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Demyelination in Parkinson's disease: Not just a secondary bystander, but also as an active contributor to pathogenesis

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Abstract

Parkinson's disease (PD) primarily affects the gray matter, with a gradual loss of dopaminergic neurons in the substantia nigra and the buildup of intraneuronal α-synuclein. Recent neuroimaging and neuropathological studies have indicated widespread alterations in white matter microstructure, raising a vital question: Is demyelination merely a consequence of axonal degeneration, or does it actively drive neurodegeneration? This review discusses the role of demyelination in PD and highlights future research directions. A literature search was conducted using keywords such as "myelin,""demyelination," "bystander," "remyelination," "impact of demyelination," "causes of Parkinson's," Parkinson's disease," "myelination," "functional magnetic resonance imaging," "neurodegeneration," "factors affecting Parkinson's," "PD," "α-synuclein," "synucleinopathy," and "aging" across Scopus, Web of Science, OpenGrey, PubMed, ResearchGate, Cochrane Library, and Google Scholar. These terms were systematically combined using Boolean operators and linked to Parkinsonism. The review prioritized peer-reviewed studies published in the last 10 to 15 years to highlight recent findings, with a few older key studies included. The collected evidence presents a complex picture: the "bystander" hypothesis, which posits that neuronal death triggers Wallerian degeneration and myelin breakdown, is supported; however, multiple lines of evidence also suggest an early, active role for oligodendrocytes. α-synuclein buildup disrupts cellular metabolic support, leading to energy deficits in axons and heightened oxidative stress before neurons are visibly lost. Furthermore, neuroinflammatory responses associated with early demyelination exacerbate the toxic environment, accelerating dopaminergic neuron loss. In conclusion, demyelination is both a consequence and an active contributor to PD progression. Recognizing these dynamics offers new opportunities for therapies that protect myelin, potentially transforming the course of PD.

Keywords: Bystander; Demyelination; Myelin; Neurodegeneration; Parkinson's disease; Remyelination

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1. Introduction

Parkinson's disease (PD) is a growing global health challenge characterized by the gradual loss of dopaminergic neurons in the substantia nigra compacta. Although it predominantly affects individuals over the age of 60, early-onset cases can occur in adults as young as 40 years.[1-3] The substantia nigra compacta, a midbrain structure,

contains dopaminergic neurons that produce dopamine, which is essential for regulating precise movements.[4,5] PD's exact cause is unclear, but both genetic and environmental factors are believed to play roles.[6,7] It manifests as tremors, bradykinesia, rigidity, and postural instability.[8] Diagnosis relies on clinical symptoms and medical history, with neurological exams and imaging used to rule out other conditions.[9] Levodopa, a dopamine precursor, helps alleviate motor symptoms.[10] As PD progresses, symptoms worsen, impacting quality of life. The aging population has contributed to an increasing prevalence of PD, indicating it as a global pandemic.[11]

Healthcare practitioners may prescribe supplementary medications such as dopamine agonists and monoamine oxidase B inhibitors.[12] PD progresses gradually, with symptoms varying among individuals.[13] In advanced stages, patients may struggle with speech, swallowing, and cognition. Non-motor symptoms such as sleep issues, mood changes, and cognitive decline are common, and regular physical activity, especially exercises for balance and flexibility, helps manage symptoms and improve well-being.[14,15] Ongoing research aims to understand PD mechanisms and develop better treatments, with increased awareness proposed as vital for early detection and intervention.[16] Patients or caregivers who notice PD symptoms should seek prompt neurologist evaluation; early treatment can improve the quality of life for PD patients.[17,18] In 2019, over 8.5 million people worldwide had PD, which caused 5.8 million disability-adjusted life years, an 81% increase since 2000, and 329,000 deaths, more than double since 2000.[19] Data on PD burden obtained from the Global Burden of Disease 2016 showed an increase in PD from 1990 to 2016, but age-standardized rates increased by only 22%.[19] In 2021, cases reached 11.76 million, with 7.47 million disability-adjusted life years and 388,000 deaths.[20] As life expectancy increases, a greater proportion of individuals with PD are expected to progress to advanced stages.[21-23] PD is currently irreversible, with pathological changes occurring long before the onset of clinical symptoms.[20,24]

Several risk factors, such as aging, genetics, environment, head trauma, and medications, have been linked to PD, but their specific impact on neuronal axons remains unclear.[25-27] Myelin sheaths, produced by oligodendrocytes, protect axons from injury, inflammation, and toxic substances, thereby maintaining neuronal integrity. Disruptions in myelination can be detrimental and may contribute to neurodegenerative processes. Identifying risk factors and enabling early intervention are critical for preventing and slowing disease progression. In this context, exploring mechanisms such as neuronal demyelination is essential for advancing our understanding of PD.

2. Methodology

A comprehensive review of research was conducted, assessing studies on demyelination, myelination, myelin, and functional magnetic resonance imaging, and their links to PD. The search was performed across Scopus, Web of Science, OpenGrey, PubMed, ResearchGate, the Cochrane Library, and Google Scholar, using keywords such as "demyelination," "myelination," "remyelination," "myelin," "functional magnetic resonance imaging," "impact of demyelination," Parkinson's disease," "bystander," "causes of Parkinson's," "factors affecting Parkinson's," "PD," "α-synuclein," "synucleinopathy," and "aging," with Boolean operators. Filters based on publication date and article type ensured relevance. Peer-reviewed, reputable studies, mainly from the past 10–15 years, were included to provide current insights into demyelination, remyelination, and PD, though some older, key studies were also considered.

