]); some oligodendrocytes predominantly [81] myelinate a specific molecular type of neurons induce the clustering of Na^+ -channels in the nodes of Ranvier [42], and are involved in motor learning and long-term memory [82]	
	type II			
	type III	• involved in myelinating a smaller number of larger-diameter axon bundles, sometimes predominantly enveloping only certain axons [67,68]		
	type IV			
	small process-forming branched, smooth	• not established		
<i>Astrocytes</i>	stellate,	• not established		
<i>Astrocytes</i>	fibrous	• remain poorly characterized [69]; they are postulated to mediate neuromodulation through process-to-synapse connectivity [70] • modulate interneuron communication and locally integrate information from a large number of synapses [70];	form and maintain the blood-brain barrier, provide synaptogenesis and synaptodestruction, neurotransmission and metabolic regulation [86,87]	
	protoplasmic	• via gap junctions with oligodendrocytes, they transfer lipids and secrete <i>FGF2</i> and <i>CNTF</i> [4,83,84]; • in certain pathologies, they become activated (astrogliosis), promoting the removal of myelin debris, and recruiting microglia [85]		
<i>Ependymocytes</i>	ciliated (typical)	• form the blood-(cerebrospinal fluid)-brain barrier, ensure the transport of ions and water to and secrete the cerebrospinal fluid [7,88,89]; • secrete neuroendocrine molecules [90]	cells synthesize cerebrospinal fluid, and their cilia facilitate its circulation [7]; directly promote the regeneration of CNS axons and their remyelination after injury [7,73]; exhibit plasticity and provide neuroendocrine control of metabolic functions [8,71,88]	
	process-bearing (tanycytes)	• neuroendocrine functions (glucose homeostasis) and reproductive function (secretion of gonadotropin-releasing hormone [91]) [71,92]; • a contact-conduction function with certain hypothalamic nuclei [72,74]		
<i>Microglia</i>	amoeboid	• exhibit high motility, as well as phagocytic and proliferative capacity [76]; • present antigens and remodel the extracellular matrix [75]	promote neurogenesis, the formation of neural networks, and the remodeling and elimination of vascular networks and synapses [77]; support oligodendrocyte development [10,76]; activated microglia are plastic and can adopt various transcriptional and functional phenotypes depending on the damaging factor [9,96]; guide axon growth [5]	
	ramified	• resting, non-activated glia; moderate phagocytic capacity and surveillance of the CNS status [10,76]; • establishes contacts with neurons and modulates their activity [76]		
	rod-shaped	• serves as a neuropathological marker for several conditions: general paresis, cerebral atrophy, multiple sclerosis [76], typhoid fever, and syphilis [75]		
	reactive	• participates in microgliosis and accompanies neuropathologies where it eliminates certain neurons (including those with $\text{A}\beta$ -protein) [76,93]; • secrete neuroinflammatory regulators (cytokines) [94,95]		
<i>Neurolemmocytes</i>	myelinating (Schwann)	• form the myelin sheath around medium- and large-caliber axons, shape the structure of developing nerves (by organizing blood vessels and the endoneurial, perineurial, and epineurial layers) [56]; • secrete regulatory growth factors and cytokines [97,98]	key element of the PNS, providing trophic, mechanical, and functional support to axons [99,100] for normal impulse conduction;	

Table 1. Continued.

Type of Cell	Morphofunctional subpopulation	Function	
		<i>Specific</i>	<i>General</i>
	non-myelinating (Remak)	• associate with small-caliber axons (<1 μm) [57], segregate them, and bundle them into a single non-myelinated Remak bundle; • perform trophic, metabolic, and organizational functions [12,37,56]	regulate the activity and efficacy of neuro-organ and neuromuscular synapses [101,102]; in response to injury, they switch to a reparative profile and facilitate the restoration of PNS function [103]
<i>Satellite glial cells</i>	satellite glial cells of sensory ganglia	• modulation of pain perception (promote neuronal hyperexcitability), secretory function [79,104]; • can differentiate into functional sensory neurons [15]; • secretory function (cytokines) [105]	regulate the microenvironment, providing support, nourishment, and protection to neurons under pathological conditions; following nerve injury, they can differentiate into sensory neurons [15,106];
	satellite glial cells of autonomic ganglia	• modulate the metabolism of sympathetic neurons, their survival, neurotransmitter homeostasis, activity, and autonomic functions [78,79]; • release neurotrophic factors (<i>NGF</i>) and regulate short-term plasticity [104]	participate in regulating synaptic transmission, are themselves capable of transmitting Ca^{2+} -mediated signals, and are involved in nervous system development [106]; exert a protective activity for ganglion neurons [107,108]

Table 2. Correlation of pathologies with corresponding myelin alterations.

Classification	Diagnostic criterion (Clinical/Neuropathological/MRI-visual)	Alteration in myelin structure/Composition
Primary diseases (Multiple sclerosis; MS)	For non-progressive MS: • key MRI characteristics: T2-weighted MRI reveals ≥ 2 lesions in ≥ 2 of the following areas: periventricular/(juxta-)cortical/infratentorial/spinal cord; • ≥ 2 clinical attacks with objective clinical evidence occurring in ≥ 2 cases [164]; • in all other cases, additional clinical and MRI studies are required [164] For progressive MS [165]: • clinical deterioration observed over a period of 1 year (independent of the presence of clinical relapses);	Abnormal isoforms of MBP form in the compact myelin of the CNS, leading to altered myelin properties, weakened membrane contact, and disruption of the myelin structure (which triggers an immune response against MBP isoforms and their appearance in the cerebrospinal fluid) [141]; ↑ Phospholipids, deiminated arginine residues, ↓ sphingolipids [142]
	• supporting paraclinical evidence, confirmed by either: T2-hyperintense lesions in at least one area of the brain characteristic of MS/T2-hyperintense spinal cord lesions/presence of specific oligoclonal bands in the cerebrospinal fluid For pediatric MS (>12 years old) [165]: • ≥ 2 clinical attacks, not associated with encephalopathy, with a presumed inflammatory cause, separated by >30 days and involving >1 area of the CNS; • 1 non-encephalopathic attack, typical for MS, with supporting MRI findings; • 1 ADEM attack followed by a non-encephalopathic clinical attack ≥ 3 months after symptom onset, with MRI evidence; • first, single, acute episode in a child that does not meet the symptoms of ADEM (see below)	
Primary diseases (Multiple sclerosis variants; MSV)	Myelinoclastic diffuse sclerosis (MDS; Schilder's disease) [166]: • clinical and histopathological characteristics are consistent with the course of classic MS; • bilateral, large demyelinating lesions in the cerebral white matter measuring $\geq 2 \times 3 \text{ cm}^2$ with discontinuous ring-like enhancement, involving the frontal/parietal lobes; • absence of oligoclonal bands, fever, preceding viral/mycoplasma infection, or vaccination before to the onset of neurological symptoms Neuromyelitis optica spectrum disorders (NMOSD; Devic's disease) [165]: • core clinical characteristics: optic neuritis, acute myelitis, "area postrema" syndrome, acute brainstem syndrome, or acute diencephalic syndrome (with NMOSD-typical MRI lesions), symptomatic narcolepsy;	
	• <i>AQP4-IgG</i> testing, which is used to diagnose NMOSD if we noticed (<i>positive test</i>, ≥ 1 core clinical characteristic, and exclusion of alternative diagnoses) (<i>negative test</i>, but fulfillment of the MRI criteria according to [167]: (<i>unknown/unavailable test result</i>, ≥ 2 core clinical characteristics from the following: optic neuritis/acute myelitis with LETM/area postrema syndrome, occurring as a result of one clinical attack and demonstrating dissemination of the lesions) Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids (CLIPPERS) [168]: • subacute pontocerebellar dysfunction with possible other CNS symptoms (cognitive impairment), responsive to corticosteroid therapy;	

Table 2. Continued.

Classification	Diagnostic criterion (Clinical/Neuropathological/MRI-visual)	Alteration in myelin structure/Composition
	• on MRI: homogeneous, gadolinium-enhancing nodules, predominantly in the pons and cerebellum, measuring <3 mm in diameter; • dense lymphocytic inflammation with a predominance of perivascular and parenchymal diffuse infiltrates (may involve both white and gray matter); • predominant T-cell infiltration (CD44, CD8, CD3) with a macrophage component; • presence of intense inflammation/focal secondary myelin loss Amyotrophic lateral sclerosis (ALS; Charcot's disease/Lou Gehrig's disease) [169]: • progressive motor impairment, with previously normal function; • presence of upper and lower motor neuron dysfunction in ≥ 1 body region or declining motor neuron function in ≥ 2–3 regions (for upper motor neurons: hyperreflexia and spasticity, presence of pathological reflexes (Babinski sign, etc.), poorly coordinated voluntary movements, not attributable to lower motor neuron signs/Parkinson's disease symptoms) (for lower motor neurons — on EMG: large motor unit potentials, polyphasia and instability of motor units, increased duration/amplitude, fibrillation potentials/fasciculations) Acute malignant multiple sclerosis (AMMS; Marburg's disease) [170]: • clinical manifestations: thrombocytopenia, leukopenia, proteinuria, coagulopathy (due to elevated aspartate aminotransferase and alanine aminotransferase activity); • <i>early stage</i>: detection of viral antigen by enzyme-linked immunosorbent assay (ELISA)/immunohistochemical methods (antibodies <i>Mab2A7</i>, <i>Mab2H6</i>); • <i>late stage</i>: serotype determination by detection of specific <i>IgM</i> and <i>IgG</i> (via indirect immunofluorescence assay/enzyme-linked immunosorbent assay/polymerase chain reaction) Concentric periaxial sclerosis (CPS; Baló's disease) [171]: • acute onset and rapid progression; • no gray matter involvement is observed; • on MRI: reveals a distinctive concentric pattern of alternating rings of myelinated and unmyelinated tissue (pathophysiology of process is not established, similar to a response to hypoxic demyelination); oligoclonal bands may be absent; • on brain biopsy, histopathological examination with myelin staining is performed to reveal similar alternating concentric rings of demyelination MOG antibody-associated disease (MOGAD) [172]: • clinically presents as NMOSD, myelitis, cerebral mono- or polyfocal deficit, brainstem/cerebellar deficit, cortical encephalitis; for “+”-diagnosis requires: • detection of <i>MOG-IgG</i> in serum/CSF, which confirms the diagnosis in patients with similar phenotypic MRI findings across different pathologies (NMOSD exacerbation, H-shaped spinal cord lesion, T2-weighted hyperintense lesions, negative <i>AQP4-IgG</i>); • infiltration by CD4-cells, as opposed to the CD8-cell predominance seen in typical MS	For MDS: $\downarrow$ cerebroside, total phospholipids, sulfatides, cholesterol, sphingomyelin, gangliosides, $\uparrow$ cholesterol esters [143] For neuritis: splitting of myelin lamellae, disorganization of vesicles [144]; For acute myelitis: <i>AQP4-IgG</i>; $\uparrow$ lactate, glutamate, formate, $\downarrow$ glucose (E-exchange), N-acetylaspartate (myelin lipid synthesis), scyllo-inositol ($A\beta$-protein binding) [145] For CLIPPERS: currently, data have not been reliably established [146,147] For ALS: a subset of cases is mediated by <i>Sod1</i> mutations, leading to $\downarrow$ expression of MBP and <i>Olig1/2</i> [148]; others — by <i>TDP43</i> accumulation, leading to myelin sheath thinning and disruption of interlamellar contacts [149] For AMMS: with relative preservation of axons, the charge and mass of MBP are altered (due to deimination of arginyl residues), causing myelin splitting [150,151]; For CPS: $\uparrow$ expression of <i>HSP70</i> and <i>HIF-1 α</i> [152], $\downarrow$ MAG and CNP in oligodendrocytes [153]; overall $\downarrow$ NAA, $\uparrow$ lactate, choline, and lipids [154]; For MOGAD: during demyelination, a complex is formed: T-cell receptor, MOG, antigen (HLA); in mice, it is associated with <i>C9neo</i> deposition [155]
Secondary Disorders	Acute disseminated encephalomyelitis (ADEM) [173]: • onset of a multifocal CNS disease, presumed to have a viral/inflammatory cause;	

Table 2. Continued.

