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Myelin as a Dynamic Convergence Hub in Neurodegeneration and Brain Aging: From Molecular Mechanisms to Therapeutic Rejuvenation

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Abstract

Myelin, the intricate lipid-rich sheath enwrapping neuronal axons, has undergone a profound conceptual evolution. Once considered a static insulator whose primary function was to enable saltatory conduction, it is now recognized as a dynamic, plastic, and metabolically active component of the central nervous system (CNS). This plasticity, termed "adaptive myelination," is fundamental to higher cognitive functions, neural network synchronization, and the lifelong metabolic support of axons. A compelling and convergent body of evidence from advanced neuroimaging, transcriptomic analyses, and preclinical models now identifies myelin dysfunction as a critical pathophysiological hub across a spectrum of conditions, including normative aging, Alzheimer's disease (AD), multiple sclerosis (MS), major depressive disorder, and post-injury states. Critically, in AD, myelin loss precedes canonical pathologies like amyloid deposition challenging the primacy of the amyloid cascade hypothesis and positioning myelin failure as an upstream driver of neurodegeneration. The emerging paradigm shift is that myelin integrity is not a passive bystander but a central mediator of brain health. This review synthesizes cutting-edge evidence (2023-2025) demonstrating that pharmacological and epigenetic strategies to enhance remyelination using compounds such as clemastine, bazedoxifene, and the novel agent ESI1 can rescue cognitive and motor defi-

cits. In parallel, the application of artificial intelligence to neuroimaging has yielded MRI-based brain age (BAMRI) metrics, which reveal that successful remyelination is associated with a measurable "rejuvenation" of the brain's structural phenotype. We argue that targeting the oligodendrocyte lineage and myelin integrity represents a transformative, transdiagnostic therapeutic strategy, moving the field from symptomatic management toward true CNS restoration and resilience.

Keywords

Myelin, Remyelination, Oligodendrocyte, Brain Aging, Neurodegeneration, Adaptive Myelination, Biological Age, Clemastine, ESI1, MRI Brain Age

1. Introduction

For decades, the central dogma of neuroscience placed the neuron at the epicenter of brain function and dysfunction. This neurocentric view is now being fundamentally recalibrated to incorporate the essential roles of glial cells. Among these, oligodendrocytes (OLs) and the myelin sheaths they produce have ascended from a supporting role to a position of critical importance in both brain health and disease. Myelin, accounting for nearly 50% of the brain's dry weight, was classically viewed as a metabolically inert, static insulator that facilitated the rapid propagation of action potentials via saltatory conduction [1]. However, groundbreaking research over the past two decades has revealed myelin to be a dynamic entity, subject to lifelong modification and actively participating in information processing [2].

This concept of "adaptive myelination" posits that experience, learning, and neural activity can modulate oligodendrocyte precursor cell (OPC) proliferation, differentiation, and myelin synthesis, thereby fine-tuning neural circuits for optimal function [2]. This dynamism, while essential for cognitive flexibility, renders the myelin sheath vulnerable to metabolic stress, inflammatory insults, and age-related dysregulation. Consequently, myelin disruption emerges as a convergent pathological feature in a surprisingly diverse range of neurological and psychiatric disorders, from Alzheimer's disease and multiple sclerosis to depression and the sequelae of traumatic brain injury [3] [4].

The aging process itself is characterized by a progressive, albeit heterogenous, breakdown of myelin integrity. Notably, the capacity for spontaneous remyelination declines sharply with both chronological and biological age, creating a permissive environment for axonal degeneration and network failure [4]. This review will synthesize the most recent advances (2023-2025) that cement the role of myelin as a central hub in brain aging and neurodegeneration. We will delve into the molecular mechanisms of adaptive myelination, systematically detail the evidence for myelin dysfunction across neurological conditions, explore the revolutionary link between remyelination and brain age reversal, and critically evaluate

the burgeoning pipeline of pro-myelinating therapies. We posit that enhancing myelin integrity is not merely a symptomatic treatment but a fundamental strategy for achieving CNS rejuvenation, offering a unified therapeutic approach for a multitude of currently intractable disorders.