3. The brain's myelin landscape

The brain is more than neurons; it is a biologically designed entity. Its effectiveness relies mainly on non-neuronal elements, especially myelin, which surrounds axons with a lipid-rich, multilayered sheath.[28] This "landscape" is vital for cognition, network coordination, and brain processing. Unlike a static insulator, myelin is dynamic and adaptable, influencing timing and communication across brain networks.[29] As shown in Figure 1, this landscape's composition and architecture are crucial for nerve signal transmission, brain rhythms, development, and adaptability, and are linked to neurological and psychiatric conditions. Oligodendrocytes produce myelin in the central nervous system (CNS), extending processes to encase axonal segments, forming internodes separated by nodes of Ranvier.[30] This structure varies across axon diameters, brain regions, and parts of the same axon. Myelin integrity depends on key structural proteins such as myelin basic protein and proteolipid protein, within a composition comprising approximately 70–80% lipid and 20–30% protein.[31] The structural heterogeneity of myelin is tightly regulated, with precise control of internode length and myelin thickness. This organization enables efficient saltatory conduction, whereby thicker myelin and longer internodes reduce capacitance and increase resistance, enabling rapid jumps in action potentials between nodes.[32]

Harris and Attwell[33] demonstrated that myelination decreases energy use during neural signaling while boosting conduction speed by up to 100 times compared to unmyelinated axons. Researchers have visualized this *in vivo*, primarily using quantitative magnetic resonance

imaging techniques such as myelin water imaging.[33] These imaging findings reveal a "core" of fast-transmission pathways, characterized by substantial myelination early in life, encompassing deep brain structures and essential sensory and motor pathways. Conversely, the prefrontal cortex and other association cortices, which handle higher-level integration, myelinate later and may retain a more adaptable, distinct myelin arrangement into adulthood.[34]

3.1. The myelin beyond insulation

The primary function of myelin is to facilitate rapid and efficient nerve impulse transmission; however, it also serves additional roles beyond insulation, regulating conduction velocity, and maintaining synchronization within the brain, which is essential for processes such as memory formation, motor coordination, and sensory perception.[37] According to Fields,[29] temporal coherence refers to the phenomenon in which messages from different neurons reach their respective targets simultaneously due to myelination, as shown in Figure 2. For example, the coordination of signals from multiple brain regions is necessary to execute complex motor tasks smoothly, a capability enabled by the carefully regulated myelination of these pathways.[38,39] Furthermore, myelin is increasingly recognized as an active participant in neuronal metabolism. By supplying lactate, a vital energy substrate, via monocarboxylate transporters, oligodendrocytes support axonal function.[40,41] Maintaining axonal health, particularly during periods of elevated energy demand, depends on this metabolic connection. Disruption of this support, as observed in demyelinating disorders (Figure 2), can lead to irreversible functional impairment and progressive axonal damage.[42]

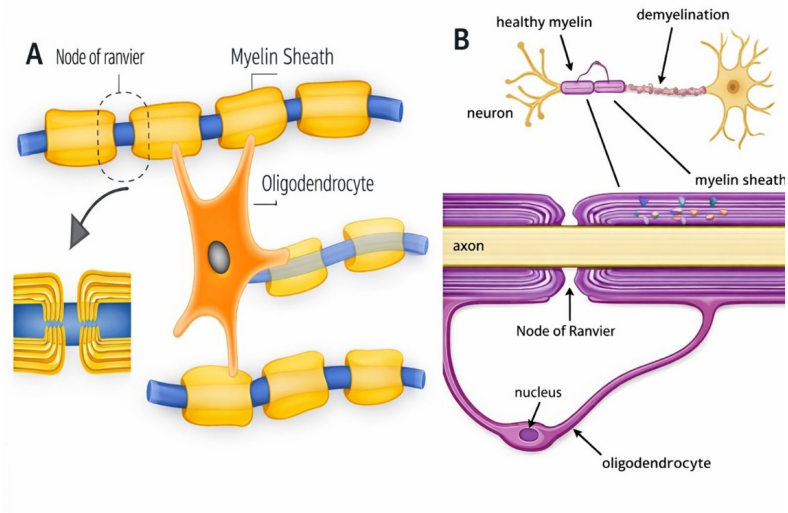


Figure 1. The structure of the myelin sheath in the central nervous system (CNS). (A) A schematic diagram illustrating a mature oligodendrocyte contributing to the myelin sheaths of three individual axons. Reprinted from Abu-Rub and Miller.[35] (B) Key components of the myelin sheath, the protective layer surrounding axons. Reprinted from Pi *et al.*[36]