Classification	Diagnostic criterion (Clinical/Neuropathological/MRI-visual)	Alteration in myelin structure/Composition
	• fever and encephalopathy in the acute phase, defined as stupor/lethargy/behavioral changes (drowsiness/irritability) not explained by fever, systemic illness, or post-traumatic symptoms; • typical brain MRI findings include (acute phase abnormalities): presence of diffuse, poorly demarcated, large (>1–2 cm in diameter) T2-hyperintense lesions predominantly affecting the cerebral white matter (thalamic/basal ganglia involvement possible); T1-lesions are rare Acute hemorrhagic leukoencephalitis (AHLE; Hurst's disease) [174]: • clinical presentation: extensive focal lesions, fulminant course often leading to coma/death within days; possible increased intracranial pressure due to significant edema; • focal neurological signs are present, varying by location; • histochemical analysis of cerebrospinal fluid shows granulocytic pleocytosis; in blood — leukocytosis with neutrophilia; histopathology reveals small vessel necrosis, perivascular fibrin exudation, “ring-shaped” hemorrhages, infiltration by neutrophils and macrophages, demyelination in late stages; proteinuria; • MRI shows significant edema and petechial hemorrhages (perivascular microhemorrhages); lesion location varies, most severely affecting the parietal and frontal lobes, brainstem, spinal cord, and basal ganglia may be involved; (resembles ADEM but occurs more often in adults than in children; symptoms typically appear 2–12 days after a nonspecific upper respiratory tract infection or vaccination) Hereditary motor and sensory neuropathy (HMSN; Charcot-Marie-Tooth Disease) [175]: • <i>typical clinical presentation</i>: onset in adolescence (10–20 years), slowly progressive course, presence of deformities such as “pes cavus”/Achilles’ tendon retraction, sensory impairments (not reaching the level of paresthesia); • initial manifestations often affect the lower limbs, accompanied by weakness and progressive muscle atrophy in the distal muscles; over time, it progresses to involve the upper limbs (clawed fingers); muscle stretch reflexes are reduced/absent; • for some forms (CMT1A), specific signs are observed (thickening of peripheral nerves); • MRI is used to obtain muscle cross-sections (T1-weighted imaging) to detect fatty infiltration Acute polyradiculoneuritis (GBS; Guillain-Barré Syndrome) [176]: • <i>typical clinical presentation</i>: progressive weakness in the arms and legs, reduced/absent tendon reflexes in the affected limbs, progressive deterioration over 4 weeks (supportive features: symmetry, mild/absent sensory impairments, cranial nerve involvement, autonomic and respiratory failure, muscular radicular pain in the back/limbs, antecedent infection (<6 weeks); • elevated CSF protein with a normal cell count (albuminocytological dissociation) Infectious, toxic, diabetic, dysmetabolic polyneuropathies [177,178]: fundamentally similar to the previous point; additional investigations are required.	<i>For ADEM</i>: myelin development and compaction were not halted; complement deposition was observed in active lesions, but not in astrocytes/glia [156] <i>For AHLE</i>: currently, data have not been reliably established; <i>For HMSN</i>: mutations in <i>PMP22</i>, <i>GJB1</i>, <i>MFN2</i>, <i>MPZ</i> [157], <i>Litaf</i>, <i>Erg2</i>, and <i>Nefl</i> [158] lead to the appearance of isoforms; in some cases — ↑ aggregation propensity, ↓ stability, protein dynamics / fatty acid binding, and their membrane interaction kinetics [159]; overall, organization and lipid metabolism are disrupted [160]; <i>For GBS</i>: splitting was most frequent in the Schmidt- Lanterman incisures; complement deposition was observed in the nodes of Ranvier/paranodal regions [161]; rare antibodies to <i>MPZ</i>, <i>P2</i>, <i>PMP22</i> [162]

(Notice for Table 2: increased signal intensity on T1- and T2-weighted MRI may be caused not only by the destruction of myelin itself but also by the accumulation of metabolic water, which is normally displaced by tightly wrapped myelin sheaths and becomes detectable on MRI in pathological conditions [163]). Upper arrow ↑ is Increased level. Downward arrow ↓ is Decreased level.

Table 3. Correlation of alterations in the biochemical composition of myelin with corresponding pathologies.

Component			Content in CNS ¹ , %	Content in PNS ² , %	Associate gene	Regulatory molecules	Associated neurological diseases ³
Proteins & their modifications ⁴	proteolipid protein (PLP)		38	0.2	<i>PLP1</i>		Pelizaeus-Merzbacher disease, SP2 [DB]
	myelin basic protein (MBP)		30	18	<i>MBP</i>	<i>Foxp2</i> [182], <i>Celf4</i> [183], <i>Npas4</i> [184]	Classic multiple sclerosis [141,191]
	cyclic nucleotide phospho-diesterase (CNP)		5	0.3	<i>CNP</i>	<i>c-fos/jun</i> [185], general transcriptional [186] and epigenetic factors [187], hormones [188,189], neurotrophic factors [190]	HML20, multiple sclerosis, schizophrenia [DB]
	myelin associated glycoprotein (MOG)		1	NE	<i>MOG</i>		MOGAD, NMOSD, TM, forms of ADEM, MS [192], narcolepsy [DB], pathology development in rubella virus infection [193]
	oligodendrocyte specific protein		1	NE	<i>CLDN11</i>		Deafness (in mouse models), leukodystrophy [DB]
	myelin protein zero (MPZ; P0)		NE	44	<i>MPZ</i>		Charcot-Marie-Tooth disease (CMT1B, CMT3), CDN [DB]
	periaxin (PRX)		NE	15	<i>PRX</i>		Charcot-Marie-Tooth disease (CMT4f, CMT3) [DB]
	cluster of differentiation (CD9)		0.06	0.8	<i>CD9</i>		Neoplastic processes (e.g., glioma) [DB; 194]
	β -spectrin, erythrocytic-1	non-	NE	0.5	<i>SPTBN1</i>		Delays in cognitive, motor, and speech functions [195,196]
	α -spectrin, erythrocytic-1	non-	NE	0.4	<i>SPTAN1</i>		EIEE-5, PBA, SIDWCM, diffuse cortical atrophy [DB; 197]
Lipid molecules	other components		24.9	20.8	—		—
	galactosylceramide (GC)		17	10	<i>Galc</i>	<i>PPARβ</i> , <i>SREBP</i> , <i>SCAP</i> , <i>mTOR</i> , <i>QKI</i>	Globoid-cell leukodystrophy (Krabbe disease) [DB; 66]
	cholesterol (ChOL)		46	41	<i>Dhcr7</i>	<i>Pls2G6</i> ; <i>Pemt</i>	Congenital malformations, mental retardation [66], Smith-Lemli-Opitz syndrome [DB] [198,199], <i>Fasn</i> [66], <i>For Pla2G6</i> : dystonia-parkinsonism, early-onset parkinsonism, atypical neuroaxonal dystrophy [204]
	phosphatidylcholine (PC)		7	10			<i>For Pemt</i> : schizophrenia [205], defects of nervous system, AD [206]
	plasmalogen (PG)		13	13	<i>Agps</i> ; <i>Gnpat</i>		<i>For Agps</i> : rhizomelic chondrodysplasia punctata, type 3 and Zellweger syndrome [DB]
							<i>For Gnpat</i> : rhizomelic chondrodysplasia punctata [DB]
							<i>For Smpd1</i> : Niemann-Pick disease type A and B [DB]
	sphingomyelin (SM)		6	13	<i>Smpd1</i> ; <i>Npc1/Npc2</i> ; <i>Sgms1</i>		<i>For Npc1</i> : Niemann-Pick disease type C [DB]
							<i>For Npc2</i> : the same as for <i>Npc1</i> , atrophy of the frontal lobes [DB]
							<i>For Sgms1</i> : hearing loss [207]
Lipid molecules	glycerophosphatides (GP)		7	7	<i>Gapdh</i>		Development of pathology in AD [208]
	sulphatide (ST)		3	1	<i>Arsa</i> ; <i>Sumf1</i>		<i>For Arsa</i> : metachromatic leukodystrophy [DB]
	other components		1	5	—		<i>For Sumf1</i> : multiple sulfatase deficiency [DB]

Table 3. Continued.

Component	Content in CNS ¹ , %	Content in PNS ² , %	Associate gene	Regulatory molecules	Associated neurological diseases ³
<i>Carbohydrates (glycans) combined with proteins and lipids</i>	MN, α LF, NAG, GAG [209]; diverse [210], quantitatively comparable to the proteins they are associated with	—	—	typical enzymes glycolysis, gluconeogenesis [211]	currently, data have not been reliably established

Abbreviations for Table 3: SP2, spastic paraplegia 2-nd type; HML20, hypomyelinating leukodystrophy-20; CDN, congenital demyelinating neuropathy; TM, transverse myelitis; EIEE-5, early infantile epileptic encephalopathy-5; PBA, progressive brain atrophy; SIDWCM, severe intellectual disability with cerebellar malformations; AD, Alzheimer's disease; MN, mannose; α LF, α -L-fucose; NAG, N-acetylglucosamine; GAG, glycosaminoglycans. The three most common proteins of the "young" PNS myelin (MPZ, MBP, PRX) the absolute amount does not change with aging [212].

¹For proteins, refer to [213]; for lipids — [179,214].

²For proteins, refer to [215]; for lipids — [179,214].

³For cells marked with [DB], the information was retrieved from the [NCBI](#) gene database by querying the gene name from the "Associated Gene" column.

⁴Due to the vast number of myelin proteins [180,181], only the 5 most common ones by relative content in the CNS and PNS are listed.

Table 4. Functional significance of selected biological regulators associated with myelin.