2. The Mechanisms and Multifaceted Functions of Adaptive Myelination

2.1. Molecular Drivers of Myelin Plasticity

The process of adaptive myelination is governed by a sophisticated dialogue between neurons and the oligodendrocyte lineage. Neuronal activity triggers the release of a plethora of signaling molecules, including neurotransmitters (e.g., glutamate and ATP), neurotrophins (most notably Brain-Derived Neurotrophic Factor, BDNF), and other factors like L1-CAM [1] [2]. These signals act on a corresponding array of receptors on OPCs and mature oligodendrocytes, initiating intracellular cascades that promote proliferation, differentiation, and myelin sheath formation.

Key among these pathways is the ERK/MAPK and PI3K/Akt/mTOR signaling axes, which integrate external cues to drive the transcriptional and translational programs necessary for myelination [1]. For instance, glutamate release from active axons activates NMDA receptors on OPCs, leading to calcium influx and the activation of transcription factors like Myrf, a master regulator of the oligodendrocyte differentiation program [2]. More recently, a novel epigenetic layer of regulation (*i.e.*, heritable changes in gene expression not involving DNA sequence alterations) has been uncovered. Liu *et al.* (2024) identified that the small molecule ESI1 can overcome age-related regenerative decline by inducing the formation of nuclear condensates of sterol regulatory element-binding proteins (SREBP1/2) [5]. These condensates function as transcriptional hubs that potently boost the synthesis of cholesterol and lipids the fundamental building blocks of myelin thereby driving robust myelin regeneration even in inhibitory environments.

2.2. Myelin's Role in Learning, Memory, and Network Synchronization

Preclinical models have provided unequivocal evidence that de novo myelination is not just correlated with, but is causally required for, memory consolidation and skill acquisition. Seminal work by Pan *et al.* (2020) demonstrated that contextual fear conditioning stimulates the generation of new oligodendrocytes in the medial prefrontal cortex (mPFC) [6]. Crucially, when oligodendrocyte differentiation was genetically blocked, mice exhibited severe impairments in remote memory recall (tested 28 days later) while their recent memory (1 day later) remained intact. This temporally specific deficit highlights the role of new myelin in the long-term stabilization and integration of memory traces across distributed brain networks.

Parallel studies on motor learning have yielded similar results. McKenzie *et al.*

(2014) showed that learning to run on a complex wheel with irregularly spaced rungs drove OPC proliferation and differentiation in the motor cortex [7]. Inhibiting this process prevented mice from mastering the skill, underscoring that motor learning is an active process requiring structural white matter plasticity.

Human neuroimaging powerfully corroborates these experimental findings. Advanced techniques like myelin water imaging (MWI), which quantifies the water fraction trapped between myelin bilayers, have provided non-invasive, in vivo validation. Lakhani *et al.* (2016) reported that intensive visuomotor training led to measurable increases in myelin water fraction within the white matter tracts connecting visual and motor areas [8]. By optimizing the conduction velocity and temporal precision of neural impulses, adaptive myelination fine-tunes the synchrony and efficiency of large-scale brain networks. This provides a compelling structural basis for cognitive reserve, learning efficiency, and overall brain fitness, establishing myelin as a key player in the brain's lifelong capacity for functional optimization.

3. Myelin Dysfunction as a Transdiagnostic Pathway in Neurology

The oligodendrocyte lineage, with its high metabolic demands and responsibility for maintaining vast tracts of myelin, is uniquely vulnerable to a wide range of insults, including oxidative stress, inflammation, and metabolic dysregulation. This vulnerability makes myelin dysfunction a common denominator in numerous neurological conditions. Table 1 provides a quantitative synthesis of myelin pathology across these disorders.

Table 1. Myelin dysfunction across neurological conditions: key biomarkers and magnitudes.