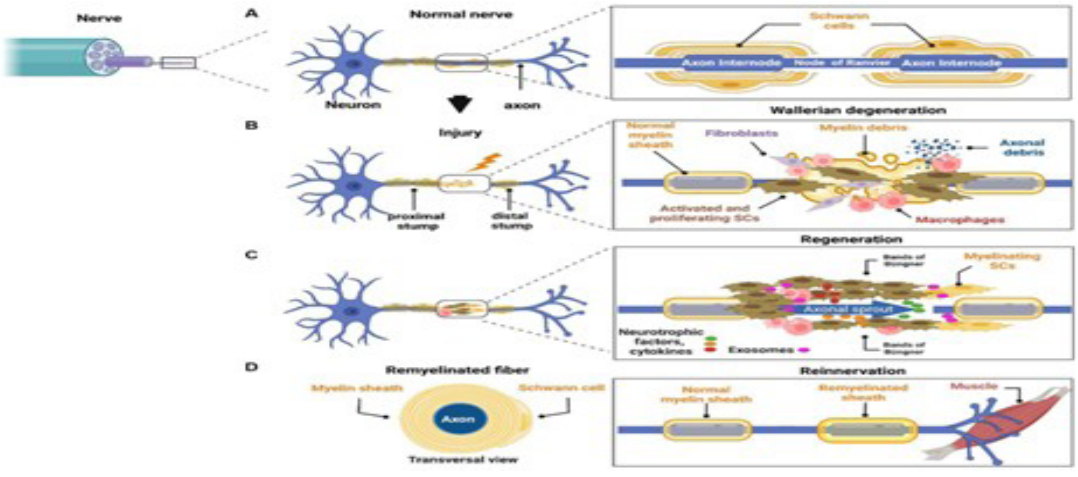


Figure 2. Illustration of the process of neuron myelination in the central nervous system (CNS). Reprinted from Oliveira *et al.*[43]

3.2. Myelin in Parkinson's disease

Parkinson's disease is a progressive neurodegenerative condition characterized by the loss of dopaminergic neurons in the substantia nigra.[44] Although it has been traditionally seen as a disorder involving dopamine depletion and basal ganglia dysfunction, recent evidence suggests that myelin abnormalities also contribute to disease progression. Myelin, which surrounds axons, is essential for effective neural transmission, and its impairment can worsen both motor and non-motor symptoms.[45] Neuroimaging studies have identified widespread white matter changes in PD, indicating that myelin integrity may be affected beyond the dopaminergic system.[46] Diffusion tensor imaging shows decreased fractional anisotropy in multiple brain regions, reflecting microstructural damage.[47] These results suggest that PD involves not only gray matter degeneration but also significant white matter pathology, which impairs neural connectivity and contributes to the motor and cognitive issues experienced by patients. At the molecular level, myelin dysfunction in PD may be associated with oxidative stress and neuroinflammation. Oligodendrocytes, which produce myelin, are vulnerable to oxidative damage due to their high metabolic activity and lipid-rich makeup.[44] In PD, increased reactive oxygen species and cytokines impair oligodendrocytes, leading to demyelination, reduced axonal support, disrupted neuronal communication, and accelerated neurodegeneration. Genetic studies show that variants in genes such as *GBA* and *LRRK2* affect lipid metabolism and myelin maintenance, possibly hindering repair and worsening PD.[48] Postmortem studies reveal changes in myelin proteins, such as myelin basic protein, indicating that myelin pathology plays a key role.[49] Myelin issues in PD also relate to non-motor symptoms such as cognitive decline and depression.[49] Therefore, therapies that promote myelin repair, oligodendrocyte regeneration, or lipid metabolism might benefit patients with PD (Figure 3).

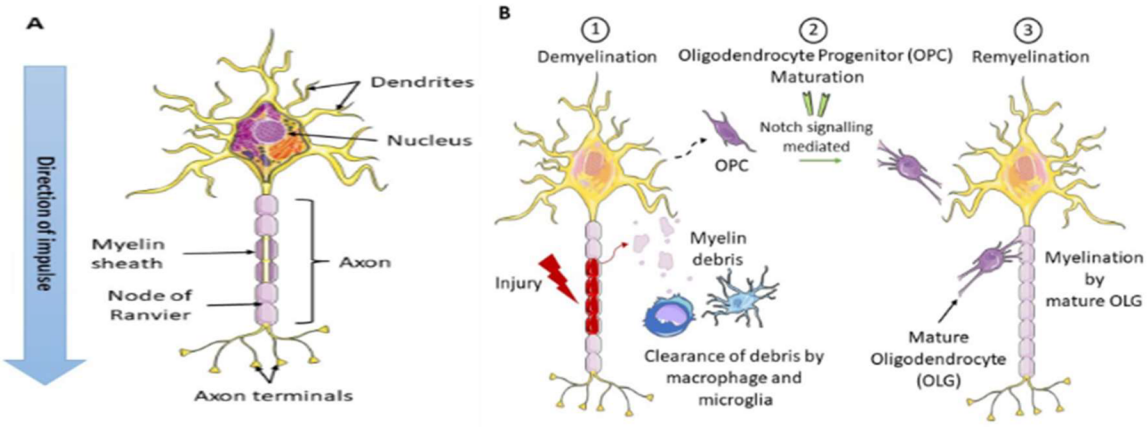


Figure 3. Myelin anatomy and the processes of demyelination and remyelination. (A) The myelinated neuron and (B) the demyelination process resulting from injury, followed by oligodendrocyte progenitor cell maturation, and remyelination. Reprinted from Parilla *et al.*[50]

4. Demyelination as a secondary bystander in Parkinson's disease

Parkinson's disease has been recognized for decades as a synucleinopathy, characterized by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta and the presence of Lewy bodies, which are intraneuronal protein aggregates primarily composed of misfolded α-synuclein.[51-53] The principal clinical symptoms, bradykinesia, tremor, rigidity, and postural instability, are directly associated with this nigrostriatal dopamine deficiency. Nevertheless, mounting evidence from neuropathological and neuroimaging studies indicates that PD pathology extends beyond the dopaminergic system and the nervous system. One notable non-neuronal pathology is demyelination, which involves damage or loss of myelin sheaths surrounding axons. In the context of PD, demyelination is not considered a primary etiological factor but rather a significant secondary process that exacerbates neurodegeneration and influences clinical progression.[54]