Active Substance	Function, associated with nervous system and myelin
<i>Ions of micro- and macroelements</i>	Fe²⁺: • directly involved in the production of myelin (a cofactor of cholesterol biosynthesis) and indirectly — in oxidative metabolism [221] (including β-oxidation of fatty acids [222] and non-enzymatic lipid peroxidation [223]); • participates in the activation of microglia [224]; Zn²⁺: • interacts with the myelin basic protein (MBP) and acts as cofactor of matrix metalloproteinase [224]; Cu²⁺: • cofactor of superoxide dismutase-1, monoamine oxidase, dopamine-β-hydroxylase, cytochrome-c-oxidase [225]; Mn²⁺: • poorly studied [226,227]; presumably, it is localized in synaptic vesicles, a cofactor of arginase and the enzyme of inactivation of reactive oxygen species [226]; Ca²⁺: • participates in axon-myelin signaling [228,229], release of mediators [230], forming of cytoskeleton and cell processes [229,231]; Na⁺: • transported through channels in the area of Ranvier's node, responsible for the initiating of a nerve impulse and its saltatory conduction [216], participates in maintaining the electrochemical gradient [232]; • presumably, able to attract microglia (shown in multiple sclerosis) [233]; K⁺: • transported through channels in the juxtaparanode region, responsible for the stabilization of axonal conduction, regulates the releasing of neurotransmitters in nerve terminals [216,234]; • together with Na⁺, participates in the initiation of a nerve impulse, maintains water-salt, acid-base and electrochemical balance [235]; Cl⁻: • similarly to Na⁺ and K⁺ participates in homeostasis, impulse conduction; gives reactivity to astroglia [236]
<i>Lipid components</i>	cholesterol: • one of the main isolating components of myelin [140,237], regulates the fluidity of formed biological membranes [237]; • It is necessary for the normal development of the brain, directs the growth of axons, forms dendrites [238,239], participates in synaptogenesis, synaptic transmission and plasticity [237,239]; sphingolipids: • carry out membrane transport, signal transmission, and cytoskeleton organization [240]; • regulate cell differentiation, process growth, myelination, ion channel modulation, and neuroplasticity [227]; glycerolipids (including gangliosides): • involved in neuritogenesis, axon growth and regeneration, and myelin formation and stability [241,242], in processes of adhesion, modulation of receptor functions, maintenance of Ca²⁺ homeostasis, signal transduction [241,243]
<i>Some proteins and their modifications</i>	myelin protein zero (MPZ; P0-protein): • participates in maintaining the integrity and compactness of the myelin sheath; enhances the growth of axons [218,244]; P2-protein: • lipid-binding protein that reduces lipid dynamics in membrane [245] and participates in the elongation of chains and transport of fatty acids in the process of myelination [246]; • causes inflammatory demyelination in experimental allergic neuritis [245];

Table 4. Continued.

Active Substance	Function, associated with nervous system and myelin
	myelin-associated glycoprotein (MAG): - transmembrane protein that is located in the periaxonal region and participates in the organization of lemmocyte-axon contact and in the process of myelination after injury [247,248,249]; - participates in axoglial signal transmission [250]; - regulates axon thickness, expression, and phosphorylation of axonal cytoskeleton proteins [251]; proteolipid protein (PLP): - the most common CNS myelin protein (38% of dry weight) is involved in the convergence of myelin membranes [244] и maintaining contacts/integrity of myelin sheaths [140]; prevents axonal degeneration [140]; - promotes the increase of cholesterol content in myelin by association and cotransport [252]; 2', 3'-cyclic nucleotide 3'-phosphodiesterase (CNP): - oligodendrocyte-specific, has catalytic activity, binds to RNA, microtubules and actin [253] to regulate the formation of cytoplasmic cavities in compact myelin (in interaction with MBP) [140]; - in mitochondria, CNP is associated with the opening of the transition pore complex, a proapoptotic mechanism leading to the release of Ca^{2+} into the cytoplasm [254]; prevents axonal degeneration [140]; myelin basic protein (MBP): - interacts with other proteins and participates in the transmission of extracellular signals to the cytoskeleton and the formation of dense contacts in compact myelin [140]; affects the intracellular level of Ca^{2+} [255]; - responsible for the adhesion of cytosolic surfaces [256]; myelin-associated oligodendrocytic basic protein (MOBP): - presumably, participates in the formation of tight membrane junctions in the compact myelin of CNS [244,257]; juxtanodine (JUX): - participates in formation of oligodendrocyte branching processes [244] and ensures their mobility [258]; - may be involved in the myelination of the CNS and the specialization of the Ranvier node [258]; periaxin (PRX): - the most common protein in non-compact myelin of the PNS, which forms properly matured myelin [244]; - support its integrity and stability in contact with cytoskeleton and cytolemma proteins [259]; myelin oligodendrocyte glycoprotein (MOG): - cytoskeleton formation and microtubule stabilization depend on the interaction of MOG with MBP, which includes a complement activation factor [156]; - provides interaction with the immune system [260]; actine-myosine filaments (Act): - actin polymerization promotes early glial cell differentiation, and depolymerization promotes myelin formation [219,220,261]; - modify the growing membrane that surrounds the axon along the radius and expands longitudinally, participate in the formation of stable molecular complexes mediating glia-axon and glia-matrix interactions [54]; - destruction of the cytoskeleton is noted in some neuropathologies (Charcot-Marie-Tooth disease) [54,261]; peripheral myelin protein-22 (PMP22): - crucial for the proper homeostasis of cholesterol in myelin through its interaction with the ATP-binding cassette protein family 1 (ABCA1) in Schwann cells and the regulation of its outflow [262]; - support binding to proteins, participates in the process of apoptosis, synaptic transmission, and cell differentiation [DB];

Table 4. Continued.

Active Substance	Function, associated with nervous system and myelin
	connexins; gap junction proteins (including CX26, CX29, CX30, CX32, CX43): • form intercellular communication channels for intercellular exchange of ions and metabolites and create syncytial-like communities of cells connected by gap junctions [263, DB]; • provides the activity of the gap cell junctions, binding to proteins, participates in cellular and intercellular signaling, sensory perception of sound, transmembrane transport [DB; DB]; neurofascins; contactins (including NFC154): • participates in the growth of neurites, the organization of the axonal mound, and Ranvier node during early development, organizes voltage- dependent sodium channels, and binds the extracellular matrix of interneuronal synapses to the intracellular cytoskeleton [DB]; • cell adhesion molecule of the neuronal membrane, presumably forms axonal connections in the developing nervous system, promotes the binding of carbohydrates and proteins, provides activity of the synaptic cleft mediator, participates in the Notch signaling pathway and the orientation of axonal growth [DB]; • promotes proliferation, orientation of axonal growth in the developing cerebellum, migration of GABAergic interneurons, clustering of voltage-dependent potassium channels [DB];
Others	vitamins (as coenzymes): • B₁₂ — pain treatment and restoration of the myelin sheath of neurons [264,265]; for the elderly ↓ B₁₂ associated with ↓ cognitive decline, Alzheimer’s disease, peripheral neuropathies [266]; • B₉ — affects the expression of MBP in the brain and spinal cord of pregnant and lactating rats [267,268]; improves the condition of oligodendrocyte progenitor cells after exposure to sevoflurane [269]; effective in ↓ frequency of neural tube defects, enhances growth, repair, and restores damaged central nervous system [270]; • B₇ — in combination with Mg²⁺, it significantly ↓ markers of inflammation, oxidative stress, ↑ expression of synaptic transmission proteins, participates in axon regeneration, oligodendrocyte growth, improvement of cognitive performance [271]; • B₆ — synthesis of neurotransmitters (dopamine from L-DOPA, serotonin from 5-HTP, GABA from glutamate), affects the adren-, serotonin-, and glutamatergic systems; presumably, have neuroprotective function [265,272]; • B₅ — synthesis of acyl chains of myelin and acetylcholine, play an important role in neurodegeneration and cognitive impairment in age-related dementia (Huntington’s and Alzheimer’s diseases) and energy metabolism of the brain [273,274]; • B₃ — promotes axon remyelination through microglial stimulation [275]; • B₂ — antioxidant protection, participation in oxidative dehydrogenation reactions improves motor neurological disorders in animals with a model of multiple sclerosis, expression of BDNF genes and proteins [276]; • B₁ — participates in the synthesis of neurotransmitters, which leads to focal thalamic degeneration (in the form of Wernicke encephalopathy/Wernicke-Korsakoff syndrome) [265,277,278]; • E, C — antioxidants, restore some molecules from the oxidized form [279,280]; • D — neuroprotective [281] and an immunomodulatory role (in multiple sclerosis), accelerates the differentiation of oligodendrocytes [282]; in rat models, the <i>active form of D2</i> ↑ diameter of axons, promotes nerve regeneration in injury, and the <i>active form of D3</i> ↓ hyperreflexia in paraplegia [283]; hormones: • thyroid (T_{4(inact.)}, T_{3(act.)}) — involved in the maturation of the nervous system, oligodendrocytes, glial cells, neurons, their metabolism [284]; T₃ controls the expression of genes for myelination, differentiation, migration, signaling, and process formation [285]; neuroprotective function may be manifested [286,287]; • sex hormones (estrogens and androgens) — stimulate the immune response (based on the model of experimental autoimmune encephalomyelitis), which leads to ↓ inflammation [189,287,288]; <i>estrogens (progesterone)</i>: stimulates <i>in vivo</i> and <i>in vitro</i> the maturation of oligodendrocytes and the restoration of myelin, and also reduces the severity of symptoms of experimental autoimmune encephalomyelitis [189]; <i>androgens (testosterone)</i>: proliferation of oligodendrocyte precursors into mature forms [189]; • glucocorticoids (cortisol) — responsible for the overall metabolic balance [289]; provide interaction between astro- and oligodendrocytes [290]; regulates oxidative phosphorylation of brain mitochondrial enzymes and brain morphology (in animal models) [291]; oxydants (free radicals RO•, ROO• [3], reactive oxygen [217] and nitrogen species): • in response to activation of microglia and astrocytes, oxidative damage is induced, which is enhanced by the release of Fe²⁺ from degenerating cells into the extracellular space (as a result of the Fenton reaction) [292,293]

(Notice for Table 4: For citations marked with “[DB]”, the information was retrieved from the [NCBI](#) gene database by querying the gene name from the “Associated Gene” naming).

molecular types in human in sporadic vestibular schwannoma [132]. For Remak cells, these variants have not been established.

2.2.6 Satellite Glial Cells of Peripheral Nerve Ganglia

They originate primarily from migrating neural crest cells [78].

Morphological varieties are represented by the following forms:

(1) *satellite cells of sensory ganglia* — laminar cells that typically form a sheath of several glial cells surrounding each neuron [133];

(2) *satellite cells of autonomic ganglia* — have a polygonal, flattened shape and long, branched cytoplasmic processes on the surfaces facing the neurons. Their organization is similar to sensory satellite cells [79].

Studies of gene expression profiles and molecular markers distinguish approximately 5 variants of ganglionic satellite cells [134]. ScRNA-seq has demonstrated over 9 clusters of trigeminal ganglion cells, with several types showing induced expression of genes related to cellular adhesion and extracellular matrix remodeling [135].

We have provided a brief description of the main cell subtypes in the human nervous system. Different cells have different functions, locations, morphologies, and distributions. But all are associated with one specific feature: enabling the formation of the myelin sheath in the CNS and PNS. This demonstrates that axonal ensheathment is a very complex and important structure for the proper function of the entire nervous system.

For a long time, it was thought that myelin's only function was to accelerate the conduction of nerve impulses. Current research shows that myelin is involved in plasticity, adaptive processes, memory, the selection and integration of useful information, and the active remodeling of the nervous system during inflammatory and degenerative processes and regeneration after injury.

In our study, we summarize the main information about myelin in health and pathology, but further research is needed to explore these molecular mechanisms and their significance in normal life and in disease. In the next step, we will describe the fundamental properties of the physiological and biochemical organization of myelin and its special role in the normal functioning of CNS, PNS.

2.3 Physiology and Biochemistry of Axonal Sheathing

Many neuronal circuits strictly regulate the timing of impulse conduction to ensure the synchronous arrival of excitatory potentials at specific brain centers. Myelination also plays an important role in regulating the temporal accuracy of excitatory potential transmission [136,137]. New concepts differ from earlier ideas that axonal ensheathment is needed only to maximize the conduction velocity of nerve impulses [138,139]. Myelin helps maintain the small diameter of some nerve fibers (due to space limitations in the cranial cavity) and minimizes conduction delay [140].