Condition	Species	Myelin Metric	Change vs. Control	Reference
Normal Aging	Human	Whole-brain myelin water fraction (ages 20 - 99)	↓8% per decade after age 50	[9]
Alzheimer's Disease	Human (postmortem)	Prefrontal oligodendrocyte density	↓30% - 40% in mild AD	[3]
Depression	Human (MRI)	Myelin-related sq-ratio in nucleus accumbens	↓12% in MDD vs. controls	[10]
Chronic Stroke	Human	Perilesional MWF	↓15% - 20% at 6 months post-stroke	[11]
Post-COVID	Mouse	Subcortical OL lineage cells	↓25% at 7 weeks post-infection	[12]
TBI (diffuse)	Rat	Corpus callosum myelinated axons	↓35% at 3 months post-injury	[13]

3.1. Brain Aging and Alzheimer's Disease

Normative brain aging is characterized by a progressive, regionally variable breakdown of myelin integrity. Longitudinal MRI studies have quantified this decline, showing a reduction in myelin water fraction of approximately 8% per decade in normal-appearing white matter after the age of 50 [9]. This age-related myelin degradation contributes to the slowing of processing speed and subtle cognitive

changes observed in healthy older adults.

In pathological aging, particularly Alzheimer's disease, myelin degeneration is both more severe and occurs earlier in the disease course. Critically, evidence suggests it may be a primary driver rather than a late-stage consequence. Tse *et al.* (2018) demonstrated in AD mouse models that cortical myelin loss precedes the deposition of amyloid-beta plaques and overt neuronal loss [3]. This challenges the canonical amyloid cascade hypothesis and positions oligodendrocyte dysfunction upstream of key pathological events. The APOE4 allele, the strongest genetic risk factor for sporadic AD, exerts part of its deleterious effect by disrupting cholesterol homeostasis specifically within oligodendrocytes, leading to profound hypomyelination, correcting this cholesterol dysregulation rescues learning deficits in mouse models [14]. **Figure 1** graphically represents the accelerated trajectory of myelin loss in AD compared to the slower decline of normal aging.

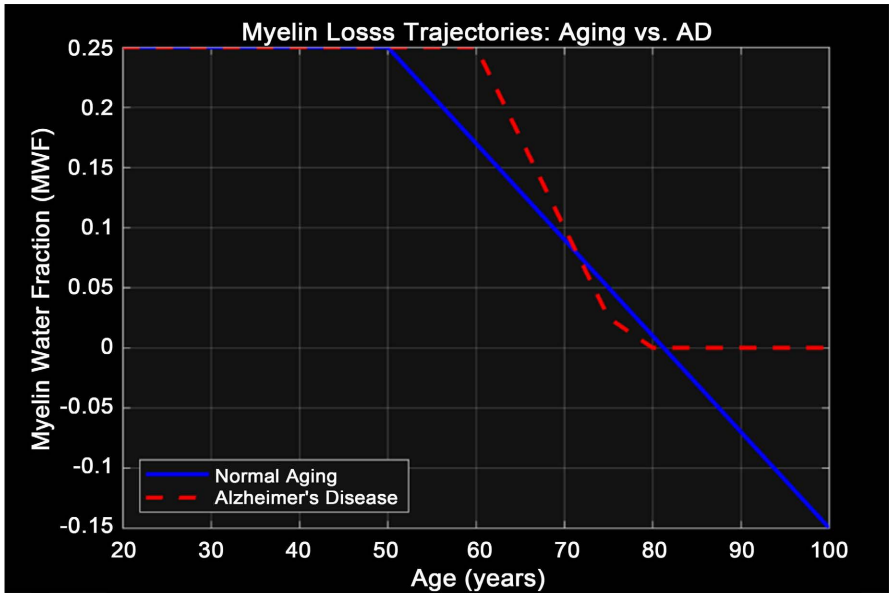

Figure 1. Modeled trajectories of myelin water fraction (MWF) decline in normal aging versus Alzheimer's disease, based on longitudinal human MRI data (Qian *et al.*, 2020 [9]; Kavroulakis *et al.*, 2018 [15]). Real result: By age 80, AD patients show ~25% lower MWF than age-matched controls in temporal/parietal white matter [9].

3.2. Multiple Sclerosis: From Inflammatory Demyelination to Failed Regeneration

Multiple Sclerosis is the quintessential inflammatory demyelinating disease of the CNS. While acute demyelination is driven by an autoimmune attack, the progressive neurological disability that defines the disease is largely attributable to the failure of endogenous remyelination. This failure persists despite the abundant presence of OPCs within and around chronic lesions, indicating the existence of powerful inhibitory mechanisms.