4.1. The "bystander" hypothesis

Oligodendrocytes are myelinating cells within the CNS that facilitate the rapid conduction of action potentials and support the integrity of axons and neurons.[55] Their

progenitor cells are distributed throughout the adult brain, serving as a continual source for oligodendrocyte replacement and enabling myelin adaptation.[56] Recent research has increasingly recognized that oligodendrocytes, their progeny, and myelin play crucial roles in the development and progression of neurodegenerative diseases, thereby enriching our understanding of these pathological conditions.[57,58] The "secondary bystander" hypothesis posits that demyelination in PD is not the primary causative factor but rather a consequence of the principal neurodegenerative processes, such as α-synuclein pathology and neuroinflammation.[56] In this context, myelinating oligodendrocytes and their myelin sheaths become passive "bystanders" damaged by the toxic environment generated by neuronal dysfunction and death. This secondary demyelination subsequently aggravates neuronal injury, thereby establishing a detrimental cycle that further debilitates neurons and accelerates disease progression.[55,59]

4.2. Key mechanisms linking Parkinson's disease pathology to secondary demyelination

4.2.1. Toxicity and disruption of axoglial signaling

Oligodendrocytes, responsible for producing myelin in the CNS, are susceptible to aggregated α-synuclein.[60,61] Additionally, some studies suggest that oligodendrocytes may naturally express low levels of α-synuclein, rendering them vulnerable to misfolding and aggregation similar to those observed in neurons.[62] Neurons and oligodendrocytes constantly communicate to sustain myelin. In PD, ongoing neuronal dysfunction and loss disrupt these essential signals, leading to failure of myelin maintenance and ultimately its breakdown.[63]

4.2.2. Chronic neuroinflammation and oxidative stress

Parkinson's disease brains exhibit ongoing neuroinflammation, characterized by activated microglia, the brain's resident immune cells, and elevated levels of pro-inflammatory cytokines.[64,65] This inflammatory state is highly harmful to oligodendrocytes. Activated microglia can produce reactive oxygen species (ROS) and pro-inflammatory molecules such as tumor necrosis factor-alpha, which can hinder the differentiation of oligodendrocyte precursor cells and cause direct damage to mature oligodendrocytes and myelin sheaths.[66] The high energy requirements for myelination and the susceptibility of oligodendrocytes to oxidative stress make them key targets in a brain environment marked by mitochondrial dysfunction and oxidative damage, both of which are well-established features of PD.[67,68]

4.3. Implications of secondary demyelination in Parkinson's disease

The demyelination observed in PD is not merely a secondary effect; it has significant functional implications.[69] Myelin is essential for providing metabolic and trophic support to axons.[70-72] When demyelination occurs, axons become exposed, energy-deficient, and more prone to degeneration, thereby worsening the initial neuronal loss.[73,74] It also hampers or halts the conduction of electrical impulses along axons, disrupting the timing of neural signals within the basal ganglia and other areas. This affects motor functions and also contributes to non-motor symptoms such as cognitive decline and depression.[75,76] The integrity of white matter pathways, particularly those connecting cortical areas, is crucial for the execution of higher cognitive functions. Extensive demyelination offers a plausible basis for the cognitive decline and dementia often seen in advanced PD.[77,78]

5. Theory of axon degeneration

5.1. The Wallerian theory

Waller, in 1850, documented axon and myelin degeneration after a hypoglossal nerve transection in frogs, reporting that the distal part of the nerve naturally degenerated, a process now known as Wallerian degeneration (WD).[79,80] This was initially regarded as passive, a view that changed in 1989 when Lunn *et al.*[81] found that the "Wallerian Degeneration Slow" (Wlds) mouse strain showed WD.[82,83] In these mice, sciatic nerve transection allowed distal axons to stay intact for up to two weeks, whereas in Wlds-type mice, distal axon preservation lasted less than two days. Electron microscopy revealed delayed degeneration of presynaptic terminals, with synaptic breakdown occurring about a week later, indicating that CNS degeneration progresses more slowly than in the peripheral nervous system (PNS).[84] These findings demonstrate that axons have an intrinsic, active self-destructive mechanism, making this model a breakthrough that shifted WD understanding from a passive to an actively regulated state. In 1850, Waller called WD "neuronal cytoplasmic trophoblastic axons" or "neuronal cytotoxic axons."[85] According to Rozon *et al.*,[86] the "neuronal theory" was proposed by Cajal in 1906, while Weiss and Hiscoe in 1948 linked axonal transport to WD, according to Tian *et al.*[85] Hickey *et al.*[87] modeled myelin breakdown using ultrastructural and biochemical data. Figlewicz *et al.*[88] showed that debris clearance in young animals is faster, indicating a higher regenerative capacity. Ultrastructural studies in 1985 by Ohara and Ikuta[89] identified early WD stages in mouse nerves, including axonal degeneration, myelin breakdown, endothelial detachment, and macrophage

invasion. Endothelial fibroblasts form Buengner bands to assist regeneration. Lindholm *et al.*[90] found increased interleukin-1 post-injury, which activates macrophages and raises nerve growth factor mRNA. The discovery of the Wlds transgenic mouse (C57BL/6/Ola) advanced the understanding of WD. It showed that WD of distal axons is an active, intrinsic process, independent of the presence of intact axons, recruited cells, myelin debris, or Schwann cell proliferation. The Wlds gene encodes a protein combining Ube4b (an E3 ligase) and nicotinamide mononucleotide adenylyltransferase 1. Unlike wild-type axons, which quickly degenerate after injury, Wlds-expressing axons exhibit delayed degeneration and can remain functional for several weeks.[21,85]