These facts show that myelin function has a great effect on precise actions (e.g, fine motor skills in children's brain development). It is also involved in the balance between excitation and inhibition in the nervous system, providing proper control of inspiration/expiration centers, etc. New theories suggest the impact of myelin plasticity and its adaptive role in sensory perception, the formation of feelings (especially pain and motivation), and their integration and analysis in higher centers.

We described associations of changing myelin morphology with some human neurological pathologies in Table 2 (Ref. [141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178]). Also, we discussed current biochemical structure of myelin with connected diseases in Table 3 (Ref. [66,141,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202,203,204,205,206,207,208,209,210,211,212,213,214,215]). And the function of the listed molecules for the nervous system and myelin is described in detail in Table 4 (Ref. [3,54,140,156,189,216,217,218,219,220,221,222,223,224,225,226,227,228,229,230,231,232,233,234,235,236,237,238,239,240,241,242,243,244,245,246,247,248,249,250,251,252,253,254,255,256,257,258,259,260,261,262,263,264,265,266,267,268,269,270,271,272,273,274,275,276,277,278,279,280,281,282,283,284,285,286,287,288,289,290,291,292,293]).

2.3.1 Aspects of Normal Formation and Components of Myelin Sheaths

The CNS is almost entirely myelinated (unlike the PNS), but CNS sheaths do not cover every single fiber. Even axons within a single reflex arc can vary in their degree of myelination [5].

Schwann cells envelop axons, produce myelin in such a way that the length of internodal gaps and myelin thickness is proportional to axon diameter [54]. For a given axon diameter, the maximal impulse velocity will be achieved only with an optimal myelin thickness (*g-ratio*). This is why a very thick sheath around a very thin axon results in a very slow impulse conduction velocity [11].

Oligodendrocytes, similarly, form thicker myelin around larger axons [80,140]. Some oligodendrocytes preferentially myelinate a specific type of neuron [81]. This contributes to saltatory nerve impulse conduction in myelinated fibers compared to unmyelinated ones.

For the CNS, various myelination patterns have been described along the entire axon length (myelin sheaths in the CNS are often much shorter than in the PNS). This significantly affects the speed and precision of impulse conduction, even over short axonal segments [139,140]. Moreover, even a slight elongation of short myelin sheaths can begin to reduce conduction velocity [139,294,295]. In the

brain's auditory system, the length of myelinated segments varies even among different axonal branches of a single neuron [139,216]. Factors determining the conduction velocity in myelinated axons include: the axon's morphology [296], its caliber (cross-sectional diameter) [295,297], and the internodal length [298]. In our opinion, these findings may inform the development of additional neurostimulation mechanisms or compensatory mechanisms for maintaining the degenerating brain. They may also be associated with emotional behavior. To date, there are not many proper studies on this. For details, also see *Khelifaoui et al., 2024; Chen et al., 2019* [299,300].

CNS axons with a diameter less than 0.5–1 μm are typically unmyelinated, and larger-diameter axons are myelinated. Some myelinated axons exceed a giant diameter of 50 μm . Despite this, axon caliber is a signaling factor that regulates the formation and thickness of the myelin sheath. In the PNS, myelin supports further growth of axon diameter, which is dependent on myelin thickness [139,140]. Some authors suggest that oligodendrocytes provide metabolic support to neurons *via* the myelin sheath [216]. Due to its unique biochemical composition, myelin can influence axonal metabolism and the plasticity of neuronal networks [54].

From a biochemical perspective¹ (Detailed composition of myelin is presented in Table 3. Detailed description of active molecules associated with myelin is presented in Table 4.), myelin sheath is a modified, repeatedly wrapped bilipid biological membrane around axons [140]. Space between the membrane layers filled with water [301,302]. Both myelin sheath and other cell membranes consist of three main components — water, lipids, and protein molecules — in varying proportions. In dehydrated myelin, the lipid component predominates over the protein component [179,303]. But myelin sheath has qualitative differences from other biological membranes. It obtains *unique ratio of main lipid components* (approximately 40% cholesterol, 40% phospholipids [sphingomyelin and phosphatidylcholine], 20% glycolipids) [140,303]. Besides, myelin is characterized by a high content of galactosphingolipids, and long-chain saturated fatty acids [304]. CNS myelin contains more glycolipids and less sphingomyelin compared to PNS myelin [305].

Axonal ensheathment is very sensitive to changes in molecular composition. This is why even minor alterations can affect intermembrane adhesive properties and impulse conduction, leading to the disruption of myelin structure and serious neurological diseases [216,302,306,307].

Mass spectrometry has revealed over 1200 different proteins in CNS myelin and approximately 545 different proteins in PNS myelin [180,181]. In the PNS, the regulation of myelination is primarily determined by axonal signals. In the CNS, myelination is also controlled by special mechanisms such as the spatial density of oligodendrocytes, electrical activity, signals from other glial cells [179,305].

Also, myelin differs from other cellular membranes in its qualitative protein composition [66,179]. Differences between PNS and CNS myelin sheaths may explain why some diseases (e.g., acute inflammatory demyelinating polyneuropathy) affect only peripheral myelin, while others (e.g., multiple sclerosis) affect only central myelin [140]. However, other studies present contrasting data on the presence of identical myelin proteins (*MBP, MAG*) that can induce autoimmune reactions in both the CNS and PNS [305].

Now, thanks to developing proteomic, transcriptomic, and connectomic studies, we know much about the quantitative values of certain myelin components. But our knowledge of qualitative values is limited. New single-cell RNA-sequencing methods that explore specific gene activation in different subtypes under physiological and pathological conditions offer perspectives in this area.

According to Table 4, lipids provide mechanical stability, isolation, axon growth, proper embryo development, perception and signaling of myelin sheath. Lipid metabolism is tightly regulated by *SREBPs, mTOR complexes, PPARs, QKI*. These materials correlated with studies of dietary effects with prevalence of certain lipid components and studies with individual molecules (ketogenic, and other). Thus, oh human babies researches examine the effect on cognitive and social-emotional development [308]. In rat models β -hydroxybutyrate increase protection oligodendrocytes and reduce axonal damage [309].

According to Table 4, proteins provide adhesive, transporting, and compacting properties, as well as the transmission of extracellular signals for the myelin sheath. Some protein components are connected with cell activation in pro-inflammatory and anti-inflammatory profiles.

In our opinion, we need to pay more attention to observing people with endocrine and immune disorders, because many studies show an impact on myelin from external factors (stress, diet, cognitive function, infection). However, molecular research often provides individual data about a certain organism and a certain cell subtype, without analyzing complex interactions with other cells and the nervous system's "microenvironment". Most studies have not described the long-term consequences of different molecules. Many authors provide controversial data from clinical trials and pharmaceutical products that have uncertain effects on different patients. The majority of current experiments are on animal models, and most positive effects remain in those models and are not applicable to humans. Modern approaches in gene sequencing open up new receptors, new proteins, and new regulatory pathways, but the materials lack critical analysis and discussion.

All of the above describes the individual properties of some separate molecules. There is no idea how these factors work together to provide the unique human brain function associated with myelin. Most of our current knowledge is based on pathological studies. The fundamental function of

myelin in normal conditions and the healthy brain remains a mystery. But even successes in pathological research do not provide new therapies, new visualization methods, and so on. Neurological disorders remain idiopathic diseases with no observed mechanism of induction and progression. Furthermore, most neurological disorders have only symptomatic therapy, with no major treatment modifications for over 50 years (e.g., DOPA therapy in Parkinson's disease).

In summary, we can underline that our development of experimental and clinical experience with the nervous system and myelin has only just begun. We need new theories and new laboratory approaches to help us correctly understand the unknown nervous system.

2.3.2 Aspects of Pathological Formation and Components of Myelin Sheaths

According to Table 3, majority of myelin associated diseases connected with dysfunction and disruption of proteins. Main neurological disorders include subtypes of multiple sclerosis. And according to Table 2, MRI and CT-visualization show different myelin predictors of cognitive impairment in multiple sclerosis (content of ^{11}C -PIB, etc.). Some studies describe new criteria for observing remyelination in MRI q-space myelin map. Thus, many neurological diagnostic and visualization methods obtain new use with understanding of myelin biology.

Furthermore, mutations of *CNP* and *phosphatidylcholine* genes are connected with schizophrenia and other psychological diseases. *PLP* knockout in mice is connected with specific OPC proliferation in the subventricular area, impaired odor perception, impaired perseverative behavior, and increased anxiety. This provides great theories about new mechanisms for developing addiction, deviant behavior, neurosis, and psychosis. But these are only individual studies that apply theoretical information and are not clinically approved.

We describe our view on myelin's impact on the maintenance of the developing and aging brain.

In the first case, myelin can serve as a "vector" for cell migration and participate in axonal orientation, trophic support, and regulating growth and remodeling. This is similar to the role of blood vessels in early development, where other cells organize around the vessel and perform a complex set of paracrine regulations and interactions with the extracellular matrix.

In the second case, we probably have two variants of interactions.

(1) Alterations of myelin induce secondary cellular remodeling and activation:

(a) in multiple sclerosis metabolic disruption in sheath impact oligodendrocyte activity and function;

(b) in sensory perception (visual/auditory cortex) sheaths modulate their morphology, provide connected changes in activity of neocortical neurons.

(2) Molecular and cellular mechanisms induce secondary myelin degeneration:

(a) myelin alterations occur with degenerative diseases of brain gray matter (Alzheimer/Parkinson disease, etc.);

(b) myelin alterations occur with external factors (behavioral experience/neuronal activity, etc.).

In our opinion, both variants manifest in human nervous system in balance. Primary myelin alterations involved in PNS and neurocognitive dysfunction. Secondary myelin degeneration caused by inflammation, trauma or infection of CNS and provide its progression and complications.

Moreover, small level of myelination increases risks of some diseases (Lewy body pathology) [310]. Also examined correlations of poor myelination in nigrostriatal pathways and their increased vulnerability in Parkinson disease [311].

If there is more evidence of myelin's significance in various neurological disorders (even those not primarily related to myelin), it will cause a "small neuroscience revolution" and provide new therapeutic targets, new diagnostic criteria, and new neuroprotection measures, disease prevention.

2.3.3 Mechanisms of Brain Maintaining Biochemical and Metabolic Homeostasis

As we described previously, different cells and molecular signals provide support to the myelin sheath. Due to this, the human brain has well-developed resistance mechanisms to oxidative stress, inflammation, and degeneration. Astrocytes [6,292,312,313,314] and microglia [217,315,316] are the primary participants in these reactions. Two mechanisms are distinguished:

(1) *antioxidant*, associated with preventing of free radicals' synthesis, their trapping, absorption, and removal. Can be

– enzymatic, include catalase, glutathione peroxidase, superoxide dismutase, heme oxygenase-1, quinone oxidoreductase-1, γ -glutamylcysteine ligase [6,280,317];

– non-enzymatic, include thioredoxin system and endogenous reducing agents (vitamins C and E, glutathione, NADPH, uric acid, bilirubin, and melatonin — neutralize O_2^-) [6,279,280];

(2) *reparative-protective*, associated with restoration of damaged structures or their degradation and removal before they form complexes with each other. They involve specific repair mechanisms and protective components that promote regeneration and restitution of DNA, lipids, and proteins to their normal configuration [3,6].

Energy molecules such as ATP/ADP [318], UTP/UDP [217,319], and diadenosine polyphosphates, in addition to their energy storage function, have a regulatory effect in the CNS. Their extracellular hydrolysis limits synaptic transmission and participates in neuronal survival, differentia-

tion *in vitro*, and neuronal development *in vivo* [318,319]. These molecules serve a specific function as local neurotransmitters in the enteric nervous system [320,321,322].