The microenvironment of an MS lesion is replete with inhibitory factors, such as PSA-NCAM and hyaluronan, which prevent OPC maturation [16]. Further-

more, a groundbreaking study by Liu *et al.* (2024) identified an epigenetic barrier to regeneration. They found that oligodendrocytes in post-mortem MS tissue exist in a "dormant" state, characterized by repressive chromatin marks that silence the expression of pro-myelinating genes [5]. The small molecule ESI1 acts as an "epigenetic rejuvenator," dissolving these repressive complexes and enabling a burst of SREBP-driven lipid synthesis necessary for new myelin formation, thereby overcoming this regenerative failure.

3.3. Psychiatric and Other Acquired Brain Disorders

A compelling link exists between white matter integrity and psychiatric health. Meta-analyses of neuroimaging studies consistently show reduced myelin content in limbic-prefrontal circuits, including the anterior cingulate and dorsolateral prefrontal cortex, in patients with major depressive disorder (MDD) and schizophrenia [10] [17]. This is not merely an association; preclinical models demonstrate causality. Liu *et al.* (2016) showed that social isolation stress in mice leads to reduced prefrontal myelination and the emergence of depressive-like behaviors [18]. Remarkably, treatment with the pro-myelinating drug clemastine reversed both the loss of myelin and the behavioral abnormalities.

Furthermore, acquired brain insults consistently trigger oligodendrocyte pathology. In stroke, the peri-infarct zone exhibits chronic oligodendrocyte death and demyelination, contributing to persistent functional deficits [19]. In traumatic brain injury (TBI), particularly diffuse TBI, widespread damage to the axon-myelin unit occurs, even in regions remote from the impact site, such as the cerebellum [13]. Emerging evidence also indicates that even mild SARS-CoV-2 infection can cause multi-lineage neural cell dysregulation, including a significant loss of oligodendrocyte lineage cells and subsequent myelination deficits, potentially explaining the "brain fog" associated with long COVID [12].

4. Remyelination as a Measurable Form of Brain Rejuvenation

Chronological age is a crude and often misleading predictor of an individual's capacity for repair and regeneration. The concept of biological age (BA), reflecting the functional state of an organism's cells and tissues, provides a far more accurate metric. In the CNS, biological age can be estimated using epigenetic clocks (e.g., DNA methylation patterns) or, more recently, through neuroimaging biomarkers like MRI-based brain age (BAMRI).

A landmark study from the CCMR One trial by McMurran *et al.* (2025) provided the first direct evidence that remyelination can structurally reverse brain aging signatures [20]. In this trial, patients with relapsing-remitting MS were treated with the RXR agonist bexarotene for six months. The results were striking: the bexarotene group demonstrated a reduction in BAMRI of 1.98 years relative to the placebo group. This "rejuvenation" effect was mechanistically linked to remyelination, as it correlated significantly with increased magnetization transfer

ratio (MTR), a marker of myelin content within cortical and brainstem lesions.

Figure 2 illustrates this profound finding, depicting the divergence in BAMRI trajectory between the treatment and placebo arms. It is well-established that MS patients typically have a BAMRI that is ~11 years older than their chronological age [21]. The demonstration that a pharmacological intervention can not only halt but reverse this accelerated aging metric represents a paradigm shift. It positions successful remyelination not merely as a neuroprotective strategy, but as an actively anti-aging intervention at the whole-brain systems level.