Research shows that WD in the PNS and CNS causes axonal degeneration and myelin clearance, highlighting the crucial roles of these systems in neuronal maintenance and repair. Axons degenerate early after injury, with both proximal and distal segments degenerating within 30 minutes, a phenomenon known as "acute axonal degeneration."[91] Chronic or WD develops over 8–24 hours, with axonal swelling preceding the loss of continuity. CNS reacts quickly, forming axonal spheroids within six hours; PNS shows minimal changes up to 37–44 hours.[92,93] Treatments such as calpain inhibitors or calcium chelators do not prevent membrane breakdown, indicating the presence of unknown calcium-independent mechanisms. Over time, cytoskeletal components, influenced by increased actin and tubulin assembly, break down, affecting transport and regeneration.[94] Granular disintegration of the axonal cytoskeleton (GDC) involves ubiquitin–proteasome system-dependent microtubule dismantling and calpain-driven neurofilament degradation.[80,94] Evidence suggests calpain activation occurs early after injury, promoting degeneration.[95] Elevated calcium and potassium ions prolong degeneration; the release of calcium from stores triggers secondary WD.[96] Axonal GDC is crucial in WD, with myelin changes and immune cell infiltration following GDC.[97] A one-week gap exists between axonal degeneration and GDC in humans, offering a potential intervention window.[80,98]

Myelin is a lipid–protein sheath produced by Schwann cells in the PNS and by oligodendrocytes in the CNS, wrapping around axons to support, protect, and facilitate impulse transmission. Schwann cells develop from precursors in three stages: from cristae to Schwann cell precursors, to immature Schwann cells, then to pre-myelinating or non-myelinating (Remak) Schwann cells. Pre-myelinating Schwann cells undergo "radial sorting" of myelinating axons > 1 μm, and some produce myelin.[28,41] Demyelination typically results from inflammatory responses to peripheral nerve injury, primarily through WD, which delays myelin formation and causes breakdown.[73] In the PNS, this accelerates debris clearance and aids regeneration.[55] Research indicates that demyelination precedes axonal cytoskeleton degeneration. Early WD is characterized by increased sodium current, which occurs more rapidly than conduction failure and axonal disintegration, suggesting that sodium channel blockers may be a potential therapeutic approach.[99]

6. Aging as a comorbidity

Parkinson's disease affects more than 1% of the population over the age of 60 in the United Kingdom, accounting for over 127,000 individuals, and approximately 500,000 in the United States. Among individuals aged 85 and older, the prevalence increases by 5%, underscoring the heightened risk associated with aging.[93,100,101] Although often considered an age-related disorder, around 5% of patients exhibit symptoms before age 60, primarily due to mutations in an expanding list of genes that influence protein metabolism or mitochondrial function.[102] Aging remains the predominant risk factor, with incidence rising sharply after age 60 and increasing exponentially in subsequent decades.[103] Approximately 5–10% of cases are familial PD, which is inherited in a Mendelian manner. At the same time, genome-wide association studies have identified common genetic variants associated with increased susceptibility.[104] The majority of cases are sporadic or idiopathic. Environmental factors, including exposure to pesticides and traumatic brain injury, elevate the risk, whereas protective factors such as tobacco use and physical activity have been observed to reduce it.[105] Although aging, genetics, and environmental influences all contribute to disease development, the majority of cases are likely the result of complex interactions among these factors.[106]

Many studies have measured neuronal loss in other brain regions with aging, although none have shown a degree of cell loss comparable to that observed within the substantia nigra.[107-111] Neuronal numbers have been shown to remain relatively stable throughout old age within the hippocampus, putamen, medial mammillary nucleus, hypothalamus, and the nucleus basalis of Meynert. At the same time, it was estimated that the neocortical neurons might show a loss of only 10% over the entire lifespan.[112,113] However, in other dopaminergic populations, including the ventral tegmental area and the retrorubral area, cell loss may reach 50%.[107,114] According to previous studies[115,116] Dopaminergic neuronal populations appear to be preferentially vulnerable to loss with aging compared with many other brain regions and those affected by other neurodegenerative disorders, e.g., the hippocampus. The

selective vulnerability of dopaminergic neurons in the substantia nigra pars compacta to aging is a multifaceted phenomenon.[114,117,118] However, recent advances in animal models of PD have established a central pathophysiological role of oxidative stress, mitochondrial dysfunction, and neuromelanin accumulation.[109,117,119] Despite these advances, there is currently no comprehensive theory that unifies selective vulnerability with other factors implicated in PD pathophysiology, such as Lewy pathology, immune responses, and blood–brain barrier disruption.