Glycolysis and oxidative phosphorylation induce pro- and anti-inflammatory activation of microglia due to the generation of reactive oxygen and nitrogen species [6,292]. This fact is associated with the *Warburg effect* (a transition that leads to a phenotypic switch from pro-inflammatory to anti-inflammatory, and vice versa) [217]. During reactive cellular changes, fatty acid metabolism causes the generation of free radicals [292,323].

It is interesting that neurodegeneration is accelerated in people with metabolic disorders, including obesity and diabetes [324]. Cellular response to stress is strictly regulated by short-term (non-transcriptional) and long-term (transcriptional-translational) homeostatic mechanisms [325].

These data may encourage neurologists to consider complex therapies for endocrine and autoimmune disorders to prevent various complications and revise associated methodological standards. In the CNS, the effect of endocrine, immune, and toxic factors is associated with the blood-brain barrier (involving astrocytes) and the blood-(cerebrospinal-fluid)-brain barrier (involving ependymocytes) [326].

In the PNS, this barrier function is assumed by satellite glial cells [107,108].

2.4 Relationships Between Enteric Microbiota, Neuronal Cell Environment and Myelination

In recent decades, a new popular topic has emerged regarding the interaction between the intestinal (gut) microbiota and various systems of the human body, especially the immune and nervous systems [327,328]. *Microbiota* — it is a collection of microorganisms colonizing a specific niche, including not only bacteria but also other microbes such as fungi, archaea, viruses, and protozoa. Many authors have tried to describe the great and crucial role of these commensal microorganisms. All the materials below predominantly relate to the preliminary or speculative nature of the evidence. There are not enough evidence-based studies.

Some studies showed potential effect microbiota on different levels.

(1) *cellular components*:

- autoimmune demyelination [329];

- differentiation and maturation of oligodendrocytes regulated by synthetic short-chain fatty acids [330] and microglia [331];

- dysregulation in immune responses and neuronal differentiation caused by dysbiosis during early infancy microbial colonization [332];

- modulate the blood-brain barrier integrity [333] and permeability and other structural specialties [334];

(2) *ultrastructural/genetic components*:

- appropriate and dynamic regulation of myelin-related genes with clear implications for cortical myelination [335];

- epigenetic regulation of myelination processes [336,337];

(3) *pathological conditions (not approved reliably on humans)*:

- Parkinson's disease [338];

- Huntington's disease [339];

- Alzheimer's disease [340], others [331,341,342].

In mice models observed alterations of myelin thickness in corpus callosum with decreased levels of myelin proteins and mature oligodendrocytes in prefrontal cortex [343].

However, there is also a lot of controversial data and a lack of evidence-based studies in humans or cohort studies in mice. The microbiota is very sensitive to different effects, including diet, living conditions, and stress factors, which complicates obtaining reliable data. Individual characteristics such as gender, age, and metabolic rate play a crucial role in the state of the microbiota and are not always considered. The multiple ways of interaction in the “gut-brain” axis and the current molecular mechanisms are not well known (most studies observe only correlations). Difficulties in determining cause-and-effect relationships (we cannot always distinguish primary/secondary manifestations).

Reliable data show current impact on human emotions [344], human behavior [345], cognitive and intellectual function [346]. Probiotics, prebiotics, and fecal transplantation therapies can aid researchers in identifying more comprehensive causes and the effects of underlying pathways [347]. In the previous section, we described the complex impact of internal factors on myelin function and structure but did not explore external ones. These can be stress, environment, psychological status, and now we have added the enteric microbiome. We cannot explain the direct or indirect signaling to neuronal or glial cells; however, we see clinical complications and correlations that relate to our commensal microorganisms. This is a time for new experiments and new theories.

Thus, we do not understand the proper pathways of regulatory signals from the intestine to the nervous system. Probably, we examine external factors impacting the microbiota (diet, antibiotics, etc.) but do not observe different internal regulations and microorganism homeostasis. We know about the production of bacterial secretory molecules with paracrine effects, but it is too early to assume reliable information about gut-brain interactions.

All these facts show that microbiota effects are very complex, and we need many studies to better understand the current mechanisms of these interactions. Perhaps the medical community should more carefully consider antibiotic therapy in neurological diseases, infancy, and preg-

nancy, pay more attention to environmental status (diet, stress, etc.), and gather more data and experience in these cases.

2.5 Structural Differences Between CNS and PNS Myelin

In addition to the physiological and biochemical features of myelin described above, there are concomitant structural and functional differences in its organization.

At the microanatomical level, a common feature of myelinated segments across different parts of the nervous system is the division into compact and non-compact myelin [54,305].

However, organization differs:

(1) for CNS:

(a) *compact myelin (predominant)* consists of tightly apposed double-layered glial plasma membranes formed by the processes of oligodendrocytes [218,305];

(b) *non-compact myelin* is presented only in specific areas:

– a system of cytoplasmic channels along the perimeter of the oligodendrocytic process — the adaxonal region (adjacent to the axon) and the abaxonal region (located on the outer side) [348];

– paranodes (zone of specific contacts with the axon) [305,349]; and juxtaparanodes (zone containing specific K^+ -channels) [350]. These regions also contain connexin pores [66,305];

(2) for PNS:

(a) *compact myelin (predominant)* is fundamentally similar to CNS compact myelin but differs in cellular organization (Schwann cells) and specific proteins responsible for myelin packing and adhesive properties (contacts between layers) [66];

(b) *non-compact myelin* is represented by:

– Schmidt-Lanterman incisures (clefts in the major dense lines of myelin improving fiber tropism and flexibility) [140,351];

– bands of Cajal (structures surrounding cytoplasmic channels, containing a significant number of microtubules) [54,352];

– paranodes and juxtaparanodes [305,349];

– mesaxons (a duplication of the myelin sheath) [353].

Both CNS and PNS are characterized by interruptions in myelin sheath at Ranvier nodes [354]. A distinctive feature of PNS is the presence of special outgrowths (microvilli) from cytoplasm of abaxonal region [54,355], which contain actin filaments [356]. Their function is discussed [357].

Current views explored only a small part of myelin dynamic changes. The majority of studies provide experiments on the compact part of myelin and Ranvier nodes. Some researches in rodents and zebrafish show correlation of the activity in several neuronal networks (especially, visual) and modulation of Ranvier nodes length [358,359]. But there are no studies of myelin alterations with differ-

ent activity of motor circuits, associative and commissural fibers, other parts of brain (cerebellum, brain stem).

These facts provide great opportunities for further researches. Probably, myelin structure remodulation will play a key role in treatment of peripheral neuropathies, such as paresis, palsy, nerve injury. Because even now there is no effective therapy, except physiological rehabilitation, stimulation, physical activity. We have perspectives in stem cell therapy. But most effects shown for *in vitro* studies, despite this with better understanding of molecular biology, interactions with other cells and extracellular neuronal matrix, we may get results in recovery after stroke and other diseases.

Huge number of researches provide experiments with demyelinating agents (cuprizone, etc.), enriched environment, or individual molecules/dietary effects.

In our opinion, technical development allows to examine other features of myelin structure.

(1) Cytoskeleton organization and remodeling in health and pathology:

(a) actin-myosin filaments connected with membrane stability, flexibility, interaction with “outside” molecules;

(b) exocytosis/endocytosis factors involved in proper conduction of nerve impulses.

(2) Correlations of synaptic and myelin remodeling with astrocytic/microglial activation:

(a) perform neurotransmitters/vesicle impact on myelin organization and properties in neuronal contact;

(b) extracellular signaling impact ion channels and membrane receptors.

(3) Observations of external factors (education, music, sport, etc.) on myelin architecture:

(a) different activities prevent most of aging brain disorders;

(b) educational, memory training, active rest provide increased cognitive/intellectual skills;

(c) fine motor skills, writing on paper improve neuronal function and activity.

We also have improving visualization methods (diffusion tensor imaging) that can help us in interpretation of occurring changes (*for details see [360]*).

A schematic representation of myelin microstructure is provided below in Figs. 3,4, which were compiled based on data from sources [354,361,362,363,364]. The relationship between structure and resulting pathologies is described in [365].

A distinctive feature of CNS myelin is the presence of radial components in the form of interlamellar strands traversing the sheath. They prevent the diffusion of substances, making the membrane less permeable [140,305,351]. Another feature is the existence of a system of myelin channels — an analogue of Schmidt-Lanterman incisures [362,366]. There is no basal lamina or microvilli in the paranodes of CNS myelin sheaths, and some areas of the nodes of Ranvier are in contact with perinuclear astro-

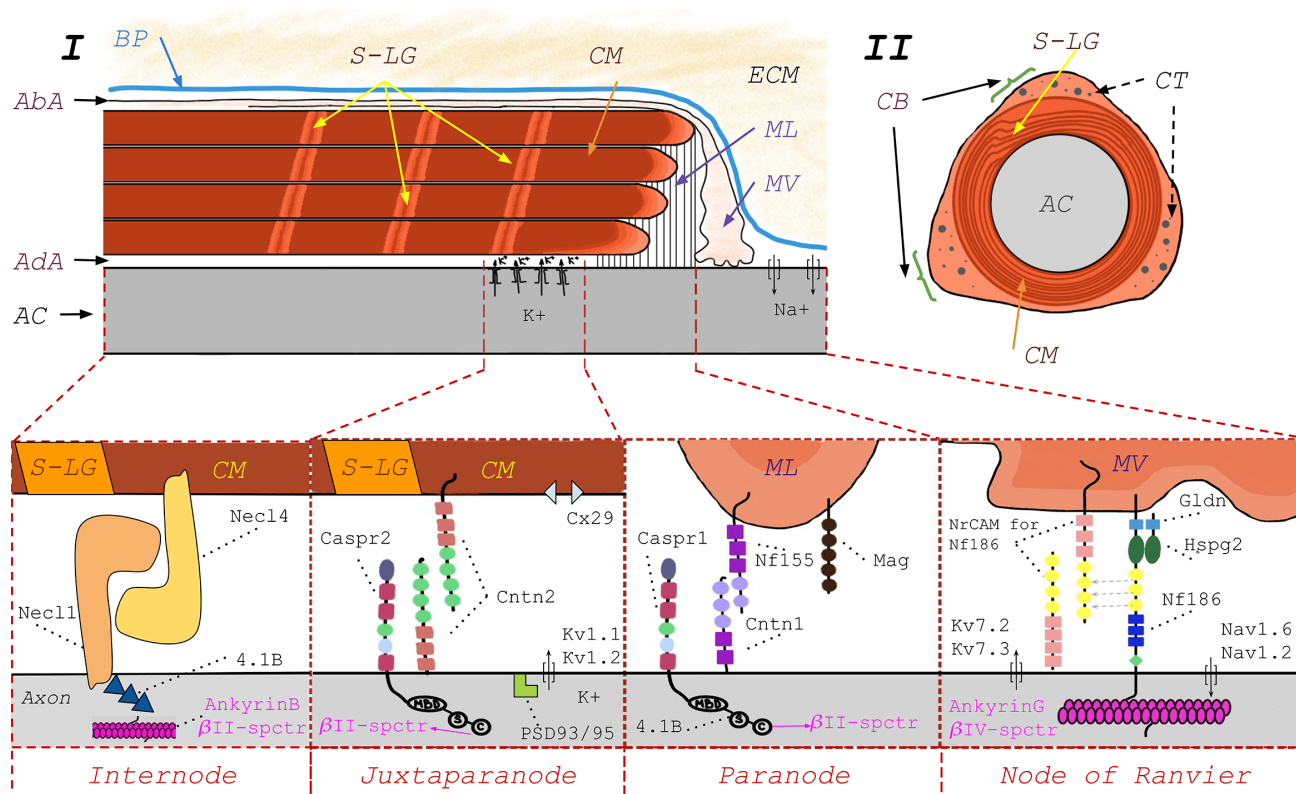


Fig. 3. Schematic diagram of the structural organization of the PNS myelin sheath relative to an axonal segment. I — PNS myelin organization scheme (sagittal section): AdA — adaxonal area (adhesive, metabolic microenvironment of the axon), AbA — abaxonal area, which in the node of Ranvier (RN) turns into microvilli (MV). AbA is adjacent to the basal plate (BP) at the border of endoneurium and extracellular matrix (ECM). AC — axial cylinder of the axon, covered with compact myelin (CM). In CM there are stratifications or Schmidt-Lanterman grooves (S-LG), at the same time, in the paranode region, CM continues into myelin loops (ML). They attach myelin and separate the zone of K^+ -channels of juxtaparanode and Na^+ -channels of RN. II — PNS myelin organization scheme (frontal section): CB — Cajal bands (membrane seals) around cytoplasmic tubules (CT).

cytes or processes of oligodendrocyte precursor cells [305]. In turn, the basal lamina, together with extracellular collagen fibrils, protects peripheral axons from stretching and compression injuries [367]. Schwann cells also limit the radial growth of axon diameters *via* a mechanism involving the chemokine-like factor *CMTM6* [355]. Questions regarding the genomic and proteomic regulation of myelination remain open [219,220].