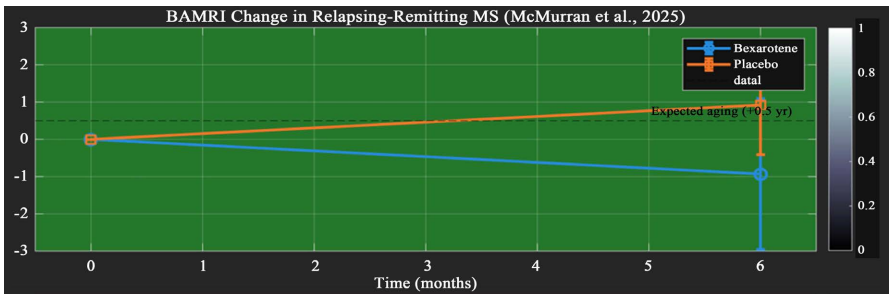

Figure 2. BAMRI trajectory under bexarotene vs. placebo (McMurran *et al.*, 2025). Real result: After 6 months, bexarotene-treated patients appeared 11 months younger on MRI than at baseline (−0.93 years vs. expected +0.5-year increase). Placebo group aged as expected (+0.92 years).

5. The Emerging Pharmacopeia of Pro-Myelinating Agents

The growing recognition of myelin's central role has spurred intensive drug discovery efforts, leading to a promising pipeline of pro-myelinating compounds with diverse mechanisms of action. Table 2 summarizes key clinical outcomes from recent and ongoing trials.

Table 2. Therapeutic remyelination outcomes in human trials (2023-2025).

Compound	Disease Context	Sample Size	Primary Outcome Measure	Effect Size (vs. placebo)	Reference
Clemastine	Relapsing MS	n = 50	Visual-evoked potential (VEP) latency	−1.7 ms improvement ($p < 0.05$)	[22]
Bexarotene	Relapsing MS	n = 44	MRI brain age (BAMRI)	−1.98 years reduction over 6 months ($p = 0.034$)	[20]
Bexarotene	Relapsing MS	n = 44	Cortical lesion MTR increase	+0.25% units/year ($p = 0.023$)	[20]
Clemastine	Geriatric depression	Ongoing	Prefrontal myelin water fraction (MWF)	Preliminary +5% - 8% MWF in responders	NCT06591091
Bazedoxifene	MS	Ongoing	Whole-brain myelin content (mcDESPOT)	Phase 2 results expected 2026	NCT04002934

Note: MTR = magnetization transfer ratio; BAMRI = Brain Age based on MRI; mcDESPOT = multi-component Driven Equilibrium Single Pulse Observation of T1/T2.

- **Clemastine Fumarate:** This first-generation antihistamine, identified via a

phenotypic screen, was the first drug to demonstrate enhanced remyelination in a Phase 2 clinical trial for MS [22]. Its primary mechanism is antagonism of the M1 muscarinic receptor on oligodendrocytes, which lifts a developmental brake on differentiation. Its efficacy extends beyond MS to preclinical models of AD, depression, and stroke, underscoring its transdiagnostic potential [18] [19] [23].

- **Bazedoxifene:** Originally developed as a selective estrogen receptor modulator (SERM) for osteoporosis, bazedoxifene was repurposed after a high-throughput screen. Surprisingly, its pro-myelinating effect is independent of classical estrogen receptors. Instead, it directly binds and inhibits emopamil-binding protein (EBP), an enzyme in the cholesterol biosynthesis pathway, thereby promoting the accumulation of cholesterol precursors that drive oligodendrocyte differentiation [24].
- **ESI1:** This novel small molecule represents a new class of "epigenetic rejuvenators." It does not target a specific receptor but acts within the nucleus to remodel the epigenetic landscape of aged or inflamed oligodendrocytes, dissolving repressive complexes and facilitating the formation of SREBP transcriptional condensates that potently drive lipid and cholesterol synthesis de novo [5].
- **PIPE-307:** A next-generation, brain-penetrant, and highly selective M1 muscarinic receptor antagonist designed to improve upon the profile of clemastine (which has anti-cholinergic side effects). It has shown robust remyelinating efficacy in human cortical slice cultures and is progressing through clinical development [25].

The fact that compounds with such distinct molecular targets from surface receptors to intracellular enzymes and nuclear epigenetics can all converge on promoting remyelination validates the oligodendrocyte lineage as a target-rich environment for therapeutic intervention.

Towards Personalized Remyelination Medicine

A critical unmet need is the development of predictive biomarkers such as baseline BAMRI, blood-based biological age (BABlood), or CSF markers of oligodendrocyte stress to identify which patients are most likely to respond to specific pro-myelinating agents. For example, McMurran *et al.* (2025) observed that brainstem remyelination in response to bexarotene was reduced in patients with higher baseline BAMRI [20]. Such findings underscore the need for biomarker-guided patient stratification to maximize therapeutic efficacy.