7. Demyelination as a potential contributor to Parkinson's disease pathogenesis

Demyelination, the targeted destruction of the myelin sheath that insulates neuronal axons, is a fundamental pathological process underlying a wide range of neurological disorders.[120-122] Although PD is mainly considered a gray matter disease, recent research highlights white matter changes.[123] In PD, α-synuclein misfolds and aggregates in neurons, while in multiple system atrophy, it accumulates in oligodendrocytes, forming glial cytoplasmic inclusions. This distinction is not absolute, as glial cytoplasmic inclusion-like structures appear in PD oligodendrocytes with α-synuclein mutations.[124] Additionally, some PD cases show demyelinating lesions across brain regions. Biochemical studies also reveal changes in oligodendrocytes in PD.[125] The myelin sheath, formed by oligodendrocytes in the CNS and Schwann cells in the PNS, enables fast saltatory conduction and efficient neuronal communication.[126] Its loss disrupts axonal support, leading to degeneration and neurological disability.[127] Evidence indicates that demyelination is a key driver of disease and a therapeutic target.[128]

Demyelination is a key pathological cause in many neurological disorders.[57,129] Evidence indicates that immune-mediated attacks, genetic factors, and oligodendrocyte dysfunction can trigger demyelination. Neuroimaging techniques enable early detection, while physiological studies reveal a pathogenic cascade progressing from conduction failure to metabolic stress and eventual axonal loss.[130] Effective therapeutic strategies should therefore aim to suppress detrimental immune responses while promoting remyelination and neuroprotection, thereby preserving axonal integrity.

8. Evidence supporting demyelination as a contributing factor

8.1. Neuropathological evidence

The role of demyelination as an underlying factor in PD has become more apparent through neuropathological examinations of individuals with PD, which have historically defined PD by the presence of Lewy bodies and the deterioration of dopaminergic neurons in the substantia nigra pars compacta.[131,132] Studies have shown that, on postmortem examination, PD brains exhibit widespread structural abnormalities, including white matter and myelin degeneration, with specific areas of the cortex and subcortex demonstrating reduced myelin and oligodendrocyte density, indicating that myelin loss may increase the vulnerability of cells that require the integrity of myelinated axons.[133-137] By disrupting axonal integrity, myelin breakdown impairs signal transmission and increases the likelihood of degeneration, suggesting that the degree of demyelination correlates with PD severity, particularly in individuals with cognitive decline.[138] According to Xie *et al.*,[139] numerous genes responsible for producing various components of myelin are dysregulated in PD brains. This dysregulation affects both the structure and function of myelin, supporting the view that demyelination may occur alongside neuronal loss rather than solely as a downstream consequence. The location of white matter lesions in individuals with PD shows considerable overlap with sites of both motor and non-motor symptomatology, suggesting that demyelination contributes to the variance in PD characteristics, with a growing body of neuropathological evidence supporting that demyelinating events play an important yet underappreciated role in PD pathophysiology.[15,131,140,141]

8.2. Neuroimaging evidence

Research using neuroimaging techniques has provided strong evidence that demyelination is an important factor in the pathogenesis of PD.[142] Diffusion tensor imaging, magnetization transfer imaging, and myelin water fraction (MWF) mapping show that white matter abnormalities are present throughout the brain in individuals with PD, with decreased fractional anisotropy and increased mean diffusivity, both of which are consistent with damaged myelin.[143,144] Recent studies of white matter lesions have demonstrated a clear correlation between the extent of myelin loss in motor-related tracts and the severity of motor impairment. These lesions are observed not only in motor regions but also in areas associated with cognition and mood.[75,145,146] This finding corresponds to clinical observations that patients with PD often show decreased cognitive ability or depressive symptoms, which may be related to myelin loss and increased microglial cells.[147] Imaging methodologies are currently being studied to evaluate their potential as biomarkers of myelin loss/microglial cell activation, providing information on the development of PD before the occurrence of significant neuronal loss.[148] Evidence from longitudinal studies

shows that ongoing demyelination occurs as the disease progresses, further supporting a role for demyelination in the pathophysiology of PD.[149] Therefore, neuroimaging evidence provides considerable support for the notion that demyelination plays a significant role in contributing to motor and non-motor symptoms associated with PD.

8.3. Physiological evidence

The role of myelin in supporting rapid and efficient nerve transmission has been well established, and disruptions to myelin can impair communication between cortical and subcortical regions of the brain, with demyelination already shown to slow conduction velocity, impair neural network synchronization, and limit neural plasticity, all of which contribute to classic motor symptoms (bradykinesia, rigidity, and tremor).[150] The relationship between increased white matter lesions and increased cognitive decline/psychiatric symptoms indicates that the effects are magnified by the absence of dopaminergic neurons.[151] Biochemical evidence of tissue loss due to demyelination has also been found in cerebrospinal fluid through an increase in myelin basic protein, suggesting that demyelination is an active pathological process rather than a passive consequence.[152,153] Electrophysiological studies in patients with PD demonstrate reduced long-range cortical excitability and weakened long-range cortical connectivity. These findings indicate impaired myelin function, supporting the role of demyelination in the physiological basis of both motor and non-motor symptoms and highlighting its significant contribution to PD pathogenesis.[154,155]

8.4. Genetic and molecular evidence

Demyelination has been strongly implicated in PD by genetic and molecular analyses, with over 200 genes involved in PD pathology, many of which are associated with myelin formation, maintenance, and repair, including mutations in *PRKN*, *PINK1*, and *LRRK2*. These genes play roles in mitochondrial function and cellular stress response pathways that indirectly affect oligodendrocyte survival and myelin integrity.[156-158] Transcriptomic studies have shown a downregulation of myelin-related gene expression in the brains of people with PD, which is involved in oligodendrocyte differentiation and myelin sheath stability.[159,160] Furthermore, there have been examples of epigenetic alterations in the expression of these genes, suggesting that environmental factors may further increase genetic susceptibility to demyelination.[147,161] Overall, both genetic and molecular evidence indicate that demyelination is integral to the molecular architecture of PD and suggest that targeting myelin repair pathways may represent a potential therapeutic strategy for PD.