There are different ways of so-called “myelin clearance” (myelin utilization) [368,369]. In the CNS, myelin fragments can persist at the site of injury for several months or longer, where they suppress key repair mechanisms [368]. The primary cells responsible for removing CNS myelin debris are microglia [370,371]. Studies on mouse brains have shown a significant age-related increase in microglia with a hypertrophied lysosomal compartment. This increased burden on microglia is caused by the accumulation of indigestible myelin residues in lipofuscin, contributing to age-related dysfunction [216]. The involvement of astroglia in clearance processes has also been suggested [84,372]. In the PNS, “clearing” involves two cell types: microglia with phagocytic function and Schwann cells with

myelino-phagic function. These interactions provide effective removal of unnecessary myelin [369,373].

For the restoration of the insulating sheath in the CNS, oligodendrocyte precursor cells realize their potential. However, recent studies on zebrafish have shown that mature forms can also participate in remyelination, albeit to a lesser extent with less precision in axon orientation [96,374].

In the PNS, remyelination is again the responsibility of Schwann cells [12], which act as “universal soldiers”, performing a wide range of functions almost single-handedly. These cells are the subject of extensive research, for example, in the field of regenerative therapy.

Under certain conditions, demyelinated axons in the CNS can also be remyelinated by Schwann cells (in multiple sclerosis, neuromyelitis optica, and in patients with spinal cord injuries) [11,12]. Thus, the CNS and PNS have different mechanisms of structural organization and its maintenance. Interestingly, the PNS has more complex molecular and cellular interactions. Also, remyelination begins with the induction of proinflammatory cytokines ($TNF-\alpha$ activates oligodendrocytes [375]). These

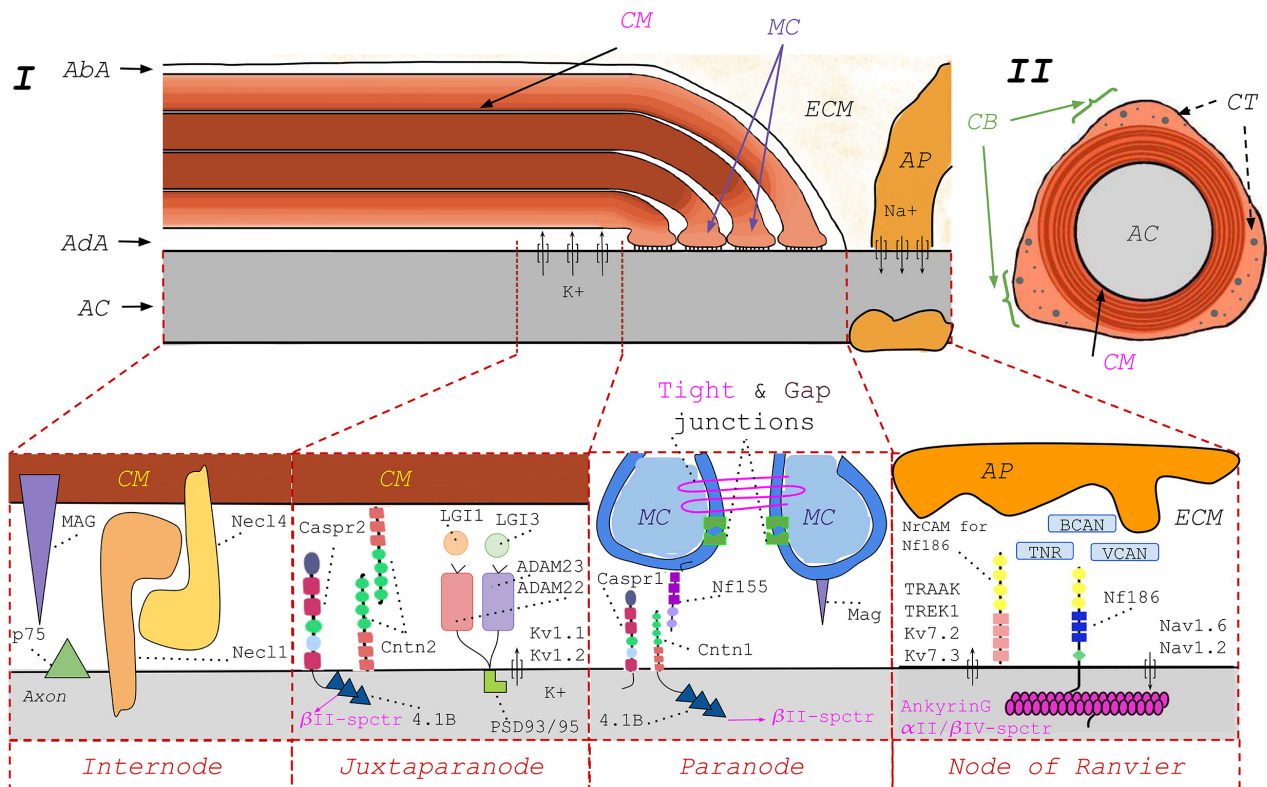


Fig. 4. Schematic diagram of the structural organization of the CNS myelin sheath relative to an axonal segment. I — CNS myelin organization scheme (sagittal section): AdA — adaxonal area (adhesive, metabolic microenvironment of the axon), AbA — abaxonal area, where the compact myelin (CM), enveloping the axial cylinder (AC), continues into special myelin channels (MC) that promote trophic function. AbA is the most distal part of lemmocyte from the AC. ECM is able to mediate chemical signaling (vesicle conduction) and provide mechanical signaling. In the area of the wrapping gap, the axon contacts the astrocytic pedicle (AP), which is involved in regulation of nerve impulse conduction. II — CNS myelin organization scheme (frontal section): CB — Cajal bands (membrane seals) around cytoplasmic tubules (CT).

facts suggest that, in neurodegeneration and neuroinflammation, anti-inflammatory molecules may disrupt proper remyelination. For the correct function of microglia and the fine migration of precursor and specialized Schwann cells, pro-inflammatory factors may be necessary. Further steps could include describing the pro-inflammatory activation of the immune and microglial systems by specific cytokines in autoimmune pathological disorders.

2.6 Signaling Pathways of Myelinogenesis and Demyelination

Damage to a peripheral nerve by mechanical trauma, transection, crush injury, or a pathological condition can affect sensory, motor, and autonomic PNS function. Primary degradation of the axon begins with *Wallerian degeneration* in the distal part of the nerve. It involves the breakdown of the axonal cylinder and disintegration of the myelin sheath, followed by differentiation and proliferation of Schwann cells [376,377]. In the CNS, damage is more frequently caused by internal processes such as neuronal degeneration and neuroinflammation, and less frequently by trauma.

Glia plays a role in remyelination and participate in the formation and remodeling of synapses, neurotransmitter recycling, trophic support, and the formation and maintenance of the blood-brain barrier [96,374,378]. Due to this, most of the molecular signals transduced *via* the extracellular matrix are provided by glia. Changes in the neuronal microenvironment impact glial cells.

The extremely subtle regulation of signaling processes can be used as targets in pharmacological therapy, because these molecular mechanisms convey information to neuronal cells and their microenvironment about the initiation of specific “action programs”. Cell biology allows us to observe the specific gene regulation of signaling molecules and excitatory/inhibitory mediators.

Molecular signaling pathways of myelinating cells in the CNS and PNS are described below.

2.6.1 Role of MAPK/Erk1-2, PI3K/Akt/mTOR, Fyn-Kinase, and Wnt/ β -Catenin Signaling Pathways in Regulating CNS Myelination and Demyelination

Proteins of the MAPK/Erk1/2 signaling pathway belong to the family of mitogen-activated protein kinases (MAPK) and extracellular signal-regulated kinases (Erk). They are playing key role in regulation of cell proliferation, differentiation, and survival [379].

The pathway involves activation of Erk1/Erk2 by growth factors (*BDNF*, *Nrg-1*, *Igf-1*, *Fgf-2*), neurotrophins (*NGF*, *NT-3*), or cellular stress. Process goes in 4 stages [380,381]:

- (1) ligand binding to the receptor → recruitment of adapter proteins (*Shc*, *Grb2*);
- (2) activation of small GTPases (*Ras*) → phosphorylation of *Raf* (*MAP3K*);
- (3) kinase cascade: *Raf* → *MEK1/2* (*MAP2K*) → phosphorylation of *Erk1/2* (at Thr and Tyr);
- (4) nuclear translocation of *Erk1/2* → regulation of transcriptional factors (*Olig1/2*, *Sox10*, *Nkx2-2*) controlling the expression of myelin genes (*MBP*, *PLP*).

In vivo expression of specific MAPKs leads to hypermyelination [380,382], while pharmacological inhibition of these same proteins (*PD98059*) suppresses myelination *in vitro* [383].

Interaction with other signaling pathways includes cross-regulation with the PI3K/Akt/mTOR pathway. It controls the overall synthetic function for myelin proteins and prevents apoptosis. This pathway being influenced by thyroid hormones [384,385]. *Akt* activation is stimulated by *IGF-1* via *PI3K*, which inhibits *GSK3 β* and stabilizes β -catenin (an adhesion protein). It promotes normal contact of myelin sheaths [386]. Inhibition of *Akt* enhances *Erk1/2* activity via *IRS-1* [387,388].

Experiments on animal models have shown that *Fyn*-kinase knockout leads to hypomyelination in brain and particularly in corpus callosum. It also provides normal myelination in spinal cord [389]. *Fyn* is localized in lipid rafts. It activates *Ras/Erk* cascade, interacts with *TrkB* receptors [390], modulates the cytoskeleton [391], and coordinates signaling with the *mTOR* pathway [392]. *Fyn* integrates extracellular signals and intracellular processes involved in myelin sheath formation. It makes these pathways a promising target for the therapy of demyelinating diseases.