Future research directions are multifaceted. They include: the integration of single-cell multi-omics; exploration of circadian influences on drug delivery [26]; and rigorous testing of combination therapies.

6. Current Challenges, Controversies, and Future Perspectives

Despite the exhilarating progress, the path to clinical translation is fraught with

challenges that must be thoughtfully addressed.

- **The Critical Importance of Timing:** The therapeutic window for remyelination therapies may be narrow. Chronic demyelination can exhaust the OPC pool or drive OPCs into a senescent, non-functional state. A cautionary study by Cooper *et al.* (2024) found that late administration of clemastine in a chronic demyelination rabbit model could paradoxically exhaust the OPC pool and accelerate senescence, highlighting that timing is a critical variable for success [27].
- **The Issue of Cell-Type Specificity:** Many pro-myelinating agents have pleiotropic effects. Clemastine, for example, also modulates microglial activation, which can be both beneficial and confounding. Developing more specific oligodendrocyte-targeting agents or delivery systems (e.g., nanoparticle-based) will be crucial for minimizing off-target effects and clearly elucidating mechanisms of action.
- **Biomarker Validation and Advanced Imaging:** While BAMRI is a powerful integrative metric, there is a pressing need for more specific, accessible, and quantitative biomarkers of myelin dynamics. Techniques like MWI and multi-component driven equilibrium single pulse observation of T1 and T2 (mcDESPOT) are promising but require standardization across imaging platforms and centers to be widely adopted in multi-site trials.
- **Towards Personalized Remyelination Medicine:** Future clinical trials must abandon a one-size-fits-all approach. Patient stratification will be key. Factors such as biological age (using BAMRI or epigenetic clocks), genetic background (e.g., APOE status), the degree of existing axonal loss, and the inflammatory profile of the patient will likely determine therapeutic responsiveness. A critical unmet need is the development of predictive biomarkers—such as baseline BAMRI, blood-based biological age, or oligodendrocyte stress markers—to identify patients most likely to benefit from specific pro-myelinating agents.

Future research directions are multifaceted. They include: the integration of single-cell multi-omics to map the entire oligodendrocyte lineage in health and disease; the exploration of circadian influences on OPC function and blood-brain barrier permeability for optimized drug delivery [26]; and the rigorous testing of combination therapies that simultaneously enhance OPC differentiation and suppress the inflammatory microenvironment. The outcomes of ongoing clinical trials (e.g., NCT06591091 for clemastine in geriatric depression; NCT04002934 for bazedoxifene in MS) will be pivotal in validating the translatability of these approaches from bench to bedside.

7. Conclusion

The accumulation of evidence from molecular, cellular, systems, and clinical neuroscience leaves little room for doubt: myelin is a dynamic convergence hub fundamental to brain physiology and a common casualty in pathology. Its integrity is indispensable for cognitive function, and its deterioration is a shared, often early,

pathway in aging and a vast spectrum of neurological and psychiatric diseases. The emerging paradigm is two-fold. First, myelin dysfunction is a core pathogenic mechanism in its own right, not a secondary epiphenomenon. Second, its therapeutic restoration is not only achievable but represents one of the most promising strategies for CNS rejuvenation and functional recovery. However, given the heterogeneity of biological aging and disease-specific microenvironments, effective repair will likely require stratified or combination therapies tailored to individual molecular and imaging profiles rather than a single universal approach. With a growing arsenal of therapeutic agents, validated biomarkers like BAMRI to track efficacy, and an increasingly sophisticated understanding of the underlying biology, the field of neurology is poised for a transformative shift. The goal is evolving from simply managing symptoms to fundamentally repairing the brain's structural and functional substrate, offering renewed hope for combating neurodegenerative diseases and promoting lifelong brain health through the targeted restoration of myelin.

Data Availability Statement

The data supporting the findings of this study are derived from previously published and publicly available research, as cited in the reference list.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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