9. Synthesizing the evidence: The vicious cycle in Parkinson's disease

Traditionally, PD was mainly characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta and the accumulation of misfolded α-synuclein in Lewy bodies.[162] However, recent studies show that other brain cells, especially oligodendrocytes, are actively involved.[163,164] This has led to a "vicious cycle" model where neuronal dysfunction and oligodendrocyte abnormalities reinforce each other, speeding up the disease's progression. According to this model, neuronal damage triggers oligodendrocyte dysfunction, which, in turn, exacerbates neuronal dysfunction, thereby explaining the self-perpetuating nature of neurodegenerative diseases such as PD.[165] Disrupting this cycle is now a key goal for future therapies. Factors such as mutations, toxins, or aging damage neurons,[166] leading to α-synuclein misfolding and aggregation. Stressed neurons release toxic α-synuclein, which damages oligodendrocytes and myelin.[167] Oligodendrocytes are particularly vulnerable to α-synuclein. When they internalize α-synuclein, it induces endoplasmic reticulum stress and mitochondrial dysfunction, leading to demyelination and challenges with remyelination, even in the presence of neuronal regeneration. Additionally, oligodendrocytes may spread pathology via exosomes, contribute to remyelination deficits, and promote neuron regeneration.[168]

Axonal damage and energy deficits in the CNS lead to the loss of healthy myelin, with severe consequences for neurons.[169] When demyelination occurs, it disrupts the transmission of electrical impulses along axons, leading to slower or blocked signals.[170] Myelin is essential for the rapid saltatory conduction of action potentials, and its depletion forces neurons to use significantly more energy to maintain signaling. Moreover, oligodendrocytes support axonal metabolism by providing lactate, a vital energy source whose failure leads to a localized energy crisis for the axon.[171] The combined issues of impaired signaling and energy deficiency increase neuronal stress, promoting further α-synuclein aggregation and cell death, creating a damaging cycle that intensifies over time, which then continues with even greater intensity.[172]

9.1. The bidirectional model

The neuron-to-oligodendrocyte and oligodendrocyte-to-neuron models emphasize reciprocal interactions between neurons and oligodendrocytes, providing a more comprehensive understanding of PD pathogenesis.[173] It transcends a neuron-centered perspective by underscoring the importance of oligodendrocytes and myelin integrity.[174] Therapeutic strategies aimed at protecting

oligodendrocytes, promoting remyelination, or supporting their metabolic functions present promising new opportunities to decelerate or cease the progression of PD by disrupting this detrimental cycle.[175] This cycle involves two primary communication pathways, each exhibiting a distinct direction of flow.

9.1.1. Neuron-to-oligodendrocyte signaling

This is referred to as "the initiating and propagating arm," which elucidates how compromised neurons adversely affect oligodendrocyte health.[173] This signaling pathway contributes significantly to white matter deterioration, a phenomenon frequently observed in neuroimaging studies of patients with PD.[176,177] The extent of damage results not solely from axonal loss but also involves active myelin degradation. The primary etiological factor in this degeneration, or myelin disintegration, is α-synuclein-induced toxicity.[57,178,179] Oligomers and fibrils of α-synuclein originating from neurons are detrimental to oligodendrocytes. Empirical evidence demonstrates that exposure to these aggregates induces oligodendrocyte apoptosis and decreases the levels of myelin basic protein, an essential constituent of myelin.[180-182] Neuroinflammation occurs when microglia and astrocytes are activated in response to neuronal injury and α-synuclein release, leading to the production of pro-inflammatory cytokines such as tumor necrosis factor-α and interleukin-1β.[183,184] This inflammatory response damages oligodendrocytes and hampers the maturation of oligodendrocyte precursor cells, hindering their ability to repair myelin.[185] Additionally, the regular release of survival and support factors by neurons, which bolster oligodendrocyte function, is likely disrupted, leaving oligodendrocytes more vulnerable to damage in PD.[185-187]

9.1.2. Oligodendrocyte-to-neuron signaling

The amplifying arm delineates the role of dysfunctional oligodendrocytes in neuronal degeneration.[188] This signaling from oligodendrocytes to neurons exacerbates axonal damage, accelerates neurodegeneration, and impacts non-motor symptoms of PD, such as cognitive decline and depression, which are linked to broader network dysfunction beyond the nigrostriatal pathway.[189,190] Healthy oligodendrocytes function as metabolic partners to axons by supplying lactate, produced through their enhanced glycolytic activity, via monocarboxylate transporters.[191] Neurons utilize this lactate to generate adenosine triphosphate. In PD, dysfunctional oligodendrocytes fail to provide this essential metabolic support, leading to energy deprivation in axons and heightened vulnerability to degeneration. The deterioration of axonal integrity leads to myelin sheath degradation, exposing axons to a detrimental ionic environment.[192-194] This exposure causes ion channel dysfunction, leading to increased sodium and calcium influx and increased energy demands on the neuron to restore ionic homeostasis. However, these energy requirements are unmet due to an existing energy deficit.[195] Emerging evidence suggests that oligodendrocytes may contribute to the propagation of α-synuclein pathology; they may sequester the protein, but upon cell death, release it into the surrounding environment, potentially facilitating aggregation in adjacent neurons.[196-200]