The Wnt/*GSK3 β* / β -catenin pathway plays a dual role [393]. At early stages, it suppresses the differentiation of oligodendrocyte precursors via *GSK3 β* -dependent degradation of β -catenin [394]. At later stages, it inactivates *GSK3 β* , promoting the stabilization of β -catenin [395].

Even individual molecules, such as *Nogo-A*, can make a substantial contribution to the development of pathology. *Nogo-A* accumulates under conditions of chronic demyelination, and its increased expression leads to alterations in the composition of the extracellular matrix [396]. This protein can modulate the functional state of glial cells, induc-

ing a transition of astrocytes to an anti-synaptogenic profile with a reduced ability to uptake glutamate and impaired synaptic regulation [376]. *Nogo* alters the migratory capacity, and adhesive and phagocytic properties of microglia, which impacts myelin clearance of degradation products [397]. Conversely, experimental reduction of *Nogo-A* levels is associated with enhanced synaptogenesis [398].

2.6.2 Role of Signaling Pathways in Regulating Myelination and Demyelination in PNS

Survival, proliferation, migration, and differentiation of Schwann cells are primarily controlled by factors of neuregulin (*Nrg*) family. Signal passes through ErbB tyrosine kinase receptors [399].

Based on this evidence, a number of studies have focused on the application of exogenous *Nrg1* to improve axonal regeneration, remyelination, and functional recovery after peripheral nerve injury [400]. While some authors suggest that activation of *ErbB2/3* in Schwann cells by *Nrg1* promotes *ERK* activation and induces Schwann cell demyelination. Other researches assume that *Nrg1* triggers *Rac1/JNK* activation, which activates *c-Jun* (factor involved in cell migration and orientation) [401,402,403]. *c-Jun* is also responsible for myelin repair after injury and myelin clearance [404,405].

The MAPK/ERK pathway is responsible for the plasticity of Schwann cells, their metabolic activity, proliferation, and apoptosis [406]. Its antagonist is *Rac1/JNK* pathway, which regulates the proper degeneration of damaged myelin [405,407]. And the *Notch* signaling promotes formation of Schwann cells from their precursors [390,408], but inhibits OPC differentiation and myelination.

One of the enzymes involved in the cleavage of *Nrg1* is the β -amyloid-converting enzyme (*BACE1*) — β -secretase present in axon. Studies have shown that *BACE1* knock-out leads to reduced *Nrg1* cleavage rates, decreased PNS myelin content, and diminished capacity for axon myelination [409]. Mice decreasing *BACE1* demonstrate faster clearance of axonal and myelin debris, as well as enhanced axonal regeneration and target reinnervation [410]. Opposite effect is exhibited by tumor necrosis factor- α -converting enzyme (*TACE*) and neuronal α -secretase that destroy *Nrg1* [411].

This section has described the primary pathways under normal physiological conditions. In addition to the mentioned pathways, there are other types of chemical signaling (glutamatergic [26], pathological ABCA1/ApoE/HDL [412], others [413]) and mechanical signaling, involving the extracellular matrix [26].

2.6.3 Disruption of Signaling Pathways, Metabolic Support and Brain Aging

In demyelinating diseases (multiple sclerosis, etc.), shown reduced activity of *Erk1/2*, leading to impaired remyelination. Dysregulation of *Akt/mTOR* provide decreased synthesis of myelin.

There are different active molecules impacting myelin properties:

(1) *rolipram* (*PDE4 inhibitor*): indirectly improves myelin repair [414];

(2) *diosgenin*: stimulates Erk1/2-dependent MBP expression [415], and other medicines.

Some of the described substances impact glial cells (especially, microglial). It changes neurotransmitter/signaling molecule recycling and impact blood-brain barrier function [96,374]. This can disrupt initiation, termination, and switching of various cellular programs.

Relevant studies show in *RHEB*-knockout mice increased level of *Dlk1* and decreased oligodendrocyte function in aging brains [416]. Also demonstrated age-dependent *Sestrin-Gator2* signaling changes [417]. These and other regulatory mechanisms acquire proper metabolic support. Oligodendrocytes provide dynamic energy supply of myelinating cells by lactate and pyruvate according to activity level [418]. Current data approves that myelin maintenance concentrates potential of all nervous system. It makes myelin one of the key players in CNS and PNS functioning together with neurons and synapses.

Besides, the transport of all regulating and trophic molecules involves cytosolic myelin channels and myelin loops. Changes in their structure may be associated with early markers of neuronal degradation due to metabolic disruption. These alterations are not described in the literature. In our opinion, protein conformation changes, along with associated gene-regulated anti-myelinating, anti-proliferating, and anti-adhesive factors, play a key role in age-related myelin degradation.

Thus, we assume that vertebrate brain aging may be connected not only with neuronal degradation but also with myelin alterations, disruption of signaling pathways, and gene expression of inhibitory anti-myelinating and anti-proliferating agents. We do not fully understand the full spectrum of intracellular and intercellular molecular interactions, but they all relate to dysfunction of adaptive myelination and increase myelin's vulnerability to aging and pathology.

2.7 Classification of Demyelinating Diseases

Based on conventional topographic criteria, emerging demyelinating pathologies are divided into central and peripheral [419,420].

Central demyelinating diseases include [419,421]:

(1) Multiple sclerosis, including its variants (central pontine myelinolysis, acute disseminated encephalomyelitis);

(2) Osmotic demyelination syndrome;

(3) Myelopathies;

(4) Leukodystrophies, and others.

Peripheral demyelinating diseases include [420]:

(1) Guillain-Barré syndrome;

(2) Chronic inflammatory demyelinating polyradiculoneuropathy;

(3) POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, M-protein, Skin);

(4) Charcot-Marie-Tooth disease, and others.

Earlier researches assume different classifications of myelin associated disorders. First were based on clinical symptoms and their time of onset. Next were based on pathogenetic factors. Others — on histochemical studies and the morphological substrate. More relevant studies suppose comprehensive classification by, which considered the listed factors and included hereditary diseases [422,423]. And one of the newest classifications of myelodegenerations into primary and secondary based on etiopathogenesis [419,424].

Currently, attempts are also being made to further subdivide and categorize major pathologies into subgroups of leukodystrophies [425] and multiple sclerosis [426].

Exogenous factors have been shown to contribute most significantly to the pathogenesis of demyelinating pathologies. These include infections (especially viral), metabolic disorders due to nutritional deficiencies, immunodeficiency diseases, and intoxications [419,422]. The main endogenous pathogenetic factors of primary demyelination are diverse genetic mutations [427,428].

There are no reliable and comprehensive methods for treating acquired and hereditary demyelinating pathologies [429,430,431,432]. This underscores the importance of conducting such research and developing new methods for diagnosing, identifying, and differentiating the relevant pathologies.

The relationship between demyelinating pathologies and the structural/biochemical changes in myelin is described further (Tables 2,3,4). Thus, even minor alterations of myelin components (in a single protein, etc.) can cause a wide range of neurological diseases associated with the axonal sheath.

(1) *Motor and sensory disorders:*

(a) ↓ MBP and *Olig1/2* or *TDP43* accumulation induce amyotrophic lateral sclerosis. In our opinion, it is connected with disruption of interlamellar contacts of the myelin sheath.

(b) *PMP22*, *GJB1*, *MFN2*, *MPZ*, *Litaf*, *Erg2*, *Nefl* mutations induce hereditary motor and sensory neuropathy. In our opinion, it is connected with decreased stability, protein dynamics, fatty acid binding, and membrane kinetics.

(c) PLP mutations induce spastic paraplegia, second type. In our opinion, it is connected with impaired cholesterol integrity and myelin sheath disruption due to divergence of lipid and protein membrane kinetics

(d) Sphingomyelin decreasing associated with hearing loss.

(2) *Autoimmune disorders:*

(a) MBP (with deamination of arginyl residues) induce acute malignant multiple sclerosis. In our opinion, it is

connected with dysfunction of MBP associated with Zn^{2+} -matrix metalloproteinase and cytoskeletal proteins.

(b) MOG (with T-cell activation) induces MOG-antibody-associated disease, narcolepsy, rubella virus infection. In our opinion, it is connected with the formation of a specific complex (T-cell receptor, MOG, HLA-antigen).

(c) ↓ glucose, ↓ N-acetylaspartate, ↓ scyllo-inositol (with *AQP4-IgG*) induce neuromyelitis optica spectrum disorders. In our opinion, it is connected with disruption of myelin lipid synthesis and Aβ-protein binding.

(3) *Cognitive disorders:*

(a) MBP and CNP induce multiple sclerosis. In our opinion, it is connected with disruption of *WNT/β-catenin* pathway and activation of PPAR-γ (despite the classic view of multiple sclerosis as autoimmune pathology).

(b) ↓ MAG and CNP induce concentric periaxial sclerosis. In our opinion, it is connected with disruption of cytoskeletal proteins and cytoplasmic cavities, with associated impaired axoglial signaling

(c) CNP mutations and decreasing of phosphatidylcholine induce schizophrenia

(d) β-spectrin and α-spectrin induce delays in cognitive, motor, and speech functions. In our opinion, it is connected with improper integrity and connection between axon and myelin, which critically disrupt its structure.

(4) *Inflammatory disorders:*

(a) MPZ and MBP induce acute polyradiculoneuritis (with rare antibodies to MPZ, P2, PMP22). In our opinion, it is connected with splitting in Schmidt-Lanterman incisures, alterations of Ranvier nodes, and paranodal regions.

(b) Unknown molecular changes induce myelinoclastic diffuse sclerosis and CLIPPERS.

(5) *Other types of disorders:*

(a) infections, toxic, diabetic, dysmetabolic polyneuropathies.

This is a conditional classification due to multiple manifestation symptoms of listed diseases. Most of the etiopathogenetic factors are not described in the literature, and we suggest our opinion.

In common, we can assume that all described alterations are involved in *maladaptive myelin plasticity*. A healthy brain maintains normal myelin plasticity. This includes de novo myelination, morphological and biochemical myelin remodeling, restructuring of nodes of Ranvier, myelin cytoplasmic channels and loops, cytoskeleton formation, and the permeability of ion channels in paranodes/juxtaparanodes. Maladaptive plasticity may occur on three levels: (1) structural; (2) cellular; and (3) molecular. These changes may occur due to: (1) gene dysregulation; (2) post-translational protein/lipid modification; (3) interruption of neuroprotective mechanisms; (4) changes in “glial microenvironment” and the induction of activated cell types; (5) other idiopathic reasons.

In our opinion, the most severe and complex disorders are connected with microstructural changes. They induce a vicious cycle of alterations in neuronal activity/molecular signaling (paracrine regulation) and lead to further pathological complications involving more of the pathogenetic factors (1)–(5). This is the main problem of neurodegenerative and neuroinflammatory disorders because proper therapy should affect all of the described parameters. We are interested in understanding the fundamental properties of the myelin sheath to develop effective treatments.

Current research explores demyelination as pathogenesis pathway in Alzheimer’s disease, besides the classic amyloid theory [433,434,435]. Other authors describe poor myelination in nigrostriatal pathways and their increased vulnerability in Parkinson’s [310] and Huntington’s disease [436].

In our opinion, this could initiate the creation of new principal pathophysiological concepts for the majority of different neurological disorders. We propose “*myelin vulnerability*” as an additional criterion for testing neurological function and treatment quality. Myelin support is absolutely necessary for rehabilitation after stroke and spinal cord injury. We may be describing a new way of modulating neuronal activity according to myelin thickness, node of Ranvier length, and so on. This provides fundamental knowledge of excitatory conduction in different nervous centers, their synchronous and rhythmic activation, and complex integrity in higher associative brain regions.