10. Future directions

10.1. Diagnostic and prognostic biomarkers

According to previous studies,[201,202] there have been significant advancements in the management of PD. Currently, PD diagnosis relies on clinical symptoms, which often only manifest after considerable neuronal loss.[203] Biomarkers such as the α-synuclein seed amplification assay (SAA) facilitate biological diagnosis, substantially reducing the incidence of misdiagnosis and enabling detection during the prodromal phase.[204] Biomarkers indicative of the core pathology of PD may enhance early diagnostic accuracy, facilitate subtype identification, and accelerate clinical research.[205,206] The disease is characterized by the accumulation of misfolded, aggregated α-synuclein within the substantia nigra and other brain regions, with aggregates also observed in PNS tissues.[204] Techniques that amplify misfolded proteins—originally devised to detect the self-replicating scrapie isoform of the prion protein in prion diseases—have been adapted to detect α-synuclein seeds in PD and related disorders.[207] These include real-time quaking-induced conversion, protein misfolding cyclic amplification, and, more recently, the SAA.[208,209] These biomarkers can forecast disease progression and crucial symptoms, thereby supporting personalized therapeutic strategies. For example, elevated blood levels of neurofilament light chain are associated with accelerated cognitive decline.[210,211] They serve as quantifiable indicators of disease activity, which are essential for evaluating novel therapies in clinical trials.[212] Extensive multicenter studies are imperative to validate biomarkers like SAA across diverse populations.[202,213] The prospective approach involves integrating multiple biomarkers, such as imaging modalities (DaTSCAN, novel PET ligands), biofluids (SAA, neurofilament light chain), and digital biomarkers derived from wearable devices, to achieve a comprehensive understanding.[214,215] The primary objective is to develop more accessible diagnostic techniques for cerebrospinal fluid-based testing, including blood-based assessments[207,211,212] or skin biopsies.[205]

Common *in vivo* magnetic resonance imaging methods for evaluating myelin in the CNS include MWF, diffusion-weighted imaging, and magnetization transfer ratio.[203] The MWF model relies on the different relaxation times of water within myelin compared to water in other areas, such as intracellular and extracellular spaces.[216] In multicomponent T2 neuroimaging, these components are distinguished by their T2 relaxation times: short T2 times reflect myelin water, intermediate T2 times indicate intra- and extracellular water, and long T2 times are linked to cerebrospinal fluid.[217] Measuring the proportion of myelin water signal provides a specific marker for myelin health. However, MWF has limitations, as it relies on complex multi-echo T2 sequences that require precise timing, calibration, and advanced data analysis.[203] Diffusion-weighted imaging also helps evaluate myelin and white matter integrity by providing structural information through water diffusion properties in various tissue compartments.[203,218] Diffusion tensor imaging is a specialized diffusion-weighted imaging technique that leverages the anisotropic diffusion of white matter fibers to offer insights into microstructure and potential myelin condition.[219-221]

10.2. Emerging therapeutic alternatives

The focus is shifting from symptomatic dopamine replacement to strategies that target the root causes of PD.[222,223] The goal is to develop therapies that slow, stop, or reverse disease progression. These treatments may be personalized based on patient-specific PD subtypes identified by genetic and biomarker profiles. When reliable biomarkers are validated, clinical trials can include patients in the early, prodromal stage, using biomarker changes as surrogate endpoints to improve trial efficiency.[165] Currently, advanced clinical testing is underway for immunotherapies, such as prasinezumab, and active vaccines aimed at removing pathological α-synuclein.[213,224] These approaches include gene delivery of neurotrophic factors, such as *GDNF*, and targeting genetic variants, including *LRRK2* and *GBA*.[225] Emphasizing lysosomal and *GBA1* therapies is crucial for progress, given their key role in PD diagnosis. Given the fundamental role of lysosomal function, boosting this system with GCase modulators shows promise.[226] Additionally, developing drugs to combat chronic neuroinflammation remains an important area of research.[227] This review highlights that oligodendrocytes may be affected early in PD and could contribute to disease development. Evidence indicates the presence of pathological α-synuclein in oligodendrocytes, along with associated myelin damage, which can impair neural signaling and trophic support, potentially accelerating neurodegeneration.[228] If demyelination is an initial event, remyelination therapies might serve as effective neuroprotective strategies.[229,230] Imaging techniques to assess myelin integrity could serve as useful prodromal biomarkers, suggesting that PD may also be called "gliopathy" rather than a synucleinopathy.[166,231]

11. Conclusion

There is growing evidence from neuropathological and neuroimaging studies suggesting the pathology of PD extends beyond the dopaminergic system and brain tissues. Demyelination, a major non-neuronal pathological process, is characterized by the loss or deterioration of the myelin sheaths that surround axons. Although traditionally considered a secondary phenomenon that exacerbates neurodegeneration and influences clinical progression, accumulating evidence indicates that it may also play a more active role in disease pathogenesis. Recognizing the role of demyelination provides new insights into PD mechanisms and highlights potential therapeutic strategies to promote remyelination, preserve axonal integrity, and slow disease progression.

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