Furthermore, we poorly understand myelin’s role in the autonomic nervous system. We do not understand the mechanisms of myelin’s reaction to chronic stress and pain, or its correlations with other pathologies of the cardiovascular system.

These topics are becoming more interesting but need more clinical confirmation.

2.8 Perspectives and Future Directions

The intricate biology of myelin, as detailed in this review, has transitioned from a static structural view to a dynamic paradigm of adaptive myelination. Thus, the myelin sheath plays a crucial role in nervous system function, plasticity, aging and disease. This evolving understanding opens several promising avenues for future research and therapeutic development, while also highlighting significant difficulties that could be overcome with future development.

(1) *Translating Myelin Biology into Therapeutic Strategies*

A primary goal is to translate our knowledge of myelinating cell biology into effective treatments for demyelinating and neurodegenerative diseases. But the fundamental differences in regenerative capacity between the CNS and PNS remain a central challenge. Future research must focus on unlocking the latent regenerative potential of the CNS. This could involve:

(a) Targeting inhibitory signals to develop strategies to overcome molecules like *Nogo-A*, which we discussed for its role in inhibiting regeneration and altering glial function.

(b) Harnessing cell plasticity when we could use the remarkable plasticity of Schwann cells to potentially reprogram oligodendrocytes or recruit endogenous repair cells more effectively. The observation that Schwann cells can remyelinate CNS axons in some pathologies provides a compelling, albeit challenging, blueprint.

(c) Biomaterials and engineering. According to advances in biomaterials development for peripheral nerve repair, future work could design “smart-scaffolds” that deliver precise spatiotemporal signals (e.g., growth factors like *Nrg1*, or inhibitors of specific signaling pathways like *Notch*) to guide axonal regrowth and remyelination in the CNS.

We can also describe pharmacological modulation of signaling pathways. The complex signaling networks (*MAPK/Erk*, *PI3K/Akt/mTOR*, *Wnt/β-catenin*, *Fyn-kinase*) that govern myelination are ripe for therapeutic intervention. The challenge lies in achieving cell-type and context-specific modulation. For instance, while enhancing *PI3K/Akt/mTOR* signaling might promote remyelination, its systemic activation carries oncogenic risks. Future directions include developing drugs that target downstream effectors or that can be delivered specifically to myelinating glia; exploring the role of metabolic regulators, such as thyroid hormones and dietary factors, which have shown promise in modulating these pathways and supporting myelin health.

(2) Unraveling the “Gut-Brain Axis” in Myelin Health

The correlations between the gut microbiota and myelination represent a nascent but exciting field. In this area, we should move beyond correlation to causation.

(3) Deconstructing Myelin’s Role in Neurodegeneration and Aging

The concept of “myelin vulnerability” as an early driver of neurodegeneration in diseases like Alzheimer’s and Parkinson’s is a paradigm shift. This perspective suggests new research priorities:

(a) Myelin as an early diagnostic biomarker. Developing advanced neuroimaging techniques (e.g., advanced diffusion MRI, myelin water imaging) capable of detecting subtle, pre-clinical changes in myelin integrity. These could serve as early biomarkers for neurodegenerative diseases, allowing for earlier intervention.

(b) Understanding age-related myelin failure. Research should focus on the molecular mechanisms of age-related myelin degradation, particularly the role of lipid metabolism dysregulation and the cumulative burden of indigestible myelin debris on microglial function. The transcriptomic data showing that aged microglia resemble those in disease states is a critical clue that needs further exploration.

(c) The myelin-autonomic connection. The role of myelin in the autonomic nervous system and its potential involvement in conditions like chronic stress, pain syndromes, and cardiovascular disease is a significant knowledge gap. Future studies should investigate how myelin plasticity in autonomic ganglia and nerves contributes to systemic pathophysiology.

(4) Technological and Conceptual Horizons

Progress is contingent on embracing new technologies and refining our conceptual frameworks.

(a) Single-Cell and Spatial Omics. As highlighted in this review, scRNA-seq is revolutionizing our understanding of cellular heterogeneity. Future work must integrate these transcriptomic maps with proteomic, lipidomic, and spatial data to understand how different cell subtypes interact within their niche in health and disease. This is essential for moving beyond descriptive cell atlases to functional insights.

(b) Advanced modeling. While animal models (like cuprizone or genetic mutants) remain invaluable, there is a pressing need for more sophisticated human-relevant models. Induced pluripotent stem cell (iPSC)-derived oligodendrocytes and complex co-culture systems (including neurons, astrocytes, and microglia) can help model patient-specific diseases and screen for novel therapeutics.

(c) Refining the concept of adaptive myelination. We must dissect the precise contribution of de novo myelination versus structural remodeling of existing sheaths in learning, memory, and cognitive function. This requires developing tools to visualize and manipulate myelin dynamics *in vivo* with cellular and molecular precision.

In conclusion, the field of myelin biology is at a thrilling inflection point. The recognition of myelin as a dynamic and adaptive structure has opened new frontiers in our understanding of the nervous system. The major challenges ahead lie in translating this foundational knowledge into a new class of therapies that can not only halt demyelination but actively promote repair and protect against neurodegeneration. Overcoming these challenges will require a concerted, multidisciplinary effort, bridging molecular biology, neuroscience, bioengineering, and clinical research.

3. Discussion

We have demonstrated the impact of pathology on the structures of myelinated fibers and their compensatory responses aimed at preventing the pathological process. We examined contemporary views on the cell populations responsible for myelinogenesis, demyelination, and remyelination, describing their origin and functional significance under normal and pathological conditions (inflammation, trauma, etc.). Key physiological aspects and principles of myelinated fiber function are outlined, highlighting the vast diversity of myelin’s biochemical composition, the mechanisms of its fine-tuned maintenance, and the fundamental

structural differences between central and peripheral nervous system myelin.

A correlation between certain demyelinating pathologies and their associated myelin alterations is provided. Changes in the biochemical composition of myelin that regulate its adhesive, insulating, and trophic properties are also indicated, along with the appearance of reactive forms among surrounding cells (astro- and microgliosis, activated Schwann cell phenotypes). This leads to the development of demyelinating and other diseases. Due to ongoing myelination in the CNS throughout life, we observe both classic age-related changes (accumulation of undegraded myelin in microglia, impaired antioxidant defense in astrocytes and microglia) and specific dynamic changes in myelination patterns and the response of the microenvironment (activation of signaling pathways and morphological changes such as the formation of astrocytic processes around axons). In contrast, myelination in the PNS virtually ceases with age; however, in response to injury, inflammation, and other pathological reactions, cells actively proliferate and acquire various stem cell, reparative, autophagic, and other phenotypes.

Alterations in myelin at the earliest stages of pathology, sometimes preceding the main cellular degeneration (in Alzheimer's disease, etc.), are examined. This underscores the diagnostic importance of monitoring the state of nerve fibers and axonal insulating sheaths.

Thus, the organization of the nervous system's conductive elements is not limited solely to myelination processes induced during early ontogeny. Associated processes of remyelination and preceding demyelination, which exist in a dynamic equilibrium, also play a significant role in maintaining healthy nerve fiber functionality. The cellular populations organizing the nerve fiber in the peripheral and central nervous systems necessarily respond to the course of these processes. For instance, it has been established that extensive axonal degeneration is a necessary condition for the proliferation of astrocytes and Schwann cells, but it is insufficient for microglial activation.

The combination of these mechanisms, among other things, contributes to the implementation of "myelin plasticity" (by analogy with synaptic plasticity). From certain perspectives, distinguishing this mechanism is justified by the fact that myelination processes are reliably involved in adaptive responses during aging, memory formation, and learning (changes in the hippocampus and medial prefrontal cortex), which also highlights its importance in the context of neurodegeneration. In addition to the sheath's role in cognitive processes, its involvement in sensory and motor reactions of the organism is noted (also see [437]). Following the initial ensheathment of the axon, myelin undergoes changes based on incoming impulses, which adapt neuronal conduction and optimize the pathway through which the impulse travels. This form of plasticity (adaptive myelination) is supported both by pre-existing oligodendrocytes

involved in myelin remodeling and by newly differentiated myelinating cells. Adaptive myelination plays an important role in cognitive functions, as well as in emotional and motor learning [438].

Myelin degradation is an early sign of various pathologies (including Alzheimer's disease and amyotrophic lateral sclerosis). Furthermore, signs of impairment manifest not only in old age but also in adolescents with schizophrenia, bipolar disorder, and congenital autism [439]. The next stage of research could focus on the cooperative changes in white and gray matter in demyelinating and neurodegenerative pathologies.

The myelination profile differs across cortical layers [302], as do the myelination patterns themselves [440]. The restoration of these patterns (the alternation of myelinated and unmyelinated segments) is the primary goal of remyelination and nerve fiber regeneration. Targeting these processes potentially holds therapeutic value.

Many aspects of the topic were not discussed or were discussed without sufficient detail due to the constraints of the text length and the format of a "Review Article". More than 150 years have passed since the discovery of myelin. This work has successfully summarized the accumulated data on its structure and the relationship between this structure and existing pathologies of the CNS and PNS axonal sheaths. Promising and currently developing research directions have also been outlined.

4. Conclusions

This work presents a structured literature review and summarizes the results and conclusions of previous studies. It is a descriptive, yet critical and multifaceted, analysis of published literature on a specific topic and research question, without strict limitations on the material search strategy.

Updated evidence indicates that myelin not only ensures rapid saltatory impulse conduction but, primarily, facilitates the synchronized delivery of incoming signals to various nerve centers, enabling the integration and interpretation of received information/experience into developing neural circuits. This is significant, considering that central nervous system myelination occurs throughout life, albeit with reduced intensity in older age.

Following terminal differentiation, the myelin sheath is potentially capable of additional forms of structural and molecular plasticity, including changes in myelin thickness, compaction, internode length, sheath positioning, and the extent of individual nodes of Ranvier. In addition to structural changes, the expression and distribution of molecules and transporters involved in providing metabolic support to myelinated axons are altered. These changes can occur in response to varying neuronal activity and throughout the lifespan. Each of these forms of plasticity, ranging from the generation of new myelinating cells to more subtle alterations in internode length, can modulate conduction ve-

locity, axonal status, and neural circuit activity, and is described as “adaptive myelination”.

Among potential therapeutic approaches are the regulation of signaling pathways and the stimulation of myelinating cells and their microenvironment (mechanically, electrically, or chemically). However, it is necessary to account for the high sensitivity and specificity of myelin to changes in composition, cell activity, and environmental properties. For instance, the expression of *Nrg1 type III* is sufficient to initiate myelination by Schwann cells, whereas for oligodendrocytes, these conditions are insufficient, and the involvement of astroglia is required (for details, see [305], and others).

To date, there have been successes in developing biomaterials for peripheral nerve repair [441], novel therapeutic methods [97], and models for assessing the progression of certain neurological diseases [432]. Further research on the topic is required to understand the fundamental aspects and realize the most promising developments.

Author Contributions

NVN: Conceptualisation, Data Curation, Formal Analysis, Validation, Methodology. OMV: Conceptualisation, Data Curation, Writing. RAN: Conceptualisation, Data Curation, Writing. BA: Methodology, Data Curation. KA: Visualization, Writing. ZMV: Investigation, Visualization, writing, formal Analysis. ABV: Conceptualisation, Writing. SRE: Investigation, Writing, Validation. UK: Writing, Validation. MAA: Writing, Validation, Investigation, Formal Analysis. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflicts of Interest

The authors declare no conflicts of interest.

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